



HAL
open science

Diagnosis and clinical outcomes of extrapulmonary tuberculosis in antiretroviral therapy programmes in low- and middle-income countries: a multicohort study

Kathrin Zürcher, Marie Ballif, Sasisopin Kiertiburanakul, Henri Chenal, Marcel Yotebieng, Beatriz Grinsztejn, Denna Michael, Timothy Sterling, Kapella Ngonyani, Anna Mandalakas, et al.

► To cite this version:

Kathrin Zürcher, Marie Ballif, Sasisopin Kiertiburanakul, Henri Chenal, Marcel Yotebieng, et al.. Diagnosis and clinical outcomes of extrapulmonary tuberculosis in antiretroviral therapy programmes in low- and middle-income countries: a multicohort study. *Journal of the International AIDS Society*, 2019, 22 (9), 10.1002/jia2.25392 . hal-04607288

HAL Id: hal-04607288

<https://ut3-toulouseinp.hal.science/hal-04607288v1>

Submitted on 11 Jun 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.











L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

SHORT REPORT

Diagnosis and clinical outcomes of extrapulmonary tuberculosis in antiretroviral therapy programmes in low- and middle-income countries: a multicohort study

Kathrin Zürcher^{1§} , Marie Ballif¹ , Sasisopin Kiertiburanakul² , Henri Chenal³, Marcel Yotebieng⁴ , Beatriz Grinsztejn⁵ , Denna Michael⁶ , Timothy R Sterling^{7,8} , Kapella M Nkonyani⁹, Anna M Mandalakas¹⁰, Matthias Egger^{1,11} , April C Pettit^{7,8} , and Lukas Fenner¹  for the International Epidemiology Databases to Evaluate AIDS (IeDEA) consortium

§Corresponding author: Kathrin Zürcher, Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland. Tel: +41 31 631 38 67. (kathrin.zuercher@ispm.unibe.ch)

Abstract

Introduction: Extrapulmonary tuberculosis (EPTB) is difficult to confirm bacteriologically and requires specific diagnostic capacities. Diagnosis can be especially challenging in under-resourced settings. We studied diagnostic modalities and clinical outcomes of EPTB compared to pulmonary tuberculosis (PTB) among HIV-positive adults in antiretroviral therapy (ART) programmes in low- and middle-income countries (LMIC).

Methods: We collected data from HIV-positive TB patients (≥ 16 years) in 22 ART programmes participating in the International Epidemiology Databases to Evaluate AIDS (IeDEA) consortium in sub-Saharan Africa, Asia-Pacific, and Caribbean, Central and South America regions between 2012 and 2014. We categorized TB as PTB or EPTB (EPTB included mixed PTB/EPTB). We used multivariable logistic regression to assess associations with clinical outcomes.

Results and Discussion: We analysed 2695 HIV-positive TB patients. Median age was 36 years (interquartile range (IQR) 30 to 43), 1102 were female (41%), and the median CD4 count at TB treatment start was 114 cells/ μ L (IQR 40 to 248). Overall, 1930 had PTB (72%), and 765 EPTB (28%). Among EPTB patients, the most frequently involved sites were the lymph nodes (24%), pleura (15%), abdomen (11%) and meninges (6%). The majority of PTB (1123 of 1930, 58%) and EPTB (582 of 765, 76%) patients were diagnosed based on clinical criteria. Bacteriological confirmation (using positive smear microscopy, culture, Xpert MTB/RIF, or other nucleic acid amplification tests result) was obtained in 897 of 1557 PTB (52%) and 183 of 438 EPTB (42%) patients. EPTB was not associated with higher mortality compared to PTB (adjusted odd ratio (aOR) 1.0, 95% CI 0.8 to 1.3), but TB meningitis was (aOR 1.9, 95% CI 1.0 to 3.1). Bacteriological confirmation was associated with reduced mortality among PTB patients (aOR 0.7, 95% CI 0.6 to 0.8) and EPTB patients (aOR 0.3 95% CI 0.1 to 0.8) compared to TB patients with a negative test result.

Conclusions: Diagnosis of EPTB and PTB at ART programmes in LMIC was mainly based on clinical criteria. Greater availability and usage of TB diagnostic tests would improve the diagnosis and clinical outcomes of both EPTB and PTB.

Keywords: extrapulmonary tuberculosis; pulmonary tuberculosis; tuberculosis; HIV-positive patients; low- and middle-income countries; diagnostics; mortality; lost to follow-up

Received 22 January 2019; Accepted 9 August 2019

Copyright © 2019 The Authors. *Journal of the International AIDS Society* published by John Wiley & Sons Ltd on behalf of the International AIDS Society.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

1 | INTRODUCTION

In low- and middle-income countries (LMIC), tuberculosis (TB) accounts for approximately 40% of HIV/AIDS-related deaths among adults, and half of those TB cases are undiagnosed at the time of death [1]. TB predominantly affects the lungs (pulmonary tuberculosis [PTB]), but can affect extrapulmonary sites as well (EPTB). Globally, about 25% of all TB cases are estimated to be EPTB [2]. EPTB is a common presentation in HIV-positive individuals, particularly in those with low CD4

cell counts [3,4]. EPTB is most frequently identified in the lymph nodes, pleura, bones and joints, abdomen, meninges and genitourinary tract [5]. TB meningitis is considered the most severe form of EPTB with mortality as high as 70% in low-income countries [6].

The diagnosis of EPTB is particularly difficult and is often solely based on clinical signs and symptoms. A bacteriological confirmation of EPTB often requires invasive specimen collection by biopsy or fine needle aspiration [7,8], followed by use of adequate diagnostic tests [9,10]. Much progress has been

made in developing new diagnostic tests for TB, including the Xpert MTB/RIF and other nucleic acid amplification tests (NAAT), which have higher sensitivity than smear microscopy and can also be used to diagnose both PTB and EPTB [11]. This study assessed diagnostic modalities and TB treatment outcomes of EPTB compared to PTB in HIV-positive adults in clinical care in antiretroviral therapy (ART) programmes in six International epidemiology Databases to Evaluate AIDS (IeDEA) regions in sub-Saharan Africa, Asia-Pacific, Caribbean, Central and South America Central and South America.

2 | METHODS

2.1 | Study setting and study population

IeDEA (www.iedea.org) is a large consortium of ART programmes predominantly located in LMIC [12]. ART programmes in six IeDEA regions participated in this study are mostly public but often supported by NGOs or academia: East Africa; Central Africa; West Africa; Southern Africa; Asia-Pacific; Caribbean, Central and South America.

We reviewed records of consecutive 3165 HIV-positive patients diagnosed with any form of TB between January 1, 2012 and December 31, 2014 in participating ART programmes. Patient records missing data on sex, date of birth or site of disease were excluded from the analysis (35 records). We studied only adults and excluded paediatric cases (age <16 years, 396 records). In case of multiple TB episodes, only

the patient's first episode was included in the study (39 duplicate records deleted). This resulted in the inclusion of 2695 adult HIV-positive TB patients from 22 ART programmes (Figure 1).

