

TB Case Fatality Ratio by patient stratum for Spectrum TB

Definition

Case Fatality Ratio (CFR): “fraction of individuals with active TB that will die *due to TB*, during that TB episode, regardless of the duration of that episode”. This follows the definition used by Straetemans et al, and included deaths recorded as ‘with TB as contributory cause’, ‘attributable to TB’ or ‘related to TB’. [1]

Methods (see tables in appendix for details)

The CFR differs from the proportion of TB cases that die *during TB treatment*, which does not include TB cases not receiving TB treatment and does not take into account the substantial proportion of deaths among TB cases that are not due to TB, in particular in HIV positive, ART naïve individuals. [1,2]

The Spectrum TB model considers TB cases in HIV/ART and TB notification status strata (see Table). Here, we assume notification equals TB treatment status, although some non-notified cases could receive TB treatment outside the NTP, or not be reported. The population receiving ART is further divided in 2 strata, those on ART for more than 12 months before their TB episode, and those receiving ART for less than 12 months, or started on ART during TB therapy. Patients starting ART after TB treatment completion are considered as HIV positive, not on ART.

Within each stratum, the CFR does not differentiate by TB type or age group. Where data sources only provided mortality by sputum smear status, the CFR was calculated as a weighted average (see appendix). For HIV negative and HIV positive-ART naïve population strata, we made use of existing systematic literature reviews and WHO reports. For the ART receiving strata, a new review of existing data was carried out. Preliminary results from this review are used here where possible.

Note of caution

These CFR estimates were generated to fit the strata of Spectrum TB, and as such represent a strong simplification of TB epidemiology and mortality. The uncertainty that follows from such simplifications is, to an extent, captured by the wide ranges around the point estimates.

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TABLE: Case Fatality Ratios (CFRs) for Spectrum TB

Population stratum	CFR (range)	Sources	Explanation
HIV negative			
Not on TB treatment	0.43 (0.28- 0.53)	[2-4]	Appendix (A.1)
On TB treatment	0.03 (0.00-0.07)	[1]	Appendix (A.2)
HIV positive not on ART			
Not on TB treatment	0.78 (0.65-0.94)	[2]	Appendix (A.3)
On TB treatment	0.09 (0.03-0.15)	[1,2,5]	Appendix (A.4)
HIV positive, on ART for less than one year before TB episode			
Not on TB treatment	0.62 (0.39-0.86)	Data from review + assumptions	Appendix (A.5)
On TB treatment	0.06 (0.01-0.13)	Data from review + assumptions	Appendix (A.6)
HIV positive, on ART for one year or more before TB episode			
Not on TB treatment	0.49 (0.31-0.70)	Assumptions	Appendix (A.7)
On TB treatment	0.04 (0.00-0.10)	Assumptions	Appendix (A.8)

References

1. Straetemans M, Glaziou P, Bierrenbach AL, Sismanidis C, van der Werf MJ (2011) Assessing tuberculosis case fatality ratio: a meta-analysis. PLoS One 6: e20755.
2. Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, et al. (2003) The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch Intern Med 163: 1009-1021.
3. Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ (2011) Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. PLoS One 6: e17601.
4. WHO (2012) Global Tuberculosis Report 2012 - Annex 1: Methods used to estimate the global burden of disease caused by TB. Geneva: WHO - Stop TB department.
5. Mukadi YD, Maher D, Harries A (2001) Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. AIDS 15: 143-152.

Appendix: calculation for CFRs

Table A.1: HIV negative, not on TB treatment

Point estimate	Smear positive: 70%, Smear negative: 20% agreement between [2] and [3] No confidence interval given in Tiemersma et al. [3] Proportion smear positive: 45% [2] Value = $(0.7*0.45)+(0.2*0.55) = 0.43$
Lower bound	Lower bound of estimate of CFR: smear positive: 55%, smear negative 10% [2] Lower bound of estimated proportion smear positive: 40% [2] Value = $(0.55*0.4)+(0.1*0.6) = 0.28$
Upper bound	Upper bound of estimate of CFR: smear positive: 75%, smear negative 30% [2] Upper bound of estimated proportion smear positive: 50% [2] Value = $(0.75*0.5)+(0.3*0.5) = 0.53$
Notes	This range overlaps with not high income country estimate in WHO 2012 report [4]

