ORIGINAL RESEARCH

Tuberculosis mortality in HIV-infected individuals: a cross-national systematic assessment

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Objective: Tuberculosis (TB) is a leading cause of death in human immunodeficiency virus (HIV)-positive individuals. We sought to compare mortality rates in TB/HIV co-infected individuals globally and by country/territory.

Design: We conducted a cross-national systematic assessment.

Methods: TB mortality rates in HIV-positive and HIV-negative individuals were obtained from the World Health Organization (WHO) Stop TB department for 212 recognized countries/territories in the years 2006–2008. Multivariate linear regression determined the impact of health care resource and economic variables on our outcome variable, and TB mortality rates.

Results: In 2008, an estimated 13 TB/HIV deaths occurred per 100,000 population globally with the African region having the highest death rate ([AFRH] ≥4% adult HIV-infection rate) at 86 per 100,000 individuals. The next highest rates were for the Eastern European Region (EEUR) and the Latin American Region (LAMR) at 4 and 3 respectively per 100,000 population. African countries' HIV-positive TB mortality rates were 29.9 times higher than non-African countries (95% confidence interval [CI]: 16.8–53.4). Every US$100 of government per capita health expenditure was associated with a 33% (95% CI: 24%–42%) decrease in TB/HIV mortality rates. The multivariate model also accounted for calendar year and did not include highly active antiretroviral therapy (HAART) coverage.

Conclusions: Our results indicate that while the AFRH has the highest TB/HIV death rates, countries in EEUR and LAMR also have elevated mortality rates. Increasing health expenditure directed towards universal HAART access may reduce mortality from both diseases.

Keywords: tuberculosis, HIV, antiretroviral therapy, mortality

Introduction

Tuberculosis (TB) and human immunodeficiency virus (HIV) are two devastating global infectious diseases. TB is one of the deadliest diseases of the 20th century and continues to claim millions of lives.[1–4] The global HIV epidemic also continues to claim many lives, despite the global scale-up of antiretroviral (ARV) therapy. In 2008, an estimated 33.4 million people worldwide were living with HIV, and 2.7 million were newly infected. More than 25 million people worldwide have died from HIV since the epidemic began.[5]

Immune-suppressed HIV-positive individuals are more likely to become co-infected with TB,[6] which is a leading cause of death in this population,[7] especially among those who reside in Sub-Saharan Africa.[8,9] The dual burden of TB and HIV infection increases the likelihood of dying compared with having either disease separately.[10–14] Previous studies have examined the effect of TB on mortality in HIV-infected individuals within

specific cohorts. For example, a recent study of TB patients in Nigeria found that 15.5% of HIV-positive individuals on treatment died, compared with 3.1% of HIV-negative individuals.[13] There remains a dearth of research on global TB mortality in HIV-positive individuals.

The purpose of this analysis was to investigate the global burden of TB incidence and mortality in people with HIV. Our objectives were to determine rates of TB mortality in HIV-positive individuals compared with HIV-negative individuals by World Health Organization (WHO) designated regions, and to assess the effect of health care resources and economic variables on reducing TB/HIV co-infection mortality.

Methods
Data sources
The estimated number of TB (all forms) deaths among HIV-positive and HIV-negative individuals, along with health care resources and economic data by country/ territory were gathered from our prospectively maintained Globally Accumulated health Indicator Archive (GAIA) of publicly accessible health statistics for the years 2006–2008. The last available data was from 2008. Source data on TB death rates and incidence per 100,000 general population and the proportion of HIV among TB incident cases originated from statistics produced by the WHO's Stop TB department. The 'Year', 'Region', and 'Percent of HIV-positive new pulmonary smear-positive cases cured' were obtained from WHO's Stop TB department. 'Percent HAART coverage' data were obtained from WHO's Towards Universal Access 2009 report.[15] 'GDP' (gross domestic product) in current international dollars (PPP, purchasing power parities), and 'Percent of women and men who received HIV testing in the last 12 months and know their results' were obtained from UNDATA.[16] Data for 'Number of AIDS deaths' were taken from UNAIDS.[5] 'Per capita government expenditure on health at average exchange rate (US$)' and 'Personal expenditure on health as % of total expenditure on health' (year 2006 only) were obtained from WHO's World Health Statistics 2009 report.[17] 'Average exchange rate' specifies the observed annual average rate at which a currency is traded in the banking system. All source data were publicly accessible through the Internet.