2.2 | Data collection

Standardized electronic case report forms (CRFs), available in English or French, were used to record age, sex, date of TB diagnosis, site of TB disease, site of EPTB manifestation (predominant organ), start date of TB treatment, body mass index (BMI) at start of TB treatment, ART status at TB diagnosis, CD4 cell count at start of TB treatment, previous history of TB, TB drug resistance, results from TB diagnostic tests (smear microscopy, culture, Xpert MTB/RIF and other NAAT) and TB treatment outcomes [13]. All data were collected using REDCap (www.project-redcap.org) [14]. Local IeDEA site investigators completed CRFs for TB patients. Data were entered between January 2012 and January 2016. During data collection, routine audits were made to ensure data quality [15]. Furthermore, we used programme-level data previously collected in the same ART programmes in 2012 [16].

2.3 | Definitions

We categorized TB as PTB (involving the lungs only), mixed PTB/EPTB and EPTB only [5]. For binary outcome analyses, we used the categories PTB and EPTB (includes mixed

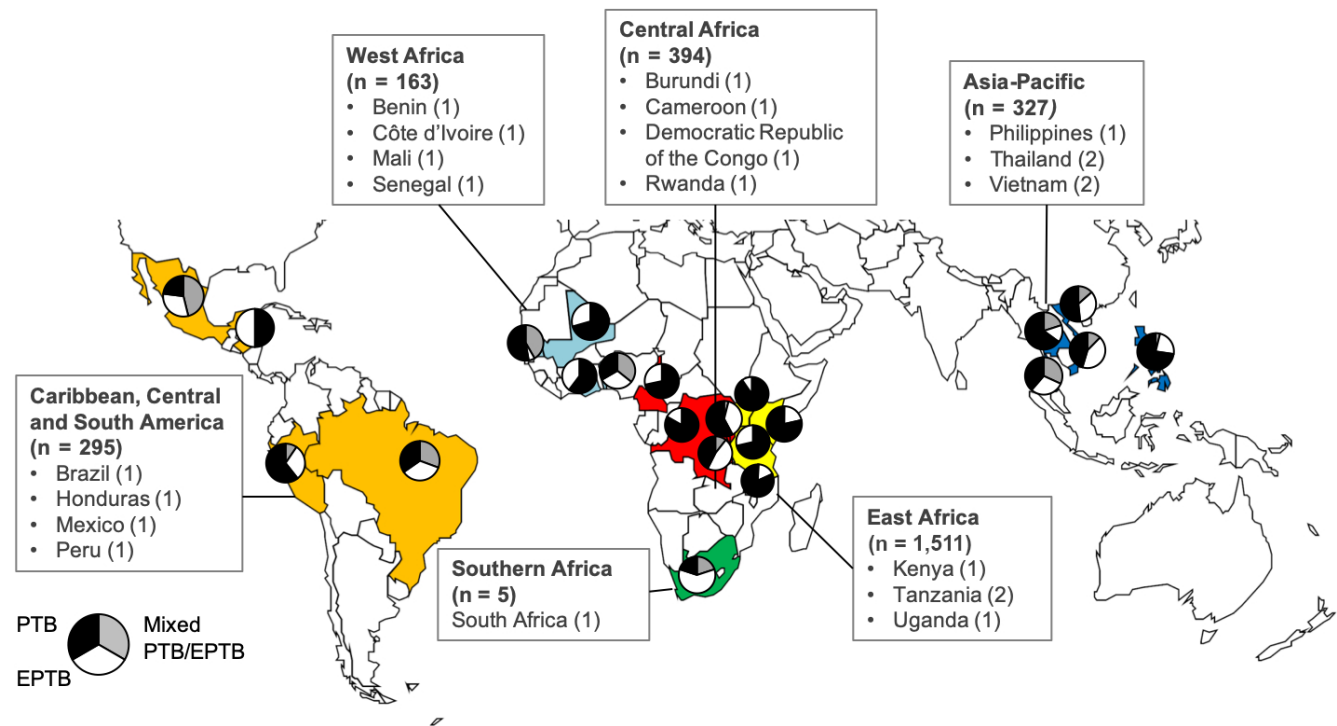


Figure 1. Geographical distribution of 22 antiretroviral treatment (ART) programmes treating HIV-positive patients (≥ 16 years) in low- and middle-income countries.

The proportions of pulmonary (black), mixed pulmonary/extrapulmonary (grey), and extrapulmonary tuberculosis cases (white) diagnosed at each site are indicated in the pie charts; n indicates the number of patients included in the study by IeDEA region; the numbers in parentheses following the country names indicate the number of ART programmes participating in the study by country. EPTB, extrapulmonary tuberculosis; IeDEA, International Epidemiology Databases to Evaluate AIDS; PTB, pulmonary tuberculosis.

PTB/EPTB cases) as previously defined [17]. Miliary TB was categorized as EPTB. Furthermore, we categorized bacteriological confirmation as “test performed” if at least one of the tests (smear microscopy, culture, Xpert MTB/RIF and/or other NAATs) was performed regardless of whether the result was positive or negative; “positive” bacteriological confirmation (any positive test result); “negative” (all performed tests were negative); and “no test performed.” TB treatment outcomes were categorized as cured, treatment completed, treatment failed, died, lost to follow-up (LTFU) and not evaluated [5]. The category “not evaluated” included patients who were still on treatment, transferred out and those whose treatment outcome was unknown. The category “treatment success” included cured patients and patients who completed TB treatment.

2.4 | Statistical analyses

We used descriptive statistics to characterize both programme-level and patient-level data, as well as diagnostic modalities. Differences between groups were assessed using chi-square, Fisher’s exact or Wilcoxon rank-sum tests as appropriate. We used univariate and multivariate logistic regressions to assess risk factors for mortality and LTFU during TB treatment. These associations were presented as unadjusted odds ratios (ORs) and ORs adjusted (aORs) for age, sex, BMI at start of TB treatment, previous history of TB, ART status at TB diagnosis and CD4 cell counts at start of TB treatment, taking into account heterogeneity across regions (clustering by treatment programmes). In separate models, we obtained the estimates for EPTB sites, (adjusted for the same co-variables). Patients without documented treatment outcomes were excluded from the primary analysis. However, we performed a sensitivity analysis considering patients LTFU as having died. To account for missing data we used multiple imputations by chained equations to impute missing BMI, ART status at TB diagnosis, CD4 cell counts at start of TB treatment and previous history of TB. The quality of the imputation can be improved by adding variables outside the analysis [18], therefore in addition to the outcome and the covariates used in the analysis, we also considered the date of TB treatment start, leDEA region, setting, level of care for imputation. We ran the model on 20 imputed datasets for each analysis and used the Rubin rule to pool the estimates. All analyses were performed in STATA (version 14.1, Stata Corporation, Texas, USA).

2.5 | Ethics statement

Local institutional review board or ethics committee approval was obtained at all local study sites. Informed consent was obtained where requested per local regulations. The Vanderbilt University Medical Center Institutional Review Board, Nashville, Tennessee (USA), and the Cantonal Ethics Committee Bern (Switzerland) approved the analyses for this specific project.

