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Mortality rate and determinants of death in HIV-associated extrapulmonary tuberculosis: A ten-year retrospective cohort study

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Abstract

Background

Extrapulmonary tuberculosis (EPTB) is a leading cause of death among people living with HIV (PLHIV) in sub-Saharan Africa, yet site-specific mortality patterns and risk factors remain poorly characterised. We aimed to describe EPTB localisations and assess mortality rates and determinants of death among HIV-infected adults with EPTB in Abidjan, Côte d'Ivoire.

Methods

We conducted a retrospective cohort study including all HIV-infected adults (≥ 18 years) treated for presumptive or confirmed EPTB at the Infectious and Tropical Diseases Department of Treichville University Hospital between January 1, 2010, and March 31, 2019. Data were extracted from medical records. Survival was estimated using Kaplan–Meier methods. Risk factors for death were identified using a stratified Cox proportional hazards model.

Results

Of 2,046 TB/HIV co-infected patients, 1,240 (60.6%) had EPTB. The most frequent localisations were lymph nodes (32.0%), miliary tuberculosis (23.6%), and tuberculous meningitis (TBM, 16.4%). Overall mortality was 38% (470/1,240), reaching 58% for TBM, 49% for serous membrane TB, and 43% for miliary TB. Most deaths occurred within the first 60 days of anti-tuberculosis treatment. In multivariable analysis, independent risk factors for death were TBM (adjusted hazard ratio [aHR] 2.20; 95% confidence interval [CI] 1.28–3.74) and serous membrane TB (aHR 1.77; 95% CI 1.02–3.09). Miliary TB showed a trend toward increased mortality (aHR 1.66; 95% CI 0.98–2.82). Protective factors included cotrimoxazole prophylaxis (aHR 0.65; 95% CI 0.53–0.80) and a CD4 count ≥ 100 cells/mm³ (aHR 0.26; 95% CI 0.18–0.36).

Conclusions

EPTB is frequent and highly lethal among HIV-infected patients in Côte d'Ivoire, particularly TBM and serous membrane TB. The first two months of treatment are a critical period for survival. Cotrimoxazole prophylaxis and preserved CD4 counts are strongly protective. These findings support earlier HIV diagnosis, prompt ART initiation, and strengthened diagnostic algorithms for disseminated EPTB in resource-limited settings.

Introduction

Tuberculosis (TB) is the tenth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS (1). According to the World Health Organization's (WHO) global tuberculosis report, there were approximately 10.8 million people who developed tuberculosis worldwide in 2023, resulting in 1.23 million deaths (1). *Carabalí-Isajar et al*., in a recent review, described that TB can disseminate from the initial site of infection via various pathways to affect almost all organs, challenging the historical perception of tuberculosis as solely a pulmonary disease (2). Extrapulmonary tuberculosis (EPTB) is defined by World Health Organisation (WHO) classification criteria as an infection by *Mycobacterium tuberculosis* (MTB) affecting tissues and organs outside the pulmonary parenchyma, representing between 20 and 25% of all TB cases (3). In clinical practice, diagnosis is challenging due to the frequently low bacillary load in affected tissues and the procedural difficulty in acquiring deep organ specimens. According to the 2013 WHO definition, a diagnosis of EPTB is based on either a positive culture, a positive histology from an organ biopsy, or strong clinical evidence consistent with active EPTB (4). While, in resource-limited countries, confirmation of an EPTB diagnosis is often based on presumptive evidence with limited confirmatory proof.

Among TB patients, high mortality rates have been associated with diagnostic delays, which occur most frequently in smear-negative pulmonary TB and EPTB (5–7). TB remains a leading cause of death among people living with HIV (PLHIV) in sub-Saharan Africa (8, 9). HIV-associated TB is more likely to present as smear-negative pulmonary TB or EPTB (10, 11). For example, the most lethal and disabling form of TB is tuberculous meningitis (TBM), with an estimated 164,000 new cases per year, representing around 6% of EPTB cases (12–14).

