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# Mortality Among People With HIV Treated for Tuberculosis Based on Positive, Negative, or No Bacteriologic Test Results for Tuberculosis: The IeDEA Consortium

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***Background.*** In resource-constrained settings, many people with HIV (PWH) are treated for tuberculosis (TB) without bacteriologic testing. Their mortality compared with those with bacteriologic testing is uncertain.

***Methods.*** We conducted an observational cohort study among PWH ≥15 years of age initiating TB treatment at sites affiliated with 4 International epidemiology Databases to Evaluate AIDS consortium regions from 2012 to 2014: Caribbean, Central and South America, and Central, East, and West Africa. The exposure of interest was the TB bacteriologic test status at TB treatment initiation: positive, negative, or no test result. The hazard of death in the 12 months after TB treatment initiation was estimated using a Cox proportional hazard model. Missing covariate values were multiply imputed.

***Results.*** In 2091 PWH, median age 36 years, 53% had CD4 counts ≤200 cells/mm$^3$, and 52% were on antiretroviral therapy (ART) at TB treatment initiation. The adjusted hazard of death was higher in patients with no test compared with those with positive test results (hazard ratio [HR], 1.56; 95% confidence interval [CI], 1.08–2.26). The hazard of death was also higher among those with negative compared with positive tests but was not statistically significant (HR, 1.28; 95% CI, 0.91–1.81). Being on ART, having a higher CD4 count, and tertiary facility level were associated with a lower hazard for death.

***Conclusions.*** There was some evidence that PWH treated for TB with no bacteriologic test results were at higher risk of death than those with positive tests. Research is needed to understand the causes of death in PWH treated for TB without bacteriologic testing.

**Keywords.** adults; epidemiology; HIV; mortality; tuberculosis.

Diagnosing tuberculosis (TB) in people with HIV (PWH) remains a challenge in resource-limited settings. In 2017, only 56% of the 5.5 million global pulmonary TB cases reported to the World Health Organization (WHO) were bacteriologically confirmed (ie, positive for smear microscopy, culture, or nucleic acid amplification test [NAAT]) [1]. In autopsy studies of TB in HIV-related deaths, TB was prevalent in 37% of deaths but was not diagnosed by the time of death in half of cases [2].

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The rollout of NAATs such as the Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), which are more sensitive and specific than smear microscopy, has helped close this gap [3]. However, limited impact on mortality has been observed with the use of Xpert MTB/RIF, in part due to high baseline rates of empiric TB treatment in high–TB burden settings [3–5]. Additionally, despite the higher sensitivity of Xpert compared with direct smear microscopy and increasing use of Xpert globally, there has not been a general increase in the proportion of notified pulmonary TB cases that are bacteriologically confirmed in low- and middle-income countries, including in the 30 high–TB burden countries [6]. A better understanding of mortality among PWH treated for TB in the setting of varying TB test results, or the absence of TB testing, is needed to inform the management of PWH treated for TB in resource-limited settings.

Acquiring a TB bacteriologic diagnosis in resource-limited settings can be challenging for multiple reasons. Despite increases in TB bacteriologic test coverage in sub-Saharan Africa,

smear microscopy and culture are estimated to be available at only 1.4 and 0.7 laboratories per 100 000 population, respectively [7, 8]. Many labs suffer from weak supply systems, outdated equipment, poor quality control, and insufficient staffing [7, 9–11]. Smear microscopy for acid-fast bacilli (AFB) is often the only TB test available but is poorly sensitive in PWH, with 30%–60% of pulmonary TB cases reported to be smear negative [12–14]. Clinicians may not order TB bacteriologic testing among PWH due to lack of knowledge about TB (or, conversely, knowledge of smear microscopy's limitations), or in cases of suspected extrapulmonary TB for which invasive tissue sampling cannot be performed [5, 9, 15, 16]. Patients may not be able to produce a sputum sample for bacteriologic testing or access TB testing sites due to the distance or cost of transport [9, 17, 18].

Empiric TB treatment in PWH, either because a bacteriologic test was negative or no test was performed, is thus common in resource-limited settings [4, 5, 14, 19, 20]. However, mortality in the absence of TB bacteriologic testing is not well defined [21–24]. The objective of this study was to describe the characteristics and risk of death among PWH treated for TB in the context of positive, negative, or no TB bacteriologic test results.

