

Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa

Ya Diul Mukadi, Dermot Maher^a and Anthony Harries^b

Background: Tuberculosis is a leading cause worldwide of morbidity and mortality among HIV-infected people. The HIV era has seen a dramatic increase of the tuberculosis case fatality rate (CFR) in high HIV prevalence populations. Providing care for HIV-infected people must include measures to tackle this high tuberculosis CFR.

Aims: To analyse the extent of the increased tuberculosis CFR in high HIV prevalence populations in sub-Saharan Africa, the reasons for this increase and the causes of death, in order to identify possible ways of tackling this problem.

Methods: References were obtained by searching the MEDLINE on 'tuberculosis', 'HIV infection', and 'mortality' (MeSH or textword). In addition, available data from National Tuberculosis Programme reports were reviewed.

Findings: Tuberculosis CFR is closely linked to HIV prevalence. Limited autopsy data suggest that death from HIV-related diseases other than tuberculosis is probably the main reason for the increased CFR in HIV-infected tuberculosis patients. Among HIV-infected tuberculosis patients, the higher tuberculosis CFR in sputum smear-negative and extrapulmonary than in sputum smear-positive tuberculosis cases can also be attributed to misdiagnosis of HIV-related diseases as tuberculosis. The adverse effect of the HIV/AIDS epidemic on general health service performance probably accounts for the higher tuberculosis CFR among HIV-negative tuberculosis patients in high prevalence populations than that in low HIV-prevalence populations.

Conclusion: Tackling the problem of the increased tuberculosis CFR in high HIV prevalence populations requires collaboration between tuberculosis control and HIV/AIDS programmes in implementing measures such as improved health services, tuberculosis and HIV control services, preventive treatment for HIV-related diseases and anti-HIV treatment.

© 2001 Lippincott Williams & Wilkins

AIDS 2001, **15**:143–152

Keywords: Tuberculosis, HIV, mortality, sub-Saharan Africa

Introduction

In the era before anti-tuberculosis chemotherapy tuberculosis was a feared disease with a high case fatality rate

(CFR). Those populations benefiting from the effective application of anti-tuberculosis chemotherapy saw a dramatic decrease in the CFR. In the HIV/AIDS era, tuberculosis has again become a feared disease, as a

From the HIV/AIDS Prevention and Care Department, Family Health International, Arlington, Virginia, USA, the ^aCommunicable Diseases Control, Prevention and Eradication Department, World Health Organization, Geneva, Switzerland, and the ^bNational Tuberculosis Control Programme, Lilongwe, Malawi.

Requests for reprints to: Ya Diul Mukadi, HIV/AIDS Prevention and Care Department, Family Health International, 2101 Wilson Boulevard, Suite 700, Arlington, VA 22201, USA.

Received: 15 June 2000; revised: 26 October 2000; accepted: 9 November 2000.

leading cause worldwide of morbidity and mortality among HIV-infected people, and, in high HIV prevalence populations in sub-Saharan Africa, with a high CFR once again. This review aims to analyse the extent of the increase in tuberculosis CFR in high HIV prevalence populations in sub-Saharan Africa, the reasons for this increase, and the causes of death in HIV-infected persons with tuberculosis, in order to identify measures to decrease the tuberculosis CFR in high HIV prevalence populations.

Terminology

One of the international definitions of outcome of treatment in cohorts of tuberculosis patients is the proportion of tuberculosis patients dying during treatment (without specification of cause, as the cause of death can rarely be determined in low-income, high tuberculosis prevalence countries) [1,2]. Strictly speaking, the proportion of cases of a specified disease, which are fatal within a specified time is the fatality case ratio, often called the case fatality rate (CFR) [3]. For reason of common usage, we therefore refer to the proportion of tuberculosis patients dying during treatment as the 'tuberculosis CFR'. The tuberculosis CFR is a key National Tuberculosis Programme (NTP) performance indicator [4].

Background

The tuberculosis CFR was high in the era before the introduction of effective anti-tuberculosis chemotherapy. Survival analysis of confirmed pulmonary tuberculosis patients diagnosed between 1925 and 1934 in a large town in Denmark showed that the probability of dying ranged between 17% and 29%, 32% and 43% and 42% and 55% respectively 1 year, 3 years and 5 years following tuberculosis diagnosis [5]. In an observational study of sputum-positive tuberculosis patients diagnosed between 1928 and 1938 Thompson reported that the probability of dying in the first year following tuberculosis diagnosis was 40% [6]. With the application of effective anti-tuberculosis chemotherapy, the CFR decreased to the point that tuberculosis deaths were considered an exceptional occurrence and were no longer useful as an epidemiological index of disease magnitude and trend [7].

Data on the tuberculosis CFR in the pre-chemotherapy era in sub-Saharan Africa are lacking. Data from clinical trials of combination chemotherapy in Eastern Africa in the 1970s showed a very low CFR in the pre-HIV era [8]. The advent of the HIV epidemic in sub-Saharan Africa has seen not only a

dramatic increase in the incidence of tuberculosis cases in the region, but also a dramatic increase in the tuberculosis CFR and the number of people dying from what was previously considered to be a curable disease. With treatment regimens which are generally highly effective in HIV-negative pulmonary tuberculosis patients, the CFR for HIV-positive pulmonary tuberculosis patients in some sub-Saharan African countries is now as high as 20% for sputum smear-positive cases and 50% for sputum smear-negative cases [9–13]. Tuberculosis deaths represent an important indicator of the severity of the effect of HIV on tuberculosis epidemiology.

