

Tuberculosis control in the era of HIV

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Abstract | Without HIV, the tuberculosis (TB) epidemic would now be in decline almost everywhere. However, instead of looking forward to the demise of TB, countries that are badly affected by HIV are struggling against a rising tide of HIV-infected patients with TB. As a consequence, global TB control policies have had to be revised and control of TB now demands increased investment. This paper assesses what is being done to address the issue and what remains to be done.

HIV and tuberculosis (TB; also known as the ‘white plague’¹) are the major infectious killers of adults in the developing world, and about 13 million people are infected with both causative organisms². An estimated 8.8 million new cases of TB occurred in 2003 and 1.7 million people died from the disease³, whereas a total of 39 million people were living with HIV at the end of 2004 and the annual death toll from HIV/AIDS was about 3.1 million⁴. The biggest impact has been in sub-Saharan Africa, where TB notifications have, on average, trebled since the mid 1980s, and death rates on treatment have reached 20% compared with the 5% that can be achieved by good TB-control programmes without HIV^{3,5}. Elsewhere, HIV-associated TB is less common but its impact is still important.

An international framework has been established to guide the direction of global development efforts until 2015, with both TB and HIV/AIDS featuring prominently⁶. Millennium development goals (MDGs) covering a wide range of topics have been set

by the United Nations Millennium Project⁶. The ambitious targets related to improving health include halving the 1990 levels of prevalence and mortality arising from HIV and other infectious diseases, such as TB, by 2015. To achieve these targets, the WHO (World Health Organization) has set an additional goal of treating 3 million people with antiretroviral therapy (ART) by the end of 2005 — generally referred to as the ‘3-by-5’ Initiative⁷. Provision of the necessary financial resources is anticipated through the existing networks of multilateral agencies (for example, the World Bank and regional development banks) and bilateral agencies (notably the Presidential AIDS Initiative of the US Government⁸ and the innovative Global Fund to Fight AIDS, TB and Malaria — GFATM⁹). Technical standards and guidelines are being set by the WHO for the control of TB¹⁰ and HIV/AIDS¹¹. The Commission for Macroeconomics and Health¹² has set the standard for financial contributions from both developing governments and donor countries. Various international forums, not least the World Health Assembly, will monitor progress and attempt to hold governments and agencies accountable.

HIV has undoubtedly delivered a body blow to TB control. We describe what is required in the era of HIV to reach the goals of the international community for TB control.

The biological link between HIV and TB

One-third, or two billion, of the world population is estimated to be infected with *Mycobacterium tuberculosis*¹³. Infection follows the ingestion and multiplication

of inhaled bacilli by non-specifically activated alveolar macrophages if the bacilli are sufficiently virulent to withstand the proteolytic enzymes in the macrophage phagolysosomes¹⁴. Two to four weeks after infection, cell-mediated immune processes lead to the formation of granulomas (aggregations of activated macrophages), the histological hallmark of TB¹⁵. In most infected people, competent immunity keeps the tuberculous bacilli inside these granulomas, thereby arriving at a balance between the bacilli and host immunity. CD4⁺ T cells are essential to this balance through their role in activating macrophages by the production of cytokines. Alternatively, the bacilli die, often leaving a calcified nodule visible on chest radiography. About 5–10% of infected people develop TB disease during their lifetime (BOX 1), mostly within 5 years of infection¹⁶. In those infected with HIV, however, CD4⁺ T-cell counts steadily decline as the infection progresses and the ability to restrict the tuberculous bacilli to a few infected macrophages is lost. The risk of developing TB disease in those that are co-infected with HIV by reactivating a latent tuberculous infection increases to 5–15% annually^{17,18}, rising as immune deficiency worsens¹⁹. Rapid progression from infection to TB disease can also occur in markedly immunosuppressed patients.

The epidemiology of TB and HIV

The WHO estimates that about 8% of the 8.8 million new cases of TB in 2003 were HIV infected. Of the 1.7 million people that are thought to have died with TB in 2003, 229,000 were probably infected with HIV³. Africa is the only continent where TB incidence is rising; however, this trend is sufficient to cause a global increase of about 1.0% per year and HIV is clearly the main underlying cause.

The pandemic of HIV/AIDS is now a quarter of a century old. The highest prevalence of infection (that is, the proportion of individuals infected at a given point in time) is seen in eastern and southern Africa (FIG. 1a).

