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Effect of tuberculosis on the survival of HIV-infected men in a country with low TB incidence

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Abstract

Evidence regarding the effect of tuberculosis disease (TB) on HIV disease progression at the population level remains inconclusive. We estimated the effect of incident TB on time to acquired immunodeficiency syndrome (AIDS)-related death, using a marginal structural Cox model. Between 1984 and 2005, 2,882 HIV-infected men in the Multicenter AIDS Cohort Study contributed 21,914 person-years while followed for a median of 5.4 years. At study entry, the median CD4 cell count and HIV-1 RNA viral load were 533 cells/mm³ (interquartile range [IQR], 365 – 737) and 12,953 copies/ml (IQR, 2,453 – 48,540), respectively. This study was performed in a setting with a modest exposure to HAART; 8,295 of 23,801 (35%) person-years were followed during the HAART era. Fifteen men incurred incident TB, yielding a TB incidence of 7 (95% confidence interval [CI]: 4, 14) per 10,000 person-years, and 1,072 died of AIDS-related causes. Accounting for potential confounders, including CD4 cell count and viral load, the hazard of AIDS-related death was 2.4 times larger for the person-time with TB, compared to the person-time without TB (95% CI: 1.2, 4.7). Results underscore the importance of avoiding TB by using preventive interventions, such as treatment of latent TB infection, particularly in populations with a large prevalence of HIV/TB co-infected individuals.

Evidence regarding the effects of tuberculosis disease (TB) on the progression of human immunodeficiency virus (HIV) disease at the population level remains inconclusive [1]. An inverse-variance-weighted pooled estimate of data on 22,296 HIV-infected men and women with 11,044 deaths in eight papers published during the last decade [2-9] suggests that TB is associated with a slight increase in the risk of death of HIV-infected individuals, with a summary relative risk of 1.1 (95% confidence interval [CI]: 1.0, 1.2). However, the analytical approaches used in those studies may have underestimated a harmful effect of TB on mortality [10]. Specifically, controlling confounding due to HIV stage by stratifying on time-varying markers of immunosuppression, such as CD4 cell count [7-9] may have provided, at best, only estimates of the effects of TB on mortality that are not mediated through such markers. Using appropriate analytic methods [11,12] that allow estimation of direct and indirect effects, we recently reported a four-fold increase in mortality associated

with TB in HIV-infected women [10]. Here we estimate the effect of incident pulmonary and extra-pulmonary TB on AIDS-related mortality in a large prospective cohort of HIV-infected men.

Methods

Study population

The Multicenter AIDS Cohort Study (MACS) [13] is an ongoing prospective study of HIV-1 infection among men in four US cities: Baltimore/Washington DC, Chicago, Pittsburgh, and Los Angeles. Beginning in 1984, the MACS enrolled 2,884 HIV-1 seropositive and 4,089 HIV-1 seronegative homosexual men, 622 of whom subsequently seroconverted. Participants undergo semiannual physical examinations and provide specimens for laboratory measurements, including lymphocyte subset counts by flow cytometry at NIAID certified labs [14] and plasma HIV-1 RNA viral load by reverse transcriptase-polymerase chain reaction (Roche Molecular Systems, Branchburg, New Jersey) with a lower limit of detection of 50 copies/ml. Participants also respond to interviewer-administered questionnaires about medical history and health care utilization, including use of antiretroviral therapy (ART). The present study is limited to 2,882 (82%) of the 3,506 (=2,884+622) MACS participants who were HIV-infected by November 2005. Excluded were HIV-infected men with incomplete data for the variables of interest at study entry ($n = 163$, 5%), a history of TB at study entry ($n = 4$, <1%), and those with only a single study visit ($n = 457$, 13%).

Endpoint ascertainment

Men were followed from the first MACS semiannual visit at which they were HIV-infected (hereafter known as study entry) until the first of: death, dropout, or the date of analysis on 5 November 2005. Follow-up methods used in the MACS to ascertain vital status have been described elsewhere [15]. The endpoint of interest was AIDS-related mortality. Deaths were classified as AIDS-related if a) a cause listed on the death certificate was an AIDS-defining condition (ADC) according to the 1993 CDC classification system for HIV infection [16] or b) "AIDS" or "HIV" was listed as a cause, without further specification.