## METHODS

### Setting and Patient Population

This observational cohort study utilized data collected from PWH enrolled in HIV care programs affiliated with 4 participating regions of the International epidemiology Databases to Evaluate AIDS (IeDEA) consortium: Caribbean, Central and South America (CCASAnet) and Central, East, and West Africa [25]. IeDEA is a National Institutes of Health (NIH)–funded consortium that pools and harmonizes patient data collected in the context of routine care [26]. All participating facilities provided standard-of-care HIV and TB treatment services per their respective national guidelines. The study population included all PWH ≥15 years of age who initiated TB treatment between January 2012 and December 2014. Patients were excluded if an alternative diagnosis was established and TB treatment was stopped. Recurrent TB cases within the study period were excluded (n = 41), so a patient could not contribute >1 TB case. Patients receiving a drug-resistant TB treatment regimen were also excluded, defined by WHO criteria as any injectable agent (except streptomycin), fluoroquinolones, or oral bacteriostatic agent [27]. Patients with these characteristics were excluded in order to reduce the potential for confounding, given associations of these characteristics with adverse treatment outcomes and mortality in other studies [21, 28]. The reporting of this study conforms to the STROBE statement (Supplementary Table 1) [29].

### Ethics Statement

Independent Ethics Committee or Institutional Review Board approval for this study was obtained by each of the local IeDEA sites as well as from Indiana University (Supplementary Table 2).

### Data Management

TB cases were identified through review of local TB registries by site staff. An electronic case report form developed in Research Electronic Data Capture in English and French was used to collect medical record data [30]. Data entry into case report forms was performed by local IeDEA investigators. Patient-level HIV data were obtained from the IeDEA regional HIV care and treatment data repositories for patients with completed case report forms. Site-level data were obtained from surveys of antiretroviral therapy (ART) sites participating in IeDEA conducted between March 1 and July 1, 2012 [31, 32]. Routine audits were performed to ensure data quality. Regional IeDEA data were transferred to the IeDEA-East Africa Regional Data Center, where they were merged and additional data quality assessments undertaken before analysis.

### Study Definitions

Adult patients were defined as patients who were ≥15 years of age, consistent with WHO and other national and regional TB programs [33, 34]. The primary exposure of interest was the TB bacteriologic test status at TB treatment initiation: The *positive test* group included patients with ≥1 positive result including acid fast bacilli (AFB) smear, culture, or NAAT (Xpert MTB/RIF); the *negative test* group included patients for whom 1 or more of these bacteriologic tests were performed and none were positive; the *no test* group includes patients for whom no bacteriologic test was performed or results reported [35]. Patient-level variables at TB treatment initiation included age, sex, body mass index (BMI), ART status at TB treatment initiation, CD4 count (nearest value within 180 days before or 30 days after TB treatment initiation), TB disease site, and type of bacteriologic TB test (smear, culture, NAAT). Data on lipoarabinomannan (LAM) testing, which was recommended by the WHO for routine use in PWH in 2015 and was not used routinely at the time of the study, were not collected [36]. Specimen type (eg, respiratory vs nonrespiratory) was also not available. TB disease site was categorized into pulmonary and extrapulmonary according to WHO and Centers for Disease Control and Prevention definitions [33, 35, 37].

Site-level variables included IeDEA region, setting (urban, peri-urban), facility level (secondary [ie, district or provincial] vs tertiary [ie, regional or referral]), availability of specialized clinic/ward with dedicated staff for TB patients, physical proximity of HIV/TB clinical services, and the nature of active screening for TB performed for all PWH at enrollment. Site-level variables were applied to each patient as individual characteristics. The main outcome variable was death. Patients were followed from TB treatment initiation until death or censoring within the 12 months following treatment initiation or June 1, 2015. Nondeath events within this period were considered censored events.

