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Epidemiology of HIV-associated tuberculosis Running Head: Epidemiology of TB /HIV

Stephen D. Lawn[a,b] and **Gavin Churchyard**[b,c,d]

[a]The Desmond Tutu HIV Centre, Institute for Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

[b]Clinical Research Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK

[c]Aurum Institute for Health Research, Johannesburg, South Africa

[d]Nelson R. Mandela School of Medicine, University of KwaZulu Natal, Durban, South Africa

Abstract

Purpose of review—We review literature concerning the epidemiology of HIV-associated tuberculosis (HIV-TB), focussing on articles published between 2007-2008.

Recent findings—An estimated 1.37 million new cases of HIV-TB occurred in 2007, representing 15% of the total global burden of TB. In addition, an estimated 456,000 HIV-TB deaths accounted for 23% of global HIV/AIDS mortality. Sub-Saharan Africa is the worst affected region with 79% of the disease burden. The epicentre of the co-epidemic lies in the south of the continent, with South Africa alone accounting for over one quarter of all cases. A critical overlap between HIV and the global multi-drug resistant TB (MDR-TB) epidemics is emerging. Although it is as yet unclear whether HIV is driving a disproportionate increase in MDR-TB cases at a population level, HIV has nevertheless been a potent risk factor for institutional outbreaks, especially in South Africa and Eastern Europe. Increasing data have highlighted the risk of TB among HIV-infected health-care workers in resource-limited settings. However, many studies also show the major benefits to be derived from antiretroviral therapy in high- and low-income countries.

Summary—HIV-TB remains a major challenge to global health that requires substantial increases in resource allocation and concerted international action.

Keywords

HIV; tuberculosis; antiretroviral; epidemiology

Correspondence: Stephen D. Lawn, Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory 7925., Cape Town, South Africa. Tel +27 21 650 6957 Fax +27 21 650 6963 stevelawn@yahoo.co.uk.

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Introduction

From the early stages of the HIV epidemic, a strong association with tuberculosis (TB) was apparent [1] and HIV subsequently emerged as one of the key factors undermining global TB control [2]. The epicentre of this co-epidemic is in southern Africa and where TB incidence rates have risen to unprecedented levels [3**]. The situation has been further compounded by the intersection with the growing global epidemic of multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (and XDR-TB), especially in Eastern Europe and South Africa. In this paper, we review the current global disease burden, recent epidemiological studies that provide insights into the epidemic and the impact of the increasing availability of antiretroviral therapy (ART) in both high- and low-resource settings.

Global burden of HIV-Associated TB

Between 1990 and 2003, HIV infection was one of the key factors underlying an approximately 1% annual increase in the global TB incidence. World Health Organization (WHO) estimates that global TB incidence peaked at 142 cases per 100,000 population in 2004 and that it is now decreasing slowly [3**]. However, as a result of global population growth, the absolute number of TB cases globally continued to rise in 2007. Trends in recent years also suggest that the annual number of incident cases of HIV-associated TB (HIV-TB) peaked at 1.39 million cases in 2005 and is now decreasing [3**].

In 2007 there were an estimated 9.3 million new cases of TB worldwide. Among these there were 1.37 million (14.8%) cases of HIV-TB and approximately 456,000 HIV-TB deaths [3**]. Sub-Saharan Africa accounted for the vast majority (79%) of cases, with the co-epidemic being particularly concentrated in the countries of southern Africa countries where HIV prevalence is highest (Figures 1 and 2). The South-East Asian region accounted for 11% of cases [3**].

These estimates released by WHO in 2009 represent a substantial increase from previous estimates, with an approximately two-fold greater disease burden [3**,4*]. These new estimates have arisen because of the substantial increase in HIV-testing among TB patients, particularly in Africa where the proportion of TB patients being tested for HIV has increased greatly in recent years, reaching 37% of TB patients in 2007 [3**]. Thus, much more reliable data on the prevalence of HIV in TB patients are now available. Using these data, the relative risk of HIV-infected people developing TB compared to HIV-negative people has been revised. Previously this ratio was estimated to be approximately 6 in populations with a generalized HIV epidemic but has now been revised to 20.6 (95%CI, 20.4-34.9) [3**, 4*]. These revised estimates indicate that the scale of the challenge of HIV-TB is considerably greater than previously thought.