Assessment of TB

The exposure of interest was confirmed incident TB; defined as the first self-report of pulmonary or extra-pulmonary TB at any semiannual visit six months beyond study entry, confirmed by culture, cytology, or clinical or radiological assessment. Incident TB was modeled as a time-varying binary indicator that was set to zero for all men at study entry and changed to one after the onset of TB.

Assessment of covariates

Age, CD4 cell count, and viral load at study entry were modeled as time-fixed continuous covariates; white ethnicity was modeled as a time-fixed binary indicator. During follow up, CD4 cell count and nadir, as well as viral load and peak, were modeled as time-varying continuous covariates. Also during follow up, time-varying binary indicators were created for: (1) anti- *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis (i.e., trimethoprim, co-trimoxazole, dapsone, or aerosolized pentamidine), (2) use of ART, (3) HIV-related symptoms (i.e., persistent fever or night sweats), (4) incident PCP, (5) incident *Mycobacterium avium* complex disease (MAC), and (6) the remaining clinical ADCs excluding TB, PCP and MAC. To assure a correct time sequence, all time-varying covariates were lagged one visit and therefore measured before TB onset. To allow a flexible (e.g., curvilinear) relation between continuous covariates and incident TB, censoring

and mortality, we used restricted cubic splines with knots at the 5th, 35th, 65th and 95th percentiles.

Statistical analysis

In the presence of time-varying confounders affected by previous TB, conventional methods (i.e., stratification or regression) may at best provide an estimate of the direct, rather than the total, effect of TB on mortality. In particular, TB may induce faster HIV replication [17] or subsequent reductions in CD4 cell counts [18] which, in turn, predict higher mortality [19] and also, lower CD4 cell counts or higher HIV RNA levels predict TB. As in women [10], we used a marginal structural Cox proportional hazards model, which appropriately controls for time-varying confounding by weighting each man's person-time contribution proportionally to the inverse probability of his observed incident TB status, estimated as a function of the history of time-varying covariates [11,20]. Assuming no unmeasured confounding, no informative censoring, and no model misspecification, this method allows estimation of the total effect of TB on mortality. The marginal structural model included as time-fixed regressors: white ethnicity, study entry date, age, CD4 cell count, and viral load; as well as time-varying regressors: incident TB and follow up time. The inverse probability weights were stabilized and taken as the product of incident TB and censoring weights [11,21]. Inverse probability-of-incident-TB weights were estimated using time-fixed regressors: white ethnicity, study entry date, and CD4 cell count; as well as time-varying regressors: CD4 cell count, CD4 nadir, log₁₀ viral load, peak viral load, PCP, anti-PCP prophylaxis, other ADC, HIV symptoms, and follow up time. Inverse probability-of-censoring weights were estimated using time-fixed regressors: white ethnicity, study entry date, CD4 cell count, log₁₀ viral load, ART, and PCP-prophylaxis; as well as time-varying regressors: incident TB, CD4 cell count, log₁₀ viral load, PCP, MAC, other ADC, HIV symptoms, and follow up time. The mean (standard deviation) of the final weights was 1.00 (0.10). To ameliorate the impact of extremely influential values, weights were censored at the first and 99th percentiles, namely, 0.64 and 1.6 [22].

The effect of TB on mortality was measured by the hazard ratio (HR), and the 95% CI was used as a measure of precision. Robust CI [23] were used for the marginal structural model [21]. Neither a plot of log-log survival by time nor an interaction between incident TB and follow-up time (robust p for homogeneity = 0.86) suggested a strong departure from the proportional hazards assumption. Analyses were performed with SAS version 9 (SAS Institute, Cary, NC).

Results

At study entry, the 2,882 HIV-1 infected men had a median age of 35 years (interquartile range [IQR], 31 – 41), 71% were white, 17% African-American, and 10% Hispanic. Median calendar year was 1985 (IQR, 1985 – 1988), median CD4 count was 533 cells/mm³ (IQR, 365 – 737), and median viral load was 12,953 copies/ml (IQR, 2,453 – 48,540) (Table 1). 2,201 of 2,882 (76%) men entered into the analysis before 1 January 1996, the date when highly active ART became widely available.

During follow-up, 0.5% (15 of 2,882) incurred incident TB, yielding an incident TB rate of 7 (95% CI: 4, 14) per 10,000 person-years. Culture or cytology confirmed 12 of 15 TB reports and either radiological or clinical criteria confirmed the remaining three; 10 TB reports were pulmonary and five were extra-pulmonary.