### Data Analysis

Patient characteristics were summarized by each bacteriologic test group using frequencies and proportions for categorical

variables and medians and interquartile ranges for continuous variables. Differences between groups were assessed, as appropriate, using 1-way analysis of variance (ANOVA), the Pearson chi-square test, and the Fisher exact test. Survival for each group was estimated using the Kaplan-Meier method. The log-rank test was used to test the equality of survival among the groups. The Cox proportional hazard model was used to estimate the univariate and multivariable associations of covariates and the hazard of death. Independent variables included in this model were sex, age, BMI, CD4 count, ART status at TB treatment initiation, TB disease site, IeDEA region, and facility level. These variables were selected a priori because of their associations with adverse TB treatment outcomes in prior studies [21, 38–46].

The impact of missingness on the observed hazard associations was assessed by refitting the models after imputing missing patient-level covariate values selected because of their independent associations with mortality in patients with TB/HIV co-infection in prior studies [21, 42]. Missing values for CD4 count, BMI, and ART status at TB treatment initiation were multiply imputed using the fully conditional specification (FCS), where these covariates were assumed to be jointly distributed [47]. Imputation was performed 100 times following Rubin's scheme [48, 49]. Imputation analysis was performed using the PROC MI procedure in SAS [50]. Analyses were performed at the $\alpha = 0.05$ level.

In a secondary analysis, the hazard of death was compared among those with any bacteriologic test (positive or negative) vs no test results using the Cox model. Owing to the aforementioned missing values and the covariate imbalance among those with and without test results, the analysis was performed sequentially as follows: 1) Missing values were imputed separately for those with and without a test result. 2) The propensity for having a bacteriologic test result was modeled using logistic regression while adjusting for the covariates considered in the primary analysis. 3) Propensity scores were used to construct stabilized inverse probability weights (IPWs) (Supplementary Table 3). 4) The hazard of death was modeled conditional on having a bacteriologic test while adjusting for stabilized IPWs. In step 4 of the sequence, the estimate of the log hazards ratio and its robust standard error estimate were obtained. Steps 1–4 were repeated 100 times; resulting log-hazards ratio estimates and their standard errors were pooled using Rubin's rules.

## RESULTS

### Patient- and Site-Level Characteristics

Among 2140 patients in the database, 49 were excluded for initiating TB treatment outside of the study period (n = 32) or before the TB diagnosis date (n = 1), for documentation errors (n = 13), or for receiving drug-resistant TB treatment regimens (n = 3). Thus, 2091 patients were included in the analysis. These patients received care in 12 countries in 4 participating IeDEA regions (Figure 1). The characteristics of patients stratified by TB bacteriologic test status are presented in Table 1. Overall, 30% of patients had positive TB bacteriologic tests, 43% had negative tests, and 27% had no test results. Table 2 presents the patient distribution by site characteristics.

AFB smear was performed in 71% of patients (Supplementary Table 4). Culture and NAAT were performed in 8% and 3% of patients, respectively. Among patients with a positive test (whereby ≥1 test type may be performed for each patient), 90% had a positive AFB smear, 16% had a positive culture, and 6% had a positive NAAT. Among patients with results from >1 test type, 35% (27 of 78) with a negative AFB smear had a positive culture and 38% (14 of 37) with a negative smear had a positive NAAT (Supplementary Table 5).

A total of 243 (12%) deaths were reported: 64 (10%) deaths among those with a positive test, 99 (11%) among those with a negative test, and 80 (14%) in those with no test results ($P = .099$). Figure 2 shows the survival summary for the 2091 patients. The corresponding log-rank test suggested evidence of a difference in survival among the 3 groups ($P = .017$).

### Primary Analysis

Of the 2091 patients, 1258 (60%) were complete cases with respect to the analysis model (see Table 1 for proportion of missing values for each variable). Both the univariate and multivariable analyses were therefore restricted to these 1258 subjects (Table 3). In the univariate and multivariable models, there was not sufficient evidence of a difference in hazards of death among the 3 groups within 12 months after TB treatment initiation. The multivariable model did suggest that being on ART and having a higher CD4 count at TB treatment initiation were associated with lower hazards for death.

