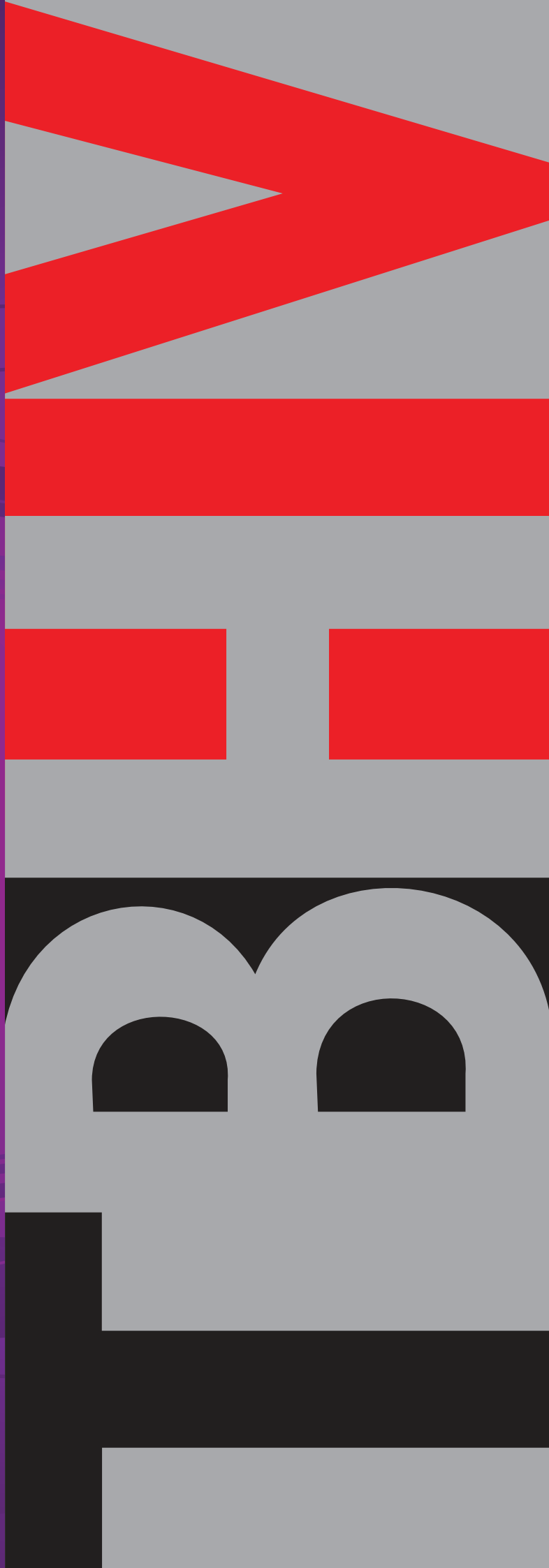
Priority research questions for TB/HIV in HIV-prevalent and resource-limited settings



World Health Organization

TB/HIV Working Group

Stop TB Partnership

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CONTENTS

ABBREVIATIONS

aHR	adjusted hazard ratio
AIDS	acquired immunodeficiency syndrome
aOR	adjusted odds ratio
BCG	bacille Calmette-Guérin
CI	confidence interval
CYP	cytochrome P450
DNA	deoxyribonucleic acid
ELISPOT	enzyme-linked immunosorbent spot
HIV	human immunodeficiency virus
HR	hazard ratio
IGRA	interferon-gamma release assay
IRIS	immune reconstitution inflammatory syndrome
MDR	multidrug resistant
MODS	microscopic-observation drug susceptibility
OR	odds ratio
P	p-value
PCR	polymerase chain reaction
RCT	randomized controlled trial
RNA	ribonucleic acid
RR	relative risk
TB	tuberculosis
TDR	UNDP/UNICEF/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund
WHO	World Health Organization
XDR	extensively drug resistant

EXECUTIVE SUMMARY

In November 2008, the Global TB/HIV Working Group of the Stop TB Partnership, in collaboration with the WHO Stop TB and HIV/AIDS departments and the UNDP/UNICEF/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) called for the revision of the 2005 TB/HIV research priorities agenda for resource-limited settings.

Literature review was conducted to assess the current state of research and to identify knowledge gaps in six key pre-defined areas of TB and HIV coinfection: TB prevention; intensified TB case-finding; TB treatment in people living with HIV; drug-resistant TB and HIV; childhood and maternal TB and HIV; and integration of TB and HIV services. The results of the literature review, together with discussions held during an international meeting on TB/HIV research issues in Cape Town, South Africa in July 2009 form the basis of the document.

The process was advised by international TB and HIV experts in a form of an Advisory Group and a Peer Review Committee. Members included technical experts and researchers in the field of TB and HIV, health policy-makers, people living with HIV and their advocates, TB and HIV programme managers, representatives of donor agencies, and WHO staff. Members of the Advisory Group and the Peer Review Committee reviewed the document and were also asked to list their three top-priority questions under each pre-defined area based on the review of the document and their view. This allowed compiling a list of 77 questions for all areas. These questions were then rated for prioritization based on defined criteria that considered effectiveness, deliverability, answerability and equity issues around each question. Priority scores were eventually produced by calculating the mean of the scores for each of the 77 questions, and questions were ranked under each area based on the score. A password protected web-based consultation system was used for the prioritization process.

The top research question for *TB prevention among people living with HIV* include the need for an optimal TB screening algorithm to be used across different settings, with different TB and HIV disease burden, to safely initiate preventive TB therapy; the best infection control interventions that effectively reduce *M. tuberculosis* transmission in health-care settings, at home and in the community; and the optimal duration, safety, efficacy and cost-effectiveness of isoniazid preventive therapy alone or added with antiretroviral therapy in reducing the risk of active TB compared to antiretroviral therapy alone among people living with HIV, particularly under programme conditions.

In the area of intensified TB case-finding, the question for a simple and rapid point-of-care "TB dipstick test" to diagnose all types of TB in all patients, including children and people living with HIV was the topmost priority identified. Likewise the optimal TB screening and diagnostic algorithm for use across all settings with different HIV and TB diseases burdens to enable screening of all forms of TB, and that can be integrated into routine care; and the programmatic impact of the most promising diagnostic tools currently available for rapid TB diagnosis, including diagnosis of drug resistance and of smear-negative patients identified through large-scale evaluation studies were identified as priorities.

The safety, efficacy and pharmacokinetic parameters of new and novel drugs that could replace rifampicin and shorten TB treatment, to cure susceptible and drug-resistant TB in people living with HIV, with or without antiretroviral therapy; the best first and second-line antiretroviral therapy regimens in terms of safety, efficacy, tolerability, optimal dosage of drugs and drug interactions, to use in combination with a rifampicin-based TB regimen; and the optimal time to start antiretroviral therapy in HIV-infected patients who have active TB disease, both drug-susceptible and drug-resistant types were the priority research questions identified In the area of *TB treatment for people living with HIV*.

The three top-priority questions for *drug-resistant TB and HIV infection* were the programmatic impact and benefit to individual treatment outcomes of line probe assays and other non-culture-based assays for diagnosis of drug-resistant TB at the peripheral level of care; the true burden, predictors and transmission dynamics of MDR-TB and XDR-TB in high HIV prevalence and resource-limited settings; and the best model of care for drug-resistant TB in settings with high burden, in light of basic public and individual patient rights.

Under *maternal and childhood TB and HIV coinfection*, the priority questions identified include the best clinical algorithms and diagnostic tools to improve TB screening and diagnosis in HIV-infected infants and children, including diagnosis of BCG-related TB, TB-IRIS and drug-resistant TB; the effect of antiretroviral therapy in preventing TB in children; and the optimal antiretroviral therapy to use in combination with a rifampicin-based TB regimen in HIV-infected infants and children and the optimal time to initiate antiretroviral therapy in children being treated for TB.

The research priorities identified in the *TB and HIV services integration* area include the best strategies and optimal models to integrate and deliver joint TB/HIV interventions, including antiretroviral therapy, at community and health sector levels to HIV-infected TB adults, children and families; the best operational models to increase and scale-up laboratory capacity, including implementing new TB diagnostic techniques and drug-susceptibility testing, and improve diagnosis of TB at all levels of care; and identifying the barriers to HIV care for people living with HIV, adults, children and families, and to access HIV and TB care, and antiretroviral therapy for those coinfected with TB, from patient and health-care worker's perspective, and how to address them.

The priority questions reflect a wide range of research needs in basic, epidemiology, clinical, and operational research. Implementation of research priorities should capitalize on financial resources mobilized through the Global Fund for AIDS, Tuberculosis and Malaria, and the United States President's Emergency Plan for AIDS Relief among others. Concomitant to increasing the scientific interest of the research community towards these questions, enhancing fund allocation by national governments of resource constrained settings is very crucial. It is believed the priority research questions identified in this document provide guidance on what needs urgent scientific interest and funding to address the dual TB and HIV epidemic.

INTRODUCTION

Rationale

Tuberculosis (TB) is a leading killer among people living with human immunodeficiency virus (HIV). At least one in four deaths among people living with HIV can be attributed to TB, and many of these deaths occur in resource-limited settings. Collaborative TB/HIV activities are essential to prevent, diagnose and treat TB among people with HIV and HIV among TB patients, and to ensure that HIV-positive TB patients are identified and treated appropriately. In recent years, the implementation of collaborative TB/HIV activities has been rising globally. This has created the need for additional research into how to deliver quality and integrated services for TB and HIV prevention, treatment and care, and thus prevent unnecessary deaths.

In 2005, TB/HIV research priorities for resource-limited settings were defined during an expert consultation convened by the Global TB/HIV Working Group of the Stop TB Partnership (*1*). The consultation was undertaken in collaboration with the World Health Organization (WHO) Stop TB Department and Department of HIV/AIDS, and the United Nations Development Programme (UNDP)/ United Nations Children's Fund (UNICEF)/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). Five priority areas for research were identified: preventive therapy for TB; co-trimoxazole prophylaxis; antiretroviral therapy for people living with HIV, who have or develop TB; intensified TB case-finding; and new tools and diagnostic algorithms to improve the diagnosis of smear-negative TB. Cross-cutting issues were also identified.

The consultation also formulated 30 research questions falling under the five priority areas. Partners, donors, research agencies and countries were encouraged to implement the research priorities they considered crucial for improving TB and HIV control.

To determine whether the 2005 TB/HIV research agenda stimulated research, a literature review was conducted in 2009 using the United States National Library of Medicine PubMed database[1] and key words pertinent to each of the 30 research questions. A total of 209 research publications published between 2004 and 2009 were identified (Annex 1). The number of published manuscripts relevant to the 30 questions increased each year; 20 relevant manuscripts were published in 2004, increasing to 56 in 2009 (Annex 1).

In addition to these published studies, there are ongoing randomized control trials (RCTs) that address some of the priorities set in 2005. For example, questions currently being studied through RCTs include the optimal time to initiate antiretroviral therapy in HIV-infected TB patients, and strategies to improve TB case detection. Results from these trials are expected in the next year or two. Also, since 2005, the WHO has released two relevant publications:

- Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults, released in 2006
- Improving the diagnosis of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents. Recommendations for HIV-prevalent and resource constrained settings, released in 2007.

In view of the impact of the 2005 TB/HIV research agenda in stimulating research publications, and the current unmet needs, the Global TB/HIV Working Group of the Stop TB Partnership, in collaboration with the WHO Stop TB and HIV/AIDS departments and the TDR, called for revision of the TB/HIV research priorities agenda for resource-limited settings. This publication provides the revised research agenda, and explains how it was achieved.

Purpose

This document is intended to raise awareness about TB/HIV research priorities (i.e. areas that require urgent funding and scientific interest), help coordinate advocacy efforts, and encourage research funding. The aim is to increase the implementation of high-quality, integrated TB/HIV interventions in resource-limited settings. The document outlines a revised research priority agenda based on the latest evidence in six key areas of TB and HIV coinfection (covered in Chapters 1-6):

[1] Available at http://www.ncbi.nlm.nih.gov/pubmed

- TB prevention
- intensified TB case-finding
- TB treatment in people living with HIV
- drug-resistant TB and HIV
- childhood and maternal TB and HIV
- integrated TB and HIV services.

Target audience

This document is intended for researchers, representatives from funding agencies, activists and policy-makers in the TB and HIV fields.

Document preparation process

From March to June 2009, a writing group from the WHO Stop TB and HIV/AIDS departments conducted a literature review of the current state of research progress in the six key areas described above, using the PubMed database, and identified knowledge gaps in these critical areas. The results of the literature review form the basis of this document, which was prepared with the assistance of members of an Advisory Group and a Peer Review Committee. The membership of these groups (listed in the Acknowledgements) included technical experts in the TB and HIV fields, policy-makers, people living with HIV and their advocates, international and national TB and HIV programme managers, representatives of donor agencies, and members of the WHO Research Policy and Cooperation Department and the TDR. The document content was also informed by discussions held at the international meeting on TB/HIV research issues entitled *Catalysing HIV/TB research: innovation, funding and networking*, Cape Town, South Africa, July 2009.

Prioritization of research questions

Research questions were prioritized based on their potential to:

- guide and accelerate universal and effective implementation of collaborative TB/HIV activities in resource-limited settings
- prevent unnecessary morbidity and mortality due to TB among people living with HIV.

In June 2009, members of the Advisory Group and Review Committee were asked to contribute their three top-priority research questions under each of the six key areas identified above. By October 2009, a list of 77 research questions had been compiled. Each of these 77 questions was then graded, based on defined criteria of effectiveness, deliverability, answerability and equity, adapted from the Child Health Nutrition Research Initiative (*2*) (Annex 2).

Final priority scores were produced in November 2009 by calculating the mean of the scores for each of the 77 questions. Questions with the highest rated priority scores were assigned to the appropriate chapter of this document; they are listed at the end of each chapter. These questions were discussed by the Global TB/HIV Working Group of the Stop TB Partnership on 3 November 2009.

The prioritization method that was used has some limitations. For example, there is a limited role for non-experts, each question needs to be detailed, and it is not possible to rank the importance of a question relative to other questions. Nevertheless, this method values principles of fairness, legitimacy and objectivity; allows experts to independently score the questions; and documents the prioritization process using a transparent and repeatable method that can be reviewed, challenged and revised at any time.

