

 Tuberculosis 3

The HIV-associated tuberculosis epidemic—when will we act?

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This is the third in a [Series](#) of eight papers about tuberculosis

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Despite policies, strategies, and guidelines, the epidemic of HIV-associated tuberculosis continues to rage, particularly in southern Africa. We focus our attention on the regions with the greatest burden of disease, especially sub-Saharan Africa, and concentrate on prevention of tuberculosis in people with HIV infection, a challenge that has been greatly neglected. We argue for a much more aggressive approach to early diagnosis and treatment of HIV infection in affected communities, and propose urgent assessment of frequent testing for HIV and early start of antiretroviral treatment (ART). This approach should result in short-term and long-term declines in tuberculosis incidence through individual immune reconstitution and reduced HIV transmission. Implementation of the 3Is policy (intensified tuberculosis case finding, infection control, and isoniazid preventive therapy) for prevention of HIV-associated tuberculosis, combined with earlier start of ART, will reduce the burden of tuberculosis in people with HIV infection and provide a safe clinical environment for delivery of ART. Some progress is being made in provision of HIV care to HIV-infected patients with tuberculosis, but too few receive co-trimoxazole prophylaxis and ART. We make practical recommendations about how to improve this situation. Early HIV diagnosis and treatment, the 3Is, and a comprehensive package of HIV care, in association with directly observed therapy, short-course (DOTS) for tuberculosis, form the basis of prevention and control of HIV-associated tuberculosis. This call to action recommends that both HIV and tuberculosis programmes exhort implementation of strategies that are known to be effective, and test innovative strategies that could work. The continuing HIV-associated tuberculosis epidemic needs bold but responsible action, without which the future will simply mirror the past.

Introduction

“Only those who dare to fail greatly can ever achieve greatly.”

Robert Kennedy

We are at a watershed with the dual epidemic of tuberculosis and HIV. About 30 years ago, an ancient pathogen, *Mycobacterium tuberculosis*, and a new pathogen, HIV, began to interact to escalate the burden of disease, death, and misery in human populations. Our response to this onslaught, particularly in the killing fields of east and southern Africa, has been timid, slow, and uncoordinated. If this situation had been a war—more deaths from AIDS have been recorded than there were military deaths in World War II—our efforts would have been ridiculed as half-hearted and ineffectual. Implementation of effective policies, strategies, and guidelines has been inadequate, particularly for tuberculosis prevention.

This call to action focuses on sub-Saharan Africa, the epicentre of the HIV-associated tuberculosis epidemic. We begin by listening to people with HIV infection who have developed tuberculosis, to understand what they want from health services. We review the interim international policy

Key messages

- The WHO interim policy on collaborative tuberculosis and HIV activities (2004) was a milestone in the fight against the two diseases, but it failed to emphasise the crucial preventive role of antiretroviral treatment (ART) or to provide adequate guidance on management of suspected HIV-associated tuberculosis. The policy needs urgent revision and updating to incorporate recent data and field experience.
- Many people with HIV infection start ART too late, especially in Africa, and have already developed tuberculosis by the time that they present to health services for care. Rigorous implementation of recent international guidelines to ensure early start of ART could prevent some of these failed opportunities.
- Findings from mathematical models suggest that an innovative approach of frequent universal HIV testing combined with immediate or much earlier start of ART has the potential to greatly reduce tuberculosis incidence and HIV transmission. A research priority is how to use ART for maximum benefit to prevent HIV infection and HIV-associated tuberculosis.
- Much morbidity and mortality from tuberculosis could be prevented in people with HIV infection, even with the limitations of diagnostic technologies, by application and scale-up of the 3Is (intensified case finding, infection control, and isoniazid preventive therapy) in HIV and ART clinical services. This approach complements the effects of early start of ART and must be scaled up.
- Because early start of ART and efforts to prevent tuberculosis have not yet been implemented to scale, provision of good HIV care is vital for all HIV-infected patients with tuberculosis through provider-initiated HIV testing and counselling, co-trimoxazole prophylaxis, and ART. ART should be given to all tuberculosis patients co-infected with HIV, and given as early as possible during antituberculosis treatment.

Search strategy and selection criteria

We searched PubMed and Google Scholar with search terms that included, but were not restricted to, “tuberculosis HIV”, “tuberculosis HIV testing”, “tuberculosis cotrimoxazole prophylaxis”, “tuberculosis antiretroviral therapy”, “isoniazid preventive therapy”, “intensified TB case finding”, “tuberculosis infection control”, and “tuberculosis Africa”. Further publications were identified from references cited in relevant articles, reports, workshops, and conference proceedings. We reviewed only papers published in English. No date restrictions were placed on searches.

guidelines for collaborative tuberculosis and HIV activities, and argue for a different conceptual approach that focuses on early diagnosis and treatment of HIV infection, which we believe will have the greatest effect in mitigation of the HIV-associated tuberculosis epidemic. We examine the logistics for delivery of tuberculosis prevention and HIV care, and make practical recommendations to scale up diagnosis, prevention, and treatment.

What do HIV-infected people with tuberculosis want from health services?

By the time people with HIV infection seek help from health services because of cough, fever, and weight loss, they are weak and frightened, and poorer because of transport and other costs that are imposed on their often meagre household budgets (panel 1). The health facility that greets them is overcrowded, with few health-care workers and no privacy. People with HIV infection might not know why they are ill, but they do know what they need: rapid and free-of-charge diagnosis of HIV infection and tuberculosis; information and support about what these diagnoses mean; free treatment of both diseases within the same facility with clear instructions about drugs, side-effects, and the need for adherence; and courtesy, respect, and discretion.¹

Yet, in most countries with dual HIV and tuberculosis epidemics, these simple, often unspoken, expectations are rarely honoured. In Brazil, for example, integration of tuberculosis and HIV services has been discussed at state and national level, but implementation has occurred in only a few municipalities: Rio de Janeiro and São Paulo.² Similar problems are encountered in the Democratic Republic of the Congo,³ Malawi,⁴ and Ghana.⁵ Never-ending queues, long waiting times, and indirect costs associated with travel to different clinics could be mitigated by implementation of integrated collaborative activities within the same facility.