3 | RESULTS AND DISCUSSION

3.1 | Study sites and patient characteristics

The 2695 HIV-positive TB patients participating in this study were treated at 22 ART programmes in 19 countries (Figure 1). Eighteen sites were urban, three were peri-urban and

one site was rural. The level of care was mostly tertiary, at 17 sites, followed by secondary at four sites and primary at one site. For TB diagnostics a free-of-charge cost model was available at 11 of the 22 sites, a cost sharing model was available at 10 of the 22 sites and one site had a mixed cost model.

The median patient age was 35.5 years (interquartile range (IQR) 29.9 to 42.8), and 1102 patients (40.9%) were female. Among the 2695 patients, 1930 had PTB (71.6%) and 765 had EPTB (28.4%); 131 patients (4.9% overall) had both. At the time of TB diagnosis, 1270/2695 (47.1%) TB patients had not started ART and 763/2695 (28.3%) TB patients were on ART; the ART status of the remaining patients was unknown. Of the TB patients on ART, 342/763 (44.8%) were more than six months on ART before TB diagnosis and 421/763 (55.2%) were six or less months on ART. Among the 765 EPTB patients, the most frequent sites of disease were the lymph nodes (24.4%), pleura (14.2%), abdomen (11.1%), and meninges (6.3%). Complete patient characteristics are given in Table 1. When stratifying CD4 cell counts at the time of TB treatment (0 to 49 cells/ μ L; 50 to 199 cells/ μ L; \geq 200 cells/ μ L; missing CD4 values), the frequencies of sites of EPTB manifestations remained similar over all groups.

3.2 | Diagnostics of EPTB and PTB

Diagnostic capabilities varied according to sites. Sputum smear microscopy was available at all sites. Culture was not available at one site each in East Africa (1/4) and Central Africa (1/4), and Xpert MTB/RIF was not available at half of the sites: two in East Africa (2/4), three in Central Africa (3/4), two in West Africa (2/4), one in Asia-Pacific (1/5), and three in Caribbean, Central and South America (3/4) and other NAATs were not available in half of the sites: two in East Africa (2/4), two in Central Africa (2/4), two in West Africa (2/4), three in Asia-Pacific (3/5), and two in Caribbean, Central and South America (2/4). Bacteriological confirmation of PTB, EPTB only, and PTB/EPTB was sought in varying proportions in the three groups, and test results in groups varied as well. A confirmatory bacteriological test was performed in 438 of 765 EPTB (including mixed PTB/EPTB) patients (57.3%) and 1557 of 1930 PTB patients (80.7%). Bacteriological confirmation by any test (positive test result) was obtained in 183 of those 438 EPTB patients (41.8%), 103 of 334 patients with only EPTB (30.8%) and 807 of the 1557 PTB patients (51.8%). The diagnoses of the remaining EPTB and PTB patients who were not tested or whose test results were negative were based on clinical criteria (Table 2).

Among EPTB patients, smear microscopy was the most frequently performed diagnostic test (in 416 of 765 patients, 54.4%) and Xpert MTB/RIF was the least frequently performed diagnostic test (in 35 of 584 patients, 6.0%), but had the highest proportion of bacteriological confirmation (in 23 of 35 patients, 65.7%). The highest proportion of bacteriological confirmation was found among patients with lymph node TB, (in 77 of 131 patients, 58.8%).

3.3 | Patient factors associated with LTFU and mortality

In a multivariate model, LTFU during TB treatment was equivalent in EPTB patients’ (including both PTB/EPTB) compared

Table 1. Characteristics of HIV-positive patients diagnosed with pulmonary tuberculosis and extrapulmonary tuberculosis at the start of TB treatment in 22 antiretroviral treatment programmes from lower income countries

	All	PTB	EPTB		
			EPTB	Mixed PTB/EPTB	EPTB only
Total, n (%)	2695 (100)	1930 (71.6)	765 (28.4)	131 (4.9)	634 (23.5)
Age, year					
16 to 29	588 (21.8)	414 (21.4)	174 (22.8)	28 (21.4)	146 (23.0)
30 to 39	1105 (41.0)	793 (41.1)	312 (40.8)	59 (45.0)	253 (39.9)
40 to 49	696 (25.8)	503 (26.1)	193 (25.2)	35 (26.7)	158 (24.9)
50	306 (11.4)	220 (11.4)	86 (11.2)	9 (6.9)	77 (12.2)
Sex, n (%)					
Male	1593 (59.1)	1134 (58.8)	459 (60.0)	90 (68.7)	369 (58.2)
Female	1102 (40.9)	796 (41.2)	306 (40.0)	41 (31.3)	265 (41.8)
BMI at start of TB treatment kg/m ² , median (IQR)	18.7 (16.8 to 20.9)	18.6 (16.7 to 20.8)	18.8 (16.9 to 21.1)	18.1 (16.4 to 19.8)	18.9 (17.0 to 21.4)
No. of observations (%)	2115 (78.5)	1553 (80.5)	562 (73.5)	82 (62.6)	480 (75.7)
CD4 count at TB treatment start, median (IQR), cells/ μ L	114 (40 to 248)	124 (45 to 263)	92 (32 to 212)	55 (19 to 129)	105 (34 to 228)
No. of observations (%)	2196 (81.5)	1575 (81.6)	621 (81.2)	108 (82.4)	513 (80.9)
ART status at TB diagnosis					
Not on ART	1270 (47.1)	936 (48.5)	334 (43.7)	51 (38.9)	283 (44.6)
On ART	763 (28.3)	599 (31.0)	164 (21.4)	12 (9.2)	152 (24.0)
6 + months at TB diagnosis	342 (12.7)	268 (13.9)	74 (9.7)	4 (3.1)	70 (11.0)
<6 months at TB diagnosis	421 (15.6)	331 (17.2)	90 (11.8)	8 (6.1)	82 (12.9)
Missing	662 (24.7)	395 (20.5)	267 (34.9)	68 (51.9)	199 (31.4)
Previous history of TB, n (%)					
Yes	55 (2.0)	37 (1.9)	18 (2.4)	3 (2.3)	15 (2.4)
No	2304 (85.5)	1705 (88.3)	599 (78.3)	82 (62.6)	517 (81.5)
Unknown	336 (12.5)	188 (9.7)	148 (19.3)	46 (35.1)	102 (16.1)
TB treatment outcomes, n (%)					
Treatment success ^a	1908 (70.8)	1383 (71.7)	525 (68.6.9)	75 (57.3)	450 (71.0)
Treatment failed	15 (0.6)	13 (0.7)	2 (0.3)	1 (0.8)	1 (0.2)
Died	281 (10.4)	194 (10.1)	87 (11.4)	13 (9.9)	74 (11.7)
Lost to follow-up (default)	136 (5.0)	100 (5.2)	36 (3.2)	16 (12.2)	20 (3.2)
Not evaluated ^b	355 (13.2)	240 (12.4)	113 (14.0)	24 (18.3)	89 (14.0)
Organs involved in EPTB, n (%)					
Lymph nodes ^c	187 (6.9)	-	187 (24.4)	31 (23.7)	156 (24.6)
Pleura	109 (4.0)	-	109 (14.2)	15 (11.5)	94 (14.8)
Abdomen	85 (3.2)	-	85 (11.1)	13 (9.9)	72 (11.4)
Meninges	48 (1.8)	-	48 (6.3)	10 (7.6)	38 (6.0)
Miliary ^d	32 (1.2)	-	32 (4.2)	10 (7.6)	22 (3.5)
Joints and/or bones	22 (0.8)	-	22 (2.9)	4 (3.1)	18 (2.8)
Pericardium	13 (0.5)	-	13 (1.7)	3 (2.3)	10 (1.6)
Genitourinary tract	3 (0.1)	-	3 (0.4)	1 (0.8)	2 (0.3)
Larynx	1 (<0.1)	-	1 (0.1)	-	1 (0.2)
Unknown	265 (9.8)	-	265 (34.6)	44 (33.6)	221 (34.9)
leDEA region, n (%)					
Caribbean/C-S America	295 (11.0)	160 (8.3)	135 (17.6)	42 (32.1)	93 (14.7)
Asia-Pacific	327 (12.1)	176 (9.1)	151 (19.7)	45 (34.4)	106 (16.7)
West Africa	163 (6.0)	87 (4.5)	76 (9.9)	30 (22.9)	46 (7.3)
Central Africa	394 (14.6)	262 (13.6)	132 (17.3)	9 (6.9)	123 (19.4)

