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TB:HIV

STRATEGIC FRAMEWORK TO DECREASE THE BURDEN OF TB/HIV

TB:HIV

WORLD HEALTH ORGANIZATION

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STRATEGIC FRAMEWORK TO DECREASE THE BURDEN OF TB/HIV

Stop TB Department and Department of HIV/AIDS

World Health Organization
Geneva - Switzerland

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Contents

List of abbreviations

AIDS	**A**cquired **I**mmuno**D**eficiency **S**yndrome
ALHI	**A**dult **L**ung **H**ealth **I**nitiative
ARV	**A**nti **R**etro**V**iral
BCG	**B**acille **C**almette-**G**uérin
CIDA	**C**anadian **I**nternational **D**evelopment **A**gency
CMV	**C**yto**M**egalo**V**irus
DFID	**D**epartment **F**or **I**nternational **D**evelopment (United Kingdom)
DOTS	The brand name of the internationally recommended tuberculosis control strategy (**D**irectly **O**bserved **T**reatment, **S**hort-course)
GNP	**G**ross **N**ational **P**roduct
HAART	**H**ighly **A**ctive **A**nti **R**etroviral **T**reatment
HCW	**H**ealth **C**are **W**orker
HIPC	**H**ighly **I**ndebted **P**oor **C**ountries
HIV	**H**uman **I**mmunodeficiency **V**irus
IMCI	**I**ntegrated **M**anagement of **C**hildhood **I**llnesses
IPT	**I**soniazid **P**reventive **T**reatment
KS	**K**aposi's **S**arcoma
PMTCT	**P**revention of **M**other **T**o **C**hild **T**ransmission
NGO	**N**on **G**overnmental **O**rganization
NORAD	**N**orwegian **A**gency for **D**evelopment
PCP	**P**neumocystis **C**arinii **P**neumonia
PLWH	**P**eople **L**iving **W**ith **H**IV/AIDS
ProTEST	WHO-coordinated initiative to **Pro**mote **TEST**ing for HIV by increasing access to a range of HIV/AIDS and tuberculosis prevention and care interventions
STI	**S**exually **T**ransmitted **I**nfection
TB	**T**u**B**erculosis
TB/HIV	The intersecting epidemics of **TB** and **HIV**
UNAIDS	The joint **U**nited **N**ations programme on HIV/**AIDS**
UNICEF	**U**nited **N**ations **C**hildren's **F**und
VCT	**V**oluntary **C**ounselling and **T**esting (for HIV)
WHO	**W**orld **H**ealth **O**rganization


TB:HIV

1 Executive summary

The unprecedented scale of the epidemic of HIV-related tuberculosis demands effective and urgent action. The strategic goal is to reduce tuberculosis transmission, morbidity and mortality (while minimising the risk of anti-tuberculosis drug resistance), as part of overall efforts to reduce HIV-related morbidity and mortality in high HIV prevalence populations. This evidence-based paper concentrates specifically on tuberculosis control in high HIV prevalence populations, while addressing those aspects of the HIV epidemic relevant to tuberculosis. It is complementary to the Global Health Sector Strategy against HIV/AIDS under development by WHO. It sets out a new WHO/UNAIDS strategic framework to decrease the burden of the intersecting epidemics of tuberculosis and HIV (TB/HIV). Instead of the previous "dual strategy for a dual epidemic", the new framework represents a strengthened unified health sector strategy to control HIV-related tuberculosis as an integral part of the strategy for HIV/AIDS.

The interaction between tuberculosis and HIV has implications for the public health approach to tuberculosis control among HIV-infected people. Untreated HIV infection leads to progressive immunedeficiency and increased susceptibility to infections, including tuberculosis. Tuberculosis in high HIV prevalence populations is a leading cause of morbidity and mortality, and HIV is driving the tuberculosis epidemic in many countries (especially in sub-Saharan Africa). Tuberculosis programmes and HIV programmes therefore share mutual concerns: prevention of HIV should be a priority for tuberculosis control; tuberculosis care and prevention should be priority concerns of HIV/AIDS programmes. The public health approach to decreasing the burden of TB/HIV requires more effective delivery of the available interventions by health service providers, with increased population coverage. Whereas previously tuberculosis programmes and HIV/AIDS programmes have largely pursued separate courses, they need to exploit synergies in supporting health service providers to deliver these interventions.

Up to now, the efforts to control tuberculosis among HIV-infected people have mainly focused on implementing the DOTS strategy for tuberculosis control, i.e. identifying and curing infectious tuberculosis cases (among patients presenting to general health services). This targets the final step in the sequence of events by which HIV fuels tuberculosis, namely the transmission of *Mycobacterium tuberculosis* infection by infectious tuberculosis cases. **The expanded scope of the new strategy for tuberculosis control in high HIV prevalence populations comprises interventions against tuberculosis (intensified case-finding and cure and tuberculosis preventive treatment) and interventions against HIV (and therefore indirectly against tuberculosis), e.g. condoms, STI treatment, safe injecting drug use (IDU) and highly active antiretroviral treatment (HAART).**

Common communicable diseases, including tuberculosis, and their complications comprise the largest part of the burden of HIV-related disease. The vast majority of HIV-infected people do not know their HIV status and seek health care from general health service providers. Therefore tuberculosis and HIV programmes must strengthen

the general health service providers' ability to respond to the health care needs of people in high HIV prevalence populations. The proposed framework for a coherent health response to TB/HIV incorporates tuberculosis control interventions as part of a comprehensive general health service response to HIV/AIDS.

The countries most badly affected by HIV/AIDS are low-income countries, where there has often been little substantial progress so far in meeting the most basic health needs of the general population, and in particular of people infected with HIV. Substantial increases in funding are necessary to strengthen the general health infrastructure to enable an effective comprehensive response to HIV/AIDS. Since it is not possible to achieve everything desirable all at once, explicit and rational criteria are necessary for prioritising implementation of interventions.

The proposed framework indicates the applicability of health service interventions in response to HIV/AIDS at different levels of the health care system according to a country's income level. The interventions to decrease the burden of TB/HIV are applicable in the home and community and at primary, secondary and tertiary health care levels. The interventions applicable at the secondary and tertiary levels of the health care system are additional to those applicable at the primary and secondary levels respectively. The interventions are part of a package of prioritised HIV/AIDS care interventions which general health service providers should deliver in low-income countries.

Several requirements are necessary for countries to strengthen general health service providers in implementing the interventions to control tuberculosis as part of the overall health service response to HIV/AIDS. These include: increased funding (by national governments and the donor community); changes in international and national policy away from specific HIV/AIDS activities towards responding to the care needs of high HIV prevalence populations through strengthened general health services; improved general health service capacity to deliver interventions (human resources, infrastructure and commodities); operational research to find out how best HIV/AIDS and tuberculosis programmes can work together to help general health services deliver an effective response; effective coordination of activities on the part of the many role players often involved.

This paper provides the technical basis to inform and guide the development of national implementation strategies for joint tuberculosis and HIV programme activities in delivering the available interventions. The Global Working Group on TB/HIV aims to harness the efforts of many partners to support a strengthened health service response in the most badly affected countries. In response to demand for operational guidelines for joint tuberculosis and HIV programme activities, WHO will coordinate the development of these guidelines by a Scientific Panel of the Global Working Group. The guidelines will reflect the principles of the framework and lessons learned so far from field sites with experience of comprehensive health service provision of interventions to decrease the burden of TB/HIV.

2 Introduction

The unprecedented scale of the epidemic of HIV-related tuberculosis demands effective and urgent action. The strategic goal is to reduce tuberculosis transmission, morbidity and mortality (while minimising the risk of anti-tuberculosis drug resistance), as part of overall efforts to reduce HIV-related morbidity and mortality in high HIV prevalence populations. The current policy statement from UNAIDS on tuberculosis in high HIV populations describes "a dual strategy for a dual epidemic".[1] The dual strategy consists of a strategy for HIV/AIDS care (that doesn't take tuberculosis very much into consideration) and the DOTS (Directly Observed Treatment, Short-course) strategy (that doesn't take HIV/AIDS very much into consideration). However, there is increasing recognition of tuberculosis as one of the leading causes of HIV-related morbidity and mortality, and of the extent to which HIV is fuelling the tuberculosis epidemic in high HIV prevalence populations. This overlap justifies a strengthened unified health sector strategy to control tuberculosis among HIV-infected people as an integral part of the strategy for HIV/AIDS, rather than as "a dual strategy for a dual epidemic". **Tackling tuberculosis should include tackling HIV as the most potent force driving the tuberculosis epidemic; tackling HIV should include tackling tuberculosis as a leading killer of PLWH.**

This evidence-based paper concentrates specifically on tackling the problem of tuberculosis in high HIV prevalence populations, while addressing those aspects of the HIV epidemic relevant to tuberculosis. A document in preparation "Global Health Sector Strategy for HIV/AIDS" describes the overall WHO strategic approach to HIV, and information about the UNAIDS strategic approach is available on the UNAIDS website (www.unaids.org). The focus of the framework is on the roles within the overall health system of HIV/AIDS programmes and tuberculosis programmes in supporting the response of health service providers to the needs of people in high HIV populations. Health service providers include governments, NGOs, employers, private practitioners and religious organizations. Government health service provision includes not only the Ministry of Health but also other relevant ministries, e.g. Ministry of Justice or Ministry of Interior responsible for prison health services.

