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Tuberculosis disease characteristics associated with mortality, severe morbidity and unsuccessful treatment in people living with HIV treated for tuberculosis – a secondary analysis of the ANRS 12300 Reflate TB2 trial

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Abstract

Background Tuberculosis is a severe disease, not only due to its lethality but also to a significant morbidity occurring in people living with HIV (PLWH). If factors associated to mortality, severe morbidity and unsuccessful treatment related to the host are well identified in PLWH, there is scarce knowledge on factors related to the disease itself such as bacillary load, extent of lung involvement and disease dissemination to other organs. We sought to assess whether tuberculosis-related factors were associated with key patient outcomes in PLWH using data from an international clinical trial.

Methods We conducted a secondary analysis of the ANRS 12300 Reflate TB2, an international phase III open-label randomized trial that assessed different antiretroviral regimens in PLWH treated for tuberculosis. We evaluated whether bacillary load (smear positivity grade), extent of lung involvement (cavitation on chest x-ray) and disease dissemination (urine LAM positivity) were associated with mortality using Cox proportional hazard models, and to severe morbidity and unsuccessful tuberculosis treatment using logistic regressions.

Results Of 457 participants included in this study, 90 (20.4%) had grade 2 + or 3 + smear positivity, 39 (10.8%) had cavitation on chest X-ray, and 147 (32.2%) had a positive urinary LAM. Overall, 19 (4.2%) participants died, 113 (24.7%) presented severe morbidity, and 33 (7.2%) had unsuccessful tuberculosis treatment. Factors that remained independently associated with mortality were cavitation on chest x-ray (aHR = 7.92, 95% CI, 1.74–35.94, $p = .0073$) and LAM positivity (aHR = 5.53, 95% CI, 1.09–28.06, $p = .0389$). The only factor that remained significantly associated with severe morbidity was LAM positivity (aOR = 2.04, 95% CI, 1.06–3.92, $p = .0323$). No factor remained significantly associated with unsuccessful tuberculosis treatment.

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Conclusions In PLWH with tuberculosis enrolled in a trial, tuberculosis disease characteristics related to disease severity were cavitation on chest x-ray and urine LAM positivity. Early identification of these factors could help improve the management of PLWH with tuberculosis and improve their survival.

Keywords Tuberculosis, HIV, Mortality, Severe morbidity, Unsuccessful treatment, Bacillary load, Extent of lung involvement, Disease dissemination

Background

Tuberculosis (TB) is the leading cause of death from a single infectious agent, with 1.25 million deaths estimated in 2023 [1]. In people living with Human Immunodeficiency Virus (PLWH), TB is the leading opportunistic infection, with 662 000 cases in 2023, and the first cause of death, accounting for 161 000 deaths in the same year [1], as also shown by autopsy studies [2–6]. As such, in PLWH, TB is a severe disease, not only due to its lethality but also to significant morbidity requiring hospitalization or prolonged hospitalization, paradoxical clinical deterioration due to Immune Reconstitution Inflammatory Syndrome (IRIS), delayed cure, treatment failure or relapse [7–12].

Individuals admitted with HIV-associated tuberculosis are frequently acutely ill, with high incidence of inpatient deaths occurring early during hospitalization [2, 3, 13], despite appropriate antituberculosis treatment [13]. This highlights the urgent need for improving patient management strategies to increase survival in PLWH with tuberculosis, requiring a better understanding of the main determinants of severe morbidity and mortality. A better knowledge of factors associated with TB disease itself in mortality, severe morbidity or unsuccessful treatment in PLWH is then needed as it would help to identify those factors early and could contribute to improve the management of most severe patients with closer medical monitoring or a possible intensification of their treatment [14–16].

Most studies evaluating risk factors associated with TB mortality, severe morbidity or unsuccessful treatment in PLWH typically focus on factors related to the host, such as male sex [17–21], advanced age [8, 12, 17, 20, 22–25], co-morbidities [8, 23, 24, 26–35], poor adherence to treatment [24, 32, 36, 37], smoking [26, 38], alcohol use [29, 31, 32] or low socio-economic level [38, 39]. Very few studies focused on important characteristics of the TB disease itself such as bacillary load [8, 22, 40], extent of lung involvement on chest x-ray [36, 41–43], or disease dissemination [17, 44, 45]. Furthermore, most studies are retrospective and were not specifically designed for PLWH. Clinical trials are known to be the gold standard design in medical research, and even when only a secondary analysis with an aim different from that of the initial trial is conducted, the prospective collection of data on the outcomes of interest could provide more valid results than retrospective cohort studies, especially by reducing the risk of recall bias or inaccurate reporting.

We sought to assess the association between TB severity (mortality, severe morbidity and unsuccessful treatment) and three important characteristics of TB reported to be associated with the disease severity (bacillary load, extent of lung involvement on chest x-ray, and disease dissemination) in antiretroviral treatment (ART) naive PLWH enrolled and followed up in the ANRS 12300 Reflate TB2 trial, an international phase III open-label randomized trial assessing different antiretroviral regimens for treatment of HIV infection in PLWH treated for tuberculosis [46].