Regional trends in the overall rate of HIV-TB are uncertain at present. However, overall TB notification rates in many countries in southern Africa have started to decrease between 2003 and 2006 (Figure 3) [4**]. These trends are perhaps most likely to reflect the natural evolution of the HIV epidemic; the contribution, if any, of other potential factors such as scale-up of ART are as yet unknown. South Africa and Swaziland are the exception to this

trend, with rates continuing to rise in 2007 and this may reflect the later development of the HIV epidemic in these countries [3**]. With just 0.7% of the world's population, South Africa accounted for 28% of the global burden of HIV-associated TB in 2006 (Figure 2) [4*].

HIV-TB is also an important public health challenge in Eastern Europe. Here, the overlap of the HIV and antituberculosis drug resistance epidemics is an important factor in the rising TB rates observed in the region (Figure 3). A study of 25 of the highest burden countries in the WHO European Region found that the proportion of TB cases testing positive increased from 2.1% in 2004 to 3.3% in 2005, with Ukraine accounting for much of this [5*]. The highest incidence rates of HIV-TB were in Portugal, followed by Ukraine, Estonia, the Russian Federation and Latvia. England and Wales were not included in this study but here HIV prevalence among TB cases has increased from 3.1% in 1999 to 8.3% in 2003 [6*]. HIV-coinfected cases contributed almost one third to the increase in overall TB notifications in England and Wales in this period and the majority were non-UK born. In marked contrast, the United States experienced a three-fold decrease in the number of HIV-TB cases between 1993 and 2004, coinciding with improvements in TB control and advances in HIV diagnosis and treatment [7].

HIV-associated TB and Mortality

Patients with HIV-TB have high mortality risk [8-13] and TB is a leading cause of death in HIV-infected patients in TB endemic countries, including those with free access to ART such as in Brazil [14*]. TB is also associated with an increased risk of AIDS-related deaths in men and women living in the United States [15*,16]. WHO estimates that there were a total of 456,000 HIV-TB deaths in 2007 [3**]. This numbers equates to 33% of the number of incident HIV-TB cases that year. Moreover, this represents 23% of the estimated 2 million deaths from HIV/AIDS in 2007. Such deaths are routinely classified as 'HIV deaths' rather than 'TB deaths' in the International Statistical Classification of Diseases (ICD-10).

Deaths from HIV-TB have exacted a huge toll on the worst-affected communities in sub-Saharan Africa. In a rural South African community with high HIV prevalence, there has been an increasing trend in TB mortality since 1994 in HIV-infected but not HIV-uninfected TB patients, especially in young adults [12]. In recent years the excess HIV-TB mortality has been 1.6-fold greater in women compared to men. Observed regional differences in death rates in Ugandan and Malawian patients with HIV-TB are likely be due to differences in patient age and stage of HIV epidemic [9].

Consistent with previous randomized clinical trials, co-trimoxazole prophylaxis significantly reduced mortality risk in HIV-infected pulmonary TB patients in Zambia [8]. Together with post-mortem data from South Africa [17*], these data highlight bacterial sepsis as a likely frequent cause of death in these patients.

HIV and Recurrent TB

A systematic review of 32 studies [18] and recently published data from Rio de Janeiro, South African gold mines and San Francisco [19**,20*,21*] confirm that HIV-TB patients

are at increased risk of recurrent disease, especially those with low CD4 cell counts. Consistent with an earlier study [22], molecular epidemiological data from South African gold mines [20*] suggest that exogenous reinfection accounts for approximately two-thirds of recurrent disease. This contrasts with data from the low TB burden setting of San Francisco where the relapse rate among HIV-infected patients was substantially reduced by increased duration of TB treatment, suggesting the importance of relapse in this setting [18*]. Increased duration of TB treatment, use of antiretroviral treatment and secondary isoniazid prophylaxis are all strategies that may reduce recurrence rates [19**,21*,23].