Box 1 | Tuberculosis – the disease and its management

Tuberculosis (TB) is a potentially fatal infectious disease. Almost all infections occur after the inhalation of infected droplets expelled through coughing by someone with pulmonary TB. Normally, only 5–10% of those infected develop the disease during their lifetime, but the risk that a new or latent infection will progress to disease is increased by a compromised immune system. Globally, the most important cause of compromised immune responses is HIV infection.

About two-thirds of all TB cases are pulmonary (slightly less in those infected with HIV) and present with a cough for more than 2–3 weeks that is productive of purulent sputum. Some patients also cough up blood. Weight loss and fever are common. Before the availability of treatment, over half of all patients died within 5 years. Extrapulmonary TB is most often pleural, lymphatic, spinal or urogenital.

The clinical picture that is typical of HIV-negative patients with TB, comprising pulmonary cavitating disease in the upper lobes and bacilli visible in the sputum, shifts with advancing HIV infection to one in which there is a greater probability of extrapulmonary disease or infiltrating non-cavitating pulmonary lower lobe disease with no bacilli visible in the sputum. However, a large number of HIV-positive patients with TB present with typical smear-positive pulmonary TB.

In resource-poor countries, diagnosis is made by microscopic examination of at least three samples of sputum smeared on a glass slide and stained, usually by the Ziehl–Neelsen method. Effusion fluid or tissue can be treated similarly. Where resources permit, diagnosis is confirmed by culture, but this can take up to 10 weeks. Treatment with a combination of usually four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) is required for at least 6 months.

In some African countries, the increase in prevalence has slowed in recent years²⁰, in others it is decreasing (REFS 21,22; National AIDS and STD Control Programme, unpublished data) and in a few, such as Nigeria, it might yet increase significantly.

TB incidence and notification rates (BOX 2) are strongly associated with HIV infection (FIG. 1b) and 12 of the 15 countries with the highest TB notification rates are in sub-Saharan Africa³. In eight such southern and eastern African countries (FIG. 1c), more than 50% of all adult patients with TB are co-infected with HIV.

Trends in incidence rates over time are illustrated in FIG. 2. In African countries where the prevalence of HIV in adults is below 4%, TB notification rates have either remained steady or increased slowly. In African countries where the prevalence of HIV is above 4%, TB notification rates have increased by more than three times, on average, with much greater increases in some countries than in others.

TB case notifications mirror increases in HIV prevalence. In the Kisumu district of Kenya (FIG. 3), which was affected relatively early and severely by HIV, increases in TB follow rises in HIV by approximately 7 years (K. Chebet, A. Kutwa, J. Mansoer and L. Marum, personal communication). This delay can be explained by the facts that healthy people have approximately 1,000 CD4⁺ T cells per microlitre of blood, which decline at a rate of about 100 cells

per microlitre per year after HIV infection, and the median CD4⁺ T-cell count at which people develop TB is 187 per microlitre per year¹⁹. As the HIV epidemic matures, more people present with TB and show greater immunosuppression.

Already, TB incidence is highly dependent on HIV prevalence in the general population, but the ultimate impact of HIV on TB will be determined by whether TB is being transmitted from HIV-infected patients back to the much larger HIV-uninfected population. Data on this crucial topic are scarce.

In Karonga, Malawi²³, where a good, directly observed therapy short-course (DOTS) programme (BOX 2) has existed for nearly 20 years, the proportion of new smear-positive TB cases attributable to HIV rose from 17% in 1988–1990 to 57% in 2000–2001, while the estimated number of smear-positive

“The impact of HIV on TB has been devastating, with approximately 10% of all global TB cases now attributable to HIV — were it not for HIV, TB would already be declining worldwide.”

TB cases among HIV-uninfected people fell from 78 to 45 per 100,000. Among South African gold-miners, the duration of smear-positive disease is about 2 months if they have HIV infection, and about 14 months if they do not²⁴. This sevenfold difference in duration can be explained by the faster progression to active TB in HIV-infected people, which results in them seeking treatment quickly or dying early. The shorter the duration of illness, the less transmission occurs. In addition, each HIV-positive person with TB is, on average, less likely to transmit the infection than is an HIV-negative person with TB, because of the lower frequency of cavity formation and reduction in the bacillary content of sputum²⁵. It is important to remember, however, that gold-miners in South Africa are an unusual group: approximately 30% of the work force has radiological silicosis, which is itself associated with a threefold increase in the risk of TB and the effect is synergistic with HIV²⁶. Furthermore, in some mines²⁷, the HIV-uninfected population has seen TB rates rise, suggesting that there might indeed be transmission of TB from HIV-infected to HIV-uninfected individuals.