Methods

Study design and population

We conducted a secondary analysis of the ANRS 12300 Reflate TB2 trial, a multicenter, open-label, randomized, phase 3 trial that assessed non-inferiority of raltegravir- versus efavirenz-based antiretroviral therapy (ART) in ART-naive HIV-1 infected adults with bacteriologically confirmed or clinically diagnosed TB enrolled in six clinical sites in five countries (Brazil, Côte d'Ivoire, France, Mozambique, and Vietnam) between September 2015 and January 2018. The trial design and results, which did not show non-inferiority of raltegravir, have been reported elsewhere [46]. Participants who were on rifampicin-containing TB treatment for a maximum of 8 weeks, initiated ART with either raltegravir 400 mg 1 pill twice daily or efavirenz 600 mg once daily, to which they were randomly assigned, both in association with tenofovir 300 mg plus lamivudine 300 mg once daily. Participants with HIV-2 infection, TB meningitis, rifampicin-resistant TB, impaired hepatic or renal function, severe anemia, and those who were pregnant or breastfeeding were excluded. In the present study, we included all participants enrolled in the ANRS 12300 Reflate TB2 trial that were included in the intention to treat analysis and we considered follow-up until week 24, i.e. 6 months in the trial.

A screening visit was performed at any time between TB treatment initiation and TB treatment initiation + seven weeks, provided that inclusion would be

feasible no later than eight weeks after tuberculosis treatment initiation, and within the first two weeks in participants whose CD4 T-cell count was known to be < 50 cells/μL. Smear microscopy, Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), mycobacterial cultures on expectorated sputum, relevant extrapulmonary samples and chest radiographs performed at the time of tuberculosis diagnosis were collected, or done at the screening visit, if not already available. Once participants had provided written informed consent and eligibility criteria had been checked, they were randomized into one of the two trial arms. The inclusion (W0) visit was the ART initiation visit performed within 2 weeks of the screening visit.

All participants received standard TB treatment with isoniazid (4–6 mg/kg/day), rifampicin (8–12 mg/kg/day), pyrazinamide (20–30 mg/kg/day), and ethambutol (15–20 mg/kg/day) for 2 months (intensive phase), followed by isoniazid (4–6 mg/kg/day) and rifampicin (8–12 mg/kg/day) for 4 months (maintenance phase). As recommended by WHO, participants were initiated on ART after 2–8 weeks of tuberculosis treatment (depending on CD4 cell counts). Patients were offered trimethoprim-sulfamethoxazole (cotrimoxazole) prophylaxis against toxoplasmic encephalitis, *Pneumocystis jirovecii* pneumonia, and severe bacterial diseases, following national recommendations.

Follow-up visits were organized bi-monthly for the first month of follow-up in the trial, every month thereafter until W24. TB follow-up exams included sputum smear microscopy and culture in participants with pulmonary TB at month 2 and month 5 of treatment and chest radiographs at month 2 and month 6 of tuberculosis treatment. TB follow up exams were not performed at fixed visits in the trial but at different time points depending on the duration of TB treatment at inclusion.

Investigators recorded frequency, grade, and type of adverse events during the 48 weeks of the study in an unsolicited manner. Time to adverse events was collected and an endpoint review committee validated all grade 3 and 4 adverse events. Deaths were recorded as the outcome of a serious adverse event. Time to death and death certificates were collected whenever possible.

Outcomes and definitions

We focused on three main outcomes in the present study: 1) death during tuberculosis treatment, 2) severe morbidity during tuberculosis treatment and 3) unsuccessful tuberculosis treatment. We considered deaths due to all causes occurring between inclusion and the W24 visit in the trial. We defined severe morbidity as a composite outcome comprising i) hospitalizations due to any cause with a duration of at least 7 days, ii) grade 3 or 4 ART or tuberculosis related drug-induced adverse event and/or paradoxical TB-associated IRIS validated by the endpoint review committee, using experts' opinion for ART or tuberculosis related drug-induced adverse events and INSHI (International Network for the Study of HIV-associated IRIS) criteria for IRIS [47].We defined unsuccessful tuberculosis treatment as a composite outcome comprising i) death and/or ii) treatment failure, i.e., a treatment regimen that needed to be terminated or permanently changed to a new regimen or treatment strategy and/or iii) loss to follow up, i.e., participants whose treatment was interrupted for 2 consecutive months or more [48].

Main independent variables

Our main independent variables of interest were three important characteristics of TB reported to be associated with disease severity: 1) bacillary load documented through smear positivity grade, or gene expert positivity level, or delay to culture positivity, 2) extent of lung involvement on chest x-ray including presence of cavitation and proportion of the lung field, and 3) disease dissemination documented through urine lipoarabinomannan assay (LAM) positivity, involvement of other organs or miliary TB.