Of the 833 patients with missing values, imputation was not performed for 138 cases due to missing facility level, TB disease site, or simultaneously missing BMI, ART status, and CD4 count. Each imputed data set thus had 1953 patients. In the univariate analysis, after imputing missing values, there was evidence of a difference in the hazards of death among the 3 test groups ($P = .030$) (Table 3). However, after adjusting for other covariates, the effect of the test status on the hazard of death was not significant at the $\alpha = 0.05$ level ($P = .058$). At the pairwise level, however, the hazard of death was 56% higher among those with no TB test results compared with positive tests (adjusted hazard ratio [aHR], 1.56; 95% CI, 1.08–2.26) (Table 3). The hazard of death was also higher among patients with negative tests compared with positive tests but was not significant at the $\alpha = 0.05$ level (aHR, 1.28; 95% CI, 0.91–1.64). Finally, the multivariable analysis also suggested that increasing age was associated with an increased hazard of death, while increasing CD4 count, being on ART at TB treatment initiation, and receiving care from a tertiary facility were associated with a decreased hazard of death.

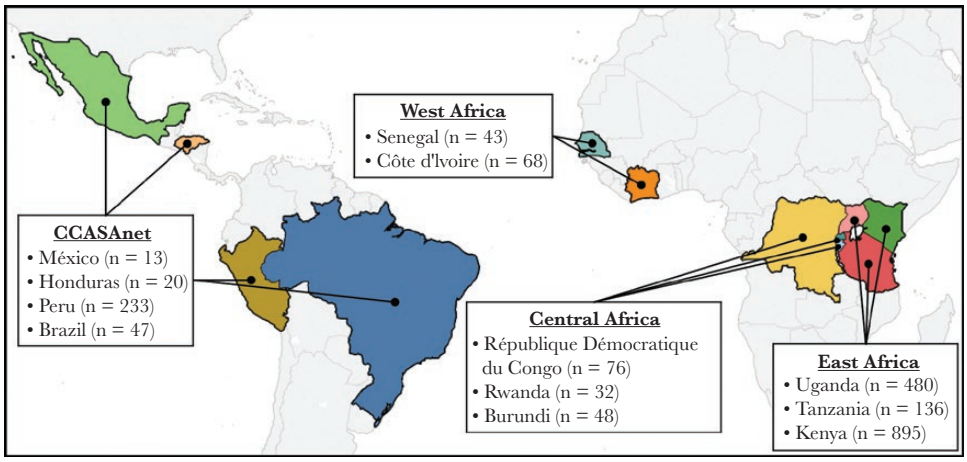



**Figure 1.** Patients included in the analysis by International epidemiology Databases to Evaluate AIDS region and country.

**Table 1. Patient Characteristics Stratified by TB Bacteriologic Test Status**

| Characteristic | Bacteriologic Test Status | | | | |
|---|---|---|---|---|---|
| | Total (n = 2091), No. (%) | Positive Test (n = 615), No. (%) | Negative Test (n = 907), No. (%) | No Test Result (n = 569), No. (%) | *P* Value[a] |
| Age, median (IQR), y | 36 (30–43) | 35 (30–42) | 36 (30–43) | 36 (29–44) | .779 |
| Female sex | 910 (44) | 266 (43) | 385 (42) | 259 (46) | .505 |
| BMI, median (IQR), mg/kg$^2$ | 19 (17–21) | 18 (17–21) | 19 (17–21) | 19 (17–22) | .001 |
| Missing | 374 (18) | 86 (14) | 89 (10) | 199 (35) | |
| ART status at TB treatment initiation | | | | | .069 |
| On ART | 1084 (52) | 346 (56) | 475 (52) | 216 (38) | |
| Not on ART | 790 (38) | 215 (35) | 359 (40) | 263 (46) | |
| Missing | 217 (10) | 54 (9) | 73 (8) | 90 (16) | |
| CD4 count, cells/mm$^3$ | | | | | .612 |
| <100 | 716 (34) | 204 (33) | 309 (34) | 203 (36) | |
| 100–200 | 391 (19) | 114 (19) | 174 (19) | 103 (18) | |
| 201–350 | 306 (14) | 85 (14) | 148 (16) | 73 (13) | |
| 351–500 | 161 (8) | 44 (7) | 73 (8) | 44 (8) | |
| >500 | 118 (6) | 36 (6) | 59 (7) | 23 (4) | |
| Missing | 399 (19) | 132 (21) | 144 (16) | 123 (21) | |
| TB disease site[b] | | | | | <.001 |
| Pulmonary | 1646 (79) | 564 (92) | 732 (81) | 350 (62) | |
| Miliary | 18 (1) | 0 (0) | 13 (2) | 5 (1) | .011 |
| Extrapulmonary | 422 (20) | 49 (8) | 172 (19) | 201 (35) | |
| Pleural | 79 (22) | 3 (10) | 36 (23) | 40 (20) | <.001 |
| Lymphatic | 73 (20) | 20 (67) | 26 (17) | 27 (13) | .149 |
| Bone and/or joint | 12 (34) | 1 (3) | 5 (3) | 6 (3) | .129 |
| Abdominal[c] | 34 (10) | 3 (10) | 18 (11) | 13 (7) | .027 |
| Pericardial | 7 (2) | 0 (0) | 4 (3) | 3 (2) | .276 |
| Genitourinary | 1 (<1) | 1 (3) | 0 (0) | 0 (0) | .566 |
| CNS and/or meningeal | 21 (6) | 1 (3) | 13 (8) | 7 (3) | .042 |
| Laryngeal | 1 (<1) | 0 (0) | 1 (1) | 0 (0) | 1.000 |
| Other | 25 (7) | 0 (0) | 11 (7) | 14 (7) | <.001 |
| Not specified | 23 (1) | 2 (<1) | 3 (<1) | 18 (3) | <.001 |

