Mortality among people with HIV treated for tuberculosis based on positive, negative, or no bacteriologic test results for tuberculosis: the IeDEA consortium

John M. Humphrey, MD, MS, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, United States

Philani Mpofu, MS, Department of Biostatistics, Indiana University Fairbanks School of Public Health, Indianapolis, IN, United States

April C. Pettit, MD, MS, Vanderbilt University Medical Center, Nashville, TN, United States; Vanderbilt Tuberculosis Center, Nashville, TN, United States

Beverly Musick, MS, Department of Biostatistics, Indiana University Fairbanks School of Public Health, Indianapolis, IN, United States

E. Jane Carter, MD, Department of Medicine, Brown University School of Medicine, Providence, RI, United States

Eugène Messou, PhD, University of Bordeaux, Centre INSERM U1219, Bordeaux Population Health, Bordeaux, France; Centre de Prise en charge de Recherche et de Formation (Aconda-CePReF), Abidjan, Côte d'Ivoire

Olivier Marcy, MD, PhD, University of Bordeaux, Centre INSERM U1219, Bordeaux Population Health, Bordeaux, France; Epidemiology and Public Health Unit, Institut Pasteur du Cambodge, Phnom Penh, Cambodia

Brenda Crabtree-Ramirez, MD, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

Marcel Yotebieng, MD, MPH, PhD, The Ohio State University, College of Public Health, Columbus, OH, United States

Kathryn Anastos, MD, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, United States

Timothy R. Sterling, MD, Vanderbilt University Medical Center, Nashville, TN, United States; Vanderbilt Tuberculosis Center, Nashville, TN, United States

Constantin Yiannoutsos, PhD, Department of Biostatistics, Indiana University Fairbanks School of Public Health, Indianapolis, IN, United States

Lameck Diero, MBChB, Mmed, Department of Medicine, Moi University College of Health Sciences, Eldoret, Kenya

Kara Wools-Kaloustian, MD, MS, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, United States

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

Key words: tuberculosis; HIV; mortality; adults; epidemiology

Corresponding author
John M. Humphrey, MD, MS
Indiana University School of Medicine
545 Barnhill Drive, Suite 421
Indianapolis, IN 46202
humphrjm@iu.edu
Phone +1 630-346-0133
Fax +1 317-274-1587

Alternate correspondence
Kara Wools-Kaloustian
Indiana University School of Medicine
545 Barnhill Drive, Suite 421
Indianapolis, IN 46202
kwools@iu.edu
Phone +1 317-274-8115
Fax +1 317-274-1587

40-word summary: In this observational cohort of 2,091 HIV-positive adults initiating tuberculosis (TB) treatment, the adjusted hazard of death was higher in patients treated for TB with no TB bacteriologic test results compared to those treated for TB with positive test results.

Abstract

Background: In resource-constrained settings, many people with HIV (PWH) are treated for tuberculosis (TB) without bacteriologic testing. Their mortality compared to 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 four International epidemiology Databases to Evaluate AIDS consortium regions from 2012-2014: 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 following TB treatment initiation was estimated using Cox proportional hazard model. Missing covariate values were multiply imputed.

Results: In 2,091 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 to positive test results (HR 1.56, 95% CI 1.08-2.26). The hazard of death was also higher among those with negative compared to 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.

Conclusion: 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.

Introduction

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) globally were bacteriologically confirmed (i.e. 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]. The rollout of nucleic acid amplification tests (NAAT) such as the Xpert MTB/RIF (Cepheid, Sunnyvale, CA), 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 to 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 is 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 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 four 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 more than one 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 ≥ 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: *Positive test* group included patients with ≥ 1 positive result including acid fast bacilli (AFB) smear, culture, or NAAT (Xpert MTB/RIF); *Negative test* group included patients for whom ≥ 1 of these bacteriologic tests were performed and none were positive; *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 (e.g. respiratory vs. non-respiratory) was also not available. TB disease site was categorized into pulmonary and extrapulmonary according to WHO and CDC definitions [33, 35, 37].