Table 1. (Continued)

	All	PTB	EPTB		
			EPTB	Mixed PTB/EPTB	EPTB only
East Africa	1511 (56.1)	1244 (64.5)	267 (34.9)	4 (3.1)	263 (41.5)
Southern Africa	5 (0.2)	1 (<0.1)	4 (0.5)	1 (0.8)	3 (0.5)

ART, antiretroviral therapy; BMI, body mass index; Caribbean/C-S America, Caribbean, Central and South America; EPTB, extrapulmonary tuberculosis; IQR, interquartile range; MDR, multidrug-resistant; n, number; PTB, pulmonary tuberculosis; TB, Tuberculosis.

^aTreatment success includes cured patients and patients who completed TB treatment; ^bnot evaluated includes on treatment, transfer out, and unknown; ^cextra- and intrathoracic; ^dmiliary TB defined as EPTB.

to PTB patients (aOR 0.92, 95% CI 0.36 to 2.32). It was also equivalent in EPTB patients' only compared to PTB patients (aOR 0.58, 95% CI 0.30 to 1.13). However, patients with both PTB/EPTB had at higher odds for LTFU compared to PTB patients (aOR 2.59, 95% CI 1.06 to 6.32, Table 3). EPTB mortality was similar to that of PTB (aOR 1.03, 95% CI 0.84 to 1.27; Table 3). However, TB meningitis was associated with increased mortality (aOR 1.85, 95% CI 1.00 to 3.10) compared to PTB, and overall mortality was also higher in patients with CD4 cell counts <50 cells/ μ L compared to those with CD4 cell counts \geq 200 cells/ μ L (aOR 2.60, 95% CI 1.46 to 4.64; Table 3). Sensitivity analyses (Table 3) considering patients LTFU as having died showed similar results. From a separate model, bacteriological confirmation was associated with reduced mortality among PTB patients (aOR 0.68, 95% CI 0.61 to 0.76) and EPTB patients (aOR 0.32 95% CI 0.13 to 0.79) compared to all other TB patients with a negative test result.

The lymph nodes, pleura, abdomen, and meninges were the most frequently involved organs in this large, multicohort study of HIV-positive EPTB patients treated in ART programmes in sub-Saharan Africa, Asia-Pacific, and Caribbean, Central and South America. Diagnosis were mainly based on clinical criteria, and bacteriological confirmation was seen less frequently in EPTB than PTB patients. Mortality was reduced among EPTB patients and PTB patients with a positive diagnostic test result compared to all other TB patients with a negative result. The observation that CD4 cell count in patients with EPTB was frequently lower than that of PTB patients was similar to the report of a South African study, that found that EPTB was generally more common in HIV-positive patients with lower CD4 cell counts, and three times more frequent among those with HIV and a CD4 count <50 cells/ μ L than among HIV-negative individuals [4]. Similarly, the predominating involvement of the lymph nodes that we observed is consistent with

Table 2. Diagnostic testing (smear microscopy, culture, Xpert MTB/RIF and/or nucleic acid amplification tests) of PTB and EPTB in HIV-positive patients: proportion of bacteriologically confirmed results (any positive result/any confirmatory test performed (positive and negative)), and proportions by specific diagnostic tests (smear microscopy, culture and Xpert MTB/RIF)

	Total n (%)	Bacteriological confirmation ^a Proportion n/n, (%)	Smear microscopy confirmation Proportion n/n, (%)	Culture confirmation Proportion n/n, (%)	Xpert MTB/RIF confirmation Proportion n/n, (%)
Site of disease					
PTB	1930 (100)	807/1557 (51.8)	805/1531 (52.6)	95/191 (49.7)	53/77 (68.8)
EPTB	765 (100)	183/438 (41.8)	118/416 (28.4)	75/133 (56.4)	23/35 (65.7)
EPTB only	634 (100)	103/334 (30.8)	58/317 (18.3)	43/84 (51.2)	12/20 (60.0)
Mixed PTB/EPTB	131 (100)	80/104 (76.9)	60/99 (60.6)	32/49 (65.3)	11/15 (73.3)
Organs involved in EPTB					
Lymph nodes	187 (100)	77/131 (58.8)	46/115 (40.0)	17/32 (53.1)	15/18 (75.0)
Meninges	48 (100)	14/29 (48.3)	5/22 (22.7)	4/7 (57.1)	4/4 (100)
Abdomen	85 (100)	18/58 (31.0)	9/45 (20.0)	3/8 (27.5)	1/1 (100)
Pleura	109 (100)	14/49 (28.6)	7/47 (14.9)	3/6 (50.0)	-
Joint/bones	22 (100)	6/12 (50.0)	4/11 (36.4)	3/4 (75.0)	0/1 (0)
Miliary	32 (100)	5/20 (25.0)	3/17 (17.6)	5/5 (100)	1/1 (100)
Other	17 (100)	3/10 (30.0)	2/9 (22.2)	1/1 (100)	1/1 (100)
Unknown	265 (100)	58/154 (37.7)	42/150 (28.0)	39/70 (55.7)	1/9 (11.1)

EPTB, extrapulmonary tuberculosis; n, numbers; PTB, pulmonary tuberculosis.

^aBacteriological confirmation was defined as confirmed if any diagnostic test result was positive (smear microscopy, culture, Xpert MTB/RIF and/or nucleic acid amplification tests).

