

Original Contribution

Effect of Tuberculosis on the Survival of Women Infected with Human Immunodeficiency Virus

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Evidence regarding the effect of tuberculosis (TB) disease on progression of human immunodeficiency virus (HIV) disease is inconclusive. The authors estimated the effect of time-varying incident TB on time to acquired immunodeficiency syndrome (AIDS)-related mortality using a joint marginal structural Cox model. Between 1995 and 2002, 1,412 HIV type 1 (HIV-1)-infected women enrolled in the Women's Interagency HIV Study were followed for a median of 6 years. Twenty-nine women incurred incident TB, and 222 died of AIDS-related causes. Accounting for age, CD4 cell count, HIV-1 RNA level, serum albumin level, and non-TB AIDS at study entry, as well as for time-varying CD4 cell count, CD4 cell count nadir, HIV-1 RNA level, peak HIV-1 RNA level, serum albumin level, HIV-related symptoms, non-TB AIDS, anti-*Pneumocystis jiroveci* prophylaxis, antiretroviral therapy, and household income, the hazard ratio for AIDS-related death comparing time after incident TB with time before incident TB was 4.0 (95% confidence interval (CI): 1.2, 14). The effect of incident TB on mortality was similar among highly active antiretroviral therapy (HAART)-exposed women (hazard ratio = 4.3, 95% CI: 0.9, 22) and non-HAART-exposed women (hazard ratio = 3.9, 95% CI: 0.9, 17; interaction $p = 0.91$). Although results were imprecise because few women incurred TB, irrespective of HAART exposure, incident TB increases the hazard of AIDS-related death among HIV-infected women.

acquired immunodeficiency syndrome; causality; disease progression; HIV infections; models, statistical; survival analysis; tuberculosis; women

Abbreviations: AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HR, hazard ratio; PCP, *Pneumocystis jiroveci* pneumonia; TB, tuberculosis; WIHS, Women's Interagency HIV Study.

Approximately 25 million people worldwide are coinfectd with human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* (1). Tuberculosis (TB) disease is the most common opportunistic infectious disease among

HIV-infected persons (2), and HIV infection is the strongest known risk factor for TB disease (3). A synergistic impact of TB disease and HIV infection may produce quicker depletion of CD4-positive T lymphocytes (CD4 cells) (4–6) and

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shorten survival. However, the epidemiologic evidence regarding the effect of TB disease on the progression of HIV disease is inconclusive (7).

Most prior studies of HIV-infected persons that have found TB disease to increase the hazard of death have had a prospective design but have determined participants' TB disease status only at study entry (8–13). Such simple categorization neglects the sequence of TB and non-TB acquired immunodeficiency syndrome (AIDS)-defining conditions. Conversely, investigators who have concluded that TB disease does not increase mortality among HIV-infected persons have conducted mainly retrospective studies or have compared groups defined by the first AIDS-defining condition, which may or may not have been TB disease (14–17). Such approaches prevent investigators from estimating the effect of TB disease among persons who already have AIDS. Finally, some researchers have controlled for confounding due to HIV stage by stratifying results on time-varying markers of immunosuppression, such as CD4 cell count (12, 13, 17). Researchers who stratify their data on such markers may underestimate the TB effect by estimating, at best, only the effects of TB disease that are not mediated through such markers.

If TB disease shortens HIV-related survival, it is imperative to improve efforts to prevent TB disease among HIV-seropositive persons through interventions such as treatment for latent TB infection. We estimated the effects of incident pulmonary and extrapulmonary TB disease on AIDS-related and all-cause mortality among HIV-infected women enrolled in a large prospective cohort study. We hypothesized that TB disease would increase the risk of death but have a reduced effect among women who had received highly active antiretroviral therapy (HAART).

MATERIALS AND METHODS

Study population

The Women's Interagency HIV Study (WIHS) (18) is an ongoing, prospective multicenter study of HIV type 1 (HIV-1) infection among women in the United States. In 1994 and 1995, WIHS personnel recruited 2,056 HIV-seropositive women and 569 HIV-seronegative women at high risk of HIV infection from primary-care and hospital-based medical units, community support groups, and research and drug rehabilitation programs in six US locations: Brooklyn, New York City; the Bronx, New York City; Chicago, Illinois; Southern California and Hawaii; the San Francisco Bay Area; and Washington, DC. At study entry, participants at all sites had similar sociodemographic and immunologic characteristics (18).