CHAPTER 1: TB PREVENTION

People living with HIV are at increased risk of developing active TB disease. The WHO's *Policy on collaborative TB/HIV activities* recommends a combination of measures to reduce the burden of TB among HIV-infected individuals (*3*). These measures include intensified case-finding, isoniazid preventive therapy, infection control and antiretroviral therapy. This chapter examines research topics that could contribute to improve TB prevention among people living with HIV, including preventive TB therapy, TB infection control, antiretroviral therapy and TB vaccines. The chapter also discusses assays to detect latent TB infection.

1.1 Preventive TB therapy

Meta-analyses of RCTs have shown that, compared to placebo, TB therapy (i.e. any anti-TB drugs) reduces the risk of active TB by 32% in people living with HIV (relative risk [RR] 0.68, 95% confidence interval [CI]: 0.54 to 0.85), and by 62% (RR 0.38, 95% CI: 0.25 to 0.57) in those who are tuberculin skin test positive (*4*). Isoniazid preventive therapy reduces the risk of TB by 33% (RR 0.67, 95% CI: 0.51 to 0.87) in both skin test positive and skin test negative people living with HIV, and by up to 64% (RR 0.36, 95% CI: 0.22 to 0.61) among those with a positive tuberculin skin test (*5*).

Isoniazid preventive therapy has similar efficacy to short-course rifampicin and pyrazinamide in HIV-infected and uninfected individuals (*6*). Similarly, an RCT among HIV-infected tuberculin-positive patients in South Africa did not show any difference in efficacy between intermittent three-month regimens of rifampicin or rifapentine with isoniazid, and isoniazid preventive therapy (*7*).

Multidrug preventive regimens were more likely to be discontinued due to adverse events than isoniazid preventive therapy, which in turn was more likely to be discontinued than placebo (*5*). Results from a multicentre RCT in Brazil, Canada and Saudi Arabia showed that daily rifampicin therapy for four months compared to daily isoniazid for nine months was associated with less severe adverse events among HIV-infected and uninfected patients (risk difference –2.3%; 95% CI: –5% to –0.1%) (*8*). In a trial in South Africa, isoniazid, taken continuously for up to four years, was associated with higher rates of severe adverse events compared to intermittent three-month regimens of rifampicin or rifapentine combined with isoniazid, or daily isoniazid for six months (*7*).

The duration of the protective effect of preventive TB therapy is not well known. In a trial in Uganda, people living with HIV with a positive tuberculin skin test receiving isoniazid for six months, or combined rifampicin and isoniazid for three months, had a lower chance of developing TB over four years of follow-up compared to individuals receiving placebo (*9*). Other studies suggest that the duration of protective benefit of isoniazid preventive therapy among people living with HIV ranges from 18 to 24 months (*10-11*).

Systematic reviews have found that rates of TB reinfection increased in people living with HIV and in areas of high TB incidence (*12-13*). Among South African miners, HIV infection was associated with a 19-fold increase in the incidence of TB after reinfection, without an increase in TB reactivation rate (*14*). In areas with high exposure to, and transmission of *Mycobacterium tuberculosis*, isoniazid preventive therapy was found to reduce the risk of TB among people living with HIV by 82% (RR 0.18, 95% CI: 0.04 to 0.83) when given directly after the cure of a first TB episode, and by 55% (RR 0.45, 95% CI: 0.26 to 0.78) when given some time after the cure of a first TB episode (*15-16*).

The implementation of isoniazid preventive therapy may be limited by many factors, including the difficulty of excluding active TB before preventive therapy, and concerns about selecting for isoniazid resistant *M. tuberculosis* strains. A meta-analysis of 12 RCTs and one observational study was performed to examine the risk of isoniazid resistance among HIV-infected and uninfected individuals who received isoniazid preventive therapy for 6–12 months. In this analysis, since the overall number of incident resistant TB cases was small, an increased risk of isoniazid resistance could not be ruled out (RR 1.45, 95% CI: 0.85 to 2.47) (*17*). However, a cluster-randomized trial in mine shacks in South Africa found a similar prevalence of isoniazid resistance in first and retreatment TB episodes among miners previously exposed to isoniazid preventive therapy and controls (*18*). No data are available to assess the impact of isoniazid preventive therapy on isoniazid resistance under routine preventive programme conditions. The limited data available

from Malawi, South Africa and Zambia showed that adherence to isoniazid preventive therapy is low, ranging from 24% to 59% (*19*).

Knowledge gaps identified:

- Optimal TB preventive therapy regimen that is effective, safe, well tolerated and accepted, with no interactions with major HIV medications.
- Optimal TB preventive therapy in special populations such as pregnant women and people with underlying liver disease (e.g. hepatitis B or C coinfection).
- Optimal dosing schedules of preventive TB therapy (repeated courses or lifelong therapy) in those receiving or not receiving antiretroviral therapy.
- Duration of the protective effect of isoniazid preventive therapy and other multidrug short-course preventive regimens.
- Role of isoniazid preventive therapy and other multidrug short-course preventive regimens in reducing the risk of recurrent TB, either reinfection or reactivation, among people living with HIV.
- Optimal TB screening algorithms to effectively rule out active TB disease among people living with HIV in settings with various burdens of TB and HIV disease.
- Rapid tests to rule out TB before initiating preventive TB therapy in people living with HIV at all levels of immunosuppression.
- Effect of preventive TB therapy on the emergence of drug resistance, including under routine programme conditions.
- Operational models for scaling-up isoniazid preventive therapy in HIV care settings, in patients receiving or not receiving antiretroviral therapy.
- Safety, tolerability, efficacy and impact of presumptive TB therapy as preventive therapy on TB incidence and mortality among people living with HIV.

1.2 TB infection control

M. tuberculosis transmission can take place where people living with HIV come into contact with infectious TB cases: at home, in the community, in congregate settings and in health facilities. The incidence of latent TB infection and TB disease among health workers in health-care facilities exceeds the incidence among the general population. The incidence of latent TB infection and TB disease among individuals in congregate settings and in household settings also exceeds the incidence among the general population.

M. tuberculosis transmission may occur in HIV outpatient clinics, emergency rooms, inpatient wards and laboratories (*20*). A study of TB transmission measured by fingerprinting *M. tuberculosis* strains transmitted from hospitalized HIV-infected TB patients to guinea pigs breathing ward air found that multidrug resistant (MDR) TB patients who received suboptimal drug therapy accounted for 90% of TB transmission (*21*).

Sound infection control methods are therefore essential to prevent *M. tuberculosis* transmission among people living with HIV. The *WHO policy on TB infection control* includes managerial activities at the national and subnational levels; and facility-level measures, including (*22*):

- administrative controls – triage, separation of infectious cases, cough etiquette and reduced hospital stay
- environmental controls – natural or mechanical ventilation systems and upper room ultraviolet germicidal irradiation
- personal protective interventions – respirators and prevention and care packages for HIV-infected health workers.

The implementation of comprehensive infection control measures reduces transmission of *M. tuberculosis* in health-care facilities (*23-25*). Consequently, all facilities, public and private, caring for patients with infectious TB, or suspected of having infectious TB, should immediately implement administrative infection control measures. Other interventions that are best suited to the programmatic, environmental and socioeconomic conditions of the particular care facility should also be implemented (*22*).

Few studies have investigated the effectiveness of individual infection control measures in reducing *M. tuberculosis* transmission. Infection control measures are usually implemented together as a package, and they lack appropriate monitoring parameters. A study in Peru found that opening windows and doors, especially in clinical areas with high ceilings and large windows, could provide high rates of air exchange and greatly reduce the risk of TB transmission compared to mechanical ventilation (*26*). The use of ultraviolet lights in a hospital TB/HIV ward with adequate room air mixing was found to significantly reduce TB transmission, by about 70% (*27*). However, modelling indicates that a synergistic combination of mask use, reduced hospitalization time, improved ventilation, rapid drug-susceptibility testing, antiretroviral therapy and TB isolation could prevent 48% (range 34–50%) of drug-resistant TB cases (28). More studies are needed to determine the most effective infection control measures for the prevention of *M. tuberculosis* transmission at the facility level. Studies are also needed to monitor the implementation and outcome of infection control measures.

Knowledge gaps identified:

- Predictors of infectiousness of HIV-infected TB patients, especially in those with drug-resistant TB.
- Methods for detecting the concentration of viable *M. tuberculosis* droplet nuclei to facilitate the monitoring and evaluation of TB infection control measures.
- Effectiveness, including cost-effectiveness, of individual infection control measures in reducing TB transmission in health-care and congregate settings.
- Best mix of infection control measures to reduce TB transmission in health-care and congregate settings.
- Operational models to implement and monitor infection control measures in health-care and congregate settings.

1.3 Antiretroviral therapy

In countries with either a high or low burden of TB, the use of antiretroviral therapy is associated with a substantial reduction in TB incidence rates in treatment cohorts, ranging from 54% to 92% (*29*), both at individual (*30*) and population levels (*31-32*). A prospective study in South Africa showed that the incidence of TB was reduced threefold in the second and third years of antiretroviral therapy compared to the first year of treatment (13.4/100 and 4.5/100 person-years respectively, p-value (P) < 0.001) (*33*). Despite this important reduction in TB incidence with highly active antiretroviral therapy, long-term TB risk remains elevated among patients receiving antiretroviral therapy compared to the general population (*34*). The long-term risk for developing active TB was also found to be strongly correlated to the length of time that patients had CD4 cell counts below 500 cells/mm^3 (*35*). Mathematical models suggest that early initiation of antiretroviral therapy in the course of HIV infection, high population coverage and high adherence levels would be needed to effectively reduce the number of TB cases and TB mortality rates (*36-37*). Rates of recurrent TB, due to either reinfection or reactivation, were halved during antiretroviral therapy in Brazil (*38*). In South Africa, TB risk reduction occurred equally among patients with or without a previous history of TB who received antiretroviral therapy (*33, 35*).

Two observational studies showed a greater reduction in TB risk among patients with a positive tuberculin skin test who received both antiretroviral and isoniazid preventive therapy. The TB risk reduction was 76% (adjusted hazard ratio [aHR] 0.24, 95% CI: 0.11 to 0.53) compared to naïve patients in Brazil and 89% (aHR 0.11, 95% CI: 0.02 to 0.78) in South Africa (*39-40*). However, the incremental benefit of combining both therapies over antiretroviral therapy alone was small.

Knowledge gaps identified:

- Impact of early initiation of antiretroviral therapy on the incidence of TB and the risk of developing active TB in high TB prevalence areas.
- Efficacy and safety of antiretroviral therapy, alone and coadministered with preventive TB therapy, in reducing the risk of recurrent TB among people living with HIV.

1.4 TB vaccines

Bacille Calmette-Guérin vaccine (BCG) is administered at birth, and confers reasonable protection against disseminated TB disease, especially TB meningitis, in the first 10 years of life. However, the protective efficacy of BCG against pulmonary TB disease in adults is variable across the world. This variable efficacy may be due to exposure to environmental mycobacteria. Strategies to improve the efficacy of TB vaccination and the prevention of active pulmonary disease include the use of a recombinant BCG, and boosting with recombinant proteins or nonreplicating viral vectored vaccines. Mathematical modelling suggests that, if introduced in 2015, this novel prime-boost vaccination strategy could decrease TB incidence by 39–52% by 2050 (*41*).

Phase 2 trials of candidate TB vaccines are presently being conducted or are about to start in several populations in Africa. Several TB vaccine candidates have been found to be safe and immunogenic in people living with HIV (*42*). However, efficacy data are limited. A subanalysis indicated that inactivated *M. vaccae*, used as a series of injections to boost BCG vaccine, reduced the number of culture-confirmed TB cases among people living with HIV in Tanzania (CD4 count of 200–500 cells/mm^3). The data demonstrate a modest vaccine efficacy of 37% with this strategy (*43*).

Knowledge gaps identified:

- Best TB vaccine in HIV-infected and uninfected patients, both adults and children.
- Safety and efficacy of new TB vaccine candidates in adults and children living with HIV (including those with severe immunosuppression).

1.5 Interferon-gamma release assays

Interferon-gamma release assays (IGRAs) measure the amount of interferon-gamma released from sensitized human T cells after exposure to *M. tuberculosis* antigens; mainly early secreted antigen target (ESAT)-6 and culture filtrate protein (CFP)-10. These antigens are more specific than antigens in a purified protein derivative, because they do not cross-react with BCG or *M. avium* complex (*44*). Thus, IGRAs have been expected to detect latent TB infection with more sensitivity and specificity than the traditionally used tuberculin skin test. IGRAs offer the advantages of a single test on a blood sample, with results available in 24 hours, and no requirement for a second clinical contact to assess the test result (*45*).

Two IGRA-based diagnostics are currently commercially available:

- the QuantiFERON-TB Gold test (Cellestis, Carnegie, Australia), which measures interferon gamma directly in solution
- the T-SPOT.TB assay (Oxford Immunotec, Oxford, United Kingdom [UK]), which measures interferon gamma and cells producing this cytokine in an enzyme-linked immunosorbent spot (ELISPOT) assay.

A recent meta-analysis of these diagnostics reported a pooled specificity of QuantiFERON-TB of 96% (95% CI: 94% to 98%) and of T-SPOT.TB of 93% (95% CI: 86% to 100%). These tests were conducted in BCG-vaccinated populations where the specificity of the tuberculin skin test was reported to be low and highly variable (*46*). Most studies assessing IGRA specificity have been conducted in settings with low TB incidence. The pooled sensitivity of QuantiFERON-TB was 76% (95% CI: 72% to 80%) and of T-SPOT.TB was 90% (95% CI: 86% to 93%), with almost all studies evaluating IGRA sensitivity being conducted in adults uninfected with HIV (*46*).

The performance of IGRAs in the diagnosis of latent TB infection in HIV-infected adults or children is an area of expanding research. A study using an ELISPOT assay for people living with HIV in Senegal found that the sensitivity of the assay decreased with decreasing CD4 counts (*47*). A study among Zambian patients with smear-positive TB found a statistically significant decrease in the sensitivity of the QuantiFERON-TB test among HIV positive individuals (63%) compared to HIV negative individuals (84%) (*48*). Similarly, low CD4 count was associated with indeterminate or false-negative results. Poor agreement between IGRAs and tuberculin skin tests has also been observed among HIV-infected adults and children in South Africa (*49*).

IGRAs have some limitations. They are immune-based tests, and therefore cannot differentiate latent infection from active or past TB disease (*50*). They cannot identify the individuals with latent TB infection who are at greatest risk of progressing to active TB, although those individuals would benefit from preventive TB therapy (*46*). IGRAs require sophisticated equipment and technologies. Appropriate transportation systems or the use of portable incubators are required to process blood samples within 16 hours of collection. These resources may only be available at district or higher level hospitals in many resource-limited settings. Finally, IGRAs require specialized and highly trained laboratory staff (*45*).