Epidemiological studies in sub-Saharan Africa

The WHO DOTS strategy has proven insufficient to control TB in high HIV prevalence communities in southern Africa [24]. Adjunctive interventions are needed but must be based upon sound epidemiological data derived from community-based studies.

A study of an HIV-seroconverter cohort of gold-miners found that TB risk did not increase during the HIV seroconversion period but that TB risk rapidly increased three-fold within the first 2 years of HIV infection. Thereafter, TB incidence increased steadily with time such that by 11 years from seroconversion nearly half the HIV-infected men had developed TB [25**].

In a township in Cape Town, South Africa, the annual TB notification rate reached 1,500/100,000 in 2004 [24] and exceeded 2,000/100,000 in 2006 [26**]. This rate is almost unprecedented in era of multi-drug TB treatment and has been driven by high HIV prevalence in the context of poverty and over-crowding [24]. Despite a reasonably well-functioning DOTS service in this community achieving a 67% case-finding rate in HIV-uninfected adults, a cross-sectional survey found a very high prevalence of undiagnosed TB (5%) among HIV-infected people and a case finding proportion of just 37% [27*]. TB disease duration (and period of infectiousness) in the community was similar among HIV-infected and uninfected individuals, contrasting with earlier studies from South African gold miners and Zimbabwean factory workers in which disease duration was substantially shorter in HIV-infected people [28, 29**]. Various factors may underlie this difference, including health-seeking behaviour, access to care, efficiency of TB treatment services and stage of evolution of the HIV epidemic. Studies from Cape Town and Harare, however, agree that a significant proportion of patients with culture-positive TB identified through active screening have sub-clinical disease [27*,29**].

The high prevalence of undiagnosed TB is the key driver of transmission in these communities. The annual risk of infection among school children in a poor community in Cape Town was found to be approximately 4-5% [26**]. As a result, approximately 50% were infected by the age of 15 years and were thus primed for development of TB in the event of subsequent HIV acquisition in early adult life. Among adults in South African townships and gold mines, the prevalence of TB infection is 77-89% [30-32]. Enhanced case finding such as that described in a work place intervention in Harare, Zimbabwe [29**], may be a key intervention to reduce high transmission rates.

HIV-TB is generally less infectious and the impact of this disease burden on overall transmission in high burden communities is not clear. Consistent with previous data, the study by Middelkoop *et al.* [26**] provides no evidence that the HIV-TB epidemic has resulted in increased TB transmission to children, which largely occurs in the home. However, in some settings within communities, large numbers of HIV-TB cases may outweigh any effect of reduced infectiousness and result in increased transmission among adults. For example, Glynn *et al.* [25**] suggested that increased secondary transmission accounted for rising TB rates in both HIV-infected and non-infected workers in a South African gold mine, which contrasts with an earlier study [33]. Collectively these data suggest that the contribution of HIV-TB to transmission is variable and may be age-specific.

HIV and MDR- and XDR-TB Epidemics

Approximately 425,000 MDR-TB cases occur annually worldwide, representing nearly 5% of the world's annual TB burden [34]. The interrelationship between the MDR-TB and HIV epidemics has been comprehensively reviewed elsewhere [35**]. By fuelling increased TB incidence rates, HIV may also be contributing to increases in absolute numbers of MDR-TB cases. However, the evidence to support a disproportionate association between the two diseases at a population level has not been conclusive [35**]. Nevertheless, a more recent study from the Ukraine (where the rates of MDR-TB are among the highest in the world) found a significant independent association between HIV and MDR-TB (adjusted odds 1.7, 95%CI 1.3-2.3) [36*]. It is also notable that more than half of the XDR-TB patients reported in the United States between 1993-2007 were HIV-infected [37].

HIV infection is associated with institutional outbreaks of MDR-TB as first described in industrialized countries in the late 1980s and early 1990s [35**]. The risk associated with newly expanding HIV care and treatment services in resource-limited settings was vividly exemplified by the Tugela Ferry hospital outbreak in rural Kwazulu Natal in South Africa in 2005 and 2006 [38]. Surveillance during this outbreak found that 39% of patients had MDR-TB and 6% had XDR-TB. Of those with XDR-TB, only half had previously received TB treatment, two-thirds had a recent hospital admission and genotyping found that 85% of strains were similar. All those tested were HIV-infected [38] and 52 of 53 patients died with median survival of 16 days from diagnosis; two deaths were among health care workers.