The main focus of this paper is on sub-Saharan Africa, since this region bears the overwhelming brunt of HIV-related TB. However, the framework is also relevant to all regions where high or increasing rates of HIV infection may fuel the tuberculosis epidemic. Adaptation is necessary in different regions according to their particular epidemiological and health service situations. For example, in medium to low HIV prevalence populations, HIV-related tuberculosis is mostly in certain risk groups. The priority is to strengthen surveillance and ensure referral of members of risk groups to the different services providing diagnosis and care of tuberculosis and other HIV-related diseases.

This document describes the background to the global problem of HIV-related tuberculosis, with a brief review of global HIV epidemiology, the causes of the main burden of HIV-related disease, the epidemiology of HIV-related tuberculosis, and the

place of tuberculosis in the course of progression of HIV infection. There is a description of the evolving international response to TB/HIV and the main interventions available.

We propose a framework for a coherent health service response, indicating the interventions applicable at different levels of the health care system according to available resources, and the criteria for determining priorities. We suggest ways forward for collaboration (leading to integration if demonstrably beneficial) between HIV/AIDS and tuberculosis programmes in supporting general health service providers. We conclude with a summary of priority research needs in developing new and improved interventions, monitoring their impact, and implementing national strategies to decrease the burden of TB/HIV.

This paper provides the technical basis to inform the development of national implementation strategies for joint tuberculosis and HIV programme activities in delivering the available interventions. The Global Working Group on TB/HIV aims to harness the efforts of many partners to support a strengthened health service response in the most badly affected countries. In response to demand for technical and operational guidelines for joint tuberculosis and HIV programme activities, WHO will coordinate the development of these guidelines by a Scientific Panel of the Global Working Group. The guidelines will reflect the principles of the framework and lessons learned so far from field sites with experience of comprehensive health service provision of interventions to decrease the burden of TB/HIV.

3 Background

3.1 Global HIV epidemiology

The overwhelming share of the global HIV burden is borne by developing countries, where 95% of HIV-infected people live.[2] Of the global total of 36.1 million people living with HIV/AIDS (PLWH) at the end of 2000, 25.3 million (70.1%) are in sub-Saharan Africa and 5.8 million (16.1%) are in South East Asia.[3] Out of 24 countries in the world with an adult HIV seroprevalence rate in 1999 above 5%, 23 are in sub-Saharan Africa (the only other country with an adult HIV seroprevalence greater than 5% is Haiti).[2] In 8 countries (all in Southern Africa), the adult HIV seroprevalence rate is above 15%.[2] Sub-Saharan Africa thus bears the largest burden of the HIV/AIDS epidemic. However, certain countries in other regions are also badly affected by HIV, with an adult HIV seroprevalence of 1-5%, e.g. Myanmar, Thailand and Cambodia (South East Asia) and Haiti, Surinam, Guyana, Panama, Belize, Guatemala and Honduras (the Americas).[2] The trend of HIV seroprevalence appears to be stabilising in sub-Saharan Africa but still increasing in other large populations, e.g. in the former Soviet Union.

3.2 The burden of HIV-related disease

The pathogens which cause disease and the type of clinical disease they cause depend on the degree of progression of HIV infection and the associated extent of immunosuppression. In the course of HIV infection, high-grade pathogens (which may be pathogenic in healthy individuals) can cause disease at any stage, e.g. the pneumococcus, non-typhoid salmonellae and *Mycobacterium tuberculosis*; low-grade pathogens (which are rarely pathogenic in healthy persons) cause disease in the more advanced stages, e.g. candida, *Cryptococcus neoformans*, toxoplasma, *Pneumocystis carinii* and atypical mycobacteria. Disseminated infections become increasingly common in advanced stages of HIV infection with more severe imunosuppression. Infections caused by the high-grade pathogens tend to be easier to diagnose and treat than those infections caused by the low-grade pathogens.[4]

The spectrum of disease in PLWH varies among regions.[5] Dominating the picture in sub-Saharan Africa are the high-grade pathogens (bacterial and mycobacterial) such as the pneumococcus, non-typhoid salmonellae and *Mycobacterium tuberculosis*, which are endemic, highly associated with poverty, and intensely transmitted in overcrowded unsanitary environments.[6] Tuberculosis has become the leading cause of death among people with HIV infection, accounting for about a third of AIDS deaths worldwide.[2] There has also been recent recognition of the association between HIV infection and increased frequency of clinical malaria.[7] In this region, some low-grade opportunistic pathogens are important (particularly cryptococcus and toxoplasma), but those which dominate the picture in the industrialised countries, such as *Pneumocystis carinii* and atypical mycobacteria, are relatively rare.[8] Although the spectrum of disease in PLWH has not been as fully characterised in other regions, a similar pattern is likely to be seen throughout the developing world.

Nearly 90% of all PLWH live in developing countries in Africa and SE Asia. Thus worldwide, the main burden of disease in PLWH arises from a limited number of common infectious agents to which PLWH are particularly susceptible, namely tuberculosis, the pneumococcus and non-typhoid salmonellae.[6] Diagnosis of these infections is usually possible at health centres or district hospitals, and they are generally amenable to successful treatment with cheap, affordable and effective antimicrobials.[6] For example, the cost of the drugs for a course of tuberculosis treatment may be as little as US$10-20 in some countries (although higher in sub-Saharan Africa). WHO has developed an essential drugs list for the treatment of common HIV-related diseases.[9] In many parts of the world the treatments for a variety of HIV-related infections (including herpes simplex virus, cytomegalovirus and atypical mycobacteria) and cancers (including Kaposi's sarcoma and non-Hodgkin's lymphoma) are more expensive and not widely available.[10]

3.3 How HIV fuels the tuberculosis epidemic

HIV fuels the tuberculosis epidemic in several ways.[11] HIV promotes progression to active tuberculosis both in people with recently acquired[12] and with latent[13] *M tuberculosis* infections. HIV is the most powerful known risk factor for reactivation of latent tuberculosis infection to active disease.[14] The annual risk of developing tuberculosis in a PLWH who is co-infected with *M tuberculosis* ranges from 5-15%.[13] HIV increases the rate of recurrent tuberculosis,[15] which may be due to either endogenous reactivation (true relapse) or exogenous re-infection.[16] Increasing tuberculosis cases in PLWH pose an increased risk of tuberculosis transmission to the general community, whether or not HIV-infected.

3.4 Global TB/HIV epidemiology

Work is under way in collaboration between WHO and UNAIDS to update and refine the most recent (1997) estimates[17] of HIV-related tuberculosis burden by country. About a third of the 36.1 million PLWH worldwide at the end of 2000 are co-infected with *M tuberculosis*. Since 68% of those co-infected live in sub-Saharan Africa, this region also carries the overwhelming burden of the global epidemic of HIV-associated tuberculosis. However, with 22% of those co-infected, South East Asia also bears a considerable burden of HIV-associated tuberculosis. PLWH coinfected with *M tuberculosis* are at risk of tuberculosis through reactivation of latent *M tuberculosis*. In addition, PLWH exposed to intense transmission of *M tuberculosis* in high TB prevalence populations are highly susceptible to developing acute primary tuberculosis or re-infection tuberculosis.

Escalating tuberculosis case rates over the past decade in many countries in sub-Saharan Africa and in parts of SE Asia (e.g. northern Thailand) are largely attributable to the HIV epidemic.[18] Since the mid-1980s, in many African countries, including those with well-organised programmes,[19,20] annual tuberculosis case notification rates have risen up to fourfold, reaching peaks of more than 400 cases/100,000 population.[21] Up to 70% of patients with sputum smear-positive pulmonary tuberculosis are HIV-positive in some countries in sub-Saharan Africa.[13]

There is thus strong epidemiological justification for TB programmes and HIV programmes sharing mutual concerns. Since HIV drives the tuberculosis epidemic, **prevention of HIV should be a priority for the control of tuberculosis.** Since up to half of PLWH develop tuberculosis,[22] and tuberculosis may have an adverse effect on HIV progression (some studies show that the host immune response to *M tuberculosis* enhances HIV replication and might accelerate the natural progression of HIV infection),[23,24] **tuberculosis care and prevention should be a priority concern of HIV/AIDS programmes.**

3.5 Tuberculosis in the course of HIV infection

During the course of HIV infection, PLWH suffer at different times from a number of different HIV-related illnesses, including tuberculosis. Since the mean CD4+ cell count is around 300/mm^3 in HIV-infected tuberculosis patients,[25] tuberculosis often occurs after PLWH have already suffered from several different illnesses. For example, among HIV-infected tuberculosis patients in a study in Haiti, 64% had symptomatic HIV infection before the diagnosis of tuberculosis.[15]

At the level of immunodeficiency at which PLWH develop tuberculosis, susceptibility to a range of diseases is associated with high case fatality rates by the end of tuberculosis treatment, typically about 20% for new sputum smear-positive and up to 50% for new sputum smear-negative cases.[26] Yet many of the illnesses and causes of death in HIV-infected tuberculosis patients are potentially treatable or preventable.[27]

3.6 The clinical picture of HIV-related tuberculosis

The clinical picture of tuberculosis depends on the stage of HIV infection and associated degree of immunodeficiency.[13] In early HIV infection with mild to moderate immunodeficiency, the features are characteristic of post-primary tuberculosis (due to reactivation or reinfection) and resemble those seen in the pre-HIV era. More advanced immunodeficiency is associated with an increased frequency of pulmonary disease resembling primary pulmonary tuberculosis and of extrapulmonary (including disseminated) disease. Tuberculosis is therefore generally easier to diagnose in early HIV infection, when there is a higher proportion of patients with sputum smear-positive pulmonary tuberculosis, than in later HIV infection, when there is a higher proportion of sputum smear-negative pulmonary and extrapulmonary (including disseminated) tuberculosis.