It is a priority to determine whether this element of optimism from Malawi applies elsewhere. From a control perspective, however, it is also essential to scale-up HIV prevention to bring the HIV prevalence down in countries that are already heavily affected, and to prevent it rising at all in countries that are at risk, especially in Asia and the former Soviet Union. How this should be done remains a challenge, but is outside the scope of this review.

HIV, TB and the health system

As HIV boosts the number of TB cases, the performance of TB-control programmes deteriorates²⁸. Recording and reporting become less accurate, with serious consequences for the follow-up of patients. Shortcuts are taken with diagnosis: sputum examination is not a popular job at the best of times, but as the workload mounts the number of sputum examinations done per patient falls from the recommended three to one²⁹. The sheer number of patients extends waiting times while cutting the time for consultation. HIV-related clinical complications prolong patient stays in hospital³⁰ and congest wards, with as many as four patients per bed in the worst-affected countries.

This increase in demand calls for expansion of budgets and trained staff, and increased investment in hospitals, clinics and vehicles. Unsurprisingly, the response

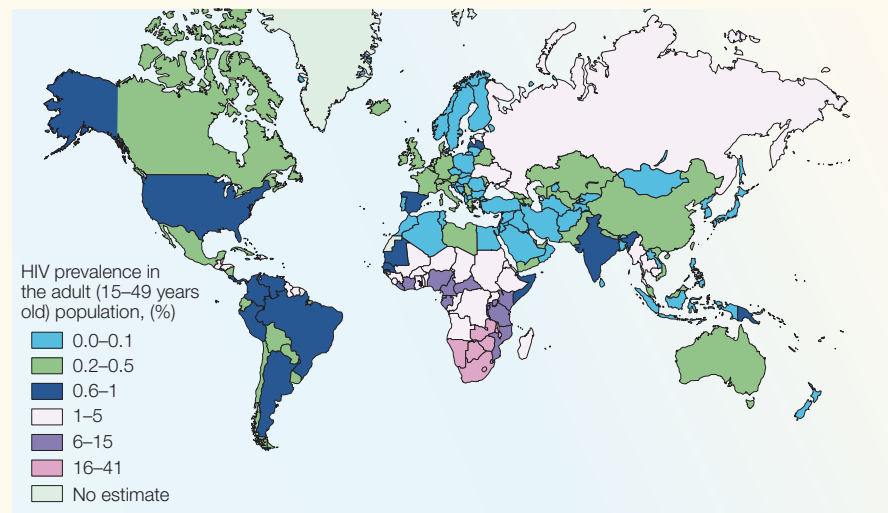
has varied, with the poorer countries, especially in sub-Saharan Africa, being least able to respond. Only recently has additional funding through the World Bank, and particularly the GFATM, begun to make improvements³.

The lack of human resources is now a major bottleneck for expansion of services in developing countries following the cutbacks resulting from economic-reform policies over the past 25 years (REF. 31). Health-worker density is clearly related to health-system performance³². The current quality of staff is also inhibiting the scale up of TB- and HIV-control interventions³³. Pressures to expand primary care, cut costs, decentralize and privatize have led staff to seek greener pastures by leaving public service, going into private practice (legally or otherwise) and migrating to richer countries, often in Europe and the United States³⁴. Staff themselves have been particularly badly hit by the HIV and TB epidemics³⁵. The net effect is that numbers of health personnel have generally not increased to meet the additional demand over the past 15 years. In Malawi, for example, 33% of the 21,337 health posts are currently vacant, 64% of the nursing posts are unfilled and only one-sixth of the recommended complement of doctors is practicing³⁶. Only the best-performing TB programmes have succeeded in increasing staff.