Further molecular epidemiological studies of patients with more than one TB episode confirm that exogenous reinfection was frequently the source of drug resistant disease at this hospital in Kwazulu Natal [39*]. The causal strain has been identified as F15/LAM4/KZN and this has been associated with MDR-TB in the province as early as 1994 and with XDR-TB from 2001 [40*]. The lack of drug susceptibility testing and drug resistance surveillance permitted the evolution of the XDR-TB strain to go undetected until the Tugela Ferry outbreak.

The Tugela Ferry outbreak developed in the context of a very poorly functioning provincial TB control programme. Moreover, there was a critical lack of TB infection control measures within this health facility where the prevalence of both HIV and TB were high [41]. Evidence is growing that this was not a sporadic localised outbreak. Cases have been

identified in patients attending approximately 60 different health facilities in Kwazulu Natal Province and in all 9 provinces of South Africa [42]. Such outbreaks threaten to overwhelm public health programmes and undermine the successes of ART. However, the extent to which HIV-associated MDR- and XDR-TB will lead to a rise in drug resistant TB in the general community remains to be determined.

Nosocomial TB transmission and infection control

Studies of the infectiousness of hospital in-patients with HIV-TB have been conducted in Peru using an air sampling system that exposed guinea pigs to exhaust air within an animal facility above the ward [43,44**]. These studies found that the infectiousness of patients receiving treatment varied greatly and that a small number of inadequately treated HIV patients with MDR-TB were responsible for almost all transmission events [43, 44**]. Patients enrolling in ART clinics in resource-limited settings have a high prevalence of untreated TB [45, 46]. Patients with sputum smear-positive disease are most infectious and yet represent a minority of the disease burden and can be rapidly diagnosed by sputum examination. In contrast, there are often substantial delays in diagnosis among the large number of those with smear-negative culture-positive pulmonary TB and such patients are a potentially important source of nosocomial transmission [47].

The risk of TB among health-care workers in low- and middle-income countries is an increasingly recognised problem [48]. In Zimbabwe, nursing students had an extremely high risk of acquiring TB infection (19.3/100PYs) [49*]. In a systematic review, the median annual incidence of TB infection attributable to health-care work in low-resource settings was 5.8% compared to 1.1% in high-income countries [50]. This has major implications for countries where a significant proportion of health-care workers are HIV-infected. In Kenya, for example, HIV-infected health-care workers were found to have a much higher risk of developing TB (adjusted odds 29.1; 95%CI, 5.1-167) [51**].

TB infection control in health facilities in resource-limited settings has been hugely neglected, but in the era of rapid expansion of HIV care and treatment services and increasing MDR-TB prevalence, this is increasingly recognised as a high priority [52*]. Simple low-cost interventions such as increased natural ventilation, upper-room ultra-violet lights and negative air ionization may be very effective [53*,54**]. An epidemiological modelling study based on the Tugela Ferry outbreak of XDR-TB suggested that if no TB infection control measures were instituted about 1300 cases of XDR-TB would occur by the end of 2012 [55**]. However, implementation of a combination of administrative, environmental and personal infection control measures was estimated to nearly halve this number of cases.

Tuberculosis and antiretroviral therapy

In recent years, access to ART has been rapidly scaled up in resource-limited settings where the burden of TB is highest. Increasing data from around the world indicate the substantial impact that ART has on HIV-TB.

