The Growing Burden of Tuberculosis

Global Trends and Interactions With the HIV Epidemic

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Background: The increasing global burden of tuberculosis (TB) is linked to human immunodeficiency virus (HIV) infection.

Methods: We reviewed data from notifications of TB cases, cohort treatment outcomes, surveys of *Mycobacterium tuberculosis* infection, and HIV prevalence in patients with TB and other subgroups. Information was collated from published literature and databases held by the World Health Organization (WHO), the Joint United Nations Programme on HIV/Acquired Immunodeficiency Syndrome (UNAIDS), the US Census Bureau, and the US Centers for Disease Control and Prevention.

Results: There were an estimated 8.3 million (5th-95th centiles, 7.3-9.2 million) new TB cases in 2000 (137/100 000 population; range, 121/100 000-151/100 000). Tuberculosis incidence rates were highest in the WHO African Region (290/100 000 per year; range, 265/100 000-331/100 000), as was the annual rate of increase in the number of cases (6%). Nine percent (7%-12%) of all new

TB cases in adults (aged 15-49 years) were attributable to HIV infection, but the proportion was much greater in the WHO African Region (31%) and some industrialized countries, notably the United States (26%). There were an estimated 1.8 million (5th-95th centiles, 1.6-2.2 million) deaths from TB, of which 12% (226 000) were attributable to HIV. Tuberculosis was the cause of 11% of all adult AIDS deaths. The prevalence of *M tuberculosis*–HIV coinfection in adults was 0.36% (11 million people). Coinfection prevalence rates equaled or exceeded 5% in 8 African countries. In South Africa alone there were 2 million coinfected adults.

Conclusions: The HIV pandemic presents a massive challenge to global TB control. The prevention of HIV and TB, the extension of WHO DOTS programs, and a focused effort to control HIV-related TB in areas of high HIV prevalence are matters of great urgency.

Arch Intern Med. 2003;163:1009-1021

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H UMAN immunodeficiency virus (HIV) infection is a potent risk factor for tuberculosis (TB). Not only does HIV increase the risk of reactivating latent *Mycobacterium tuberculosis* (MTB) infection,[1] it also increases the risk of rapid TB progression soon after infection or reinfection with MTB.[2,3] In persons infected with MTB only, the lifetime risk of developing TB ranges between 10% and 20%.[4,5] In persons coinfected with MTB and HIV, however, the annual risk can exceed 10%.[1,6,7] The TB burden in countries with a generalized HIV epidemic has therefore increased rapidly over the past decade, especially in the severely affected countries of eastern and southern Africa.[8-12] Tuberculosis is one of the most common causes of morbidity and the most common cause of death in HIV-positive adults living in less-developed

countries,[13-26] yet it is a preventable and treatable disease.

It is possible that, in addition to increasing individual susceptibility to TB following MTB infection, the increased burden of HIV-associated TB cases also increases MTB transmission rates at the community level, threatening the health and survival of HIV-negative individuals as well.[27] In several countries HIV has been associated with epidemic outbreaks of TB, and many of the reported outbreaks involved multidrug-resistant strains[28-31] responding poorly to standard therapy.[32,33]

In 1997 the World Health Organization (WHO) carried out a study designed primarily to assess the global burden of TB.[34] In the present study we advance that work by focusing on the relationship between TB and HIV, and on the growing magnitude of the TB problem. The estimates of HIV-related TB are limited to per-

Formulas	Definitions
1. $I = T/d$ and $I_s = T_s/d_s$	N = Population
	I = Incidence of TB (No. of New Cases of TB per Year)
2. $P = tI$ and $P_s = t_s I_s$	P = Prevalence of TB Disease
3. $I_s/N = \lambda k$	T = TB Case Notifications (per Year)
	D = Deaths From TB
4. $D = fI$ and $D_s = fI_s$	IRR = TB Incidence Rate Ratio (TB Incidence Rate in Human Immunodeficiency Virus [HIV]-Positive Persons/TB Incidence Rate in HIV-Negative Persons)
5. $I = I_a^+ + I_a^- + I_n$	d = Proportion of Cases Notified (Case Detection Rate)
or	t = Average Duration of TB Disease (Years)
$I = m_a^+ r_a^+ N_a^+ + m_a^- r_a^- N_a^- + m_n r_n N_n$	λ = Rate of Infection With *Mycobacterium tuberculosis* (MTB) (Annual Rate of TB Infection per Person per Year)
	k = Ratio of Incidence of Smear-Positive TB to Rate of MTB Infection
6. $IRR = \dfrac{m_a^+ r_a^+}{m_a^- r_a^-} = \dfrac{I_a^+/N_a^+}{I_a^-/N_a^-}$	f = Proportion of TB Patients Who Die From TB (Case Fatality Rate [CFR])
	m = Prevalence of Infection With MTB
7. $\dfrac{I_a^+}{I_a^-} = \dfrac{IRR\,(N_a^+/N_a^-)}{1+(N_a^+/N_a^-)\,(IRR-1)}$	r = Rate of Progression to TB Disease in MTB-Infected Individuals (per Person per Year)
	s = Sputum Smear-Positive TB (No Subscript Implies All Forms)
	a = Adult (15-49 Years Old)
8. $I_a^* = I_a^+ - \dfrac{I_a^-}{N_a^-}\,N_a^+$	n = Other Age Groups (<15 or >49 Years Old), Assumed HIV-Uninfected
9. $D_a^* = D_a^+ - f^-\,(I^+ - I_a^*)$	+ = HIV Positive
	− = HIV Negative
	* = Attributable to HIV Infection

Figure 1. Formulas for estimating tuberculosis (TB) incidence, prevalence, and deaths.

sons aged 15 through 49 years because of the insufficient and conflicting data regarding HIV-associated TB in children,[35] and because of the lack of HIV prevalence estimates in older adults. Our objectives were to develop and enumerate a range of indicators of the burden of HIV-related TB, thereby providing a firm basis for setting disease control targets, and for monitoring trends as well as the impact of interventions.

METHODS

The estimates are based on TB notifications and treatment outcomes, on surveys of TB infection and disease, and on surveys of HIV prevalence in TB patients and other population groups (eg, pregnant women). Country-specific estimates of the prevalence of HIV infection among persons aged 15 through 49 years (hereafter referred to as adult HIV prevalence) were obtained from the Joint United Nations Programme on HIV/AIDS (UNAIDS).[36] Essential formulas are given in **Figure 1**.

ESTIMATES OF TB INCIDENCE

At the start of 2000 WHO published TB incidence estimates stratified by age group and smear status for 209 countries and territories.[37] They consisted of previously published estimates[34] updated using trends in notification rates.

AGE-SPECIFIC TB RATES

The age distribution of smear-positive cases used in these calculations was assumed to be the same as the age distribution of smear-positive cases notified to WHO.[37] The age distribution of all cases was then obtained using published data on the proportion of cases that are smear-positive in each age group.[38] Estimates by the United Nations Population Division of total country populations[39] and the number of individuals aged 15 through 49 years[40] were used to convert incidence rates per capita (and the prevalence and mortality rates indicated below) to total numbers.