The interim policy on collaborative tuberculosis and HIV activities

From the mid-1980s, tuberculosis programmes in countries with high prevalence of HIV infection, particularly in sub-Saharan Africa, faced increasing challenges: rising tuberculosis case notifications; disproportionately more patients with smear-negative disease⁶ and drug-related side-effects;⁷ high case fatality;⁸ high rates of tuberculosis recurrence;⁹ and increased transmission of *M tuberculosis* within congregate settings. In industrialised countries in the 1990s, outbreaks of multidrug-resistant (MDR) tuberculosis occurred in HIV-infected people in health facilities,¹⁰ only to be re-enacted in the well publicised outbreak of extensively drug-resistant (XDR) tuberculosis in HIV-infected people in Tugela Ferry, KwaZulu Natal, South Africa, in 2005–06.¹¹

This devastating outbreak underscored the virtually complete absence of infection control and diagnostic

Panel 1: Health-care needs of a patient in sub-Saharan Africa

"I am on treatment for tuberculosis and antiretroviral treatment for AIDS. I collect tuberculosis drugs close to my home, but I have to take two minibuses to get my antiretroviral drugs. I have missed some doses of antiretroviral drugs because when it was time to return to the clinic for refills I had no money for transport. I asked the doctor if I could be given antiretroviral drugs to last more than 1 month, but he told me it was not allowed."

challenges in health-care facilities in countries of low and middle income, particularly in sub-Saharan Africa. Stigma and adverse perceptions about the link between tuberculosis and HIV, at both community and individual level,¹² led to delayed diagnosis, poor treatment outcomes, and increased transmission of infection. In the period before AIDS, impressive gains had been made through the expansion of directly observed therapy, short-course (DOTS) programmes, but these were threatened by the escalating incidence of HIV-associated tuberculosis, leading to acceptance by the turn of the century that DOTS alone could not contain the epidemic.¹³ At the same time, tuberculosis was recognised in HIV programmes as one of the most common causes of morbidity, and, in many African countries, as the leading cause of death in adults with HIV infection.¹⁴

In 2004, a WHO interim policy on collaborative tuberculosis and HIV activities was formulated, and laid out the interventions needed to decrease the joint burden of tuberculosis and HIV (panel 2).¹⁵ Because the evidence base for the policy recommendations was insufficient, the guidance was promoted as interim in nature, to be updated as new data and experience became available.

The interim policy, along with a strategic framework to decrease the burden of tuberculosis and HIV¹⁶ and guidelines for implementation of collaborative programmes,¹⁷ was a milestone. Until 2003, tuberculosis and HIV/AIDS programmes had had little interaction at global, national, or district level, mainly because of different philosophies: tuberculosis programmes were public health based and emphasised case detection and treatment of active tuberculosis, whereas HIV/AIDS programmes emphasised individual rights, did not prioritise HIV diagnosis, and focused on HIV prevention.¹⁸ The subsequent scale-up of antiretroviral treatment (ART) in resource-limited settings and the emergence of MDR and XDR tuberculosis in the context of HIV infection¹¹ identified issues of relevance to the two programmes and drew attention to the urgent need for effective collaboration.

In hindsight, the component of the interim policy that aimed to decrease the risk of tuberculosis in people with HIV infection failed to emphasise the crucial preventive role of ART. Early studies in South Africa¹⁹ and Brazil²⁰ showed that in cohorts of people with HIV infection,

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ART significantly reduced rates of tuberculosis, and these benefits increased with length of time on effective treatment.²¹ Nevertheless, with most patients starting ART at low CD4 cell counts, tuberculosis risk still remained substantial in the presence of HIV treatment.^{22,23} The interim policy also failed to provide adequate guidance on how to manage HIV-infected people with suspected but unconfirmed tuberculosis, thus missing a valuable opportunity to prioritise and steer such people into HIV care and tuberculosis prevention. The 2004 interim policy on collaborative tuberculosis and HIV activities needs to be reviewed and updated to incorporate experience and evidence garnered in the past 6 years.

The 2004 interim policy was incorporated into the Stop TB Partnership's 10-year Global Plan to Stop TB, 2006–2015,²⁴ and the Stop TB Strategy.²⁵ In 2007, of an estimated 9.27 million tuberculosis cases globally, 1.37 million (15%) cases were HIV-positive: 79% of people with HIV infection and tuberculosis were in the WHO Africa region and 11% were in southeast Asia.²⁶ In the same year, 456 000 deaths occurred in HIV-infected people with tuberculosis, representing 23% of the estimated 2 million deaths from HIV infection for that year. These estimated numbers of HIV-related tuberculosis cases and deaths were nearly double those reported in previous years, which is indicative of improved data and methodology rather than a real change in epidemiology. Southern Africa remains the epicentre of the dual epidemic, with nine countries (South Africa, Swaziland, Lesotho, Namibia, Botswana, Mozambique, Zambia, Zimbabwe, and Malawi) accounting for nearly 50% of the global burden of HIV-associated tuberculosis.

The Global Plan provides yearly milestones or targets for collaborative tuberculosis and HIV activities that serve as a benchmark against which progress can be assessed. Table 1 shows results for 2006, 2007, and 2008.^{26–28} Tuberculosis case finding and isoniazid preventive therapy remain at minimum levels of implementation. Much better progress has been made with HIV testing in patients with tuberculosis, although the numbers of patients with HIV infection and tuberculosis who have started on co-trimoxazole preventive therapy and ART are still unsatisfactory. The need to scale up prevention and treatment interventions is urgent.

HIV testing and early start of ART for tuberculosis prevention

Although use of ART results in major reductions in rates of tuberculosis in HIV treatment cohorts,^{29–32} the effect on tuberculosis control in the community is limited by the fact that so many patients, particularly in sub-Saharan Africa, are diagnosed with HIV and start ART at low CD4 cell counts of 100–150 cells per μL .³³ A large proportion of people with HIV infection first presents with active tuberculosis and a CD4 cell count of less than 200 cells per μL .^{22,23,29–32,34} HIV diagnosis and start of ART are therefore too late with regard to

Panel 2: Recommended collaborative tuberculosis and HIV activities

Establish mechanisms for collaboration

- Set up a coordinating body for tuberculosis and HIV activities that is effective at all levels of the health system
- Conduct surveillance of HIV prevalence in patients with tuberculosis
- Undertake joint tuberculosis and HIV planning for resources, capacity building, communication, community participation, and operational research
- Monitor and evaluate activities

Decrease the burden of tuberculosis in people infected with HIV/AIDS

- Establish intensified tuberculosis case finding
- Introduce isoniazid preventive therapy
- Ensure tuberculosis infection control in health-care and congregate settings

Decrease the burden of HIV in patients with tuberculosis

- Provide HIV testing and counselling, and link with HIV prevention
- Introduce co-trimoxazole prophylaxis
- Ensure care and support for HIV/AIDS
- Introduce methods to prevent HIV
- Provide antiretroviral treatment to HIV-infected patients with tuberculosis

Adapted from the WHO interim policy on collaborative tuberculosis and HIV activities.¹⁵

tuberculosis prevention. Furthermore, in patients who start ART and have not yet developed tuberculosis, the risk of tuberculosis is high for CD4 cell counts of less than 500 cells per μL .²⁹ An important first step that requires immediate implementation is the promotion of earlier HIV diagnosis (ie, before clinical presentation with tuberculosis) and earlier start of ART within existing guidelines. WHO guidelines published in 2006 recommended start of HIV treatment at CD4 cell counts of less than 200 cells per μL .³⁵ The latest WHO advice to start treatment at CD4 cell counts of less than 350 cells per μL ³⁶ provides a welcome opportunity for more people infected with HIV to start ART before tuberculosis develops.