All 212 recognized countries and territories listed in the WHO annual TB reports were included and classified into regions based on WHO designation. Regional classification were as follows: AFR, African countries with a low HIV-infection rate (where 'low' refers to a generalized infection rate <4% in adults aged 15–49 years in 2004) (N = 20 in 2006–2008); AFRH, African countries with a high HIV-infection rate (N = 26 in 2006–2008); CEUR, Central European region (N = 10 in 2006–2008); EEUR, Eastern European region (N = 16 in 2006–2008); EMR, Eastern Mediterranean region (N = 17 in 2006–2008); EME, established market economies (N = 56 in 2006–2008); LAMR, Latin American region (N = 31 in 2006–2008); SEAR, South-East Asia region (N = 11 in 2006–2008); and WPR, Western Pacific region (N = 25 in 2006–2008). Mortality rates were available for all countries/territories for each year (2006–2008) and are presented per 100,000 people for each country/territory. Each country's total population size was taken from WHO's Stop TB department statistics. To assess the difference in magnitude of HIV-positive to HIV-negative TB deaths, a ratio of the TB death rate in HIV-positive over HIV-negative individuals was calculated using each country's mortality rates. A regional and global estimate of mortality rates was calculated for each year.

TB/HIV mortality model
The WHO produces estimates of TB incidence prevalence and mortality that are published in their annual TB report entitled, 'Global Tuberculosis Control: Surveillance, Planning, Financing'.[1–3] The most up-to-date estimates were based on data collected in 2009. The model involves creating a time-series of country-specific HIV-positive TB incidence distributions. These distributions incorporate two distributions of case fatality rates (in notified and nonnotified cases) among those co-infected with TB/HIV. Using simulations, the incidence rate distributions were multiplied with the case fatality rate distributions. A more detailed description of the changes to the modeling process from previously published 'Global Tuberculosis Control' reports can be found in an update to the 2009 report.[18]

Analyses
Pearson's correlation coefficient was used to assess the linear relationship between TB death rates in HIV-positive individuals and all explanatory variables aside from year, region, and highly active antiretroviral therapy (HAART) coverage for the years 2006–2008 and for the year 2008 only. All relationships were evaluated graphically, and proper transformations were applied to render them linear. HAART coverage had to be dichotomized. The magnitude and sign of the coefficient represented the strength and direction of the linear relationship. P-values were calculated to test whether the correlation coefficient was significantly

different from 0. Each test was based on different N values based on available data for each variable. 'GDP' was deemed redundant and therefore excluded from multivariate analyses. 'Percent of women and men who received HIV testing in the last 12 months and know their results' and 'Percent of HIV-positive new pulmonary smear-positive cases cured' were also excluded since they were poorly populated.

Countries and territories were re-categorized into African (AFR and AFRH) and non-African (CEUR, EEUR, EMR, EME, LAMR, SEAR, and WPR) for bivariate and multi-variate analyses. *T*-tests for the linear regression coefficients were used to assess regional, yearly, and HAART coverage differences in the TB/HIV mortality rates from 2006–2008, and similarly for region and HAART coverage in the year 2008 only. Separate multivariate linear regression analyses were then carried out to examine the effect of these variables on TB/HIV co-infection mortality for year 2006–2008 data and year 2008 data only. A total of 122 countries/territories were included for the year 2006–2008 analyses for a total of 346 observations. Observations could have been from year 2006, 2007, or 2008. A total of 114 countries/territories were included in the year 2008 analyses for a total of 114 observations. The primary outcome measure in multivariate analysis was HIV-positive TB mortality rate per 100,000 general population, which was natural log-scaled in order to nor-malize the distribution. The normality of the outcome was assessed using QQ-plots and Kolmogorov–Smirnov tests, both suggesting that the normal assumption was reasonable.[19] To standardize the scale of each explanatory variable's data, 'AIDS deaths' data were converted to a rate (number of AIDS deaths over the HIV-positive population). Percent HAART coverage was calculated by dividing the number of persons receiving HAART treatment at the end of 2006, 2007, and 2008 by the total estimated need for HAART in 2007.[15] In the 3-year model, repeated measures were accounted for using unstructured correlation matrices in the GENMOD procedure.[46] Health expenditure units were converted to the format 'current $100 US per capita'. Model selection was achieved through minimization of the Akaike information criterion (AIC)[20] and applying the additional constraint that all coefficient *P*-values be below 0.20.