Abbreviations: ART, antriretroviral therapy; BMI, body mass index; CNS, central nervous system; IQR, interquartile range; TB, tuberculosis.

[a] *P* values comparing the 3 groups were calculated using analysis of variance F-test, chi-square test, Kruskal-Wallis test, and Fisher exact test.

[b] Percentages of extrapulmonary sites refer to the total extrapulmonary sites; each patient could have >1 extrapulmonary site.

[c] Includes peritoneum, omentum, liver, spleen, and colon.

**Table 2. Patient Distribution by Site Characteristics, Stratified by TB Bacteriologic Test Status**

| Characteristic | Bacteriologic Test Status | | | | |
|---|---|---|---|---|---|
| | Total (n = 2091), No. (%) | Positive Test (n = 615), No. (%) | Negative Test (n = 907), No. (%) | No Test (n = 569), No. (%) | *P* Value[a] |
| IeDEA region | | | | | <.001 |
| CCASAnet | 313 (15) | 126 (21) | 77 (8) | 110 (19) | |
| Central Africa | 156 (8) | 52 (8) | 44 (5) | 60 (11) | |
| East Africa | 1511 (72) | 397 (64) | 734 (81) | 380 (67) | |
| West Africa | 111 (5) | 40 (7) | 52 (6) | 19 (3) | |
| Setting | | | | | <.001 |
| Urban | 537 (26) | 198 (32) | 151 (17) | 188 (33) | |
| Peri-urban | 986 (47) | 286 (46) | 393 (43) | 307 (54) | |
| Rural | 480 (23) | 84 (14) | 324 (36) | 72 (13) | |
| Missing | 88 (4) | 47 (8) | 39 (4) | 2 (<1) | |
| Facility level | | | | | <.001 |
| Secondary | 234 (12) | 96 (15) | 56 (6) | 82 (14) | |
| Tertiary | 1769 (88) | 472 (77) | 812 (90) | 485 (85) | |
| Missing | 88 (4) | 47 (8) | 39 (4) | 2 (<1) | |
| Specialized TB clinic/ward on site | | | | | <.001 |
| Yes, on site | 1951 (93) | 550 (89) | 858 (95) | 543 (95) | |
| Yes, off site/by referral | 20 (1) | 3 (<1) | 5 (<1) | 12 (2) | |
| Not available | 32 (2) | 15 (2) | 5 (<1) | 12 (2) | |
| Missing | 88 (4) | 47 (8) | 39 (4) | 2 (<1) | |
| Physical proximity of HIV/TB services | | | | | <.001 |
| Same facility or same-day appointments | 1440 (69) | 341 (55) | 709 (78) | 390 (69) | |
| Cross-referral between HIV and TB service points | 401 (19) | 158 (26) | 84 (9) | 159 (28) | |
| Provision of TB and HIV services under the same roof | 114 (5) | 52 (8) | 44 (5) | 18 (3) | |
| None of these models | 48 (2) | 17 (3) | 31 (3) | 0 (0) | |
| Missing | 88 (4) | 47 (8) | 39 (4) | 2 (<1) | |
| Active screening for TB for all PWH at enrollment | | | | | <.001 |
| All, but only symptom screening | 199 (10) | 91 (15) | 32 (4) | 76 (13) | |
| All, symptom screening plus additional diagnostics[b] | 1689 (81) | 425 (69) | 785 (86) | 479 (84) | |
| In case of clinical suspicion | 115 (5) | 52 (8) | 51 (6) | 12 (2) | |
| Missing | 88 (4) | 47 (8) | 39 (4) | 2 (<1) | |