Since 2010, Côte d'Ivoire (CI) has integrated joint TB/HIV control into 160 TB care facilities. In 2015, the incidence of TB in CI was 159 cases per 100,000 population; of 22,879 TB cases, 5,165 (24%) were co-infected with HIV (15). In 2023, WHO reported 119 new cases per 100, 000 population (15). Between 2010 and 2015, the rate of HIV counselling and testing among TB patients increased from 73% to 95% (16). The Service des Maladies Infectieuses et Tropicales (SMIT) at the Treichville University Hospital in Abidjan was designated as a TB diagnosis and treatment centre. Since then, it has been supplied with tools from the National Tuberculosis Control Program for case collection and

treatment with anti-TB drugs. Studies conducted to date have focused primarily on overall tuberculosis prevalence data (17). While tuberculous meningitis is regarded as the most fatal form of EPTB, the diversity of anatomical sites involved calls for a better understanding of mortality patterns in the different forms of EPTB. The choice of adjuvant therapy, including corticosteroid regimens, and the treatment duration which can extend to 18 months depending on the anatomical site are key determinants of patient prognosis. In the present study, we aimed to describe the pattern of disease in patients registered as presumptive EPTB, and to assess mortality rates and risk factors for death in HIV-infected adults with EPTB enrolled in a ten-year retrospective cohort at SMIT.

Methods

Study design, site and population

This retrospective cohort study was conducted at the SMIT of the Treichville University Teaching Hospital, a primary health facility in Abidjan, the economic capital of Côte d'Ivoire. SMIT is the National Reference Centre for HIV/AIDS Care, Research, and Training, collaborating with several other institutions nationally, within Africa, and in Europe. Since its inception, over 21,413 HIV-infected patients have been cared for at SMIT, and more than 20,000 patients have received antiretroviral therapy (ART). The current active caseload is estimated at 3,379 patients. All ART-naive patients initiated first-line antiretroviral treatment with a WHO-recommended regimen containing at least two nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI) (18). Second- and third-line treatment strategies are based primarily on WHO recommendations (19). Cotrimoxazole prophylaxis was prescribed according to national guidelines.

The study population consisted of all adult patients (aged 18 years or older) with TB/HIV co-infection followed at the TB Diagnosis and Treatment Centre, who were registered in the SMIT database between January 1st, 2010, and March 31st, 2019, and had a presumptive, confirmed, or probable TB diagnosis along with HIV-positive serology confirmed by Western Blot. These patients were either under active follow-up at SMIT or referred from another centre and were either ART-naive or had previously received ARV treatment prior to their admission to SMIT. The study period 2010-2019 was selected to capture a homogeneous era of HIV/TB management in Côte d'Ivoire, corresponding to stable WHO-based ART initiation criteria (CD4 ≤ 350 cells/mm³) and pre-COVID healthcare conditions, while ensuring sufficient sample size and data completeness.

Data collection

All the patients registered in the Directly Observed Therapy Short Course (DOTS) clinic from the study period were included. Patients' registration numbers were used to obtain corresponding files from the medical records department. From each medical case file, data were collected using a standardized form that captured sociodemographic data, date of tuberculosis diagnosis, laboratory investigations, HIV status, CD4 count at TB diagnosis, ART status, TB classification (pulmonary, extrapulmonary, organ involved, disseminated), and TB treatment outcome. The initial assessment for TB/HIV co-infection included sputum acid-fast bacilli (AFB) testing, chest X-ray, abdominal ultrasound, histological examination, TB LAM, GeneXpert, culture, HIV type, CD4 lymphocyte count, and ART status.

All patients diagnosed with TB are registered in a TB register before initiating therapy. The diagnosis and treatment of TB are based on the national guidelines of the National Tuberculosis Control Program (NTCP), adapted from WHO guidelines and the recommendations of the International Union Against Tuberculosis and Lung Disease (The Union) (20, 21).

Pulmonary TB, Smear-Positive

defined as a pulmonary presentation with at least one sputum smear positive for acid-fast bacilli (AFB) on direct microscopic examination. This group included new cases (first episode), relapse cases, and retreatment cases (subsequent episodes).

Pulmonary TB, Smear-Negative

defined as a patient with symptoms suggestive of TB, with at least two sputum specimens negative for AFB by microscopy, and chest radiographic abnormalities consistent with active pulmonary TB (including interstitial or miliary opacities); or a patient with two sets of at least two sputum specimens collected at least two weeks apart that were negative for AFB by microscopy, demonstrating radiographic abnormalities consistent with pulmonary TB and no clinical response to one week of broad-spectrum antibiotic therapy.