Statistical analysis

We described baseline characteristics using frequency and proportions for qualitative variables, and median and interquartile range (IQR) for quantitative variables. We compared characteristics across groups using Wilcoxon tests for quantitative variables, and $\chi 2$ or Fisher's exact test for qualitative variables as appropriate.

We used Cox proportional hazard models to assess factors associated with mortality from inclusion to W24 and logistic regressions to assess factors associated with severe morbidity and unsuccessful tuberculosis treatment at W24. We tested in univariate models variables that we selected based on previous evidence from the literature and clinical relevance. Since three variables documenting bacillary load (smear positivity grade, gene expert positivity level, delay to culture positivity) are highly correlated, we selected for inclusion in the models the one with most data available. We selected the presence of cavitation to document extent of lung involvement on chest x-ray because the proportion of the lung field affected was not assessed in the original trial. We selected LAM positivity to document disease dissemination because, as a laboratory test, it appears more reliable than involvement of other organs or miliary TB which are subjective to the investigator's judgement. In multivariate models, we included variables with a level of significance $p = 0.20$ in univariate models, along with CD4 count and HIV viral load. We derived final models using stepwise descending selection, retaining in the model all variables

with a level of significance of $p=0.05$ along with the three main variables of interest (bacillary load, cavitation and LAM positivity).. We analyzed data using the SAS® Studio software (version 3.82).

Results

We included 457 participants in this study, excluding 3 participants (2 with HIV 2 infection and 1 with HIV-1 RNA < 50 c/ml). Most participants were male (60.2%), their median age was 35.3 years, (IQR, 28.9–42.9), their median CD4 count was 103.0 cells per mm^3, (IQR, 38.0–238.5) and a majority had pulmonary tuberculosis (Table 1).

Tuberculosis diagnosis was done before the start of tuberculosis treatment and confirmed at enrollment. The median duration of TB treatment before enrollment was 20 days (IQR, 15–27).

Key tuberculosis disease characteristics are presented in Table 1. Regarding bacillary load, 90 (20.4%) participants had grade 2 + or 3 + smear positivity, 101 (23.6%) had medium or high Xpert positivity level and 198 (44.8%) had a time to MTB culture positivity > 14 days; regarding extent of lung involvement, 39 (10.8%) participants had cavitation on chest X-ray, 225 (49.2%) had bilateral lesions and 227 (50.2%) had cavitation or bilateral location; regarding tuberculosis disease dissemination, 147 (32.2%) of 305 participants with LAM available had a positive urinary test, 87 (19%) had involvement of other organs and 10 (2.2%) had miliary patterns (Table 1). How variables characterizing bacillary load and tuberculosis disease dissemination cross with each others is presented in supplementary tables S1, S2 and S3 in appendix.

Overall, 21 (4.6%) participants died from inclusion to W24, at a median time of 58 (IQR: 45—107) days; 6 (1.31%) participants were lost to follow up; 1 (0.21%) was transferred; and 429 (93.87%) were followed up until W24, for a total of 202.19 person-years (PY) of follow-up accrued during the study. The mortality rate was estimated to 10.4 (95% CI 5.96–14.83) deaths per 100 person-years (PY). Forty-six participants (10.1%) were hospitalized (≥ 7 days) at least once for a median duration of 17 (IQR, 12–28) days; the first hospitalization occurred at a median time of 49 (IQR, 32–79) days after tuberculosis treatment initiation, and 24 (IQR, 13–49) days after ART initiation. Overall, 121 (26.47%) participants presented grade 3 or 4 drug induced adverse events, 61 (13.3%) presented grade 3 or 4 IRIS; 6 (1.3%) experienced tuberculosis treatment failure, 37 (8.1%) had unsuccessful tuberculosis treatment cases, and a total of 118 (25.8%) participants were defined as having severe morbidity.

Factors that remained independently associated with mortality were cavitation on chest x-ray (aHR = 7.92, 95% CI, 1.74–35.94, $p=0.0073$) and LAM positivity (aHR = 5.53, 95% CI, 1.09–28.06, $p=0.0389$); mortality was not associated with smear positivity grade ($p=0.2963$) (Table 2).

The only factor that remained significantly associated with severe morbidity was LAM positivity (aOR = 2.04, 95% CI, 1.06–3.92, $p=0.0323$); severe morbidity was neither associated with cavitation on chest x-ray ($p=0.2499$) nor with smear positivity grade ($p=0.0824$) (Table 3).

Unsuccessful tuberculosis treatment was neither associated with cavitation on chest x-ray ($p=0.1174$), nor with smear positivity grade ($p=0.3812$), nor with LAM positivity ($p=0.0766$) (Table 4).

Discussion

In this secondary analysis of the Reflate TB2 trial, mortality was associated with cavitation on chest x-ray and LAM positivity; severe morbidity was associated with LAM positivity. These results show that characteristics selected as potential markers of tuberculosis disease severity, reflecting the extent of lung involvement and disease dissemination, were indeed associated with key patient outcomes.