The increased CFR of tuberculosis patients in high HIV prevalence populations in sub-Saharan Africa may change the popular perception of tuberculosis as a curable disease and threaten the reputation of NTPs. This may have an adverse influence on the willingness of tuberculosis suspects to come forward for diagnosis and on the ability of the NTP to ensure that tuberculosis patients complete treatment. NTP face the challenge not only of ensuring the effective diagnosis and treatment of increasing numbers of tuberculosis patients, but also of trying to identify and implement ways of lowering the CFR.

The focus of this review is on sub-Saharan Africa. Countries in the developing world and especially in sub-Saharan Africa are the most affected by the tuberculosis epidemic. Worldwide it is estimated that 95% of tuberculosis cases and 98% of tuberculosis deaths occur in developing countries [14]. Sub-Saharan Africa, with an estimated annual incidence rate of tuberculosis of 110 per 100 000 population, is the region with the highest tuberculosis incidence in the world [15]. The HIV epidemic has fuelled the tuberculosis epidemic in the region. By the end of 1999 it was estimated that more than two-thirds of the HIV-infected persons in the world were living in sub-Saharan Africa [16]. It is also estimated that 68% of the people worldwide co-infected with HIV and *Mycobacterium tuberculosis* are living in sub-Saharan Africa [17]. These co-infected people have at least a 30% lifetime risk of developing active tuberculosis, thus contributing to the increase in the number of tuberculosis cases in the region.

Since the start of the HIV epidemic there have been 18.8 million AIDS deaths worldwide, with the majority of them occurring in sub-Saharan Africa, and overall about one-third attributed to tuberculosis [16]. Using projected estimates for the year 2000, of the 500 000 HIV-attributable tuberculosis deaths worldwide, 239 000 (47.8%) will occur in Africa [14]. The focus of this review is therefore sub-Saharan Africa, the region of the world most severely affected by the HIV/tuberculosis co-epidemic.

Methods

A MEDLINE search provided references for this review, using 'tuberculosis' (MeSH or textword), 'HIV infection' (MeSH or textword) and 'mortality' (textword). The review included any study reporting tuberculosis case fatality and HIV infection in sub-Saharan Africa and any additional available data from NTP.

It is useful to review the limitations in the sources of tuberculosis CFR data, available according to different types of tuberculosis, and classed as tuberculosis (all forms), smear-positive and smear-negative pulmonary tuberculosis, and extrapulmonary tuberculosis. Tuberculosis CFR data are available through published reports in the medical literature and through the results of cohort analysis of treatment outcomes conducted by NTP and reported to the World Health Organization (WHO) [15]. Tuberculosis CFR obtained from routine NTP data are likely to be less accurate than those from clinical trials of the efficacy of anti-tuberculosis treatment. For example, less accurate diagnosis of tuberculosis in NTP means that a proportion of patients with 'tuberculosis' who die do not in fact have tuberculosis [18], and less accurate reporting of treatment outcomes in NTP means that a proportion of patients reported as 'lost to follow-up' are in fact dead (one-third in a study in Malawi) [19].

Findings: the extent of the increase in tuberculosis CFR

Overall tuberculosis CFR in high HIV prevalence populations

Because HIV testing is not routinely available to tuberculosis patients in high HIV prevalence populations, routine NTP reporting of treatment outcomes provides an overall CFR without a breakdown by HIV status.

Tuberculosis (all forms)

NTP do not usually provide outcomes, including CFR, for tuberculosis (all forms), as they routinely report outcomes for patients with sputum smear-positive pulmonary tuberculosis, and not usually for patients with sputum smear-negative or extrapulmonary tuberculosis. In a study in Zomba, Malawi, tuberculosis (all forms) CFR was 31% (CFR for patients with sputum smear-positive, sputum smear-negative and extrapulmonary tuberculosis were respectively 19%, 46% and 37%) [20]. In 1998 the district of Kiboga in Uganda reported a tuberculosis CFR (all forms) of 21% (unpublished data).

Smear-positive pulmonary tuberculosis

Fig. 1 shows the correlation between observed tuberculosis CFR of sputum smear-positive tuberculosis patients and HIV prevalence in adults in selected sites in sub-Saharan African countries [9–13,21–27].

Data on tuberculosis CFR trends against time are not routinely available in many countries in sub-Saharan Africa. However, data from Malawi and South Africa have shown an increase in tuberculosis CFR, which has paralleled the increase in HIV prevalence in the general population, as reflected in sentinel groups (e.g. pregnant women attending antenatal clinics and tuberculosis patients). In Malawi, tuberculosis CFR nationally in sputum smear-positive patients increased from 6% in 1987 to 21% in 1996 (Malawi NTP reports); during the same period the HIV prevalence in tuberculosis patients increased from 26% in 1986 to 77% [20, 28–31] (Table 1). Similar trends were described in Lilongwe, Malawi, where parallel increases in tuberculosis CFR among smear-positive tuberculosis patients and the prevalence of HIV in pregnant women attending antenatal clinic were reported (Fig. 2). A study in Hlabisa district in South Africa also showed a similar increase in HIV prevalence among antenatal clinic attenders from 4.2% in 1991 to 25.9% by 1997 [21]. During the same period the CFR in smear-positive tuberculosis patients increased from 4.4% to 10.3%.

Smear-negative pulmonary tuberculosis

Data are limited from NTP on CFR among sputum smear-negative tuberculosis patients. In Zomba, Malawi, the CFR was twice as high in smear-negative (46%) as in smear-positive (19%) tuberculosis patients [20]. In Hlabisa, South Africa, the CFR in smear-negative tuberculosis patients increased from 13% in 1991 to 24.7% in 1995 when the HIV prevalence in women attending antenatal clinic was also increasing in the same period [21].