PREVALENCE OF HIV IN NEW TB CASES, AND THE PROPORTION OF TB CASES ATTRIBUTABLE TO HIV

The prevalence of HIV in new TB cases was estimated for each country by using available data to derive regional estimates of the incidence rate ratio (IRR), as detailed below. The IRR is the ratio of the incidence rate of TB in HIV-positive persons, I_a^+/N_a^+, to the incidence rate in HIV-negative persons, I_a^-/N_a^- (Figure 1, equation 6).

HIV Prevalence in TB Patients Compared With General Populations

A literature and database search was conducted for data on HIV prevalence in patients with TB (I_a^+/I_a) that could be matched with adult HIV prevalence (N_a^+/N_a) in the same region and time period. Equation 7 in Figure 1 (derived from equation 6) relates these 2 sets of data to IRR, which can then be estimated by maximum likelihood of fit. Equation 6 makes it clear that IRR depends on both relative MTB infection rates (m_a^+/m_a^-) and rates of progression to active disease (r_a^+/r_a^-). Since relative MTB infection rates are likely to vary from country to country, as may progression rates, IRR is expected to vary, too.[41] We attempted to identify regional IRR variations within limits set by the quality of data.

TB Attributable to HIV

The number of TB cases attributable to HIV is the number of extra cases resulting from the higher incidence rate among HIV-infected individuals, as defined in equation 8. We calculated both the number and the proportion of TB cases attributable to HIV.

Both of these quantities are uncontrolled for confounding. Confounding could be caused by any factor that is associated with HIV infection and has an independent effect on susceptibility to TB. One such factor is MTB infection (equation 6) since HIV and MTB infections share risk factors,[41] and MTB infection is a prerequisite for TB. Because we did not make adjustments for the likely positive association between MTB and HIV infections, attributable proportions are overestimated in this article. However, the data presently available do not warrant a more sophisticated approach.

PROPORTION OF TB CASES TREATED

Because the quality of treatment influences the duration of illness and the case fatality rate, WHO developed DOTS, a strategy for TB control comprising 5 elements: political commitment, diagnosis by direct smear microscopy, a mechanism to secure drug supplies, standardized recording and reporting, and use of standardized short-course chemotherapy with direct observation of treatment.[37] We used notifications to WHO to estimate the proportions of patients treated through DOTS; of patients treated outside DOTS programs (non-DOTS patients); and of patients untreated. We assumed that DOTS cases are

notified, but non-DOTS ones not necessarily so.[37] Patients treated in the private sector, of whom many receive nonstandard drug regimens,[42] are included among non-DOTS patients.

In our estimation of the proportions of HIV-positive and HIV-negative patients with TB who received TB treatment, the proportion of those who received TB treatment was taken to be independent of HIV status. This probably underestimated the proportion of HIV-associated TB patients who were left untreated in resource-poor settings.[16-20,22-26]

TB PREVALENCE AND HIV-ASSOCIATED TB TRANSMISSION

Estimates of TB prevalence were calculated from the product of incidence and the estimated duration of illness (equation 2), as previously described.[34] The exception was China, where the prevalence rate of smear-positive TB was measured directly by a survey carried out in 2000. We assumed that duration of illness differed when patients were smear positive or smear negative, HIV infected or not, treated through DOTS or other programs, or untreated (**Table 1**).[34]

The point prevalence of active, smear-positive disease is closely correlated with current TB transmission.[53,70] We used the HIV-infected proportion of prevalent smear-positive cases as a measure of the proportion of TB transmission events that were likely to be from HIV-positive patients. This assumes that the impact of HIV on TB infectivity is related to likelihood and duration of smear-positive disease, but that infectivity per unit of time is independent of HIV status.

TB DEATHS AND PROPORTION ATTRIBUTABLE TO HIV

The number of TB deaths is the product of incidence by the case fatality rate (CFR) (equation 4). Tuberculosis deaths include those of patients who die without ever being treated or while receiving treatment, as well as late deaths from relapse or posttuberculous complications.

A literature search was conducted for mortality during treatment; risk of TB relapse and late complications; and autopsy series for the cause of death in patients with TB according to HIV status, smear status, and regimen.[47,48,56-69,71-84] These data, along with treatment results reported to WHO and revised country-specific estimates calculated for 1997,[34] were used to estimate CFRs for patients with TB.[34] In nonindustrialized countries the estimated CFRs for pa-

Table 1. Global Values of Parameters Used in Estimations, With Ranges for Uncertainty Analysis and Sources*

Parameters	Value	Range	References
TB incidence rate ratio of HIV-infected to HIV-uninfected individuals			
Industrialized countries	60	41-77	43-46
Other countries	6.0	3.5-8.0	10, 36, 39, 47-52
Proportion of smear-positive TB cases			
Among HIV-uninfected TB cases	0.45	0.4-0.5	38
Among HIV-infected TB cases	0.35	0.3-0.4	9, 34, 53
Ratio of annual risk of MTB infection to incidence rate of smear-positive TB			
Countries where risk of infection is constant	50	30-70	54, 55
Countries where risk of infection is falling†	60	40-80	54, 55
Case fatality rate for untreated TB (deaths from TB)			
HIV uninfected, smear positive	0.7	0.55-0.75	54, 56, 57
HIV uninfected, smear negative	0.2	0.1-0.3	56, 58
HIV infected, smear positive, from TB	0.81	0.7-0.99	59-62
HIV infected, smear negative, from TB	0.76	0.63-0.9	59-62
Ratio of smear-negative to smear-positive case fatality rates for treated cases not infected with HIV	0.5	0.4-0.67	63-66
Ratio of HIV-infected to HIV-uninfected case fatality rates for treated TB cases			
Smear positive, DOTS	1.0	0.5-1.5	48, 67-69
Smear positive, non-DOTS	1.27	0.5-3	Assumed: no data
Smear negative, DOTS	2.0	0.5-3	48, 69
Smear negative, non-DOTS	3.3	2-10	Assumed: no data
Duration of illness, untreated TB cases, y			
HIV uninfected	2.0	1.5-2.5	54, 56, 57
HIV infected	0.5	0.25-1	59

Abbreviations: DOTS, the internationally recommended strategy for TB control; HIV, human immunodeficiency virus; MTB, *Mycobacterium tuberculosis*; TB, tuberculosis.

*Parameters in this table are those used for all countries; parameters with values specific to different countries or groups of countries are available at www.who.int/gtb/tbestimates or from the corresponding author.