EPTB

defined as tuberculosis affecting organs other than the lungs, such as lymph nodes, abdomen, genitourinary tract, skin, joints and bones, pericardium, pleura, and meninges. Diagnosis of EPTB was based on fine-needle aspiration cytology, biochemical analyses of cerebrospinal/pleural/ascitic fluid, histopathological examination, or strong clinical evidence consistent with active EPTB, leading to a

clinician's decision to treat with a full course of anti-tuberculosis chemotherapy (bacteriologically confirmed or. a clinically presumed EPTB that responded to ATT at 2–3 months or the end of treatment). In all cases of EPTB, sputum examinations and chest radiographs were performed to assess for concomitant lung parenchyma involvement. Usually, because of difficulties in accessing and obtaining specimens from different biological sites, TB treatment is started based on symptoms and other circumstantial evidence that includes laboratory investigations and radiographic abnormalities.

Disseminated Tuberculosis

Defined as the co-occurrence of pulmonary TB and extrapulmonary TB with involvement of two or more non-pulmonary organs.

Patients were classified as deceased if death was certified in the electronic hospital records or if the information was provided during phone follow-up. Death from any cause was considered as mortality. Patients who responded on the phone follow-ups or had continuous notes in the hospital records until the end of the study were considered alive. Patients were marked as lost to follow up if they were unreachable by phone at 2–3 months and at the conclusion of antituberculosis treatment (ATT).

Therapeutic management of co-infection HIV-TB

Anti-tuberculosis treatment (ATT) consisted of a first-line anti-TB regimen with rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E) for the first two months (2RHZE) followed by rifampicin and isoniazid for four months (4RH). The second-line regimen, for patients who failed or relapsed, consisted of rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin for the first two months (2RHZES), followed by rifampicin, isoniazid, pyrazinamide, and ethambutol for one month (1RHZE), then rifampicin, isoniazid, and ethambutol for five months (5RHE). According to WHO guidelines, the standard 6-month regimen (2HRZE/4HR) is recommended for most forms of extrapulmonary tuberculosis. Nevertheless, expert groups suggest extending treatment to 9–12 months for tuberculous meningitis (given the serious risk of disability and mortality) and to 9 months for osteoarticular TB (owing to difficulties in assessing treatment response)(22)

ART was firstly prescribed according to the 2010 WHO recommendations and national guidelines with adjustments based on changes in recommendations over time (18). Cotrimoxazole prophylaxis was recommended for all patients known to be HIV-positive at or after TB/HIV diagnosis.

The outcome of tuberculosis treatment was classified according to WHO definitions into five categories (23): "cured," "treatment completed," "deceased," "lost to follow-up," or "transferred." Patients who successfully completed treatment comprised those who were "cured" and those who "completed treatment".

Statistical methods

All selected data were exported from Microsoft Excel version 2010 (Microsoft, USA) to RStudio software version 2022.02.0-443. We compared characteristics between groups using Wilcoxon tests (comparison of medians) for quantitative variables, and the χ 2 or the Fisher exact tests for qualitative variables, as appropriate. Survival time was measured in days, calculated as the interval between the date of anti-TB treatment initiation and the date of death or censoring. The Kaplan-Meier method was used to estimate the survival probability after anti-TB initiation. The log-rank test was used to compare survival between tuberculosis diagnostic groups and CD4 cell count range. A stratified Cox proportional hazards model was used to estimate the effect of each predictor on mortality. “A univariate analysis identified variables with $p < 0.25$. The assumption of proportional hazards was tested for each variable in the final multivariate model. Variables violating this assumption were stratified (*patient type, Haemoglobin level, ALT level*). This approach resulted in a statistically validated final model using a stepwise selection procedure, retaining all variables with a level of significance (P = 0.05)

Results

Study population characteristics

A total of 2046 patients were included in the study (**table I**). Among them, 872 (43%) were male. The median age was 40 years (IQR; 34–47). The EPTB and PTB groups were comparable in terms of age, sex, and weight. However, significant differences were observed regarding occupation, marital status, and place of residence. Current tobacco smoking was significantly lower in the EPTB group (9.7% vs. 23%, $p < 0.001$), which aligns with the primarily pulmonary nature of exposure to this risk factor. The most striking difference concerns patient category ($p < 0.001$). While nearly all PTB patients (99%) were new cases, almost one-third (28%) of EPTB patients were retreatment cases following a relapse. The distribution of HIV types (predominantly HIV-1) and antiretroviral therapy (ART) status were similar between groups.