Results

All 212 countries included in the analyses had a TB incidence rate, a value for the proportion of HIV among TB incident cases, and a TB/HIV mortality rate for years 2006–2008.

Table 1 is a global summary of all nine regions' HIV-associated average TB mortality and incidence rates per

100,000 people and proportion of HIV among TB incident cases for the years 2006–2008 with low and high uncertainty bounds. Of note, the AFR and AFRH had 13 and 86 HIV-positive TB mortality rates in 2008, respectively. AFRH had a HIV-positive TB mortality rate 2.2 times greater than its HIV-negative TB mortality rate in the same year. AFRH TB/HIV mortality rates were approximately 717 times higher than EME in 2008. Figure 1 shows TB/HIV mortality rates by region in 2008.

Bivariate analyses of the relationship between the explan-atory variables and TB death rates in HIV-positive individu-als for the years 2006–2008 revealed that 'AIDS death rate' showed a positive linear relationship with TB/HIV mortality rates over the three years (Pearson's correlation coefficient: 0.350) while 'Government health expenditure', 'GDP', and 'Percentage of men and women who know HIV test results' showed an overall negative linear relationship (Pearson's correlation coefficient: −0.741, −0.384, and −0.172, respec-tively). All explanatory variables were correlated to TB/HIV mortality rates overall ($P < 0.05$).

Table 2 shows the median and interquartile ranges for TB/HIV mortality rates by year and region. All regions' mortality rates differed significantly from each other in each year from 2006 to 2008 ($P < 0.001$). In those years, African (AFR and AFRH countries) mortality rates were significantly different from non-African countries ($P < 0.001$). The overall median HIV mortality rates in each of those three years also differed significantly from each other ($P = 0.002$).

The unadjusted and adjusted multivariable regres-sion analyses for 122 countries/territories for the years 2006–2008 are reported in Table 3. In unadjusted analyses, region, government health expenditure, proportion of per-sonal health expenditure out of total health expenditure, AIDS death rate, and HAART coverage were signifi-cantly associated with HIV-positive TB mortality rates ($P < 0.001$). Countries with HAART coverage <15% were associated with a TB/HIV mortality rate 3.6 times higher than countries with >15% coverage ($P = 0.0004$). In adjusted analyses, region and government health expenditure were independently associated with TB/ HIV mortality rates ($P < 0.05$). Year was marginally independently associated with TB/HIV mortality rates ($P < 0.2$). Compared with elsewhere in the world, HIV-positive TB mortality rates increased by 29.9 times in African countries ($P < 0.0001$). In 2008, HIV-positive TB mortality rates increased by 1% compared with 2006. A US$100 increase in government health expenditure per