Accounting for ethnicity, calendar year, CD4 cell count, and viral load at study entry, the average CD4 count over follow-up was 341 for the person-time with TB and 471 cells/mm³ for the person time without TB; Δ = 130 cells/mm³ (95% CI: 68, 192). The average viral

load over follow-up was 4.5 log₁₀ copies/ml for the person-time with TB and 3.8 log₁₀ copies/ml for the person-time without TB; $\Delta = 0.76$ log₁₀ copies/ml (95% CI: 0.39, 1.1). Presence of HIV-related symptoms (HR = 3.6, 95% CI: 1.0, 13), PCP (HR = 1.9, 95% CI: 0.5, 7.1), or anti-PCP prophylaxis (HR = 3.5, 95% CI: 0.9, 15) were each associated with incident TB.

From November 1984 to November 2005, the 2,882 men were followed for a median of 5.4 years (IQR, 2.4 – 11). 1,202 of 2,882 (42%) men died and 502 (17%) were lost to follow-up before the date of analysis. 12 of 15 men with TB died, all from AIDS-related causes. Among the 1,190 deaths occurring in 2,867 men without TB, 1,060 were from AIDS-related causes other than TB.

In the marginal structural model (which accounts for the confounding variables listed in the methods and footnote of Table 2), the hazard of AIDS-related death was 2.4 times (95% CI: 1.2, 4.7) larger for the person-time with TB compared to the person-time without incident TB (Table 2). Adjustment for the same set of time-fixed and time-varying covariates using a standard Cox proportional hazards model yielded a HR for AIDS-related mortality of 1.3 (95% CI: 0.6, 2.5), which is similar to the summary of prior evidence; whereas standard adjustment for only time-fixed covariates yielded a HR of 3.0 (95% CI: 1.6, 5.9).

Discussion

In this prospective study of 2,882 HIV-1 infected men, we estimated incident TB to be associated with more than a two-fold increase in the hazard of AIDS-related mortality. This finding is in contrast to a summary HR of 1.1 based on prior evidence [2-9]. However, using statistical methods similar to those used in prior work we also produced a HR of 1.3, which we believe is an underestimate of the true association due to over-control for biomarkers on the pathway between TB and mortality. Moreover, prior work treating TB and covariates as time-fixed in analyses [3,7,8] has borne out a positive association between TB and mortality; we also replicate this result, but believe the 3-fold HR overestimates the true association because of uncontrolled time-varying confounding. Our primary result of greater than a two-fold association does not block pathways between TB and mortality nor does it allow uncontrolled time-varying confounding by measured variables.

We previously reported a four-fold increase in the hazard of AIDS-related death (95% CI: 1.2, 14) associated with TB among HIV-1 infected women [10]. Here, in men, we found TB is associated with a 2.4 times (95% CI: 1.2, 4.7) increase in the hazard of AIDS-related death. This is 40% ($=1 - 2.4/4$) smaller than the HR reported for women, but the fact that each CI overlaps to include the other HR [24] cautions against over-interpreting this difference. Assuming that random error explains the difference in the two HR, the resultant inverse-variance-weighted average of HR for AIDS-related mortality is 2.7 times greater (95% CI: 1.5, 4.9) with incident TB in HIV-1 infected men and women.

The present work has limitations. First, we could not examine whether highly active ART modifies the effect of incident TB on mortality because only three men incurred TB during the era of highly active ART. Second, the small number of men who incurred TB precluded the determination of whether CD4 cell count at study entry modifies the effect of incident TB on mortality [8]. Third, as with all observational studies, it is possible that unmeasured or residual confounding exists. Specifically, rather than a cause of mortality, incident TB may be a surrogate for immune suppression not captured by CD4 cell count and viral load, or a marker of social or behavioral conditions that predispose to increased mortality. In such a scenario, intervening on TB would not decrease subsequent mortality.

The strengths of this work include relatively modest attrition given 21 years of follow up and comprehensive use of active and passive methods for determining vital status, making emigrative selection bias and information bias due to misclassification of endpoints, respectively, unlikely explanations for the findings. Additionally, serial collection of blood specimens allowed longitudinal control for markers of HIV disease progression. In conclusion, among these HIV-1 infected men, incident TB was associated with more than a two-fold increase in the hazard of AIDS-related mortality. Assuming a causal association, these results underscore the importance of avoiding TB by using preventive interventions, such as treatment of latent TB infection, particularly in populations like those in Sub-Saharan Africa, with a large prevalence of HIV/TB co-infected individuals.