A statistically significant, though modest, difference was noted for cotrimoxazole (CTX) prophylaxis, which was less frequent in the EPTB group (34% vs. 38%, p = 0.041).

Table I: Baseline characteristics of adults HIV-infected patients with extrapulmonary tuberculosis and pulmonary tuberculosis, Treichville University Teaching Hospital, 2010–2019, N = 2046

Characteristic	Overall N = 2046[1]	EPTB N = 1240[1]	PTB N = 806[1]	p-value[2]
Gender				0.3
Female	57% (1174/2046)	57% (701/1240)	59% (473/806)	
Male	43% (872/2046)	43% (539/1240)	41% (333/806)	
Age				0.12
Median (IQR)	40 (34–47)	40 (34–47)	41 (34–48)	
Occupation				< 0.001
No	38% (778/2046)	35% (428/1,240)	43% (350/806)	
Yes	62% (1,264/2046)	65% (812/1,240)	57% (455/806)	
Couples				< 0.001
No	50% (1,020/2,046)	47% (577/1,240)	55% (443/806)	
Yes	50% (1,026/2,046)	53% (663/1,240)	45% (363/806)	
Residence				< 0.001
Rural	6.9% (141/2,046)	8.6% (107/1,240)	4.2% (34/806)	
Urbain	93% (1,905/2,046)	91% (1,133/1,240)	96% (772/806)	
Weight (Kg)				0.3
Median (IQR)	50 (43–58)	50 (43–58)	50 (42–57)	
Tobacco habit				< 0.001
Never	81% (1,656/2,046)	86% (1,063/1,240)	74% (593/806)	
Current smoker	15% (303/2,046)	9.7% (120/1,240)	23% (183/806)	
Ex-smoker	4.3% (87/2,046)	4.6% (57/1,240)	3.7% (30/806)	
Patient category				< 0.001
New	83% (1,689/2,046)	72% (891/1,240)	99% (798/806)	
Relapse	17% (348/2,046)	28% (342/1,240)	0.7% (6/806)	
Retreatment	0.4% (9/2,046)	0.6% (7/1,240)	0.2% (2/806)	
HIV type				0.5
HIV-1	97% (1,990/2,046)	97% (1,202/1,240)	98% (788/806)	
HIV-2	2.3% (47/2,046)	2.5% (31/1,240)	2.0% (16/806)	
HIV-dual reactive	0.4% (9/2,046)	0.6% (7/1,240)	0.2% (2/806)	
ART Status				0.10
Naive	37% (752/2,046)	38% (467/1,240)	35% (285/806)	
Pretreated	61% (1,239/2,046)	59% (734/1,240)	63% (505/806)	
Unknow	2.7% (55/2,046)	3.1% (39/1,240)	2.0% (16/806)	
CTX prophylaxis				0.041
No	64% (1,314/2,046)	66% (818/1,240)	62% (496/806)	
Yes	36% (732/2,046)	34% (422/1,240)	38% (310/806)	

[1]% (n/N)

[2]Pearson's Chi-squared test; Wilcoxon rank sum test

Note

ART, Antiretroviral therapy; **CTX**, Cotrimoxazole; **EPTB**: Extrapulmonary tuberculosis; **IQR**: Interquartile; **HIV**: Human immunodeficiency virus; **PTB**: Pulmonary tuberculosis (Sputum Smear-positive & Sputum Smear-negative); **ALT**: Alanine aminotransferase.

Table I: Baseline demographic characteristics and HIV-status in patients with extrapulmonary tuberculosis and pulmonary tuberculosis, Treichville University Teaching Hospital, 2010–2019, N = 2046 (continued).