Participants in the study undergo semiannual physical examinations and provide specimens for laboratory measurements, including lymphocyte subset counts and plasma HIV-1 RNA levels. In addition, participants answer interviewer-administered questionnaires about health status, medication use, use of health services, and health-related behaviors. The 259 HIV-seropositive participants from Washington, DC, were excluded because TB registry data were unavailable. The present analysis focused on 1,412 (79 percent) of

the remaining 1,797 HIV-infected WIHS participants with no reported history of TB disease and no HAART use who had complete data available for the variables of interest at study entry and had attended at least two study visits.

Endpoint ascertainment

Participants were followed from the second WIHS visit until death, dropout, or the date of analysis on September 29, 2002—whichever came first. Thus, participants could contribute a maximum of 7 years to the analysis. Participants from Southern California were censored on December 31, 1999, because TB registry data were unavailable after this date. The endpoints of interest were AIDS-related mortality and all-cause mortality. Dates and causes of death were ascertained through death certificate abstraction via the National Death Index. Deaths were classified as AIDS-related if 1) the cause of death listed on the certificate was an AIDS-defining condition (19) or 2) the last recorded CD4 cell count was below 200 cells/mm³ and the declared cause of death was either a nonspecific infection or organ failure (e.g., pneumonia with an unidentified microorganism, sepsis, multiple organ failure) or AIDS without further specification (20).

Assessment of TB disease

The WIHS uses a mixed protocol of active and passive detection to ascertain clinical events (18). Self-reporting of selected AIDS-related medical conditions, including TB disease, triggers confirmation by medical record abstraction (21). TB disease is considered confirmed by a medical record upon isolation of *M. tuberculosis* in tissue or fluid. Independent of self-reports, personnel at all WIHS sites except Washington, DC, conduct periodic searches of the TB registries of state or local public health departments. The exposure of interest was confirmed incident TB disease, defined as 1) the first self-report of pulmonary or extrapulmonary TB disease at any semiannual visit undertaken 6 months beyond enrollment in the WIHS, confirmed by medical record abstraction, or 2) incident TB disease found by active surveillance of TB registries or death certificates. After exploration of various functional forms, incident TB disease was modeled as a time-varying dichotomous indicator that was set to 0 for all women at study entry and changed to 1 after onset of TB disease.

Assessment of covariates

The definition of HAART was based on the guidelines of a US Department of Health and Human Services panel (22) and has been previously published (23). Typical HAART regimens consisted of two or more nucleoside or nucleotide reverse transcriptase inhibitors in combination with at least one protease inhibitor or one nonnucleotide reverse transcriptase inhibitor. A binary time-varying indicator of HAART initiation was set to 0 for all women at study entry (before HAART was introduced), was changed to 1 at the first visit at which a woman reported using HAART, and was

then changed back to 0 if a woman discontinued HAART. Antiretroviral therapies not meeting the definition of HAART were classified as either monotherapy or combination therapy and were represented by separate dichotomous time-varying indicators.

Age at study entry was obtained from each woman. Levels of T cells and their subsets were determined by immunofluorescent flow cytometry at laboratories participating in the National Institute of Allergy and Infectious Diseases quality assurance program (24). Plasma HIV-1 RNA level was measured using the isothermal nucleic acid sequence-based amplification (NASBA/Nuclisens) method (Organon Teknika Corporation, Durham, North Carolina), and the data were log₁₀-transformed. CD4 cell count, CD4 cell count nadir, HIV-1 RNA level, peak HIV-1 RNA level, and serum albumin level (25) measured at each visit during follow-up were modeled as continuous time-varying variables. Self-reports of low income (annual household income below \$12,000), use of anti-*Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia (PCP) prophylaxis (i.e., trimethoprim, cotrimoxazole, dapsone, or aerosolized pentamidine), HIV-related symptoms (i.e., persistent fever or night sweats, and unintentional weight loss), and AIDS-defining conditions were represented as binary indicators that were allowed to vary over follow-up. TB disease, low CD4 cell count/CD4 cell percentage and invasive cervical cancer were excluded from the definition of AIDS-defining conditions. For the 28 percent of longitudinal data points that were missing, the most recently observed values were carried forward.