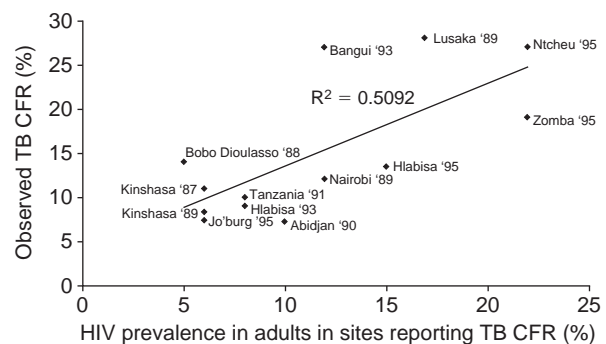


Fig. 1. Correlation between tuberculosis (TB) CFR and HIV prevalence in adults in selected sites in sub-Saharan African countries.

Table 1. Case fatality rates (CFR) in new smear-positive pulmonary tuberculosis (PTB) patients registered nationally in Malawi: relationship to HIV-seroprevalence rates in tuberculosis (TB) patients (all forms) measured at different sites.

Year	National notification and CFR in new smear-positive PTB patients		HIV-seropositive rates in TB patients (all forms)		
	Number of patients	CFR (% died)	Number of patients	HIV positive (%)	Reference
1986	1788	6	125	26	28
1987	1959	6			
1988	2720	8	153	52	29
1989	3312	10			
1990	4355	10			
1991	4071	11	187	67	30
1992	5366	12			
1993	5462	16	665	75	31
1994	6285	16			
1995	6278	19	793	77	20
1996	6702	21			

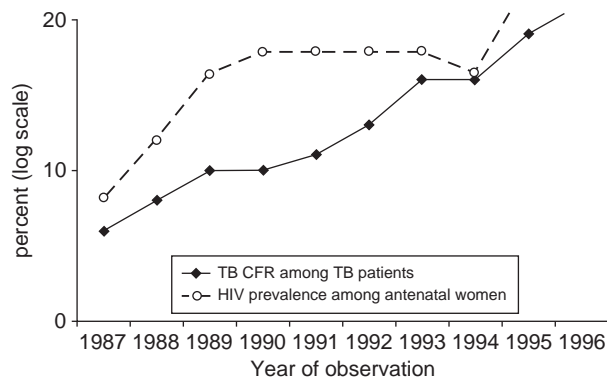


Fig. 2. Tuberculosis in CFR smear-positive pulmonary tuberculosis cases and HIV prevalence in women attending antenatal clinics in Lilongwe, Malawi (1987–1996). Source: Malawi National TB Programme unpublished data) and US Bureau of the Census, HIV/AIDS Surveillance Data Base, 1998.

Tuberculosis CFR by HIV status

Tuberculosis (all forms)

Table 2 shows reported tuberculosis CFR among tuberculosis patients (all forms) by HIV status. Tuberculosis CFR are higher in HIV-positive than in HIV-negative patients. It is noteworthy that among HIV-negative tuberculosis patients the tuberculosis CFR is higher in high HIV prevalence populations (e.g. Malawi, Zambia) than in low HIV prevalence populations (e.g. Mali, Comoros) [17]. In Zomba, Malawi, tuberculosis (all forms) CFR was 2.5 times higher in HIV-positive than in HIV-negative patients [20].

Sputum smear-positive pulmonary tuberculosis

Among patients with pulmonary tuberculosis positive by sputum smear or culture, several studies have shown a higher CFR in HIV-positive than in HIV-negative

Table 2. Tuberculosis CFR among tuberculosis patients (all forms) in relation to HIV status.

Study location	Year	Treatment regimen ^a	Tuberculosis CFR		Comment
			HIV-positive	HIV-negative	
Burkina Faso [9]	1988–1990	2SRHZ/4RH	26.9%	8.95	After 18 months, CFR was 32.5% in HIV-positive versus 11.4% in HIV-negative
Tanzania [22]	1991	2SRHZ/6TH	16%	8%	
Zaire [10]	1987	2STH/10TH	31.3%	4.4%	
Zambia [11]	1989	2STRHZ/6TH or 2STH/10TH	35%	9	

^aThe number before a phase is the duration of that phase in months. Treatment with the indicated drugs was daily. Year, Year in which study was conducted; S, streptomycin; R, rifampicin; H, isoniazid; Z, pyrazinamid; T, thiacetazone.

individuals (Table 3). The CFR in HIV-positive and HIV-negative patients with sputum smear-positive pulmonary tuberculosis were respectively 6.1% and 0.4% in Cote d'Ivoire [32], 18% and 10% in Zomba, Malawi [20], 29% and 8% in Ntcheu, Malawi [13], 14% and 0.5% in Johannesburg, South Africa [25], and 13% and 0% in Zaire [26]. The lowest tuberculosis CFR in HIV-positive patients was reported in Côte d'Ivoire and should be interpreted cautiously given that one-third of the HIV-positive patients were lost to follow-up.

Sputum smear-negative pulmonary tuberculosis

A study in Malawi in patients with sputum smear-negative pulmonary tuberculosis reported a higher CFR in HIV-positive (59%) than in HIV-negative (26%) individuals [20]. For comparison, the corresponding CFRs in sputum smear-positive patients were 18% in HIV-positive and 10% in HIV-negative patients.

