

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

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[^] Membership in the IeDEA consortium for the participating programs is provided in the Supporting Information (S8 Table).

Short title: Mortality among adults with HIV treated for TB

1 **Abstract**

2 **Background**

3 In resource-constrained settings, people living with HIV (PLWH) treated for tuberculosis (TB)
4 despite negative bacteriologic tests have a higher mortality than those treated with positive tests.
5 Many PLWH are treated without bacteriologic testing; their mortality compared to those with
6 bacteriologic testing is uncertain.

7 8 **Methods**

9 We conducted an observational cohort study among PLWH ≥ 15 years of age who initiated TB
10 treatment at clinical sites affiliated with four regions of the International epidemiology Databases
11 to Evaluate AIDS (IeDEA) consortium from 2012-2014: Caribbean, Central and South America,
12 and Central, East, and West Africa. The primary exposure of interest was the TB bacteriologic
13 test status at TB treatment initiation: positive, negative, or no test result. The hazard for death in
14 the 12 months following TB treatment initiation was estimated using the Cox proportional
15 hazard model, adjusted for patient- and site-level factors. Missing covariates were multiply
16 imputed.

17 18 **Results**

19 Among 2,091 PLWH included, the median age at TB treatment initiation was 36 years, 44%
20 were female, 53% had CD4 counts ≤ 200 cells/mm³, and 52% were on antiretroviral treatment
21 (ART). Compared to patients with positive bacteriologic tests, the adjusted hazard for death was
22 higher among patients with no test results (HR 1.56, 95% CI 1.08-2.26) but not different than

23 those with negative tests (HR 1.28, 95% CI 0.91-1.81). Older age was also associated with a
24 higher hazard for death, while being on ART, having a higher CD4 count, West Africa region,
25 and tertiary facility level were associated with lower hazards for death.

26

27 **Conclusion**

28 PLWH treated for TB with no bacteriologic test results were more likely to die than those treated
29 with positive tests, underscoring the importance of TB bacteriologic diagnosis in resource-
30 constrained settings. Research is needed to understand the causes of death among PLWH treated
31 for TB in the absence of positive bacteriologic tests.

32 **Introduction**

33 Although tuberculosis (TB) accounted for 300,000 deaths among people living with HIV
34 (PLWH) in 2017, diagnosing TB in resource-limited settings remains a challenge [1]. In 2017,
35 only 56% of the 5.5 million pulmonary TB cases reported to the World Health Organization
36 (WHO) globally were bacteriologically confirmed (i.e. positive for smear microscopy, culture, or
37 nucleic acid amplification test [NAAT]) [1]. Among studies reporting the autopsy prevalence of
38 TB in HIV-related deaths, TB was prevalent in 37% of deaths, but in half of those cases, TB was
39 not diagnosed by the time of death [2]. The rollout of nucleic acid amplification tests (NAAT)
40 such as the Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), which are more sensitive and
41 specific than smear microscopy, has helped close this diagnostic gap [3]. However, limited
42 impact on mortality has been observed with the use of Xpert MTB/RIF, in part due to high
43 baseline rates of empiric TB treatment (i.e. based on clinical symptoms or radiographic signs) in
44 high TB burden settings [3-5]. A better understanding of the risk of death among PLWH in the
45 context of varying TB test results, or the absence of TB testing, is needed to inform the
46 management of PLWH treated for TB in resource-limited settings where the risk of TB is high.

47
48 Acquiring a bacteriologic diagnosis of TB in resource-limited settings can be hampered by
49 economic, clinical and test-related factors. Despite recent increases in TB diagnostic test
50 coverage in sub-Saharan Africa, smear microscopy and culture is estimated to be available at
51 only 1.4 and 0.7 laboratories per 100,000 population, respectively [6, 7]. Many labs in resource-
52 constrained settings suffer from weak supply systems, outdated equipment, poor quality control,
53 and insufficient staffing [6, 8-10]. Smear microscopy for acid-fast bacilli (AFB) is often the only
54 TB test available in such settings but it is poorly sensitive among PLWH, with 30-60% of

55 pulmonary TB cases reported to be smear negative [11-13]. Clinicians may not order
56 bacteriologic testing for TB among PLWH due to lack of knowledge about TB (or conversely,
57 knowledge of the limitations of smear microscopy), or in cases of suspected extrapulmonary TB
58 requiring invasive tissue sampling that is not feasible to perform [5, 8, 14, 15]. Patients may not
59 be able to produce a sputum sample for bacteriologic testing or access TB testing sites (e.g. for
60 serial sputum collection) due to the distance or cost of transport [8, 16, 17].

61
62 Empiric TB treatment in PLWH, either because a bacteriologic test was negative or no test was
63 performed, is thus common in resource-limited settings [4, 5, 18-20]. However, mortality in the
64 absence of TB bacteriologic testing is not well defined [21-24]. The objective of this study was
65 to describe the characteristics and risk of death among PLWH treated for TB in the context of
66 positive, negative, or no TB bacteriologic test results.