Characteristic	Overall N = 2,046[1]	TBEP N = 1,240[1]	TPB N = 806[1]	p-value[2]
				0.1
Hb (g/l) Median	10.00 (9.00–11.10)	10.00 (9.00–11.40)	10.00 (9.00–11.00)	
Hb_group				0.7
< 10	41% (754/1,837)	42% (478/1,149)	40% (276/688)	
>= 10	59% (1,083/1,837)	58% (671/1,149)	60% (412/688)	
Unknown	209	91	118	
				0.022
Lymph (/mm^3) Median	1,100 (748–1,560)	1,090 (720–1,560)	1,160 (789–1,567)	
Lymp_group				0.5
< 1500	46% (836/1,837)	48% (546/1,149)	42% (290/688)	
>= 1500	54% (1,001/1,837)	52% (603/1,149)	58% (398/688)	
Unknown	209	91	118	
				0.001
ALT (U/l) Median	31 (21–42)	29 (19–42)	34 (24–44)	
ALT_group				0.075
< 40	70% (1,272/1,830)	71% (808/1,138)	67% (464/692)	
>= 40	30% (558/1,830)	29% (330/1,138)	33% (228/692)	
Unknown	216	102	114	
				0.009
CD4 (/mm3) Median	36 (23–85)	35 (22–89)	36 (27–79)	
CD4_group				0.2
< 100	78% (882/1,130)	77% (567/734)	80% (315/396)	
>= 200	11% (126/1,130)	11% (79/734)	12% (47/396)	
100–200	11% (122/1,130)	12% (88/734)	8.6% (34/396)	
Unknown	916	506	410	
[1]% (n/N)				
[2]Pearson's Chi-squared test; Wilcoxon rank sum test				

Notes: ART, Antiretroviral therapy; **CTx**, Cotrimoxazole; **EPTB**: Extrapulmonary tuberculosis; **IQR**: Interquartile; **HIV**: Human immunodeficiency virus; **Lymp**: lymphocytes cell counts; **PTB**: Pulmonary tuberculosis (Sputum Smear-positive & Sputum Smear-negative); **ALT**: Alanine aminotransferase.

Epidemiology and TB outcomes of EPTB according to different sites of infection

Of 2046 all TB cases registered during the study period, 1240 had EPTB. Lymph node 397 (32%), followed by miliary 293 (23.6%) and tuberculosis meningitis (TBM) 203 (16.4%) were the most frequent types of all EPTB cases among study participants (**Table II**). The highest

proportion of EPTB was found in the 35–44 and 45–54 age groups, with 41% and 25% respectively. Female accounted for 701 (57%) of all EPTB patients. The proportion of women was higher than men regardless of the anatomical site. Among the 1240 patients with extrapulmonary TB, 609 (49%) completed their ATT, with rates ranging from 28% for tuberculous meningitis to 74% for genitourinary TB. A total of 470 (38%) patient died, with the highest mortality rate observed in patients with tuberculous meningitis (58%) followed by serous membrane TB (49%) and miliary TB (43%). The lowest mortality rate was observed in patients with the genitourinary TB (21%). Furthermore, 135 (11%) were lost to follow-up, and 26 (2.1%) were transferred.

Table II: Age, gender and TB outcomes of EPTB according to the different sites

Characteristic	Overall N = 1,240[1]	Lymph Nodes N = 397[1]	Miliary N = 293[1]	TB meningitis N = 203[1]	Genito-Urinary N = 105[1]	Pleural effusion* N = 62[1]	Peritoneal* N = 62[1]	Pericarditis* N = 52[1]	Others N = 66
Age (years)									
25–34	21% (265/1,240)	23% (91/397)	20% (60/293)	21% (43/203)	18% (19/105)	19% (12/62)	26% (16/62)	25% (13/52)	17% (11/66)
35–44	41% (507/1,240)	41% (163/397)	42% (122/293)	41% (83/203)	37% (39/105)	44% (27/62)	35% (22/62)	40% (21/52)	45% (30/66)
45–54	25% (312/1,240)	25% (99/397)	25% (74/293)	26% (53/203)	30% (32/105)	18% (11/62)	21% (13/62)	27% (14/52)	24% (16/66)
55–64	6.5% (81/1,240)	5.3% (21/397)	5.5% (16/293)	7.9% (16/203)	10% (11/105)	8.1% (5/62)	6.5% (4/62)	3.8% (2/52)	9.1% (6/66)
≥65ans	1.4% (17/1,240)	0.5% (2/397)	1.7% (5/293)	2.0% (4/203)	0% (0/105)	4.8% (3/62)	3.2% (2/62)	1.9% (1/52)	0% (0/66)
<25ans	4.7% (58/1,240)	5.3% (21/397)	5.5% (16/293)	2.0% (4/203)	3.8% (4/105)	6.5% (4/62)	8.1% (5/62)	1.9% (1/52)	4.5% (3/66)
Gender									
Female	57% (701/1,240)	55% (219/397)	58% (171/293)	52% (106/203)	68% (71/105)	55% (34/62)	63% (39/62)	58% (30/52)	47% (31/66)
Male	43% (539/1,240)	45% (178/397)	42% (122/293)	48% (97/203)	32% (34/105)	45% (28/62)	37% (23/62)	42% (22/52)	53% (35/66)
TB Outcome's									
Completed	49% (609/1,240)	53% (210/397)	44% (130/293)	28% (57/203)	74% (78/105)	60% (37/62)	37% (23/62)	62% (32/52)	64% (42/66)
LTFU	11% (135/1,240)	14% (55/397)	11% (31/293)	11% (22/203)	4.8% (5/105)	9.7% (6/62)	13% (8/62)	1.9% (1/52)	11% (7/66)
Transferred	2.1% (26/1,240)	2.3% (9/397)	2.4% (7/293)	3.0% (6/203)	0% (0/105)	0% (0/62)	1.6% (1/62)	3.8% (2/52)	1.5% (1/66)
Death	**38% (470/1,240)**	**31% (123/397)**	**43% (125/293)**	**58% (118/203)**	**21% (22/105)**	**31% (19/62)**	**48% (30/62)**	**33% (17/52)**	**24% (16/66)**