Table A.2: HIV negative, on TB treatment

Point estimate	Directly taken from systematic review of Straetemans et al [1] Value = 0.03
Lower bound	Directly taken from systematic review of Straetemans et al [1] Value = 0.0
Upper bound	Directly taken from systematic review of Straetemans et al [1] Value = 0.07
Notes	Straetemans et al. use identical definition as this document. The studies quoted in the Mukadi 2001 paper [5] (which reviewed papers from high HIV prevalence settings), were considered in the Straetemans review. The WHO 2012 report estimates a higher CFR for this population (in not high-income countries): 0.07 (SD=0.03). [4]

Table A.3: HIV Positive, not on ART, not on TB treatment

Point estimate	CFR in smear positive: 81%, Smear negative: 76% [2] Proportion smear positive: 35% [2] Value = $(0.81*0.35)+(0.76*0.65) = 0.78$
Lower bound	Lower bound of estimate of CFR: smear positive: 70%, smear negative 63% [2] Lower bound of estimated proportion smear positive: 30% [2] Value = $(0.70*0.3)+(0.63*0.7) = 0.65$
Upper bound	Upper bound of estimate of CFR: smear positive: 99%, smear negative 90% [2] Upper bound of estimated proportion smear positive: 40% [2] Value = $(0.99*0.4)+(0.9*0.6) = 0.94$
Notes	

Table A.4: HIV positive, not on ART, on TB treatment

Point estimate	Directly taken from systematic review of Straetemans et al [1] Value = 0.09
Lower bound	Directly taken from systematic review of Straetemans et al [1] Value = 0.04
Upper bound	Directly taken from systematic review of Straetemans et al [1] Value = 0.15
Notes	We acknowledge that this value seems low, but it is supported by the data: <ul style="list-style-type: none"> - The range in Straetemans et al. [1] overlaps with the one used by Corbett et al [2]. - The range in Straetemans et al. is unaffected if only studies from Sub Saharan Africa are considered. - The Mukadi et al. review [5] showed a wider range of values, but considered deaths <u>during TB treatment</u>. <p>There is no existing estimate for this population by WHO. In the 2012 report. It suggests an assumed CFR of 0.50 for all HIV positive TB cases (not on ART), but does not specify a CFR estimate for HIV positive TB cases, not on ART, receiving TB treatment.</p>

Table A.5: HIV positive, on ART for less than 1 year before TB episode, not on TB treatment

Point estimate	<p>Assumption: ART will reduce the impact of HIV on mortality due to TB. So the difference between the HIV negative and HIV positive, ART naïve population, is reduced by a factor (see notes)</p> <p>Difference in CFR: $0.78-0.43=0.35$ Relative mortality: 0.55 (see notes) Value: $0.43+0.35*0.55=0.62$</p>
Lower bound	<p>As for point estimate, but with lower limits in each category</p> <p>Difference in CFR: $0.65-0.28=0.37$ Relative mortality: 0.3 (see notes) Value: $0.28+0.37*0.3=0.39$</p>
Upper bound	<p>As for point estimate, but with upper limits in each category</p> <p>Difference in CFR: $0.94-0.53=0.41$ Relative mortality: 0.8 (see notes) Value: $0.53+0.41*0.8=0.86$</p>
Notes	<p>The relative mortality due to TB in HIV infected individuals is based on a preliminary analysis of the review data on the impact of ART on TB mortality <u>during TB treatment</u>, and assumptions about the impact of ART on the proportion of those deaths that are due to TB. There is insufficient data to allow a direct estimate of the relative reduction (because of receiving ART) of deaths <u>due to TB</u>, and there is no mortality data on TB cases not receiving TB treatment in the ART era.</p> <p>Data: 0.22 = Relative mortality <u>during TB treatment</u> if on ART less than 1 year before TB diagnosis, or started on ART during TB treatment [PRELIMINARY RESULTS REVIEW] 0.75 = proportion of deaths during TB treatment <u>not due to TB</u> [2]</p> <p>Assumptions: 0.5 = relative reduction following ART initiation in proportion of deaths during TB treatment <u>not due to TB</u> The same reduction in relative mortality applies to TB cases not receiving TB treatment</p> <p>Calculation of relative mortality deaths due to TB: Before ART: $1-75\%=25\%$ of deaths due to TB: So in cohort of 100, <u>25 died due to TB</u></p> <p>After ART: $1-22\%=88\%$ reduction in deaths. Out of all deaths, $75\%*0.5=37.5\%$ are not due to TB. Out of 22 deaths, $22*0.375=8$ are not due to TB, leaving <u>14 dead due to TB</u>.</p> <p>Relative deaths <u>due to TB</u> in this stratum: $14/25=0.55$, i.e. 55%.</p> <p>Given the large uncertainty in the assumptions made, a wide confidence interval is applied: 55% (30% - 80%)</p>