Table 3. Risk factors for lost to follow-up and mortality during tuberculosis treatment in HIV-positive patients diagnosed with extrapulmonary and pulmonary TB

Variable	n	Lost to follow-up (LTFU)				Mortality				
		No. LTFU (%)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	No. of deaths (%)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age, years										
16 to 29	494	38 (7.7)	1	0.15	1	43 (8.7)	1	0.007	1	<0.001
30 to 39	966	58 (6.0)	0.77 (0.50 to 1.17)		0.79 (0.54 to 1.16)	109 (11.3)	1.33 (0.92 to 1.94)		1.20 (0.85 to 1.71)	
40 to 49	617	29 (4.7)	0.59 (0.36 to 0.97)		0.65 (0.49 to 0.85)	90 (14.6)	1.79 (1.22 to 2.63)		1.80 (0.84 to 3.87)	
≥50	263	11 (4.2)	0.57 (0.29 to 1.12)		0.61 (0.24 to 1.56)	39 (14.8)	1.83 (1.15 to 2.90)		1.95 (1.26 to 3.00)	
Sex										
Female	953	51 (5.4)	1	0.39	1	114 (12.0)	1	0.55	1	0.68
Male	1387	85 (6.1)	1.17 (0.82 to 1.67)		1.14 (0.74 to 1.75)	167 (12.0)	1.00 (0.78 to 1.29)		0.89 (0.50 to 1.56)	
BMI at start of TB treatment, kg/m ²	2340	-	0.91 (0.85 to 0.97)	0.004	0.88 (0.81 to 0.96)	-	0.96 (0.93 to 1.01)	0.003	0.98 (0.94 to 1.01)	0.19
History of TB										
No	2293	132 (5.8)	1	0.57	1	274 (11.9)	1	0.71	1	0.87
Yes	47	4 (8.5)	1.37 (0.47 to 3.94)		1.30 (0.32 to 5.23)	7 (14.9)	1.36 (0.59 to 3.12)		0.91 (0.29 to 2.87)	
ART status at TB diagnosis										
Not on ART	1660	104 (6.3)	1	0.13	1	200 (12.0)	1	0.20	1	0.28
On ART	680	32 (4.7)	0.73 (0.49 to 1.10)		0.75 (0.48 to 1.17)	81 (11.9)	0.99 (0.75 to 1.30)		1.21 (0.85 to 1.74)	
CD4 count at TB treatment start, cells/μL										
0 to 49	646	40 (6.2)	1.36 (0.84 to 2.21)		1.26 (0.94 to 1.69)	115 (17.8)	2.27 (1.61 to 3.19)		2.60 (1.46 to 4.64)	
50 to 199	829	59 (7.1)	1.51 (0.97 to 2.34)		1.46 (1.09 to 1.97)	89 (10.7)	1.25 (0.89 to 1.75)		1.38 (0.99 to 1.93)	
≥200	865	39 (4.5)	1	0.19	1	77 (8.9)	1	0.024	1	0.008
Site of disease										
PTB	1688	100 (5.9)	1	0.82	1	194 (11.5)	1	0.86	1	0.75
EPTB	652	36 (5.5)	0.96 (0.65 to 1.41)		0.92 (0.36 to 2.32)	87 (13.3)	1.19 (0.90 to 1.56)		1.03 (0.84 to 1.27)	
EPTB only ¹	546	20 (3.7)	0.60 (0.37 to 0.99)	0.044	0.58 (0.30 to 1.13)	74 (13.6)	1.21 (0.91 to 1.61)	0.12	1.04 (0.87 to 1.71)	0.69
Mixed PTB/EPTB ^a	106	16 (15.9)	3.03 (1.74 to 5.29)	<0.001	2.59 (1.06 to 6.32)	13 (12.3)	1.07 (0.59 to 1.96)	0.037	1.03 (0.62 to 1.71)	0.92

Table 3. (Continued)

Variable	n	Lost to follow-up (LTFU)				Mortality			
		No. LTFU (%)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	No. of deaths (%)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)
Organs involved ^b				0.72			0.67		
Lungs	1772	116 (6.5)	1		1	207 (11.7)	1	1	0.14
Meninges	43	1 (2.3)	1.71 (0.60 to 4.89)		1.76 (0.46 to 6.67)	10 (23.3)	2.28 (1.10 to 4.69)	1.85 (1.00 to 3.10)	
Miliary	26	2 (7.7)	1.39 (0.32 to 5.98)		1.52 (0.38 to 6.02)	2 (7.7)	0.63 (0.15 to 2.67)	0.74 (0.31 to 1.74)	
Other	449	18 (4.0)	1.12 (0.73 to 1.68)		1.10 (0.36 to 3.41)	62 (13.8)	1.05 (0.77 to 1.42)	0.87 (0.64 to 1.17)	

ART, antiretroviral therapy; BMI, body mass index; 95% CI, 95% confidence interval; ART, antiretroviral therapy; EPTB, extrapulmonary tuberculosis; LTFU, lost to follow-up; OR, odds ratio; PTB, pulmonary tuberculosis; TB, tuberculosis.

The main logistic regression model was adjusted for age, sex, BMI at start of TB treatment, previous history of TB, CD4 cell count at TB treatment start, ART status at TB diagnosis, and site of disease, taking into account heterogeneity across regions (clustering by treatment programmes). The model was based on 2340 patients since patients with TB treatment outcome defined as “not evaluated” (n = 355) were excluded from the analysis. The reference category is indicated with 1.

^aThese estimates were obtained from a separate model (n = 2340) comparing PTB versus EPTB only and mixed PTB/EPTB and was adjusted for age, sex, BMI at start of TB treatment, previous history of TB, CD4 cell count at TB treatment start, ART status at TB diagnosis, and taking into account heterogeneity across regions (clustering by treatment programmes). The reference category is indicated with 1; ^bthese estimates were obtained from a separate model (n = 2340) comparing involved organs lungs versus meninges, miliary, and other organs and was adjusted for age, sex, BMI at start of TB treatment, previous history of TB, CD4 cell count at TB treatment start, ART status at TB diagnosis, and taking into account heterogeneity across regions (clustering by treatment programmes). The reference category is indicated with 1.

previous publications on the presentation of EPTB in HIV-positive adults [19-24].

The diagnosis of TB is more challenging in HIV-positive than in HIV-negative patients. In PTB, this is due to reduced lung cavitation and lower bacterial load in sputum [25-28]. In line with previously published results, we observed that smear microscopy was the most commonly used diagnostic tool, even when other diagnostic modalities were available [16]. We further observed that bacteriological confirmation (positive smear microscopy, culture or Xpert MTB/RIF result) was associated with reduced mortality in PTB and EPTB patients compared to TB patients with a negative result. A study from Malawi showed similar results, but also found increased mortality among EPTB patients with a smear-negative result [29]. A systematic review explained the reduced mortality in bacteriologically confirmed PTB cases by showing that smear- and culture-negative disease is typical of advanced HIV immunosuppression compared to smear-positive TB patients with a less compromised immune system [30].