Abbreviations: CCASAnet, Caribbean, Central and South America; IeDEA, International epidemiology Databases to Evaluate AIDS; PWH, people with HIV; TB, tuberculosis.

[a]Analysis of variance F-test, chi-square test, Kruskal-Wallis test, or Fisher exact test was performed for each variable as appropriate.

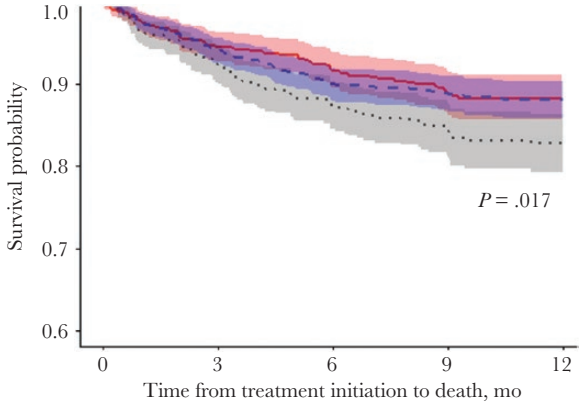
[b]Additional testing examples include sputum AFB, sputum induction, gastric lavage, tissue biopsy, chest x-ray, gene x-pert, tuberculin skin testing.

#### Secondary Analysis

The propensity model for the log-odds of having any bacteriologic test (positive or negative) vs no test result showed that CD4 count, BMI, TB disease site, facility level, and IeDEA region were associated with the probability of having a test result (Supplementary Table 6). The odds of having a test result among those with extrapulmonary TB, for example, were estimated to be about 45% lower than the odds for those with pulmonary TB ($P < .0001$) (Supplementary Table 7). The model in Supplementary Table 6 was used to calculate the propensity scores used to compute stabilized IPWs. The stabilized IPWs were used to adjust Cox models for the time to death conditional on whether a bacteriologic diagnosis was observed. The pooled adjusted hazard ratio suggested that the hazard of death, within 12 months of initiating TB treatment, was about 19% lower among those with a bacteriologic test compared with those without a test but was not significant at the $\alpha = 0.05$ level (aHR, 0.81; 95% CI, 0.61–1.07) (Supplementary Table 8).

## DISCUSSION

PWH in our cohorts treated for TB in the absence of TB bacteriologic test results had a significantly higher adjusted hazard of death than those treated for TB with positive test results in the multiple imputation analysis. This association was not significant in the complete case analysis, which included only 64% of the sample size in the multiple imputation analysis and whose coefficients were far more sensitive to adjustment. Unlike those with bacteriologically confirmed TB, it is plausible that those with no test results were a heterogenous group of individuals with TB and other life-threatening diseases (eg, opportunistic infections, cancers, chronic lung diseases) that may have




| Bacteriologic test group | Number at risk | | | | |
|---|---|---|---|---|---|
| Positive test | 615 | 556 | 475 | 373 | 0 |
| Negative test | 907 | 810 | 705 | 524 | 3 |
| No test | 569 | 452 | 382 | 297 | 3 |

**Figure 2.** Cumulative incidence of survival after tuberculosis (TB) treatment initiation, stratified by TB bacteriologic test status: red, positive test group; blue, negative test group; gray, no test result group.

mimicked TB but advanced untreated while the patient received TB treatment, resulting in excess mortality. This, along with the 12-month mortality outcome, suggests that not all patients who initiated TB treatment had TB disease and not all deaths were TB-attributable.

Consistent with the literature, being on ART and having higher CD4 count at TB treatment initiation were strongly protective against mortality in our study. This underscores the importance of early ART initiation and immune preservation on survival, regardless of TB bacteriologic testing in resource-constrained settings. Advanced HIV immunosuppression is known to be a critical risk factor for TB-related mortality, and the scale-up of ART coverage has been associated with marked reductions in TB incidence and mortality [20, 21, 42, 43, 51–53].