Site-level variables included IeDEA region, setting (urban, peri-urban), facility level (secondary [i.e. district or provincial] vs. tertiary [i.e. 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. Non-death 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 one-way ANOVA, Pearson Chi-squared test and Fisher's 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 α=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 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 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 2,140 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), documentation errors (n=13), and receiving drug-resistant TB treatment regimens (n=3). Thus, 2,091 patients were included in the analysis. These patients received care in 12 countries in four participating IeDEA regions (Figure 1). The characteristics of patients stratified by TB bacteriologic test status is 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 positive AFB smear, 16% had positive culture, and 6% had 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*=0.099). Figure 2 shows the survival summary for the 2,091 patients. The corresponding log-rank test suggested evidence of a difference in survival among the three groups (*P*=0.017).

Primary analysis

Of the 2,091 patients, 1,258 (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 1,258 subjects (Table 3). In the univariate and multivariable models, there was not sufficient evidence of a difference in hazards of death among the three groups within 12 months following 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 dataset thus had 1,953 patients. In the univariate analysis, after imputing missing values, there was evidence of a difference in the hazards of death among the three test groups (*P*=0.030) (Table 3). However, after adjusting for other covariates, the effect of the test status on the hazard of death was not significant at the α=0.05 level (*P*=0.058). At the pairwise level, however, the hazard of death was 56% higher among those with no TB test results compared to positive tests (aHR 1.56, 95% CI 1.08-2.26) (Table 3). The hazard of death was also higher among patients with negative tests compared to positive tests but was not significant at the α=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.

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 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* < 0.0001) (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 or not 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 to

those without a test but was not significant at the α=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 (e.g. opportunistic infections, cancers, chronic lung diseases) that may have 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 to those attending secondary facilities. It is possible that secondary facilities had less capacity to evaluate and manage TB or its alternative diagnoses compared to tertiary facilities [54]. However, there was not a significant difference in the adjusted hazard of death in those treated for TB with any test versus 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 dataset [55]. Differences in vital status ascertainment may also have accounted for regional differences in the hazards for death (i.e. 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 (e.g. 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 to smear-positive TB in PWH, which has been attributed to paucibacillary disease in advanced HIV, delay in diagnosis, and other opportunistic and non-communicable 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. Strengths include its large sample size from diverse regions and use of routine program data likely reflecting typical care environments. 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 stockouts suggesting this variable was missing at random. Few patients had culture or NAAT and none had LAM test results which limit 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 clinicians went to diagnose TB and other diseases or the reasons why patients had negative or no TB test results (e.g. 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 prior to TB treatment initiation in resource-constrained settings. Research is needed to understand the causes of death in PWH treated for TB without bacteriologic testing.

Funding

This work was supported by the National Institutes of Health (NIH) under award numbers: K08 AI104352 (April Pettit, PI), UL1 TR000445 (Vanderbilt Clinical and Translational Science Award), U01 AI096299 (Central Africa IeDEA), U01 AI069919 (Western Africa IeDEA), U01 AI069911 (Eastern Africa IeDEA), U01 AI069923 (CCASAnet IeDEA), and U01 AI096186 (IeDEA Network Coordinating Center). It has also been

supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through the United States Agency for International Development (USAID) under the terms of Cooperative Agreement No. AID-623-A-12-0001. The contents of this publication are the sole responsibility of the authors and do not necessarily reflect the views of the NIH, PEPFAR, or USAID.

Acknowledgements

We are grateful for the participation of the following IeDEA Collaborative sites: Brazil – INI-Fiocruz; Burundi – CPAMP-CHUK; Côte d'Ivoire – Centre Intégré de Recherches Biocliniques d'Abidjan (CIRBA), Centre Hospitalier Universitaire de Cocody, CREF/SMIT, Medicine Interne; Honduras - IHHS; Kenya – AMPATH; Mexico - INCMNSZ; Peru – IMTAvH, CoVIHS; République Démocratique du Congo – Bomoi Health Centre, Kalembelembe Paediatric Hospital; Rwanda – Rwanda Military Hospital; Tanzania – National AIDS Control Programme, Tumbi Regional Hospital, National Institute for Medical Research, Mwanza Research Centre-Kisesa Clinic; Uganda – Masaka Regional Hospital. A complete listing of participating programs and members can be found in Supplementary Table 9.

References

1. World Health Organisation. Global Tuberculosis Report 2018. Geneva, Switzerland: WHO; 2018. Available at: https://www.who.int/tb/publications/global_report/en/. Accessed December 12, 2018.

2. Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. AIDS **2015**; 29(15): 1987-2002.

3. Auld AF, Fielding KL, Gupta-Wright A, Lawn SD. Xpert MTB/RIF - why the lack of morbidity and mortality impact in intervention trials? Trans R Soc Trop Med Hyg **2016**; 110(8): 432-44.