†In industrialized countries, where risk of infection is falling steeply, infection prevalence was estimated from surveys intead.

tients treated through DOTS are lower than for patients treated through other programs because the DOTS strategy promotes rapid diagnosis and rifampicin-based drug regimens. In industrialized countries, where standard regimens for TB contain rifampicin and there is ready access to high-quality care for HIV, including highly active antiretroviral therapy (HAART), CFRs for TB were assumed to be the same whether or not treatment programs were formally classified as DOTS.[82-84]

HIV-Negative TB Patients

For smear-positive HIV-negative patients in nonindustrialized countries, estimated lifetime TB mortality rates, which included deaths from relapse and late complications, were 5% to 15% for patients treated through DOTS and 10% to 30% for patients treated through non-DOTS programs.[34,71,85] Case fatality rates for treated HIV-negative, smear-negative TB patients were assumed to be half of those for HIV-negative, smear-positive TB patients. For untreated patients with TB, we used CFRs of 70%

when they were smear positive and 20% when they were smear negative.[56-58]

HIV-Positive TB Patients

The survival rate of HIV-positive TB patients varies according to smear status and regimen. It is generally higher for smear-positive than for smear-negative patients,* and it is the lowest with rifampicin-based regimens.†

For smear-positive HIV-positive TB patients treated through DOTS in the WHO African Region we used a CFR of 10% for TB. This choice was based on the assumption that 30% of patients die during treatment, with 25% of these deaths due to TB, and that a further 2.5% will die from recurrent TB or later complications.[47,73,78,81,85,88-90] For non-DOTS patients CFRs are higher, at 38%; this assumes a mortality rate of 50% during treatment, with 50% of these deaths due

*References 47, 48, 60-63, 65-67, 69, 74-78, 80, 86, 87.

†References 47, 48, 63, 65-67, 69, 74-79, 81.

to TB, and a further 12.5% of patients dying after treatment because of late TB complications. These higher CFRs reflect the high risks of noncompliance with treatment, of treatment failure, of adverse drug reactions, and of disease recurrence with unsupervised and non–rifampicin-based regimens.[71-74,77,91]

Human immunodeficiency virus–positive patients with smear-negative TB are generally more severely immunosuppressed than those with smear-positive TB. Outcomes for them are poor, especially when drug regimens do not contain rifampicin.[65,72,74,77,92,93] For smear-negative patients treated through DOTS we used the same CFR of 10% as for smear-positive patients, assuming that the higher mortality rate during treatment is due to a higher risk of other opportunistic infections. We used a CFR of 50% for patients treated outside DOTS programs, assuming a mortality rate of 70% during treatment, with 50% due to TB, and a further 15% due to late TB deaths.[65,66,87,93-96] The mortality of untreated HIV-associated TB is extremely high, and we assumed that 90% and 95% of untreated smear-positive and smear-negative patients, respectively, would die within a few months, with 90% and 80% of deaths, respectively, due to TB. This gave CFRs of 81% and 76%, respectively.[22-24,26,61]

In established market economies, CFRs from TB in treated HIV-positive patients are lower than in sub-Saharan Africa. We assumed them to be 5% for smear-positive and 10% for smear-negative patients because more intensive medical care is available, including HAART.[82-84]

For nonindustrialized countries outside the WHO African Region, there are insufficient data on survival to base estimates on published reports. Instead, we assumed a constant ratio of HIV-positive to HIV-negative CFRs across regions, and derived HIV-positive CFRs from country-specific HIV-negative CFRs using the ratios shown in Table 1.

The overall CFR for each country was the weighted average of each category.

The number of deaths attributable to HIV is the number of extra TB deaths resulting from the higher TB incidence rates and CFRs in patients infected with the virus (equation 9). For each country and region, we calculated the proportion of all TB deaths in people with HIV infection, the proportion of those deaths attributable to HIV, and the proportion of HIV/AIDS deaths[36] that occurred primarily from TB (see below).

Classification of TB Deaths

Patients with TB who are infected with HIV are at high risk of dying from other opportunistic infections during the 6 to 8 months of TB treatment.[48,68,69,75,80] They die with TB rather than from TB.[97] Unlike the standard WHO cohort analysis of TB patient outcomes, our aim was to estimate deaths from TB.

According to the *International Classification of Diseases, 10th Revision (ICD-10)*, and as reflected in WHO's *World Health Report* for 2002,[98] deaths from TB in HIV-infected individuals are classified as AIDS deaths. However, because the timing of these deaths is influenced by TB incidence and could be delayed by effective TB treatment, they are included in this analysis and reported separately.

PREVALENCE OF MTB INFECTION AND MTB-HIV COINFECTION

The prevalence rate of MTB infection was derived from the annual risk of TB infection (back-calculated from incidence using equation 3), the rate of decline in the annual risk of TB infection,[55] and life expectancy at birth, as previously described.[34] Both annual risk of TB infection and life expectancy were taken to be independent of age, and MTB infection was assumed to be lifelong. In eastern and southern African countries, and in Eastern Europe, TB incidence has been increasing for about a decade.[37] Although the risk of infection has probably been increasing, too, we did not allow for this increase in calculating the prevalence of infection. This is because the necessary calculations are unduly complex in relation to the quality of data, and the increases may in any case be small.[27,99] The prevalence rate of MTB-HIV coinfection was calculated as the product of the prevalence rates of HIV and MTB infection; this calculation underestimates the coinfection rate if the 2 pathogens are associated via shared risk factors.

UNCERTAINTY ANALYSIS

Multivariate uncertainty analyses were used to evaluate the magnitude of the errors surrounding principal estimates of incidence, prevalence, and mortality. Ranges for parameter estimates were obtained from published literature or based on expert opinion (Table 1). When in doubt, we opted for greater uncertainty. Most input variables were assumed to be triangularly distributed, with the apex at the most likely value and lower and upper bounds fixing the width of the base. To determine the uncertainty surrounding point estimates, 1000 simulations were carried out by Latin hypercube sampling (@Risk; Palisade Decision Tools, Newfield, NY). When calculating the uncertainty in estimates for groups of countries (eg, global TB incidence), we distinguished

between parameters that varied globally (ie, in the same way across different countries during each simulation) and those that varied for each country independently. Fifth and 95th centiles were used as lower and upper bounds.

RESULTS

ESTIMATES OF REGIONAL IRRs FOR TB

Paired HIV prevalence data from patients with TB and general populations were obtained from previous publications,[10,42,43,46-51,98,99] the US Centers for Disease Control and Prevention,[45,46] the HIV database kept by the US Census Bureau,[102] and UNAIDS.[36]

Most data were from sub-Saharan Africa, as shown in **Figure 2**A and B. Data from countries outside Africa being insufficient to permit IRR estimations for each WHO global region, we divided the remaining data into data from nonindustrialized countries outside Africa and data from established market economies. Relevant data are shown in Figure 2C and D. The average for 6 groups of developing countries (3 of which are shown in Figure 2) was an IRR of 5.9, with group averages ranging from 3.5 to 8.0. On this basis, we have used an IRR of 6 for all nonindustrialized countries, with a range of 3.5 to 8 for uncertainty analysis.