The mortality rate was lower in our study than those reported in most longitudinal studies in PLHWH with TB that range between 10 and 25% [49–52]. This could be due to the fact that the most ill patients may not have been included in the trial since participants with TB meningitis, rifampicin-resistant TB, impaired hepatic or renal function, or severe anemia were excluded; another explanation could be that participants enrolled were more closely monitored in the framework of a clinical trial. The low mortality rate as well as very close monitoring in trial conditions probably contributed to low rates of loss to follow-up and treatment failure. The rate of unsuccessful treatment was also low when compared to those reported by other studies (12% to 33%) [25, 53–55]. However, the proportion of severe tuberculosis morbidity as we defined in this study was in the range between 23 and 33% usually reported [9–11, 56].

The extent of lung involvement on chest x-ray was previously reported as associated to mortality in adults with tuberculosis [41, 43]. Both the presence of cavitation and the percentage of lung affected are part of the Timika score, that predicts mortality based on chest x-ray severity in adult with smear-positive pulmonary TB [57]. Our study confirms these findings, which may be surprising in a population of PLWH with such a high immunosuppression level, since cavitations are more commonly seen at earlier stages of the HIV disease, when cellular immunity is relatively preserved [58]. Our finding shows that, even

Table 1 Baseline characteristics according to vital status at 6 months

Characteristics	Available in N′ if #N	All Participants (*N* = 457)	Available in N′ if #N	Alive (*n* = 429)	Available in N′ if #N	Dead (*n* = 21)	Available in N′ if #N	[a]Others (*n* = 7)	*P*-value
		n (%) or median (IQR)		n (%) or median (IQR)		n (%) or median (IQR)	-	n (%) or median (IQR)	
Gender female	-	182 (39.8)	-	171 (39.9)	-	10 (47.6)	-	1 (14.3)	.5611
Age (years)	-	35.3 (28.9–42.9)	-	35.3 (28.8–42.9)	-	35.3 (29.8–47.1)	-	33.6 (31.0–49.8)	.6285
BMI (Kg/m2)	-	19.0 (17.3–20.8)	-	19.0 (17.4–20.8)	-	17.6 (15.0–20.1)	-	18.5 (17.7–20.3)	.1550
Karnofsky (%)	-	80.0 (80.0–90.0)	-	80.0 (80.0–90.0)	-	80.0 (70.0–90.0)	-	80.0 (80.0–80.0)	.7030
CD4 (cells/mm^3)	-	103.0 (38.0–238.5)	-	108.0 (39.5–245.0)	-	43.0 (9.0–108.0)	-	125.0 (57.0–166.0)	.0088
HIV viral load, log10 copies/ml	-	5.5 (5.0–5.8)	-	5.5 (5.0–5.8)	-	5.8 (5.5–6.2)	-	5.6 (5.0–5.9)	.0506
Temperature	-	36.9 (36.5–37.4)	-	36.9 (36.5–37.4)	-	37.0 (36.7–37.5)	-	36.9 (36.5–37.1)	.4375
Hemoglobin (g/dL)	-	9.8 (8.5–11.3)	-	9.9 (8.5–11.4)	-	8.9 (7.1–9.7)	-	9.4 (8.5–12.9)	.0186
Tuberculosis anatomical site	-	-	-	-	-	-	-	-	.8995
Pulmonary only	-	313 (68.5)	-	297 (69.2)	-	10 (47.6)	-	6 (85.7)	-
Mixed	-	87 (19.0)	-	78 (18.2)	-	8 (38.1)	-	1 (14.3)	-
Extrapulmonary TB only	-	57 (12.5)	-	54 (12.6)	-	3 (14.3)	-	0 (0.0)	-
Extra pulmonary tuberculosis locations	-	-	-	-	-	-	-	-	-
Miliary	-	10 (2.2)	-	9 (2.1)	-	1 (4.8)	-	0 (0.0)	.8143
Pleural	-	49 (10.7)	-	46 (10.7)	-	2 (9.5)	-	1 (14.3)	.9066
Hilar/mediastinal lymph nodes	-	14 (3.1)	-	14 (3.3)	-	0 (0.0)	-	0 (0.0)	.3611
Peripheral lymph nodes	-	61 (13.3)	-	54 (12.6)	-	7 (33.3)	-	0 (0.0)	.3150
Retroperitoneal lymph nodes	-	35 (7.7)	-	31 (7.2)	-	4 (19.1)	-	0 (0.0)	.4665
Peritoneal	-	4 (0.9)	-	2 (0.5)	-	2 (9.5)	-	0 (0.0)	.0076
[b]Others	-	8 (1.7)	-	7 (1.9)	-	1 (4.8)	-	0 (0.0)	.6647
Abnormal chest radiograph	452	360 (79.6)	424	338 (79.7)	-	15 (71.4)	-	7 (100.0)	.6819
Chest x-ray features	-	-	-	-	-	-	-	-	-
Cavitation	361	39 (10.8)	339	36 (10.6)	15	3 (20.0)	-	1 (7.1)	.9534
Alveolar opacity	361	247 (68.4)	339	235 (69.3)	15	7 (46.7)	-	5 (71.4)	.3384
Interstitial opacity	361	191 (52.9)	339	179 (52.8)	15	7 (46.7)	-	5 (71.4)	.6033
Bilateral locations	452	224 (49.6)	424	211 (49.8)	-	7 (33.3)	-	6 (85.7)	.6270
Cavitation or bilateral location	452	235 (52.0)	424	220 (51.9)	-	9 (42.9)	-	6 (85.7)	.4101
Smear positive	448	208 (46.4)	421	195 (46.3)	20	7 (35.0)	-	6 (85.7)	.3395
Smear positivity grade	441	-	414	-	20	-	-	-	.3948
Negative	-	240 (54.4)	-	226 (54.6)	-	13 (65.0)	-	1 (14.3)	
Scanty or 1+	-	111 (25.2)	-	103 (24.9)	-	5 (25.0)	-	3 (42.9)	