4. Clouse K, Blevins M, Lindegren ML, et al. Low implementation of Xpert MTB/RIF among HIV/TB co-infected adults in the International epidemiologic Databases to Evaluate AIDS (IeDEA) program. PloS One **2017**; 12(2): e0171384.

5. Theron G, Zijenah L, Chanda D, et al. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. Lancet **2014**; 383(9915): 424-35.

6. World Health Organisation. Global Tuberculosis Report 2019. Geneva, Switzerland: WHO; 2019. Available at: https://www.who.int/tb/publications/global_report/en/. Accessed December 15, 2019.

7. Onyebujoh PC, Thirumala AK, Piatek A. Stronger tuberculosis laboratory networks and services in Africa essential to ending tuberculosis. Afr J Lab Med **2017**; 6(2): 519.

8. World Health Organisation. Global Tuberculosis Control: WHO Report 2011. Geneva, Switzerland: WHO; 2011. Available at: http://www.who.int/iris/handle/10665/44728. Accessed October 1, 2018.

9. Parsons LM, Somoskovi A, Gutierrez C, et al. Laboratory diagnosis of tuberculosis in resource-poor countries: challenges and opportunities. Clin Microbiol Rev **2011**; 24(2): 314-50.

10. Zumla A, Petersen E, Nyirenda T, Chakaya J. Tackling the tuberculosis epidemic in sub-Saharan Africa--unique opportunities arising from the second European Developing Countries Clinical Trials Partnership (EDCTP) programme 2015-2024. Int J Infect Dis **2015**; 32: 46-9.

11. Loveday M, Thomson L, Chopra M, Ndlela Z. A health systems assessment of the KwaZulu-Natal tuberculosis programme in the context of increasing drug resistance. Int J Tuberc Lung Dis **2008**; 12(9): 1042-7.

12. Van Deun A, Salim AH, Cooreman E, et al. Optimal tuberculosis case detection by direct sputum smear microscopy: how much better is more? Int J Tuberc Lung Dis **2002**; 6(3): 222-30.

13. Boehme CC, Nicol MP, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis

and multidrug resistance: a multicentre implementation study. Lancet **2011**; 377(9776): 1495-505.

14. World Health Organisation. Improving the diagnosis and treatment of smear-negative pulmonary and extra-pulmonary tuberculosis among adults and adolescents: Recommendations for HIV-prevalent and resource-constrained settings. Geneva, Switzerland: WHO; 2007. Available at: https://www.who.int/hiv/pub/tb/pulmonary/en/. Accessed October 1, 2018.

15. Getahun H, Harrington M, O'Brien R, Nunn P. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. Lancet **2007**; 369(9578): 2042-9.

16. Roy M, Muyindike W, Vijayan T, et al. Implementation and Operational Research: Use of Symptom Screening and Sputum Microscopy Testing for Active Tuberculosis Case Detection Among HIV-Infected Patients in Real-World Clinical Practice in Uganda. J Acquir Immune Defic Syndr **2016**; 72(5): e86-91.

17. Elbireer AM, Opio AA, Brough RL, Brooks Jackson J, Manabe YC. Strengthening Public Laboratory Service in Sub-Saharan Africa: Uganda Case Study Laboratory Medicine **2011**; 42(12): 719-25.

18. Albuquerque Mde F, Coimbra I, Batista J, et al. Empirical treatment for TB in HIV: lessons from a cohort study of people living with HIV treated in Recife, Brazil. BMC Public Health **2014**; 14: 289.

19. Hanrahan CF, Selibas K, Deery CB, et al. Time to treatment and patient outcomes among TB suspects screened by a single point-of-care xpert MTB/RIF at a primary care clinic in Johannesburg, South Africa. PloS One **2013**; 8(6): e65421.

20. Mupfumi L, Makamure B, Chirehwa M, et al. Impact of Xpert MTB/RIF on Antiretroviral Therapy-Associated Tuberculosis and Mortality: A Pragmatic Randomized Controlled Trial. Open Forum Infect Dis **2014**; 1(1): ofu038.

21. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. Int J Tuberc Lung Dis **2011**; 15(7): 871-85.

22. Hargreaves NJ, Kadzakumanja O, Phiri S, et al. What causes smear-negative pulmonary tuberculosis in Malawi, an area of high HIV seroprevalence? Int J Tuberc Lung Dis **2001**; 5(2): 113-22.