We also found that PWH attending tertiary facilities had a lower adjusted hazard of death compared with those attending secondary facilities. It is possible that secondary facilities had less capacity to evaluate and manage TB or its alternative diagnoses compared with tertiary facilities [54]. However, there was not a significant difference in the adjusted hazard of death in those treated for TB with any test vs no test, which argues against the notion that bacteriologic testing is a marker of better-resourced sites and therefore reduced mortality. Facility-level mortality differences may also have been influenced by differences in the completeness of vital status ascertainment between higher- and lower-resourced facilities, the latter being potentially more susceptible to undocumented loss to follow-up or transfer events not captured in our data set [55]. Differences in vital status ascertainment may also have accounted for regional differences in the hazards for death (ie, West Africa vs CCASAnet) in our study.

Notably, the increased mortality among PWH with no TB test results in our study was independent of patients' TB disease site and CD4 count (Table 1). This reduces the possibility that extrapulmonary TB (which was more prevalent in those with no tests than positive tests) or advanced HIV disease were driving the increased mortality in the no test group. The potential influence of extrapulmonary TB on mortality in our study nevertheless remains an important consideration. Extrapulmonary TB is known to be more common in advanced HIV disease, certain extrapulmonary TB sites (eg, disseminated or meningitis) have been associated with especially high mortality in PWH, and extrapulmonary TB has been associated with delays in diagnosis [42, 44, 45, 56–59]. The diagnosis of extrapulmonary TB and extrapulmonary disease sites may be less accurate in patients without bacteriologically confirmed TB in our study. This accuracy may improve over time with the broader use of urinary LAM, which does not require sputum collection and is not site-specific.

The use of NAAT in only 3% of patients in our study is lower than expected in light of a 2012 global IeDEA site assessment that identified that Xpert MTB/RIF to be accessible at 63% of sites (in the clinic, at the same facility, and/or offsite) [4]. This gap between accessibility and utilization of Xpert MTB/RIF may be attributable to a variety of factors, including evolving country-specific policy during the study period, lack of provider knowledge about Xpert and WHO guidelines, cartridge stock-outs, interruptions in electricity, unreliable transport of specimens at sites with off-site Xpert availability, and high operating costs in resource-limited settings. The low utilization of Xpert despite its increasing availability may also be a factor in the lack of increase in the proportion of notified pulmonary TB cases that are bacteriologically confirmed in low- and middle-income countries according to the recent WHO Global Tuberculosis Report 2019 [6].

Finally, patients with negative tests had a 28% higher hazard of death than those with positive tests in the adjusted multiple imputation analysis, but the difference was not statistically significant. Other studies have found that smear-negative TB is associated with increased mortality compared with smear-positive TB in PWH, which has been attributed to paucibacillary disease in advanced HIV, delay in diagnosis, and other opportunistic and noncommunicable diseases [15, 21–23, 60–67]. Similar findings have been shown with respect to TB culture, but such studies have not been performed for NAAT to our knowledge [68]. The lack of mortality difference in our study could thus be related to the combination of smear, culture, and NAAT used to define the groups. The positive test group may also have had higher-than-expected mortality due to more extensive TB disease (with higher bacterial burden) or inadequate treatment of drug-resistant TB [69].

Our study has strengths and limitations. The strengths include its large sample size from diverse regions and use of