Bacteraemic tuberculosis occurs typically with advanced AIDS, with median CD4 cell counts of about 100 cells/mm^3 or less.[28] *M tuberculosis* is often the most common cause of bacteraemia in febrile hospitalised HIV-infected persons, with rates of positive blood cultures for *M tuberculosis* typically in the range of 10-20%.[28] Because of difficulties in diagnosis, anatomically disseminated tuberculosis accounts for a high proportion of deaths in hospital of HIV-infected people. For example, in a study in Abidjan, tuberculosis was the prime cause of death in 80 (32%) out of an autopsy sample of 247 HIV-positive cadavers and was widely disseminated in all but 10 patients.[29]


TB:HIV

4 The international response to TB/HIV: an evolving approach

For many years, those involved primarily with tackling tuberculosis and those involved primarily with tackling HIV **have largely pursued separate courses.** Those involved primarily with tackling tuberculosis have concentrated on implementing the recommended tuberculosis control strategy based on case-finding and cure[30] (known as the DOTS strategy[31]), with little attention to HIV prevention and the care of tuberculosis patients with other HIV-related diseases. Those involved primarily with tackling HIV have largely concentrated on HIV prevention, and recently on antiretroviral treatment, with little attention to the care of people with common HIV-related diseases (including tuberculosis, pneumonia and diarrhoea). Separate funding of tuberculosis programmes and HIV/AIDS programmes has often maintained these separate courses.

WHO is leading and coordinating global efforts to ensure that all tuberculosis patients worldwide, particularly in those countries where HIV is dramatically fuelling the tuberculosis epidemic, have access to the basic essentials of tuberculosis control (effective diagnosis and treatment). The provision of tuberculosis diagnosis and treatment is often completely integrated with the general health services. Tuberculosis programmes provide the support to general health services for training, logistics (including drugs and laboratory reagents for smear microscopy diagnosis) and disease surveillance and monitoring (including evaluation of case-finding and treatment outcomes).[30]

There has been some progress in the response to TB/HIV over the past decade. International policy is now for recording and reporting, and treatment with standardised short-course chemotherapy regimens, of smear-negative pulmonary and extrapulmonary as well as smear-positive pulmonary tuberculosis patients.[30] There is clear recognition of how HIV-related tuberculosis differs in clinical presentation and outcome from non-HIV-related tuberculosis.[13] More high TB/HIV burden countries have adopted and started to implement the internationally recommended tuberculosis control strategy.[21] Available evidence from sub-Saharan Africa suggests that multi-drug resistant tuberculosis is not a widespread problem in the region.[32]

Despite considerable progress over the past decade, only 23% of all infectious tuberculosis patients worldwide in 1999 had access to the basic essentials of effective diagnosis and treatment, provided under the internationally recommended tuberculosis control strategy.[21] Failure to ensure these basic essentials in countries with severe HIV epidemics will result in an increased burden of tuberculosis (in terms of incident cases and deaths) over the coming decades.[33]

The response to HIV/AIDS involves prevention and care interventions, ideally provided in ways which mutually reinforce prevention and care.[34] One of the rationales for increasing the attention paid to previously neglected care interventions is that HIV/AIDS care provision can help to counter stigma and enhance community receptivity to take up prevention interventions.[35]

It is useful to review briefly the extent to which strategies for care of PLWH[2] have included tuberculosis. National HIV/AIDS programmes have tended to focus on providing services for the care of PLWH with known HIV status as the starting point. However, the vast majority of people in developing countries living with HIV infection do not even know they are infected with HIV. For instance in a random population sample in Zambia, only 6.5% of adults had had an HIV test previously.[36] Paradoxically, general health care services provide the vast majority of the care for most HIV-infected persons, who usually do not know their HIV status, but have received little attention from national HIV/AIDS programmes.[6] National HIV/AIDS programme efforts to improve specific HIV/AIDS services rather than to support the general health service response to the needs of high HIV prevalence populations have run the risk of becoming specialised and elitist.[35]

The general health services need to meet the needs of a population carrying an excess burden of HIV-related morbidity and mortality on top of the pre-existing burden due to non-HIV-related disease. Common infections (namely tuberculosis, pneumonia and diarrhoea) and their complications constitute a large part of the excess burden of HIV-related and non-HIV-related morbidity and mortality. General health services need to ensure that HIV-infected and non-HIV-infected persons have access to effective diagnosis and treatment of the diseases common in both groups. There has been little documented progress so far in successfully strengthening general health services on a large scale in high HIV prevalence countries.

In those countries with the highest rates of TB/HIV co-infection it is apparent that those involved primarily with tackling tuberculosis and those involved primarily with tackling HIV have common cause in supporting the general health service response to HIV/AIDS. **Tackling HIV should include tackling tuberculosis as a major killer of PLWH; tackling tuberculosis should include tackling HIV as the most potent force driving the tuberculosis epidemic.**

5 Interventions to control TB in high HIV prevalence populations

HIV has a specific impact on the dynamics of the tuberculosis epidemic. Therefore controlling tuberculosis in high HIV prevalence populations requires measures not only to achieve high rates of detection and successful treatment of cases which are handled more effectively, but also additional measures[37] beyond case-finding and treatment. Measures are also necessary to decrease morbidity and mortality in HIV-infected tuberculosis patients due to other common infections. These measures should complement ongoing efforts to develop improved specific tuberculosis control tools (e.g. a more effective vaccine[38], better diagnostic tests[39] and preventive[40] and therapeutic approaches[41]). The following description of interventions considers their efficacy and effectiveness. A discussion of rational criteria for prioritising these interventions follows in the section "A coherent health service response to TB/HIV".

5.1 Tuberculosis case-finding and treatment to ensure cure

Case-finding and treatment to ensure cure are the core tuberculosis control activities. In terms of communicable disease control, the aim is to reduce the average number of people infected by each infectious case sufficiently to interrupt transmission. In order to offset the adverse effect of HIV on the tuberculosis epidemic,[11] tuberculosis control programmes have to be more effective in diagnosing more infectious cases earlier and maximising achievable treatment success rates in order to interrupt transmission. The currently recommended approach to case-finding involves detecting cases among people presenting with symptoms (most importantly chronic cough) to general health services.[30] There is often considerable scope to improve the current approach to case-finding, since few programmes are achieving the WHO global target of 70% detection of the infectious cases.[21] It is important, however, to expand case-finding only where tuberculosis control programmes can ensure a high rate of successful treatment. Otherwise, finding more cases without being able to treat them successfully is likely to result in an increased pool of infectious cases (through decreased mortality but prolonged duration of infectivity of inadequately treated cases) and increased drug-resistance.[42] **The most efficient approach to detecting more cases and with shortened duration of infectivity involves intensified case-finding in settings where HIV-infected people are concentrated:** people with respiratory symptoms attending general health service providers in the public, private and NGO sectors (out-patients, in-patients and health care workers[43]), people attending centres for voluntary counselling and testing (VCT)[44] for HIV, prisoners,[45] and household contacts of HIV-positive index infectious tuberculosis cases.[46] Child contact screening is often neglected but is important as an intervention of benefit to individual children (rather than to decrease disease transmission, since children with tuberculosis are usually not infective to others).[47]

Tuberculosis control programmes need to support general health service providers in ensuring proper case management conditions for patients to complete a course of

effective anti-tuberculosis treatment and avoid the risk of drug resistance.[30] WHO recommends directly observed therapy as one of a range of measures aimed at promoting treatment adherence and completion.[30] WHO recommends only rifampicin-containing regimens (Table 1).[30] Among HIV-infected tuberculosis patients, cure rates are higher[48] and death[49 50] and recurrence[51 52] rates are lower with rifampicin-containing than with non-rifampicin-containing regimens.

TABLE 1

Possible alternative treatment regimens for each treatment category[30]

TREATMENT CATEGORY	TUBERCULOSIS (TB) PATIENTS	ALTERNATIVE TREATMENT REGIMENS	
		INITIAL PHASE (DAILY OR 3 TIMES PER WEEK)	CONTINUATION PHASE
I	New smear-positive pulmonary TB; new smear-negative pulmonary TB with extensive parenchymal involvement; new cases of severe forms of extra-pulmonary TB.	2 EHRZ (SHRZ) 2 EHRZ (SHRZ) 2 EHRZ (SHRZ)	6 HE 4 HR 4 H_3R_3
II	Sputum smear-positive: Relapse; Treatment failure; Treatment after interruption.	2 SHRZE / 1 HRZE 2 SHRZE / 1 HRZE	5 $H_3R_3E_3$ 5HRE
III	New smear-negative pulmonary TB (other than in Category 1); new less severe forms of extra-pulmonary TB.	2 HRZ 2 HRZ 2 HRZ	6 HE 4 HR 4 H_3R_3
IV	Chronic case (still sputum-positive after supervised re-treatment)	Refer to WHO guidelines for use of second-line drugs in specialized centres[53]	

In the standard code for TB treatment regimens, each anti-TB drug has an abbreviation: streptomycin (S), isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). A regimen consists of 2 phases. The number before a phase is the duration of that phase in months. A number in subscript (e.g. $_3$) after a letter is the number of doses of that drug per week. If there is no number in subscript after a letter, then treatment with that drug is daily. An alternative drug (or drugs) appears as a letter (or letters) in brackets.