Statistical analysis

We approximated the parameters of a joint marginal structural Cox proportional hazards model (26) using a weighted pooled logistic regression model (27). Assuming no unmeasured confounding, no informative censoring, and no model misspecification, this method allows estimation of the total effect of TB disease on mortality among HAART-exposed women and non-HAART-exposed women. These same assumptions apply to standard approaches (e.g., Cox regression). Moreover, the assumptions of the present analytical strategy are less restrictive than standard approaches when estimating the effects of time-varying exposures (26). The additional restriction of the standard approaches amounts to disallowing feedback between the time-varying exposure and time-varying confounders.

This joint marginal structural model included as regressors time-varying incident TB disease, time-varying HAART use, and a restricted cubic spline representing time since study entry, with knots at the 5th, 35th, 65th, and 95th percentiles, as well as age, CD4 cell count, HIV-1 RNA level, serum albumin level, and history of non-TB AIDS-defining conditions, all measured at study entry. Such a model appropriately controls for time-varying confounding by weighting each participant's person-time contribution proportionally to the product of 1) the inverse probability of her observed incident TB disease status and 2) the inverse probability of her observed HAART initiation

and discontinuation status, each estimated from the available data as a function of the history of time-varying predictors (23, 28).

To construct the time-varying inverse probability of incident TB disease weights, we estimated the probability of incident TB disease at a given study visit using a separate pooled logistic regression model including CD4 cell count and HIV-1 RNA level, both measured at study entry, as well as time-varying CD4 cell count, HIV-1 RNA level, serum albumin level, fever or sweats, weight loss, non-TB AIDS-defining conditions, and the indicators of HAART initiation and discontinuation. To assure the correct time sequence, data on all time-varying covariates were lagged one visit and therefore were measured before TB disease onset.

To construct the time-varying inverse probability of HAART initiation weights, we included CD4 cell count, HIV-1 RNA level, serum albumin level, and the indicator of anti-PCP prophylaxis, all measured at study entry, as well as time-varying incident TB disease, CD4 cell count, CD4 cell count nadir, HIV-1 RNA level, serum albumin level, and indicators for anti-PCP prophylaxis, previous use of combination therapy, and any non-HAART antiretroviral therapy, in a similar separate pooled logistic regression model.

Finally, to construct the inverse probability of HAART discontinuation weights, we included age and HIV-1 RNA level, both measured at study entry, as well as time-varying incident TB disease, CD4 cell count, CD4 cell count nadir, HIV-1 RNA level, serum albumin level, and indicators for weight loss, low income, and previous use of non-HAART antiretroviral therapy.

Eight percent (111 of 1,412) of the participants were lost to follow-up before the date of analysis. To reduce the potential impact of informative censoring due to measured covariates, we calculated inverse probability-of-censoring weights using CD4 cell count, HIV-1 RNA level, and anti-PCP prophylaxis, all measured at study entry, as well as time-varying TB disease, HAART initiation and discontinuation, CD4 cell count, and peak HIV-1 RNA level. The final inverse probability weights were stabilized and taken as the fourfold product of incident TB disease, HAART initiation, HAART discontinuation, and censoring weights (28, 29). To ameliorate the impact of extremely influential values, weights were censored at the first and 99th percentiles.

Results were not appreciably altered by further inclusion of ethnicity, health insurance coverage, other HIV-related symptoms (i.e., diarrhea, oral candidiasis, acral dysesthesia), total lymphocyte count, CD8 cell count, hemoglobin level, platelet level, serum creatinine or blood urea nitrogen level, education, type of housing, depression, smoking, or use of alcohol, intravenous drugs, heroin, methadone, crack cocaine, amphetamines, or marijuana (all measured at study entry or semiannually during follow-up).

Throughout the analysis, the hazard ratio was used as a measure of effect and the 95 percent confidence interval was used as a measure of precision. Bootstrap confidence intervals (30) were used for the marginal structural models (26). We explored possible modification of the effect of incident TB disease on AIDS-related death by HAART exposure and CD4 cell count less than 200 cells/mm³ measured at study entry. The effect of TB disease on mortality was not

TABLE 1. Characteristics of 1,412 HIV*-infected women at study entry (1995–1996) and averaged over a median of 6 years of follow-up (April 3, 1995–September 29, 2002), Women's Interagency HIV Study