Among the EPTB patients for whom a bacteriological confirmation test was performed, only 42% were confirmed positive. Bacteriological confirmation is challenging due to EPTB's paucibacillary nature, in tissue, body fluid, or cerebrospinal fluid and the need for invasive specimen collection for microbiological diagnosis by biopsy or fine needle aspiration [7-9]. Mycobacterial culture and Xpert MTB/RIF have been shown to reliably diagnose EPTB, but are still rarely used in resource-limited settings, even when available [13,16]. From a programmatic perspective, the introduction of new diagnostics can indeed increase the proportion of bacteriological confirmed TB patients, as shown by a study from Cape Town, South Africa [31], but this may depend on the clinical setting [32]. The newly developed, next generation Xpert MTB/RIF Ultra assay has a higher sensitivity and similar specificity than the first generation Xpert MTB/RIF assay [33], and seems to be particularly useful in EPTB and paediatric TB [34].

While overall mortality was similar in PTB and EPTB patients, the mortality of HIV-positive patients with TB meningitis was greater than that of HIV-positive patients with PTB. This is in accord with a review that reported mortality up to 69% for TB meningitis in low-income countries [6]. We observed no difference in the odds of being LTFU during treatment among PTB compared to EPTB patients, which is in line with a Nigerian study [35]. However, we found that patients with only EPTB showed lower and mixed PTB/EPTB cases slightly increased risk of LTFU compared to PTB. This could be explained by the fact that the patients with mixed PTB/EPTB diagnosis are too sick to return to the clinic, or might even have died at home. A recent study from Botswana also reported an increased risk for LTFU during treatment in EPTB patients (including mixed PTB/EPTB cases) compared to PTB patients [36].

The main limitation of our study was its potential for misclassification bias. EPTB might have been underestimated due to the limited availability of diagnostic capacities [16] and the clinical practice of not pursuing further diagnoses once a PTB diagnosis has been established. Another limitation of the study was the heterogeneity of the participating ART programmes in terms of TB and HIV treatment, availability of supportive care [16] as well as lack of data on opportunistic infections other than TB. Further analysis of treatment outcomes by

diagnostic method was not possible due to the small numbers. Although we could not assess the vital status of those LTFU, the sensitivity analysis that we conducted to assess the potential impact of misclassification of death as lost to follow-up did not show any differences in the main outcomes. In spite of these potential limitations, our study provides important evidence on the limited diagnostic capacities available for EPTB at ART programmes in LMIC, and is one of few studies investigating EPTB in this context.

4 | CONCLUSIONS

Diagnosis of EPTB in ART programmes in LMIC is based mainly on clinical symptoms, and the introduction of molecular assays is still challenging despite major efforts. We conclude that greater access to diagnostic services could improve diagnosis, increase the number of diagnosed EPTB and improve clinical management of EPTB as well as treatment outcomes.

AUTHORS' AFFILIATIONS

¹Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland; ²Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; ³Centre Intégré de Recherches Biocliniques d'Abidjan (CIRBA), Abidjan, Côte d'Ivoire; ⁴College of Public Health, The Ohio State University, Columbus, OH, USA; ⁵Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brazil; ⁶National Institute for Medical Research, Kisesa HDSS, Mwanza, Tanzania; ⁷Vanderbilt Tuberculosis Center, Nashville, TN, USA; ⁸Division of Infectious Diseases, Vanderbilt University Medical Center, Nashville, TN, USA; ⁹Tumbi Special Hospital, CTC, Kibaha Town, Tanzania; ¹⁰The Global Tuberculosis Program, Texas Children's Hospital and Baylor College of Medicine, Houston, TX, USA; ¹¹Centre for Infectious Disease Epidemiology & Research, School of Public Health & Family Medicine, University of Cape Town, South Africa

COMPETING INTERESTS

All authors have no competing interests.

AUTHORS' CONTRIBUTIONS

KZ, MB, ME and LF involved in conception and design. KZ and MB analysed the data. KZ and LF completed the final draft of the manuscript. MB, SK, HC, MY, BG, DM, TRS, KMN, AMM, ACP and ME provided input into the study design, analyses and drafting of the paper. All authors reviewed and approved the final version of the manuscript.

ACKNOWLEDGEMENTS

We thank the sites that participated in the survey and the patients whose data were used in the study. We are indebted to the leDEA Tuberculosis Working Group for following the project's progress. We also thank the regional data centers which contributed not only to coordinating the study but also to recording and entering data. The authors thank Christopher Ritter for editorial assistance.

FUNDING

The International Epidemiology Databases to Evaluate AIDS (leDEA) is supported by the U.S. National Institutes of Health's National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Cancer Institute, the National Institute of Mental Health, and the National Institute on Drug Abuse: Asia-Pacific, U01AI069907; CCASAnet, U01AI069923; Central Africa, U01AI096299; East Africa, U01AI069911; NA-ACCORD, U01AI069918; Southern Africa, U01AI069924; West Africa, U01AI069919; Pettit K08 AI104352. This work is solely the responsibility of the authors and does not necessarily represent the official views of any of the institutions mentioned above.

PARTICIPATING SITES

Benin, CNHU Cotonou; Brazil, INI-Fiocruz; Burundi, CHUK Bujumbura; Cameroon, Military Hospital of Yaoundé; Côte d'Ivoire, CIRBA Adultes; Honduras, IHHS; Kenya, AMPATH; Mali, Point G, Bamako; Mexico, INCMNSZ; Peru, IMTAvH, CoVIHS; Philippines, Research Institute for Tropical Medicine; République Démocratique du Congo; Rwanda, Military Hospital; Senegal, Dakar; Tanzania, National Institute for Medical Research, Mwanza Research Centre, Kisesa Clinic, Mwanza; Tanzania, National AIDS Control Programme (NACP), Tumbi Regional Hospital; Thailand, HIV-NAT; Thailand, Faculty of Medicine Ramathibodi Hospital; Uganda, Masaka Regional Hospital; Vietnam, Bach Mai Hospital; Vietnam, National Hospital for Tropical Diseases. Membership of the leDEA collaboration for participating programmes is shown in Additional File 3.

MEMBERSHIP OF THE INTERNATIONAL EPIDEMIOLOGY DATABASES TO EVALUATE AIDS (leDEA) CONSORTIUM FOR PARTICIPATING

leDEA Caribbean, Central, and South America (CCASAnet), www.ccasanet.org; Instituto Nacional de Infectologia-Fiocruz, Brazil: Beatriz Grinztajn, Valdilea Veloso, Paula Luz, Raquel de Boni, Sandra Cardoso Wagner, Ruth Friedman, Ronaldo Moreira. Instituto Hondureño de Seguridad Social, Honduras: Denis Padgett. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico: Juan Sierra Madero, Brenda Crabtree Ramirez, Paco Belaunzarán, Yanink Caro Vega. Instituto de Medicina Tropical Alexander von Humboldt, Peru: Eduardo Gotuzzo, Fernando Mejía, Gabriela Carriquiry. Vanderbilt University Medical Center, USA: Catherine C McGowan, Bryan E Shepherd, Timothy Sterling, Karu Jayathilake, Anna K Person, Peter F Rebeiro, Mark Giganti, Jessica Castilho, Stephany N Duda, Fernanda Maruri, Hilary Vansell.

leDEA Asia Pacific, www.amfar.org/treatasia: R Ditangco, E Uy and R Bantique, Research Institute for Tropical Medicine, Manila, Philippines; A Avihingsanon, S Gatechompol, P Phanuphak and C Phadungphon, HIVNAT/Thai Red Cross AIDS Research Centre, Bangkok, Thailand; S Kiertiburanakul, A Phu-phuakrat, L Chumla and N Sanmeema, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; KV Nguyen, HV Bui, DTH Nguyen and DT Nguyen National Hospital for Tropical Diseases, Hanoi, Vietnam; DD Cuong, NV An and NT Luan, Bach Mai Hospital, Hanoi, Vietnam; AH Sohn, JL Ross and B Petersen, TREAT Asia, amfAR - The Foundation for AIDS Research, Bangkok, Thailand; MG Law, A Jiamsakul and DC Boettiger, The Kirby Institute, UNSW Australia, Sydney, Australia.