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References

1. Del Amo J, Malin AS, Pozniak A, De Cock KM. Does tuberculosis accelerate the progression of HIV disease? Evidence from basic science and epidemiology. *AIDS*. 1999; 13:1151–1158. [PubMed: 10416517]
2. Perneger TV, Sudre P, Lundgren JD, Hirschel B. Does the onset of tuberculosis in AIDS predict shorter survival? Results of a cohort study in 17 European countries over 13 years. *AIDS in Europe Study Group. Bmj*. 1995; 311:1468–1471. [PubMed: 8520334]
3. Leroy V, Salmi LR, Dupon M, Sentilhes A, Texier-Maugein J, Dequae L, et al. Progression of human immunodeficiency virus infection in patients with tuberculosis disease. A cohort study in Bordeaux, France, 1988–1994. The Groupe d'Epidemiologie Clinique du Sida en Aquitaine (GECSA). *Am J Epidemiol*. 1997; 145:293–300. [PubMed: 9054232]
4. Mocroft AJ, Lundgren JD, d'Armino Monforte A, Ledergerber B, Barton SE, Vella S, et al. Survival of AIDS patients according to type of AIDS-defining event. The AIDS in Europe Study Group. *Int J Epidemiol*. 1997; 26:400–407. [PubMed: 9169177]
5. Petruckevitch A, Del Amo J, Phillips AN, Johnson AM, Stephenson J, Desmond N, et al. Disease progression and survival following specific AIDS-defining conditions: a retrospective cohort study of 2048 HIV-infected persons in London. *Aids*. 1998; 12:1007–1013. [PubMed: 9662196]
6. Del Amo J, Petruckevitch A, Phillips A, Johnson AM, Stephenson J, Desmond N, et al. Disease progression and survival in HIV-1-infected Africans in London. *Aids*. 1998; 12:1203–1209. [PubMed: 9677170]

7. Whalen CC, Nsubuga P, Okwera A, Johnson JL, Hom DL, Michael NL, et al. Impact of pulmonary tuberculosis on survival of HIV-infected adults: a prospective epidemiologic study in Uganda. *Aids*. 2000; 14:1219–1228. [PubMed: 10894287]
8. Badri M, Ehrlich R, Wood R, Pulerwitz T, Maartens G. Association between tuberculosis and HIV disease progression in a high tuberculosis prevalence area. *Int J Tuberc Lung Dis*. 2001; 5:225–232. [PubMed: 11326821]
9. Del Amo J, Perez-Hoyos S, Hernandez Aguado I, Diez M, Castilla J, Porter K. Impact of tuberculosis on HIV disease progression in persons with well-documented time of HIV seroconversion. *J Acquir Immune Defic Syndr*. 2003; 33:184–190. [PubMed: 12794552]
10. Lopez-Gatell H, Cole SR, Hessol NA, French AL, Greenblatt RM, Landesman S, et al. Effect of tuberculosis on the survival of women infected with human immunodeficiency virus. *Am J Epidemiol*. 2007; 165:1134–1142. [PubMed: 17339383]
11. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000; 11:550–560. [PubMed: 10955408]
12. Petersen ML, Wang Y, van der Laan MJ, Bangsberg DR. Assessing the effectiveness of antiretroviral adherence interventions. Using marginal structural models to replicate the findings of randomized controlled trials. *J Acquir Immune Defic Syndr*. 2006; 43 1:S96–S103. [PubMed: 17133209]
13. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR Jr. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. *Am J Epidemiol*. 1987; 126:310–318. [PubMed: 3300281]
14. Calvelli T, Denny TN, Paxton H, Gelman R, Kagan J. Guideline for flow cytometric immunophenotyping: a report from the National Institute of Allergy and Infectious Diseases, Division of AIDS. *Cytometry*. 1993; 14:702–715. [PubMed: 8243200]
15. Dudley J, Jin S, Hoover D, Metz S, Thackeray R, Chmiel J. The Multicenter AIDS Cohort Study: retention after 9 1/2 years. *Am J Epidemiol*. 1995; 142:323–330. [PubMed: 7631636]
16. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep*. 1992; 41:1–19.
17. Lederman MM, Georges DL, Kusner DJ, Mudido P, Giam CZ, Toossi Z. Mycobacterium tuberculosis and its purified protein derivative activate expression of the human immunodeficiency virus. *J Acquir Immune Defic Syndr*. 1994; 7:727–733. [PubMed: 8207650]
18. Toossi Z. Virological and immunological impact of tuberculosis on human immunodeficiency virus type 1 disease. *J Infect Dis*. 2003; 188:1146–1155. [PubMed: 14551885]
19. Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med*. 1997; 126:946–954. [PubMed: 9182471]
20. Cole SR, Hernan MA, Margolick JB, Cohen MH, Robins JM. Marginal structural models for estimating the effect of highly active antiretroviral therapy initiation on CD4 cell count. *Am J Epidemiol*. 2005; 162:471–478. [PubMed: 16076835]
21. Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology*. 2000; 11:561–570. [PubMed: 10955409]
22. Cole SR, Hernan MA, Anastos K, Jamieson BD, Robins JM. Determining the effect of highly active antiretroviral therapy on changes in human immunodeficiency virus type 1 RNA viral load using a marginal structural left-censored mean model. *Am J Epidemiol*. 2007; 166:219–227. [PubMed: 17478436]
23. Lin DY, Wei LJ. The Robust Inference for the Cox Proportional Hazards Model. *Journal of the American Statistical Association*. 1989; 84:1074–1078.
24. Schenker N, Gentleman JF. On judging the significance of differences by examining the overlap between confidence intervals. *American Statistician*. 2001; 55:182–186.