Characteristic	Study entry (1,412 women)		Follow-up (15,381 women-visits)	
	Median	IQR*	Median	IQR
Age (years)	37	32–42	40	35–45
Body mass index†,‡	26	22–29	26	23–30
CD4 cell count (cells/mm ³)	336	171–517	360	203–547
HIV-1 RNA level (copies/ml)	21,000	<4,000–99,500	4,400	580–36,000
Serum albumin level (g/dl)	4.2	3.9–4.5	4.1	3.8–4.4
	%	No.	%	No.
Ethnicity§				
African-American	53	741	55	8,376
Latina	25	352	24	3,722
White	20	281	19	2,911
Other	<2	22	<2	223
Ever use of illegal drugs				
Intravenous drugs	11	158	8	1,167
Crack cocaine	18	254	13	2,066
Heroin	13	184	9	1,359
Possession of health insurance	83	1,174	45	6,915
Annual income <\$12,000	66	934	62	9,457
Nontuberculosis AIDS*-defining condition	27	382	28	4,271

* HIV, human immunodeficiency virus; IQR, interquartile range; AIDS, acquired immunodeficiency syndrome.

† Weight (kg)/height (m)².

‡ Data on body mass index were unavailable for 55 women (182 women-visits).

§ Ethnicity was unspecified for 16 women (149 women-visits).

modified by geographic region (East Coast vs. West Coast and Chicago) (robust *p* for homogeneity = 0.74). Neither a plot of log-log survival by time nor a term for the interaction between incident TB disease and follow-up time (robust *p* for homogeneity = 0.76) suggested a strong departure from the proportional hazards assumption. Analyses were performed with SAS, version 9 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The study population was demographically similar to all HIV-infected women in the United States; 53 percent of participants were African-American, 25 percent were Latina, and 20 percent were White (table 1). At study entry, 27 percent reported a history of non-TB AIDS-defining conditions. The median CD4 cell count was 336 cells/mm³ (interquartile range, 171–517), and the median quantitative HIV-1 RNA level was 21,000 copies/ml (interquartile range, <4,000–99,500). A total of 258 participants were observed in Brooklyn, 323 in the Bronx, 225 in Chicago, 337 in Southern California/Hawaii, and 269 in San Francisco.

During follow-up, 46 (3 percent) of the 1,412 participants self-reported incident TB disease. Four of these self-reports were confirmed by medical record abstraction, four by registry match, and 10 by both methods. Additionally, 11 unreported incident TB events were found through active surveillance (one in medical records, seven by registry match, two in death certificates, and one by both registry and death certificate). Thus, the total number of women who incurred confirmed incident TB disease was 29 out of 1,412 (2 percent), yielding an incident TB disease rate of 4.3 (95 percent confidence interval (CI): 3.0, 6.2) per 1,000 person-years (figure 1). Twenty of 29 TB events were pulmonary, six were extrapulmonary, and three were mixed. Women who incurred TB disease were evenly distributed across study sites; Brooklyn and the Bronx each had eight TB events, Chicago and Southern California/Hawaii each had five TB events, and the remaining three TB events occurred in San Francisco. During 3,365 HAART-free person-years of follow-up, 929 (66 percent) of the 1,412 women initiated HAART, yielding a HAART initiation rate of 276 (95 percent CI: 259, 294) per 1,000 person-years.

Incident TB disease was independently predicted by variables measured both at study entry and over the course of

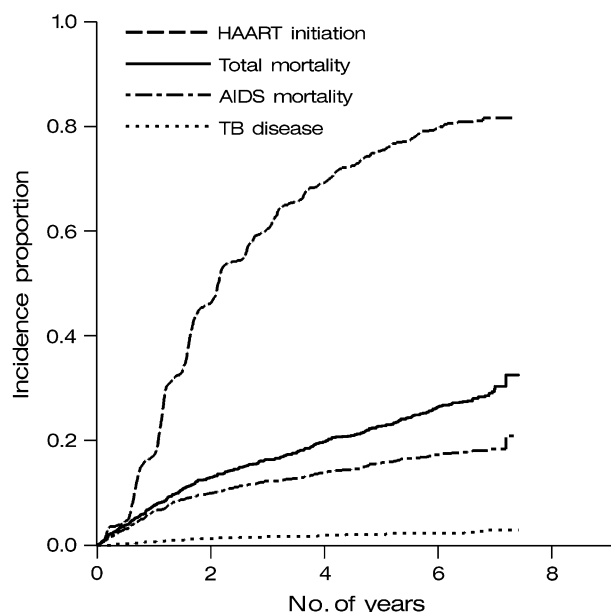


FIGURE 1. Initiation of highly active antiretroviral therapy (HAART), total (all-cause) mortality, acquired immunodeficiency syndrome (AIDS)-related mortality, and incidence of tuberculosis (TB) disease per 100 women among 1,412 human immunodeficiency virus (HIV)-infected women followed for a median of 6 years in the Women's Interagency HIV Study, April 3, 1995–September 29, 2002.