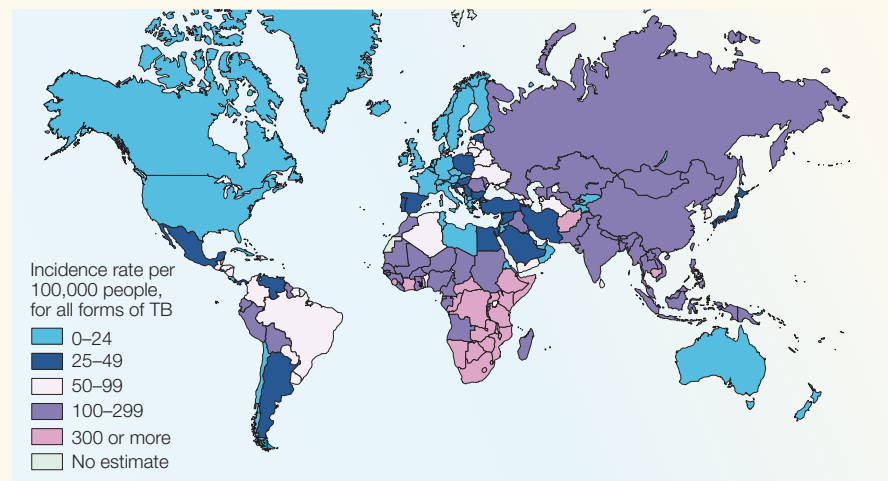
How should policy makers respond when these problems extend beyond the health system? There have been recent calls for an improved analysis of the needs and gaps in the health workforce in developing countries³⁷, although steps need to be taken before the knowledge base is perfected. Better management of the existing workforce could help existing staff and provide the information needed to develop new policies³³. Delegation of TB-control tasks to expanded auxiliary cadres with qualifications that are not recognized internationally is one successful approach³⁷. TB programmes have led the way in involvement of the private sector³⁸ and communities, especially in rural areas³⁹, and this might be key to avoid the impact of TB-control staff moving to better resourced ART programmes. Greater use of incentives, more local training opportunities, and better international efforts to limit the drain of such scarce resources all need proper evaluation.

Despite the increased difficulties, most national TB control programmes have survived and continue to provide reasonably good services⁴⁰, although rates of cure and treatment completion remain unacceptably low³.

a HIV prevalence in the adult population, 2003



b Estimated TB incidence rate, 2003



c Estimated HIV prevalence in TB cases, 2003

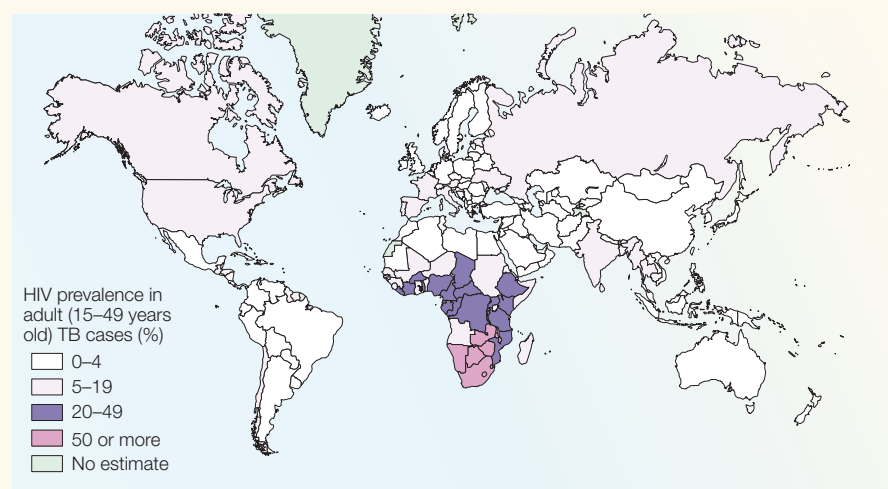


Figure 1 | **Map illustrating tuberculosis (TB) and HIV interactions.** **a** | Prevalence of HIV among adults (15–49 years). **b** | Estimated rates of TB incidence in 2003. **c** | Proportion of people with TB that are also infected with HIV.

Box 2 | Directly observed therapy short-course strategy

As a relatively common and potentially fatal disease, tuberculosis (TB) control demands a public-health approach. This requires a simplified, standardized set of activities that can be carried out by health workers with only basic training. The current international standard for TB control is the WHO (World Health Organization) directly observed therapy short-course (DOTS) strategy.