To examine an innovative approach to eliminate HIV transmission, Granich and colleagues³⁷ used a mathematical model that included the case reproduction number (stochastic model), long-term dynamics of the HIV epidemic (deterministic transmission model), and data from South Africa as representative of a generalised heterosexual epidemic. A strategy in which all adults were tested for HIV every year and in which ART was started immediately after diagnosis of HIV could reduce HIV incidence and mortality by 95% in 10 years, and HIV prevalence to less than 1% within 50 years.

Findings from a further modelling analysis show that this type of innovative strategy could substantially

	Global Plan target for 2006	Country reports for 2006*	Global Plan target for 2007	Country reports for 2007*	Global Plan target for 2008	Country reports for 2008*
Number of HIV-infected people who were actively screened for tuberculosis	11 000 000	314 000 (2.9%)	14 000 000	630 000 (4.5%)	16 000 000	1 385 000 (8.7%)
Number of eligible HIV-infected people who were offered isoniazid preventive therapy	1 200 000	27 000 (2.3%)	1 500 000	29 000 (1.9%)	1 900 000	48 000 (2.5%)
Number of tuberculosis patients who were tested and counselled for HIV infection	1 600 000	687 000 (42.9%)	2 000 000	1 122 000 (56.1%)	2 300 000	1 374 000 (59.7%)
Number of HIV-positive tuberculosis patients who started co-trimoxazole treatment	500 000	147 000 (29.4%)	600 000	196 000 (32.7%)	700 000	229 000 (32.7%)
Number of HIV-positive tuberculosis patients who started antiretroviral treatment	220 000	66 000 (30.0%)	300 000	90 000 (30.0%)	300 000	109 000 (36.3%)

Adapted from WHO Global Tuberculosis Control 2009,²⁶ the Global Plan to Stop TB 2006–2015,²⁷ and WHO Global Tuberculosis Control.²⁸ *Numbers are rounded to nearest thousand; percentages are the proportion of the Global Plan target.

Table 1: Progress against collaborative tuberculosis and HIV targets in the Global Plan to Stop TB, 2006–2015

reduce the incidence of HIV-associated tuberculosis (BGW and KMDC, personal communication). If ART could be started within 5 years of HIV seroconversion, the incidence of HIV-related tuberculosis could be more than halved. If ART was started even earlier, within 1 year of seroconversion, the direct effect on HIV-related tuberculosis would not be much greater, but such treatment would be expected to reduce HIV transmission substantially, resulting in fewer people infected with HIV and thereby greatly reducing the long-term risk of HIV-associated tuberculosis.

Although models are useful to understand certain situations and predict the effects of various interventions, they are dependent on underlying assumptions. Research is needed to assess such an approach for efficacy, feasibility, safety, cost, and effect on the population.³⁸ Four operational issues will need attention: community acceptability and protection of human rights; tolerability of drug regimens; health-system constraints that include human resources; and assurance of adequate monitoring and reporting.

Prevention of tuberculosis with the 3Is

While early HIV diagnosis and treatment is being evaluated and scaled up, much morbidity and mortality from tuberculosis in people infected with HIV could be prevented by application of the 3Is—intensified case finding, infection control, and isoniazid preventive therapy—even with the limitations and constraints of current diagnostic technologies. Intensified case finding promotes early start of tuberculosis treatment, which reduces HIV-related tuberculosis disease and death, and simultaneously contributes to infection control by reducing transmission of tuberculosis in communities and health facilities.^{14,39} Isoniazid preventive therapy treats latent tuberculosis infection, thereby reducing progression to active disease, and simultaneously prevents new infections from becoming established.⁴⁰

Major barriers to effective implementation of tuberculosis screening and preventive therapy include

the difficulty of diagnosis of both tuberculosis infection and disease, and the length and toxic effects of available antituberculosis treatment regimens. Such barriers result in underdiagnosis and undertreatment of both infection and disease in the community and in specialist facilities. Interventions in both the community and health facilities are likely to have a much greater effect than are facility interventions alone. Community interventions are increasingly recognised as effective, more equitable, and able to greatly extend coverage especially in poor and rural populations, and to have better rates of retention, with similar or better individual patient outcomes, than are facility interventions alone.^{41,42} Moreover, community interventions are not necessarily more expensive if delivered by supervised community workers.⁴³

Intensified case finding in the community

In surveys in southern Africa, undiagnosed, culture-positive tuberculosis occurred in 0.7–1.6% of general populations, and undiagnosed, smear-positive tuberculosis occurred in 0.3–0.8%, despite good DOTS coverage.^{44–48} HIV-positive individuals had 1.7–4.4 times higher prevalence of culture-positive tuberculosis and 0.8–3.5 times higher prevalence of undiagnosed smear-positive tuberculosis than did HIV-negative individuals: 0–34% of the total burden of smear-positive disease was directly attributable to HIV.^{44–48} Most of these patients reported no previous contact with health services, which is consistent with long-term infectiousness before presentation at health facilities.¹⁴

Findings from two studies in Zimbabwe showed that in populations with high prevalence of HIV, provision of easy access to tuberculosis diagnosis in occupational clinics⁴⁴ or in outreach facilities⁴⁹ can substantially reduce undiagnosed tuberculosis (to 0.3% and 0.4% culture-positive disease, and to 0.1% and 0.2% smear-positive disease, respectively). Improved diagnosis was one of the factors associated with rapid declines in tuberculosis incidence in the northern hemisphere during the first half of the last century.⁵⁰ Approaches include door-to-door screening for chronic

cough, use of mobile vans to obtain sputum samples, or open access to smear microscopy. Such methods need to be evaluated and then scaled up in several different settings, with the yield dependent on HIV prevalence in the target population, the national prevalence of tuberculosis, and the screening strategy used.⁵¹