Table 1 (continued)

Characteristics	Available in N′ if #N	All Participants (*N* = 457)	Available in N′ if #N	Alive (*n* = 429)	Available in N′ if #N	Dead (*n* = 21)	Available in N′ if #N	[a]Others (*n* = 7)	*P*-value
		n (%) or median (IQR)		n (%) or median (IQR)		n (%) or median (IQR)	-	n (%) or median (IQR)	
2 + or 3 +	-	90 (20.4)	-	85 (20.5)	-	2 (10.0)	-	3 (42.9)	
Xpert MTB/RIF positive	431	266 (61.7)	404	250 (61.9)	20	11 (55.0)	-	5 (71.4)	.9960
Xpert MTB/RIF positivity level	427	-	400	-	20	-	-	-	.4328
Negative	-	165 (38.6)	-	154 (38.5)	-	9 (45.0)	-	2 (28.6)	-
Very low or low	-	161 (37.7)	-	154 (38.5)	-	5 (25.0)	-	2 (28.6)	-
Medium or high	-	101 (23.6)	-	92 (23.0)	-	6 (30.0)	-	3 (42.9)	-
MTB culture positive	442	228 (51.6)	415	214 (51.6)	20	9 (45.0)	-	5 (71.4)	.6646
Time to culture positivity	-	30.0 (21.0–44.0)	-	30.0 (21.0–44.0)	-	35.0 (22.0–50.0)	-	28.0 (24.0–29.0)	.5490
MTB culture and time to culture positivity	442	-	415	-	20	-	-	-	.7317
Negative	-	214 (48.4)	-	201 (48.4)	-	11 (55.0)	-	2 (28.6)	-
Positive, results available ≤ 14 days	-	30 (6.8)	-	28 (6.7)	-	1 (5.0)	-	1 (14.3)	-
Positive, results available > 14 days	-	198 (44.8)	-	186 (44.8)	-	8 (40.0)	-	4 (57.1)	-
LAM positive	305	147 (32.2)	288	134 (46.5)	13	10 (76.9)	4	3 (75.0)	.0252
ART allocation	-	-	-	-	-	-	-	-	.8807
Efavirenz	-	227 (49.7)	-	209 (49.6)	-	10 (47.6)	-	4 (57.1)	-
Raltégravir	-	230 (50.3)	-	212 (50.4)	-	11 (52.4)	-	3 (42.9)	-

[a] Others = lost to follow up and transferred out;

[b] Others = Intestinal, ocular or adrenal glands *N* = total number *N′* = number of participants with the variable; % = percentage; *IQR* = Inter quartile range; *MTB* = Mycobacterium Tuberculosis; Scanty = 1–9 Acid Fast Bacilli (AFB) in 100 fields; 1 + = 10–99 AFB in 100 fields; 2 + = 1–10 AFB per field; 3 + = more than 10 AFB per field; ART = Antiretroviral Treatment

if uncommon at late stages of HIV infection, the presence of cavitation is a key marker of TB severity in PLWH, as it is in the general population [41, 43]. Beside cavitation, the proportion of lung affected is the other characteristic of the extent of lung involvement reported to be related to tuberculosis disease severity [41, 42, 59].

TB disease dissemination as captured by urine LAM positivity was associated with mortality and severe morbidity in our study. We chose LAM positivity as a marker of TB dissemination since it is associated with renal tuberculosis on autopsy [60], presence of mycobacteria in the urine [61] and in blood [62, 63], hence evidence that, beside the lungs, other organs are certainly also affected by Mycobacterium Tuberculosis. Even in immunocompetent patients, disseminated TB is a severe condition with a high risk of death [44, 64]; the impact of disseminated disease is even worse in PLWH [65–67]. In a study conducted in PLWHs hospitalized in South Africa, TB dissemination was quantified with a three-point score based on urine Xpert MTB/RIF, urine LAM test and blood culture; a higher dissemination score (ranging 0 to 3) was associated with higher mortality [68]. This confirms that the disease dissemination is a key marker of TB severity in PLWH.

