Published in final edited form as:
AIDS. 2012 March 27; 26(6): 770–773. doi:10.1097/QAD.0b013e328351f6b8.

Prevalent tuberculosis and mortality among HAART initiators

Daniel Westreich[1], **Matthew P. Fox**[2,3], **Annelies Van Rie**[4], and **Mhairi Maskew**[3]

[1]Department of Obstetrics and Gynecology and Duke Global Health Institute, Duke University, Durham NC

[2]Department of Epidemiology, School of Public Health, Boston University, Boston MA and Center for Global Health and Development, Boston University, Boston MA

[3]Health Economics and Epidemiology Research Office, Johannesburg, South Africa and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[4]Department of Epidemiology, University of North Carolina, Chapel Hill, USA

Abstract

The effect of tuberculosis on mortality in people initiating highly active antiretroviral treatment (HAART) remains unclear; here, we strengthened a previous cohort analysis. Multivariate Cox proportional hazards models were used to assess the association of baseline tuberculosis and time to all-cause mortality among HAART initiators. In reanalysis, treatment for tuberculosis at time of HAART initiation remained unassociated with increased risks of all-cause mortality, with adjusted hazard ratios ranging from 1.00 to 1.09.

In 2010, Straetemans et al. published a meta-analysis of the effect of tuberculosis on mortality in HIV positive people[1]. In a sub-analysis of six studies, they found an overall hazard ratio of 1.08 (95% confidence limits 0.91, 1.27) for the effect of TB on all-cause mortality in HIV-positive individuals where at least 50% of the cohort reported use of HAART. Nonetheless the authors concluded that insufficient data were available to draw strong conclusions about the effect of TB on all-cause mortality among individuals receiving HAART. The largest contributor to that sub-analysis was a 2009 report in this journal by Westreich et al., which examined the effect of prevalent pulmonary tuberculosis being treated at time of HAART initiation on time to mortality among patients all of whom were initiating HAART in Johannesburg, South Africa[2]. We found an adjusted (weighted) hazard ratio of 1.06 (95% confidence limits 0.75, 1.49) in these individuals, indicating no increased risk of death among those with prevalent tuberculosis at time of HAART initiation.

While our findings were in line with that of at least some other studies[1, 3–5], our study had two, related limitations. First, there was a high rate of loss to follow-up in our study; second, we had a low recorded incidence of mortality. We attempted to account for these effects[2] by using inverse probability of censoring weights[6]. However, inverse probability of censoring weights rely on assumptions that data are censored (missing) at random[7–9], an assumption which, similar to an assumption of no uncontrolled confounding[10], is not verifiable. Since the publication of our report, additional mortality information has been obtained from the South African National Death Registry[11] for a

Correspondence: Daniel Westreich, PhD, Duke University Medical Center, Department of OB/GYN, Box 3084 Med Center, Durham, NC 27710, daniel.westreich@duke.edu.

DISCLOSURE

The authors have no financial, consultant, institutional or other conflict of interest to declare.

subset of patients in the database. This allowed an opportunity to enhance our analysis with better mortality data[11], extend follow-up by 18 months, and check the validity of modeling assumptions and overall results from the original publication in three analyses.

Details on TB screening, treatment for TB and HIV at the Themba Lethu Clinic and South Africa more generally, and on clinical care and research procedures of the clinic has been described in detail [2, 11, 12]. In the *original cohort analysis*, we examined impact of being in treatment for TB at baseline (initiation of HAART) on time to all-cause mortality among all patients initiating HAART at the Themba Lethu Clinic between 1 April 2004 and 31 March 2007[11]. In the *updated analysis*, we used the same set of individuals and same time-frame, but updated vital status outcomes and dates of death. In the *extended analysis*, we extended follow-up (including opportunity for death) until 1 October 2008, allowing up to 18 additional months of follow-up in all subjects. In the original report[2] we found no changes in estimates of effect when using inverse probability of censoring weights[6] compared to traditional adjusted Cox proportional hazards models, so these analyses used traditional Cox models, adjusted for confounding by factors as in the original report[2].