Innovative approaches to providing patients with the necessary support to complete treatment involve community health workers and community members.[54] Results from five pilot projects (in Botswana, Kenya, Malawi, South Africa and Uganda) emphasising the roles of community and primary care facility in tuberculosis treatment show that these approaches are generally lower cost and more cost-effective, while maintaining satisfactory effectiveness (treatment success), compared to the traditional approach using hospital in-patient care.[55]

Useful indicators of programme performance include the treatment success rate (interpreted to take into account the high tuberculosis case fatality rate in high HIV prevalence populations) and the rate of treatment interruption (default).[30] Few tuberculosis control programmes in high HIV prevalence countries are achieving adequate treatment outcomes.[21] The consequences include not only an increasing burden of tuberculosis, but also the increased risk of drug resistance,[56] (which enormously complicates, and increases the costs of, tuberculosis control).[57]

Increased funding of tuberculosis programmes has rarely kept pace with the increasing case-load fuelled by HIV.[58] Adequate resources and technical expertise are necessary for programmes to achieve and maintain quality performance. In high TB/HIV burden countries, good national tuberculosis control programmes have succeeded in blunting the impact of HIV on tuberculosis (in terms of case notification rates[59] and annual risk of tuberculosis infection[60]).

Ongoing tuberculosis transmission occurs during delays in diagnosis and starting treatment, which may occur even in relatively well organised national tuberculosis programmes.[61 62] Therefore to increase the effectiveness of case-detection and cure in decreasing tuberculosis transmission, it is necessary to minimise diagnostic and treatment delays. Achieving this requires investment in programmes to improve the management of the services and make them more user-friendly and accessible (including through sensitivity to gender). As a potential area of collaboration, tuberculosis programmes could benefit from HIV programme experience of communication and social mobilisation aimed at promoting sexual behaviour change, in order to use these means to promote adherence to tuberculosis treatment.

5.2 Additional measures beyond tuberculosis case-finding and treatment

The interrupted arrows in Figure 1 (page 23) show the steps in the sequence of events by which HIV infection fuels the tuberculosis epidemic:[11, 13] HIV probably increases risk of *M tuberculosis* infection following exposure; HIV promotes progression to active tuberculosis in people with recently acquired and with latent *M tuberculosis* infections; increasing tuberculosis cases in PLWH pose an increased risk of tuberculosis transmission to the general community; HIV increases the risk of recurrent tuberculosis.

The current strategy of effective case-finding and cure addresses the end of this sequence of events, by interrupting disease transmission by infectious cases. To counteract the impact of HIV, **a significant expansion in scope of the strategy for tuberculosis control is required beyond effective case-finding and cure, through interventions aimed elsewhere in this sequence of events.** Figure 1 shows the interventions beyond case-finding and cure acting directly against tuberculosis and those acting against HIV (and therefore indirectly against tuberculosis). **The expanded scope of the new strategy for tuberculosis control in high HIV prevalence populations comprises: intensified tuberculosis case-finding and cure; tuberculosis preventive treatment; and interventions against HIV (and therefore indirectly against tuberculosis).**

5.2.1 *Interventions directly against tuberculosis*

5.2.1.1 *Preventive tuberculosis treatment*

Preventive tuberculosis treatment may be aimed at decreasing the risk of a) a first ever episode of tuberculosis (in someone exposed to infection or with latent infection), or of b) a recurrent episode (in someone who has previously had tuberculosis).

a) Aimed at decreasing the risk of a first ever episode of tuberculosis

People at high risk of developing tuberculosis may benefit from preventive treatment, as an intervention currently for individual benefit rather than as a public health measure to control tuberculosis. For example, WHO has for many years recommended isoniazid preventive treatment (IPT) for those children who are household contacts of infectious index cases of tuberculosis, and who, after screening, are found not to have tuberculosis.[63]

In high tuberculosis prevalence countries, between 3.4% and 10% of tuberculin-positive PLWH may develop tuberculosis per year.[22] Studies in this group have shown that IPT reduced the risk in the short term of developing tuberculosis to around 40% of what it would have been without such treatment, but did not prolong survival.[22] WHO and UNAIDS recommend IPT for 6 months for tuberculin-positive HIV-infected individuals who do not have tuberculosis (while recognising that in some settings where tuberculin-testing is not feasible, IPT may still be valuable in HIV-infected individuals at high risk of tuberculosis).[22] Among PLWH, IPT is likely to provide protection against the risk of developing tuberculosis through decreased risk of progression of recent, and of reactivation of latent, *M tuberculosis* infection. In high tuberculosis prevalence populations, continued exposure to *M tuberculosis* infection probably accounts for the limited duration of benefit (up to 2.5 years[64]) following completion of a 6-month course of IPT. The duration of protection depends on the duration of preventive treatment.[65]

The process of delivery by the health services, and completion by the patient, of IPT involves several steps, with a proportion of PLWH who could potentially benefit falling out at each step. The proportion of PLWH who in practice do complete a course of IPT is small.[44] In the short term, WHO and UNAIDS recommend promoting IPT as an intervention for the benefit of HIV-infected individuals rather than as a public health measure to control tuberculosis. In the medium to long term, in order for IPT to be effective as a public health measure to control tuberculosis, it is necessary to find ways of minimising the fall-out at each step of the process and to expand the provision of services for voluntary counselling and testing (VCT) for HIV.[66]

b) Aimed at decreasing risk of a recurrent episode of tuberculosis

Studies in the former Zaire (now DR Congo)[67] and in Haiti[15] showed a higher rate of recurrent tuberculosis in HIV-infected individuals than in non-HIV-infected individuals treated with a 6-month regimen containing rifampicin throughout (the regimen used

in the study in Zaire had a 4-drug initial phase and that in Haiti had a 3-drug initial phase). In both studies, post-treatment prophylaxis (isoniazid and rifampicin in the study in Zaire and isoniazid in the study in Haiti) decreased the risk of tuberculosis recurrence in HIV-infected individuals, but did not prolong survival.[67, 15] Further studies are needed to confirm the benefit, establish the optimum regimen (drugs and duration) and assess operational feasibility, before widely recommending treatment aimed at decreasing risk of tuberculosis recurrence.

5.2.1.2 *BCG immunisation*

BCG has little or no effect in reducing the number of adult cases of infectious pulmonary tuberculosis, and so has limited impact on tuberculosis control.[68] WHO has collaborated with UNICEF in establishing guidelines for childhood immunisation. In high tuberculosis prevalence countries, the benefit of BCG is in protecting young children against disseminated and severe tuberculosis, e.g. meningeal and miliary tuberculosis. Even where HIV is common, the possible benefits of BCG outweigh the possible disadvantages. WHO recommends BCG for all children in high tuberculosis prevalence countries except children with symptoms of HIV disease or AIDS.[69]

5.2.2 *Interventions against HIV*

5.2.2.1 *Interventions to decrease HIV transmission*

Since HIV fuels the tuberculosis epidemic, interventions to decrease HIV transmission should contribute to decreasing the tuberculosis burden. Increased condom use, treatment of STIs, reduction in the number of sexual partners, safe injecting behaviour, and drugs to prevent mother-to-child transmission have all been shown effective in preventing HIV infection in pilot projects, controlled trials, or national programmes in less-developed countries.[70] The key to stopping the HIV/AIDS epidemic is to bring the case reproduction number of HIV (the average number of susceptible people infected by an infected person over their lifetime) to below one.[71] When that happens the epidemic will eventually die out.

The most efficient way to constrain the spread of HIV in the whole population is to prevent transmission among those for whom the case reproduction number is very high, e.g. those with the most sexual partners.[72] Pilot projects have shown the effectiveness of reducing HIV transmission among those with the riskiest sexual behaviour in preventing secondary transmission.[73,74] Thailand has shown the effectiveness of this approach on a national scale.[75] Epidemiological models have shown that even in a generalised AIDS epidemic, such as in many countries in sub-Saharan Africa, this strategy is key to lowering prevalence in the whole population.[76] Yet no government in sub-Saharan Africa has systematically attempted on a national scale to reduce HIV transmission among those with the riskiest sexual behaviour.[77] While HIV seroprevalences have fallen in Uganda, “how much of the decline is due to the efforts of intervention programmes is open to question”.[78]

The nature and the extent of the evidence of effectiveness in decreasing HIV transmission varies between the different measures. Among the range of measures aimed at decreasing HIV transmission,[76] the immediate proximate interventions of proven efficacy in decreasing HIV transmission are condom use[75] and the treatment of STIs.[79 80] By the nature of the cultural and other determinants of sexual behaviour[81], the evaluation of behavioural interventions aimed at a reduction in number of sexual partners is complex and it is difficult to demonstrate that declining HIV incidence is due to behaviour change consequent upon public policy.[78] School health education on HIV/AIDS and life skills development have been effective in sustaining safe sex behaviour among young people.[82] A randomised trial in Kenya, Tanzania and Trinidad showed the effectiveness of VCT in reducing unprotected intercourse, as reported by trial participants,[83] and mathematical modelling has indicated the cost-effectiveness of VCT based on the assumption that the self-reported changes in sexual behaviour would translate into decreased transmission of STIs, including HIV.[84]

The scale of ongoing HIV transmission and the inadequacy of current funding for HIV/AIDS, especially in sub-Saharan Africa, testify to the pressing need to implement interventions of proven effectiveness, cost effectiveness and affordability in decreasing HIV transmission. However, assessment of the impact on transmission of HIV infection of interventions aimed at promoting sexual behavioural change awaits the results of ongoing controlled trials.