Abbreviations

ADC	AIDS-defining condition
AIDS	Acquired immunodeficiency syndrome
CD4	CD4-positive lymphocytes
CI	Confidence interval
ART	Antiretroviral therapy
HIV	Human immunodeficiency virus
HR	Hazard ratio
IQR	Interquartile range
PCP	Pneumocystis jiroveci pneumonia
RNA	Ribonucleic acid
TB	Tuberculosis disease
MACS	Multicenter AIDS cohort study

Table 1
Characteristics of 2,882 HIV-infected men at study entry and averaged over a median of 5.4 years of follow up. Multicenter AIDS Cohort Study, 1984 – 2005

Characteristic: *	Study Entry (2,882 men)	Averaged over Follow-up (45,729 semiannual visits)
Age, years	35 (31, 41)	41 (35, 47)
Race, % (n) †		
White	71 (2,059)	80 (36,558)
African-American	17 (501)	12 (5,278)
Hispanic	10 (284)	7 (3,353)
Other	1 (38)	1 (540)
CD4 cell count, cells/mm ³	533 (365, 737)	438 (267, 633)
CD4 cell count category, % (n)		
< 50	2 (52)	5 (2,468)
50 – 199	7 (211)	12 (5,517)
200 – 249	14 (398)	19 (8,842)
350 – 499	22 (638)	22 (10,254)
500 +	55 (1,583)	41 (18,648)
HIV-1 RNA, copies/ml	12,953 (2,45, 48,540)	10,172 (1,020, 45,620)
HIV-1 RNA category, % (n)		
< 400	14 (408)	20 (9,191)
400 – 9,999	31 (902)	30 (13,559)
10,000 +	55 (1,572)	50 (22,979)

* Median and quartiles unless otherwise noted

† Percentages may not add up to 100 due to rounding

Table 2
Effect of incident TB on all-cause mortality among 2,882 HIV-infected men followed for a median of 5.4 years. Multicenter AIDS Cohort Study, 1984 – 2005

Person-years of follow-up		AIDS-related mortality (1,072 deaths)		
		Number of Deaths	Hazard Ratio	95% Confidence Interval
Marginal structural model *				
No TB-disease	21,873	1,060	1	
TB-disease	41	12	2.4	1.2, 4.7
Unadjusted				
No TB-disease	21,873	1,060	1	
TB-disease	41	12	6.0	3.1, 11
Baseline adjusted †			3.0	1.6, 5.9
Fully adjusted ‡			1.3	0.6, 2.5

* White ethnicity, age, calendar year, and CD4 cell count and viral load at study entry were included as regressors. Time-varying CD4 cell count, nadir of CD4 cell count, viral load, peak viral load, PCP, anti-PCP prophylaxis, fever or sweats, MAC, and non-TB ADC were used to compute weights for inverse probability of TB, and censoring (see text)

† Adjusted for all time-fixed variables listed above

‡ Adjusted for all time fixed and time-varying variables listed above