Intensified case finding in health facilities

For people newly diagnosed with HIV infection who are attending health facilities, tuberculosis screening with mycobacterial culture has a high yield, with culture-positive tuberculosis in 5–25% of otherwise unselected patients.^{46,52–56} Unfortunately, screening by culture is not feasible in most resource-poor settings, and the only practical approaches are screening for symptoms and by sputum smear microscopy, neither of which is ideal. Less than a third of culture-positive patients will be smear positive, and the overlap between symptoms of tuberculosis and HIV results in low specificity of symptom-based enquiries.^{46,52–56}

The most consistently discriminating questions concern cough of any duration, weight loss, fever, and night sweats. Sensitivity is challenging since long-term cough is reported by only 35–65% of culture-positive patients, and up to 21% deny any tuberculosis symptoms at all. Specificity is reduced by attempts to increase sensitivity by asking a broader range of questions or enquiring about a history of contact with tuberculosis cases: up to 74% of patients who do not have tuberculosis are identified as needing further investigation. In a study of HIV-positive people in southeast Asia, cough of any duration, fever of any duration, or night sweats lasting 3 or more weeks in the previous month identified tuberculosis with a sensitivity of 93% and specificity of 36%.⁵⁷ Enquiries about the combination of these three symptoms rather than just cough seemed to be effective to exclude a diagnosis of tuberculosis. The role of screening by chest radiography is controversial. Some studies show value and others do not,^{58–60} and radiography is often unavailable in primary care.

The inability to readily confirm or exclude active tuberculosis in people with HIV infection has delayed routine implementation of the 3Is because patients need to be accurately classified before they receive isoniazid preventive therapy. New tuberculosis diagnostic techniques that can be used at all levels of the health system, particularly in people infected with HIV and in children, are urgently needed.⁶¹ An example is the GeneXpert System (Cepheid, Sunnyvale, CA, USA), which is an *M tuberculosis* integrated nucleic acid amplification test that uses a common platform to diagnose tuberculosis and rifampicin resistance.⁶² With results provided in less than 2 h and with no risk of contamination, this system needs urgent evaluation in district hospitals, clinics, and microscopy centres.

Until new diagnostic techniques are available, a pragmatic approach is needed. People with HIV infection

who are asymptomatic for tuberculosis on symptom screen could be considered for isoniazid preventive therapy without further investigation. In all settings except those with the highest tuberculosis risk, the prevalence of culture-positive tuberculosis in such patients is not more than 1–2%. People with HIV infection who are symptomatic need investigation by smear microscopy, supplemented by chest radiography. A variable proportion will have tuberculosis diagnosed and treated,⁵¹ but in the remainder tuberculosis cannot be reliably excluded. Although use of isoniazid preventive therapy should be avoided in these symptomatic patients, this group should be referred to routine HIV care and considered for early start of ART as a priority, because otherwise these patients are likely to be lost to follow-up and mortality will be extremely high.⁶³ Preventive treatment with isoniazid could then be considered later when the diagnosis of tuberculosis is easier to confirm or exclude as a result of immune recovery.^{29,64}

Infection control in health facilities

Exposure in health facilities has almost certainly accounted for an appreciable but generally unrecognised proportion of the total risk of tuberculosis infection, affecting patients repeatedly attending for chronic care.³⁹ In areas of high HIV prevalence, HIV-related tuberculosis accounts for a large proportion of all admissions and outpatient consultations, resulting in intense tuberculosis transmission within congested facilities and presenting a very difficult challenge to infection control.⁶⁵ Data are also emerging about the crucial link between HIV and spread of MDR and XDR tuberculosis in institutional settings such as hospitals and prisons.⁶⁶

WHO's tuberculosis infection control guidelines have recently been updated (panel 3).⁶⁷ Infection control relies on early identification, isolation, and treatment of tuberculosis suspects, combined with infrastructure modifications and organisation to avoid congestion and ensure appropriate airflow and patient-flow within facilities. Germicidal ultraviolet upper-room light is also effective, but needs electricity and reliable maintenance.⁶⁸ Findings from a series of studies in Peru have provided key lessons for interventions to control infection in low-resource settings.^{69,70} First, natural ventilation is a low-cost environmental measure for tuberculosis infection control. Maximum natural ventilation can be achieved with open windows and doors, enlarged or additional windows, open skylights for cross-ventilation, and rebuilding of waiting rooms in the open air.⁶⁹ These measures provide much higher airflow than do costly mechanical ventilation systems, many of which function well below recommended levels because of poor maintenance. Second, unrecognised or inadequately treated MDR tuberculosis can be a key source of nosocomial transmission, which further emphasises the importance of environmental control measures in crowded health-care settings, and

the importance of rapid testing for drug susceptibility to allow effective treatment to be started promptly.⁷⁰

Control of tuberculosis transmission within HIV care clinics is especially important, but also extremely difficult, because of the high burden of undiagnosed active tuberculosis in patients entering HIV care, of whom not all will have identifiable tuberculosis-related symptoms.^{52–56} Outbreaks can continue for long periods, affecting many patients from the same clinic, but might not be clearly distinguishable from background rates unless the outbreaks are due to drug-resistant tuberculosis strains causing high mortality. Concerns about hazards and challenges associated with tuberculosis infection control have left programmes reluctant to completely integrate tuberculosis and HIV services at the level of individual clinics, contributing to continuing practical difficulties with implementation of joint HIV and tuberculosis care.

Isoniazid preventive therapy

Treatment with isoniazid for 6 months reduces the overall risk of tuberculosis by 33% in individuals with HIV infection, with the protective effect predominantly in people with positive tuberculin skin tests (TSTs) and limited to 6–24 months after discontinuation of therapy.^{14,71,72} The prevalence of positive TSTs varies in populations, so use of the test should theoretically allow effective targeting of isoniazid preventive therapy (64% reduction in tuberculosis risk if TST is positive).^{71,72} Unfortunately, technical and logistical challenges hinder use of TSTs,⁷³ and have been a barrier to scale-up of isoniazid therapy. Interferon- γ release assays that use ESAT-6 or CFP-10 antigens, or both, are an improvement on TSTs, but they are also associated with technical and financial challenges,⁷⁴ and cannot yet be considered for routine use in resource-constrained settings.