5.2.2.2 *Antiretroviral therapy*

There is a need to evaluate whether combination antiretroviral (ARV) therapy in high HIV prevalence populations in sub-Saharan Africa has the same impact in reducing (or postponing) the incidence of tuberculosis as has been shown in the USA,[85] Brazil[86] and Italy.[87] A recent mathematical model estimated the impact of low-level use of ARV treatment on the AIDS epidemic in South Africa (but not specifically on tuberculosis).[88] Of an estimated 2,302,000 incident AIDS cases that would be expected between 2000-2005 with negligible ARV use, 431,000 (19%) cases would be prevented by the use of triple combination ARV treatment in 25% of HIV-1-infected adults. It is not yet clear whether these are cases of tuberculosis and AIDS that would be postponed as opposed to prevented.

The call for “pilot projects to pioneer the use of highly active anti retroviral therapy (HAART) in settings with a heavy burden of HIV but without laboratories capable of performing CD4 counts or viral loads”[34] has implications for tuberculosis control. Such pilot projects would enable the evaluation of the impact of HAART on risk of developing tuberculosis in resource-poor settings.[89]

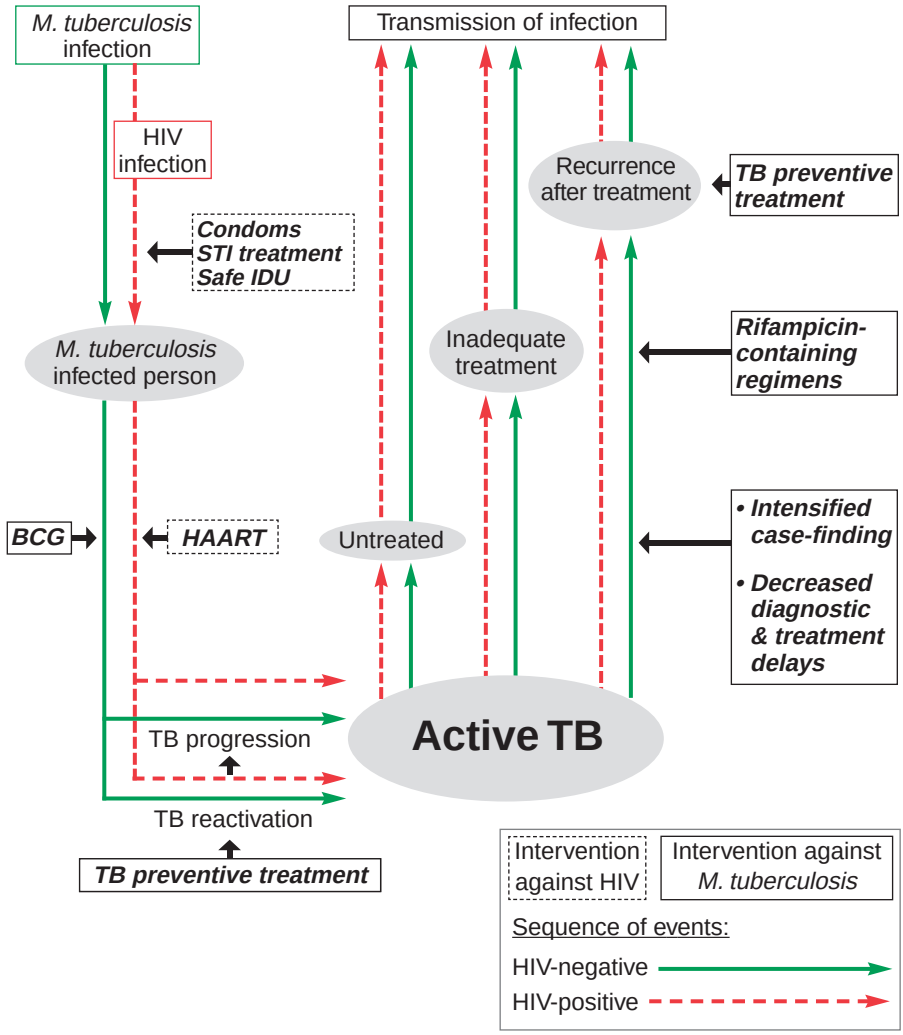
5.2.2.3 *Interventions against other HIV-related diseases to decrease morbidity and mortality in HIV-infected tuberculosis patients*

Common HIV-related infections (e.g. pneumonia and diarrhoea and their complications, and fungal infections) cause considerable morbidity during treatment of HIV-infected tuberculosis patients, and contribute to the increased case fatality rate.[13, 26]

Prophylaxis against these intercurrent infections represents a possible way forward in decreasing morbidity and mortality in HIV-infected tuberculosis patients. Studies in PLWH in Cote d'Ivoire have shown the benefit of cotrimoxazole prophylaxis against some bacterial causes of pneumonia and diarrhoea and their complications.[90 91] UNAIDS and WHO have provisionally recommended the use of cotrimoxazole prophylaxis in HIV-infected individuals in Africa as part of a minimum package of care.[92] Further studies are necessary to evaluate the benefit and the duration of effectiveness in other sites, and the feasibility and effectiveness of this intervention under routine conditions.

Evaluation of pneumococcal polysaccharide vaccine in HIV-infected adults in Uganda did not show a benefit in protecting against pneumococcal disease.[93]

FIGURE 1 **Interventions to interrupt the sequence of events by which HIV fuels the TB epidemic**




TB:HIV

6 A coherent health service response to TB/HIV

6.1 Rational criteria in determining priority interventions

Those countries most badly affected by HIV/AIDS are those with the least resources: of the 24 countries in the world with an adult HIV seroprevalence in 1999 greater than 5%, 23 are in sub-Saharan Africa and the other country is Haiti.[2] In most of these countries, basic health care is scant and to provide even the basic health needs of newly identified HIV patients would require large investments in order to increase training of personnel, to improve infrastructure to deliver services and to ensure sustainable improvements.[94]

No health system can achieve everything possible and desirable all at once, and all health systems face resource constraints. Therefore systematic, rational and explicit ways of identifying priorities are necessary. From the human rights perspective, making decisions on resource allocation in other ways runs the risk that "inappropriate health resource allocation can lead to discrimination that may not be overt".[95] The greater the resource constraints, the more important prioritisation becomes, in order to ensure the most effective use of the limited resources available.

In determining public health priorities among the many problems faced by a population, rational criteria include: a) the extent of the disease burden; b) the availability of interventions to alleviate this burden; c) the potential to reduce or alleviate poverty; d) the extent to which available interventions are characterised by market failures; e) the cost (affordability) and cost-effectiveness (value-for-money) of available interventions; f) the social, economic and political consequences of failing to implement the interventions. The UN strategy for access to HIV-related drugs recommends a stepwise approach to implementing interventions, starting with the most cost-effective, and aiming for the greatest impact within available resources.[96]

Although the burden of disease associated with tuberculosis and HIV is extensive, there are several interventions currently available to address it. The following four sub-sections discuss poverty alleviation, market failure, cost, and cost-effectiveness.

6.1.1 *Poverty alleviation*

A growing body of evidence shows that better health contributes to greater economic security and growth.[97] Within the poorest 20% of the world's population, communicable diseases represent the greatest burden (and in adults the three leading causes of communicable disease burden are tuberculosis, HIV and malaria). Among this group, communicable diseases are responsible for 59% of deaths and 64% of DALYs lost. Among the richest 20% of the globe, the figures are 8% and 11% respectively.[98] The contribution to poverty reduction is thus one justification for investment in TB/HIV interventions.

6.1.2 *Market failure*

Market failures exist when resources are not allocated in the most efficient way by a free market. Interventions may be assessed in relation to market failure by asking the following questions:

- Is the intervention a public good, i.e. is it both non-rival (consumption by one individual does not affect the amount that can be consumed by other individuals) and non-excludable (once provided, no one can be prevented from consuming it)? Public goods will not be provided by a free market because it is not possible to ensure that those who consume the good pay for this consumption.
- Is the intervention associated with important externalities, i.e. the benefits and/or the costs of the intervention extend beyond the individual receiving the intervention? For example, cure of a communicable disease will have benefits beyond the individual treated due to reduced transmission.
- Is the intervention a "catastrophic financial risk" but insurance is not available to cover costs when needed? A catastrophic financial risk occurs when the costs of an intervention are high in relation to an individual or household's income, but there are failures in the health insurance market that mean that insurance cover for such risks is not available. Such failures may arise on the supply or demand side. Supply failures include unwillingness of insurers to cover people assessed to be bad risks (which could include people known to be HIV-infected or at high risk of becoming infected). Demand failures include the possibility that individuals have imperfect information regarding their risk status.
- Are market outcomes associated with the intervention unacceptable for reasons besides those listed above? Outcomes could be considered unacceptable for a variety of reasons, including poor quality of care and treatment outcomes in the private sector, and equity concerns – for example, if only those with higher socio-economic status gain access to the intervention.

TABLE 2 **Interventions in relation to market failure**

INTERVENTION	PUBLIC GOOD	EXTERNALITIES	CATASTROPHIC FINANCIAL RISK COMBINED WITH INSURANCE MARKET FAILURES	MARKET OUTCOME MAY BE UNACCEPTABLE DUE TO EQUITY CONCERNS/POOR QUALITY OF CARE
Tuberculosis treatment	No	Yes	Yes	Yes
Interventions to increase tuberculosis case detection and cure rates	??	Yes	??	??
Cotrimoxazole prophylaxis, HIV-positive tuberculosis patients	No	No	?? < tuberculosis	?? treatment
BCG immunization	No	Yes	No	??
Preventive tuberculosis treatment	No	Yes	?? < tuberculosis treatment	??
Interventions to reduce HIV incidence	??	Yes	??	??
Antiretroviral treatment	No	??	Yes	Yes

Note: ?? indicates that either "Yes" or "No" may apply. In the case of public goods, ?? are included for two of the intervention areas because these interventions may sometimes have the characteristics of a public good, e.g. health promotion campaigns may be non-rival and non-excludable

Table 2 provides an assessment of the major types of intervention related to tuberculosis and HIV prevention and treatment with respect to market failure. This shows that most interventions are associated with some form of market failure, the most common being externalities.