The five principles of DOTS are as follows:

- Government commitment to TB control
- Diagnosis by smear microscopy, mostly on self-reporting symptomatic patients
- Standardized short-course chemotherapy under proper case-management conditions, including direct observation of treatment, at least during the initial phase
- Secure system of regular high-quality drug supply
- Outcome evaluation of each patient through a standardized recording and reporting system

Progress in the control of TB is monitored by the WHO. Each year, through regional offices, countries notify the headquarters of the WHO in Geneva about all cases of TB detected. Both incidence (the total number of cases) and notifications are expressed in terms of cases per 100,000 of the population in that year. The WHO estimates that in 2003, countries notified 45% of all smear-positive cases. Standard outcomes of treatment are also reported. Notably, a death from any cause, while on TB treatment, is counted as a 'TB death'. Death is significantly more common among HIV-infected patients with TB compared with those not infected with HIV, especially those who are not on ART.

Strategies available to control TB

The DOTS strategy. During the 1990s, following the pioneering work of Styblo⁴¹, the international community reached consensus on a strategy for controlling TB, based on finding and treating infectious cases. The strategy is known as DOTS⁴², and has five core components⁴³ (BOX 2). The targets for the DOTS strategy are to detect 70% of sputum smear-positive cases and to successfully treat 85% of them by 2005 (REF. 44). Achieving these targets reduces the transmission of TB and, in the absence of HIV, incidence falls⁴⁵. Initially, resources were limited and priority was given to the infectious, smear-positive cases that were likely to spread disease. Over the past decade, as the cost of TB drugs has fallen steeply and financial resources in some parts of the world have increased³, policy makers, health workers, and especially activists, have taken a more human-rights-based approach, which argues that everyone suffering from TB is entitled to be treated⁴⁶.

DOTS is clearly effective in reducing mortality^{47,48}, prevalence⁴⁹ and incidence⁴⁷ in the absence of HIV. A well-executed programme can reduce notifications by 6–8% per year⁵⁰. However, so far no developing country with a major HIV epidemic has succeeded in sustainably reducing TB notifications, which raises the important question of whether DOTS will achieve this in areas with rapidly rising TB notification rates due to HIV⁵¹. Clearly, DOTS cannot prevent TB from occurring in HIV-infected people who are already infected with TB. Preventing this

requires additional measures, notably preventive therapy (see below). However, if the results from Malawi and the South African gold-mines hold true elsewhere, then successful DOTS programmes will bring down TB notifications once HIV prevalence has levelled off, with a delay of about 7 years (FIG. 3). Although DOTS might not be sufficient, recent modelling studies indicate that it is necessary: finding and curing active TB is still the most efficient and cost-effective way to minimize the number of TB cases and deaths (REF. 52; C. S. M. Currie, K. Floyd, B. G. Williams and C. Dye, unpublished observations) in the short term (5–10 years). In the long term, reducing HIV incidence will have a greater impact.

TB/HIV collaborative activities. Additional control measures are necessary to limit the increase of HIV-associated TB. These TB/HIV 'collaborative activities' have been developed in response to pleas for help from the countries that are worst affected by HIV and are summarized in BOX 3 (REF. 53). These activities take into account the practical realities of disease control in resource-poor countries, and identify the additional responsibilities of TB and AIDS control programmes, while avoiding the creation of a 'third' programme. Measuring the effectiveness of this broader approach is a priority.

Mechanisms for collaboration between TB and HIV/AIDS programmes are essential for joint strategic planning, but how this is achieved will vary by country. Guidelines on how to conduct HIV surveillance among

patients with TB⁵⁴ and on the monitoring and evaluation of joint activities⁵⁵ have recently been published.

Intensified TB case finding is the search for symptoms and signs of TB in all settings where HIV-infected people are concentrated⁵¹, such as HIV counselling and testing facilities, clinics for sexually transmitted diseases and ART, and outreach programmes for intravenous drug users. If active TB is excluded, clients are eligible for isoniazid preventive therapy (IPT), which eliminates the small number of bacilli present in latent TB infection. Several studies have shown the efficacy of IPT in the prevention of TB (a risk reduction of about 60%)^{56–60}, but its effectiveness in the field has yet to be established⁶¹. A major investment in infrastructure is necessary to deliver enough IPT to have a significant public health impact, but this could be linked to the scaling up of ART. Particularly in care and congregate settings, TB infection control should also be carried out using early recognition and treatment of TB, improved ventilation, personal protection and the separation of infectious patients with TB from those who are highly susceptible⁶².