However, the choice of an IRR of 6 greatly underestimates HIV prevalence for TB patients in industrialized countries.[42-44] We derived a better IRR estimate of 60 for the United States from national statistics on adult HIV prevalence and on HIV prevalence in TB patients aged 25 to 44 years (Figure 2D, 1998 data).[44,45] This estimate is the approximate midpoint of a lower bound (IRR=41) obtained by assuming that the 60% of TB patients tested for HIV infection in 1998 included all those who were HIV infected, and an upper bound (IRR=77) derived from the assumption that those tested were a representative sample of all patients with TB.[45] No other industrialized country monitors HIV prevalence in TB patients systematically, but single nationally representative estimates of HIV prevalence in TB patients have
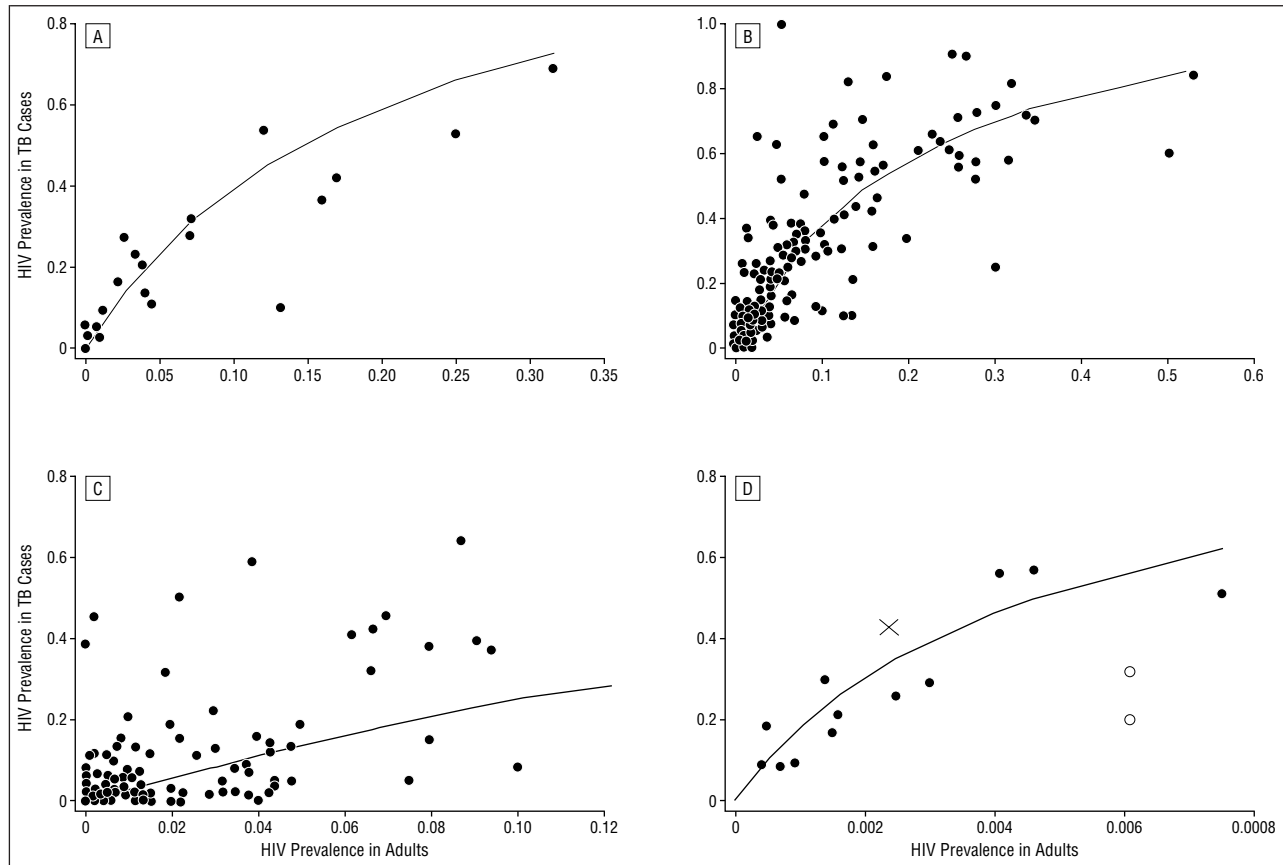
Figure 2. Human immunodeficiency virus (HIV) prevalence in patients with tuberculosis (TB) vs HIV prevalence in the adult (15-49 years old) population. A, Matched data where *x* and *y* variables were measured in the same study populations. B-D, Data were obtained from the same part of each country, but not necessarily the same populations. A and B, African countries. C, Nonindustrialized countries outside Africa. D, 12 states of the United States. Black circles indicate the weighted average for these states; open circles, lower and upper estimates of the national average of HIV prevalence in adult patients with TB; and ×, the weighted average for the 12 states. Regression lines in A-D were obtained from the maximum likelihood estimate of incidence rate ratio derived by fitting equation 6 of Figure 1 to data represented by the points. This assumes that incidence rate ratio is constant for each region.

been published for the United Kingdom (≥3.3%)[44] and Spain (15%).[43] When paired with general population estimates for HIV (0.11% and 0.6%, respectively),[36] these give IRRs of 31 and 29, respectively. In the absence of better information we used an IRR of 60 (range, 41-77), a ratio based on US data, for all industrialized countries.

ESTIMATES OF THE TB BURDEN AND THE IMPACT OF HIV

Here we present an overview of the TB burden that focuses on the impact of HIV. Statistics are given for the world as a whole; for each of the 6 WHO regions (**Table 2**); and for each of 22 high-burden countries with the largest numbers of cases, which together account for approximately 80% of the world's new TB cases (**Table 3** and **Figures 3**, **4**, and **5**). These 22 countries include 5 of the

15 countries with the highest incidence rates per capita (**Figure 6**). A list of estimates for all countries, together with updates, can be found at www.who.int/gtb/tbestimates, or obtained from the corresponding author.

There were an estimated 8.3 million (7.3-9.2 million) new TB cases in 2000, or 137 (121-151) per 100 000 population; 3.7 million (3.1-4.0 million) were smear positive, ie, 61 (51-66) per 100 000 population. Most new cases were in adults aged 15 to 49 years (5.4 million; 172/100 000). Among WHO regions, the African Region (essentially sub-Saharan Africa) had by far the highest annual incidence rates (290/100 000), while the South-East Asian Region had the largest number of cases (3.0 million). Half the new cases (4.4 million) were in the top 5 countries, all in Asia. Of 15 countries with the highest incidence rates per capita, 13 were in Africa (Figure 6).

The global burden of TB is growing. The total number of new TB cases increased at a rate of 1.8% per year between 1997 and 2000, and incidence rates per capita (all ages) at a rate of 0.4% per year. Case numbers increased much more quickly in the former Soviet Union (6.0% per year) and in the WHO African Region (6.4% per year).