The greatest power of IGRAs may be in the detection of latent TB infection without interference from prior BCG vaccination.

Knowledge gaps identified (51):

- Accuracy and reliability of IGRAs in the diagnosis of latent *M. tuberculosis* infection and active TB disease in HIV-infected adults and children.
- Role of IGRAs in enhancing the effective application of preventive TB therapy in people living with HIV.
- Identification of IGRAs CD4 count cut-off points in people living with HIV.
- Prognostic ability of IGRAs, compared to the tuberculin skin test, to accurately identify people living with HIV at higher risk for progression from latent to active TB.
- Role of IGRAs in monitoring response to latent and active TB treatment in HIV-infected individuals.
- Feasibility, suitability, acceptability and cost-effectiveness of implementing wide-scale use of IGRAs.
- Most appropriate tool at the peripheral health system level to diagnose latent TB infection among people living with HIV.

1.6 Priority research questions in the area of TB prevention

RESEARCH QUESTION	SCORE
What is the optimal TB screening algorithm to be used across different settings, with different TB and HIV disease burden, to safely initiate preventive TB therapy?	9.6
What are the best infection control interventions that effectively reduce *M. tuberculosis* transmission (both drug susceptible and resistant) in health-care settings, at home and in the community?	9.0
What is the optimal duration, safety, efficacy and cost-effectiveness of isoniazid preventive therapy alone or added with antiretroviral therapy in reducing the risk of active TB compared to antiretroviral therapy alone among people living with HIV, particularly under programme conditions?	8.9
How early to start antiretroviral therapy (i.e. at what CD4 count level) among HIV-infected TB patients, to achieve maximum reduction in the risk of developing TB?	8.8
What are the operational models to scale-up isoniazid preventive therapy in HIV care settings, including frequency of symptom screening, monitoring tools and measures to maintain high adherence among health workers?	8.6
What is the optimal TB preventive therapy regimen in terms of efficacy, safety, tolerability and duration of protection to be used in HIV-infected adults and children, and other special populations, such as pregnant women and people with underlying liver disease?	8.4
What is the best administration schedule of preventive TB therapy in HIV-infected patients (repeated courses or lifelong preventive therapy)?	8.4
What is the safety, tolerability and efficacy impact of presumptive TB treatment (e.g. for two months) on TB incidence mortality in people with advanced HIV infection, either before or soon after initiation of antiretroviral therapy?	8.3
What are the best operational models (i.e. practical, feasible, easily reproducible and effective), to implement and monitor infection control measures in health facilities?	8.2
What is the best TB vaccine (either BCG booster vaccine or new replacement vaccine) in terms of immune response, safety and efficacy, for HIV-infected children and adults at all levels of immunosuppression?	8.1
What is the durability of effect of different combination of preventive TB therapy (isoniazid preventive therapy and other multidrug short course regimens)?	8.1
What is the effect of isoniazid preventive therapy on the emergence of drug resistance (especially on isoniazid and rifampicin)?	7.9
What is the best tool to diagnose latent TB infection among people living with HIV – adults and children – at peripheral health level?	7.5
What are the best operational models to assess the impact of infection control measures in reducing the spread of *M. tuberculosis* to HIV-infected adults and children?	7.5
What are the best models of surveillance to quantify nosocomial transmission of *M. tuberculosis* so as to allow the monitoring of infection control measures?	7.1
What is the role of IGRAs in diagnosing latent TB to start TB preventive therapy in HIV-infected patients – adults and children – at all level of immunosuppression?	6.5
What are the best air-sampling methods for viable TB droplet nuclei, to facilitate monitoring and evaluation of infection control measures?	6.3
How to improve IGRAs so they can effectively differentiate between infection and active disease for use in adults and children?	6.2
What are the best predictors of infectiousness of TB patients including MDR and extensively drug resistant (XDR) patients on therapy?	6.2
Does routine, widespread use of N95 respirators accompanied by a respiratory fit testing programme in health-care workers reduce TB transmission compared with usual practices?	5.9

CHAPTER 2: INTENSIFIED TB CASE-FINDING

All people living with HIV should be evaluated for latent *M. tuberculosis* infection and TB disease at the time of initial HIV diagnosis and during follow-up. This will facilitate the initiation of preventive and curative TB therapy, and will improve the safety of antiretroviral initiation (*3*). This chapter examines research issues and new technologies that could contribute to improved TB case-finding and treatment among people living with HIV.

2.1 Clinical screening and diagnostic algorithms

A chronic cough alone lasting for two to three weeks may be an insensitive predictor of TB disease in people living with HIV. Diagnosis of TB requires a combination of symptoms (*52-58*); however, the most appropriate combination of symptoms is not known.

A number of cross-sectional studies have been conducted in various settings to evaluate screening methods. The screening typically consisted of an evaluation of multiple symptoms, with or without a chest X-ray. Results from these studies have been extremely variable in sensitivity and specificity, and have probably been affected by CD4 counts (*56, 58*). Active TB was defined in different ways in these studies. The definitions ranged from a positive culture for *M. tuberculosis* or positive sputum smear, to response to TB therapy. Other limitations of these studies included the enrolment of prescreened patients with suspected TB, and poor generalizability of studies conducted in referral or hospital settings, or in single-centre study sites.

The role of a chest X-ray in the diagnosis of TB in people living with HIV remains unclear. A study in South Africa found that a chest X-ray increased the sensitivity of screening up to 91% (*52*). In Ethiopia, chest X-ray screening had a sensitivity of 60% and a specificity of 83%. The authors estimated that an additional 10% of all TB cases would have been detected if a chest X-ray had been performed on all of the people living with HIV screened for TB (*56*). In Cambodia, an abnormal chest X-ray was found to be a significant predictor of smear-negative pulmonary TB (adjusted odds ratio [aOR]: 4.9, 95% CI: 2.7 to 8.6) However, inter-reader variability was considerable; 51% of the chest X-rays were classified as abnormal on site compared to 19% reviewed by external readers (*59*). In contrast, in a study from Botswana, only 0.2% of people living with HIV who were screened for TB presented with suggestive chest radiographic findings (*60*). In South Africa, chest radiographs were not sensitive enough to improve the performance of clinical TB diagnosis (*53*). A chest X-ray was normal in up to 29% of HIV-infected patients with sputum culture-positive TB, and a higher proportion of normal radiographic results was seen in those with severe immunosuppression (*61-64*).

A number of studies have also reported culture-confirmed TB in asymptomatic HIV patients (*65*), and high rates of undiagnosed TB in the community (*57, 66*). The significance of positive cultures in asymptomatic patients is not clear; they may indicate the progression of clinical disease, or transient excretion of *M. tuberculosis* in patients who later self-cure or convert to latent TB infection. Alternatively, such cultures may be due to laboratory or clerical errors.

Knowledge gaps identified:

- Optimal TB algorithm to diagnose TB with high sensitivity, specificity and predictive values, that can be applied across different settings and in patients with different TB and HIV disease burdens.
- When, where and who should administer the TB algorithm and at what frequency.
- Impact of implementing an evidence-based algorithm to diagnose TB on reducing TB incidence and mortality in people living with HIV.
- Role of chest X-ray in assisting TB diagnosis in people living with HIV.
- Clinical predictors and best screening methods for TB in asymptomatic patients.

2.2 TB Diagnostic tools

Sputum-smear microscopy remains the cornerstone of TB diagnosis in resource-limited settings. However, the sensitivity of this test can be as low as 20% in HIV-infected patients and children (*67*). Mycobacterial culture as a diagnostic tool for TB has several advantages; it is more sensitive than smear microscopy, permits the definitive

diagnosis of smear-negative disease and enables drug-susceptibility testing. The disadvantages of mycobacterial culture are that it requires specimen transport, complex biosafety facilities and trained laboratory technicians.

Smear-negative pulmonary TB is common in the HIV population. It is associated with poor treatment outcomes and excessive early mortality compared with smear-positive disease. Smear-negative TB is also associated with delayed diagnosis (*68*). Patients with smear-negative pulmonary TB cases may contribute to TB transmission (*69*).

Several new diagnostic tools to improve TB case detection and drug-susceptibility testing are presently being developed, or are being evaluated in the laboratory or field.

2.2.1 Microscopy

Systematic reviews showed that the use of sodium hypochlorite (bleach) sedimentation improves the yield and sensitivity of conventional smear microscopy (*67*). Studies in settings with high HIV prevalence showed that the addition of household bleach to sputum, followed by overnight sedimentation, increased the number of TB cases detected by up to 17% (*70-72*).

Front-loaded smear microscopy is defined as the collection and examination of the first two sputum specimens on the same day. This method was found to have similar yields to the standard approach of collecting one specimen on the spot and one early morning specimen on the following day, among patients presenting with chronic cough (*73*).

Fluorescence microscopy was found to increase the sensitivity of conventional smear microscopy by an average of 10% (*74*). However, two studies comparing fluorescence microscopy and Ziehl-Neelsen smear in samples from people living with HIV found a difference in sensitivity of 37% and an incremental increase in yield of 26% (*75-76*). The use of light-emitting diodes (LEDs), which reduce power consumption and improve acceptance by laboratory technicians, is being assessed for both light and fluorescence microscopy.

2.2.2 Culture-based methods

Due to the slow replication time of *M. tuberculosis*, solid media cultures need to be incubated for 2–8 weeks before colonies may be visible. Conversely, liquid culture systems that rely on nonradiometric detection of *M. tuberculosis* growth provide results within 7–16 days (*68, 77*). However, the use of liquid culture systems is still restricted in resource-limited settings. The inability to perform rapid culture techniques hinders the prompt diagnosis and management of susceptible and drug-resistant TB.

Microscopic-observation drug susceptibility (MODS) – a low-cost manual liquid culture technique – was found to have high sensitivity and specificity, and to detect *M. tuberculosis* much more rapidly than automated liquid or conventional solid culture (*78*). This technique has been tested under research conditions in settings with high HIV prevalence such as Brazil, Ethiopia and Honduras (*79-80*). However, MODS still needs to be validated in a programmatic context, particularly among people living with HIV. Quality control and inter-observer variability may also be issues that need to be addressed in programmatic settings.

Other solid culture techniques, such as the thymidine kinase colorimetric assay, nitrate reductase assay and thin-layer agar culture have also been developed. These methods can be used to detect mycobacterial growth before the appearance of visible colonies, or to visually indicate resistance to isoniazid and rifampicin (*81*). Studies are needed to validate their use in both programmatic settings and among HIV-prevalent populations.

Rapid strip speciation testing can detect a TB-specific antigen (MPB64) from positive liquid or solid cultures to confirm the presence of *M. Tuberculosis*, and differentiate its growth from other mycobacteria in culture. The test provides results in 15 minutes and is highly sensitive (98.6%) and specific (97.9%) (*45*).

2.2.3 Gene amplification technique

Nucleic acid amplification tests detect mycobacterial nucleic acid within 3–6 hours, generally using polymerase chain reaction (PCR). Meta-analyses have reported highly variable estimates of the accuracy of noncommercial and commercial

assays for the detection of *M. tuberculosis* in sputum (*82-83*). Research on the loop-mediated isothermal amplification assay is still very limited.

The Xpert MTB device (Cepheid, California, United States of America [USA]) is a promising fully automated system based on molecular detection of *M. tuberculosis*. This system has demonstrated the ability to detect TB in the majority of smear-negative samples, and screen for rifampicin resistance in 90 minutes (*84*). The sensitivity of the assay was 90.2% (95% CI: 84.9% to 93.8%) for three tests to detect smear-negative culture-confirmed TB, and 97.6% (95% CI: 94.4% to 99.0%) to identify rifampicin-resistant bacteria when compared to phenotypic drug-susceptibility testing. There are preliminary indications that it may be possible to adapt this system to also perform HIV viral load testing.

FASTPlaque TB (Biotec Laboratories, Ipswich, UK) uses phage amplification technology. This system has been well tested, including in settings with high rates of HIV infection, but has produced contradictory results (*68*).

The WHO has endorsed the use of two commercially available molecular line probe assays that use deoxyribonucleic acid (DNA) PCR, followed by DNA hybridization, to detect *M. tuberculosis*, and common mutations in *M. tuberculosis* associated with resistance to rifampicin and isoniazid (Genotype MDRTBplus, Hain Lifescience, Germany and INNO-LiPA Rif.TB, Innogenetics NV, Belgium) (*85*). Both technologies have the potential to reduce time to diagnosis and drug-susceptibility testing to two days if performed directly from patient smear-positive sputa. Molecular line probe assays require well-equipped laboratory infrastructure to carry out PCR. The laboratory requirements include separate rooms for sample preparation and analysis, proper disposal materials and methods, well-trained staff and external quality assurance. The addition of testing for *M. tuberculosis* sequences associated with resistance to fluoroquinolones and to injectables is under evaluation, and will allow line probe assays to detect extensively drug resistant (XDR)-TB (*86*).

2.2.4 Other diagnostics and point-of-care tests

A systematic review evaluating the accuracy of commercially available antibody diagnostic tests has found that such tests have limited sensitivity and inconsistent specificity (*87*). Specificity was higher in healthy volunteers than in suspected TB cases, and data were too scarce to determine the accuracy of the assays in smear-negative patients or in HIV-infected adults and children.

Studies are ongoing to develop biomarkers that can indicate active TB disease and monitor the response to therapy (cure and relapse). However, the tests available need further refinement, evaluation and validation, especially in people living with HIV. Candidate biomarkers with the potential to lead to new diagnostics include the detection of mycobacterial growth in sputum; detection of specific *M. tuberculosis* antigens (e.g. AG85); detection of *M. tuberculosis* DNA in sputum or urine; detection of immune or drug-mediated killing of *M. tuberculosis* in cultured human blood cells or in human blood; and highly multiplexed immunoassays that characterize host responses to *M. tuberculosis* infection (*88*).

Point-of-care diagnostic tests that could be used in peripheral facilities are in the early phases of development. Examples of these types of tests include urinary antigen detection via dipstick and the administration of TB skin test antigens via transdermal patch (*45, 64*). Exploratory work is also underway on a diagnostic breath test, based on detection of volatile organic molecules.

Knowledge gaps identified:

- Development of a rapid, simple and accurate point-of-care TB diagnostic tool for all patients, including children and people living with HIV, and for all types of TB disease.
- Efficacy of the revised WHO algorithm for smear-negative TB and extrapulmonary TB on mortality among HIV-infected patients with suspected TB.
- Accuracy of a comprehensive implementation of smear techniques (bleach sedimentation, concentration, fluorescence microscopy, etc) under programme conditions.