HIV counselling combined with rapid testing is the entry point for prevention, care, support and treatment for HIV/AIDS among patients with TB. Cotrimoxazole preventive therapy is promoted by the WHO and UNAIDS for the prevention of several bacterial and parasitic infections in adults and children with HIV/AIDS in Africa, including HIV-positive patients with TB^{63–65}. Access for patients with TB to HIV care and support, including good clinical management of opportunistic infections and malignancies, nursing care, nutritional support, home

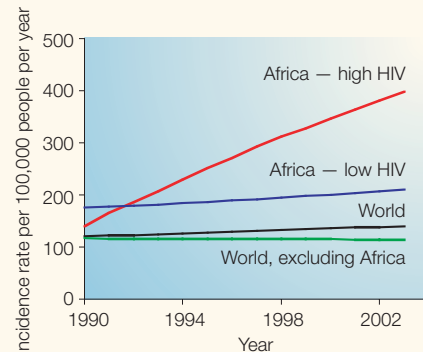


Figure 2 | Graph of rising estimated incidence rates in Africa and the rest of the world.

'Africa - low HIV' consists of all sub-Saharan African countries where HIV prevalence in the adult (15–49 years) population is less than or equal to 4%. 'Africa - high HIV' refers to those sub-Saharan African countries in which adult HIV prevalence is more than 4%.

care and palliative care, is feasible and fosters collaboration between TB and HIV/AIDS programmes⁶⁶.

Synergies in DOTS and ART delivery. ART has changed a fatal condition into a chronic and manageable disease, and annual mortality rates of patients with AIDS are now well below 5% among those treated⁶⁷. The WHO 3-by-5 Initiative and the US Presidential Initiative against AIDS both focus on rapid expansion of ART in the developing world, and by the end of 2004 some 700,000 people were estimated to be on ART⁶⁸. However, this represents only 12% of the 5.8 million people that are currently in need of treatment. Provision of ART to all those needing it would require a massive and unprecedented investment in the health systems of developing countries.

Provision of ART to HIV-positive patients with TB is, at least in sub-Saharan Africa, arguably the most important addition to DOTS in preventing premature death and achieving the MDG mortality targets for both HIV and TB⁶⁹. It is vital to ensure that patients cured of TB do not then die of other AIDS-related diseases. ART can also prevent TB, although without wide availability its effect will be limited. As TB is one of the most common life-threatening AIDS-related opportunistic infections in developing countries, and the median CD4⁺ T-cell count at which patients with TB present to health services is about 200 per microlitre¹⁹, offering HIV testing to patients with TB will probably be one of the most efficient ways of finding large numbers of people eligible for antiretroviral drugs. TB programmes are therefore an important entry point to ART. Moreover, the infrastructure established to deliver effective TB control in a country can act as a suitable model on which to build an ART-delivery system. Building political commitment, standard case definitions, quality diagnostic services, standard treatment regimens with adherence support, reliable drug supplies, and standardized recording, reporting and supervision are the key elements of the DOTS strategy and are relevant for ART delivery. In countries like Malawi, where the TB infrastructure is relatively strong, the national TB programme is playing an essential part in the rapid scale up of access to ART⁶⁸.

There are, however, significant problems to be overcome in all low-resource countries. Although money is available in unprecedented quantities, major bottlenecks remain in the use of these funds⁷⁰. Health services are not well prepared for such massive programmes after some 25 years of low

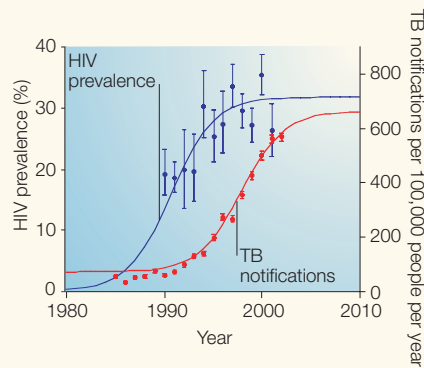


Figure 3 | HIV prevalence in adults, and tuberculosis (TB) notification rates, for Kisumu, Kenya. The HIV data are fitted to a logistic curve. An increase of 1% in the prevalence of HIV leads to an increase in the TB notification rate of about 18.7 people per 100,000, per year. Note that prevalence is defined as the proportion of a population having a particular disease at a given time or in a given period. Prevalence is a particularly useful measure for long-lasting infections such as HIV. Prevalence should not be confused with incidence, which is the number of new cases that arise during a specific period of time in a given population, usually per 100,000 of the general population in the case of TB.