When deaths occur

Survival analyses in several studies have shown that the timing of deaths differed between HIV-positive and HIV-negative groups [11,22,23,27]. Fig. 3 shows a Kaplan–Meier survival curve for HIV-positive and HIV-negative tuberculosis patients in a study in Kenya [23]. A study in Uganda described a biphasic distribu-

tion of deaths in HIV-positive patients, with the first peak of risk of death being reached within the first 3 months of treatment, and a second peak around the 21st month after first starting treatment [33]. Most other studies have reported a similar bimodal distribution [11,22,23,27].

In Hlabisa, South Africa, the probability of death for both HIV-positive and HIV-negative patients was greatest in the 2 weeks following the start of treatment. The probability of death then remained stable for HIV-negative patients at around 1% per month, whereas it continued to increase throughout the treatment period in HIV-positive patients at an average of 3% per month [21].

Studies in Kenya [23], Tanzania [22], and Zambia [34] also showed a stable probability of death in HIV-negative and an increasing probability of death in HIV-positive tuberculosis patients during and after treatment. In Kenya [23], the difference in probability of death between HIV-positive and HIV-negative tuberculosis patients increased between the second and the sixth month of treatment. In Tanzania 35% of HIV-positive patients died 4 years after the diagnosis of tuberculosis compared with 13% in HIV-negative tuberculosis patients [22]. In Zambia there were five times more deaths in HIV-positive compared with

Table 3. Tuberculosis CFR among patients with pulmonary tuberculosis (positive sputum smear/culture) by HIV status.

Study location	Year	Treatment regimen ^a	Tuberculosis CFR		Comments
			HIV-positive	HIV-negative	
Central African Republic [12]	1993–1994	2RHEZ/6EH	39	8	After 24 months CFR was 58% in HIV-positive versus 20% in HIV-negative 31% HIV-positive and 21% HIV-negative patients were lost to follow-up Treatment interruption rate higher in HIV-positive (31.6%) than in HIV-negative (21%) patients
Côte d'Ivoire [32]	1992–1993	2RHEZ/4RH	6.1	0.4	
Kenya [23]	1989–1990	1STH/11TH or 1S2HRZ/6TH	21	6	CFR 24% in patients treated with non-rifampicin-containing regimen versus 0% in those treated with rifampicin-containing regimen.
Malawi					
Ntcheu [13]	1995	2SRHZ/6TH	29%	8%	CFR higher in sputum smear-negative (59% in HIV-positive versus 26% in HIV-negative)
Zomba [20]	1995	2SRHZ/6TH	18%	10%	
South Africa					
Hlabisa [21]	1991–1995	6R ₂ H ₂ E ₂ Z ₂	18.5%	6.8%	
Hlabisa [24]	1993	6R ₂ H ₂ E ₂ Z ₂	13%	9%	
Johannesburg [25]	1995	2RHEZ/4RH	13.7%	0.5%	
Zaire [26]	1989–1990	2RHEZ/4RH	13%	0%	

^aThe number before a phase is the duration of that phase in months; a number in subscript 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 was daily). Year, Year in which study was conducted; S, streptomycin; R, rifampicin; H, isoniazid; Z, pyrazinamid; T, thiacetazone.

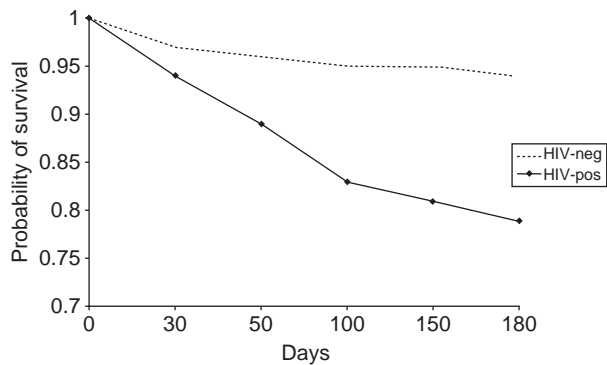


Fig. 3. Probability of survival of HIV-positive and HIV-negative tuberculosis patients during tuberculosis treatments. Source: Nunn *et al. Am Rev Respir Dis* 1992, **146**:849–854.

HIV-negative tuberculosis patients 2 years after the start of treatment [34]. Deaths in the later part of treatment and after the end of treatment are probably due to HIV-related causes other than tuberculosis.

The observation in the study in Kenya that death in HIV-negative patients was associated with tuberculosis symptoms of more than 2 months [23] suggests that early deaths may result from delay in starting treatment. The delay in initiation of tuberculosis treatment may be due to patient delay in seeking medical care, to health services failing to diagnose and initiate treatment, or to both. The local socio-economic situation and the status of the health delivery system are likely to affect patient delay in seeking medical care.

Effect of type of treatment regimen used

The type of tuberculosis treatment regimen used affects the CFR. In a study of HIV-positive tuberculosis patients in Kenya, there were no deaths reported among those who received a rifampicin-containing regimen, compared with 21 deaths among the 88 who received a non-rifampicin-containing regimen ('standard' tuberculosis regimen comprising streptomycin, thiacetazone and isoniazid) [23]. Other studies have also shown a higher CFR in HIV-positive tuberculosis patients treated with a non-rifampicin-containing regimen than in those treated with a rifampicin-containing regimen [11]. Generally, the CFR in HIV-positive tuberculosis patients treated with rifampicin-containing regimens was higher among those who received rifampicin in the initial phase of treatment only compared with those who received rifampicin throughout the initial and continuation phases of treatment (see Table 3); this may be because of the protection rifampicin affords against pyogenic infections.