When interventions are characterised by market failures, it is important to consider if these can be corrected. Three possible options include regulation of the private sector, public funding and/or direct provision of the intervention, and the use of incentives and disincentives to affect provider and consumer behaviour. If the main solution to market failure is judged to be public funding and/or provision, prioritisation among interventions should be informed by consideration of their comparative cost (affordability) and cost-effectiveness (value-for-money).

6.1.3 Cost of interventions

Data regarding the cost of the interventions listed above are scarce. Table 3 below provides a summary of the evidence regarding the unit cost of each intervention in Africa, based on existing studies.[74,84,99-116] Studies in low-income countries (LIC) and middle-income countries (MIC) are shown separately. The focus is on studies to facilitate comparisons among interventions in Africa, because this is the region most badly affected by the combined burden of tuberculosis and HIV.

TABLE 3 Cost of interventions (year 2000 US$ prices)

INTERVENTION	UNIT COST*	UNIT	REFERENCE NUMBER
Tuberculosis treatment	100-450 (LIC) 400-2100 (MIC)	Patient treated	99-101 101-103
Interventions to increase tuberculosis case detection and cure rates	??	??	None
Cotrimoxazole prophylaxis, HIV-positive TB patients	15 (LIC)	Patient treated	104
BCG immunization	1-3	Child vaccinated	105,106
Preventive tuberculosis treatment	25-48 (LIC)	Person treated	107
Interventions to reduce HIV incidence**: (a) condom distribution + STD treatment for commercial sex workers (CSWs) (b) Blood safety measures (c) Mother to child transmission prevention (nevirapine) (d) Voluntary counselling and testing (e) STD treatment	 218 (LIC) 0.5-12 (LIC) 1-33 (LIC) 4-7 (LIC) 14-30 13	 Per CHW reached Unit transfused Usable unit Per woman Per person Per client	 74 108 109-111 112,113 114,84 115
Antiretroviral treatment	>1,100***	Person year of treatment	116

* Unit costs are from the perspective of providers of services only. Patient and household costs are not included in the figures, as many studies did not assess these costs.
**Since there are several interventions in this category, a selection only are shown for illustrative purposes. Further data are available in references 114 and 116.
***Costs will be greater than US$1,100 because this is based on a restrictive subset of costs (drugs and laboratory monitoring) and does not include other important costs e.g. strengthening of health services.

Unit cost data are not particularly informative by themselves. However, they can be very useful for assessing the affordability of interventions when combined with data regarding the number of people eligible for each intervention, and available resources. Table 4 shows a hypothetical example based on data that may reflect the situation in an African country with a medium-size population and high HIV prevalence. Such data can be used to identify what interventions are feasible with available resources, or what level of intervention coverage is feasible with available resources.

TABLE 4

Assessing the affordability of interventions: a hypothetical example
(for a population of 30 million with an adult HIV seroprevalence of 14%)

INTERVENTION	APPROXIMATE NUMBER ELIGIBLE	TOTAL ANNUAL COST (US$ MILLIONS)	TOTAL COST AS % GOVERNMENT HEALTH BUDGET
Tuberculosis treatment	70,000	15	3
Interventions to increase tuberculosis case detection (CD) and cure rates (CR)	140,000 (CD) 70,000 (CR)	??	??
Cotrimoxazole prophylaxis, HIV-positive tuberculosis patients	28,000-42,000	0.4-0.6	0.1
Preventive tuberculosis treatment	150,000	3.8-7.2	0.9-1.7
Interventions to reduce HIV incidence: (a) Mother to child transmission prevention (nevirapine) (b) Voluntary counselling and testing	 900,000 15,000,000	 3.6-6.3 210-450 or 21-45 per 1% coverage	 0.8-1.5 49-105 or 4.9-10.5
Antiretroviral treatment	200,000*	220 or 22 per 1% coverage	50.9 or 5.1

*based on assumption of provision to symptomatic individuals with late-stage disease. Provision to the entire HIV-infected population could increase the numbers eligible by a factor of approximately 10.

6.1.4 *Cost-effectiveness of interventions*

Evidence regarding the cost-effectiveness of interventions is also limited. Table 5 summarizes existing evidence in terms of the cost per DALY, which is a useful generic measure allowing comparisons among different types of intervention. This indicates that tuberculosis treatment, cotrimoxazole prophylaxis for HIV-positive tuberculosis patients, and several HIV prevention interventions cost around US$50 or less in low-income settings. Highly active antiretroviral treatment is the least cost-effective.

How should these figures be interpreted? Based on the benchmark suggested by the World Bank in the World Development Report 1993, any intervention costing less than US$50 (US$62 in year 2000 prices) is highly cost-effective in the context of the poorest countries.[117] More recently, it has been suggested that a cost per DALY of under US$150 in 1995 prices (US$176 in 2000 US$ prices) is a good investment in low-income countries (defined as those with per capita incomes of less than US$765 in 1995),[118] and that interventions with a cost per DALY less than per capita GNP represent good value for money.[119,120]

TABLE 5 **Cost-effectiveness of interventions**

INTERVENTION	COST PER DALY (YEAR 2000 US$ PRICES)	REFERENCE
Tuberculosis treatment (a) New smear-positive pulmonary patients, in context of 30-70% HIV prevalence among tuberculosis patients (b) New smear-negative and extrapulmonary patients, in context of 40%-88% HIV prevalence	 2-8 (LIC) 8-68 (MIC) 13-62	 99-101 101-103 101
Interventions to increase tuberculosis case detection and cure rates	??	None
Cotrimoxazole prophylaxis, HIV+ tuberculosis patients	6	104
BCG immunization	<50	105,106
Preventive tuberculosis treatment*	169-288 (excluding transmission benefits)	107,116
Interventions to reduce HIV incidence: (a) condom distribution + STD treatment for commercial sex workers (CSWs) (b) Blood safety measures (c Mother to child transmission prevention (nevirapine) (d) Voluntary counselling and testing (e) STD treatment	 1 1-43 1-12 18-22 12	 All data summarized in 116
HAART**	>1,100	116

*analysis did not allow for the fact that compliance may be less than 100%
** the cost-effectiveness figure is an underestimate at current prices (because it is based only on drug and laboratory monitoring costs) and will be highly sensitive to drug prices

There is additional evidence regarding the cost-effectiveness of alternative ways of providing particular interventions, e.g. that rapid HIV testing is more cost-effective than ELISA testing in terms of the cost per person post-test counselled.[121]

6.2 A framework for HIV/AIDS care which incorporates interventions to address tuberculosis

Although countries determine their own priorities, the application of rational criteria for prioritisation among countries of similar resource level facing similar problems is likely to produce broadly similar results. Table 6 (pages 32 and 33) shows a framework which indicates the likely prioritisation for the main HIV/AIDS interventions applicable at different levels of the health care system according to a country's resource level.[122] The interventions applicable at the secondary and tertiary levels of the health care system are additional to those applicable at the primary and secondary levels respectively. Classification of resource level is according to low-income (per capita GNP<$635), middle-income (per capita GNP between $635 and $7,911) and high-income (per capita GNP > $7,911).[117] The framework can accommodate the possibility of significant increases in funding, which could result in the applicability of more interventions in the low- and middle-income countries, at the relevant levels of the health care system.

Tuberculosis-specific interventions within the framework should be mostly applicable in low-resource settings, where 95% of the world's tuberculosis cases and 98% of tuberculosis deaths occur.[123] Some particular aspects of TB/HIV pose challenges for which currently available interventions may be of limited value. The framework can accommodate the future development of improved interventions aimed at tackling these aspects, e.g. validated specific and sensitive diagnostic approaches for smear-negative pulmonary and extrapulmonary, including disseminated, tuberculosis.

Close collaboration is necessary between different health service providers at the different levels of the healthcare system in order to facilitate referral of patients along the "continuum of care".[124] In developing national guidelines each country needs to decide on the specific indications for referral.

6.2.1 *Home and community care*

Local responses imply people in their homes, neighbourhoods and community organizations taking responsibility for addressing HIV/AIDS as a shared community concern.[125] In the home and community, community support interventions for PLWH should include supporting tuberculosis patients to complete treatment.[54, 126] There is a need for targeted information, education and communication interventions aimed at encouraging PLWH to regard the development of features of tuberculosis as an opportunity to seek help for a treatable condition with the prospect of increased healthy life expectancy, rather than as an ominous sign of AIDS.[127]

6.2.2 *Primary care*

At primary care level, measures for detecting and treating common HIV-related diseases should include diagnosis and treatment of infectious (sputum smear-positive pulmonary) tuberculosis in people presenting to general health services with chronic cough, in congregate settings (e.g. prisons, health care facilities) and attending VCT centres. Measures for the prevention of common HIV-related diseases should include isoniazid for the preventive treatment of tuberculosis[22] and cotrimoxazole for the prevention of common bacterial infections.[92] Interventions should be implemented to decrease nosocomial risk of tuberculosis[128] and to protect healthcare workers from occupational exposure to HIV and HIV-related diseases, including tuberculosis.[43]

Information on reporting of tuberculosis cases and recording of tuberculosis treatment outcomes passes from primary care level to those responsible at district level for communicable disease surveillance. The tuberculosis surveillance system can be a starting point for the development of systems of surveillance of other HIV-related diseases, which are currently lacking or poorly developed at all levels of care.