- Large-scale evaluation of the most promising diagnostic tools currently available for rapid TB diagnosis, including diagnosis of drug resistance and of smear-negative patients under programme conditions.
- Biomarker research to distinguish infection and disease, and to monitor response to treatment.
- Development of multifunctional diagnostic platforms that allow for simultaneous or rapid sequential testing for TB and HIV infection and disease.

2.3 Priority research questions in the area of intensified TB case-finding

RESEARCH QUESTION	SCORE
What is the simple and rapid point-of-care "TB dipstick test" to diagnose all types (smear-positive and negative pulmonary, extrapulmonary drug susceptible and drug resistant) of TB in all patients, including children and people living with HIV?	9.7
What is the optimal TB screening and diagnostic algorithm for use across all settings with different HIV and TB diseases burdens to enable screening of all forms of TB, and that can be integrated into routine care?	9.1
What is the programmatic impact of the most promising diagnostic tools currently available for rapid TB diagnosis, including diagnosis of drug resistance and of smear-negative patients identified through large-scale evaluation studies?	9.1
What are the best operational models for enhanced case-finding of TB among HIV-infected patients in HIV service facilities and at the community level in both high and low HIV prevalence settings?	8.7
What is the optimal timing and frequency of systematic TB screening among people living with HIV?	8.7
What is the best model to eliminate diagnostic delay and hasten treatment initiation for TB using existing tools, including the efficacy of the revised WHO algorithm for smear-negative TB on mortality among HIV-infected patients with suspected TB?	8.6
What is the role of contact tracing in intensified TB (and HIV) case-finding at the population level?	7.8
What are the best multifunctional diagnostic platforms that allow for simultaneous or rapid sequential testing for TB and HIV infection?	7.7
How to best identify subclinical and extrapulmonary disease in HIV coinfected and uninfected individuals?	7.4
What are the best TB biomarkers to distinguish infection and disease, and to monitor response to treatment?	7.1
What are the definition, true prevalence, natural history and importance of subclinical TB, particularly for people living with HIV?	6.5

CHAPTER 3: TB TREATMENT FOR PEOPLE LIVING WITH HIV

HIV-infected TB patients should receive antiretroviral therapy as early as possible. This chapter examines research issues around the delivery of antiretroviral therapy to HIV-infected TB patients. These research issues include the optimal combination of antiretroviral and anti-TB therapy, and the optimal timing of initiation of therapy. Other treatment issues, such as immune system reconstitution and inflammatory syndrome, are also examined.

3.1 Antiretroviral and anti-TB therapeutic drug combinations

Achieving successful outcomes in HIV-infected patients with TB requires the delivery of optimal regimens for the treatment of both HIV and TB. Treatment for HIV infection generally requires three antiretroviral agents from two drug classes for first-line therapy. Second-line therapy for patients with drug resistant HIV is more complicated, and may require three or four drugs from different classes. In most settings, recommended first-line HIV therapy includes a nonnucleoside reverse transcriptase inhibitor (efavirenz or nevirapine), together with two nucleoside reverse transcriptase inhibitors. Treatment of drug-resistant HIV relies on HIV protease inhibitors, which generally include ritonavir as a boosting agent, to increase drug levels through inhibition of cytochrome P450 (CYP) 3A metabolism. Treatment of HIV is only successful when the patient is able to adhere to and tolerate the therapeutic regimen, and when drug levels are maintained at levels that prevent the emergence of drug-resistant HIV.

Rifampicin is a cornerstone of the standard TB treatment regimen, including regimens for people living with HIV. Because rifampicin is a potent inducer of the cytochrome P450 liver enzyme system, administration of rifampicin with either first or second-line HIV therapy leads to alterations in HIV drug levels metabolized through this pathway. Importantly, rifampicin reduces levels of both nonnucleoside reverse transcriptase inhibitors and HIV protease inhibitors. A brief overview of what is known about these interactions follows.

3.1.1 Rifampicin and nevirapine

The clearance of nevirapine varies with sex, presence of hepatitis B coinfection and geographical area (e.g. patients from South America and Western countries have a higher clearance of nevirapine compared to patients in Thailand and South Africa) (*89*). In addition, nevirapine bioavailability is reduced by 20–55% when coadministered with rifampicin (*90*).

There is increasing evidence from RCTs and observational cohorts that concomitant use of rifampicin and nevirapine leads to short-term subtherapeutic nevirapine plasma concentrations (*91-95*). However, results about the consequences of concomitant dosing of rifampicin and nevirapine on virological suppression are conflicting. In a study in Thailand, patients receiving nevirapine alone showed similar virological outcomes to those receiving nevirapine plus rifampicin, at 144 weeks (*96*). Excess virological failures (HIV-ribonucleic acid [RNA] ≥ 400 copies/mL) at 18 months were observed in patients in South Africa receiving rifampicin at the start of nevirapine treatment, compared to patients on nevirapine alone (*94*). None of the studies provided data on patients' previous use of single-dose nevirapine for prevention of mother-to-child transmission of HIV. The use of single-dose nevirapine had been found to increase the rate of nevirapine resistance mutations, and to compromise the success of subsequent treatment of mother and child with antiretroviral regimens that include nonnucleoside reverse transcriptase inhibitors (*97*).

Increasing the standard dose of nevirapine (i.e. 200 mg twice daily) has been suggested, to counter the reduction of nevirapine plasma concentrations due to rifampicin co-administration. Furthermore, a modelling study in South Africa based on pharmacokinetic measurements in patients receiving standard doses of nevirapine and rifampicin suggested that 300 mg twice a day may be the optimal dose to obtain recommended nevirapine serum levels in most patients (*98*). Similarly, in a small pharmacokinetic study of seven HIV-infected TB patients in India, increasing the dose of nevirapine to 300 mg twice daily resulted in therapeutic levels of nevirapine with no hepatotoxicity (*99*).

However, there is a general reluctance to increase the standard dose of nevirapine because of concerns over hepatotoxicity. In an RCT in Thailand, increasing the dose of nevirapine to 600 mg per day following a 400 mg loading-phase was associated with a higher incidence of hypersensitivity reactions (25% in the 600 mg group compared to 6% in the standard dose group) (*93*).

Finally, because of concerns over symptomatic hepatic toxicity and serious rash, nevirapine is not recommended in antiretroviral therapy-naïve female patients with CD4 counts above 250 cells/mm^3, or in male patients with CD4 counts above 400 cells/mm^3 (*100*).

3.1.2 Rifampicin and efavirenz

Rifampicin has been shown to reduce efavirenz plasma concentrations by 20–25% (*90*); a reduction that could lead to virological failure. Studies among people living with HIV established that increasing the dose of efavirenz from 600 mg to 800 mg could overcome the reduction in efavirenz levels (*101-102*). However, dose adjustment for antiretroviral drugs is rarely feasible in resource-limited settings, and many HIV-infected TB patients continue to be treated with 600 mg efavirenz.

Large variability in efavirenz plasma concentrations was observed in a cohort of 20 HIV-infected TB patients in South Africa receiving 600 mg efavirenz with rifampicin. In spite of the variability in plasma concentrations of efavirenz, 80% of the patients had an undetectable viral load at 6 months, and 65% of the patients had an undetectable viral load at 21 months (*103*). Another retrospective study in South Africa compared the virological outcomes of people living with HIV receiving efavirenz-based (600 mg) antiretroviral therapy, treated or not treated with rifampicin as part of TB treatment, and found that both regimens resulted in similar virological failures (aOR for virological failure: 1.1, 95% CI: 0.8 to 1.5) (*94*). A study in India showed that co-administration of rifampicin did not affect efavirenz plasma concentrations when given at 600 mg daily, or clinical and immunological responses to treatment. However, efavirenz plasma concentrations were significantly influenced by polymorphisms in the CYP2B6 gene (*104*). In an RCT in Thailand, there was no difference in plasma concentrations and no difference in time to undetectable viral load when efavirenz was given at doses of 600 mg or 800 mg to patients who were jointly treated with rifampicin (*105*).

Even if evidence suggests that standard doses of 600 mg efavirenz are adequate when coadministered with rifampicin, the use of efavirenz is constrained in resource-limited settings, due to its high cost. In addition, the teratogenic potential of efavirenz, particularly during the first trimester of pregnancy, makes it unsuitable for use in women of childbearing age, a population highly affected by HIV in sub-Saharan Africa.

3.1.3 Comparison of nevirapine and efavirenz for rifampicin co-administration

An RCT compared standard doses of efavirenz and nevirapine-based antiretroviral therapy in HIV-infected TB patients receiving rifampicin. This study demonstrated that 600 mg efavirenz once daily was adequate for suppression of HIV viral load, despite interpatient variability in serum drug concentrations (*106*). Nevirapine, at the standard dose of 200 mg twice daily, was also effective in achieving viral load suppression (73.2%); efavirenz was superior (71.8%) but not significantly so ($P > 0.05$). Viral load suppression was measured as HIV-RNA < 50 copies/ml at week 48.

Previous observational studies have provided conflicting results about the efficacy of efavirenz and nevirapine administered with and without rifampicin. A cohort study in Botswana showed no difference in immunological and virological outcomes throughout the first year of efavirenz and nevirapine-based antiretroviral therapy coadministered with or without rifampicin (*107*). In contrast, patients in South Africa had less favourable virological outcomes when they started nevirapine while already receiving rifampicin-based TB treatment compared to those who had started efavirenz after rifampicin (*94*). Similarly, these patients had poorer virological outcomes compared to those who initiated TB treatment while already receiving nevirapine or efavirenz-based antiretroviral therapy. All these studies had a short follow-up period for measuring antiviral activity. No studies have investigated the short-term use of efavirenz while in treatment with rifampicin for TB disease, followed by a return to nevirapine after completion of TB treatment.

One RCT examined the efficacy of once-daily drugs regimens several drug therapies coadministered with rifampicin. A once-daily regimen of didanosine, lamivudine and nevirapine led to more frequent virological failure than once-daily didanosine, lamivudine and efavirenz (38/57 and 50/59 patients, respectively, reaching undetectable viral load at 24 weeks, P = 0.038) and death (11/57 vs. 5/59) (*108*). However, in this study, nevirapine was administered as a 400 mg once-daily dose, rather than as the standard dose of 200 mg twice daily; it is probable that this contributed to its inferior activity.

Reports of safety and tolerability of these therapeutic regimens varied across observational studies. In some studies, there was no difference in adverse events between nevirapine and efavirenz when given with rifampicin (*94, 107, 109*); in others, higher rates of hepatotoxicity due to nevirapine were observed (*110*).

3.1.4 Rifampicin and protease inhibitors

When rifampicin is given with protease inhibitors in the absence of boosting doses of ritonavir, reductions in concentrations of protease inhibitors of up to 90% are observed. Pharmacokinetic studies of saquinavir (*111-112*), lopinavir (*113*) and atazanavir (*114*) – all boosted with ritonavir and coadministered with rifampicin – showed highly variable and mainly subtherapeutic plasma concentrations of the protease inhibitor. These studies, most of which were conducted in healthy volunteers, also showed a high incidence of severe adverse events, leading to discontinuation of the drug when given concomitantly with rifampicin.

3.1.5 Triple-nucleoside reverse transcriptase inhibitor regimens

Triple-nucleoside reverse transcriptase inhibitor regimens (known as "triple nukes") for first-line HIV therapy avoid the interaction between nonnucleoside reverse transcriptase inhibitors and rifampicin. However, a trial of 1147 people living with HIV in the USA showed that these regimens had inferior virological efficacy compared to nonnucleoside reverse transcriptase inhibitor regimens (*115*). One observational study investigated the triple-nucleoside reverse transcriptase inhibitor regimen abacavir, zidovudine and lamivudine in HIV-infected TB patients and reported that virological success (HIV-RNA < 50 copies/mL) was achieved in 76% of the patients at 24 weeks. No hypersensitivity reactions were observed (*116*).

3.1.6 Rifabutin-based treatment regimens

Rifabutin, a semi-synthetic derivate of rifampicin, is a less potent inducer of the CYP system, and has been administered successfully to people also receiving nonnucleoside reverse transcriptase inhibitor or protease inhibitor antiretroviral therapy. A systematic review found no difference in terms of efficacy between rifabutin and rifampicin-based TB regimens, assessed by sputum culture conversion after treatment for two, three or six months (*117*). However, this review of TB treatment was chiefly from studies in patients not infected with HIV. A retrospective study showed that changes in TB relapse rates in people living with HIV were not related to use of either rifampicin or rifabutin (*118*).

Rifabutin concentrations can be affected by nonnucleoside reverse transcriptase inhibitors and protease inhibitors; thus, dose adjustments may be required (*119*). However, the data to support current dose adjustment recommendations were primarily derived from studies conducted in Caucasian subjects. There have been reports of acquired rifamycin-resistant TB relapses occurring in HIV-infected patients receiving recommended dosages of rifabutin coadministered with boosted protease inhibitors (*120*). Pharmacokinetic studies in South Africa and Vietnam are currently investigating the use of rifabutin at different dosages, coadministered with efavirenz and nevirapine, and ritonavir- boosted lopinavir or indinavir.

Rifabutin has less effect on protease inhibitor plasma concentrations than rifampicin. Therefore, rifabutin has since been suggested as a replacement for rifampicin in people living with HIV, treated with a ritonavir-boosted protease inhibitor. Rifabutin was added to the WHO essential medicines list to make it more available and affordable in resource-limited settings (*121*). However, the absence of a formulation of rifabutin with other anti-TB drugs might limit its use in these settings.

Knowledge gaps identified:

- Optimal first and second-line antiretroviral therapy regimens, in terms of safety, tolerability, efficacy, optimal dosage of drugs and operational aspects,

to use in combination with a rifampicin-based regimen. Ideally, these optimal combinations should minimize the development of HIV drug resistance and TB relapses.

- Optimal co-treatment regimens for women of childbearing age and children.
- Better understanding of the pharmacokinetics of the most frequently used combinations of HIV and TB drugs, to better define drug–drug interactions and achievable drug levels.
- Combined use of new HIV agents in combination with existing and new TB regimens.
- Optimal dosage, safety, tolerability, efficacy and operational aspects of rifabutin in people living with HIV, with and without antiretroviral therapy (protease inhibitors or nonnucleoside reverse transcriptase inhibitors).