67

68 **Materials and Methods**

69 **Study setting and patient population**

70 This observational cohort study utilized data previously collected from PLWH who were
71 enrolled in HIV care programs affiliated with four participating regions of the International
72 epidemiology Databases to Evaluate AIDS (IeDEA) consortium: Caribbean, Central and South
73 America (CCASAnet), and Central, East, and West Africa [25]. IeDEA is a National Institutes of
74 Health (NIH)-funded consortium that pools and harmonizes baseline and follow-up patient data
75 collected in the context of routine care [26]. All participating facilities provided standard of care
76 HIV and TB treatment services per their respective national guidelines. The study population
77 included all PLWH ≥ 15 years of age who initiated TB treatment between January 2012 and

78 December 2014. Patients were excluded if an alternative diagnosis was established and TB
79 therapy was stopped. Recurrent TB cases within the study period were excluded (n = 41), so a
80 patient could not contribute more than one TB case. Patients receiving a drug-resistant TB
81 treatment regimen were also excluded, which was defined according to WHO criteria as any
82 injectable agent (except streptomycin), fluoroquinolones, or oral bacteriostatic agent (e.g. para-
83 aminosalicylic acid, ethionamide, cycloserine) [27]. The reporting of this study conforms to the
84 STROBE statement (S1 Table) [28].

85

86 **Ethics statement**

87 Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approval for this study
88 was obtained by each of the local IeDEA sites as well as from the Indiana University IRB (S2
89 Table).

90

91 **Data management**

92 TB cases were identified at participating IeDEA sites through review of local TB registries by
93 site staff. A standardized, electronic case report form developed in Research Electronic Data
94 Capture (REDCap) and available in English and French was used to collect medical record data
95 [29]. Data entry into case report forms was conducted from January 2012 through January 2016
96 by local IeDEA investigators following medical record review. Patient-level HIV data were
97 obtained from the IeDEA regional HIV care and treatment data repositories for all patients with
98 completed case report forms. Site-level data were obtained from surveys of antiretroviral
99 treatment (ART) sites participating in IeDEA conducted between March 1 and July 1, 2012 [30,
100 31]. Routine audits were performed to ensure data quality throughout data collection. Regional

101 IeDEA data were transferred to the IeDEA-East Africa Regional Data Center where they were
102 merged, and additional data quality assessments were undertaken before analysis.

103

104 **Study definitions**

105 Adult patients were defined as individuals ≥ 15 years of age to be consistent with WHO and
106 other national and regional TB programs [32, 33]. The primary exposure of interest was the TB
107 bacteriologic test status at the time of TB treatment initiation: *Positive test* group included
108 patients with one or more positive results including acid fast bacilli (AFB) smear, culture, or
109 NAAT; *Negative test* group included patients for whom one or more of these bacteriologic tests
110 were performed and none were positive; *No test* group includes patients for whom no
111 bacteriologic test was performed or results reported [34]. Patient-level variables at TB treatment
112 initiation included: age, sex, body mass index (BMI), ART status at TB treatment initiation (on
113 ART vs. not on ART), CD4 count (defined as the nearest value within 180 days before or 30
114 days after TB treatment initiation), TB disease site (pulmonary vs. extrapulmonary, and specific
115 extrapulmonary site(s)), and type of bacteriologic TB test (smear, culture, NAAT; the specimen
116 type [e.g. respiratory vs. non-respiratory] was not available). TB disease site was categorized
117 into pulmonary and extrapulmonary according to the WHO and CDC reporting definitions [32,
118 34, 35]. Accordingly, pulmonary TB included any case involving the lung parenchyma or
119 tracheobronchial tree, and miliary TB with lesions in the lungs; extrapulmonary TB included
120 cases involving organs other than the lungs; cases of combined pulmonary and extrapulmonary
121 TB were classified as pulmonary TB.

122

123 Site-level variables included IeDEA region (CCASAnet, Central Africa, East Africa, West

124 Africa), setting (urban, peri-urban [i.e. immediately adjoining urban areas], facility level
125 (secondary [i.e district or provincial facilities] or tertiary [i.e regional or referral facilities]),
126 availability of specialized clinic/ward on site with dedicated staff for TB patients (on site, off
127 site, or not available), physical proximity of HIV/TB clinical services (same facility or same day
128 appointments, cross referral between HIV and TB service points, provision of TB and HIV
129 services under the same roof, or none of these models), and active screening for TB performed
130 for all PLWH at enrollment (only symptom screening, symptom screening plus additional
131 diagnostics, or in case of clinical suspicion). Site-level variables were applied to each patient
132 within the site as an individual characteristic. The main outcome variable was death. Patients
133 were followed from TB treatment initiation until death or censoring within the 12 months post-
134 treatment initiation or June 1, 2015. All the non-death events within the 12 months of follow-up
135 were considered censored events.