6.2.3 *Secondary care*

Measures at the secondary care level should enable the diagnosis and treatment of common HIV-related diseases, including sputum smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis (diagnosis of which

requires investigations usually available only at secondary level, such as x-ray and biopsy), in addition to sputum smear-positive pulmonary tuberculosis (diagnosis of which requires sputum smear microscopy often available at primary level).

6.2.4 *Tertiary care*

At the tertiary care level, measures for diagnosis and treatment of complications of common HIV-related diseases should include specialist management of complicated forms of tuberculosis such as peritoneal and pericardial tuberculosis.[129]

6.3 Interventions to decrease the burden of TB/HIV as part of an essential package of HIV/AIDS care in low-income countries

General health service providers in a low-income country should routinely deliver an essential package of HIV/AIDS interventions shown below. These include interventions directly against tuberculosis (shown in bold) and interventions against HIV (and therefore indirectly against tuberculosis). The interventions applicable at the secondary and tertiary levels of the health care system are additional to those applicable at the primary and secondary levels respectively. Operational research is necessary to establish the feasibility, effectiveness, affordability and cost-effectiveness of provision of antiretroviral treatment as part of the essential package in low- and middle-income countries.

Home and community care

Information and education (on basics of HIV transmission and means of prevention, on common HIV-related diseases and on stigma)
Support groups, e.g. **tuberculosis patient support groups**, associations of PLWH
Community member support of tuberculosis patients (including directly observed treatment)
Breastfeeding advice

Primary care

Targeted health information and education on HIV and tuberculosis
Voluntary counselling and testing (VCT) for HIV
Prevention of sexual transmission of HIV: i) condoms, ii) treatment of sexually transmitted infections (STIs) (syndromic management)
Detection and treatment of common HIV-related diseases, e.g. pneumonia, diarrhœa, **tuberculosis (smear positive)**, candidiasis
Prevention of common HIV-related diseases, e.g. **isoniazid (tuberculosis)**, cotrimoxazole (septicaemia)
Prevention of tuberculosis transmission and of HIV transmission (e.g. safe injections) in health care settings
Pain relief
Intensified tuberculosis case finding in congregate settings
Disease surveillance, **e.g. tuberculosis recording and reporting**
Prevention of mother to child transmission (PMTCT) of HIV

TABLE 6

Framework of main prioritised HIV/AIDS interventions applicable at different levels of the health care system

Resource level	Low-Income	Middle-Income	High-Income
Current level of provision	Most low- and middle-income countries have yet to implement these basic minimum essential services		
HIV seroprevalence in adults in countries, end 1999	e.g. Zimbabwe (25%), Zambia (20%), Malawi (16%), Kenya (14%), Uganda (8.30%), Tanzania (8.10%), Haiti (5.20%) Cambodia (4%), Myanmar (2%)	e.g. Botswana (35.80%), South Africa (19.95%), Guyana (3%), Russia (0.18%)	e.g. USA (0.61%), Spain (0.58%), France (0.44%), Canada (0.30%), UK (0.11%)
Time-scale for extending access to all	10-15 years	5-10 years	0-5 years
Extra resources needed	+++	++	+
HOME & COMMUNITY			• Terminal care with advanced medical technology • Domiciliary treatment of HIV- related diseases, eg CMV, lymphoma, KS
		• Terminal care with health care professional input • Formula feeds for infant • Nutritional supplementation	***As per middle resource level***
	• Information and education (e.g. basics of HIV transmission and means of prevention, common HIV-related diseases) • Condom distribution • Palliative HIV/AIDS care • Support groups, e.g. associations of PLWH, **TB patient support groups** • **Community member support of TB patients (e.g. DOT)** • Breastfeeding advice	***As per low resource level***	***As per low resource level***
PRIMARY CARE (health centre)			Clinical and laboratory monitoring of HIV progression
		• Prevention of fungal infections	***As per middle resource level***
	• VCT for HIV • Prevention of HIV transmission: i) condoms, ii) STI treatment (syndromic management) iii)PMTCT • Detection and treatment of common HIV-related diseases, eg pneumonia, diarrhœa, **TB (smear positive)**, candida • Prevention of common HIV-related diseases, eg **isoniazid (TB)**, cotrimoxazole • Pain relief • **Intensified TB case finding in congregate settings** • Disease surveillance, **e.g. TB,** HIV testing results • Decreased nosocomial transmission and protection of HCWs, **eg TB**, HIV	***As per low resource level***	***As per low resource level***

Resource level	Low-Income	Middle-Income	High-Income
SECONDARY CARE (district hospital)			• Diagnosis and treatment of uncomplicated HIV-related diseases, eg low grade pathogens, lymphoma, KS • Post-exposure prophylaxis
		• HAART **(decreases TB incidence)** • Disease surveillance - less common HIV-related diseases • Prevention of HIV-related diseases, eg PCP, toxoplasmosis	***As per middle resource level***
	• Diagnosis and treatment of common HIV related diseases including severe pneumonia and diarrhœa and their complications (eg septicæmia), **smear negative and extra-pulmonary, including disseminated, TB** • Terminal in-patient care • Disease surveillance, **eg TB recording and reporting** • Safe blood • Post-occupational exposure prophylaxis against HIV	***As per low resource level***	***As per low resource level***
TERTIARY CARE (referral hospital)			Management of complications of HIV-related diseases
		Protection of HCWs eg post HIV exposure prophylaxis	***As per middle resource level***
	Management of complications of common HIV-related diseases, including **TB (eg pericardial, peritoneal),** and of complicated AIDS-related problems (e.g. cryptococcal meningitis, toxoplasmosis, PCP, KS)	***As per low resource level***	***As per low resource level***

Secondary care (additional to interventions in primary care)

Diagnosis and treatment of common HIV-related diseases, including severe pneumonia and diarrhœa and their complications (e.g. septicæmia), **smear negative and extra-pulmonary (including disseminated) tuberculosis**
Terminal in-patient care
Safe blood

Tertiary care (additional to interventions in secondary care)

Management of complications of common HIV-related diseases, including **tuberculosis (e.g. pericardial, peritoneal),** cryptococcal meningitis, toxoplasmosis, *Pneumocystis carinii* pneumonia, Kaposi's sarcoma

6.4 Financing of interventions

The section on the cost of interventions, and the hypothetical example of how to assess affordability, indicates that a substantial increase in resources is required to enable provision of some interventions – for example, widespread provision of voluntary counselling and testing and antiretroviral therapy. How to raise additional resources for priority health interventions is a generic issue not specific to tuberculosis and HIV/AIDS. Therefore, this document does not attempt to provide detailed recommendations regarding resource mobilisation. Readers should consult the reports of the Commission on Macroeconomics and Health, which include analysis of the funds required for scaling up a wide variety of interventions, and how such scaling up might be funded. These reports are due for publication in early 2002.

It is worth noting, however, that two prerequisites for accessing any new international funds available for TB/HIV interventions are likely to be a strategic plan and an annual implementation plan. The annual implementation plan should include a budget attached to a detailed work-plan of activities.

7 Collaboration between HIV/AIDS and tuberculosis programmes in support of general health service providers

Where there is overlapping epidemiology of tuberculosis and HIV, there are likely to be mutual benefits of joint HIV/AIDS and tuberculosis programme activities in tackling tuberculosis and HIV. There is growing recognition of **the need for increased collaboration between HIV/AIDS and tuberculosis programmes (leading to integration if demonstrably beneficial) in support of coherent health service provision of interventions against HIV-related tuberculosis.** This will lead to improved care for people in high HIV prevalence populations. Collaboration in support of coherent health service provision implies joint HIV/AIDS and tuberculosis programme support to the different service providers (including government, private practitioners, NGOs, employers). Increased collaboration between HIV/AIDS and tuberculosis programmes has the potential to yield benefits for more effective and efficient training, drug supply, case detection and management, and surveillance.

Identifying ways to yield the benefits of increased coordination and collaboration between HIV/AIDS and tuberculosis programmes requires policy analysis and operational research on the ground. Policy analysis is useful to identify the barriers which up to now have largely hindered effective collaboration and ways of overcoming them. Operational research projects, such as the WHO-coordinated Adult Lung Health Initiative and the ProTEST Initiative[130], are useful at district level to identify practical ways of collaboration and to evaluate the outcomes of a more concerted approach. Such research informs policy and strategy development.

7.1 Policy analysis

Policy analysis is necessary to contribute to the development of more effective ways by which national HIV/AIDS and tuberculosis programmes can support general health service providers. The main areas of work include:
i) critically reviewing policy development aimed at promoting the closer collaboration and integration of national HIV/AIDS and tuberculosis control programme activities;
ii) analysing barriers to national HIV/AIDS and tuberculosis programme collaboration and integration; iii) identifying opportunities and mechanisms for more effective national HIV/AIDS and tuberculosis programme collaboration and integration;
iv) identifying the relative advantages of different stakeholders in acting as the main implementers of the different interventions.

7.2 The Adult Lung Health Initiative (ALHI)

Strengthening of the general health services is crucial to ensuring that PLWH have access to care for common HIV-related diseases, including the respiratory diseases (especially pneumonia and tuberculosis) that constitute a large

part of the burden of HIV-related and non-HIV-related disease. Through the ALHI, WHO is coordinating the development of guidelines and algorithms based on a syndromic approach aimed at improving the general health service management of common respiratory problems. The ALHI will be an entry point to developing an evidence-based algorithmic approach to the common problems of adults, analogous to the Integrated Management of Childhood Illness (IMCI).