investment. Delivery systems will need to be simpler than in industrialized countries. For example, clinical criteria will have to be used initially to identify eligible patients, as it will take time for CD4⁺ T-cell counts to be available in most settings in Africa¹¹ — in current guidelines for ART, all HIV-positive patients with TB are eligible for treatment in the absence of a CD4⁺ T-cell count. Procurement of drugs is proving to

be particularly problematic. Drug interactions limit the use of some antiretroviral agents in patients receiving rifampicin⁷¹, and immune-reconstitution syndrome⁷², in which TB symptoms can worsen dramatically as a result of rising immunity, is a particular hazard for patients with TB who are receiving ART. Centralization of ART delivery might preclude access by patients with TB, most of whom can access TB treatment at their local health facility⁷³. Finally, the DOTS approach to monitoring TB control can be adapted for the delivery of ART⁷⁴.

What about using ART to prevent the development of TB in the first place? ART in Brazil has dramatically reduced the incidence of TB in people living with AIDS, and controlled trials have shown similar results, with reductions in incidence of about 80% (REF. 75) However, ART is unlikely to avert a significant fraction of TB cases unless treatment is started relatively early in the course of HIV infection, and high levels of coverage and compliance are achieved¹⁹.

Resources considerations

There have been six recent studies on the resources required to address the HIV/AIDS and TB epidemics (TABLE 1). These reports are not readily comparable because they cover different countries and different types of cost; in particular, the costing of ART for patients with TB has assumed durations of treatment varying from only during TB treatment (that is, for 6 months) up to lifetime ART. However, overall, these studies suggest that low- and middle-income countries need

Box 3 | Collaborative TB/HIV activities

The following activities address the problems that are caused by the interaction of tuberculosis (TB) and HIV/AIDS and should be carried out by the health worker.

To establish the mechanisms for collaboration

- Set up a coordinating body for tuberculosis (TB)/HIV activities that is effective at all levels
- Conduct surveillance of HIV prevalence among patients with TB
- Carry out joint TB/HIV planning
- Conduct monitoring and evaluation

To decrease the burden of TB in people with HIV/AIDS, the following steps are needed:

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

To decrease the burden of HIV in patients with TB

- Provide HIV testing and counselling
- Introduce HIV-prevention methods
- Introduce cotrimoxazole preventive therapy
- Ensure that there is care and support for people with HIV/AIDS
- Introduce antiretroviral therapy

Table 1 | Summary of studies on resources required for TB and HIV/AIDS

Topics considered (year of study)	Strategies/interventions considered	Targets to which estimates relate	Countries considered	Time period	Main results	Reference
HIV/AIDS (2001)	Range of prevention and care interventions, including ART	Feasible coverage targets given existing health-service coverage	135 low- and middle-income countries	2005	US\$9.2 billion	76
TB and HIV/AIDS (2001)	DOTS and various HIV prevention and care strategies, including ART	Feasible coverage targets given existing health service coverage by 2007 and 2015	83 countries (all low-income countries, plus any other countries in sub-Saharan Africa)	2002–2015	Additional spending of \$0.5 billion and \$1.4 billion, respectively, needed for TB and HIV/AIDS from 2002 to 2007 compared with the 2002 levels, with ART accounting for 56% of the HIV/AIDS total	12
TB control (2002)	DOTS	Global TB control targets ratified by the World Health Assembly	22 high-burden countries and all other low- and lower-middle-income countries	2001–2005	Average of \$1 billion per year needed in high-burden countries, \$1.2 billion for all countries considered	77
TB control (2002)	DOTS, DOTS-plus for MDR-TB, TB/HIV, and new drug, diagnostics and vaccine development	Global TB control targets ratified by the World Health Assembly	22 high-burden countries and all other low- and lower-middle-income countries	2001–2005	\$600 million for TB/HIV and \$6 billion for DOTS	78
HIV/AIDS (2004)	ART delivery and associated strategies, including the enrolment of large numbers of TB patients on ART	'3-by-5' Initiative (that is, enrolment of 3 million people on ART by the end of 2005)	34 countries that account for 90% of the ART needs in resource-poor countries	2004 and 2005	\$5.1–5.9 billion by the end of 2005, 43% of which is for ART	79
TB/HIV (2004)	TB/HIV collaborative activities as defined in the WHO interim policy document	Range of coverage levels for different activities	34 countries that account for 90% of the ART needs in resource-poor countries (the same definition as that used for '3-by-5' costing)	Annual costs	About \$250–300 million when ART is only considered for the 6 months of TB treatment, as much as \$1 billion if ART is also considered after TB treatment is completed; the costs are dominated by ART	80