follow-up (table 2). Incident TB disease was more frequent among women with lower CD4 cell counts during follow-up (comparing <50 cells/mm³ with ≥ 500 cells/mm³, hazard ratio (HR) = 9.0, 95 percent CI: 1.7, 48), women with higher HIV-1 RNA levels during follow-up (comparing $\geq 10,000$ copies/ml with $<4,000$ copies/ml, HR = 2.1, 95 percent CI: 0.7, 7.0), women with lower albumin levels during follow-up (comparing the lower tertile with the upper tertile, HR = 8.2, 95 percent CI: 1.8, 37), and women who self-reported involuntary weight loss at follow-up visits (HR = 3.1, 95 percent CI: 1.4, 6.8). Incident TB disease was not independently associated with age, ethnicity, previous non-TB AIDS-defining conditions, or HAART use.

Between April 3, 1995, and September 29, 2002, the 1,412 women were followed for a median of 6.0 years (interquartile range, 3.4–6.8), during which 355 deaths occurred; 222 of these deaths were AIDS-related and two were attributed to incident TB disease on the death certificate. Twelve of 29 women with TB disease died, 11 from AIDS-related causes; and 343 of 1,383 women without TB disease died, 211 from AIDS-related causes. Seventy deaths were recorded in Brooklyn, 77 in the Bronx, 73 in Chicago, 62 in Southern California, and 73 in San Francisco.

After accounting for age, CD4 cell count, HIV-1 RNA level, serum albumin level, and history of non-TB AIDS-defining conditions, all measured at study entry, as well as time-varying CD4 cell count, CD4 cell count nadir, HIV-1 RNA level, peak HIV-1 RNA level, serum albumin level, HIV-related symptoms (i.e., fever or night sweats, and

TABLE 2. Independent predictors of incident tuberculosis disease among 1,412 HIV*-infected women over a median of 6 years of follow-up, Women's Interagency HIV Study, April 3, 1995–September 29, 2002

Predictor†	Hazard ratio‡	95% confidence interval
Age >37 years	0.9	0.4, 1.9
African-American ethnicity	1.2	0.5, 2.5
CD4 cell count (cells/mm ³)		
<50	9.0	1.7, 48
50–199	5.3	1.1, 26
200–349	2.4	0.5, 13
350–499	2.4	0.4, 13
≥ 500	1	
HIV-1 RNA level (copies/ml)		
>10,000	2.1	0.7, 7.0
4,000–10,000	1.8	0.4, 7.3
<4,000	1	
Serum albumin level (g/dl)		
<3.9	8.2	1.8, 37
3.9–4.1	4.9	1.1, 22
>4.1	1	
Nontuberculosis AIDS*-defining conditions	0.7	0.3, 1.7
Use of highly active antiretroviral therapy	1.1	0.4, 2.8
Fever or sweats	1.5	0.7, 3.3
Involuntary weight loss	3.1	1.4, 6.8

* HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

† Age and ethnicity were assessed at study entry; all other variables were measured during follow-up.

‡ Adjusted for all variables listed in the table.

weight loss), non-TB AIDS-defining conditions, anti-PCP prophylaxis, previous use of combination and any non-HAART antiretroviral therapy, HAART use, and low income in the joint marginal structural model, the hazard of AIDS-related death was 4.0 times (95 percent CI: 1.2, 14) larger among women who incurred incident TB disease than among women who did not (table 3). The effect of incident TB disease on AIDS-related mortality was similar for HAART-exposed women (HR = 4.3, 95 percent CI: 0.9, 22) and non-HAART-exposed women (HR = 3.9, 95 percent CI: 0.9, 17; robust *p* for homogeneity = 0.91). Analyses restricting the exposure to the 20 women with pulmonary TB disease provided a larger but less precise estimate of the effect on AIDS-related mortality (HR = 5.3, 95 percent CI: 1.1, 25). Having a CD4 cell count less than 200 cells/mm³ at study entry did not appear to modify the effect of incident TB disease on AIDS-related mortality (*p* for homogeneity = 0.64). For all-cause mortality, the hazard ratio from the joint marginal structural model was 2.3 (95 percent CI: 0.7, 7.4); hazard ratios were similar among HAART-exposed women (HR = 2.1, 95 percent CI: 0.4, 12) and