Policy recommendations were made more than 10 years ago about the use and value of isoniazid preventive therapy,⁷⁵ but national rollout has been attempted in Botswana alone. In addition to the challenges posed by TST, use of isoniazid therapy has been hindered by: an understandable fear of treatment of patients in whom active tuberculosis cannot be completely excluded; the incomplete protective effect in patients with positive TSTs and the possibility of no protective effect in those with negative TSTs; and the need for clinical monitoring for hepatitis and peripheral neuropathy, with peripheral neuropathy exacerbated by concurrent use of stavudine.⁷⁶ The need for repeat or continuous courses is still not fully defined. Adherence could also be an issue unless isoniazid therapy is closely integrated into other aspects of routine HIV care and community-based programmes.⁷⁷

Despite these challenges, people with HIV infection increasingly recognise the need for isoniazid preventive therapy to provide important protection against the frightening, debilitating, and life-threatening experience of tuberculosis.⁷⁸ As a component of the 3Is control

strategy, isoniazid therapy needs to be routinely implemented to scale for improved control of tuberculosis transmission to be realised within health facilities and potentially the wider community. A WHO expert meeting in January, 2010, endorsed the need for scale-up in people with HIV infection, irrespective of the degree of immune suppression, and agreed that although TST should be done wherever possible to target the intervention more effectively, TST should not be a prerequisite to start preventive therapy (SDL, personal communication). Research from India, South Africa, and Botswana that is yet to be published will inform on the issue of 6 months' versus long-term isoniazid preventive therapy. Data from Botswana, for example, suggest that in HIV-infected people with positive TSTs, as compared with 6 months' treatment, long-term therapy provides obvious and sustained suppression of tuberculosis incidence.⁷⁹

Implementation of the 3Is

In April, 2008, WHO clearly stated that HIV programmes are responsible for delivery of the tuberculosis prevention package to people with HIV infection within general health systems.⁸⁰ HIV programmes at national, district,

Panel 3: Tuberculosis infection control in health-care settings

Facility-level measures

- Identify and strengthen local coordinating bodies for tuberculosis infection control
- Rethink use of available spaces, renovation of existing facilities, or construction of new facilities
- Undertake on-site surveillance of tuberculosis disease in health workers
- Address advocacy, communication, and social mobilisation for health workers, patients, and visitors
- Monitor and evaluate the set of tuberculosis infection control measures
- Participate in research efforts

Administrative measures

- Promptly identify people with tuberculosis symptoms, separate infectious patients, institute cough etiquette and respiratory hygiene, and keep time spent in health-care facilities to a minimum
- Provide a package of prevention and care interventions for health workers, including HIV prevention, antiretroviral treatment, and isoniazid preventive therapy for health workers with HIV infection

Environmental protection

- Use ventilation systems
- Use ultraviolet germicidal irradiation fixtures (if applicable)

Personal protection

- Use particulate respirators

Adapted from the WHO policy on tuberculosis infection control in health-care facilities, congregate settings, and households.⁵⁷

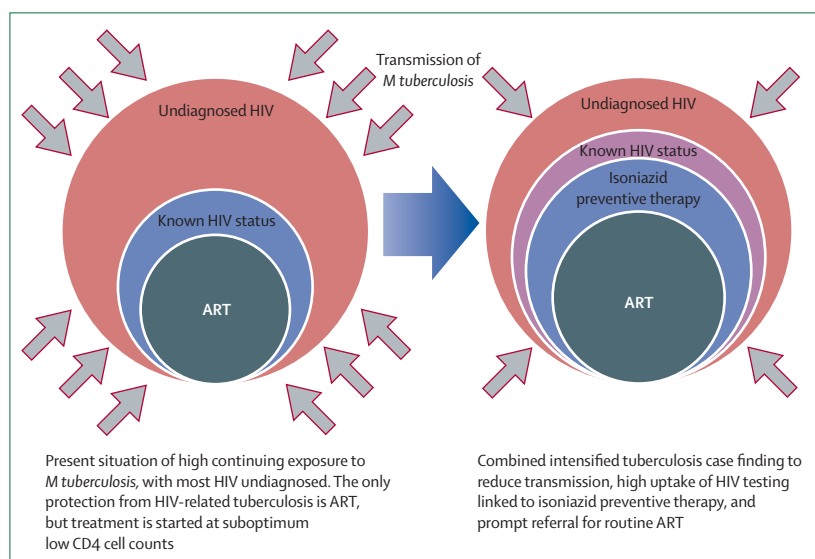


Figure: Combined effect of intensified tuberculosis case finding, HIV testing, isoniazid preventive therapy, and antiretroviral treatment (ART) on exposure and susceptibility to *Mycobacterium tuberculosis*. Arrows indicate amount of exposure to *M tuberculosis*.

facility, and clinic level should heed this call. To provide isoniazid preventive therapy, health facilities need the capacity to screen patients for tuberculosis. Adequate infection control practices are vital in clinics in which patients are screened and regularly obtain medication because otherwise the risk of tuberculosis could increase. The 3Is are therefore highly interdependent and complementary. To keep exposure and susceptibility to tuberculosis to a minimum in people with HIV infection, the three components need to be integrated to provide care before and with ART, in facilities and the community (figure).

Care before start of ART would include regular checks of clinical status and CD4 cell count, provision of cotrimoxazole prophylaxis, nutritional support, family planning, insecticide-treated bednets for prevention of malaria, regular intensified screening for tuberculosis, and isoniazid preventive therapy.⁷¹ With the scarcity of structured care before start of ART in most resource-poor settings, HIV programmes need to substantially expand their already heavy caseload to provide such services and ensure that the 3Is are implemented.

Studies from Brazil⁸¹ and South Africa⁸² suggest that sequential or concurrent use of ART and isoniazid preventive therapy could result in a synergistic decline in risk of active tuberculosis, and thus ART clinics are very suitable places in which to start implementation of the 3Is. WHO's advice for ART programmes to gradually phase out stavudine,³⁶ most probably in favour of tenofovir, will reduce the risk of additive peripheral neuropathy induced by isoniazid.⁷⁶ Most patients who are eligible for ART will not initially be suitable for isoniazid preventive therapy because at this disease stage and in busy clinics, confident exclusion of tuberculosis is too

difficult. Isoniazid preventive therapy could be considered as soon as patients are stable and asymptomatic.

A more innovative, but untested, approach would be use of empiric antituberculosis treatment in HIV-infected people who are sick, have low CD4 cell counts, and are at high risk of tuberculosis. Potential benefits would include reduction in mortality in those with tuberculosis, reduced nosocomial tuberculosis transmission, tuberculosis prevention in those who do not have tuberculosis, and ultimately a simplification of the decision-making process. Randomised trials would be needed in high-burden areas to establish whether such a strategy has a high benefit–risk ratio, which would be strongly dependent on whether this intervention was associated with a reduction in mortality.