Results from reanalysis are summarized in the Table. In the *original cohort*, the 7,512 subjects in the database experienced a recorded 298 deaths, 74 (25%) of which were in subjects exposed to prevalent TB. There were 1,423 subjects recorded as lost to follow-up. The crude hazard ratio (HR) was 1.68 (95% CL 1.29, 2.19), and the adjusted was 1.07 (95% CL 0.80, 1.44). These are nearly identical to the originally reported results[2].

In the *updated cohort*, among 7,512 subjects there were 494 deaths recorded, of which 115 (23%) occurred in prevalent TB cases; and there were 882 subjects recorded as lost to follow-up. The crude HR was 1.55 (95% CL 1.26, 1.91), and the adjusted was 1.00 (95% CL 0.80, 1.26).

In the *extended cohort*, among 7,512 subjects there were 666 deaths, of which 155 (23%) occurred in prevalent TB cases. There were 1,460 subjects recorded as lost to follow-up. The crude HR was 1.62 (95% CL 1.35, 1.94), and the adjusted HR was 1.09 (95% CL 0.90, 1.33).

This reanalysis of data from a large cohort of individuals initiating HAART in South Africa reaffirms earlier findings[2] that patients receiving active treatment for tuberculosis at HAART initiation were not at higher risk of death compared to those not being treated for TB, demonstrating that these findings were robust to more-complete collection of previously missing data. One limitation of this reanalysis is that Fox et al. were able to obtain vital registration data for only 42% of subjects presumed lost to follow-up [11]. Thus, more than 50% of those lost to follow-up may have in fact not had their vital status validated. Nonetheless, reanalysis only among those patients with valid medical ID numbers (those whose status would have been evaluated by Fox et al. if they had been presumed lost to follow-up; about 64% of all patients) yielded very similar results, with HR=0.90 (95% CL 0.68, 1.20) in the updated cohort and HR=1.01 (95% CL 0.79, 1.29) in the extended cohort.

High rates of patients becoming lost to follow-up are an unfortunate reality in both the practice and analysis of large-scale HIV clinical cohorts[13], and the missing data which results from these losses can be a significant challenge to the validity of the results of analyses in those cohorts[14–16]. When that missing data comprises missing outcome values which are caused by the true value of the missing outcomes, not only are biased effect estimates likely [17], but the bias cannot generally be eliminated through analytic approaches such as inverse probability of censoring weights or multiple imputation[17] (although these approaches[18] as well as others[14–16] may help reduce bias). However,

this bias will *not* be introduced when the true effect is null[17]; as this re-analysis demonstrates, the true effect is likely to be null, and our original report was likely unbiased.

In conclusion, our analysis substantially strengthens the evidence that TB treatment at time of HAART initiations is not associated with increased risk of mortality on HAART.

Acknowledgments

FUNDING

Clinical activities at the Themba Lethu Clinic are supported by the South African National and Gauteng provincial Department of Health, with additional funding support from the United States President's Emergency Plan for AIDS Relief (PEPFAR) in a grant by USAID to Right to Care and the Institution (674-A-00-08-00007-00).

DW received funding from the National Institute for Health NIAID grant 2P30-AI064518-06 Duke Center for AIDS Research. MPF received funding from the National Institute of Allergy and Infectious Diseases (NIAID) (K01AI083097).

The opinions expressed herein are those of the authors and do not necessarily reflect the views of NIH, NIAID, USAID, PEPFAR, the University of North Carolina, Boston University or Duke University.

The authors gratefully acknowledge the dedicated staff of the Themba Lethu Clinic and all clinic patients for allowing us to use their clinic data for research purposes.