The spatial and temporal variation in TB incidence is strongly associated with the prevalence of HIV infection (**Figure 7**). In 2000, 11% of all new TB cases in adults (612 000) occurred in persons infected with HIV, and 9% of all new TB cases were directly attributable to HIV. The prevalence rate of HIV infection in new TB cases varied markedly between regions and countries: from 1% in the WHO Western Pacific Region, to 14% in industrialized countries, and 38% in the WHO African Region; from under 1% in Afghanistan, Bangladesh,

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Table 2. Summary of TB-HIV Estimates for 2000 by WHO Regions

	Africa	Americas	Eastern Mediterranean	Europe	South-East Asia	Western Pacific	Global
Population, millions	640	832	485	874	1536	1688	6053
New cases of TB, all forms							
No. of cases, thousands	1857	382	587	468	2986	2031	8311
Incidence rate per 100 000 population	290	46	121	54	194	120	137
Change in incidence rate 1997-2000, %/y	3.9	−4.1	−1.4	2.8	−1.3	0.0	0.4
Prevalence of HIV in new adult cases (15-49 years old), %	38	5.9	1.8	2.8	3.2	1.3	11
Attributable to HIV, thousands	421	12	5.2	8.2	53	13	511
Attributable to HIV, % of adult cases	31	5.1	1.5	2.6	2.7	1.1	9
New smear-positive cases of TB							
No. of cases, thousands	785	169	264	210	1338	913	3679
Prevalence rate of SS+ TB, per 100 000 population	185	27	103	35	209	117	122
Proportion of prevalence of SS+ cases infected with HIV, %	7.5	1.0	0.2	0.5	0.3	0.1	1.4
Infection prevalence among adults							
Prevalence of MTB infection, %	31	15	27	14	46	32	30
Prevalence of MTB-HIV coinfection, %	2.7	0.1	0.1	0.0	0.3	0.0	0.4
Deaths from TB							
Deaths from TB, thousands	482	55	135	72	727	368	1839
Deaths from TB, per 100 000 population	75	6.6	28	8.3	47	22	30
Deaths from TB in HIV-positive adults, thousands	203	3.9	3.0	1.6	29	5.7	246
Adult AIDS deaths due to TB, %	12	4.1	11	10	8.1	17	11
TB deaths attributable to HIV, %	39	6.5	2.0	2.1	3.7	1.4	12

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; MTB, *Mycobacterium tuberculosis*; SS+, smear-positive sputum; TB, tuberculosis; WHO, World Health Organization.

China, and Indonesia, to 60% or more in South Africa and Zimbabwe. The proportions of cases directly attributable to HIV were necessarily smaller (eg, 31% in the WHO African Region).

The higher the prevalence of HIV infection among smear-positive TB cases, the greater the contribution of HIV to TB transmission. Our analysis suggests that 1.4% of all transmission events in 2000 were from HIV-infected, smear-positive TB cases. The proportion was higher than average in industrialized countries (2.3%), and much higher in the WHO African Region (7.5%).

The quality of TB treatment and the life expectancy of patients with TB govern the duration of illness, and hence the ratio of prevalence to incidence. We estimate that global TB prevalence was twice the incidence in 2000. The ratio varied by WHO region from 1.4 in the Americas and Europe, to 1.5 in Africa, and 2.4 in South-East Asian Region. This regional variation can be explained by regional differences in HIV prevalence rates and treatment practices, and by the local effect of large countries, such as South Africa (1.2) where high HIV prevalence rates reduces the average life expectancy of

TB patients, and India (2.5) where the poor quality of treatment extends the duration of disease. Our assumption of high access to effective treatment leads to a relatively low ratio for the European Region (1.4).

There were 1.84 million (1.59-2.22 million) deaths from TB in 2000, 226 000 attributable to HIV (12%; range, 8%-15%). The 246 000 (range, 167 000-298 000) TB deaths in adults infected with HIV represented 13% of all TB deaths and 11% of 2.3 million adult AIDS deaths, and most of these deaths (203 000) occurred in Africa. Across all countries, the aggregate CFR of HIV-infected TB cases was 40%. The number of people who died from TB was lower in the WHO African Region (482 000) than in South-East Asian Region (727 000), but the annual death rate was far higher (75 vs 47 per 100 000 population).

Tuberculosis death rates in high-burden countries varied dramatically, from 9 per 100 000 population in Brazil to 139 per 100 000 in South Africa. In these 2 countries overall CFRs for TB were 13% and 27%, respectively, and the difference was due largely to the difference in HIV infection rates.

Assuming lifelong MTB infection, and excluding effects on transmission of the recent increases in incidence in Africa and the former Soviet Union, 30% of the world population (1.8 billion people) carried MTB in 2000. Assuming no shared risk factors, the prevalence of MTB-HIV coinfection among adults aged 15 to 49 years was 0.36%, or 11.4 million people. Coinfection prevalence in adults aged 15 to 49 years equaled or exceeded 5% in 8 countries, all on the African continent. The largest numbers of coinfected adults were in South Africa (2.0 million), India (1.7 million), and Nigeria (0.9 million).

COMMENT

This analysis goes beyond previous TB-burden studies in defining the principal trends in TB incidence and in quantifying the impact of HIV. In the WHO African Region (largely sub-Saharan Africa), the impact of HIV is such that TB incidence rates are strongly associated with adult HIV prevalence. We calculated that 31% of adult TB cases were attributable to HIV in the entire African Region in 2000, about the same as determined by more direct methods for some
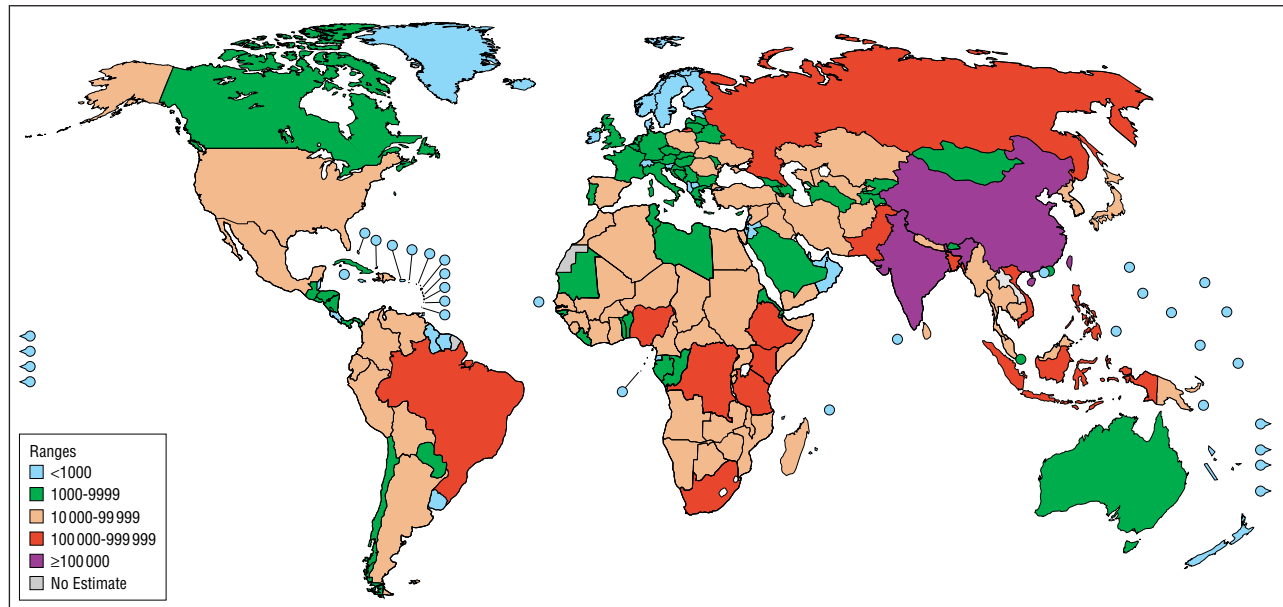
Table 3. Summary of TB-HIV Estimates for 2000 for 22 High-Burden Countries*