Table I TB deaths and death rates stratified by region and year

Region	Year	TB incidence per 100,000			Population	Proportion of HIV among TB incident cases			TB death rates per 100,000						Rate ratio** HIV+/HIV-
		Estimate	Low	High		Estimate	Low	High	HIV+ Estimate	Low	High	HIV- Estimate	Low	High	
African region (AFR) (N = 20 in 2006–2008)	2006	204.59	164.49	245.51	170,586,570	0.12	0.10	0.16	12.01	6.35	21.90	39.72	14.99	76.13	0.30
	2007	209.12	167.60	250.95	174,785,114	0.12	0.09	0.15	11.46	6.18	20.60	40.38	15.39	78.83	0.28
	2008	213.75	171.68	256.50	179,051,557	0.13	0.10	0.16	12.62	6.93	22.17	42.15	15.99	81.09	0.30
African region[a] (AFRH) (N = 26 in 2006–2008)	2006	460.40	376.43	551.50	545,123,571	0.46	0.42	0.51	91.15	52.13	148.25	47.13	22.27	84.61	1.93
	2007	452.71	367.80	542.26	558,178,947	0.45	0.38	0.52	85.45	48.46	142.15	40.38	15.14	80.30	2.12
	2008	433.43	352.19	518.84	571,509,534	0.45	0.38	0.53	86.04	48.75	142.23	38.67	14.19	77.85	2.23
Central European region (CEUR) (N = 10 in 2006–2008)	2006	38.64	33.09	45.94	213,995,783	0.04	0.03	0.05	0.90	0.46	1.67	3.91	1.97	6.98	0.23
	2007	37.21	31.25	44.26	215,334,088	0.04	0.03	0.05	0.87	0.50	1.46	3.69	1.70	6.94	0.24
	2008	24.00	21.01	28.42	151,272,379	0.01	0.01	0.01	0.02	0.01	0.04	1.84	0.68	3.62	0.01
Eastern European region (EEUR) (N = 16 in 2006–2008)	2006	112.61	94.34	135.13	312,258,156	0.02	0.02	0.03	0.88	0.46	1.49	16.14	10.81	23.73	0.05
	2007	111.75	92.21	134.10	311,759,570	0.03	0.02	0.04	1.09	0.58	1.86	15.37	9.19	24.47	0.07
	2008	108.81	90.22	130.57	311,353,225	0.09	0.07	0.10	4.11	2.21	6.84	15.17	7.41	26.99	0.27
Eastern Mediterranean region (EMR) (N = 17 in 2006–2008)	2006	96.46	78.26	115.71	587,539,640	0.03	0.03	0.04	1.51	0.86	2.55	17.51	7.06	33.70	0.09
	2007	95.32	77.35	114.34	600,219,915	0.03	0.03	0.04	1.63	0.93	2.81	16.92	6.87	32.74	0.10
	2008	94.14	76.41	112.92	613,101,289	0.03	0.02	0.04	1.62	0.92	2.77	16.35	6.69	31.74	0.10
Established market economies (EME) (N = 56 in 2006–2008)	2006	25.37	21.48	29.36	1,031,155,682	0.09	0.07	0.11	0.16	0.08	0.26	6.79	2.84	12.78	0.02
	2007	25.53	21.62	29.56	1,038,114,516	0.06	0.05	0.07	0.11	0.06	0.19	7.80	3.10	14.94	0.01
	2008	24.98	21.71	28.94	1,044,902,687	0.08	0.06	0.10	0.12	0.06	0.20	9.23	3.57	17.76	0.01
Latin American region (LAMR) (N = 31 in 2006–2008)	2006	69.73	56.58	83.66	552,171,999	0.10	0.08	0.12	3.21	1.80	5.35	9.17	4.31	17.02	0.35
	2007	68.55	55.47	82.24	558,541,591	0.14	0.11	0.17	3.42	1.91	5.76	9.21	3.76	18.23	0.37
	2008	67.37	55.12	80.83	564,800,508	0.14	0.11	0.17	3.27	1.82	5.51	8.88	3.63	17.57	0.37
South-East Asia region (SEAR) (N = 11 in 2006–2008)	2006	180.14	144.60	216.17	1,625,442,338	0.03	0.03	0.04	2.25	1.26	3.75	26.72	11.17	52.81	0.08
	2007	178.99	145.17	214.79	1,648,538,041	0.03	0.03	0.04	2.21	1.23	3.75	26.72	11.28	52.73	0.08
	2008	188.13	151.79	225.76	1,736,733,772	0.05	0.04	0.06	3.01	1.68	5.06	28.19	11.86	55.78	0.11
Western Pacific region (WPR) (N = 25 in 2006–2008)	2006	131.42	108.22	158.85	1,550,251,943	0.03	0.02	0.03	1.65	0.95	2.76	17.36	7.00	34.33	0.1
	2007	123.80	104.27	149.74	1,562,259,393	0.02	0.01	0.02	0.58	0.32	1.02	16.38	6.64	32.28	0.04
	2008	120.02	100.98	145.25	1,574,223,530	0.09	0.07	0.11	1.68	0.95	2.85	15.35	6.16	30.40	0.11
World (N = 212 in 2006–2008)	2006	146.59	119.72	175.76	6,588,525,682	0.10	0.09	0.12	12.64	7.15	20.89	20.50	9.16	38.01	0.62
	2007	144.78	118.08	173.58	6,667,731,175	0.10	0.08	0.12	11.87	6.68	19.95	19.72	8.12	37.94	0.6
	2008	141.62	115.68	169.78	6,746,948,481	0.12	0.10	0.14	12.66	7.04	20.85	19.54	7.80	38.09	0.39