136

137 **Data analysis**

138 Patient characteristics were summarized overall and by each bacteriologic test group. Categorical
139 variables were summarized using frequencies and proportions; continuous variables were
140 summarized using medians and interquartile ranges. Differences between bacteriologic test
141 groups were assessed using one-way ANOVA or Kruskal-Wallis tests for continuous variables
142 and Pearson Chi-squared test or Fisher's exact tests for categorical variables. Cumulative
143 incidence of survival, stratified by bacteriologic test group, was estimated using the Kaplan-
144 Meier method. The log-rank test was used for testing equality of survival among the levels of
145 categorical covariates. The Cox proportional hazard model was used to estimate the univariate
146 and multivariate associations of covariates and the hazard for death. Independent variables

147 included in this model were sex, age, BMI, CD4 count, ART status at TB treatment initiation,
148 TB disease site, IeDEA region, and facility level. These variables were selected a priori because
149 of their associations with adverse TB treatment outcomes in prior studies [21, 36-44]. The other
150 site variables were not included in the model due to co-linearity with each other and the facility
151 level variable.

152
153 The proportional hazards assumption was assessed using the supremum-type goodness of fit test.
154 The impact of missingness on the observed hazard associations was assessed by refitting the
155 models after imputing missing covariate values. In this analysis, missing values for CD4 count,
156 BMI, and ART status at TB treatment initiation were multiply imputed using the fully
157 conditional specification (FCS), where these covariates were assumed to be jointly distributed
158 [45]. We did not impute missing values for cases with missing facility level, TB disease site, or
159 simultaneously missing BMI, ART status, and CD4 count. Imputation followed Rubin's scheme:
160 missing values were imputed 100 times; Cox proportional hazards models were fit for the 100
161 complete datasets; and, results were pooled to obtain overall effect estimates [46, 47]. Imputation
162 analysis was performed using the PROC MI procedure in SAS [48]. Analyses were performed at
163 the 0.05 alpha level.

164
165 In a secondary analysis comparing the hazard for death among those with any bacteriologic test
166 (positive or negative) vs. no test results, we used logistic regression to build a propensity score
167 model for the log odds of having any bacteriologic test given imbalance of covariates in the test
168 groups (i.e. any test vs. no test). The independent variables included in this model were the same
169 as those used in the primary analysis. Missing values for CD4 count, BMI, and ART status were

170 also multiply imputed. The imputation and propensity model were performed as follows: 1)
171 missing values were imputed separately for those with and without a bacteriologic test; 2)
172 propensity model was fit; 3) stabilized inverse probability weights (IPWs) were constructed
173 using the predicted propensities, checking if the mean of weights was close to one (S3 Table); 4)
174 the proportional hazards model was fit for time to death conditional on having any bacteriologic
175 test, weighted by the IPWs to obtain an estimate of log hazards ratio and its robust standard error
176 estimate. These steps were repeated 100 times and the resulting log-hazards ratio estimates and
177 their standard errors pooled using Rubin's rules.

178

179 **Results**

180 **Patient and site-level characteristics**

181 Among 2,140 patients in the database, a total of 49 were excluded for initiating TB treatment
182 outside of the study period (n=32) or before the TB diagnosis date (n=1), documentation errors
183 (n=13), and receiving TB treatment regimens for drug-resistant TB (n=3). Thus, 2,091 patients
184 were included in the analysis. These patients received care in 12 countries in the four
185 participating IeDEA regions (Fig 1).

186

187 **Fig 1. Patients included in the analysis by IeDEA region and country.** Numbers in
188 parentheses indicate the number of patients contributed by participating IeDEA programs in each
189 country. Map created in January 2019 by John Humphrey using Tableau Public 2018.3.2
190 (Tableau Software, Seattle, WA).

191

192 A total of 615 (29%) had positive bacteriologic tests for TB, 907 (43%) had negative tests, and
193 569 (27%) had no test results (Table 1). The median age was 36 years, 44% were female, and the
194 median BMI was 19 kg/m². Overall, 52% were on ART at TB treatment initiation, and the

195 proportions of patients in each bacteriologic test group who were on ART at TB treatment
 196 initiation were: positive test (56%), negative test (52%), and no TB test results (38%) ($P =$
 197 0.069). The CD4 count was ≤ 200 cells/mm³ in 53% of patients. A total of 79% had pulmonary
 198 TB and 20% had extrapulmonary TB; the TB disease site was not specified in 1% of patients.
 199 The proportions of patients with extrapulmonary TB were significantly different between the
 200 three bacteriologic groups, with extrapulmonary TB in 35% of patients with no TB test result,
 201 compared to 8% of patients with a positive test and 19% with a negative test ($P < 0.001$). The
 202 most commonly reported extrapulmonary sites were bone and joint (34%) and pleura (22%).

203
 204
 205

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

Characteristic	Bacteriologic Test Status				P value ^a
	Total <i>N</i> = 2091 n (%)	Positive test <i>N</i> = 615 n (%)	Negative test <i>N</i> = 907 n (%)	No test result <i>N</i> = 569 n (%)	
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)	19 (17-21)	19 (17-21)	20 (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/mm³					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

206 ART, antiretroviral treatment; BMI, body mass index; CNS, central nervous system; IQR, interquartile range; TB,
207 tuberculosis

208 ^a P values comparing the three groups were calculated using ANOVA F-test, chi-square test, Kruskal-Wallis test,
209 and Fisher's exact test.