	India	China	Indonesia	Bangladesh	Nigeria	Pakistan	Philippines	South Africa	Russian Federation	Ethiopia	Democratic Republic of Congo
Population, millions	1009	1275	212	137	114	141	76	43	145	63	51
New TB cases, all forms											
No. of cases, thousands	1816	1437	582	325	261	245	230	220	183	178	150
Incidence rate per 100 000 population	180	113	274	237	230	173	304	509	126	284	294
Change in incidence rate 1997-2000, %/y	−1.3	0.0	−1.3	−1.3	2.4	−1.5	−1.0	8.7	5.9	2.9	2.9
HIV prevalence in new adult cases (15-49 years old), %	4.0	0.4	0.3	0.1	24	0.6	0.4	60	1.0	42	24
Attributable to HIV, thousands	41	3.1	0.8	0.2	38	0.7	0.5	80	1.1	45	22
Attributable to HIV, % of adult cases	3.4	0.4	0.2	0.1	20	0.5	0.3	50	0.9	35	20
New smear-positive cases of TB											
No. of cases, thousands	813	646	261	146	113	110	104	90	82	75	65
Prevalence rates of SS+ TB, per 100 000 population	201	122	325	214	192	181	232	219	88	186	185
Prevalence of SS+, HIV-positive cases, %	0.6	0.1	0.0	0.0	4.5	0.1	0.1	21	0.3	9.5	5.8
Infection prevalence among adults											
Prevalence of MTB infection, %	46	31	52	46	36	37	52	42	12	27	36
Prevalence of MTB-HIV coinfection, %	0.3	0.0	0.0	0.0	1.8	0.0	0.0	8.3	0.0	2.8	1.8
Deaths from TB											
Deaths from TB, thousands	453	268	146	79	76	65	44	60	33	47	36
Deaths from TB per 100 000 population	45	21	69	57	67	46	58	139	23	74	70
Deaths from TB in HIV-positive adults, thousands	24	1.4	0.5	0.1	23	0.5	0.2	38	0.4	21	11
Adult AIDS deaths due to TB, %	10	8.6	18	13	11	8.0	23	18	35	10	15
TB deaths attributable to HIV, %	4.8	0.5	0.3	0.1	28	0.7	0.5	59	1.2	41	28

	Vietnam	Kenya	United Republic of Tanzania	Brazil	Thailand	Myanmar	Zimbabwe	Uganda	Cambodia	Afghanistan	Mozambique
Population, millions	78	31	35	170	63	48	13	23	13	22	18
New TB cases, all forms											
No. of cases, thousands	143	138	117	114	86	78	76	75	75	69	48
Incidence rate, per 100 000 population	183	449	335	67	137	164	604	323	573	319	262
Change in incidence rate 1997-2000, %/y	−1.0	14	2.8	−3.9	−1.3	−1.3	3.9	0.3	2.0	−1.5	1.0
HIV prevalence in new adult cases, %	1.4	49	35	3.3	12	11	67	35	20	0.0	48
Attributable to HIV, thousands	1.0	41	25	1.8	5.1	4.8	31	16	7.7	0.0	14
Attributable to HIV, % of adult cases	1.2	41	29	2.8	10	9.1	56	29	17	0.0	40
New smear-positive cases of TB											
No. of cases, thousands	64	57	50	51	38	35	31	32	34	31	20
Prevalence rates of SS+ TB, per 100 000	96	253	207	46	101	115	282	187	548	310	124
Prevalence of SS+ HIV-positive cases, %	0.5	13	8.4	0.7	2.5	2.5	21	9.1	3.5	0.0	15
Infection prevalence among adults											
Prevalence of MTB infection, %	44	23	33	19	43	41	20	15	76	56	25
Prevalence of MTB-HIV coinfection, %	0.1	3.2	2.7	0.1	0.9	0.8	5.0	1.3	3.1	0.0	3.3
Deaths from TB											
Deaths from TB, thousands	19	35	27	15	13	19	16	19	16	20	13
Deaths from TB, per 100 000 population	24	115	77	8.8	21	40	130	82	121	92	70
Deaths from TB in HIV-positive adults, thousands	0.3	19	11	0.6	1.8	2.6	9.7	7.9	3.6	0.0	6.8
Adult AIDS deaths due to TB, %	12	12	11	3.2	3.0	6.2	7.5	8.1	30	0.0	9.8
TB deaths attributable to HIV, %	1.6	48	36	3.4	12	13	53	38	21	0.0	49

*See footnote to Table 2 for explanation of abbreviations.

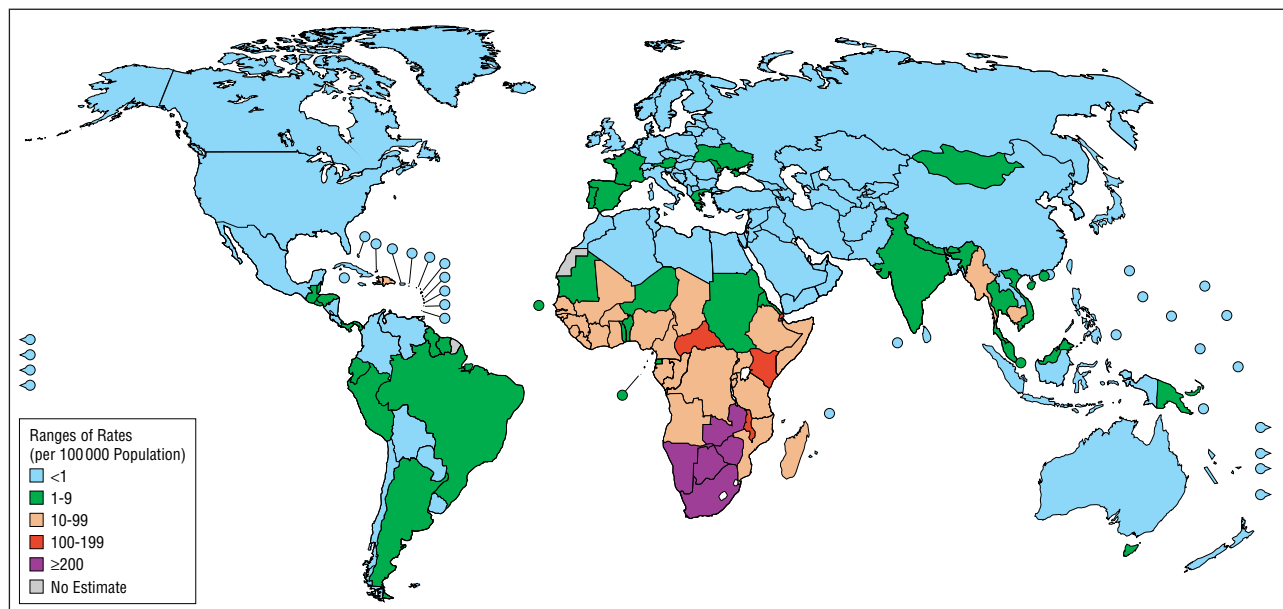**Figure 3.** Estimated numbers of tuberculosis cases by country in 2000.