Notes: Estimates are presented as averages. Complete calculations for each country and region can be found in the Appendix; [a]African countries with a generalized HIV-infection rate (≥4% in adults aged 15–49 in 2004); [b]HIV-positive TB mortality rate over the HIV-negative TB mortality rate per 100,000 general population.
Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.
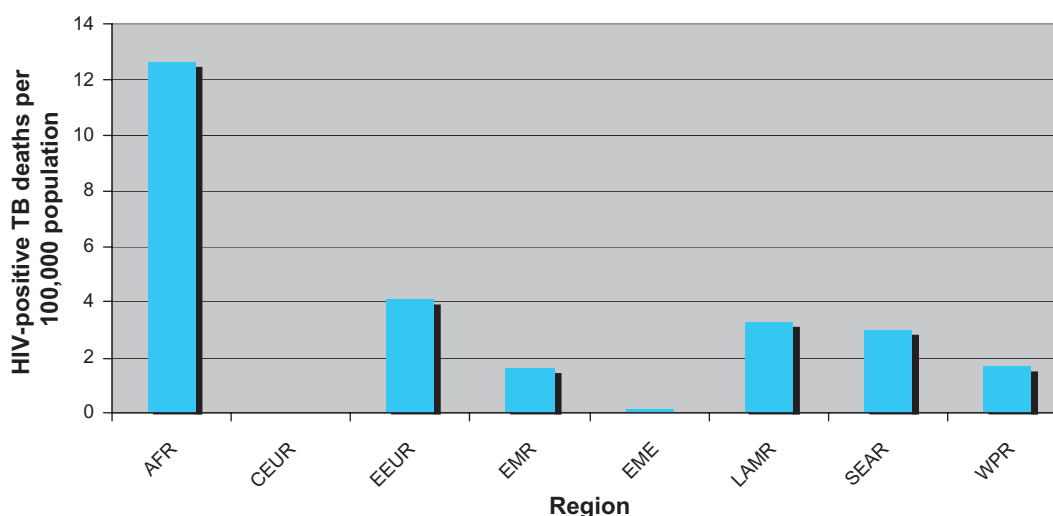
Figure 1 HIV-positive TB mortality rates by WHO-defined region, excluding African countries with high HIV-infection rate (AFRH), 2008. Africa-countries with low HIV-infection rate (AFR) (N = 20), Central European region (CEUR) (N = 10), Eastern European region (EEUR) (N = 16), Eastern Mediterranean region (EMR) (N = 17), established market economies (EME) (N = 56), Latin American region (LAMR) (N = 31), South-East Asia region (SEAR) (N = 11), and Western Pacific region (WPR) (N = 25). Total N = 212.
Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis; WHO, World Health Organization.

capita was associated with a 0.67 (95% confidence interval [CI]: 0.58, 0.76) unit increase TB/HIV mortality rates), in other words, every US$100 dollars spent on health expenditure per capita was associated with 33% reduction in mortality rates ($P < 0.0001$).