7.3 Initiatives promoting VCT for HIV as an entry point to HIV/AIDS care

At least 90% of the 25.3 million PLWHA in sub-Saharan Africa do not know that they are HIV-positive. It is likely that more people will choose to have HIV testing when services are available which link the provision of VCT for HIV with the provision of other services for the prevention and treatment of common HIV-related diseases, e.g. tuberculosis. Figure 2 shows schematically how VCT for HIV can be a point of access to a range of HIV/AIDS and tuberculosis prevention and care interventions, and how this range of interventions may serve to promote VCT for HIV.

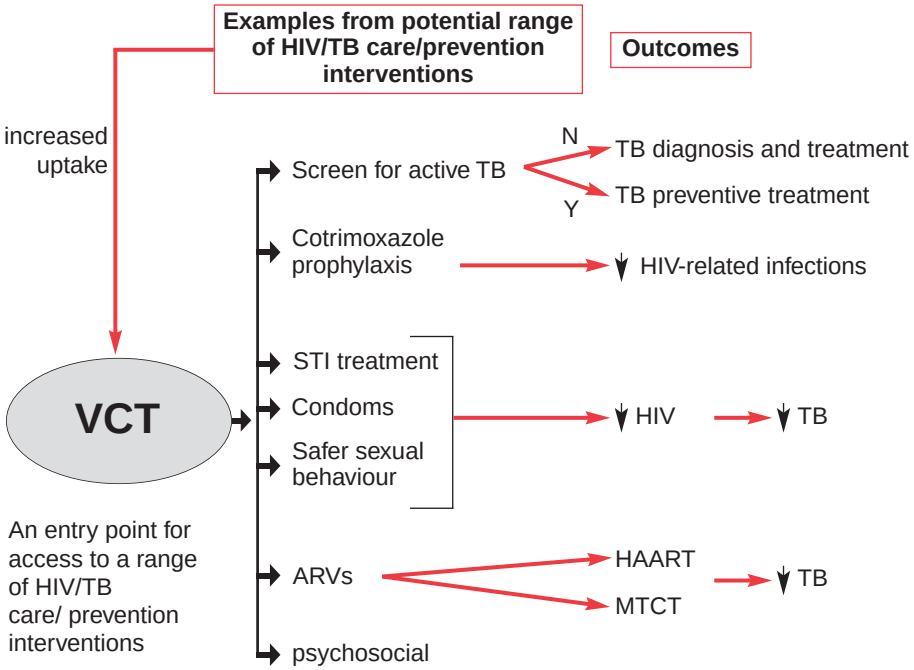
Among initiatives to promote VCT for HIV as an entry point to HIV/AIDS care, WHO Stop TB Department is facilitating the ProTEST initiative. This operational research initiative aims to promote HIV voluntary testing as a key to a more coherent response to tuberculosis in high HIV prevalence settings. The name “ProTEST” reflects the promotion of voluntary HIV testing, as an entry point for access to HIV and tuberculosis prevention and care. The initiative supports district-level field experience in several pilot sites of combining efforts against HIV and tuberculosis to reduce the combined HIV/tuberculosis burden. This will contribute to the development of a strategic approach that can be promoted as an expansion in scope of the internationally recommended tuberculosis control strategy.

Since 1999 WHO in collaboration with UNAIDS has started to establish a coordinated network of pilot sites for evaluation of integrated service delivery to reduce the burden of tuberculosis and HIV. Projects are currently under way in South Africa (funded by CIDA), Malawi (funded by NORAD) and Zambia (funded by DFID). Implementation of projects should start later this year in Uganda and in another site in Zambia (linking in prevention of transmission of HIV from mother to child). Implementation of pilot projects in different settings (e.g. urban versus rural) involves forging of links between different service providers, training of staff, strengthening of provision of services (e.g. VCT, tuberculosis preventive therapy and treatment of common HIV-related diseases, including tuberculosis.

Wide experience in several pilot sites will lead to the development of a district-based model for the integrated delivery of health care services (government, NGO, community and private sector). Experience in developing links at district level between different service providers should inform policies for the development of links at the province/region and national levels. Results from district-based pilot sites will inform the development of policy guidelines for scaling up the model on a wider scale if shown to be acceptable, effective, affordable and cost-effective. The ultimate goal of dissemination of the model is to reduce the burden of TB/HIV.

WHO Stop TB Department will set up a steering group with representatives from collaborating agencies to oversee the implementation of "ProTEST" projects belonging to the network and to promote the process of getting results into policy and practice. WHO, UNAIDS and partners will monitor and evaluate the projects and share results within the network and through the steering group. Evaluation of each pilot project will involve assessing acceptability, effectiveness, affordability and cost-effectiveness. Evaluation of scaling up will include assessment of quality and effectiveness of service provision and population coverage.

FIGURE 2 **ProTEST - operationalising the links between TB/HIV care and prevention activities**

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8 Priority research needs to decrease the burden of TB/HIV

The strategic goal is to reduce tuberculosis transmission, morbidity and mortality (while minimising the risk of anti-tuberculosis drug resistance) as part of overall efforts to reduce HIV-related morbidity and mortality in high HIV prevalence populations. Achieving this goal will require scaling up of current efforts to implement interventions of proven effectiveness, and research to determine how to implement these interventions and monitor their impact, and to develop improved and new interventions, including specific tuberculosis control tools (e.g. a more effective vaccine[38], better diagnostic tests[39] and preventive[40] and therapeutic approaches[41]).

To be able to monitor the impact of interventions on HIV-related tuberculosis, epidemiological research is necessary to address the extent of spread of tuberculosis to HIV-negative people, as reflected by the annual risk of tuberculosis infection. Mathematical modelling is useful to estimate the potential impact of different interventions and their combinations on TB/HIV, in order to inform the development of prioritised packages of interventions.

Key clinical research issues arise on account of the limitations of currently available interventions in dealing with certain aspects of HIV-related tuberculosis (e.g. diagnosis of sputum smear-negative pulmonary tuberculosis and extrapulmonary, including disseminated, tuberculosis, including in children). Further evaluation is necessary of prophylaxis against common bacterial (e.g. the pneumococcus, non-typhoid salmonellae) and fungal (e.g. cryptoccus) infections in decreasing morbidity and mortality in HIV-infected tuberculosis patients. Further studies of cotrimoxazole are necessary to evaluate the benefit and the duration of effectiveness in other sites, and the feasibility and effectiveness of this intervention under routine conditions.[92]

A key operational research issue is the identification of ways to improve coordination and collaboration between HIV/AIDS and tuberculosis programmes in order to yield potential benefits (e.g. more effective and efficient training, drug supply, case detection and management, and surveillance). It is also necessary to establish how to expand the contribution of all service providers (government, NGOs and missions, private practitioners, employers) in scaling up a coherent and coordinated response to HIV-related tuberculosis. This research includes the need to develop new policies and financing mechanisms.

The scale of provision of antiretroviral drugs is at present extremely limited in low- and middle-income countries, although the potential impact on the burden of HIV-related disease (including tuberculosis) is considerable. Operational research is therefore necessary to establish the feasibility, effectiveness, affordability and cost-effectiveness of provision of antiretroviral treatment as part of the essential package in low- and middle-income countries. It is also necessary to explore the use of the framework for effective tuberculosis control as a model for access of HIV-infected people to HAART,[131] and to examine the impact of HAART provided on a large scale (e.g. district level) on the incidence of the common HIV-related diseases, including tuberculosis, in a high HIV prevalence population.[132]


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9 Conclusion

The enormity of the global HIV/AIDS epidemic requires the scaling up, synergising and prioritising of efforts, that up to now have been too little, too fragmented and too diffusely spread. The promise of substantially increased aid flows to tackle the priority diseases of poverty, if translated into actual aid flows, represents an opportunity to scale up, synergise and prioritise the collaborative efforts of HIV/AIDS and tuberculosis programmes in support of the general health service response to the HIV/AIDS epidemic. The need is greatest in sub-Saharan Africa, where *"a tragedy of unprecedented proportions is unfolding"* (Nelson Mandela, XIII International AIDS Conference, Durban, 14 July 2000).

Efforts to combat HIV/AIDS have been substantially under-financed by governments within the heavily affected regions, and by the donor community (whose annual contribution at the end of the 1990s was only $150 million, in comparison with an estimated sum of $7.5 billion required for a meaningful response).[133] Recent events hold out the promise of substantially increased aid flows to tackle the priority diseases of poverty, including HIV/AIDS and tuberculosis, e.g. progress in the highly indebted poor countries (HIPC) initiative and the commitment of the world's most powerful countries at the G8 Summit in July 2000 in Okinawa to boost efforts against HIV, tuberculosis and malaria. Substantially increased aid flows represent an opportunity for financial and technical partners to collaborate with governments and civil society in the countries most badly affected by the HIV epidemic in substantially increasing concerted action against HIV and tuberculosis.

The development of a new strategy to decrease the burden of TB/HIV, which frames tuberculosis as part of the overall HIV/AIDS epidemic, is a step towards a level of response which matches the enormity of the HIV/AIDS epidemic. In ways which support the strengthening of the general health service response to the HIV/AIDS epidemic, the joint efforts of HIV/AIDS and tuberculosis programmes and other partners are necessary to implement the strategy, and deliver the interventions to reduce HIV/AIDS-related morbidity and mortality, including the substantial proportion due to tuberculosis.


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