23. Hargreaves NJ, Kadzakumanja O, Whitty CJ, Salaniponi FM, Harries AD, Squire SB. 'Smear-negative' pulmonary tuberculosis in a DOTS programme: poor outcomes in an area of high HIV seroprevalence. Int J Tuberc Lung Dis **2001**; 5(9): 847-54.

24. Campos LC, Rocha MV, Willers DM, Silva DR. Characteristics of Patients with Smear-Negative Pulmonary Tuberculosis (TB) in a Region with High TB and HIV Prevalence. PloS One **2016**; 11(1): e0147933.

25. International Epidemiology Databases to Evaluate AIDS (IeDEA). Available at: https://www.iedea.org. Accessed January 31, 2019.

26. Egger M, Ekouevi DK, Williams C, et al. Cohort Profile: the international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa. Int J Epidemiol **2012**; 41(5): 1256-64.

27. World Health Organisation. Treatment of tuberculosis: guidelines – 4th ed.: Geneva, Switzerland: WHO; 2010. Available at: https://www.who.int/tb/publications/2010/9789241547833/en/. Accessed November 20, 2018.

28. Koenig SP, Kim A, Shepherd BE, et al. Increased Mortality after Tuberculosis Treatment Completion in Persons with HIV in Latin America. Clin Infect Dis. **2019** Oct 20 DOI: 10.1093/cid/ciz1032. Epub ahead of print.

29. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol **2008**; 61(4): 344-9.

30. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform **2009**; 42(2): 377-81.

31. Charles MK, Lindegren ML, Wester CW, et al. Implementation of Tuberculosis Intensive Case Finding, Isoniazid Preventive Therapy, and Infection Control ("Three I's") and HIV-Tuberculosis Service Integration in Lower Income Countries. PloS One **2016**; 11(4): e0153243.

32. Fenner L, Ballif M, Graber C, et al. Tuberculosis in antiretroviral treatment programs in lower income countries: availability and use of diagnostics and screening. PloS One **2013**; 8(10): e77697.

33. World Health Organisation. Global Tuberculosis Report 2017. Geneva, Switzerland: WHO; 2017. Available at: http://apps.who.int/medicinedocs/en/m/abstract/Js23360en/. Accessed December 12, 2018.

34. GBD Tuberculosis Collaborators. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. Lancet Infect Dis 2018;18(3):261-284.

35. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision. Geneva, Switzerland: WHO; **2013**. Available at: http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf. Accessed December 12, 2018.

36. World Health Organization. The use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV. Geneva, Switzerland: WHO; **2015**. Available at: https://www.who.int/tb/publications/use-of-lf-lam-tb-hiv/en/. Accessed December 12, 2019.

37. Centers for Disease Control and Prevention (CDC). Reported Tuberculosis in the United States, **2016**. Atlanta, GA: US Department of Health and Human Services, CDC; 2017. Available at: https://www.cdc.gov/tb/statistics/reports/2016/default.htm. Accessed May 6, 2018.

38. Teklu AM, Nega A, Mamuye AT, et al. Factors Associated with Mortality of TB/HIV Co-infected Patients in Ethiopia. Ethiop J Health Sci **2017**; 27(Suppl 1): 29-38.

39. Dawood H, Hassan-Moosa R, Zuma NY, Naidoo K. Mortality and treatment response amongst HIV-infected patients 50 years and older accessing antiretroviral services in South Africa. BMC Infect Dis **2018**; 18(1): 168.

40. Lindan CP, Allen S, Serufilira A, et al. Predictors of mortality among HIV-infected women in Kigali, Rwanda. Ann Intern Med **1992**; 116(4): 320-8.

41. Tabarsi P, Chitsaz E, Moradi A, et al. Treatment outcome, mortality and their predictors among HIV-associated tuberculosis patients. Int J STD AIDS **2012**; 23(9): e1-4.

42. Schmaltz CA, Santoro-Lopes G, Lourenco MC, Morgado MG, Velasque Lde S, Rolla VC. Factors impacting early mortality in tuberculosis/HIV patients: differences between subjects naive to and previously started on HAART. PloS One **2012**; 7(9): e45704.

43. Mugusi FM, Mehta S, Villamor E, et al. Factors associated with mortality in HIV-infected and uninfected patients with pulmonary tuberculosis. BMC Public Health **2009**; 9: 409.