References

1. Straetemans M, Bierrenbach AL, Nagelkerke N, Glaziou P, van der Werf MJ. The effect of tuberculosis on mortality in HIV positive people: a meta-analysis. PLoS ONE. 2010; 5:e15241. [PubMed: 21209936]
2. Westreich D, MacPhail P, Van Rie A, Malope-Kgokong B, Ive P, Rubel D, et al. Effect of pulmonary tuberculosis on mortality in patients receiving HAART. AIDS. 2009; 23:707–715. [PubMed: 19279444]
3. Stringer JS, Zulu I, Levy J, Stringer EM, Mwango A, Chi BH, et al. Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. Jama. 2006; 296:782–793. [PubMed: 16905784]
4. Zachariah R, Fitzgerald M, Massaquoi M, Pasulani O, Arnould L, Makombe S, et al. Risk factors for high early mortality in patients on antiretroviral treatment in a rural district of Malawi. Aids. 2006; 20:2355–2360. [PubMed: 17117022]
5. Dronda F, Sobrino P, Hernandez-Novoa B, Caro-Murillo AM, Montero M, Iribarren JA, et al. Response to HAART in treatment-naive HIV-infected patients with a prior diagnosis of tuberculosis or other opportunistic infections. Curr HIV Res. 2011; 9:229–236. [PubMed: 21631429]
6. Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics. 2000; 56:779–788. [PubMed: 10985216]
7. Rubin DB. Inference and Missing Data. Biometrika. 1976; 63:581–592.
8. Little, RJA.; Rubin, DB. Statistical Analysis with Missing Data. New York: John Wiley; 1987.
9. Heitjan DF, Basu S. Distinguishing "Missing at Random" and "Missing Completely at Random". The American Statistician. 1996; 50:207–213.
10. Hernán MA. A definition of causal effect for epidemiological research. J Epidemiol Community Health. 2004; 58:265–271. [PubMed: 15026432]
11. Fox MP, Brennan A, Maskew M, MacPhail P, Sanne I. Using vital registration data to update mortality among patients lost to follow-up from ART programmes: evidence from the Themba Lethu Clinic, South Africa. Trop Med Int Health. 2010; 15:405–413. [PubMed: 20180931]
12. Sanne IM, Westreich D, Macphail AP, Rubel D, Majuba P, Van Rie A. Long term outcomes of antiretroviral therapy in a large HIV/AIDS care clinic in urban South Africa: a prospective cohort study. J Int AIDS Soc. 2009; 12:38. [PubMed: 20017918]

13. Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. PLoS Med. 2007; 4:e298. [PubMed: 17941716]

14. Geng EH, Emenyonu N, Bwana MB, Glidden DV, Martin JN. Sampling-based approach to determining outcomes of patients lost to follow-up in antiretroviral therapy scale-up programs in Africa. Jama. 2008; 300:506–507. [PubMed: 18677022]

15. Geng EH, Bangsberg DR, Musinguzi N, Emenyonu N, Bwana MB, Yiannoutsos CT, et al. Understanding reasons for and outcomes of patients lost to follow-up in antiretroviral therapy programs in Africa through a sampling-based approach. J Acquir Immune Defic Syndr. 2010; 53:405–411. [PubMed: 19745753]

16. Egger M, Spycher BD, Sidle J, Weigel R, Geng EH, Fox MP, et al. Correcting mortality for loss to follow-up: a nomogram applied to antiretroviral treatment programmes in sub-Saharan Africa. PLoS Med. 2011; 8:e1000390. [PubMed: 21267057]

17. Westreich D. Berkson's Bias, Selection Bias, and Missing Data. Epidemiology. 2012; 23:159–164. [PubMed: 22081062]

18. Daniel RM, Kenward MG, Cousens SN, De Stavola BL. Using causal diagrams to guide analysis in missing data problems. Stat Methods Med Res. 2011

Table

Summary of results from re-analyses of effect of treated tuberculosis on all-cause mortality among subjects initiating HAART in Johannesburg, South Africa.

Scenario	Deaths	Hazard ratio (95% confidence limits)	
		Crude	Adjusted
Original cohort analysis	298	1.68 (1.29, 2.19)	1.07 (0.80, 1.44)
Updated analysis	494	1.55 (1.26, 1.91)	1.00 (0.80, 1.26)
Extended analysis	666	1.62 (1.35, 1.94)	1.09 (0.90, 1.33)

HR, hazard ratio. CL, confidence limit.