Findings: possible explanations for the adverse effect of HIV on tuberculosis CFR

Tuberculosis (all forms)

Biological interaction between HIV and M. tuberculosis

HIV-induced depression of cellular immunity increases the susceptibility of individuals to develop tuberculosis either from a reactivation of latent infection [35,36] or a rapid progression of a recent infection [37]. The location and extent of tuberculosis in HIV-infected individuals depend largely on the degree of the immunosuppression, with an increased frequency of extrapulmonary and disseminated tuberculosis and lower field infiltrative pulmonary tuberculosis with more severe immunocompromise [38]. This may increase the difficulty of diagnosis and delay the initiation of treatment, resulting in an increased risk of death. Studies have shown a strong correlation both between the severity of tuberculosis and high CFR [34,38,39], and also between severe immunosuppression and mortality [23,32]. With increased immunosuppression, patients are at increased risk of dying from HIV-related conditions such as bacteraemia and pyogenic infections [40].

Immunological and virological studies indicate that the host's immune response to *M. tuberculosis* enhances HIV replication and might accelerate the natural progression of HIV infection. There is evidence that the lungs of HIV-positive tuberculosis patients have more signs of HIV replication than those of HIV-positive individuals without tuberculosis [41]. This supports the hypothesis that pulmonary tuberculosis enhances local replication of HIV. Cohort studies reported shorter survival among HIV-positive tuberculosis patients than among HIV-positive patients without tuberculosis [42–45]. Thus tuberculosis accelerates the course of HIV infection and enhances the suppression of cellular immunity, which is strongly associated with death.

HIV interactions with anti-tuberculosis treatment

Although no longer on the list of drugs recommended by WHO for use as part of anti-tuberculosis treatment regimens [1], thiacetazone is still in use in some high HIV prevalence populations and may contribute to excess tuberculosis deaths on account of the increased risk of severe and sometimes fatal drug reactions. Decreased gut absorption of anti-tuberculosis drugs could lead to decreased effectiveness of treatment regimens and impaired treatment outcomes, including death, in HIV-positive tuberculosis patients. Some studies (although not on patients in high tuberculosis prevalence populations) have shown decreased gut absorption of anti-tuberculosis drugs in HIV-positive tuberculosis patients [46,47], but another study found no evidence that HIV infection reduced plasma concentrations of anti-tuberculosis drugs [48].

Impact of the HIV epidemic on health services

HIV infection may lead to an increased tuberculosis CFR in high HIV prevalence populations through the adverse effect of the HIV epidemic on health service delivery of care. The HIV epidemic generally increases demands on over-stretched and under-resourced health services. Over-burdening impairs health service delivery. In addition, the HIV epidemic is decreasing human resource capacity (HIV-related deaths of health care workers) and performance (decreased motivation and morale and increased absence from work through illness and attendance at funerals).

Specifically, tuberculosis control may suffer as a consequence of the demands of an increased number of tuberculosis cases due to HIV infection, usually in the face of little or no increase in resources for tuberculosis control. Consequent delays in diagnosis and initiation of treatment and decreased monitoring of tuberculosis patients may lead to their suboptimal management with an increased CFR. The increase in CFR is likely to contribute to low health worker morale and further worsening of performance.

Among HIV-negative tuberculosis patients, the higher CFR in high as compared with low HIV prevalence populations probably reflects the adverse effect of the over-burdening of health services on all tuberculosis patients.

Sputum smear-negative pulmonary tuberculosis

With often hard-pressed diagnostic services, misdiagnosis may at least partly account for the high CFR in sputum smear-negative tuberculosis patients. Firstly, new sputum smear-positive patients (category 1, see WHO classification of tuberculosis patients [1]) may be misdiagnosed as sputum smear-negative (category 3), and under-treated with the category 3 regimen. Secondly, because there is no 'gold standard' diagnostic test for smear-negative patients, the tuberculosis CFR in smear-negative patients represents a mix of deaths from tuberculosis and other diseases misdiagnosed as tuberculosis. These include diseases related to HIV (e.g. *Pneumocystis carinii* pneumonia) and diseases unrelated to HIV (e.g. heart failure).

Misdiagnosis of other HIV-related diseases as sputum smear-negative pulmonary tuberculosis is also a likely explanation for the higher CFR in sputum smear-negative than in sputum smear-positive pulmonary tuberculosis patients in high HIV prevalence populations. In addition, the higher HIV seroprevalence in smear-negative than in smear-positive patients is likely to result in a correspondingly higher risk of death due to HIV-related illnesses other than tuberculosis, e.g. bacteraemia.

Findings: causes of death in HIV-positive tuberculosis patients

The two main sources of information on the causes of death in HIV-positive tuberculosis patients are from a limited number of post-mortem and clinical/microbiological studies. Post-mortem examinations are not routinely performed in most countries in sub-Saharan Africa. The general assumption is that deaths are usually due to HIV-related diseases other than tuberculosis. A study in Kenya using verbal autopsies reported that the proportion of deaths due to causes other than tuberculosis was greater in HIV-positive (23%) than HIV-negative patients (0%) [23].