44. Kourbatova EV, Leonard MK, Jr., Romero J, Kraft C, del Rio C, Blumberg HM. Risk factors for mortality among patients with extrapulmonary tuberculosis at an academic inner-city hospital in the US. Eur J Epidemiol **2006**; 21(9): 715-21.

45. Kingkaew N, Sangtong B, Amnuaiphon W, et al. HIV-associated extrapulmonary tuberculosis in Thailand: epidemiology and risk factors for death. Int J Infect Dis **2009**; 13(6): 722-9.

46. Dangisso MH, Datiko DG, Lindtjorn B. Trends of tuberculosis case notification and treatment outcomes in the Sidama Zone, southern Ethiopia: ten-year retrospective trend analysis in urban-rural settings. PloS One **2014**; 9(12): e114225.

47. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res **2007**; 16(3): 219-42.

48. Rubin DB. Inference and missing data. Biometrika **1976**; 63(3): 581-92.

49. Rubin DB. Multiple imputation for nonresponse in surveys: John Wiley & Sons, **2004**.

50. The MI Procedure. Available at: https://support.sas.com/documentation/onlinedoc/stat/141/mi.pdf. Accessed April 2, 2018.

51. Yan I, Bendavid E, Korenromp EL. Antiretroviral Treatment Scale-Up and Tuberculosis Mortality in High TB/HIV Burden Countries: An Econometric Analysis. PloS One **2016**; 11(8): e0160481.

52. Au-Yeung C, Kanters S, Ding E, et al. Tuberculosis mortality in HIV-infected individuals: a cross-national systematic assessment. Clin Epidemiol **2011**; 3: 21-9.

53. Suthar AB, Lawn SD, del Amo J, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. PLoS Med **2012**; 9(7): e1001270.

54. Saito S, Howard AA, Reid MJ, et al. TB diagnostic capacity in sub-Saharan African HIV care settings. J Acquir Immune Defic Syndr **2012**; 61(2): 216-20.

55. Bassett IV, Chetty S, Wang B, et al. Loss to follow-up and mortality among HIV-infected people co-infected with TB at ART initiation in Durban, South Africa. J Acquir Immune Defic Syndr **2012**; 59(1): 25-30.

56. Qian X, Nguyen DT, Lyu J, Albers AE, Bi X, Graviss EA. Risk factors for extrapulmonary dissemination of tuberculosis and associated mortality during treatment for extrapulmonary tuberculosis. Emerg Microbes Infect **2018**; 7(1): 102.

57. Mukadi YD, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. AIDS **2001**; 15(2): 143-52.

58. El Sahly HM, Teeter LD, Pan X, Musser JM, Graviss EA. Mortality associated with central nervous system tuberculosis. J Infect **2007**; 55(6): 502-9.

59. Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. BMC Public Health **2008**; 8: 15.

60. Djouma FN, Noubom M, Ngomba AV, Donfack H, Kouomboua PS, Saah MA. Determinants of death among tuberculosis patients in a semi urban diagnostic and

treatment centre of Bafoussam, West Cameroon: a retrospective case-control study. Pan Afr Med J **2015**; 22: 253.

61. Lawn SD, Acheampong JW. Pulmonary tuberculosis in adults: factors associated with mortality at a Ghanaian teaching hospital. West Afr J Med **1999**; 18(4): 270-4.

62. Calis J, Bakker ML, Elens RB, Borgdorff M, Harries AD. Mortality in smear-negative tuberculosis patients in Phalombe. Malawi Med J **2002**; 14(2): 13-4.

63. Harries AD, Nyirenda TE, Banerjee A, Boeree MJ, Salaniponi FM. Treatment outcome of patients with smear-negative and smear-positive pulmonary tuberculosis in the National Tuberculosis Control Programme, Malawi. Trans R Soc Trop Med Hyg **1999**; 93(4): 443-6.

64. Henegar C, Behets F, Vanden Driessche K, et al. Mortality among tuberculosis patients in the Democratic Republic of Congo. Int J Tuberc Lung Dis **2012**; 16(9): 1199-204.

65. Raviglione MC, Harries AD, Msiska R, Wilkinson D, Nunn P. Tuberculosis and HIV: current status in Africa. AIDS **1997**; 11 Suppl B: S115-23.