Notes: TB, *tuberculosis*; **Serous membrane* (***pleural effusion n = 62; peritoneal n = 62; pericarditis n = 52***); Other locations**: *Cutaneous (n = 1); Breast (n = 3); Bones and joints (n = 12); Disseminated TB (50);* **LTFU**, *lost to follow up.*

Survival probability of EPTB

Survival analysis revealed a generally poor prognosis, characterized by an accelerated decline in survival probability during the initial 60 days following anti-tuberculosis treatment (ATT) initiation, with stabilization observed after three months. A log-rank test demonstrated a statistically significant difference in survival distributions across the different tuberculosis forms within the cohort (p = 0.0001) (**Figure I**). The cumulative survival probability for tuberculous meningitis (TBM) patients was 78.8% at 20 days, 70.4% at 30 days, 54.7% at 60 days, and 44% at 90 days post-ATT initiation. Similarly, for miliary tuberculosis, the cumulative survival probability was 86.0%, 78.5%, 67.2%, and 59.7% at the same respective time points and was 86.9%, 79.5%, 67.6% and 65.9% for serous membrane TB respectively. In contrast, patients with TB involving other anatomical sites (e.g., genitourinary, lymph nodes,) exhibited a more favourable survival trajectory over time. Furthermore, immunologic status, as measured by CD4 cell count, was a critical determinant of survival. Throughout the follow-up period, patients with

CD4 counts between 100–200 cells/mm³ and those with counts ≥ 200 cells/mm³ experienced significantly better survival (63% and 90%, respectively) compared to those with severe immunosuppression (CD4 < 100 cells/mm³), who had a survival probability of only 34% (**Figure II**).

Figure I: Kaplan-Meier survival estimates according to the sites of extrapulmonary tuberculosis in the cohort, N = 1240

Figure II: Kaplan-Meier survival estimates according to the CD4 cell counts range in the cohort, N = 649

Risk factors for EPTB mortality

In univariate analysis, mortality was significantly associated with several factors. An increased hazard of death was observed for tuberculous meningitis (HR 3.23; 95% CI 1.91–5.45, p < 0.001), miliary tuberculosis (HR 2.02; 95% CI 1.20–3.40, p = 0.008), serous membrane tuberculosis (HR 1.77; 95% CI 1.02–3.09, p = 0.044), and patient retreatment category (HR 2.32; 95% CI 1.93–2.78, p < 0.001). Conversely, genitourinary tuberculosis (HR 0.85; 95% CI 0.40–1.00, p = 0.049), cotrimoxazole (CTX) prophylaxis (HR 0.69; 95% CI 0.57–0.85, p < 0.001), and a higher CD4 cell count (HR 0.27; 95% CI 0.20–0.38, p < 0.001) were significantly protective. In the multivariable Cox hazards model, adjusted for age and lymphocyte count, the following factors remained independently associated with an increased risk of death: serous membrane tuberculosis (aHR 1.77; 95% CI 1.02–3.09, p = 0.044), miliary tuberculosis (aHR 2.02; 95% CI 1.20–3.40, p = 0.059), and tuberculous meningitis (aHR 2.20; 95% CI 1.32–2.26, p < 0.001). Protective factors included cotrimoxazole prophylaxis (aHR 0.70; 95% CI 0.57–0.86, p < 0.001) and a CD4 count ≥ 100 cells/mm³ (aHR 0.26; 95% CI 0.18–0.36, p < 0.001) **(Figure III)**.