210 ^b Percentages of extrapulmonary sites refer to the total extrapulmonary sites; each patient could have > 1
211 extrapulmonary site.

212 ^c Includes peritoneum, omentum, liver, spleen, and colon.

213 The East Africa IeDEA region contributed 72% of patients overall (Table 2). In this region,
214 twice as many patients had a negative bacteriologic test (n=734) compared to a positive test
215 (n=397) or no test (n=380). In contrast, more than twice as many patients in West Africa had
216 either a positive (n=40) or negative test (n=52) compared to no test (n=19). Overall, more
217 patients attended facilities that were peri-urban (47%) than urban (26%) or rural (23%). Among
218 rural facilities, more patients had a negative test (n=324) than either a positive test (n=84) or no
219 test results (72). A total of 88% of patients overall attended tertiary facilities, and there were
220 more patients attending these facilities in the group with negative tests (n=812) than the groups
221 with positive tests (n=472) or no test results (n=485). Finally, 93% of patients attended facilities
222 with a specialized TB clinic/ward available on site, 69% attended facilities with same facility or
223 same day HIV/TB service appointments, and 81% attended facilities with active screening for
224 TB among all PLWH at enrollment that included symptom screening plus additional diagnostics.
225 Site-level differences between the three test groups were significant for all characteristics
226 measured ($P < 0.001$ for all).
227

228 **Table 2. Patient distribution by site characteristics, stratified by TB bacteriologic test**
 229 **status.**
 230

Characteristic	Bacteriologic Test Status				P value ^a
	Total	Positive test	Negative test	No test	
	<i>N</i> = 2091 n (%)	<i>N</i> = 615 n (%)	<i>N</i> = 907 n (%)	<i>N</i> = 569 n (%)	
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 PLWH 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)	

231 CCASAnet, Caribbean, Central and South America; PLWH, people living with HIV; TB, tuberculosis
 232 ^a ANOVA F-test, chi-square test, Kruskal-Wallis test, Fisher's exact test performed for each variable as
 233 appropriate.

234 ^b Additional testing examples include sputum AFB, sputum induction, gastric lavage, tissue biopsy, chest
 235 x-ray, gene x-pert, urine lipoarabinomannan (LAM), tuberculin skin testing.

236 AFB smear was performed in 71% of patients (1,493 of 2,091) (Table 3). Culture and NAAT
 237 were performed in 8% and 3% of patients, respectively. Among 618 patients with a positive test
 238 (whereby ≥ 1 test type may be performed for each patient), 90% had a positive AFB smear, 16%
 239 had a positive culture, and 6% had a positive NAAT. Among 907 patients with a negative test
 240 (also including ≥ 1 test type), 99% had a negative AFB smear, 6% had a negative culture, and
 241 3% had a negative NAAT. Among patients who had results from more than one test type
 242 reported, 75% with a positive AFB smear also had a positive culture (64 of 85) and 35% with a
 243 negative AFB smear also had a positive culture (27 of 78) (S4 Table). Among those who had
 244 AFB smear and NAAT results reported, 63% with a positive smear had a positive NAAT (10 of
 245 16) and 38% with a negative smear had a positive NAAT (14 of 37).

246

247 **Table 3. Summary of bacteriologic test results.**

248

Characteristic	Bacteriologic Test Status		
	Total tests	Positive test	Negative test
	<i>N</i> = 2091 n (%)	<i>N</i> = 615 n (%)	<i>N</i> = 907 n (%)
AFB smear			
Positive	553 (26)	553 (90)	0 (0)
Negative	940 (45)	41 (7)	899 (99)
Not performed / no result	598 (29)	21 (3)	8 (1)
Culture			
Positive	98 (5)	98 (16)	0 (0)
Negative	75 (4)	22 (4)	53 (6)
Not performed / no result	1918 (91)	495 (80)	854 (94)
Nucleic acid amplification			
Positive	38 (2)	38 (6)	0 (0)
Negative	34 (2)	11 (2)	23 (3)
Not performed / no result	2019 (96)	566 (92)	884 (97)

249 AFB, acid-fast bacilli

250

251 **Mortality outcome**

252 A total of 243 (12%) deaths were reported in the study cohort: 64 (10%) deaths among those
253 with a positive test, 99 (11%) among those with a negative test, and 80 (14%) in those with no
254 test results ($P = 0.099$). The ordering of the survival function in the Kaplan-Meier curve
255 suggested a significant difference in the cumulative incidence of survival between the three
256 bacteriologic test groups. ($P = 0.017$) (Fig 2).