Two studies have reported data on post-mortem examinations of tuberculosis patients. A post-mortem study of tuberculosis patients in Abidjan showed that tuberculosis was the primary cause of death in two out of five smear-positive HIV-positive patients who died during tuberculosis treatment [49]. Opportunistic infections other than tuberculosis were the only causes of death in patients with sputum smear-positive pulmonary tuberculosis who died after completion of treatment. In a study in South Africa, post-mortem examinations performed in half of a group of patients with sputum smear-positive pulmonary tuberculosis showed that five of the six deaths that occurred within the first month of treatment were caused by tuberculosis, whereas late deaths were most commonly due to opportunistic infections such as cryptococcal pneumonia [25]. The main limitation of these studies is the small number of cases examined. There is an urgent need for more studies to determine the cause of death in tuberculosis patients, in order to clarify the relative contributions of death from HIV-related diseases other than tuberculosis and failure of mycobacterial response to anti-tuberculosis treatment.

Two studies conducted in Africa have looked at the cause of death of HIV-positive patients basing their finding on clinical data collected on patients before their death. The study in Kinshasa considered that 25 of the 90 deaths (28%), which occurred in HIV-tuberculosis individuals were related to tuberculosis compared with one of the four HIV-negative patients who died [26]. In Zambia, tuberculosis was responsible for the death of 14 out of 42 (33%) HIV-positive individuals and three out of five (60%) HIV-negative patients [11].

Conclusion: measures to decrease the tuberculosis CFR in high HIV prevalence populations

General measures in improving health services and

specific measures are needed to counter high tuberculosis CFRs.

Health service measures

Improved general health services

General measures needed to counter high tuberculosis CFR include increased investment in improving health services and infrastructure capable of responding to increased HIV-related health needs, including tuberculosis control.

Improved tuberculosis control services

In addition to strengthening the general health services and infrastructure, specific investment is needed to improve tuberculosis control services, to ensure access of all tuberculosis patients to prompt diagnosis and initiation of safe and effective treatment and the necessary support for patients to complete treatment. There is a need for studies to establish the effectiveness, affordability and cost-effectiveness of targeted screening of high-risk groups to promote the prompt identification of sputum-positive cases, in addition to the current policy of screening of respiratory symptomatics presenting to general health services. Policy-makers in the international agencies and national governments need to consider whether all HIV-positive tuberculosis patients should receive a 6-month treatment regimen containing rifampicin throughout rather than an 8-month regimen containing rifampicin in the initial phase only. In view of the importance of preserving the efficacy of rifampicin as the most potent anti-tuberculosis drug currently available, international recommendations are needed for direct observation of rifampicin whether given in the initial or continuation phase of treatment [2]. Policy-makers need to be aware of the considerable extra resources necessary to ensure direct observation throughout the 6 months of treatment.

Improved HIV control

Controlling tuberculosis in high HIV prevalence populations will require effective HIV control measures. The implementation of measures to decrease HIV transmission is likely to not only decrease tuberculosis incidence but also to decrease the tuberculosis CFR.

Improved collaboration between tuberculosis and HIV services

The organization of care provision for tuberculosis patients must ensure the prompt diagnosis and treatment of other HIV-related diseases. This will require close collaboration between NTP and National AIDS Control Programs.

Specific measures

Preventive treatment of HIV-related causes of death other than tuberculosis

Two randomized controlled trials in Côte d'Ivoire

comparing cotrimoxazole preventive treatment and placebo in HIV-positive patients showed a lower incidence of bacterial infections in the cotrimoxazole group [50,51]. The study which enrolled HIV-positive patients with sputum smear-positive pulmonary tuberculosis reported a significantly decreased (46%) tuberculosis CFR in patients treated with cotrimoxazole [50]. A study in Cape Town, South Africa, similarly showed improved survival among HIV-positive tuberculosis patients receiving cotrimoxazole prophylaxis compared with placebo [52]. Although UNAIDS and WHO have recommended the use of cotrimoxazole prophylaxis in HIV-infected adults and children in Africa as part of a minimum package of care, this still requires further evaluation of affordability, feasibility and acceptability in a range of different settings [53].

Anti-HIV treatment

Studies in low tuberculosis prevalence populations have shown that highly active anti-retroviral therapy (HAART) decreases mortality in HIV-positive patients [54,55]. The provision of HAART to HIV-positive tuberculosis patients in high tuberculosis prevalence populations may result in a decreased tuberculosis CFR. However, current prospects for widespread use of HAART in sub-Saharan Africa are poor because of the generally weak health service infrastructure, prohibitively expensive drugs, lack of monitoring capacity, and difficulties in maintaining regular drug supplies and ensuring adherence to complex treatment regimens.

Immune modulation and micronutrient supplementation

The results of clinical trials have not confirmed the earlier hopes that immune modulation through the use of *M. vaccae* might prove beneficial to the outcome of treatment of tuberculosis patients [56]. The possible beneficial role of vitamin A supplementation is under evaluation in tuberculosis patients in high HIV prevalence populations.

References

1. Maher D, Chaulet P, Spinaci S, Harries A. *Treatment of Tuberculosis: Guidelines for National Programmes*. 2nd edn, Geneva: World Health Organization; 1997. WHO/TB/97.220.
2. Enarson DA, Rider HL, Arnadottir T, Trebucq A. *Management of Tuberculosis. A Guide for Low-Income Countries*. 5th edn, Paris: International Union Against Tuberculosis and Lung Disease (IUATLD); 2000.
3. Beaglehole R, Bonita R, Kjellstrom T. *Basic Epidemiology*. Geneva: World Health Organization; 1993.
4. Harries AD, Maher D. *TB/HIV: A Clinical Manual*. Geneva: World Health Organization; 1996. WHO/TB/96.200.
5. Buhl K, Nyboe J. **Epidemiological basis of tuberculosis eradication. Changes in the mortality of Danish tuberculosis patients since 1925.** *Bull World Health Org* 1967, 37:907-925.
6. Thompson BC. **Survival rates in pulmonary tuberculosis.** *BMJ* 1943, 2:721.
7. Styblo K. **Epidemiology of tuberculosis.** In: *Royal Netherlands Tuberculosis Association (KNCV) selected papers*. Vol.24. 1991.