Impact of ART on survival of TB/HIV patients

The apparent complexity of concurrent administration of ART during TB treatment may have resulted in either the under-utilization or delayed initiation of this key intervention. However, increasing data indicate the huge survival benefit of ART for patients with HIV-associated TB. In the Netherlands, there has been a 54% reduction in the adjusted odds of death among those with HIV-TB during the ART era [10]. In Thailand [56, 57] and Spain [58], adjusted mortality risk is estimated to be reduced by 80-93% and 63%, respectively. In Malawi, adults and children with TB receiving ART have good outcomes similar to non-TB patients [59, 60]. Surprisingly, a further retrospective observational study from Malawi found no short-term survival benefit conferred by ART started during the continuation phase of TB treatment but this study may well be subject to ART allocation bias [61]. Furthermore, most deaths occurred in the intensive phase of TB treatment [61], suggesting the need for early ART initiation [62]. Consistent with data from South Africa [45], patients developing incident TB during ART in Malawi have much poorer survival [63]. This reflects the fact that TB develops opportunistically in those patients with poor CD4 cell recovery and who already have poor survival [64].

TB and mortality in ART services

TB is a leading cause of early mortality in ART services in sub-Saharan Africa [65] although much of the true burden of disease may remain unascertained. In an ART service in South Africa, TB was associated with a 2-3-fold increased crude mortality risk [45]. However, some data from ART services in Uganda, Malawi and South Africa suggest that TB is not an independent predictor of mortality, which instead appears to be largely driven by low baseline CD4 cell counts [46,66,67]. Since patients with HIV-TB typically have advanced immunodeficiency and very high morality risk, early initiation of ART is often warranted [62]. The precise timing of this remains unclear and randomised controlled trials are awaited [68].

Impact of ART on TB prevention

The WHO DOTS strategy alone is insufficient to control the HIV-TB epidemic. ART, however, is a potent intervention for TB prevention. Adding to earlier data [69], recent studies have shown a 54-74% reduction in TB rates associated with use of ART in an adult cohorts in Spain [70, 71] and at a population level in Brazil [72**,73]. Recurrence rates were halved by ART in a study from Brazil [19]. Furthermore, in a retrospective hospital-based paediatric cohort in South Africa, the extremely high TB incidence rates (53.3 cases/100PYs) decreased by 88% during ART [74].

TB incidence rates decline with increasing duration of ART [45,46] and risk reductions observed in cohorts in high- and low-incomes countries are similar [75*]. Despite this, it remains unclear whether ART will improve TB control at the population level [69, 76]. A study from Brazil found that much HIV-TB occurs prior to HIV diagnosis [77] and early HIV diagnosis and treatment are clearly needed for TB prevention. In addition, since TB rates do not return to background during ART [45], concurrent adjunctive interventions are needed. Isoniazid preventive therapy in a routine clinical service reduces the risk of HIV-TB substantially [78]. More recent retrospective observational data from Brazil suggest that

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isoniazid preventive therapy and ART used together may have an additive effect [72**]. Concurrent use of these treatments was not associated with an increased risk of hepatitis in South African gold miners [79]. In eastern Europe where rates of HIV-associated drug-resistant disease are high, a system dynamics simulation model suggested that very high coverage (>75%) with ART combined with high TB treatment success rates would need to be achieved to substantially impact mortality rates associated with TB [80].

TB-associated immune reconstitution disease

The early phase of ART may be complicated by the development of immune reconstitution disease (IRD), alternatively known as immune reconstitution inflammatory syndrome (IRIS). Although this is associated with a wide variety of opportunistic infections, mycobacterial diseases are the most common [81]. TB accounted for 41% of IRD events in a prospective South African cohort [82*].

TB IRD was reviewed in 2008 [83*] and may present as either the clinical deterioration of pre-existing TB following ART initiation (‘paradoxical’ IRD) or the clinical presentation of sub-clinical TB present at the time of ART initiation (‘unmasking’ TB). Between 8-43% of TB patients who commence ART develop paradoxical IRD, with a tendency for lower rates to be observed in studies in resource-limited settings [83*]. The reasons for this apparent difference are not clear but recently published consensus case definitions may help standardisation of data [84*].

Although just 12% of TB patients developed IRD in a study from South Africa, the proportion was much higher (32%) among the sub-set who initiated ART in the first 2 months of TB treatment [85**]. In adjusted analyses, those initiating ART in the first month of TB treatment had a 70-fold higher risk of TB IRD compared to those initiating ART after at least 3 months of TB treatment. A further prospective study from the US found a rate of just 15% but highlighted the considerable morbidity and frequent need for interventions [86].