East Africa leDEA, www.iedea-ea.org/joomla: Diero L, Ayaya S, Sang E, MOI University, AMPATH Plus, Eldoret, Kenya; John Ssali, Mathew Ssemakadde, Masaka Regional Referral Hospital, Masaka, Uganda; Kapella Ngonyani, Jerome Lwali, Tumbi Regional Hospital, Pwani, Tanzania; Mark Urassa, Denna Michael, Richard Machemba, National Institute for Medical Research (NIMR), Kisesa HDSS, Mwanza, Tanzania; Kara Wools-Kaloustian, Constantin Yiannoutsos, Rachel Vreeman, Beverly Musick, Indiana University School of Medicine, Indiana University, Indianapolis, IN, USA; Batya Elul, Columbia University, New York City, NY, USA; Jennifer Svartsen, Ohio State University, Columbus, OH, USA; Rami Kantor, Brown University/Miriam Hospital, Providence, RI, USA; Jeffrey Martin, Megan Wenger, Craig Cohen, Jayne Kulzer, University of California, San Francisco, CA, USA; Paula Braitstein, University of Toronto, Toronto, Canada.

West Africa leDEA, www.mereva.net/iedea: Benin Cotonou: Djimon Marcel Zannou, Carin Ahouada, Jocelyn Akakpo, Christelle Ahomadegbé, Jules Bashi, Alice Gougounon-Houéto, Angèle Azone-Kouanou, Fabien Houngbé, Jean Sehonou (CNHU Hubert Maga). Côte d'Ivoire, Abidjan: Henri Chenal, Denise Hawerlander, Franck Soppa (CIRBA); Mali, Bamako: Hamar Alassane Traore, Daouda Minta, Tidiani Cissé, Mamadou Dombélé, Mohammed Doumbia, Mahamadou Fomba, Assétou Soukho Kaya, Abdoulaye M Traoré, Hamady Traoré, Amadou Abathina Toure (CH Point G). Senegal, Dakar: Moussa Seydi, Papa Salif Sow, Bernard Diop, Noël Magloire Manga, Judicael Malick Tineš, Coumba Cissé Bassabi (SMIT, CHU Fann). Executive Committee: François Dabis (Principal Investigator, Bordeaux, France), Emmanuel Bissagnene (Co-Principal Investigator, Abidjan, Côte d'Ivoire), Elise Arrivé (Bordeaux, France), Patrick Coffie (Abidjan, Côte d'Ivoire), Didier Ekouevi (Abidjan, Côte d'Ivoire), Antoine Jaquet (Bordeaux, France), Valérie Leroy (Bordeaux, France), Charlotte Lewden (Bordeaux, France), Annie J Sasco (Bordeaux, France). Operational and Statistical Team: Dieudonné Amani (Abidjan, Côte d'Ivoire), Jean-Claude Azani (Abidjan, Côte d'Ivoire), Eric Balestre (Bordeaux, France), Serge Bessekon (Abidjan, Côte d'Ivoire), Franck Bohossou (Abidjan, Côte d'Ivoire), Camille Gilbert (Bordeaux, France), Sophie Karcher (Bordeaux, France), Jules Mahan Gonsan (Abidjan, Côte d'Ivoire), Jérôme Le Carrou (Bordeaux, France), Séverin Lenaud (Abidjan, Côte d'Ivoire), Célestin Nchot (Abidjan, Côte d'Ivoire), Karen Malateste (Bordeaux, France), Amon Roseamonde Yao (Abidjan, Côte d'Ivoire), Bertine Siloué (Abidjan,

Côte d'Ivoire). Administrative Team: Gwenaëlle Clouet (Bordeaux, France), Madikona Dosso (Abidjan, Côte d'Ivoire), Alexandra Doring (Bordeaux, France), Adrienne Kouakou (Abidjan, Côte d'Ivoire), Elodie Rabourdin (Bordeaux, France), Jean Rivenc (Pessac, France). Consultants/Working Groups: Xavier Anglaret (Bordeaux, France), Boubacar Ba (Bamako, Mali), Jean Bosco Essanin (Abidjan), Andrea Ciaranello (Boston, USA), Sébastien Datté (Abidjan, Côte d'Ivoire), Sophie Desmone (Bordeaux, France), Jean-Serge Elvis Diby (Abidjan, Côte d'Ivoire), Geoffrey S Gottlieb (Seattle, USA), Apollinaire Gnigninrino Horo (Abidjan, Côte d'Ivoire), Serge N'zoré Kangah (Abidjan, Côte d'Ivoire), Denis Malvy (Bordeaux, France), David Meless (Abidjan, Côte d'Ivoire), Aida Mounkaila-Harouna (Bordeaux, France), Camille Ndongdoki (Bordeaux, France), Caroline Shiboski (San Francisco USA), Boris Tchounga (Abidjan, Côte d'Ivoire), Rodolphe Thiébaud (Bordeaux, France), Gilles Wandeler (Dakar, Senegal). Coordinating Centre: ISPED, Univ Bordeaux Segalen, Bordeaux, France Regional Office: PAC-CI, Abidjan, Côte d'Ivoire Methodologic Support: MEREVA, Bordeaux, France.

Central Africa leDEA, www.iedea.org: Jean Claude Dusingize and Eugene Mutimura, Andre Gitembagara Women's Equity in Access to Care and Treatment, Kigali Rwanda; Kathryn Anastos Albert Einstein College of Medicine and Montefiore Medical Center, New York, USA; Judy Tatwangire, Izimukwize Izabelle, Rwanda Military Hospital, Kigali, Rwanda; Theodore Niyongabo, Christelle Twizere Centre hospitalo-Universitaire de Kamenge, Bujumbura, Burundi; Evelyne Baramperanye, Centre National de Reference en matiere du VIH, Bujumbura, Burundi; Andrew Edmonds, Marcel Yotebieng Kalembelembe Pediatric hospital, Kinshasa, DRC; Innocent Azinyue Liliane Ayangma, Military Hospital of Yaoundé.

leDEA Southern Africa, www.iedea-sa.org: Data centers: Nina Anderegg, Marie Ballif, Lina Bartels, Julia Bohlius, Frédérique Chamartin, Benedikt Christ, Cam Ha Dao Ostinelli, Matthias Egger, Lukas Fenner, Per von Groote, Andreas Haas, Taghavi Katayoun, Eliane Rohner, Lilian Smith, Adrian Spörri, Gilles Wandeler, Elizabeth Zaniewski, Kathrin Zürcher, Institute of Social and Preventive Medicine, University of Bern, Switzerland; Andrew Boule, Morna Cornell, MaryAnn Davies, Victoria Iyun, Leigh Johnson, Mmamapudi Kubjane, Nicola Maxwell, Tshabakwane Nembandona, Patience Nyakato, Ernest Mokotoane, Gem Patten, Michael Schomaker, Priscilla Tsondai, Renee de Waal, School of Public Health and Family Medicine, University of Cape Town, South Africa.