TABLE 3. Effect of incident tuberculosis on AIDS*-related and all-cause mortality among 1,412 HIV*-infected women according to their use of highly active antiretroviral therapy during follow-up, Women's Interagency HIV Study, April 3, 1995–September 29, 2002

	Person-years of follow-up	AIDS-related mortality (222 deaths)			All-cause mortality (355 deaths)		
		No. of events	HR*	95% CI*	No. of events	HR	95% CI
Marginal structural model†							
Overall							
No TB*	6,748	211	1		343	1	
TB	65	11	4.0	1.2, 14	12	2.3	0.7, 7.4
No HAART*							
No TB	4,411	172	1		261	1	
TB	39	9	3.9	0.9, 17	10	2.3	0.6, 9.3
HAART							
No TB	2,337	39	1		82	1	
TB	26	2	4.3	0.9, 22	2	2.1	0.4, 12
Standard Cox model‡							
Overall							
No TB	6,748	211	1		343	1	
TB	65	11	2.5	1.2, 5.3	12	1.4	0.7, 2.7
No HAART							
No TB	4,411	172	1		261	1	
TB	39	9	3.5	1.5, 8.0	10	1.9	0.9, 3.8
HAART							
No TB	2,337	39	1		82	1	
TB	26	2	1.0	0.2, 5.2	2	0.6	0.1, 2.7

* AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; HR, hazard ratio; CI, confidence interval; TB, tuberculosis; HAART, highly active antiretroviral therapy.

† Age, CD4 cell count, HIV-1 RNA level, serum albumin level, and history of non-TB AIDS-defining conditions at study entry were included as regressors. Time-varying CD4 cell count, CD4 cell count nadir, HIV type 1 (HIV-1) RNA level, peak HIV-1 RNA level, serum albumin level, HIV-related symptoms (i.e., fever or night sweats, and weight loss), incident non-TB AIDS-defining conditions, anti-*Pneumocystis jirovecii* pneumonia prophylaxis, previous use of combination and any antiretroviral therapy, HAART use, and low household income were used to compute weights for inverse probability of TB disease, HAART initiation, HAART discontinuation, and censoring (see text).

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

non-HAART-exposed women (HR = 2.3, 95 percent CI: 0.6, 9.3; robust *p* for homogeneity = 0.90).

Standard adjustment for the same set of time-fixed and time-varying covariates using a Cox proportional hazards model produced an attenuated hazard ratio for AIDS-related mortality of 2.5 (95 percent CI: 1.2, 5.3), with hazard ratios of 1.0 (95 percent CI: 0.2, 5.2) for HAART-exposed women and 3.5 (95 percent CI: 1.5, 8.0) for non-HAART-exposed women, whereas standard adjustment for only time-fixed covariates yielded a hazard ratio of 3.5 (95 percent CI: 1.8, 6.9), with hazard ratios of 3.5 (95 percent CI: 1.7, 7.5) for HAART-exposed women and 3.4 (95 percent CI: 0.8, 15) for non-HAART-exposed women. A similar pattern was observed for all-cause mortality (table 3).

DISCUSSION

In this prospective study, we estimated the total effects of incident pulmonary and extrapulmonary TB on AIDS-related and all-cause mortality among HIV-1-infected women. Incident TB disease was associated with a fourfold increase in the hazard of AIDS-related mortality, which was largely obfuscated using standard analytical methods. Contrary to our hypothesis, exposure to HAART did not modify (i.e., attenuate) this effect. Some prior studies (12, 13) have found the TB effect on mortality in HIV-infected persons to be stronger among those with CD4 counts greater than 200 cells/mm³. We found a similar pattern, but because of the small number of women with TB, our estimates were imprecise.

The results of this analysis are consistent with those of previous studies showing shorter survival among HIV-infected persons who develop incident TB disease (9, 10, 12, 13), but the estimates of effect found here are larger. The primary outcome of this study was the effect of incident TB disease on AIDS-related mortality, rather than all-cause mortality as it was in many previous studies (12, 13). Progression of HIV disease is probably better represented by the more specific measure of AIDS-related mortality than by all-cause mortality, which, to the degree that non-AIDS-related mortality occurs, would dilute the impact of incident TB disease.