Conversely to what was shown in patients from the general population i.e. HIV and non-HIV infected with tuberculosis, bacillary load as captured by the smear positivity grade was not associated with any of the outcomes in our study [8, 22, 69]. To our knowledge, this association has not previously been reported specifically among PLWH. One reason might be that PLWH have a higher rate of smear-negative disease and lower bacillary load in

Table 2 Factors associated with mortality among people living with HIV with tuberculosis: univariate and multivariate analysis

Characteristics	Univariate						Multivariate		
	N	PY	Mortality rate (100 PY)	Crude HR	95% CI	*p*-value	Adjusted HR	95% CI	*p*-value
Gender female	10	80,71	11,2	1.34	0.54–3.30	.5193	-	-	-
Age (years)	-	-	-	-	-	.5815	-	-	-
< 35	10	98.34	10.2	1	-	-	-	-	-
≥ 35	11	103.85	10.6	1.04	0.44–2.45	-	-	-	-
BMI (Kg/m2)	-	-	-	-	-	.1534	-	-	-
≥ 18	9	127.38	7.1	1	-	-	-	-	-
< 18	12	73.35	13.6	1.92	0.78–4.74	-	-	-	-
Karnofsky (%)	-	-	-	-	-	.2125	-	-	-
≥ 80	15	160.72	8.1	1	-	-	-	-	-
< 80	6	40.01	15.0	1.85	0.70–4.86	-	-	-	-
CD4 (/mm3)	-	-	-		-	.0421	-	-	-
≥ 100	6	104.46	5.7	1	-	-	-	-	-
< 100	15	97.27	15.4	2.66	1.03–6.88	-	-	-	-
Log10 HIV viral load	-	-	-	-	-	.3138	-	-	-
< 5 log10	3	52,42	5,7	1	-	-	-	-	-
≥ 5 log10	18	148,31	10,8	1.88	0.54–6.46	-	-	-	-
Hemoglobin (g/dL)	-	-	-	-	-	.0466	-	-	-
≥ 9	9	138.75	6.5	1	-	-	-	-	-
< 9	12	61.97	16.1	2.49	1.01–6.14	-	-	-	-
Tuberculosis anatomical site	-	-	-	-	-	.1460	-	-	-
Pulmonary	10	138.39	7.2	1	-	-	-	-	-
Mixed	8	37.49	18.7	2.579	0.98–6.77	-	-	-	-
Extra pulmonary	3	24.84	8.1	1.101	0.24–5.02	-	-	-	-
Cavitation	-	-	-	-	-	.2422	-	-	.0073
No	12	141.63	8.5	1	-	-	1	-	-
Yes	3	16.52	18.2	2.12	0.60–7.53	-	7.92	1.74–35.94	-
Bilateral locations	-	-	-	-	-	.1509	-	-	.5475
No	14	102.39	13.7	1		-	1	-	-
Yes	7	99.8	7.0	0.51	0.20–1.27	-	0.64	0.15–2.67	-
Cavitation or bilateral location	-	-	-	-	-	.8658	-	-	-
No	12	102.15	11.7	1	-	-	-	-	-
Yes	9	100.04	9.0	0.92	0.37–2.27	-	-	-	-
Xpert MTB/RIF positivity level	-	-	-	-	-	.3421	-	-	-
Negative	9	72.51	11.0	1	-	-	-	-	-
Very low or low	5	72.36	5.5	0.50	0.15–1.66	-	-	-	-
Medium or high	6	43.00	14.0	1.26	0.44–3.65	-	-	-	-
Smear positivity grade	-	-	-	-	-	.5460	-	-	.2963
Negative	13	115.95	10.3	1	-	-	1	-	-
Scanty or 1 +	5	48.51	8.2	0.72	0.23–2.25	-	0.61	0.13–2.78	-
2 + or 3 +	2	39.28	5.1	0.45	0.10–2.019	-	0.15	0.01–1.61	-
TB culture and time to culture positivity	-	-	-	-	-	.5471	-	-	-
Negative culture	11	92.19	7.6	1	-	-	-	-	-
≤ 14 days	1	32.44	0.0	0.00	-	-	-	-	-
> 14 days	8	42.94	14.0	1.84	0.61–5.48	-	-	-	-
LAM result	-	-	-	-	-	.1139	-	-	.0389
Negative	3	70.63	4.2	1	-	-	1	-	-
Positive	10	63.77	12.5	2.91	0.77–10.99	-	5.53	1.09–28.06	-
ART allocation	-	-	-	-	-	.6801	-	-	-
Efavirenz	10	25.16	4.0	1	-	-	-	-	-
Raltégravir	11	25.68	4.3	1.19	0.51–2.76	-	-	-	-

N = Number of deaths; *PY* = Person years, *HR* = Hazard ratio; =; 95% CI = 95% confidence interval; *ART* = Antiretroviral Treatment