8. Tuberculosis in Kenya: follow-up of the second (1974) national sampling survey and a comparison with the follow-up data from the first (1964) national sampling survey. An East African and British Medical Research Council co-operative investigation. *Tubercle* 1979, **60**:125–149.
9. Malkin JE, Prazuck T, Simonet F, *et al.* **Tuberculosis and human immunodeficiency virus infection in West Burkina Faso: Clinical presentation and clinical evolution.** *Int J Tuberc Lung Dis* 1997, **1**:68–74.
10. Perriens JH, Colebunders R L, Karahunga C, *et al.* **Increased mortality and tuberculosis treatment failure rate among human immunodeficiency virus (HIV) seropositive compared with HIV seronegative patients with pulmonary tuberculosis treated with standard chemotherapy in Kinshasa, Zaire.** *Am Rev Respir Dis* 1991, **144**:750–755.
11. Elliott AM, Halwiindi B, Hayes RJ, *et al.* **The impact of human immunodeficiency virus on mortality of patients treated for tuberculosis in a cohort study in Zambia.** *Trans Roy Soc Trop Med Hyg* 1995, **89**:78–82.
12. Garin B, Glaziou P, Kassa-Kelembho E, Yassibanda S, Mbelesso P, Morvan J. **High mortality rates among patients with tuberculosis in Bangui, Central African Republic.** *Lancet* 1997, **350**:1298.
13. Banerjee A, Moyo S, Salaniponi F, Harries A. **HIV testing and tuberculosis outcome in a rural district in Malawi.** *Trans Roy Soc Trop Med* 1997, **91**:707–708.
14. Dolin PJ, Raviglione MC, Kochi A. **Global tuberculosis incidence and mortality during 1990–2000.** *Bull World Health Org* 1994, **72**:213–220.
15. World Health Organization. Communicable Diseases Cluster. **Global Tuberculosis Control report. WHO report 2000, WHO/CDS/TB/2000.275.**
16. Joint United Nations Programme on HIV/AIDS. **Report on the global HIV/AIDS epidemic – June 2000. UNAIDS report 2000. UNAIDS/00.13E.**
17. Dye C, Scheele S, Dolin P, Pathania V, Raviglione M. **Global burden of tuberculosis: Estimated incidence, prevalence, and mortality by country.** *JAMA* 1999, **282**:677–686.
18. Moorman J, Edgington M. **Cause of death of patients on treatment for tuberculosis: a study in a rural South African Hospital.** *Int J Tuberc Lung Dis* 1999, **3**:786–790.
19. Kruyt ML, Kruyt ND, Boeree MJ, Harries AD, Salaniponi FM, van Noord PA. **True status of smear-positive pulmonary tuberculosis defaulters in Malawi.** *Bull World Health Org* 1999, **77**:386–391.
20. Harries AD, Nyangulu DS, Kang'ombe C, *et al.* **Treatment outcome of unselected cohort of tuberculosis patients in relation to human immunodeficiency virus serostatus in Zomba hospital, Malawi.** *Trans Roy Soc Trop Med* 1998, **92**:343–347.
21. Connolly C, Davies GR, Wilkinson D. **Impact of the human immunodeficiency virus epidemic on mortality among adults with tuberculosis in rural South Africa, 1991–1995.** *Int J Tuberc Lung Dis* 1998, **2**:919–925.
22. van den Broek, Mfinanga S, Moshiro C, O'Brien R, Mugomela A, Lefi M. **Impact of human immunodeficiency virus infection on the outcome of treatment and survival of tuberculosis patients in Mwanza, Tanzania.** *Int J Tuberc Lung Dis* 1998, **2**:547–552.
23. Nunn P, Brindle R, Carpenter L, *et al.* **Cohort study of human immunodeficiency virus infection in patients with tuberculosis in Nairobi, Kenya. Analysis of early (6-month) mortality.** *Am Rev Respir Dis* 1992, **146**:849–854.
24. Wilkinson D, Moore DA. **HIV-related tuberculosis in South Africa - clinical features and outcome.** *S Afr Med J* 1996, **86**:64–67.
25. Murray J, Sonnenberg P, Shearer SC, Godfrey-Faussett P. **Human immunodeficiency virus and the outcome of treatment for new and recurrent pulmonary tuberculosis in African patients.** *Am J Respir Crit Care Med* 1999, **159**:733–740.
26. Perriens JH, St. Louis ME, Mukadi YB, *et al.* **Pulmonary tuberculosis in HIV-infected patients in Zaire. A controlled trial of treatment for either 6 to 12 months.** *N Engl J Med* 1995, **332**:779–784.
27. Kassim S, Sassan-Morokro M, Ackah A, *et al.* **Two-year follow-up of persons with HIV-1- and HIV-2-associated pulmonary tuberculosis treated with short-course chemotherapy in West Africa.** *AIDS* 1995, **9**:1185–1191.
28. Kool HE, Bloemkolk D, Reeve PA, Danner SA. **HIV seropositivity and tuberculosis in a large general hospital in Malawi.** *Trop Geogr Med* 1990, **42**:128–132.
29. Kelly P, Burnham G, Radford C. **HIV seropositivity and tuberculosis in a rural Malawi hospital.** *Trans Roy Soc Trop Med Hyg* 1990, **84**:725–727.
30. Kelly PM, Cummings RG, Kaldor JM. **HIV and tuberculosis in rural sub-Saharan Africa: a cohort study with two year follow-up.** *Trans Roy Soc Trop Med Hyg* 1999, **93**:287–293.