3.2 Optimal time to start antiretroviral therapy in HIV-infected TB patients

RCTs are ongoing in Asia and sub-Saharan Africa to identify the optimal time to initiate antiretroviral therapy in people living with HIV who are newly diagnosed with active TB and are eligible to start antiretroviral therapy. These studies will compare patients starting antiretroviral therapy within the first 4 weeks versus 8–12 weeks of initiation of TB treatment (*122*). Results from a trial in South Africa confirmed current WHO recommendations that patients should not wait until completion of TB treatment to start antiretroviral therapy. Mortality rates were significantly higher among patients who initiated antiretroviral therapy after completion of TB treatment, compared to those who started within the first two months of intensive phase TB treatment or after completing intensive phase TB therapy (*123*). A trial done in Cambodia among 661 patients found a reduction of mortality of 34% if antiretroviral therapy is initiated in the first two weeks of TB treatment compared to eight weeks (*124*).

Data from a cohort of 313 Spanish patients showed that starting antiretroviral therapy in the first two months of TB treatment, compared to starting antiretroviral treatment after three months of TB treatment, was an independent predictor of survival (hazard ratio [HR]: 0.37, 95% CI: 0.17 to 0.66) (*125*). Similarly, a study in Thailand found that the risk of death increased with the length of time that antiretroviral therapy was delayed (HR 9.0, 95% CI: 1.1 to 73.0 in those for whom antiretroviral therapy was delayed compared to those who initiated antiretroviral therapy within the first 120 days of TB treatment) (*109*). In a retrospective study in South Africa, starting antiretroviral therapy within the first 30 days of TB treatment did not increase mortality (*126*). A study in Malawi reported on the clinical management of HIV-infected patients with TB who started antiretroviral therapy two weeks after initiating TB treatment. Clinical management of the patients was complicated by the occurrence of severe adverse events such as hepatotoxicity, rash or peripheral neuropathy (*91*). Most adverse events required symptomatic treatment, but only led to discontinuation of treatment in one patient.

Knowledge gaps identified:

- Optimal time and management to start antiretroviral therapy in HIV-infected individuals who have active TB disease.

3.3 Immune reconstitution inflammatory syndrome

TB-associated immune reconstitution inflammatory syndrome (TB-IRIS) is a recognized complication of antiretroviral therapy (*127*). There is increasing consensus that TB-IRIS has two forms. Paradoxical TB-IRIS occurs when patients receiving treatment for TB are put on antiretroviral therapy and develop an immune-mediated clinical deterioration. Unmasking TB-IRIS develops in a smaller fraction of patients not on TB treatment. These patients start antiretroviral therapy and develop antiretroviral therapy-associated TB with inflammatory symptoms in the first few months. It has been suggested that unmasking TB-IRIS is triggered by antiretroviral-induced immune recovery. Clinical case definitions for use in resource-limited settings have been proposed (*128*). A prospective study from South Africa evaluating these definitions found a positive agreement between the definition of paradoxical TB-IRIS and expert opinion of 72%, and a negative agreement of 93% (*129*). Positive agreement between the definition of unmasking TB and expert opinion was 63% and negative agreement was 100%.

Paradoxical forms of TB-IRIS have been reported in 8–43% of TB patients starting antiretroviral therapy (*128*). A key differential diagnosis is for drug-resistant TB, which may similarly present with an initial clinical improvement followed by deterioration. There may be considerable overlap between these two phenomena, as reported in South Africa, where 10% of cases of suspected TB-IRIS had rifampicin-resistant TB (*130*).

To date, there is no evidence-based recommendation for the prevention or treatment of paradoxical TB-IRIS. A double-blind placebo-controlled trial of prednisone for TB-IRIS showed that a four-week course of prednisone at the time of diagnosis of paradoxical TB-IRIS reduced the duration of hospitalization and need for procedures, without an excess of adverse events or severe infections (*131*). However, many patients in this study required a longer course of treatment with steroids, which is associated with additional toxicity.

In studies that report changing TB rates over time during antiretroviral therapy, TB incidence rates are invariably highest during the initial months of therapy (*29*). Such cases may arise as a result of persistent immunodeficiency or the unmasking of TB disease during immune recovery. A report from South Africa showed epidemiological evidence that "unmasking" accounted for more than 30% of cases presenting during the first four months of antiretroviral therapy (*35*). Among those whose TB is unmasked, it is proposed that the small subset of cases that are associated with inflammatory symptoms be referred to as "unmasking TB-IRIS" (*132*). However, clinical presentation of unmasking TB-IRIS is not well defined.

Since most episodes of TB-IRIS are self-limiting and not associated with significant mortality (*133*), the risk of TB-IRIS must be balanced against the benefit of early initiation of antiretroviral therapy in patients with advanced immunosuppression.

Knowledge gaps identified:

- Evaluation and validation of the consensus clinical cases definitions for paradoxical TB-IRIS.
- Clinical case definition and clinical presentation of unmasking TB-IRIS and identification of its role in early mortality.
- Identification of immunological markers to predict and diagnose TB-IRIS.
- Development and evaluation of clinical algorithms to identify major differential diagnoses for TB-IRIS in different settings.
- Role of drug-resistant TB in HIV-infected TB patients who deteriorate rapidly after starting antiretroviral therapy.
- Prevention and optimal management of TB-IRIS, particularly in life-threatening cases.
- Role of steroids and immune modulators in the management of TB-IRIS.

3.4 TB treatment regimens

The optimal duration of TB therapy for people living with HIV is unclear. Past observational studies have shown TB recurrence rates that are slightly (but not significantly) higher in people living with HIV treated with the standard six-month short course therapy, compared to HIV-negative patients (*134*). However, a retrospective review showed that relapse rates after a six-month rifamycin-based regimen were significantly higher among people living with HIV (9.3 vs. 1.0 per 100 person-years, $P < 0.001$) (*135*). Intermittent rifamycin-based regimens in HIV-infected TB patients were also significantly associated with higher relapse rates and mortality (*108*), as were therapies with shorter duration (*135*).

Current and new drugs are being studied for the treatment of drug-susceptible TB and MDR-TB. These include the latest generation methoxy-fluoroquinolones gatifloxacin and moxifloxacin; TMC207; the nitroimidazoles OPC67683 and PA824; and SQ109 and LL3858 (*136*). In a Phase 2 study, the addition of TMC207 to standard therapy for MDR-TB increased the proportion of patients with conversion of sputum cultures, and reduced the time to conversion to negative culture compared to placebo (*137*). However, people living with HIV with a CD4 count below 300 cells/mm^3 and those receiving antiretroviral therapy were excluded from the trial. New drugs need to be tested in HIV-infected TB patients with susceptible and MDR *M. tuberculosis* strains, regardless of co-administration of antiretroviral therapy, and regardless of the patient's level of immunosuppression. In addition, novel strategies to shorten TB treatment, such as

the replacement of ethambutol with moxifloxacin, are currently being investigated (*138*). Modalities that need to be investigated include novel drugs that could replace rifampicin and facilitate the co-administration of antiretroviral and TB therapies, and shorter and more effective TB regimens compatible with antiretroviral therapy.

Knowledge gaps identified:

- Optimal length of TB treatment in people living with HIV.
- Role of empiric TB treatment in reducing mortality among people living with HIV.
- Safety and efficacy of new and novel anti-TB drugs for susceptible and resistant TB in people living with HIV, with or without antiretroviral therapy.
- Development of novel drugs to replace rifampicin and facilitate the co-administration of antiretroviral and TB therapies.
- Identification of shorter and more effective TB regimens compatible with antiretroviral therapy.

3.5 Priority research questions in the area of TB treatment for people living with HIV

RESEARCH QUESTION	SCORE
What are the safety, efficacy and pharmacokinetic parameters of new and novel drugs that could replace rifampicin and shorten TB treatment, to cure susceptible and drug-resistant TB in people living with HIV, with or without antiretroviral therapy (either first or second-line antiretroviral therapy)?	9.5
What are the best first and second-line antiretroviral therapy regimens in terms of safety, efficacy, tolerability, optimal dosage of drugs and drug interactions, to use in combination with a rifampicin-based TB regimen?	9.3
What is the optimal time to start antiretroviral therapy in HIV-infected patients who have active TB disease, both drug-susceptible and drug-resistant types?	9.1
What are the best co-treatment strategies for TB and HIV in special populations such as women in childbearing age, people with underlying liver disease and injecting drug users who are also infected with hepatitis B and C?	8.6
What are the safety, efficacy and tolerability of newer HIV agents in combination with existing and new first and second-line TB regimens?	8.5
What are the safety, efficacy, optimal dosage and drug interactions of rifabutin in curing active TB, preventing TB relapse and preventing acquired rifamycin resistant failures in people living with HIV on antiretroviral therapy, possibly including integrase inhibitor based regimens?	8.2
What are the drug interactions between antiretroviral drugs and second-line anti-TB drugs in all categories of patients including children and pregnant women?	8.2
What are the best drug formulations of antiretroviral and anti-TB drugs that may allow fixed dose combinations to facilitate compliance during times of combined treatment?	8.1
What are the best treatment regimen options for TB patients who fail first-line TB treatment or relapse within two years, in HIV and TB prevalent settings where no drug-susceptibility testing is available?	8.1
What are the optimal length and dosage of rifampicin-based TB treatment in adults and children living with HIV?	7.6
What are the optimal clinical case definitions, risk factors, predictors and strategies to prevent TB-IRIS (paradoxical and unmasking) in adults and children?	7.4

CHAPTER 4: DRUG RESISTANT TB AND HIV

Despite the increased risk of MDR-TB and XDR-TB among people living with HIV, little attention has been given to the interface between drug-resistant TB and HIV infection (*139*). WHO guidelines recommend standardized or individualized MDR-TB treatment strategies, including at least four drugs with certain or almost certain effectiveness for a duration of at least 18 months after culture conversion, irrespective of HIV status (*140*). Prevention, screening and early diagnosis of MDR-TB and XDR-TB among people living with HIV are important issues in the management of coinfected patients. This chapter examines research issues that deal with MDR-TB and XDR-TB among people living with HIV, including epidemiology, diagnostics, treatment strategies and management of contacts of drug-resistant TB patients.

4.1 Epidemiology of HIV infection and drug-resistant TB

HIV infection was closely associated with a multi-institutional outbreak of MDR-TB in New York City in the early 1990s. The outbreak was linked to poor infection control practices, and occurred before the availability of antiretroviral therapy (*141*). Coinfection with HIV and MDR-TB led to reduced survival time and high mortality rates among patients. More recently, in Tugela Ferry, South Africa, an outbreak of XDR-TB predominantly affected people living with HIV. There were 52 deaths among 53 patients within a median time of 16 days after specimen collection for drug-susceptibility testing; 44% of the patients had tested positive for HIV (*142*). Use of antiretroviral therapy did not improve survival, and all 15 people living with HIV receiving antiretroviral therapy (34% of the patients) died of XDR-TB.

There is little population-based epidemiology data about an association between HIV infection and MDR-TB, either transmitted or acquired, and the data that are available are inconsistent. Only seven countries of the Global Project on Anti-Tuberculosis Drug Resistance reported data on MDR-TB stratified by HIV status. None of these seven countries has a generalized HIV epidemic. No association between HIV infection and MDR-TB was found in five of these countries. MDR-TB was significantly associated with HIV infection in Latvia (OR: 2.1, 95% CI: 1.4 to 3.0) and Ukraine (OR: 1.5, 95% CI: 1.1 to 2.0) (*143*). A survey of 1496 TB patients from the civilian and penitentiary sectors in Ukraine reported a significant positive association between HIV status and MDR-TB (OR 1.7, 95% CI: 1.3 to 2.3) (*144*).

Several studies conducted in sub-Saharan Africa (*145-146*), South America (*147*) and South-East Asia (*148-151*), and a study conducted in 11 countries (*152*), did not observe any association between MDR-TB and HIV infection. However, most of these studies included small numbers of MDR-TB cases, and many were carried out before the dual epidemics of HIV and drug-resistant TB had significantly expanded. A systematic review including 32 studies from 17 countries could not demonstrate an overall association between MDR-TB and HIV infection. However, this analysis was limited by the lack of adjustment for potential confounders and the small sample sizes in individual studies (*153*).

The extent of MDR-TB disease among people living with HIV is poorly documented around the world, especially in sub-Saharan Africa (*139, 143*). The prevalence of HIV infection among MDR-TB patients in Africa is believed to be high (*154*), as is the prevalence of HIV among people with drug-sensitive TB. The separation of control programmes for HIV and TB might have contributed to the lack of clear data. However, TB programmes recently started to regularly test for and report HIV coinfection, and HIV programmes routinely include TB screening and reporting.

Acquired rifampicin resistance in previously susceptible HIV-infected TB patients has been well established (*154*). Recently it has been documented that, in adults, drug-resistant TB is frequently the result of the transmission of an existing resistant strain. A study in Shanghai showed that 27 out of 38 patients (84%) with pulmonary TB but unspecified HIV status had drug resistance due to transmission of a drug-resistant strain of *M. tuberculosis* (*155*). Exogenous reinfection was the cause of MDR-TB and XDR-TB among 17 patients treated in the Tugela Ferry district hospital in South Africa, 15 of whom were HIV-infected. This exogenous reinfection was demonstrated through spoligotyping of the initial and subsequent follow-up isolates (*156*). All 17 patients had previously been hospitalized. A systematic review confirmed that primary MDR-TB (direct transmission of a resistant strain) was associated with HIV infection (summary prevalence ratio 2.72, 95% CI: 2.03 to 3.66) (*153*).

Little is known about drug-resistant TB among HIV-infected and uninfected children. Due to the paucibacillary nature of TB disease in children, drug resistance is more likely to result from transmission of a resistant strain than to develop during treatment (*157*).

Knowledge gaps identified:

- Determination of the global and regional burden, as well as the predictors of drug-resistant, MDR and XDR-TB among people living with HIV.
- Impact of concurrent HIV infection on transmission, acquisition and progression of TB drug resistance in HIV-infected patients, with or without antiretroviral therapy.
- Impact of early initiation of antiretroviral therapy on MDR and XDR-TB transmission.
- Surveillance criteria that would allow facility-based MDR-TB outbreaks to be identified and rapid response initiated in low MDR-TB settings.

4.2 Diagnostic issues in the identification of drug resistant TB in people living with HIV

Laboratory support, especially for mycobacterial culture, and drug-susceptibility testing for both first and second-line anti-TB drugs are critical for the management of drug-resistant TB (as discussed in Chapter 2). Limited laboratory capacity and lack of rapid point-of-care diagnostic tools for MDR-TB and XDR-TB are major bottlenecks for scaling-up the management and control of drug-resistant TB. Other obstacles include the lack of standardized, reproducible and reliable methods for second-line drug-susceptibility testing. An additional issue is the unknown clinical relevance of *in vitro* mono-resistance and cross-resistance within second-line anti-TB drugs (*158*).