Figure 4. Estimated numbers of human immunodeficiency virus–infected tuberculosis cases per 100 000 population (all ages) by country in 2000.

countries.[8] In the same region, HIV-infected cases were responsible for an estimated 7% of all TB transmission. The spread of HIV across sub-Saharan Africa is primarily responsible for driving the number of TB cases upwards at 6% per year, though we expect growth to slow as HIV epidemics peak—and there are signs that this is beginning to happen.[103] Some countries with high incidence rates have small populations, and are therefore not included among the rankings in Table 3, which are based on numbers of cases. However, TB is

clearly a major burden for these countries, many of which are in Africa.

Our results indicate that the HIV epidemic is exacerbating TB transmission, although on a case-by-case basis disproportionately few infections come from HIV-infected patients. This is because TB patients with HIV are less likely to be smear-positive than patients without HIV, and the duration of infectiousness is relatively brief in them because they have a relatively rapid progression of disease. Our results in this respect are qualitatively consistent with those of

surveys in Africa. These surveys show either no increase,[99] or relatively small increases,[27] in the annual risk of TB infection in children, despite a severalfold increase in national TB incidence rates over the same period.

Inevitably, the burden of MTB-HIV coinfection is increasing as HIV spreads. Coinfection prevalence rates have reached startlingly high levels in African countries such as Botswana, Zimbabwe, and South Africa. And although the proportion of people coinfected in Asian countries is typically of a lower order of magnitude, the ab-
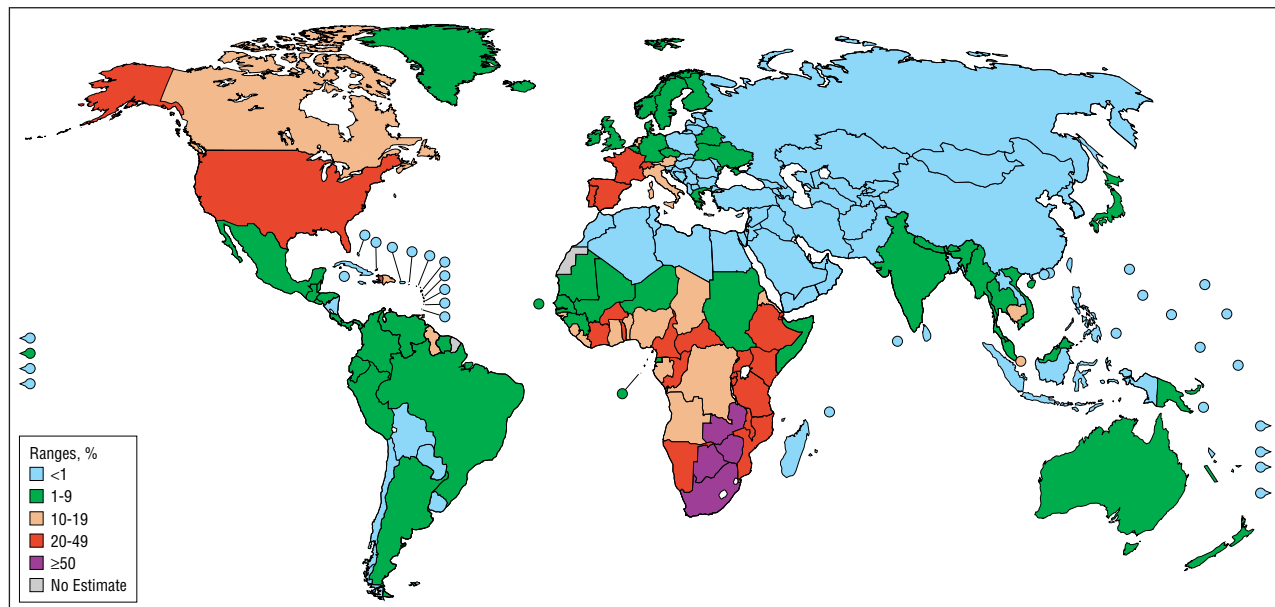
Figure 5. Proportions of adult tuberculosis cases attributable to human immunodeficiency virus by country in 2000.

Ranges, %
- <1
- 1-9
- 10-19
- 20-49
- ≥50
- No Estimate

solute number of coinfected people in Asia exceeds 2 million. Without interventions to treat HIV-induced immunosuppression, latent TB infection, or both, a high proportion of these coinfected individuals can be expected to develop active TB.[104] The estimates in this article suggest a lifetime risk of 30% to 40% for coinfected persons in Africa (assuming a mean survival time of 6 to 10 years after HIV infection). In this context, Brazil is still the only country with a large number of coinfected people (100 000), a policy of universal access to HAART, and therefore the potential to reduce the risk of HIV-related TB.[105,106]

Even in regions with low TB incidence, HIV has had a marked impact. For example, HIV prevalence rates in patients with TB are high in the United States, as are IRRs, and we estimate that 26% of TB cases were attributable to HIV. This is well above the attributable proportions calculated for Latin American and Asian countries that have higher prevalence rates of MTB infection and equal or higher HIV prevalence rates. There are at least 2 possible explanations for this. The first is that both HIV and MTB infections tend to be concentrated within the same subpopulations in countries where neither infection is generalized. In Spain, for example, both HIV and MTB infection and disease are strongly associated with intravenous drug use, and coinfection
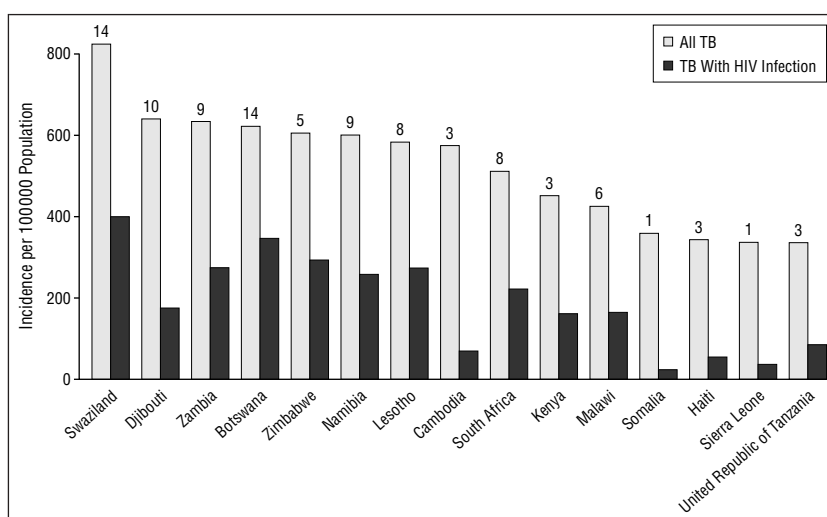
Figure 6. Fifteen countries with the highest estimated tuberculosis (TB) incidence rates per capita (all ages) and corresponding incidence rates of human immunodeficiency virus (HIV)–infected TB. Numbers above the bars are percentages of *Mycobacterium tuberculosis*–HIV coinfection.