Prevention of tuberculosis in HIV-infected infants and children: BCG vaccination

Tuberculosis is also an important cause of death and disease in children with HIV infection, and is even more difficult to diagnose than HIV-related tuberculosis in adults.⁸³ Prevention of HIV infection in parents and mother-to-child transmission of HIV infection will probably have the greatest effect on reduction of HIV-associated tuberculosis in children.

BCG, a live attenuated *Mycobacterium bovis* vaccine, is almost universally given soon after birth in sub-Saharan African countries, where the brunt of the global paediatric burden of HIV infection is concentrated. Vaccination greatly reduces an otherwise high risk of disease progression and death when HIV-negative infants and young children are infected with *M tuberculosis*, but has much less effect on the risk of adult pulmonary tuberculosis.⁸⁴ BCG can cause local and disseminated tuberculosis, with the risk of disseminated disease in HIV-infected infants recently estimated to be as high as 1%.⁸⁵ This has prompted a revision of WHO guidelines to make HIV infection in infants a full contraindication to BCG vaccination.⁸⁶

Unfortunately, serological testing cannot easily distinguish between HIV-infected infants and HIV-exposed but uninfected infants because of the passage of maternal antibodies. Early infant diagnosis on the basis of PCR is the only way to confirm HIV infection, and until very recently this diagnostic capacity was not widely available. However, access to early infant diagnosis is expanding, and immediate start of ART for those confirmed with HIV is now recommended to reduce the extremely high HIV-related mortality in the first year of life.⁸⁷

The ideal approach would be to defer BCG vaccination in infants of mothers infected with HIV until HIV-infection status has been established. In children with HIV infection, early start of ART reduces the risk of tuberculosis and can be augmented with isoniazid preventive therapy.⁸⁸ However, implementation of a deferred vaccination and early ART strategy will be logistically difficult,⁸⁹ and risks inadvertently reducing BCG coverage in HIV-exposed but uninfected infants. A safer strategy would be continuation of universal

BCG vaccination of infants in countries that are highly endemic for tuberculosis until all programmes are in place to implement a selective deferral strategy. This conundrum also underscores the urgent need for tuberculosis vaccines that can be safely given to individuals with HIV infection.

HIV care for HIV-infected patients with tuberculosis

With tuberculosis prevention efforts not yet implemented to scale, the other main emphasis of the tuberculosis and HIV interim policy is to provide good HIV care for HIV-infected people who develop tuberculosis. Provider-initiated HIV testing and counselling, co-trimoxazole preventive therapy, and ART should be regarded as the basic standard of care, and yet gaps in implementation remain large. About 40% of all patients with tuberculosis are not tested for HIV, and a large proportion with HIV infection and tuberculosis lack access to co-trimoxazole preventive therapy and ART.^{26–28} Such low service provision is unacceptable.

Provider-initiated HIV testing and counselling

WHO recommends that provider-initiated HIV testing and counselling be provided routinely,⁹⁰ and this service has been feasible and acceptable in various settings.^{91,92} The approach differs from the traditional idea of voluntary counselling and testing because HIV testing is recommended by the health-care worker as a standard test, with emphasis on opting out (ie, patients undergo HIV testing as part of the diagnostic work-up unless they specifically decline), and post-test counselling is given increased priority, particularly if the patient is HIV positive. Testing for HIV infection establishes the diagnosis, serves as the gateway to an adjunctive package of clinical treatment and care, and assists in the prevention of transmission.⁹³

Key operational considerations for success include: streamlined incorporation of early HIV testing into tuberculosis diagnosis and registration so that suspects and tuberculosis patients know their HIV-infection status; uninterrupted supply and use of rapid HIV tests; good quality counselling after HIV testing; task shifting of HIV testing to trained lay counsellors to address human resource shortages;⁴¹ community empowerment to encourage HIV testing; and reliable and regular reporting. Failure to provide HIV testing to patients with tuberculosis is a missed opportunity and should be deemed substandard care.

Co-trimoxazole prophylaxis

Co-trimoxazole (combined trimethoprim and sulfamethoxazole) is a widely available, easy to administer, cheap, and safe antibiotic with a broad spectrum of activity against pathogens that are related or unrelated to HIV infection.^{94,95} Despite initial concerns about its use in resource-poor countries, clinical studies and trials in patients with (table 2)^{96–100} and without tuberculosis^{94,95} have shown that use of the drug is feasible and safe, and

	Country	Study type	Cohort size	Co-trimoxazole resistance	Mortality reduction
Wiktor et al ⁹⁶	Cote d'Ivoire	Randomised controlled trial	771	Low	48%
Nunn et al ⁹⁷	Zambia	Randomised controlled trial	1003	High	45%
Zachariah et al ⁹⁸	Malawi (Thyolo)	Cohort study (historical controls)	2986	High	25%
Mwaungulu et al ⁹⁹	Malawi (Karonga)	Cohort study (historical controls)	717	High	22%
Grimwade et al ¹⁰⁰	South Africa	Cohort study (historical controls)	3232	High	29%

Table 2: Effect of co-trimoxazole prophylaxis on mortality in patients with tuberculosis and HIV in resource-limited settings

has major beneficial effects. These effects include a 25–46% decrease in mortality, fewer hospital visits, weight gain, improved CD4 cell counts, and reduced plasma HIV loads. This intervention is cost effective,¹⁰¹ and efficacy, which extends to malaria prevention, is maintained in areas with high bacterial resistance to co-trimoxazole.

Co-trimoxazole preventive therapy is effective across a broad range of CD4 cell counts and can be used before ART and in combination with ART. Combination of co-trimoxazole preventive therapy with ART, compared with use of one of these interventions alone, is associated with reduced 6-month mortality (by up to 40%),¹⁰² fewer episodes of malaria,¹⁰³ and increased overall life expectancy.¹⁰⁴

Despite clear WHO guidelines for co-trimoxazole preventive therapy in HIV-infected patients with tuberculosis,⁹⁵ by 2008 only 33% of patients reached the access target set by the Global Plan to Stop TB.^{26,28} Operational considerations for successful implementation include: a national policy guideline; a high HIV testing rate among patients with tuberculosis; uninterrupted supplies of co-trimoxazole; provision of free-of-charge therapy; and reliable monitoring and reporting systems. A key challenge is maintenance of secure and uninterrupted drug supplies, and ensuring that the workload in administering and dispensing medication is kept to a minimum. A practical approach in Malawi was procurement of the prophylactic adult daily dose in tins for 2 months, which removed the labour-intensive counting of drug doses from tins of 1000 tablets.