66. Onyango DO, Yuen CM, Cain KP, Ngari F, Masini EO, Borgdorff MW. Reduction of HIV-associated excess mortality by antiretroviral treatment among tuberculosis patients in Kenya. PloS One **2017**; 12(11): e0188235.

67. Macpherson P, Dimairo M, Bandason T, et al. Risk factors for mortality in smear-negative tuberculosis suspects: a cohort study in Harare, Zimbabwe. Int J Tuberc Lung Dis **2011**; 15(10): 1390-6.

68. Crabtree-Ramírez BE, Jenkins C, Jayathilake K, et al. HIV-related tuberculosis: mortality risk in persons without vs. culture-confirmed disease. Int J Tuberc Lung Dis **2019**; 23(3): 306-314.

69. Zurcher K, Ballif M, Fenner L, et al. Drug susceptibility testing and mortality in patients treated for tuberculosis in high-burden countries: a multicentre cohort study. Lancet Infect Dis **2019**; 19(3): 298-307.

Tables

Table 1. Patient characteristics stratified by TB bacteriologic test status.

Characteristic	Bacteriologic Test Status				
	Total ***N = 2091*** **n (%)**	**Positive test** ***N = 615*** **n (%)**	**Negative test** ***N = 907*** **n (%)**	**No test result** ***N = 569*** **n (%)**	**P value**[a]
Age, median years (IQR)	36 (30-43)	35 (30-42)	36 (30-43)	36 (29-44)	0.779
Female sex	910 (44)	266 (43)	385 (42)	259 (46)	0.505
BMI, median mg/kg^2 (IQR)	19 (17-21)	18 (17-21)	19 (17-21)	19 (17-22)	0.001
Missing	374 (18)	86 (14)	89 (10)	199 (35)	
ART status at TB treatment initiation					0.069
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					0.612
< 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]					<0.001
Pulmonary	1646 (79)	564 (92)	732 (81)	350 (62)	
Miliary	18 (1)	0 (0)	13 (2)	5 (1)	0.011
Extrapulmonary	422 (20)	49 (8)	172 (19)	201 (35)	
Pleural	79 (22)	3 (10)	36 (23)	40 (20)	<0.001
Lymphatic	73 (20)	20 (67)	26 (17)	27 (13)	0.149
Bone and/or joint	12 (34)	1 (3)	5 (3)	6 (3)	0.129
Abdominal[c]	34 (10)	3 (10)	18 (11)	13 (7)	0.027
Pericardial	7 (2)	0 (0)	4 (3)	3 (2)	0.276
Genitourinary	1 (<1)	1 (3)	0 (0)	0 (0)	0.566
CNS and/or meningeal	21 (6)	1 (3)	13 (8)	7 (3)	0.042
Laryngeal	1 (<1)	0 (0)	1 (1)	0 (0)	1.000
Other	25 (7)	0 (0)	11 (7)	14 (7)	<0.001
Not specified	23 (1)	2 (<1)	3 (<1)	18 (3)	<0.001

CNS, central nervous system; IQR, interquartile range

[a] P values comparing the three groups were calculated using ANOVA F-test, chi-square test, Kruskal-Wallis test, and Fisher's 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* n (%)	Positive test *N = 615* n (%)	Negative test *N = 907* n (%)	No test *N = 569* n (%)	P value[a]
IeDEA region					<0.001
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					<0.001
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					<0.001
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					<0.001
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					<0.001
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					<0.001
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)	

[a] ANOVA F-test, chi-square test, Kruskal-Wallis test, Fisher's exact test 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.

Table 3. Hazard ratios for death within 12 months following TB treatment initiation.

Characteristic	Complete Case Analysis[a]		Multiple Imputation Analysis[b]	
	Univariate HR	Multivariable HR[c]	Univariate HR	Multivariable HR[c]
	N = 1258	*N = 1258*	*N = 1953*	*N = 1953*
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (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 (years)	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)

HR, hazard ratio; CI, confidence interval; Ref., reference

[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.

Figure legends

Figure 1. Numbers in parentheses indicate the number of patients contributed by participating IeDEA programs in each country. Map created in January 2019 by J.H. using Tableau Public 2018.3.2 (Tableau Software, Seattle, WA).

Figure 2. Red, positive tess group; blue, negative test group; grey, no test result group.

Figures

Figure 1. Patients included in the analysis by IeDEA region and country.