rates within this behavioral group are extremely high.[107] In the United States, rates of both HIV and TB infections are disproportionately high in certain ethnic groups.[45,108] Nonrandom associations between HIV and MTB infections increase the likelihood of coinfection, further increasing the already high incidence rate of TB in HIV-infected individuals. The second possibility is that, unlike MTB-HIV–coinfected individuals, a relatively high proportion of HIV-uninfected MTB-infected people in low-incidence, industrialized countries are in the older age groups, and acquired their infections many

years ago, when TB transmission rates were higher than they are now. Most of these people develop TB at the low reactivation rate characteristic of long-standing infections, thereby increasing the difference between themselves and TB-HIV–coinfected individuals.[54]

Although the most alarming TB-HIV statistics are generally connected with Africa, the link between HIV and drug resistance could have greater epidemiological significance elsewhere. Multidrug-resistant TB (MDR-TB) has remained uncommon in most parts of Africa.[109] As HIV spreads into parts of Asia and

Eastern Europe where drug resistance is more firmly established, the number of persons infected with both HIV and MDR-TB is likely to increase.[109,110] As HIV generates a greater number of MDR-TB cases,[111,112] the frequency of drug resistance among new cases may increase. At the institutional level, HIV has been associated with epidemic MDR-TB transmission in a number of countries.[29-31] On a far larger scale, India has 1.7 million people coinfected with MTB and HIV, and a multidrug resistance rate of 2% to 5% among previously untreated individuals with TB.[109]

Even without the complication of drug resistance, high death rates are reported for patients treated for HIV-associated TB.[47,48,62,63,67,68,74,76-80] Deaths rates may be even higher, and it is possible that fewer than half the fatal TB cases are diagnosed before death.[22-26] The reality is that the proportion of TB deaths attributable to HIV (12%) is higher than the proportion of new TB cases (11%), and we estimate the overall CFR for HIV-related TB (in-

cluding undiagnosed cases) to be over 50% in many developing countries.

These calculations also imply that the contribution of TB to AIDS deaths is substantial: 11% of AIDS deaths are deaths primarily from TB. Even higher proportions, between 20% and 50%, have been found in autopsy studies, but these were based in high-incidence urban settings and may be unrepresentative.[22-24]

We stress that the calculations in this analysis, as in all other similar analyses, are subject to error. Our country and regional estimates were derived from a mixture of research and surveillance data and expert opinion, and the quality of the information varies from very high to very low. For this reason, we explored the variation around estimates using multivariate uncertainty analyses that aim to overstate rather than understate errors. Point estimates are commonly used to express the magnitude of the TB problem and its link with HIV, and the present article provides more statistics of this kind. However, it is crucial to appreciate that, for example, while the upper estimate of global TB incidence is roughly 25% greater than the lower estimate, for certain high-incidence countries lower and upper estimates differ by a factor of 2. Among countries ranked by incidence, Côte d'Ivoire, in 24th place, has only 5% more cases than Cameroon, in 30th place. Such rankings must therefore be used with great caution.

We were not able to carry out a full appraisal of uncertainty be-

cause some unknowns lie beyond the scope of formal, multivariate analyses. Thus, in using a single IRR value to estimate HIV prevalence in TB cases in developing countries, we did not account for the fact that IRR is likely to increase as an HIV epidemic matures in any country, and a higher proportion of HIV-infected people becomes immunosuppressed.[113] Moreover, our choice of dichotomous IRRs, set at 6 or 60, reflects the paucity of data in industrialized countries and elsewhere. There is weak (statistically nonsignificant) evidence for an IRR greater than 6 in some middle-income countries. From 22 observations in Latin America we obtained an IRR average of approximately 10, but with enormous variation (range, 0.6-412) between sites. We may therefore have underestimated the proportion of cases and deaths attributable to HIV in these countries, but the extent of any bias is presently unclear.

The IRR for TB has been measured directly in a number of cohort studies.[6,100,113-119] In Africa estimates vary from 4.9 to 26, although most are of limited precision because of a small number of HIV-negative cases.[100,113,117-119] Estimates in the present study are similar to estimates found in 2 large cohort studies: a relative risk of 7.1 in a population-based study in Malawi,[100] and an IRR of 4.9 among South African gold miners.[113] Outside Africa, IRRs of 10 and 14 were observed among American intravenous drug users with MTB infection[111] and Brazilian female prisoners,[116] respectively. However, it was previously noted that the population-based IRR would have to be many times higher than these estimates to account for the impact of HIV on TB in the United States.[120]

Most of the recent successes in TB control have been in countries with low rates of HIV infection such as China, Peru, and Vietnam.[37,121,122] Yet TB in HIV-infected patients is both treatable and preventable (**Table 4**).[1] Achieving TB control in populations with high HIV prevalence rates requires more than wide-scale implementation of the DOTS strategy.[128] There is urgent need to implement a strategy of extended
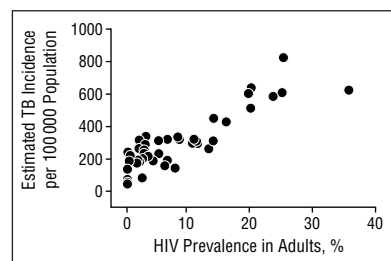
Figure 7. Estimated tuberculosis (TB) incidence in relation to human immunodeficiency virus (HIV) prevalence for 42 countries in the World Health Organization African Region.

Table 4. Interventions to Reduce TB Morbidity and Mortality Associated With HIV

Reducing risk of HIV infection
    Condom use and STD control[123-125]
    Availability of voluntary counseling and testing[126]
    Safe needles for injecting drugs[124]
Reducing TB transmission events
    Control of nosocomial and community TB transmission[127]
Reducing risk of TB among persons already infected with HIV
    Treatment of latent TB infection[1]
    Treatment of immunosuppression with antiretroviral drugs[82,105,106]
Reducing the case fatality rate of HIV-associated TB
    Prompt diagnosis[66]
    Use of rifampicin-containing short-course regimens[66]
    Concurrent administration of prophylactic cotrimoxazole[80]
    Treatment of immunosuppression with antiretroviral drugs[82,105,106]

Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis; STD, sexually transmitted diseases.

scope combining intensified TB case finding and treatment, HIV prevention, and the identification and treatment of latent MTB in coinfected individuals. Controlling HIV-related TB will require a massive global effort. The estimates in this article provide a measure of this challenge, and suggest ways to monitor the impact of efforts to control HIV-related TB.

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