REFERENCES

1. 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.
2. Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, Steingart KR. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. *Eur Respir J*. 2014; 44(2):435–46.
3. Rieder HL, Snider DE Jr, Cauthen GM. Extrapulmonary tuberculosis in the United States. *Am Rev Respir Dis*. 1990; 141(2):347–51.
4. Gupta RK, Lawn SD, Bekker LG, Caldwell J, Kaplan R, Wood R. Impact of human immunodeficiency virus and CD4 count on tuberculosis diagnosis: analysis of city-wide data from Cape Town, South Africa. *Int J Tuberc Lung Dis*. 2013; 17(8):1014–22.
5. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014). World Health Organization Document. 2014:1–47.
6. Marx GE, Chan ED. Tuberculous meningitis: diagnosis and treatment overview. *Tuberc Res Treat*. 2011; 2011:798764.
7. Chakravorty S, Sen MK, Tyagi JS. Diagnosis of extrapulmonary tuberculosis by smear, culture, and PCR using universal sample processing technology. *J Clin Microbiol*. 2005; 43(9):4357–62.
8. Norbis L, Alagna R, Tortoli E, Codecasa LR, Migliori GB, Cirillo DM. Challenges and perspectives in the diagnosis of extrapulmonary tuberculosis. *Expert Rev Anti Infect Ther*. 2014; 12(5):633–47.
9. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Second edition. World Health Organization Document. 2014:1–146.
10. World Health Organization. Improving the diagnosis and treatment of smear-negative pulmonary and extra-pulmonary tuberculosis among adults and adolescents. World Health Organization Document. 2006:1–36.
11. World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. World Health Organization Document. 2013; WHO/HTM/TB/2013.16:1–97.

12. Egger M, Ekouevi DK, Williams C, Lyamuya RE, Mukumbi H, Braitstein P, et al. Cohort Profile: the international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa. *Int J Epidemiol*. 2012;41(5):1256–64.
13. Clouse K, Blevins M, Lindegren ML, Yotebieng M, Nguyen DT, Omondi A, 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:e0171384.
14. 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.
15. Carlucci JG, Blevins M, Kipp AM, Lindegren ML, Du QT, Renner L, et al. Tuberculosis treatment outcomes among HIV/TB co-infected children in the International Epidemiology Databases to Evaluate AIDS (IeDEA) Network. *JAIDS*. 2017;75(2):156–63.
16. Fenner L, Ballif M, Graber C, Nhandu V, Dusingize JC, Cortes CP, et al. Tuberculosis in antiretroviral treatment programs in lower income countries: availability and use of diagnostics and screening. *PLoS ONE*. 2013;8:e77697.
17. Yang Z, Kong Y, Wilson F, Foxman B, Fowler AH, Marrs CF, et al. Identification of risk factors for extrapulmonary tuberculosis. *Clin Infect Dis*. 2004;38(2):199–205.
18. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393.
19. Sharma SK, Mohan A. Extrapulmonary tuberculosis. *Indian J Med Res*. 2004;120(4):316–53.
20. Fanning A. Tuberculosis: 6. Extrapulmonary disease. *CMAJ*. 1999;160(11):1597–603.
21. Karstaedt AS. Extrapulmonary tuberculosis among adults: experience at Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa. *S Afr Med J*. 2014;104(1):22–4.
22. Naing C, Mak JW, Maung M, Wong SF, Kassim AI. Meta-analysis: the association between HIV infection and extrapulmonary tuberculosis. *Lung*. 2013;191(1):27–34.
23. Leeds IL, Magee MJ, Kurbatova EV, del Rio C, Blumberg HM, Leonard MK, et al. Site of extrapulmonary tuberculosis is associated with HIV infection. *Clin Infect Dis*. 2012;55(1):75–81.
24. Kulchavenya E. Extrapulmonary tuberculosis: are statistical reports accurate? *Ther Adv Infect Dis*. 2014;2(2):61–70.
25. Brindle RJ, Nunn PP, Githui W, Allen BW, Gathua S, Waiyaki P. Quantitative bacillary response to treatment in HIV-associated pulmonary tuberculosis. *T Am Rev Respir Dis*. 1993;147(4):958–61.
26. Telzak EE, Fazal BA, Pollard CL, Turett GS, Justman JE, Blum S. Factors influencing time to sputum conversion among patients with smear-positive pulmonary tuberculosis. *Clin Infect Dis*. 1997;25(3):666–70.
27. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. World Health Organization Document. 2014:1-464.
28. Steingart KR, Ng V, Henry M, Hopewell PC, Ramsay A, Cunningham J, et al. Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis*. 2006;6(10):664–74.
29. Kang'ombe C, Harries AD, Banda H, Nyangulu DS, Whitty CJ, Salaniponi FM, et al. High mortality rates in tuberculosis patients in Zomba Hospital, Malawi, during 32 months of follow-up. *Trans R Soc Trop Med Hyg*. 2000;94(3):305–9.
30. Waitt CJ, Squire SB. A systematic review of risk factors for death in adults during and after tuberculosis treatment. *Int J Tuberc Lung Dis*. 2016;20(10):1320–5.
31. Hermans S, Caldwell J, Kaplan R, Cobelens F, Wood R. The impact of the roll-out of rapid molecular diagnostic testing for tuberculosis on empirical treatment in Cape Town, South Africa. *Bull World Health Organ*. 2017;95(8):554–63.
32. Kendall EA, Schumacher SG, Denkinger CM, Dowdy DW. Estimated clinical impact of the Xpert MTB/RIF Ultra cartridge for diagnosis of pulmonary tuberculosis: a modeling study. *PLoS Med*. 2017;14:e1002472.
33. World Health Organization. WHO meeting report of a technical expert consultation: non-inferiority analysis of Xpert MT. World Health Organization. 2017:1-11.
34. Dorman SE, Schumacher SG, Alland D, Nabeta P, Armstrong DT, King B, et al. Xpert MTB/RIF Ultra for detection of *Mycobacterium tuberculosis* and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *Lancet Infect Dis*. 2018;18(1):76–84.
35. Ifebunandu NA, Ukwaja KN. Tuberculosis treatment default in a large tertiary care hospital in urban Nigeria: prevalence, trend, timing and predictors. *J Infect Public Health*. 2012;5(5):340–5.
36. Enane LA, Lowenthal ED, Arscott-Mills T, Mathhare M, Smallcomb LS, Kgwaadira B, et al. Loss to follow-up among adolescents with tuberculosis in Gaborone, Botswana. *Int J Tuberc Lung Dis*. 2016;20(10):1320–5.