257

258 **Fig 2. Cumulative incidence of survival after TB treatment initiation, stratified by TB**
259 **bacteriologic test status.** Red, positive test group; blue, negative test group; grey, no test result
260 group.
261

262 **Complete case analyses**

263 In the unadjusted and adjusted complete case analyses (adjusted for age, sex, BMI, ART status at
264 TB treatment initiation, CD4 count, TB disease site, region, and facility level), the hazards of
265 death were not significantly higher for those treated for TB with no TB bacteriologic test results
266 (adjusted HR [aHR] 0.87, 95% CI 0.49-1.55) or negative TB tests (aHR 1.19, 95% CI 0.73-1.93)
267 compared to those with positive tests (Table 4). Factors significantly associated with a lower
268 hazard for death in the unadjusted and adjusted analyses included being on ART at TB treatment
269 initiation (aHR 0.57, 95% CI 0.39-0.84) and having a higher CD4 count at TB treatment
270 initiation (e.g. compared to those with CD4 count < 100 cells/mm³, the aHR for death among
271 those with a CD4 count of 100-200 cells/mm³ was 0.39, 95% CI 0.23-0.65).

272

273 **Table 4. Hazard ratios for death within 12 months following TB treatment initiation.**
274

Characteristic	Complete Case Analysis ^a		Multiple Imputation Analysis ^b	
	Unadjusted HR <i>N</i> = 1258 HR (95% CI)	Adjusted HR ^c <i>N</i> = 1258 HR (95% CI)	Unadjusted HR <i>N</i> = 1953 HR (95% CI)	Adjusted HR ^c <i>N</i> = 1953 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/kg²)	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)

275 ART, antiretroviral treatment; BMI, body mass index; CCASAnet, Caribbean, Central and South America; HR,
276 hazard ratio; CI, confidence interval; Ref., reference; TB, tuberculosis

277 ^a Includes all patients without missing values for the variables listed in the table.

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

281 ^c Adjusted for all of the variables listed in the table.

282 **Multiple imputation analyses**

283 Of 2,091 patients in the study, 1,258 (60%) were complete cases with respect to the analysis
284 model. Of the 833 subjects with missing values, we did not perform imputation for 138 cases.
285 Thus, each imputed dataset had 1,953 subjects. After imputation of missing CD4 count, BMI,
286 and ART status at TB treatment initiation, the unadjusted multiple imputation analysis showed
287 that the hazard for death was significantly higher among those with no test result compared to
288 those with a positive test (HR 1.57, 95% CI 1.11-2.23) (Table 4). In this analysis, older age was
289 significantly associated with a higher hazard for death (HR 1.02, 95% CI 1.004-1.03). Factors
290 significantly associated with a lower hazard for death included being on ART at TB treatment
291 initiation (HR 0.64, 95% CI 0.48-0.85), having a higher CD4 count (e.g. HR for those with CD4
292 count of 100-200 cells/mm³ was 0.66, 95% CI 0.46-0.95), and tertiary facility level (HR 0.61,
293 95% CI 0.43-0.88). In the adjusted analysis (adjusted the same covariates as in the complete case
294 analysis), the hazard for death was significantly associated with having no test result compared
295 to a positive test (aHR 1.56, 95% CI 1.08-2.26), and there was no difference between those with
296 a positive test and negative test (aHR 1.28, 95% CI 0.91-1.81). Similar to the unadjusted
297 analysis, factors associated with a lower hazard for death included being on ART at TB treatment
298 initiation, having a higher CD4 count and tertiary facility level, as well as West Africa IeDEA
299 region (aHR 0.38, 95% CI 0.16-0.91).

300

301 **Secondary analysis**

302 The propensity model for the log-odds of having any bacteriologic test (positive or negative) vs.
303 no test result demonstrated that CD4 count, BMI, TB disease site, facility level, and IeDEA
304 region were each associated with the log odds of having a test (S5 Table). In the odds ratio scale,

305 the adjusted odds of having any test among those with extrapulmonary TB, for example, was
306 45% lower than the odds for those with pulmonary TB ($P < 0.0001$) (S6 Table). This model was
307 used to estimate the propensity scores, which were in turn used to compute the stabilized IPWs.
308 For each of the 100 analyses combining multiple imputation and propensity score analysis, the
309 stabilized IPWs were found to have an average close to 1. The stabilized IPWs were then used in
310 fitting 100 adjusted Cox models for time to death conditional on whether or not a bacteriologic
311 test had been performed (i.e. test vs. no test). The pooled results for the IPW proportional
312 hazards models demonstrated that the adjusted hazard for death was 28% lower among those
313 with any bacteriologic test compared to those with no test results, but the effect was not
314 significant at the 0.05 alpha level (aHR 0.81, 95% CI 0.61-1.07) (S7 Table).

315

316 **Discussion**

317 In this study, PLWH treated for TB in our cohorts in the absence of TB bacteriologic test results
318 had a higher adjusted hazard for death than those treated for TB with positive TB bacteriologic
319 test results. Unlike those with bacteriologically confirmed TB disease (i.e. the positive test
320 group), it is plausible that those with no bacteriologic test results were a heterogeneous population
321 of individuals with TB as well as other life-threatening diseases (e.g. opportunistic infections,
322 cancers, chronic lung diseases) that may have mimicked TB but advanced untreated while the
323 patient received TB treatment, resulting in excess mortality. This, along with the 12-month
324 mortality outcome, suggests that not all patients who initiated TB treatment had TB disease and
325 not all deaths were TB-attributable.