Knowledge gaps identified (in addition to those mentioned in Chapter 2):

- Development of rapid molecular methods for drug-susceptibility detection of all second-line anti-TB drugs.
- Standardization of drug-susceptibility testing for second-line drugs and clinical relevance of second-line drug-susceptibility testing.
- Prognostic value of *in vitro* mono-resistance and cross-resistance between second-line drugs, including of fluoroquinolones.
- Operational models for scaling-up laboratory capacity in TB culture and drug-susceptibility testing.

4.3 MDR-TB treatment strategies in people living with HIV

Clinical experience in treating patients with HIV infection and drug-resistant TB is still poorly documented. This is illustrated by a meta-analysis of 34 studies of treatment outcomes among 8502 patients with MDR-TB; HIV status was inconsistently reported in these studies (*159*).

Poor treatment outcomes and high mortality rates have been reported in HIV-infected patients treated for MDR-TB (*160-162*). In Tugela Ferry, South Africa, one-year mortality in MDR-TB patients was reported at 69%, and one-year mortality in XDR-TB patients at 82%. It was also reported that 40% of the MDR-TB and 54% of the XDR-TB patients died within 30 days of sputum collection (*163*). A total of 90% of the MDR-TB patients and 97% of the XDR-TB patients were HIV-positive. Early mortality among patients with MDR-TB and HIV was also observed in Peru where 55% (17/31) of coinfected patients died within two months of diagnosis (*162*). In Thailand, MDR-TB was a risk factor for death among patients coinfected with HIV (HR 11.7, 95% CI: 2.1 to 64.9) (*164*). Between 1993 and 2007 in the USA, higher mortality despite treatment was reported for XDR-TB patients compared to those with MDR-TB or drug-susceptible TB. Eighty-one per cent (21/26) of the TB patients were HIV-positive (prevalence ratio of 1.82, 95% CI: 1.10 to 3.02) (*165*). However, a retrospective hospital-based study of 60 patients treated for XDR-TB in South Africa found no association between mortality and HIV status (HR 0.96, 95% CI: 0.52 to 1.78) (*166*).

In general, poor outcomes are reported for drug-resistant TB patients who are also infected with HIV. However, in a study in Argentina, mortality rates and survival times were improved in a cohort of HIV-infected patients treated for MDR-TB who received antiretroviral therapy, compared to historical pre-antiretroviral therapy control groups (*167*). Improved survival was also observed among

South African people living with HIV who were receiving individualized treatments for XDR-TB, with 20% (12/60) converting their TB cultures to negative. Thirty-five per cent of these patients were also receiving antiretroviral therapy (*166*).

Overlapping toxicities and drug interactions complicate the management of patients receiving antiretroviral therapy and second-line anti-TB drugs (*154, 168*). Little is known about the optimal second-line anti-TB drug combination and treatment duration in HIV coinfected patients, whether receiving antiretroviral therapy or not, or about the optimal time of initiation of antiretroviral therapy. However, given high mortality rates among patients with resistant TB and HIV coinfection, early initiation of antiretroviral therapy is recommended to prevent early mortality (*168*). In many cases, it may be beneficial to start antiretroviral therapy in HIV-infected TB patients who are still awaiting the results of drug-susceptibility testing and who may not be on optimal TB therapy.

New classes of anti-TB drugs, such as diarylquinolines, are being investigated (*136*). A recent study of a new anti-TB drug was conducted In 47 patients. However, only 13% of the patients were HIV-infected, their CD4 counts were high, and none were receiving antiretroviral therapy. The patients were receiving a five-drug MDR-TB regimen. The addition of the drug TMC207 to the regimen resulted in faster conversion to negative *M. tuberculosis* cultures at eight weeks compared to placebo (HR 11.8, 95% CI: 2.3 to 61.3, P = 0.003). A similar incidence of adverse events was seen between the treatment and placebo arms of the study (*137*). Drug interactions studies with TMC207 and antiretroviral drugs are urgently needed; a study of interaction with ritonavir is underway.

Documented nosocomial transmission of MDR and XDR *M. tuberculosis* strains has also highlighted the need to develop outpatient management and community models to care for HIV-infected patients with drug-resistant TB, and to strengthen infection control procedures at all levels (*139, 168*). Community models are discussed in Chapter 6.

Knowledge gaps identified:

- Optimal drug combinations and duration of treatment for MDR-TB and XDR-TB disease in people living with HIV, with or without antiretroviral therapy.
- Drug interactions between second-line anti-TB drugs and antiretroviral drugs.
- Documentation of clinical outcomes and clinical experience in terms of drug tolerability, safety, efficacy, acceptance, adherence and mortality rates of HIV-infected MDR-TB patients treated with various drug combinations.
- Guidance on the recognition and management of adverse events due to concomitant use of second-line anti-TB drugs and antiretroviral drugs.
- Optimal time of initiation of antiretroviral therapy in drug-resistant TB patients.
- Incidence and risk factors of immune reconstitution syndrome in HIV-infected patients with drug-resistant TB.
- Most appropriate models of care for drug-resistant TB in resource-limited settings with high HIV burden and variables to assess these best models.

4.4 Management of contacts of drug-resistant TB patients

Little is known about the management of contacts of drug-resistant TB patients, including those contacts who are HIV coinfected. Infection control measures should be in place to reduce transmission of drug-resistant TB to contacts. However, even after an *M. tuberculosis* infection in a contact has been confirmed, the susceptibility pattern of the infecting strain is not known. It cannot be inferred that it was transmitted from the household index case. A study in Peru has shown that only 17% of *M. tuberculosis* isolates from secondary cases among close contacts of MDR-TB patients had the same drug-susceptibility profile as the strain isolated from the index case (*169*). In addition, the optimal drug regimens and duration of preventive therapy for latent *M. tuberculosis* infection with a drug-resistant strain is unknown. No trials have been conducted to determine which preventive TB therapy to use in contacts of patients with MDR-TB, whether HIV-infected or not (*158*). Contacts of drug-resistant TB patients, with or without HIV infection, should be included in new TB vaccine trials (*158*).

Knowledge gaps identified:

- Optimal management of contacts of MDR-TB patients, whether HIV-infected or not, and optimal regimen (individual drugs or drug combinations that are safe and effective) for preventive TB therapy in contacts of MDR-TB patients.
- Inclusion of contacts of drug-resistant TB patients, with or without HIV infection, in new TB vaccine trials.

4.5 Priority research questions on drug-resistant TB and HIV infection

RESEARCH QUESTION	SCORE
What are the programmatic impact and benefit to individual treatment outcomes of line probe assays and other non-culture-based assays for diagnosis of drug-resistant TB at the peripheral level of care?	8.8
What are the true burden, predictors and transmission dynamics of MDR-TB and XDR-TB in high HIV prevalence and resource-limited settings?	8.6
What is the best model of care for drug-resistant TB in settings with high burden (hospital vs. community-based), in light of basic public and individual patient rights?	8.3
What is the safety, efficacy, tolerability and optimal dosage of a single drug or combination of drugs to treat contacts of MDR-TB patients to prevent TB, including children, people living with HIV and pregnant women?	8.2
What is the impact of an early start of antiretroviral therapy (in terms of CD4 count) on clinical outcomes and on transmission of drug-resistant TB?	8.1
What are rapid, molecular methods for the detection of resistance to all second-line anti-TB drugs?	8.1
What is the impact of concurrent HIV infection on transmission, acquisition and progression of drug resistant TB in people living with HIV with or without antiretroviral therapy?	8.0
What are the surveillance or clinical criteria that allow facility-based MDR-TB and XDR-TB outbreaks to be identified and responded to rapidly?	7.7
How best to recognize and manage the adverse events due to concomitant use of second-line anti-TB drugs and antiretroviral drugs?	7.5
How best to standardize drug-susceptibility testing for second-line anti-TB drugs?	7.3

CHAPTER 5: CHILDHOOD AND MATERNAL TB AND HIV

HIV-associated TB in pregnant women, nursing mothers and children is a neglected area in both programme implementation and research in many settings. This chapter examines the issues related to TB in women living with HIV, and its consequences on morbidity and mortality. This chapter also highlights the challenges of preventing, diagnosing and managing maternal and childhood TB in the era of the HIV epidemic, and identifies critical research needs.

5.1 Paediatric TB and HIV

5.1.1 Epidemiology of TB in children living with HIV

The true burden of HIV-associated TB in children worldwide is unknown. This is due to difficulties in diagnosis and poor reporting of paediatric TB cases by national programmes. In Thailand, only 279 (2%) of the 14 487 recorded TB cases over the period 2004–06 occurred in children, of whom 75 (27%) were known to be HIV-infected (*170*). In a South African population-based study, the incidence of culture-confirmed TB over the period 2004–06 was 1596/100 000 among HIV-infected infants below one year of age and 66/100 000 among HIV-uninfected infants (*171*).

HIV infection has been reported as a risk factor for TB disease in children exposed to or infected with TB. In a cohort of 2654 South African children, the risk of microbiologically confirmed TB was more than six times higher in children living with HIV than in HIV-uninfected children (RR 6.7, 95% CI: 5.5 to 8.3) (*172*). In Côte d'Ivoire, Ethiopia and South Africa, up to 10 times higher mortality rates were reported among children living with HIV treated for active TB compared to HIV-uninfected children (*173-175*). Similarly, in Thailand, in children with TB, 17% of the HIV-infected children died during TB treatment compared with 2% of children not known to be HIV infected ($P < 0.01$) (*170*).

Children living with HIV might be more frequently exposed than HIV-uninfected children to caregivers with smear-positive pulmonary TB (*176*). High rates of exposure to *M. tuberculosis*, measured as contact with a TB source case, were observed among South African HIV-exposed infants screened for isoniazid preventive therapy (*177*). Higher relapse rates after standard TB treatment were also observed in HIV-infected children compared to HIV-uninfected children (*178*). The incidence of TB disease in children living with HIV was reported to be increased by threefold in severely immunocompromised children (CD4 count < 15%) (*179*).

5.1.2 TB prevention in children living with HIV

There are limited data on the use of preventive TB therapy in children living with HIV (*180*). One RCT found a reduced risk of TB disease (HR 0.28, 95% CI: 0.10 to 0.77) and reduced mortality (HR 0.46, 95% CI: 0.22 to 0.94) in children living with HIV receiving isoniazid preventive therapy daily or thrice weekly compared to placebo, over a median follow-up period of 5.7 months (*181*). However, isoniazid preventive therapy was found to be safe but ineffective in preventing TB or death in HIV-infected or HIV-exposed but uninfected infants with no history of TB exposure or disease (*182*).

In TB-endemic areas, most infants born to HIV-infected mothers still receive BCG vaccine, since HIV infection cannot usually be ruled out in the first weeks of life. However, BCG itself can cause mycobacterial disease in both HIV-infected and uninfected children (*183*), including those receiving antiretroviral therapy. Among children living with HIV in South Africa, the incidence of disseminated BCG disease was estimated at 992 per 100 000 BGC-vaccinated children over the period 2004–06 (*184*). BCG-associated immune reconstitution inflammatory syndrome was reported in up to 7.9% (33/417) of HIV-infected infants receiving antiretroviral therapy in South Africa (*185*). BCG-associated immune reconstitution inflammatory syndrome was also found to be significantly associated with high viral loads at baseline and younger ages (below nine months of age) (*186*). In addition, reduced immune response to BCG vaccination has been shown in children living with HIV throughout the first year of life. This reduced response makes the efficacy of BCG vaccination in this population questionable (*187*). Boosting BCG with a subunit vaccine or replacing BCG are strategies to improve TB vaccination currently being investigated. However, the protective efficacy and safety of a replacement vaccine or booster for BCG will need to be evaluated for children living with HIV.

5.1.3 TB diagnosis in children living with HIV

In the absence of bacteriological confirmation, a diagnosis of childhood TB depends on clinical features, exposure history, tuberculin skin test, relevant investigations for suspected extrapulmonary or pulmonary TB (e.g. chest X-ray), and HIV testing in areas of high HIV prevalence (*188*).

Clinical features of TB were examined in a prospective cohort of 596 South African children with culture-confirmed TB, with or without HIV infection. The most common presenting symptoms found for TB disease were cough lasting more than two weeks (57.7%), weight loss or failure to gain weight (53.4%) and fever (47.7%) (*189*). In India, 49% of the children with culture-confirmed TB, including those with pulmonary TB, presented with peripheral lymph node enlargement (*190*). However these symptoms are not specific to TB disease and may be associated with other HIV-related conditions. Clinical scoring systems have been developed for features of TB, but lack standard definitions and have not been validated (*191*). In a prospective South African community-based study, a symptom-based approach was found to have limited diagnostic value for TB in children living with HIV, because as many as 25% of the children reported similar chronic symptoms in the absence of TB (*192*).

Although less sensitive in HIV-infected than in HIV-uninfected children (*174, 193*), the tuberculin skin test is still extremely useful to support the diagnosis of TB in children (*194*). Chest X-rays shows similar features in HIV-infected and HIV-uninfected children with confirmed TB, such as persistent opacification with enlarged perihilar lymph nodes (*189, 193, 195*). However, interpretation of the chest X-ray is complicated by other HIV-related conditions (*196*). Furthermore, a chest X-ray may be normal even with active TB, as reported in India in 56% of 148 children in whom both TB culture and a chest X-ray were performed (*190*).

IGRAs that show higher sensitivity than the tuberculin skin test have recently become available. The T-SPOT.TB assay was significantly more sensitive than the tuberculin skin test in South African children with TB disease and HIV infection, malnutrition, or younger age (< 36 months) (*197*). However, these assays cannot differentiate latent TB from active TB, and data on children are still limited (*46*).

5.1.4 TB treatment in children living with HIV

Current recommendations to treat active TB disease in children living with HIV are drawn from data from HIV-uninfected children and adults (*176*). TB treatment is frequently individualized (*198*). Pharmacokinetic studies of anti-TB or antiretroviral drugs in children are lacking, as are RCTs to determine how to optimally manage and treat children living with HIV who also have active TB disease. Low serum rifampicin concentrations have been reported in South Africa among HIV-infected or uninfected children receiving recommended standard dosages of rifampicin (*199*). The high relapse rates observed among South African children living with HIV treated for active TB (*178*) suggest that the currently recommended doses of anti-TB drugs and the duration of treatment should be increased (*176*). Antiretroviral therapy reduced the incidence of childhood TB by up to 50% (*198, 200*). TB incidence also decreased with the time spent on antiretroviral therapy (*200*).