For a long time ‘unmasking’ TB IRD has remained a poorly defined phenomenon but has recently been extensively reviewed [87*,88]. Both papers provide a similar conceptual framework that proposes how ART modifies the presentation of TB. This may cause a temporal clustering of cases in the initial weeks of treatment – a phenomenon referred to as ‘unmasking’. In a sub-set of these cases, there may also be an increase in the severity of manifestations due to an overt hyper-inflammatory response – a phenomenon referred to as ‘unmasking TB IRD’ [87, 88]. Although reports of the latter in the literature are relatively few, a recent case report illustrates how this is occasionally fatal [89].

Conclusion

HIV-TB accounts for a huge burden of morbidity and mortality, which, in light of revised WHO estimates in 2009 (3**), has previously been underestimated. The African continent bears the brunt of the vast majority of this disease burden and associated mortality. However, rates are also increasing in some middle- and high-income countries.

While much needs to be done to improve diagnosis and treatment outcomes, it is also clear that this epidemic cannot be controlled solely through treatment of infectious TB cases. There is a great need for scale-up of preventive interventions [90*] such as the WHO '3I's strategy' (intensified case finding, isoniazid preventive therapy and infection control) and ART. In addition a much stronger focus on prevention needs to include concerted action with regard to HIV/AIDS prevention and addressing social determinants of disease such as poverty, malnutrition and overcrowding [90*]. To accelerate progress towards epidemiological impact targets set for 2015, HIV-TB must move up the global public health agenda with increased resource allocation and concerted international action.

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Abbreviations

AIDS	acquired immune deficiency syndrome
ART	antiretroviral treatment
HIV	human immunodeficiency virus
HIV-TB	HIV-associated TB
IRD	immune reconstitution disease
IRIS	immune reconstitution inflammatory syndrome
MDR-TB	multi-drug resistant tuberculosis
TB	tuberculosis
WHO	World Health Organization
XDR-TB	extensively resistant tuberculosis

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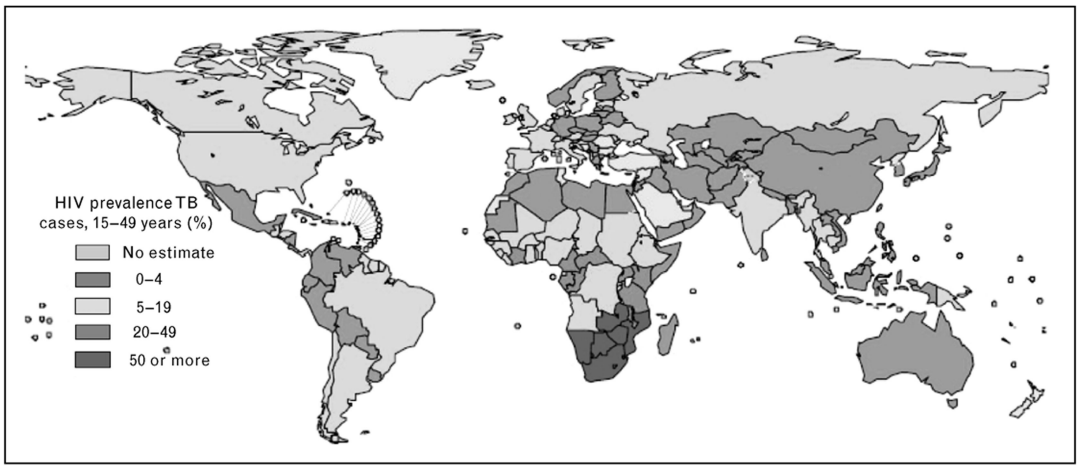

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the WHO concerning the legal status of any country or territory or concerning the delimitation of its frontiers or boundaries. World Health Organization (WHO), Geneva, 2006. http://gamapserver.who.int/mapLibrary/.

Figure 1. Country estimates of the prevalence of HIV infection in new cases of tuberculosis (TB) diagnosed in 2005.