Table 3 Factors associated with severe morbidity among people living with HIV with tuberculosis: univariate and multivariate analysis

	Univariate			Multivariate		
Characteristics	**Crude OR**	**95% CI**	***p*-value**	**Adjusted OR**	**95% CI**	***p*-value**
Gender female	1.15	0.75–1.76	.5117	-	-	-
Age (years)	-	-	.7197	-	-	-
< 35	1	-	-	-	-	-
≥ 35	0.92	0.60–1.40	-	-	-	-
BMI (Kg/m2)	-	-	.0389	-	-	-
≥ 18	1	-	-	-	-	-
< 18	1.56	1.02–2.40	-	-	-	-
Karnofsky (%)	-	-	.3876	-	-	-
≥ 80	1	-	-	-	-	-
< 80	1.25	0.75–2.07	-	-	-	-
CD4 (/mm3)	-	-	.0003	-	-	.0709
≥ 100	1	-	-	-	-	-
< 100	2.23	1.45–3.44	-	1.86	0.94–3.64	-
Log10 HIV viral load	-	-	.0459	-	-	-
< 5 log10	1	-	-	-	-	-
≥ 5 log10	1.69	1.01–2.85	-	-	-	-
Hemoglobin (g/dL)	-	-	.6322	-	-	-
≥ 9	1	-	-	-	-	-
< 9	1.11	0.71–1.74	-	-	-	-
Tuberculosis anatomical site	-	-	.0566	-	-	-
Pulmonary	1	-	-	1	-	-
Mixed	1.18	0.68–2.03	-	-	-	-
Extra pulmonary	2.06	1.14–3.74	-	-	-	-
Cavitation	-	-	.2272	-	-	.2499
No	1	-	-	1	-	-
Yes	0.59	0.25–1.38	-	0.46	0.12–1.71	-
Bilateral locations	-	-	.5799	-	-	.3941
No	1	-	-	1	-	-
Yes	0.89	0.60–1.32	-	1.31	0.70–2.44	-
Cavitation or bilateral location	-	-	.3761	-	-	-
No	1	-	-	-	-	-
Yes	0.84	0.57–1.23		-	-	-
Xpert MTB/RIF positivity level	-		.7737	-	-	-
Negative	1	-	-	1	-	-
Very low or low	1.17	0.71–1.92	-	-	-	-
Medium or high	0.99	0.56–1.76	-	-	-	-
Smear positivity grade	-	-	.1462	-	-	.0824
Negative	1	-	-	1	-	-
Scanty or 1 +	1.61	0.98–2.65	-	2.17	1.06–4.42	-
2 + or 3 +	1.02	0.57–1.81	-	1.11	0.46–2.67	-
TB culture and time to culture positivity	-	-	.6228	-	-	-
Negative culture	1	-	-	1	-	-
≤ 14 days	1.48	0.65–3.36	-	-	-	-
> 14 days	1.00	0.64–1.56	-	-	-	-
LAM result	-	-	< .0001	-	-	.0323
Negative	1	-	-	1	-	-
Positive	2.90	1.70–4.93	-	2.04	1.06–3.92	-

OR = Odds ratio; *95% CI* = 95% Confidence interval

Table 4 Factors associated with unsuccessful treatment among people living with HIV with tuberculosis: univariate and multivariate analysis

	Univariate			Multivariate		
Characteristics	**Crude OR**	**95% CI**	***p*- value**	**Adjusted OR**	**95% CI**	***p* -value**
Gender female	1.15	0.75- 1.76	.5117	0.39	0.10–1.46	.1636
Age (years)	-	-	.7249	-	-	-
< 35	1	-	-	-	-	-
≥ 35	0.88	0.45–1.73	-	-	-	-
BMI (Kg/m2)	-	-	.8048	-	-	-
≥ 18	1	-	-	1	-	-
< 18	1.09	0.54–2.19	-	-	-	-
Karnofsky (%)	-	-	.4489	-	-	-
≥ 80	1	-	-	1	-	-
< 80	1.35	0.61–2.99	-		-	-
CD4 (/mm3)	-	-	.5139		-	-
≥ 100	1	-	-	1	-	-
< 100	1.25	0.63–2.45	-	-	-	-
Log10 HIV viral load	-	-	.2062	-	-	-
< 5 log10	1	-	-	1	-	-
≥ 5 log10	1.79	0.72–4.41	-	-	-	-
Hemoglobin (g/dL)	-	-	.2502	-	-	-
≥ 9	1	-	-	1	-	-
< 9	1.51	0.74–3.07	-	-	-	-
Tuberculosis anatomical site	-	-	.5045	-	-	-
Pulmonary	1	-	-	1	-	-
Mixed	1.60	0.70–3.64	-	-	-	-
Extra pulmonary	1.33	0.48–3.70	-	-	-	-
Cavitation	-	-	.2176	-	-	.1174
No	1	-	-	1	-	-
Yes	1.91	0.68–5.35	-	3.23	0.74–14.05	-
Bilateral locations	-	-	.6524	-	-	.9821
No	1	-	-	1	-	-
Yes	0.84	0.41–1.72	-	1.01	0.27–3.77	-
Cavitation or bilateral location	-	-	.5616	-	-	-
No	1	-	-	-	-	-
Yes	1.23	0.60–2.51	-	-	-	-
Xpert MTB/RIF positivity level	-		.2067	-	-	-
Negative	1	-	-	1	-	-
Very low or low	0.56	0.23–1.38	-	-	-	-
Medium or high	1.31	0.57–3.02	-	-	-	-
Smear positivity grade	-	-	.8208	-	-	.3812
Negative	1	-	-	1	-	-
Scanty or 1 +	1.29	0.57–2.93	-	0.83	0.24–2.83	-
2 + or 3 +	1.10	0.44–2.76	-	0.29	0.05–1.67	-
TB culture and time to culture positivity	-	-	.8163	-	-	-
Negative culture	1	-	-	1	-	-
≤ 14 days	1.47	0.40–5.42	-	-	-	-
> 14 days	1.16	0.56–2.42	-	-	-	-
LAM result	-	-	.1267	-	-	.0766
Negative	1	-	-	1	-	-
Positive	2.09	0.81–5.40	-	2.84	0.89–9.02	-