326

327 Differences in TB disease site or severity between those with positive and no test results may
328 also have influenced mortality. As expected, the proportion of patients with pulmonary TB was
329 higher among those with positive tests (92%) compared to those with no test results (62%) ($P <$
330 0.001). This reflects the challenge of acquiring a bacteriologic diagnosis in suspected
331 extrapulmonary TB (which often requires invasive tissue sampling) compared to pulmonary TB
332 (which requires sputum sampling) in resource-constrained settings. Additionally, bacteriologic
333 testing for extrapulmonary TB is less sensitive in general compared to pulmonary TB,
334 extrapulmonary TB is more common in PLWH, certain extrapulmonary TB types (e.g.
335 disseminated or meningitis) are associated with especially high mortality in PLWH, and
336 extrapulmonary TB has been associated with delays in diagnosis [40, 42, 43, 49-52]. These
337 features may also have influenced clinicians to forego bacteriologic testing and initiate empiric
338 TB treatment among individuals that were already at increased risk of death. TB disease site was
339 not associated with mortality in our analyses, but we could not account for group variability in
340 extrapulmonary TB sites that may have influenced this outcome.

341
342 We also found that PLWH attending tertiary facilities had a lower adjusted hazard for death
343 compared to those attending secondary facilities. Compared to tertiary facilities, secondary
344 facilities may have had less capacity to evaluate and manage TB, or its alternative diagnoses, in
345 PLWH [53]. This finding may also have been biased by differences in the completeness of death
346 ascertainment between higher and lower-resourced facilities, the latter being potentially more
347 susceptible to undocumented loss to follow-up or transfer events not captured in our dataset [54].
348 Differences in vital status ascertainment may also have accounted for the regional differences in
349 the hazards for death (West Africa vs. CCASAnet) identified in our study.

350

351 Consistent with the literature, we found that being on ART and having higher CD4 count at TB
352 treatment initiation were both strongly protective against mortality. This underscores the
353 fundamental importance of early ART initiation and immune preservation on survival, regardless
354 of the presence or result of TB bacteriologic testing, in resource-constrained settings. Advanced
355 HIV immunosuppression is known to be a critical risk factor for TB-related mortality (including
356 mortality ≥ 1 year after completion of TB therapy), and the scale-up of ART coverage has been
357 associated with marked reductions in TB incidence and mortality in countries with high HIV and
358 TB burdens [20, 21, 40, 41, 55-57].

359

360 We did not find a significant difference in the adjusted hazard for death between those treated for
361 TB with any bacteriologic test (positive or negative) versus no test results in the secondary
362 analysis. This finding is consistent with a study in Brazil which found no difference in mortality
363 risk between PLWH who did or did not undergo TB bacteriologic testing [17]. This argues
364 against the notion that the presence of TB bacteriologic testing is a marker of better-resourced
365 sites (and therefore reduced mortality), as patients with a bacteriologic test would have been
366 expected to have a lower mortality than those who were not tested if that were the case. It is
367 possible that patients in both groups had similar survival simply by being engaged in facility-
368 based care.

369

370 Finally, we found no significant difference in the hazard for death between those with positive or
371 negative TB bacteriologic tests (Fig 2 and Table 3). This lack of significance may in part be
372 related to limited statistical power, as the adjusted hazard for death in those with negative tests

373 was similar to that for those with no test results (aHR 1.28 vs. 1.56). Nevertheless, this finding
374 contrasts with prior studies finding that smear-negative TB is associated with increased mortality
375 compared to smear-positive TB in PLWH. This finding has been attributed to paucibacillary
376 disease in the setting of advanced HIV, delay in diagnosis, and other opportunistic and non-
377 communicable diseases [14, 21-23, 58-65]. Similar findings have been shown with respect to
378 culture results among PLWH treated for TB, but no such studies have been performed for NAAT
379 to our knowledge [66]. The lack of mortality difference in our study could also be related to the
380 combination of smear, culture, and NAAT used to define the groups, overdiagnosis of TB in the
381 negative test group (yielding lower than expected mortality), or higher bacterial burden due to
382 more extensive TB disease or inadequate treatment of drug-resistant TB in the positive test group
383 (yielding higher than expected mortality) [67]. The 12-month mortality outcome used in our
384 study, which was selected due to limitations in the dataset, may also have influenced this finding.
385 A study from the Democratic Republic of Congo, for example, found that patients treated for
386 smear-negative TB had a higher risk of death within two months of TB treatment initiation, but
387 not after, compared to those treated for smear-positive TB [62].
388
389 Our study has strengths and limitations. Strengths include its large sample size from diverse
390 global regions and HIV/TB care programs and use of routine program data which likely reflects
391 typical care environments in the study settings. The use of routine program data is also a
392 limitation, as the completeness of vital status ascertainment may have been affected by loss to
393 follow-up or transfer events not captured in our dataset. We cannot be certain that patients with
394 no TB bacteriologic test results documented in their records did not actually have testing
395 performed. Still, the integration of TB-HIV services at the majority of sites supports that TB test

396 results would have been recorded in the medical records and case report forms if they were
397 available. Few patients had culture or NAAT performed, which limits the generalizability of our
398 study in settings where these tests are performed more commonly. We used multiple imputation
399 to reduce bias due to missing data, but the mortality estimate could still be biased if missingness
400 depended not only on the variables we used to impute missing values but also on the missing
401 values themselves (i.e., missing not at random).