31. Harries AD, Maher D, Mvula B, Nyangulu DS. **An audit of HIV testing and HIV serostatus in tuberculosis patients, Blantyre, Malawi.** *Tuberc Lung Dis* 1995, **76**:413–417.
32. Ackah AN, Coulibaly D, Digbeu H, *et al.* **Response to treatment, mortality, and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abidjan, Côte d'Ivoire.** *Lancet* 1995, **345**:607–610.
33. Whalen C, Okwera A, Johnson M, *et al.* **Predictors of survival in human immunodeficiency virus-infected patients with pulmonary tuberculosis.** *Am J Respir Crit Care Med* 1996, **153**:1977–1981.
34. Elliott A, M, Halwiindi B, Hayes RJ, *et al.* **The impact of human immunodeficiency virus on response to treatment and recurrence rate in patients treated for tuberculosis: two-year follow-up of a cohort in Lusaka, Zambia.** *J Trop Med Hyg* 1995, **98**:9–21.
35. Selwyn PA, Hartel D, Lewis VA, *et al.* **A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection.** *N Engl J Med* 1989, **320**:545–550.
36. Braun MM, Badi N, Ryder RW, *et al.* **A retrospective cohort study of the risk of tuberculosis among women of childbearing age with HIV infection in Zaire.** *Am Rev Respir Dis* 1991, **143**:501–504.
37. Daley CL, Small PM, Schechter GF *et al.* **An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. An analysis using restriction-fragment-length polymorphisms.** *N Engl J Med* 1992, **326**:231–235.
38. De Cock KM, Soro B, Coulibaly IM, Lucas SB. **Tuberculosis and HIV infection in sub-Saharan Africa.** *JAMA* 1992, **268**:1581–1587.
39. Abouya YL, Beaumel A, Lucas S *et al.* ***Pneumocystis carinii* pneumonia. An uncommon cause of death in African patients with acquired immunodeficiency syndrome.** *Am Rev Respir Dis* 1992, **145**:617–620.
40. Lucas SB, Hounnou A, Peacock C, *et al.* **The mortality and pathology of HIV infection in a West African city.** *AIDS* 1993, **7**:1569–1579.
41. Nakata K, Rom WN, Honda Y, *et al.* ***Mycobacterium tuberculosis* enhances human immunodeficiency virus-1 replication in the lung.** *Am J Respir Crit Care Med* 1997, **155**:996–1003.
42. Whalen C, Horsburgh CR, Hom D, *et al.* **Accelerated course of human immunodeficiency virus infection after tuberculosis.** *Am J Respir Crit Care Med* 1995, **151**:129–135.
43. Whalen C, Horsburgh CR, Hom D, *et al.* **Site of disease and opportunistic infection predict survival in HIV-associated tuberculosis.** *AIDS* 1997, **11**:455–460.
44. Leroy V, Salmi LR, Dupon M, *et al.* **Progression of human immunodeficiency virus infection in patients with tuberculosis disease.** *Am J Epidemiol* 1997, **145**:293–300.
45. Whalen C, Nsubuga P, Okwera A, *et al.* **Impact of pulmonary tuberculosis on survival of HIV-infected adults: a prospective epidemiologic study in Uganda.** *AIDS* 2000, **14**:1219–1228.
46. Peloquin CA, MacPhee AA, Berning SE. **Malabsorption of antimycobacterial medications.** *N Engl J Med* 1993, **329**:1122–1123.
47. Berning SE, Huit GA, Iseman MD, Peloquin CA. **Malabsorption of antituberculosis medications by a patient with AIDS.** *N Engl J Med* 1992, **327**:1817–1818.
48. Taylor B, Smith PJ. **Does AIDS impair the absorption of antituberculosis agents?** *Int J Tuberc Lung Dis* 1998, **2**:670–675.
49. Greenberg AE, Lucas S, Tossou O, *et al.* **Autopsy-proven causes of death in HIV-infected patients treated for tuberculosis in Abidjan, Côte d'Ivoire.** *AIDS* 1995, **9**:1251–1254.
50. Wiktor SZ, Sassan-Morokro M, Grant AD, *et al.* **Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Côte d'Ivoire: a randomised controlled trial.** *Lancet* 1999, **353**:1469–1475.
51. Anglaret X, Chene G, Attia A, *et al.* **Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in**

- Abidjan, Côte d'Ivoire: a randomised trial.** *Lancet* 1999, **353**:1463–1468.
52. Badri M, Maartens G, Wood R, Ehrlich R. **Co-trimoxazole in HIV-1 infection.** *Lancet* 1999, **354**:334–335.
 53. United Nations Joint Programme on AIDS and World Health Organization. Provisional WHO/UNAIDS secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa as part of a minimum package of care.
 54. Mocroft A, Vella S, Benfield TL *et al.* **Changing patterns of mortality across Europe in patients infected with HIV-1.** EuroSIDA Study Group. *Lancet* 1998, **352**:1725–1730.
 55. Palella FJ Jr, Delaney KM, Moorman AC, *et al.* **Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators.** *N Engl J Med* 1998, **338**:853–860.
 56. Durban Immunotherapy Trial Group. **Immunotherapy with *Mycobacterium vaccae* in patients with newly diagnosed pulmonary tuberculosis: a randomised controlled trial.** *Lancet* 1999, **354**:116–119.