OR = Odds ratio; *95% CI* = 95% Confidence interval

sputum [70, 71], with proportions of smear-negative pulmonary tuberculosis ranging from 24 to 61% [72].

Our study has limitations. A first limitation is that the Reflate TB2 trial was not initially designed to assess factors associated with tuberculosis severity. We performed a secondary analysis of trial data whose participants might differ from patients diagnosed and managed in routine non-research conditions. The standardized follow-up in the framework of a clinical trial was nevertheless an interesting strength for our study. A second limitation is the regional and epidemiological heterogeneity, since the trial was conducted in five countries representing four regions (Latin America, sub-Saharan Africa, Western Europe and Southeast Asia) among which patterns of both HIV and TB vary greatly; so we might not have the same factors associated with mortality or severe morbidity in all regions. A third limitation is the important proportion of missing data for some variables of interest such as LAM; this might impact the validity of our results since the effects found might have been underestimated or overestimated. Lastly, the analysis relied on a relatively few cases of cavitations [39] which introduced a wide confidence limit on the HR (1.74–35.94) and thus a lack of precision of the estimate.

Despite the above-mentioned limitations, this study contributes to a better knowledge of the determinants of TB disease severity. Prospective data collection in the framework of an international clinical trial may provide more valid results than previous retrospective cohort studies, notably by reducing the risk of recall bias or inaccurate reporting. Our secondary analysis of data from a clinical trial confirmed in PLWH results from previous retrospective cohort studies in the general population that had shown the association between tuberculosis severity and important disease characteristics such as bacillary load, extent of lung involvement and disease dissemination. These characteristics should be taken into account when targeting management strategies for PLWH with tuberculosis. Early identification of these factors early, could improve management of most severe disease by introducing closer medical monitoring or possible treatment intensification, which could contribute to increase survival in PLWH with tuberculosis.

Conclusion

In this secondary analysis of the Reflate TB2 trial, tuberculosis disease characteristics such as extent of lung involvement and disease dissemination were associated with disease severity and adverse outcomes. Interestingly, these important characteristics assocated with tuberculosis disease severity are not considered in existing severity scores such as the TBscore II [73], at the exception of the Timika score which includes extent of lung involvement [57]. Besides, most of these scores were not specifically designed for PLWH and may thus, not be optimal nor applicable to PLWH. Whence the need to develop a better tuberculosis severity score for PLWH including bacillary load, extent of lung involvement on chest x-ray and the disease dissemination.

Abbreviations

aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio
ART	Antiretroviral Treatment
BMI	Body Mass Index
CI	Confidence Interval
COVID	Coronavirus Disease
HIV	Human Immunodeficiency Virus
HR	Crude hazard ratio
IRIS	Immune Reconstitution Inflammatory Syndrome
LAM	Lipoarabinomannan assay
OR	Crude odds ratio
PLWH	People Living With HIV

Supplementary Information

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Supplementary Material 1.

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Data availability
All data and materials are available upon request to the ANRS 12300 Reflate TB2 group.

Declarations

Ethics approval and consent to participate
The study was approved by Comité National d'Ethique et de la Recherche (Côte d'Ivoire), CEP IPEC (Brazil), Comité de Protection des Personnes Ile-de-France II (France), Comitê Nacional de Bioética para Saúde (Mozambique) and IRB PNTH (Vietnam).
The ANRS 12300 Reflate TB2 trial protocol was registered with ClinicalTrials.gov (NCT02273765, 22 October 2014) and was conducted in accordance with the Declaration of Helsinki. All participants provided signed informed consent before enrollment in the main trial.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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