ART

Provision of ART substantially improves the prognosis of patients with HIV infection and tuberculosis. Mortality risk is reduced by 64–95%, and excellent immunological and virological responses can be achieved, tuberculosis recurrence is reduced, and frequency of bacteriological clearance can be increased.^{22,32,105–110}

Yet by the end of 2007, only 100 000 (7.3%) of an estimated 1.37 million HIV-infected tuberculosis patients worldwide were reported to have started ART.²⁶ Increase of uptake is a high priority and is likely to be

helped by the changes in WHO's 2009 guidelines for HIV treatment.³⁶ By contrast with previous guidelines,³⁵ WHO now recommends that all patients with tuberculosis, irrespective of CD4 cell count, should receive ART as soon as possible after start of tuberculosis treatment.³⁶ Removal of the CD4 cell count hurdle should simplify the process for patients with HIV infection and tuberculosis to start ART. Nevertheless, several clinical and programmatic challenges remain: how best to combine rifampicin with first-line and second-line ART regimens; management of immune reconstitution disease; the role of isoniazid preventive therapy with ART after tuberculosis treatment has ended; and where and how to provide combined therapy to best suit the patient.⁹²

Panel 4: Challenges to implementation of HIV care for patients with HIV and tuberculosis

Low uptake of HIV testing and counselling

Possible reasons

- HIV testing is provided outside tuberculosis services
- HIV testing is not provider initiated
- Lack of human resources to implement HIV testing
- Frequent absence of stock of HIV test kit
- Coercion into HIV testing
- Community stigma

Practical considerations and ways forward

- Incorporate HIV testing early into diagnosis and registration of tuberculosis^{90,91}
- Provide infrastructure and rooms for HIV testing in tuberculosis wards and clinics
- Use provider-initiated HIV testing and counselling^{90,91}
- Consider task shifting to trained lay counsellors^{41,112}
- Monitor consumption and establish a procurement and supply system through existing tuberculosis systems
- Provide training and accreditation for HIV testing sites
- Increase community empowerment and awareness

Low uptake of co-trimoxazole prophylaxis

Possible reasons

- Low frequency of HIV testing
- Co-trimoxazole prophylaxis not included in some national policies
- Frequent absence of stock of co-trimoxazole
- Patients have to pay for co-trimoxazole
- Co-trimoxazole is provided outside tuberculosis services
- Challenges with drug dispensing
- Poor data for co-trimoxazole prophylaxis uptake and compliance

Practical considerations and ways forward

- Use provider-initiated HIV testing and counselling, and ensure efficient and integrated HIV testing services^{90,91}
- Offer co-trimoxazole prophylaxis free of charge with tuberculosis drugs⁹⁴
- Offer bottles of 60 and 120 tablets of co-trimoxazole (480 mg each) and paediatric drugs⁹²
- Ensure that co-trimoxazole prophylaxis is indicated on the tuberculosis register and regularly reported⁹²

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Comprehensive HIV care

In sub-Saharan Africa, routine care of HIV-infected tuberculosis patients with DOTS regimens alone results in poor outcomes.¹¹¹ Prognosis will greatly improve with provider-initiated HIV testing and counselling, co-trimoxazole preventive therapy, and ART; and national tuberculosis programmes must show commitment and provide resources to overcome the logistical and operational hurdles of delivery of this package to all HIV-infected patients with tuberculosis. Panel 4 summarises the key challenges and approaches to scaling up of these three interventions on the basis of the authors' field experiences.¹¹²⁻¹¹⁵

Care for HIV-associated tuberculosis in the general health system

Interaction with general health systems

The organisation of disease-specific programmes has implications for the general health system, and raises two questions: what are the ways in which overall strengthening of health systems can contribute to improved performance and collaboration of HIV and tuberculosis programmes; and how can HIV and tuberculosis programmes contribute to strengthening of health systems?¹¹⁶

In response to the first question, disease-specific programmes for HIV and tuberculosis stand to benefit from improvements in the process by which health systems are reformed, by paying attention to key functions (eg, financing and regulation) and key activities of health systems (eg, policy development, human resource management, procurement of supplies and drugs, and maintenance of health infrastructure). HIV and tuberculosis programmes also cannot afford to work in isolation, but need to collaborate with one another and with other health programmes to achieve maximum benefit from global, regional, and national efforts to improve health systems. HIV and tuberculosis programmes could, for example, offer screening not just for HIV and tuberculosis but also for high blood pressure and diabetes. Programmes could also consider expansion to incorporate deworming, elimination of lymphatic filariasis and onchocerciasis, and other neglected disease initiatives as a cost-effective means to reduce morbidity and mortality.¹¹⁷

In response to the second question, disease-specific programmes at country level can assist in driving broad improvements throughout the health system, particularly in weak areas such as human resources, laboratory infrastructure, drug forecasting, data monitoring, supervision of peripheral health facilities, and quality assurance.¹¹⁸ The key issue is how to make this conceptual framework, the undoubted policy development, and the stated international commitment work in practice. Encouraging examples of progress include efforts to protect health-care workers,¹¹⁹ initiatives to share and maintain laboratory equipment across different disease-specific programmes,¹²⁰ and use of the DOTS model to

deliver chronic care to patients with non-communicable diseases such as diabetes, hypertension, and asthma.¹²¹

Collaboration

The mechanisms for collaboration between HIV and tuberculosis programmes are clearly articulated in the WHO interim policy on collaborative tuberculosis and HIV activities:¹⁵ establish coordinating bodies at all levels of the health system; undertake surveillance of HIV prevalence in patients with tuberculosis; jointly plan around resource mobilisation, advocacy, community participation, and operational research; and monitor and evaluate progress. Collaboration has indeed improved in recent years: in two-thirds of 63 tuberculosis and HIV priority countries, coordinating bodies and a joint tuberculosis and HIV plan have been established, and HIV surveillance was underway by 2007.²⁶ Patient services could be improved in three ways.