The unadjusted and adjusted multivariable regression analyses for 114 countries/territories in 2008 are reported in Table 4. In unadjusted analyses, region, government health expenditure, the proportion of personal health expenditure out of total health expenditure and the AIDS death rate were

Table 2 A comparison between TB/HIV mortality rates by region and year

Year	2006		2007		2008		All years	
Region	N[b]	Median (interquartile range)[c]	N[b]	Median (interquartile range)[c]	N[b]	Median (interquartile range)[c]	N[b]	Median (interquartile range)[c]
African region (AFR)	20	7.89 (1.25–15.90)	20	6.84 (0.52–16.37)	20	8.02 (1.97–18.25)	60	7.85 (0.70–16.51)
African region[a] (AFRH)	26	61.81 (32.30–124.59)	26	55.58 (31.13–117.34)	26	52.60 (29.70–104.59)	78	55.88 (31.13–117.34)
Central European region (CEUR)	10	0.00 (0.00–0.12)	10	0.00 (0.00–0.12)	10	0.00 (0.00–0.03)	30	0.00 (0.00–0.09)
Eastern European region (EEUR)	16	0.39 (0.24–1.25)	16	0.57 (0.39–1.86)	16	0.48 (0.27–2.24)	48	0.49 (0.29–1.88)
Eastern Mediterranean region (EMR)	17	0.05 (0.00–0.23)	17	0.07 (0.00–0.21)	17	0.05 (0.00–0.19)	51	0.05 (0.00–0.23)
Established market economies (EME)	56	0.05 (0.00–0.12)	56	0.03 (0.00–0.11)	56	0.03 (0.00–0.10)	168	0.03 (0.00–0.12)
Latin American region (LAMR)	31	1.13 (0.20–2.46)	31	1.06 (0.003–2.82)	31	1.15 (0.18–2.92)	93	1.13 (0.19–2.66)
South-East Asia region (SEAR)	11	0.05 (0.00–1.38)	11	0.06 (0.00–1.61)	11	1.36 (0.04–3.92)	33	0.08 (0.04–1.61)
Western Pacific region (WPR)	25	0.00 (0.00–0.25)	25	0.00 (0.00–0.15)	25	0.00 (0.00–0.53)	75	0.00 (0.00–0.27)
African (AFR + AFRH)	46	28.87 (8.33–64.74)	46	27.88 (6.78–64.68)	46	25.17 (8.03–64.85)	138	27.45 (8.01–64.74)
Non-African	166	0.10 (0.00–0.76)	166	0.08 (0.00–0.84)	166	0.08 (0.00–1.03)	498	0.09 (0.00–0.85)
TOTAL (all regions)	212	0.20 (0.004–3.33)	212	0.15 (0.00–3.14)	212	0.18 (0.00–3.43)	636	0.19 (0.00–3.25)

Notes: [a]African countries with a generalized HIV-infection rate (≥4% in adults aged 15–49 in 2004); [b]N represents the number of countries from each region with TB/HIV mortality rates; [c]Per 100,000 general population.
Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.

Table 3 Multivariate analyses of factors associated with HIV-positive TB mortality rate (year 2006–2008), N = 122 countries/territories (N = 115 countries in 2006, N = 117 countries in 2007, and N = 114 countries in 2008; total of N = 134 observations)

Variable		HIV-positive TB mortality rate[a]			
		Unadjusted relative risk		Adjusted relative risk	
		Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Region	Non-African	1 (–)	<0.0001	1 (–)	<0.0001
	African	76.17 (44.99–128.98)		29.93 (16.76–53.44)	
Year	2006	1 (–)	0.1908	1 (–)	0.0919
	2007	0.59 (0.27–1.3)		0.67 (0.38–1.18)	
	2008	0.91 (0.41–2.03)		1.01 (0.57–1.79)	
Government health expenditure at average exchange rate (logarithm of, US$100 per capita)		0.45 (0.39–0.51)	<0.0001	0.67 (0.58–0.76)	<0.0001
Personal health expenditure as a percentage of total health expenditure (%)		1.05 (1.03–1.07)	<0.0001	Not included in final model	
AIDS death rate (logarithm of)		1.34 (1.14–1.57)	0.0003	Not included in final model	
HAART coverage (%)	<15%	3.6 (1.76–7.35)	0.0004	Not included in final model	
	≥15%	1 (–)			

Note: [a]Natural log-scaled HIV-positive TB mortality rate.
Abbreviations: AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; TB, tuberculosis.

significantly associated with HIV-positive TB mortality rates ($P < 0.0001$).