ART, antiretroviral therapy; DOTS, directly observed therapy short-course; MDR, multidrug resistant; TB, tuberculosis; WHO, World Health Organization.

about US\$1.5 billion per year for the core elements of the DOTS strategy, from \$0.3 billion to over \$1 billion per year for TB/HIV collaborative activities, and at least \$10 billion per year for HIV/AIDS prevention and care.

The extent to which these resources are already available is unknown. New funding has become available since these studies were undertaken and it is not clear how much is already being spent. In addition, many countries are underestimating their requirements, particularly for TB/HIV collaborative activities as they are new and as yet are not well understood³. There is also no clear consensus on how much of the bill countries should foot themselves. Nevertheless, around \$10–15 billion of external funding per year could be needed for HIV/AIDS and TB control (including TB/HIV collaborative activities) in the next 5 years. The US Presidential Initiative on AIDS will provide about \$3 billion per year between 2004 and 2008, and the GFATM has approved grants of almost \$0.9 billion per year for the next

5 years or so. Therefore, although substantial new resources have already been mobilized, considerably more are still required.

Future perspectives

The impact of HIV on TB has been devastating, with approximately 10% of all global TB cases now attributable to HIV — were it not for HIV, TB would already be declining worldwide. So what are the prospects for reducing the incidence of TB and achieving the MDG targets against the background of the HIV epidemic?

DOTS is clearly having an impact on the epidemiology of TB. Even in communities with high levels of HIV, DOTS is capable of driving down TB incidence in those who remain HIV uninfected. Once HIV prevalence levels off, DOTS will probably bring down TB incidence rates even among HIV-infected individuals, provided that good health-system performance is maintained. The two assumptions implicit in this statement, however, are not assured. HIV has a

strong negative impact on the health system, and there are other major, unresolved problems affecting performance, notably the lack of sufficient human resources. In addition, DOTS still needs to expand geographically to provide access to those currently outside the public health system, especially in Africa. HIV prevalence might have reached its peak in parts of Africa and is even falling in a few countries, such as Uganda. Outside Africa, the potential for further increases of HIV is enormous, with possible negative consequences for TB control. However, resources in these countries are generally greater than those in Africa, and with foresight, political will and the spectre of Africa behind them, there will be no excuse for allowing HIV to get further out of control.

Whether the MDG targets for TB control will be reached by 2015 depends on whether DOTS programmes everywhere can adapt to the challenges of HIV co-infection and on the yet to be proven effectiveness of the TB/HIV collaborative activities. In particular,

as the incidence of TB is increasing only in Africa and is stable or decreasing in all other continents, global achievement against the MDGs will depend on progress in Africa. TB programmes need to play their part in the care of patients infected with HIV, including the provision of ART, to ensure that they do not survive TB only to die from other HIV-related complications. Similarly, those providing ART need to ensure that this expensive investment is not wasted by failure to identify and treat TB. The challenge is to ensure that the TB and HIV programmes work together effectively to achieve these aims. Strong global and national leadership, provision of adequate financial resources, sustained country support (particularly in human resources), simplified and standardized tools for ART delivery, and an effective and reliable supply of medicines and diagnostics will all be needed in strong measure. The global system that is now pursuing accelerated development of the least-developed nations must ensure that all those responsible for the necessary resources play their part. Careful monitoring of progress will be essential, and nations and institutions must be held accountable.

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Competing interests statement
The authors declare no competing financial interests.

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