Table A.6: HIV positive, on ART for less than 1 year before TB episode, on TB treatment

Point estimate	<p>The same approach was taken as in table A.5</p> <p>Difference in CFR: $0.09-0.03=0.06$ Relative mortality: 0.55 (see notes) Value: $0.03+0.06*0.55=0.06$</p>
Lower bound	<p>As for point estimate, but with lower limits in each category</p> <p>Difference in CFR: $0.04-0.00=0.04$ Relative mortality: 0.3 (see notes) Value: $0.00+0.04*0.3=0.01$</p>
Upper bound	<p>As for point estimate, but with upper limits in each category</p> <p>Difference in CFR: $0.15-0.07=0.08$ Relative mortality: 0.8 (see notes) Value: $0.07+0.08*0.8=0.13$</p>
Notes	<p>The same calculation as shown in table A.5</p>

Relative deaths due to TB in this stratum: 55% (30% - 80%)
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Table A.7: HIV positive, on ART for 1 year or more before TB episode, not on TB treatment

Point estimate	See notes. A further reduction of deaths due to TB was applied to the values in table A.5 (using values in table A.1 as reference) Difference in CFR: $0.62-0.43=0.19$ Relative mortality: 0.33 (see notes) Value: $0.43+0.19*0.33=0.49$
Lower bound	As for point estimate, but with lower limits in each category Difference in CFR: $0.39-0.28=0.11$ Relative mortality: 0.25 (see notes) Value: $0.28+0.11*0.25=0.31$
Upper bound	As for point estimate, but with upper limits in each category Difference in CFR: $0.86-0.53=0.33$ Relative mortality: 0.5 (see notes) Value: $0.53+0.33*0.5=0.70$
Notes	The review of TB mortality in patients on ART yielded insufficient data to allow data based calculations for this stratum. An assumption was made about the further reduction in deaths due to TB, that prolonged ART would further reduce (by two thirds) the difference between HIV negative and HIV positive individuals receiving ART for less than a year: $0.33 =$ relative mortality. Confidence interval 0.25 – 0.50

Table A.8: HIV positive, on ART for 1 year or more before TB episode, on TB treatment

Point estimate	See notes. A further reduction of deaths due to TB was applied to the values in table A.6 (using values in table A.2 as reference) Difference in CFR: $0.06-0.03=0.03$ Relative mortality: 0.33 (see notes) Value: $0.03+0.03*0.33=0.04$
Lower bound	As for point estimate, but with lower limits in each category Difference in CFR: $0.01-0.00=0.01$ Relative mortality: 0.25 (see notes) Value: $0.00+0.01*0.25=0.00$
Upper bound	As for point estimate, but with upper limits in each category Difference in CFR: $0.13-0.07=0.06$ Relative mortality: 0.5 (see notes) Value: $0.07+0.06*0.5=0.10$
Notes	The review of TB mortality in patients on ART yielded insufficient data to allow data based calculations for this stratum. As stated in table A.7, a relative mortality was assumed: $0.33 =$ relative mortality. Confidence interval 0.25 – 0.50