In adjusted analyses, region and government health expenditure were independently associated with TB/HIV mortality rates ($P < 0.05$). The proportion of personal health expenditure out of total health expenditure was marginally independently associated with TB/HIV mortality rates ($P < 0.2$). Compared with elsewhere in the world, HIV-positive TB mortality rates were higher by 28.9 times in African countries ($P < 0.0001$). Increasing the proportion of personal health expenditure out of total health expenditure was associated with a 2% increase in TB/HIV mortality rates ($P = 0.1168$). A one hundred dollar increase in health expenditure per capita was associated

with a 0.73 (95% CI: 0.56, 0.95) unit increase in TB/HIV mortality rates, meaning, every one hundred US dollars spent on government health expenditure per capita was associated with a 27% reduction in mortality rates ($P < 0.05$).

Discussion

Our results indicate that in 2008, the highest TB mortality rates among HIV-positive individuals were in Africa, followed by the EEUR, LAMR, and SEAR. Multivariate analyses confirmed that Africa had significantly higher TB/HIV mortality rates than non-African regions. Our adjusted multivariate analysis for the year 2008 revealed an association between government health expenditure and lower

Table 4 Multivariate analyses of factors associated with 2008 HIV-positive TB mortality rate, N = 114 countries/territories

Variable		HIV-positive TB mortality rate[a]			
		Unadjusted relative risk		Adjusted relative risk	
		Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
Region	Non-African	1 (–)	<0.0001	1 (–)	<0.0001
	African	68.17 (30.26–153.57)		28.88 (11.71–71.21)	
Government health expenditure at average exchange rate (logarithm of, US$100 per capita)		0.44 (0.36–0.53)	<0.0001	0.73 (0.56–0.95)	0.0178
Personal health expenditure as a percentage of total health expenditure (%)		1.06 (1.03, 1.08)	<0.0001	1.02 (1.00–1.05)	0.1168
AIDS death rate (logarithm of)		3.72 (2.07–6.69)	<0.0001	Not included in final model	
HAART coverage (%)	<15%	1.47 (0.5–4.3)	0.9548	Not included in final model	
	≥15%	1 (–)			

Note: [a]Natural log-scaled HIV-positive TB mortality rate.
Abbreviations: AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; TB, tuberculosis.

TB/HIV mortality rates. Personal health expenditure was associated with higher TB/HIV mortality rates.

Regions known to have a high HIV prevalence were identified to have proportionally higher HIV-positive TB death rates in our results.[5] High TB incidence and mortality among HIV-positive individuals in the African region lends support to our findings that African countries bear the highest burden from both diseases.[1,8,9] However, non-African regions containing countries/territories known to have a high-burden of TB also had elevated TB/HIV mortality rates, suggesting that this burden is not limited to Africa.[1] The ratio (>1) of HIV-positive to HIV-negative TB mortality rates in the AFRH confirms the greater mortality risk in TB/HIV co-infected individuals.

Our study revealed that increasing per capita government health expenditure might lower TB/HIV mortality rates. Since developing regions in the world bear the highest TB/HIV burden, these regions would benefit the most from an increase in financial resources. There is a critical need for increased collaboration between HIV and TB management due to the overlapping impact of the diseases. For example, provider-initiated HIV-testing for TB patients in developing regions is poorly implemented,[21] even though this has been regarded as a key entry point into ARV therapy for undiagnosed individuals.[22–25] Furthermore, the "Three I's" principle of Isoniazid preventative therapy, Intensified TB case finding, and Infection control is widely viewed as an effective TB management strategy in HIV-infected individuals.[26–30] However, a lack of formal resources has compromised these initiatives, including basic laboratory services that detect HIV-associated TB, particularly smear-negative disseminated and drug resistant forms.[31,32] Before strategy becomes common practice, developing infrastructure and relevant operational details to supplement policy can ensure service delivery to individuals in need.[33]

In contrast, our findings also showed that increasing the proportion of personal health expenditure out of total health expenditure might increase TB/HIV mortality rates. Research on treatment-seeking behavior in the African setting revealed a lower proportion of patients actively seeking health care prior to requiring mandatory hospitalization when out-of-pocket payments were required.[34] Other studies have shown that out-of-pocket payments increase the likelihood of patients self-medicating or delaying treatment until their condition worsens.[35,36] This evidence suggests that countries with the highest TB/HIV burden may need to increase public health care expenditure.