402

403 In conclusion, PLWH treated for TB with no TB bacteriologic test results in our study were more
404 likely to die than those who were treated and had positive tests. Every effort should be made to
405 establish a diagnosis of TB prior to initiating TB treatment in resource-constrained settings.
406 Further research is needed to understand the causes of death among PLWH treated for TB in the
407 absence of positive bacteriologic test results.

408

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Supporting Information

591
592
593 **S1 Table. STROBE checklist.**

594
595 **S2 Table. Independent Ethics Committee or Institutional Review Board approvals obtained by**
596 **participating IeDEA sites.**

597
598 **S3 Table. Computation of stabilized inverse probability weights.**

599
600 **S4 Table. Summary of the number (%) of positive and negative bacteriologic test results in patients with**
601 **more than one test type performed.** (A) AFB smear + culture, (B) AFB smear + NAAT, (C) Culture +
602 NAAT.

603
604 **S5 Table. Propensity model results in the log of odds ratio scale.**

605
606 **S6 Table. Propensity model results in odds ratio scale.**

607
608 **S7 Table. Inverse probability weighted Cox proportional hazards model for hazard of death within 12**
609 **months following TB treatment initiation conditional on receiving a TB bacteriologic test (positive or**
610 **negative).** Includes imputation of CD4 count, body mass index (BMI), and antiretroviral treatment (ART) status
611 at TB treatment initiation.

612
613 **S8 Table: Membership of the International Epidemiology Databases to Evaluate AIDS (IeDEA)**
614 **participating programs.**