Treatment issues for adults – such as drug interactions, overlapping side-effects and when to initiate antiretroviral therapy – also apply in children. A prospective observational study demonstrated adequate and safe lopinavir plasma concentrations after dose adjustment in 13 of 15 (93%) children living with HIV and receiving rifampicin; 70% achieved an undetectable viral load at six months (*201*). However, subtherapeutic concentrations of efavirenz were reported during and after rifampicin-based TB treatment in 15 South African HIV-infected TB children (*202*).

The choice of antiretroviral drugs regimen in children is also complicated by prior maternal and infant nevirapine exposure for prevention of mother-to-child HIV transmission (*203*). Significant virological failure at six months occurred more frequently in HIV-infected infants who received a single dose of nevirapine at birth and subsequent nevirapine-based antiretroviral therapy, compared to those who were not exposed to nevirapine at birth or who received subsequent lopinavir-based antiretroviral therapy (*204-205*) .

TB-IRIS is poorly described in children living with HIV. A few studies found that the onset of TB-IRIS in children ranges from four weeks to four months

(*198, 206*). A retrospective case series of 11 TB-IRIS cases showed that 4 had paradoxical deterioration and 7 had unmasking of undiagnosed TB (*207*).

5.1.5 Drug-resistant TB in children living with HIV

Drug-resistant TB in children is more likely to result from the transmission of a resistant strain than from acquired resistance, since TB is often paucibacillary in children (*157*). However, the acquisition of drug resistant TB in children previously treated for TB has been reported, especially in children living with HIV (*208*). The range of prevalence of isoniazid resistant TB was 7–13%, and of MDR-TB was 4–10%. Up to 48% of these children were also HIV-infected (*189, 208*). Experience with second-line anti-TB drugs in children is limited. A retrospective study of 38 children treated for MDR-TB for 18–24 months in Peru showed a cure rate of 95%, with a 2.5% mortality rate and defaulter rate (*209*). Adverse events occurred in 42% of the children, but no event required treatment discontinuation for more than five days. Like the management of drug-resistant TB in adults, little is known about cross-reactions between second-line anti-TB drugs and antiretroviral drugs.

Knowledge gaps identified:

- True global and regional burden of *M. tuberculosis* infection and TB disease in children, HIV-infected and uninfected.
- Effect of the HIV epidemic on incidence, burden and trends of childhood TB.
- Most effective strategies for enhanced TB case-finding among HIV-exposed and HIV-infected children.
- Efficacy of TB preventive therapy in children living with HIV including: the optimal TB preventive regimen; the benefit of isoniazid preventive therapy in the context of antiretroviral therapy use with age of child; the optimal duration of isoniazid preventive therapy and other preventive regimens; the duration of the protective effect of preventive TB therapy; and the long-term adverse events associated with preventive TB therapy.
- Effect of antiretroviral therapy in preventing TB in children living with HIV.
- Optimal clinical TB algorithm to improve TB screening and diagnosis in children, with and without HIV infection.
- Pharmacokinetic studies of anti-TB and antiretroviral drugs in children, to assess the influence of age, nutritional status and HIV infection on drug concentrations and clinical outcomes.
- Appropriate paediatric drug formulations and paediatric drug pharmacology for existing first and second-line anti-TB and antiretroviral drugs.
- Optimal antiretroviral therapy regimens and timing of initiation of antiretroviral therapy in children living with HIV being treated for TB.
- Efficacy and safety of new and novel drugs for the treatment of drug-resistant TB in conjunction with antiretroviral drugs in children living with HIV.
- Better understanding and better guidance for the diagnosis and management of TB-IRIS, including BCG-associated IRIS, in children living with HIV.

5.2 Maternal TB and HIV coinfection and mother-to-child transmission

TB and HIV infection are independent risk factors for maternal mortality and unfavourable perinatal outcomes, and have a greater effect on maternal and infant outcomes when combined (*210*). A prospective study in South Africa found that the rates of active TB were 10 times higher in pregnant women living with HIV (7.75/1000) than in those without HIV infection (0.73/1000) (*211*). Studies done in South Africa and India among pregnant women living with HIV showed that the prevalence of undiagnosed TB ranged from 1.5% to 11% (*212-213*). Several studies reported that TB in the mother became apparent after a diagnosis was made in the infant (*214-215*).

HIV-associated TB has been associated with increased maternal mortality. A prospective study from South Africa reported maternal mortality rates of 121.7/1000 live births among mothers living with HIV and TB, compared to 38.5/1000 among mothers with TB but without HIV infection (*216*).

Other complications observed with HIV-associated TB include higher rates of antenatal hospitalization and poorer perinatal outcomes, such as prematurity, small for gestational age, low birth weight and perinatal death (*217-218*). A study in South Africa reported a perinatal mortality rate attributed to TB of 65.2/1000 in women living with HIV compared to 0/1000 in those HIV-uninfected (*219*). Otherwise, data are very limited on the effect of HIV-associated TB on obstetrical and perinatal outcomes.

Vertical mother-to-child transmission of TB may occur in utero and during the intrapartum period, and is believed to be due to either haematogenous dissemination, or aspiration and ingestion of infected amniotic fluid. TB transmission can also occur during the postpartum period by inhalation or ingestion of respiratory droplets or breast milk (*220*). Among 107 South African pregnant women with TB, 77% of whom were HIV-infected, 16% of neonates had *M. tuberculosis* bacilli detected in gastric aspirates or cerebrospinal fluid samples within the first three weeks of life (*219*). A study among 42 HIV-infected pregnant women with TB reported that 19% of their babies acquired vertical HIV infection, which is higher than the usual range of 5–10% (*221*). However, data are too limited or inconsistent to know whether pregnancy aggravates TB in women living with HIV (*210*).

High maternal TB incidence during the postpartum period (5.0/100 person-years, 95% CI: 3.2 to 7.4) has been reported in a cohort study of Indian women living with HIV who were followed for one year after delivery (*222*). Mothers with postpartum TB were more likely to transmit HIV to their infant compared to mothers without TB (37.5% vs. 9.1% of HIV infection in the infants by one year of age, respectively, $P < 0.001$). Infants of mothers with postpartum TB were also at increased risk of death (incidence rate ratio of 3.4, 95% CI: 1.2 to 10.6).

Intensified TB case-finding, provision of isoniazid preventive therapy, or prompt and effective treatment of TB in pregnant women living with HIV are key interventions to lower maternal and perinatal mortality, but their implementation remains challenging. Pharmacokinetic studies are currently being conducted to assess the combined use of anti-TB and antiretroviral drugs during pregnancy.

Knowledge gaps identified:

- Understanding the key immunological changes that occur during pregnancy and that may affect risk, diagnosis, transmission and treatment of maternal TB.
- Evaluation of the dual effect of HIV and TB on mother-to-child transmission of HIV and TB and on maternal and infant outcomes.
- Roles of the tuberculin skin test, IGRAs, sputum and chest X-rays for screening for latent *M. tuberculosis* infection during pregnancy.
- Most effective strategies for screening for latent *M. tuberculosis* infection in pregnant women living with HIV in settings with a high burden of TB and HIV.
- Optimal timing (antenatal vs. postpartum) for preventive TB therapy.
- Safety, efficacy and cost-effectiveness of isoniazid preventive therapy and other multidrug short course regimens in pregnancy, conducted in well-designed RCTs.
- Most effective strategies for detecting active TB in pregnant women living with HIV.
- Impact of antiretroviral therapy in preventing mother-to-child transmission of HIV, and on maternal and child TB epidemiology.
- Safety, tolerability, pharmacokinetics and drug interactions of new and novel anti-TB drugs in pregnant women and nursing mothers.

5.3 Priority research questions in maternal and childhood TB and HIV coinfection

RESEARCH QUESTION	SCORE
What are the best clinical algorithms and diagnostic tools to improve TB screening and diagnosis in HIV-infected infants and children, including diagnosis of BCG-related TB, TB-IRIS and drug-resistant TB?	8.7
What is the effect of antiretroviral therapy in preventing TB in children?	8.7
What is the optimal antiretroviral therapy to use in combination with a rifampicin-based TB regimen in HIV-infected infants and children, and the optimal time to initiate antiretroviral therapy in children being treated for TB?	8.7
What are the pharmacokinetic profiles and drug interactions of antiretroviral and anti-TB drugs (including rifabutin and new anti-TB drugs) in children, and what is the influence of age, nutritional status and HIV infection?	8.4
What are the global and regional burden and dynamics of childhood TB and the impact of HIV?	8.2
What are the safety, tolerability, pharmacokinetic parameters and drug interactions of new and novel anti-TB drugs in pregnant women and nursing mothers?	8.0
What is the impact of maternal isoniazid preventive therapy given alone or with antiretroviral therapy on maternal and child outcomes?	7.8
What is the optimal timing for preventive therapy in pregnant women and nursing mothers (antenatal vs. postnatal)?	7.5
What is the impact of antiretroviral therapy to prevent mother-to-child transmission of HIV on maternal and child TB transmission and epidemiology?	7.2
What are the clinical and immunological dual effects of HIV and TB on mother-to-child transmission of HIV and TB, and maternal and perinatal outcomes?	7.2
What is the role and best strategy to improve BCG vaccine efficacy and safety in HIV-infected infants and children, including deferring BCG until HIV-infection status is known?	6.7
What is the role of BCG in prevention of TB in HIV-infected infants?	6.3

CHAPTER 6: INTEGRATED TB AND HIV SERVICES

The implementation of collaborative TB/HIV interventions requires sound policy and a programme environment that gives due consideration to the local context, the epidemiology of TB and HIV, and the status of health systems and infrastructure that will determine the service-delivery models. Cultural and system-wide differences between HIV and TB care providers and stakeholders, as well as operational difficulties for providing effective and appropriate interventions, have contributed to less implementation or scaling-up of collaborative TB/HIV activities. This chapter examines research issues that could facilitate wider implementation and scaling-up of collaborative TB/HIV interventions through effective service-delivery models, including community-based interventions.

6.1 TB and HIV service delivery

The best delivery model of collaborative TB/HIV interventions is unknown. However, different models for collaboration between TB and HIV care programmes are already implemented in several countries. In India, Malawi and Mozambique, TB and HIV services are provided separately, with strengthened cross-referrals (*223-225*). Partial integration, including provision of co-trimoxazole prophylaxis and antiretroviral therapy in TB clinics, or TB screening and directly observed TB treatment in HIV clinics, is used in Rwanda and Tanzania (*226-227*). Fully integrated models with "one-stop service" for TB patients with HIV were reported in Malawi and in South Africa (*228-229*). However, each model has advantages and disadvantages.

Strengthened referral models between TB and HIV services have been shown to improve ascertainment of HIV status among TB patients, provision of co-trimoxazole prophylaxis to HIV-infected TB patients, and TB screening and TB diagnosis among people living with HIV.

In Malawi, the percentage of TB patients tested for HIV increased from 8% to 26% from 2002 to 2004, and to 86% in 2007 (*230*). More than 95% of those who tested HIV-positive received co-trimoxazole prophylaxis therapy (*228*). Referral between voluntary HIV counselling and testing centres and TB services in India allowed diagnosis of TB in 83 of the 336 patients (29%) who had suspected TB at the voluntary counselling and testing centre, and were then referred to TB clinic (*225*). However, the number of cross-referrals remains insufficient for adequate TB and HIV control.

Loss of follow-up of patients between TB and HIV services is common. Up to 17% (177/1065) of the HIV-infected people with suspected TB referred to microscopy centres in Tamil Nadu, India did not show up (*231*). In Cambodia, compliance with HIV testing was halved when TB patients had to travel more than 15 minutes to HIV counselling and testing centres, compared with HIV testing on site (RR 0.6, 95% CI: 0.5 to 07) (*232*). Some sites provide a patient escort. In Mozambique, patients referred between TB and HIV services are accompanied by a TB/HIV focal nurse. In certain districts in India, the patient is accompanied by a directly observed therapy supporter. These efforts have greatly minimized the number of patients lost to follow-up (*224, 233*). However, the need to refer TB patients for HIV testing or HIV care was perceived as a barrier to implementing collaborative TB/HIV interventions in Kenya. Uptake of HIV testing and co-trimoxazole preventive therapy increased when these services were offered on site by TB clinic staff (*234*).

In Mozambique, TB patients found to be HIV-infected were referred to antiretroviral therapy services, with 68% (15/22) of them immediately being enrolled for antiretroviral therapy (*224*). Data from seven African countries and Myanmar showed that each antiretroviral therapy facility was shared by five TB treatment centres in these countries. These figures may explain the low antiretroviral therapy uptake in HIV-infected TB patients; they emphasize the need to combine TB and antiretroviral therapy services in one location (*230*).

Partial integration of TB/HIV services has been established in rural Rwanda by provider-initiated HIV testing and counselling of TB patients, and implementation of a standard TB screening questionnaire for inpatients on medical wards and for HIV-infected outpatients. The percentage of TB patients tested for HIV increased from 82% in 2004–05 to 93% in 2005–06 ($P < 0.001$) (*226*). Similar outcomes were achieved in Tanzania and Thailand when HIV counselling, testing, care and treatment were offered in TB clinics. In addition, TB screening was introduced in HIV care and treatment centres (*227, 235*). A qualitative study in the Democratic Republic of Congo revealed that 96% of health-

care workers and 99% of TB patients preferred incorporating HIV testing into routine TB care, compared to referral to a voluntary counselling and testing centre (*236*).

However, partial integration may bring additional burdens to already strained health workers. A shortage of staff trained in the care and treatment of HIV was a concern in Tanzania, while the Rwandan programme had to hire additional staff.

As an illustration of full integration, a "one-stop service" for HIV-infected TB patients was introduced in South Africa in 2006. This service resulted in 87% (765/881) of TB patients accepting HIV testing, 98% of HIV-infected TB patients receiving co-trimoxazole prophylaxis, and 73% of HIV-infected TB patients receiving antiretroviral therapy (*237*). In contrast, while 92% of the Malawian TB patients attending the first integrated clinic in Lilongwe were tested for HIV infection, only 36% (300/830) of the eligible coinfected patients initiated antiretroviral therapy (*229*). Patients' reluctance about receiving dual therapy and fear of side effects explained this low uptake of antiretroviral therapy among eligible HIV-infected TB patients.

These experiences have highlighted several challenges in implementing collaborative TB/HIV interventions, including space constraints; shortage of trained human resources; and the need for sound infection control and staff protection measures, sensitive TB screening tools, enhanced and flexible referral systems between TB and HIV services during and after TB treatment, and integrated monitoring and reporting systems (*224, 226-227, 229, 237*).