HIV disease progression is a predictor of both incident TB disease and mortality. Therefore, to reduce confounding when estimating the effect of incident TB disease on mortality, one needs to account for HIV disease progression. When using standard statistical methods, investigators adjust for or stratify on time-varying markers of HIV disease progression, such as CD4 cell count or HIV-1 RNA level (15–17). However, adjusting for or stratifying on these markers of HIV disease progression will not allow unbiased estimation of the total (i.e., direct and indirect) effect of incident TB disease on mortality (28) and may induce selection bias (31) whenever there is a time-varying confounder affected by previous exposure. In particular, CD4 cell count is probably an intermediate variable on the pathway from incident TB to death. This is evidenced by the fact that, in our study, fully adjusted standard methods, which did not allow the effect of incident TB to be transmitted through time-varying CD4 cell count, showed a markedly attenuated effect of incident TB on AIDS-related mortality. Therefore, we employed a joint marginal structural model, which, like standard methods, assumes no unmeasured confounding, no informative censoring, and no model misspecification; but unlike standard methods, it allows consistent estimation of the total effect of incident TB on mortality (28, 29).

Some of the effects of TB disease on mortality are probably mediated by anti-TB treatment. Unfortunately, we do not have detailed information on TB treatment for these women. With the exception of the two TB-related deaths, it is likely that these women received TB treatment because they survived for more than 6 months after TB onset. If all women were properly and promptly treated when TB arose, the effect of TB on mortality would probably be smaller than our estimate. Conversely, if no women were properly and promptly treated, the effect of TB on mortality would probably be larger than our estimate.

To our knowledge, this is the first study assessing the effects of incident TB disease on mortality among HAART-exposed and -unexposed women. Despite the known benefits of HAART in reducing AIDS incidence and extending the survival of HIV-infected persons (23, 32–34), we did not find modification of the effect of incident TB disease on mortality by HAART. We may have failed to detect true modification by HAART for the following reasons: 1) a relatively small number of women incurred incident TB disease during follow-up; 2) our assumption that women continuously adhere to HAART between initiation and discontinuation may have led to misclassification of HAART-exposed and non-HAART-exposed women; 3) anti-TB

drugs (e.g., rifampicin and isoniazid) may impair the efficacy of HAART by reducing blood concentrations of some antiretroviral drugs (35); 4) resistance due to accumulated viral mutations may have reduced HAART effectiveness (36); or 5) some women may have experienced immune reconstitution disease, a paradoxical deleterious response to HAART (37) that may offset the beneficial effects of HAART and shorten the survival of women with TB disease.

The present study had several potential limitations. First, during the course of follow-up, only 29 women incurred confirmed incident TB disease. This small proportion of exposed participants is evident in our relatively wide confidence intervals. Second, the WIHS is a study of women, and the results may or may not be generalizable to men; however, we have no reason to believe that the results would differ appreciably by sex. Third, the WIHS study population is largely socioeconomically disadvantaged, and the results may or may not apply to persons at differing socioeconomic levels. Fourth, the WIHS cohort is an HIV-seroprevalent cohort; duration of HIV infection was unknown, and the comparison between women who incurred incident TB disease during follow-up and those who did not may have been influenced by differences in HIV disease beyond CD4 cell count and HIV-1 RNA level. However, it has been shown that time-varying information on CD4 cell count and HIV-1 RNA level suffices to control for differences in duration of infection (38). Fifth, although incident TB disease was confirmed through medical records or registries, misclassification of TB disease may have remained. Sixth and last, as with all observational studies, it is possible that the findings could be explained by unmeasured confounding. The combined impact of these potential limitations is difficult to predict.

The strengths of this work include the low rate of attrition and the use of the National Death Index for classifying endpoints, making emigrative selection bias and information bias due to misclassification of endpoints, respectively, unlikely explanations for the findings. Additionally, serial collection of biologic samples allows longitudinal control for markers of HIV disease progression. In conclusion, among these HIV-infected women, irrespective of HAART exposure, incident TB disease appeared to induce a fourfold increase in the hazard of AIDS-related death. Assuming that our findings have a causal interpretation, they emphasize the need for preventive interventions (e.g., treatment of latent TB infection) to avoid the occurrence of TB disease and the resultant increased mortality among HIV-infected persons, irrespective of HAART use.

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