TB/HIV health care services have been favored for expansion,[33] such as provider-initiated HIV testing and elements of the "Three I's" program which have been evaluated for cost-effectiveness.[37,38] Recently, increasing HAART coverage combined with early ARV treatment has been championed as a strategy to decrease TB incidence.[39] Yet, national budgets in high TB-burdened countries have allocated limited funds to support TB/HIV collaborations.[3] When examining the resources dedicated to each disease separately, HIV/AIDS health expenditure has expanded dramatically compared with other related sectors.[40] In stark contrast, financial resources dedicated to TB have been a fraction of that,[3,40] allocated mostly to DOTS (directly observed treatment, short-course), the recommended strategy for TB control.[41] Yet, DOTS has been questioned as an effective method for controlling the disease.[25,42] HAART coverage was significantly associated with lower TB/HIV mortality rates in bivariate analysis (2006–2008), but was not independently associated with these same rates in our multivariate model. This suggests that HAART coverage is dependent on public health expenditure. Given that HIV/AIDS and TB are both devastating infectious diseases, the striking disparity in TB to HIV funding not only calls for greater financial resources dedicated to combat TB, but also, more specifically, investment in programs such as widespread HAART distribution that may enhance treatment for both diseases.

There are limitations to consider with this analysis. Since our primary source of data was from WHO, our analyses relied on estimates based on their calculation methodology. Their source data were based on a dearth of documented mortality cases reported to them from each country/territory.[1–3,18] In a cohort study and literature review assessing the burden of TB, similar limitations may have led to an underestimation of TB deaths among the HIV-positive population.[4,43] In addition, many countries that do report vital statistics do not subcategorize an HIV death as being TB-associated. Moreover, TB incidence, a mortality model input, is not directly measureable and instead relies on obtaining expert opinion. No country has ever completed a national survey of TB incidence nor established criteria for verifying the reliability of a country's routine TB surveillance system. However, continued improvements have been made to WHO data collection methodologies from years past, such that the rise of HIV-testing in TB patients has contributed to a substantial increase in the number of reported TB deaths associated with HIV.[3,44,45] Additionally, not all countries/territories from a region may share the same mortality burden, since those with a high rate of TB/HIV mortality would have skewed regional average mortality rates.

A lack of comprehensive and complete country data on health care resources limited our bivariate and multivariate analyses. Since our sample size was restricted to countries with data available for every explanatory variable, our findings may not be applicable to all regions. Additionally, we were limited by a lack of recent statistics. For example, ARV treatment coverage for year 2008 was calculated using statistics from 2007 while health expenditure for 2008 was extrapolated from 2006 data. These findings underscore the need for more comprehensive and updated global health statistics.

Our findings on the global burden of TB mortality in HIV-positive individuals call for additional investigation in this area. This study is unique because it relates the worldwide burden of HIV-related TB mortality to the latest publicly available health indicator data. We found incomplete national health indicator data which limits thorough and ideal global analyses. Nevertheless, our study encourages further discussion on the issue of reducing these diseases' death toll, especially in developing nations. Finally, it is clear that there is an urgent need for increased public funding toward TB health care services that have long-term effectiveness in high HIV-prevalence settings. This funding should be directed towards developing widespread HAART distribution programs.

Contributors

CG Au-Yeung, A Anema, JSG Montaner, RS Hogg, and EJ Mills designed the study. CG Au-Yeung, S Kanters, E Ding, and P Glaziou performed the analyses. CG Au-Yeung prepared the first draft of the manuscript. EJ Mills supervised the study. All authors revised the manuscript critically for important intellectual content. All authors approved the final version for publication.

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