Source: World Health Organization (WHO), Geneva, 2006. Available at: http://gamapserver.who.int/mapLibrary/ The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the WHO concerning the legal status of any country or territory or concerning the delimitation of its frontiers or boundaries.

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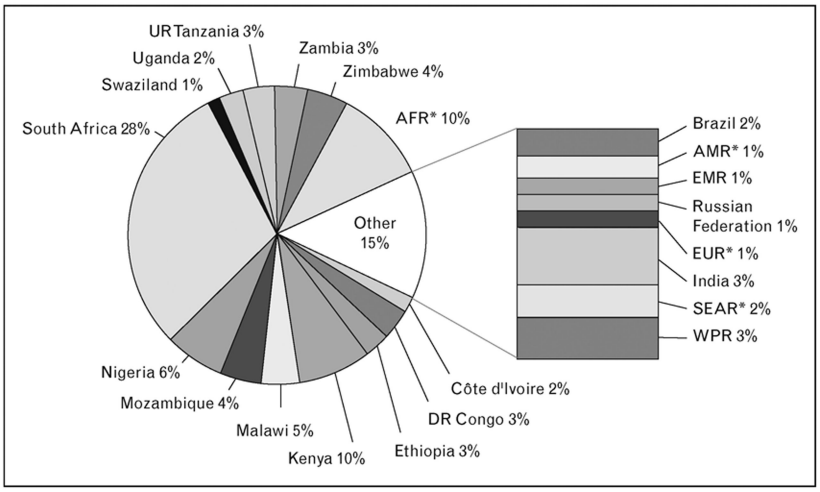

Figure 2. Geographical distribution of estimated HIV-associated TB cases in 2006.

For each country or region, the estimated number of cases is shown as a percentage of the global total. AFR* represents all countries in the WHO African region except for those shown separately. AMR* is the WHO Region of the Americas, excluding Brazil. EUR* is the WHO European Region, excluding the Russian Federation. SEAR* is the WHO South-East Asia Region, excluding India. Source: WHO, 2008 [4*].

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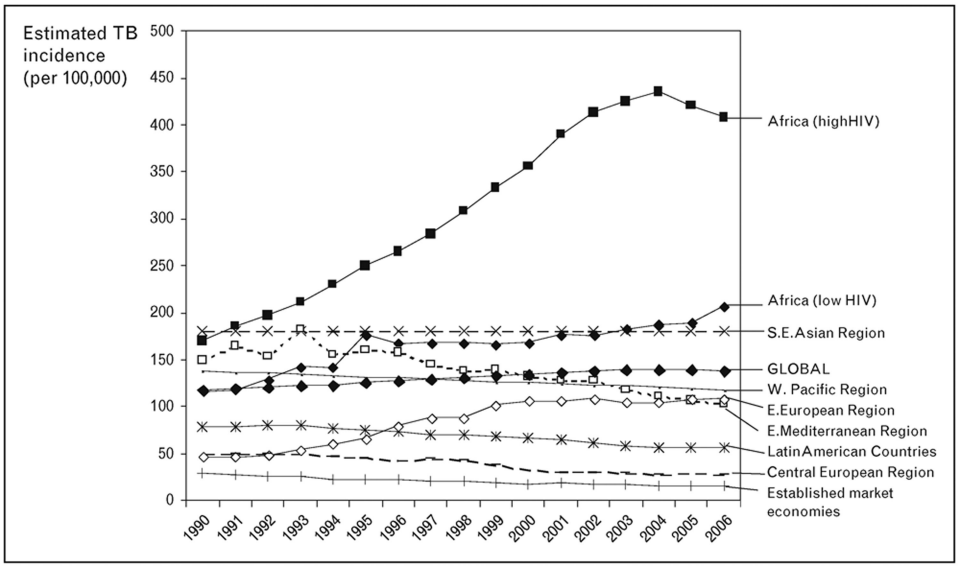

Figure 3. Trends in estimated tuberculosis incidence rates (per 100,000 per year) for the period 1990-2006.

Data are from the 134 countries with the most reliable surveillance systems. Global data and data from nine sub-regions are shown. Source: WHO, 2008 [4*].