Another major challenge in implementing collaborative TB/HIV interventions is the scaling-up of laboratory capacity in resource-limited settings. Laboratory capacity is needed to implement existing tests that can significantly improve TB detection, and to facilitate integration of point-of-care diagnostic tests when they become available (*77*). One operational research study in rural South Africa evaluated integrated home-based TB and HIV treatment. This study revealed that most of the deaths among HIV-infected TB patients (10/13) occurred in patients coinfected with MDR-TB or XDR-TB (*163*). To prevent further increases in the prevalence of drug-resistant TB, it will be crucial to integrate more rapid and simple technologies for drug-susceptibility testing that detect MDR-TB and XDR-TB within days as opposed to weeks (*154*).

Further operational research is needed to define how best to link TB and HIV services, as well as where and how to optimally deliver antiretroviral therapy to HIV-infected TB patients at a larger scale.

Knowledge gaps identified:

- Best service delivery model, including cost-effectiveness, to provide collaborative TB/HIV interventions at the health-sector level.
- Appropriate constellations of resources, including human resources, to provide TB and HIV treatments in different settings.
- Identification of the barriers to access antiretroviral therapy faced by HIV-infected TB patients.
- Optimal health-care settings to provide antiretroviral therapy to HIV-infected TB patients.
- Optimal models that enable effective uptake and retention of TB patients into antiretroviral programmes.
- Reasons why HIV-infected TB patients do or do not attend health-care settings, and why health-care staff do or do not request TB investigations in integrated services.
- Operational models to integrate TB and antiretroviral therapy programmes, including programmes at the health sector and community levels.
- Operational models to increase and scale-up laboratory capacity, including implementing new TB diagnostic techniques and improved diagnostics at all levels of care.

6.2 Community-level interventions

High levels of undiagnosed TB observed in communities may drive the dynamics of the TB and HIV epidemics at the community level (*238*). A cross-sectional survey among home-based care beneficiaries in Cambodia found a prevalence of pulmonary TB of 12% (54/441), with a ratio of undetected to detected TB cases of three to one (*54*). In a South African community with high HIV prevalence, prevalence rates of undiagnosed smear-positive pulmonary TB were 2837/100 000 among people living with HIV and 175/100 000 among HIV-uninfected individuals (*66*). TB prevalence rates in two communities of Zambia, one rural and one urban, were 650/100 000 and 1200/100 000, respectively, while TB notification rates were 275/100 000 and 438/100 000, respectively (*57*).

People living with HIV are less likely to transmit TB to their close contacts compared to HIV-uninfected people (*239-240*). Most TB transmission may be attributed to HIV-uninfected individuals, while those at highest risk for developing TB are people living with HIV (*241*). Hence, interventions to control TB in the community, such as active case-finding of undiagnosed TB, treatment of latent *M. tuberculosis* infection and effective TB care are needed, and should include HIV-uninfected individuals (*238*). Mathematical models suggest that improved TB case-finding and treatment of infectious TB cases are the most efficient and cost-effective interventions for controlling TB (*242-243*).

There are documented experiences with community-based implementation of interventions. For example, in the pre-HIV era, community-wide isoniazid preventive therapy reduced TB transmission and incidence by 59% in Alaska (*244*). Similarly, isoniazid preventive therapy was found to be effective among people living with HIV and routinely screened for TB in public primary care clinics in Brazil (*39*).

The "Community TB care in Africa" project, conducted in six sub-Saharan African countries with high HIV prevalence, demonstrated that community-based TB care – delivered by either community health workers, traditional healers or caregivers – was efficient, cost-effective, affordable and acceptable (*245-250*).

Several cluster-randomized trials are presently being conducted in settings with high HIV prevalence, to evaluate various strategies to enhance TB case-finding (among other interventions, including the feasibility and the impact of community-wide isoniazid preventive therapy on TB incidence) (*251-252*)

Community-based MDR-TB treatment was considered successful in Peru when 83% of the 66 MDR-TB patients receiving outpatient care became culture and sputum-smear negative after four months of therapy (*253*). The death rate during treatment was 8% (5/66), and only one patient continued to have positive cultures after six months of therapy. High cure rates were also observed among MDR-TB children treated in the community (*209*). Given the risk of nosocomial transmission of drug-resistant TB among people living with HIV, the cost and insufficient availability of hospitalized-based treatment, and the low acceptance of enforced hospitalization, community-level treatment for MDR-TB should be urgently developed (*168*).

However, the risk of household transmission of MDR-TB even after treatment initiation, in people with or without HIV, is unknown. The appropriate management of contacts of drug-resistant TB patients is also unknown (*158*). Proper infection control measures should be in place to protect contacts and the community as a whole, but the specific implications of such community initiatives on prevention of TB in people living with HIV are unknown.

TB control programmes need to be comprehensive, and to include interventions addressing the risk factors for developing TB, such as prevention and treatment of HIV (*254-255*). A mathematical model of universal HIV testing with immediate initiation of antiretroviral therapy indicated that the incidence and mortality of HIV could be reduced to less than one case per 1000 people within 10 years with the implementation of prompt and universal antiretroviral therapy. This outcome could potentially reduce the incidence of TB (*256*). However, other models indicated that additional factors may be needed to effectively reduce the number of TB cases and TB mortality. These factors include early initiation of

antiretroviral therapy in the course of HIV infection, high population coverage with antiretroviral therapy (≥ 75%) and high compliance levels (100%) (*36-37, 243*). Large-scale community interventions need to be assessed for efficacy, feasibility, acceptability and cost-effectiveness, as well as relevant ethical issues, before full implementation is recommended.

Knowledge gaps identified:

- Community-level interventions, including family care, and the best way to deliver these interventions to effectively reduce the prevalence of TB in communities highly affected by HIV.
- Community-level impact of implementation of collaborative TB/HIV interventions on TB and HIV transmission.
- Cost-effectiveness of collaborative TB/HIV interventions delivered through a community approach.
- Efficacy, feasibility and acceptability of community-based compared to hospital-based models for MDR-TB treatment and management, and the implications of these models for people living with HIV.
- Household risk of transmission of MDR-TB after initiation of treatment and patient discharge from hospital, for HIV-infected and uninfected household members.
- Efficacy, feasibility and acceptability of mass or targeted interventions for TB and HIV prevention and care in HIV-prevalent settings.
- Best practices in community research partnerships, particularly how to engage communities for better research outcomes.
- Best advocacy practices to promote awareness and the mobilization of community involvement, and the adoption of appropriate policies by governments, to respond effectively to the TB/HIV dual epidemic.

6.3 HIV-associated TB in special populations

Collaborative TB/HIV interventions should also be provided to most-at-risk populations (i.e. drug users, men who have sex with men, female and male sex workers) and people living in congregate settings such as prisoners, internally displaced people and refugees. People who are most at risk and those living in congregate settings have a higher risk of TB, including MDR-TB, HIV and drug use in many countries (*257-258*). This situation is usually aggravated by crowded living conditions, poor nutritional status and other coexistent illnesses. Similarly, the epidemic of drug use has become closely linked with the HIV and the TB epidemics. Injecting drug use is a major mode of HIV transmission in several regions of the world. Drug users also have an increased risk of TB infection, whether living with HIV or not (*259*).

The WHO, in collaboration with the Joint United Nations Programme on HIV/AIDS (UNAIDS) and United Nations Office on Drug and Crime, developed guidelines to deliver collaborative TB/HIV services for drug users, and highlighted questions for further research in this area (*259*).

Knowledge gaps identified:

- The best delivery models of collaborative TB/HIV interventions to most-at-risk populations and special populations in all settings with different TB and HIV epidemiology and epidemic states.
- Best models of collaborative TB/HIV interventions delivery within the context of a harm-reduction programme, including opioid-substitution therapy.
- Evidence on the safe use of antiretroviral therapy among injecting drug users living with HIV who are also TB-infected, particularly among those who are coinfected with hepatitis B or C.

6.4 Priority research questions in TB and HIV services integration

RESEARCH QUESTION	SCORE
What are the best strategies and optimal models to integrate and deliver joint TB/HIV interventions, including antiretroviral therapy, at community and health sector levels to HIV-infected TB adults, children and families?	10
What are the best operational models to increase and scale-up laboratory capacity, including implementing new TB diagnostic techniques and drug-susceptibility testing, and improve diagnosis of TB at all levels of care?	9.0
What are the barriers to care for people living with HIV, adults, children and families, to access HIV and TB care, and antiretroviral therapy for those coinfected with TB, from patient and health-care worker's perspective, and how to address them?	8.7
What are the best models of community participation (i.e. effective, feasible, acceptable and sustainable) for enhanced TB case-finding and early HIV detection, to reduce delay in initiation of TB and HIV care, and their impact on reducing TB and HIV transmission?	8.6
What are the best models to enable effective uptake and retention of TB patients into antiretroviral programmes?	8.6
What are the best strategies to promote and scale-up integrated screening of HIV infection and TB infection and disease among household contacts of HIV-infected TB patients?	8.6
What is the efficacy, feasibility and acceptability of community-based models for MDR-TB treatment and management, and what are the implications on *M. tuberculosis* transmission, particularly among people living with HIV, and on resource allocation?	8.4
What is the efficacy, feasibility and acceptability of community-wide or targeted community interventions for TB and HIV prevention and care in HIV-prevalent settings?	7.6
What is the cost-effectiveness of joint TB/HIV interventions delivered through a community approach and through health facilities?	7.6
What are the best models of delivery of collaborative TB/HIV interventions to most-at-risk and special populations in all settings with different TB and HIV epidemiology and epidemic states?	7.4
What is the household risk of transmission of MDR-TB once treatment is started and patients discharged from hospital for HIV-infected and uninfected household members?	7.3
What is the relative contribution of community versus health facility transmission of susceptible and drug-resistant TB?	7.1
How to improve routine surveillance and monitoring and evaluation systems to allow programmes to prioritize TB prevention at community and clinic level?	7.0

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ANNEX 1

Table A1:

Number of publications from January 1, 2004 to December 31, 2009 identified through PubMed related to the research priorities identified in the *2005 TB/HIV research priorities in resource-limited settings* document per topic area.

RESEARCH AREA	RESEARCH PRIORITIES	NUMBER OF PUBLICATIONS
Preventive therapy for TB	Macro-level barriers to implementing isoniazid preventive therapy	10
	Outcomes of national isoniazid preventive therapy programme in Botswana	0
	Effectiveness in special populations and regions with elevated isoniazid resistance	4
	Optimum algorithm to exclude TB disease	9
	Added benefit of isoniazid preventive therapy among people receiving antiretroviral therapy	2
	Subgroups of people who are likely to benefit from isoniazid preventive therapy	1
	Effectiveness of isoniazid preventive therapy among infants and children	3
Co-trimoxazole prophylaxis	Role of co-trimoxazole in the context of antiretroviral therapy	7
	Optimal time to start co-trimoxazole among people living with HIV/AIDS and TB (with and without antiretroviral therapy)	0
	Determinants that influence efficacy of co-trimoxazole prophylaxis	7
	Best delivery strategies to improve the uptake of co-trimoxazole prophylaxis	7
Antiretroviral therapy for people living with HIV/AIDS who have TB or develop TB	Optimal time to start antiretroviral therapy among people living with HIV/AIDS who have active TB or develop TB	5
	Best antiretroviral therapy regimens, with dose adjustment required, to use with TB treatment regimens	18
	Efficacy and safety profile of alternative antiretroviral therapy regimens (e.g. “triple nukes”)	5
	Best clinical definition for immune reconstitution inflammatory syndrome, for use in resource-limited settings (validation studies)	11
	Cost-effectiveness of different regimens and strategies	1
	Minimal requirements for clinical and laboratory monitoring for outcomes related to efficacy and safety	1
	Best strategies for measuring and enhancing adherence for people receiving tuberculosis and antiretroviral therapy	6

RESEARCH AREA	RESEARCH PRIORITIES	NUMBER OF PUBLICATIONS
Intensified case-finding	Prevalence surveys	16
	Threshold for starting intensified case finding activities for national TB programmes and national HIV/AIDS control programmes	0
	Improving case-detection strategies in clinical settings	13
	Validating screening methods	8
	Systems to routinely record and report additional cases of TB detected through intensified case-finding	11
Smear-negative TB	Diagnostic algorithms to shorten the time required for establishing a diagnosis of smear-negative pulmonary TB and to include diagnosis of extrapulmonary TB	7
	Validating adapted diagnostic algorithms in children	3
	New diagnostic tools	18
	Utility of chest radiography in the diagnostic process	5
	Feasibility of promising techniques, such as bleach method and fluorescence microscopy	20
	Developing appropriate technology	10
	Improving reporting procedures	1
TOTAL		**209**

Table A2:

Number of publications per year from January 1, 2004 to December 31, 2009 related to the research priorities identified in the WHO publication TB/HIV research priorities in resource-limited settings 2005. Publications were identified through the United States National Library of Medicine PubMed database.

YEAR	NUMBER OF PUBLICATIONS
2004	20
2005	23
2006	29
2007	31
2008	50
2009	56
TOTAL	**209**

ANNEX 2

Table A3:

Definitions of the priority criteria and grading scale used to rank the research questions identified by the Advisory Committee and Review Board. The research question rankings were submitted through a web-based survey.

PRIORITY CRITERIA	DEFINITION	GRADING SCALE	SCORE
Effectiveness	The question provides knowledge, evidence and strategies to effectively decrease the burden of TB (morbidity and mortality) among people living with HIV, in a timely and cost-effective manner	Unlikely	0
		Somewhat likely	1
		Likely	2
		Very likely	3
Deliverability	The question provides knowledge, evidence and strategies deliverable in large-scale settings in a patient-friendly manner	Unlikely	0
		Somewhat likely	1
		Likely	2
		Very likely	3
Answerability	The question provides knowledge, evidence and strategies in an ethical way (i.e. protecting the rights of HIV and TB coinfected people, avoiding harming them, and maximizing their wellbeing) and in sound methodological manner (i.e. randomized trials, well-conducted prospective studies)	Unlikely	0
		Somewhat likely	1
		Likely	2
		Very likely	3
Equity	The question provides knowledge, evidence and strategies to reduce the burden of TB and HIV (morbidity and mortality) in all groups, particularly in most-at-risk groups such as poor or marginalized persons, children and women	Unlikely	0
		Somewhat likely	1
		Likely	2
		Very likely	3
Total score (minimum score 0 – low priority; maximum score 12 – high priority)			

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