First, centres for tuberculosis diagnosis and treatment and for HIV care and treatment need to be located together, integrated, or better matched quantitatively and geographically; patients themselves plead for this to happen. Where tuberculosis services are decentralised, as is the case in many African countries, HIV treatment clinics need to become decentralised. The argument that decentralisation of ART services is impossible because of lack of trained staff, weak infrastructure, and poor drug security is unpersuasive; health centres in rural areas can achieve good treatment outcomes with ART.¹²² International policy calls for task shifting in HIV care^{41,112,123} have been heeded, and effective nurse-driven ART in primary care is already a reality.¹²⁴ At least in the short-to-medium term, equivalent ART outcomes can be achieved through a public health approach without the need for sophisticated laboratory monitoring.¹²⁵ HIV programmes must move quickly to decentralise ART services to peripheral facilities and the community, and provide tuberculosis and ART services within the same facility. Two unresolved issues are whether these joint services should be provided in the same room, and whether services can be provided in the community by home-based care teams.¹²⁶⁻¹²⁸

Second, tuberculosis and HIV programmes must reliably monitor and report on one another's parameters. The revised international guide to monitoring and evaluation of collaborative tuberculosis and HIV activities will help to promote this approach; such assessment will require revision of treatment cards, registers, and cohort reporting forms.¹²⁹ For collection and reporting of reliable data, regular supervision is needed from provincial, regional, and central units, otherwise mistakes remain uncorrected and accumulate.¹³⁰ Tuberculosis and HIV programmes need to plan how such joint supervision can be put into practice, including the appropriate design of forms and data collection instruments.

Third, HIV programmes must take responsibility and be held accountable for provision of improved prevention and care of HIV-associated tuberculosis

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Low uptake of ART

Possible reasons

- CD4 cell counts not available to assess eligibility
- ART is deferred until the continuation phase of tuberculosis treatment when sickest patients might have died and survivors feel well enough not to start ART
- In the continuation phase, tuberculosis treatment is decentralised whereas ART is often still centralised, requiring several visits to different facilities¹¹³
- Tuberculosis and ART services operate in a vertical manner in the health facility, making access of ART difficult for patients with tuberculosis
- Specific clinical challenges of combined management: optimum time to start ART; how best to combine rifampicin-containing regimens with first-line and second-line ART; consideration of rifabutin instead of rifampicin; management of immune reconstitution disease; role of isoniazid preventive therapy after completion of tuberculosis treatment
- Inadequate empowerment of patients and community groups on the benefits of combined ART and tuberculosis treatment

Practical considerations and ways forward

- Increase access to CD4 cell count testing, possibly by point-of-care test
- Start all HIV-infected tuberculosis patients on ART, irrespective of CD4 cell count
- Decentralise ART to health centres where tuberculosis care is decentralised¹¹³
- Bring HIV services to tuberculosis clinics so that patients can obtain antituberculosis drugs, co-trimoxazole prophylaxis, and ART from the same office⁹²
- In settings of high HIV prevalence, an HIV clinician can be deputised to the tuberculosis clinic to provide HIV services and ART¹¹⁴
- Clinical studies and operational research are needed to find solutions to the clinical challenges of combined management
- Engage expert patients and community groups to advocate for ART for tuberculosis patients¹¹⁵

ART=antiretroviral treatment.

throughout the health system and in the community. More engagement is needed with and from civil society. Existing HIV networks, with help from government, non-governmental organisations, and other interested stakeholders, should ensure that people with HIV infection and those who have been cured of tuberculosis are able to develop the knowledge, capacity, and confidence to monitor HIV and tuberculosis services on the ground, challenge the status-quo, and demand that substandard care is improved. Established activist organisations need to join forces with fledgling organisations in low-income countries, and, through example and from previous experience, show how to persuade national and district decision-making organisations to effect change. Proactive activism needs to replace sporadic reactivism that is all too common in response to disasters such as XDR tuberculosis in Tugela Ferry.¹¹ The media, especially radio, is an excellent source of information and education for poor communities and should be used far more than at present. HIV programmes need to promote and develop mechanisms so that community and patient groups can be heard, progress can be celebrated, and, conversely, concerns can be acted on in a timely way.

Financing of collaborative HIV and tuberculosis activities

The Global Plan estimated that US\$6.7 billion would be needed during 2006–15 to fully implement collaborative tuberculosis and HIV activities.²⁴ Notably, the Plan proposed to scale up most activities towards universal access by 2010 in line with goals of UNAIDS and the UN General Assembly Special Session goals for HIV/AIDS activities.¹³¹ In 2009, the WHO report on global tuberculosis control showed that ten of the 22 high-burden tuberculosis countries had financial shortfalls in implementation of collaborative tuberculosis and HIV activities.²⁶ However, these funding gaps might have been exaggerated because costly interventions such as HIV testing, co-trimoxazole preventive therapy, and ART were part of budgets for national AIDS programmes rather than national tuberculosis programmes.

With the continuing economic downturn and restricted financial support by donor countries for achievement of universal access in the immediate future, intensified advocacy is needed to ensure equitable and adequate financing to address this epidemic. Notably, short-term costs might be set to increase because of the movement towards early start of ART with drugs that are more durable and tolerable, but also more expensive. Since 2000, several large disease-specific global health initiatives have changed the way in which international donors provide health assistance. Such changes have provided an important opportunity for HIV and tuberculosis programmes to collaborate and assist in creation of synergies between global health initiatives, disease-specific programmes, and countries' health systems.^{132,133}

Conclusions

The advent of ART has been the most important event in tuberculosis control since the epidemic of HIV-associated tuberculosis began. However, the full potential of ART, in combination with HIV testing, tuberculosis screening, infection control, and isoniazid and co-trimoxazole preventive therapy, has yet to be realised. HIV programmes, particularly at the level of service delivery, need to take tuberculosis far more seriously than at present and engage more actively with civil society in implementation of collaborative HIV and tuberculosis activities. From the perspective of tuberculosis control, a sound theoretical base supports much earlier start of ART, which could additionally reduce mortality from HIV/AIDS.^{134–136} Moreover, isoniazid preventive therapy could further reduce tuberculosis incidence for those on ART. Worldwide, more than a third of the burden of HIV and almost half of the burden of HIV-associated tuberculosis is concentrated in southern Africa¹³⁷—affected countries should examine such innovative strategies with urgency. Without imaginative use of available and potential strategies, the epidemic of HIV-associated tuberculosis will continue long term, robbing countries of years of productive and useful citizens' life. Rarely has there been such a need for leadership, bold

thinking, willingness to take calculated risks, and action “to take death away from the young and make it the monopoly of the old, worldwide”.¹³⁸

Contributors

ADH and KMDC were responsible for the outline and the collation of the final report. First drafts of sections of the report were written by: ERSF and RC (patient perspective); ADH and KMDC (interim policy on collaborative tuberculosis and HIV activities); BGW (HIV testing and early start of ART for tuberculosis prevention); ELC (prevention of tuberculosis with the 3Is and BCG vaccination); RZ and SDL (HIV care for HIV-infected patients with tuberculosis); and DM, MH, ETSF, RC, and ADH (health-system strengthening, programmatic collaboration, and financing). All authors contributed to, read, and approved the final paper.

Steering committee

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Conflicts of interest

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