615

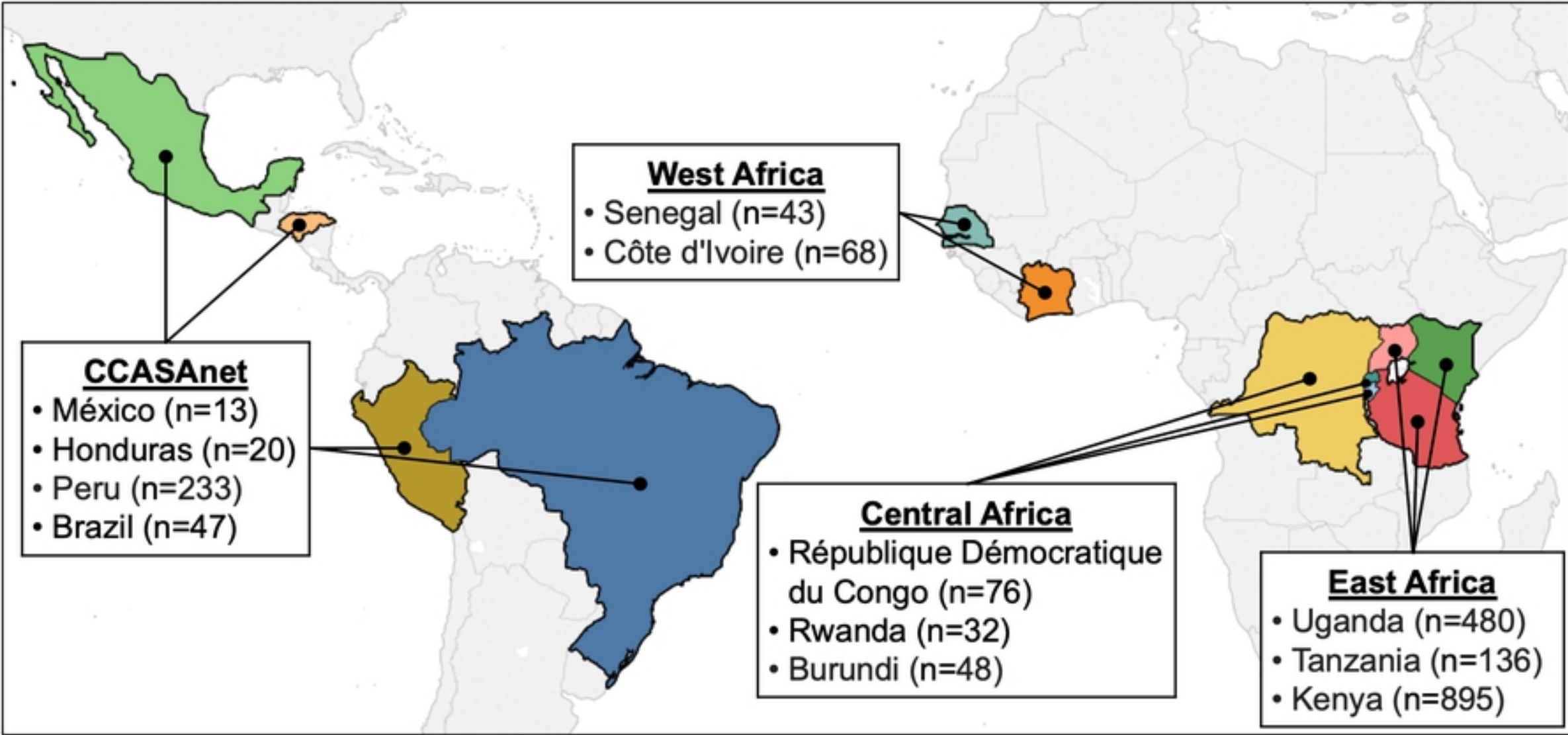
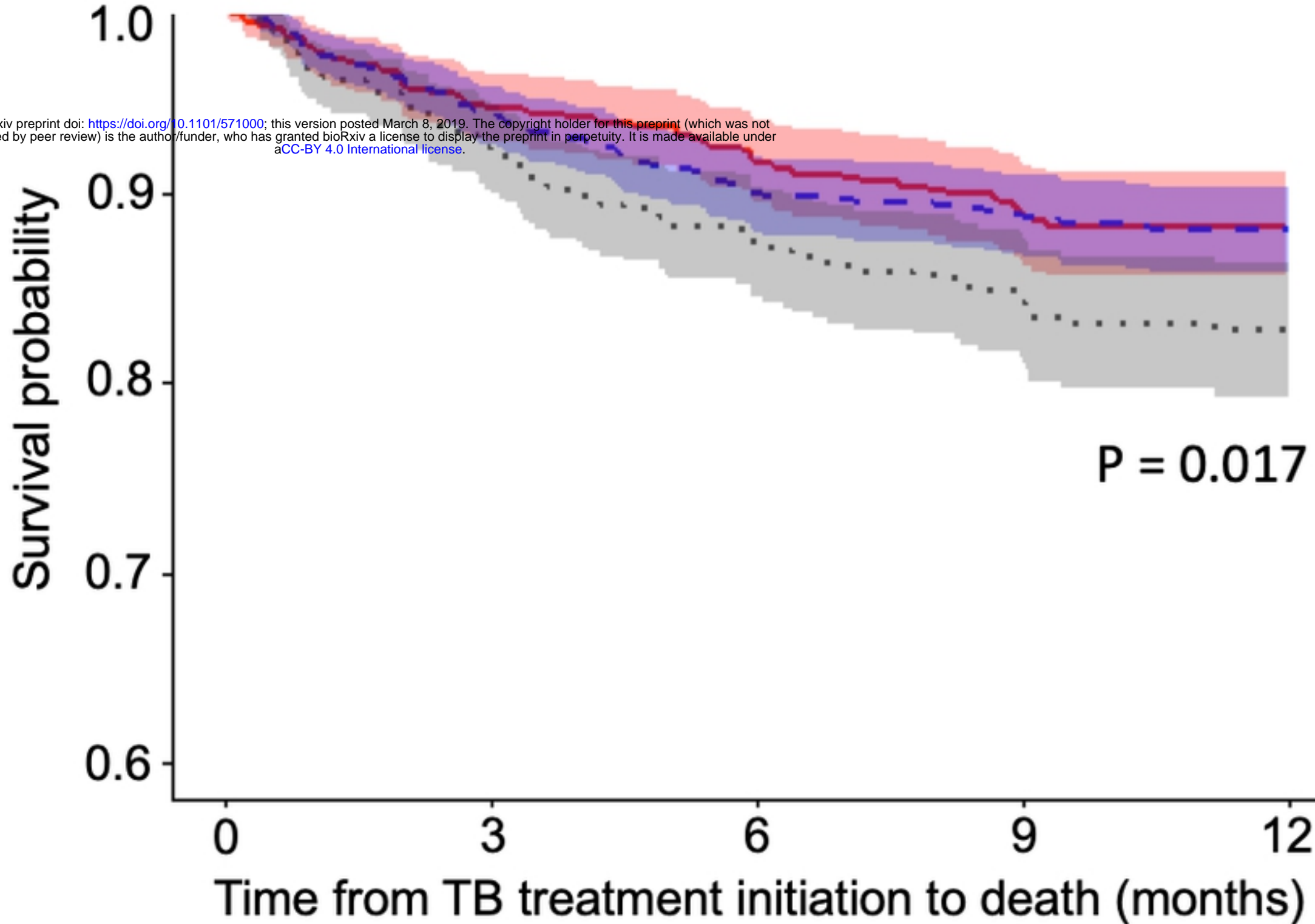


Fig 1

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<u>Bacteriologic test group</u>	<u>Number at risk</u>				
Positive test	615	556	475	373	0
Negative test	907	810	705	524	3
No test	569	452	382	297	3

Fig 2