**Table 3. Hazard Ratios for Death Within 12 Months of TB Treatment Initiation**

| | Complete Case Analysis[a] (n = 1258) | | Multiple Imputation Analysis[b] (n = 1953) | |
|---|---|---|---|---|
| Characteristic | Univariate HR (95% CI) | Multivariable HR[c] (95% CI) | Univariate HR (95% CI) | Multivariable HR[c] (95% CI) |
| Bacteriologic test | | | | |
| Positive | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| Negative | 1.34 (0.86–2.09) | 1.19 (0.73–1.93) | 1.18 (0.85–1.64) | 1.28 (0.91–1.81) |
| None | 1.21 (0.70–2.08) | 0.87 (0.49–1.55) | 1.57 (1.11–2.23) | 1.56 (1.08–2.26) |
| Age, y | 1.01 (0.99–1.03) | 1.01 (0.99–1.02) | 1.02 (1.004–1.03) | 1.02 (1.003–1.03) |
| Sex | | | | |
| Female | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| Male | 1.23 (0.85–1.78) | 1.15 (0.78–1.69) | 1.24 (0.95–1.63) | 1.20 (0.91–1.59) |
| BMI, mg/kg$^2$ | 0.97 (0.92–1.02) | 0.98 (0.92–1.03) | 0.97 (0.93–1.01) | 0.97 (0.93–1.002) |
| ART status at TB treatment initiation | | | | |
| Not on ART | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| On ART | 0.63 (0.44–0.91) | 0.57 (0.39–0.84) | 0.64 (0.48–0.85) | 0.61 (0.47–0.80) |
| CD4 count | | | | |
| <100 | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| 100–200 | 0.39 (0.23–0.66) | 0.39 (0.23–0.65) | 0.66 (0.46–0.95) | 0.69 (0.49–0.97) |
| 201–350 | 0.44 (0.26–0.75) | 0.42 (0.24–0.71) | 0.56 (0.37–0.85) | 0.56 (0.38–0.81) |
| 351–500 | 0.16 (0.05–0.51) | 0.15 (0.05–0.48) | 0.47 (0.25–0.87) | 0.46 (0.27–0.79) |
| >500 | 0.21 (0.07–0.66) | 0.19 (0.06–0.62) | 0.26 (0.10–0.68) | 0.27 (0.12–0.64) |
| TB disease site | | | | |
| Pulmonary | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| Extrapulmonary | 1.10 (0.70–1.72) | 1.10 (0.68–1.76) | 1.21 (0.88–1.64) | 1.09 (0.79–1.51) |
| IeDEA region | | | | |
| CCASAnet | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| Central Africa | 1.04 (0.36–3.01) | 1.08 (0.35–3.33) | 0.92 (0.53–1.62) | 0.52 (0.27–1.02) |
| East Africa | 0.97 (0.52–1.81) | 0.98 (0.49–1.96) | 0.81 (0.58–1.13) | 0.77 (0.54–1.11) |
| West Africa | 1.51 (0.62–3.64) | 0.89 (0.25–3.22) | 1.06 (0.53–2.10) | 0.38 (0.16–0.91) |
| Facility level | | | | |
| Secondary | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| Tertiary | 0.69 (0.40–1.18) | 0.63 (0.27–1.47) | 0.61 (0.43–0.88) | 0.41 (0.25–0.67) |

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CCASAnet, Caribbean, Central and South America; CI, confidence interval; HR, hazard ratio; IeDEA, International epidemiology Databases to Evaluate AIDS; TB, tuberculosis.

[a]Includes all patients without missing values for the variables listed in the table.

[b]Missing values were imputed for CD4 count, BMI, and ART status at TB treatment initiation. This model includes all patients without missing values for the variables listed in the table, including those for whom CD4, BMI, and ART status was imputed.

[c]Adjusted for all of the variables listed in the table.

routine program data, likely reflecting typical care environments. The limitations include the use of multiple imputation if the variables used to impute missing values were not missing at random, although missing CD4 counts, for example, were often attributable to reagent stock-outs, suggesting that this variable was missing at random. Few patients had culture or NAAT, and none had LAM test results, which limits the generalizability of our study in current settings where these tests are used more commonly. Finally, the use of retrospective data limited our ability to understand the extent of clinicians' efforts to diagnose TB and other diseases or the reasons why patients had negative or no TB test results (eg, clinical or laboratory system failures).

In conclusion, there was some evidence that PWH treated for TB with no TB bacteriologic test results were at higher risk of death than those treated for TB with positive bacteriologic tests. Every effort should be made to establish a bacteriologic diagnosis of TB before TB treatment initiation in resource-constrained settings. Research is needed to understand the causes of death in PWH treated for TB without bacteriologic testing.

## Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.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Regional Hospital. A complete listing of participating programs and members can be found in Supplementary Table 9.

***International Epidemiology Databases to Evaluate AIDS (IeDEA) Consortium.*** Membership in the IeDEA consortium for participating programs is provided in Supplementary Table 9.

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