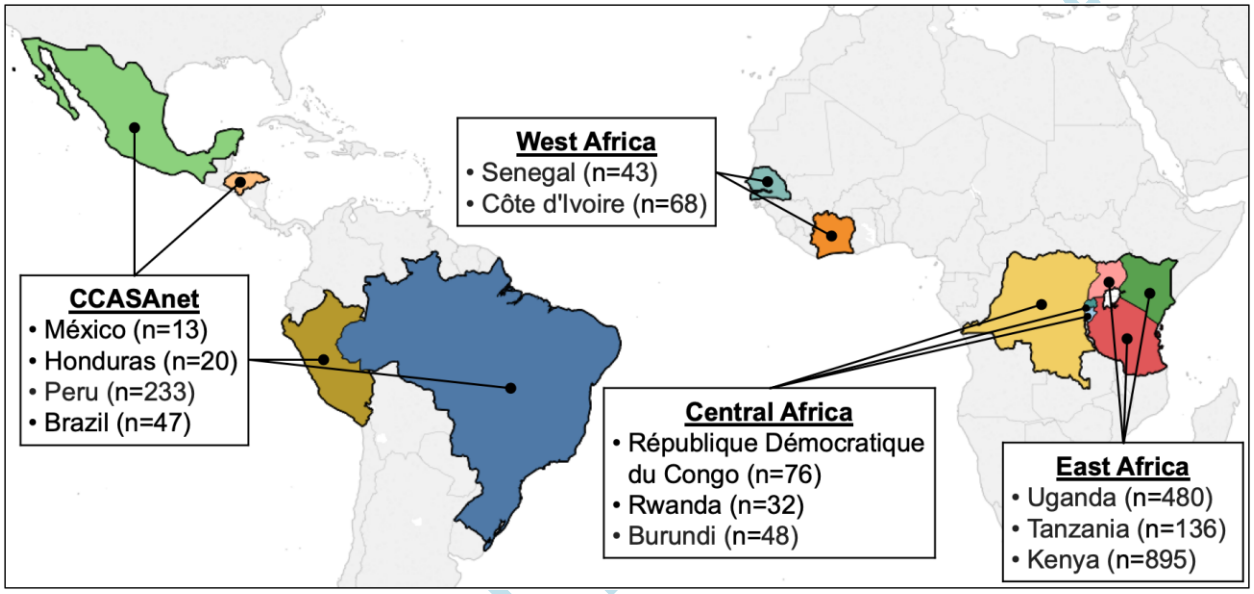
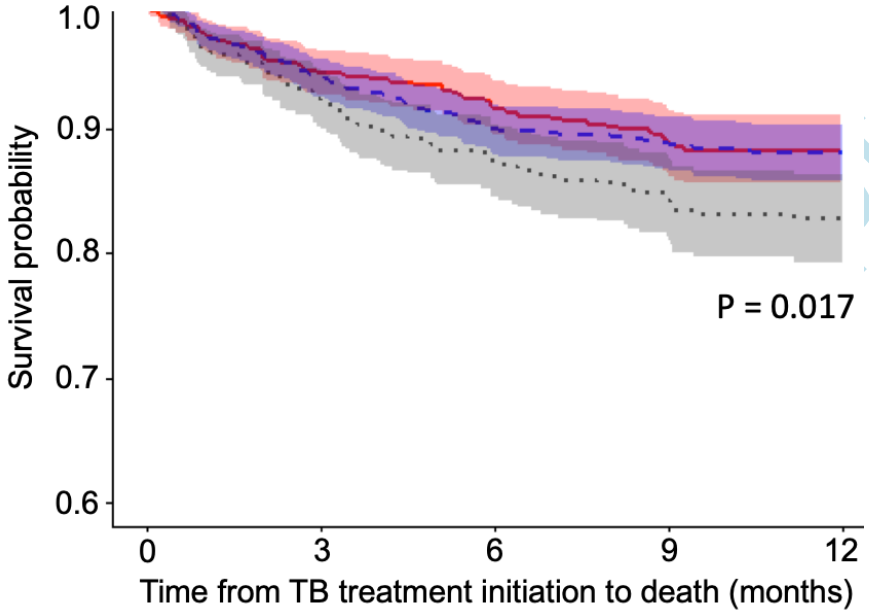


Figure 2. Cumulative incidence of survival after TB treatment initiation, stratified by TB bacteriologic test status. Red, positive test group; blue, negative test group; grey, no test result group.



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