Figure III. Forest plot for stratified cox proportional hazards model of factors associated with overall survival (OS) of EPTB patients, N = 1240

Notes: EPTB, extrapulmonary tuberculosis; **HR**, Hazard Ratio; **TB**, tuberculosis, **Serous membrane (***pleural effusion n = 62; peritoneal n = 62; pericarditis n = 52***); Other locations**: *Cutaneous (n = 1); Breast (n = 3); Bones and joints (n = 12); Multifocal (50)*

Discussion

In this large retrospective cohort of HIV-infected patients in Abidjan, Côte d'Ivoire, extrapulmonary tuberculosis (EPTB) accounted for more than 60% of all TB cases and was associated with a high mortality rate of 38% while the mortality rates are 17% and 22%, respectively, for pulmonary tuberculosis (Sputum Smear-positive & Sputum Smear-negative). The most frequent EPTB localizations were lymph node (32%), miliary (23.6%) and tuberculous meningitis (TBM, 16.4%). Mortality was highest for TBM (58%), followed by serous membrane TB (49%) and miliary TB (43%), with a sharp decline in survival during the first 60 days of anti-tuberculosis treatment (ATT). Independent risk factors for death included TBM, miliary TB and serous membrane TB, while cotrimoxazole prophylaxis and a CD4 count ≥ 100 cells/mm³ were strongly protective.

Our findings confirm that EPTB is a predominant and severe form of TB among HIV infected individuals in sub–Saharan Africa (24). This figure aligns with recent reports from similar high-burden settings, underscoring that EPTB remains a critical driver of mortality in people living with HIV (PLHIV) despite widespread antiretroviral therapy (ART) access (14, 25–27). The very high mortality associated with TBM and miliary TB is consistent with previous reports, where old age and limited access to intensive care contribute to poor outcomes(28, 29). The rapid decline in survival during the first two months of treatment underscores the urgent need for early diagnosis and prompt initiation of ATT and ART.

The high mortality rate found in our study may be attributed to the distinctive profile of SMIT as a tertiary referral centre to manage HIV-infected patients. The department predominantly admits complex cases, including patients pretreated at other sites, those with a history of prior therapeutic failure and extended treatment pathways, and critically ill individuals presenting with multiorgan dysfunction. This critical condition typically stems from advanced-stage co-infection, frequently compounded by concurrent opportunistic infections. The stark differential mortality by anatomical site is a key contribution. Furthermore, the significantly accelerated mortality within the first 20 days of treatment, particularly for tuberculous meningitis (TBM) and miliary TB, highlights a perilous "critical period" where current diagnostic and therapeutic strategies are insufficient. It is important to note also the significant mortality associated with other conditions, particularly those affecting the serous membranes (pericardium, pleural effusion and peritoneal). These cases are underreported or even underestimated, certainly due to the diagnostic challenges involved. Pleural TB can be complicated by massive effusion leading to respiratory compromise in the short term, and pleural thickening, fibrosis, and pleural adhesions causing impaired respiratory function in the medium- to long-term (30). Tuberculous (TB) pericarditis (TBP), is widespread in sub-Saharan Africa, often resulting in conditions such as pericardial effusion, cardiac tamponade, and constrictive pericarditis(31, 32) Administrating corticoids therapy is almost always the case. However, the actual clinical effectiveness of supplementary glucocorticoids remains uncertain. Abdul-Karim Iddrisu and al. reported that There is an increased hazard of

death among patients who received prednisolone compared to those who received a placebo. It is essential to interpret this result with caution(33).

The multivariable analysis provides crucial insights into modifiable and non-modifiable determinants of survival. The most powerful protective factor was immune reconstitution, evidenced by the four-fold increase in mortality (aHR 0.25 for CD4 ≥ 100) associated with severe immunosuppression (CD4 < 100 cells/mm³). This reinforces the imperative of early HIV diagnosis and rapid ART initiation to prevent advanced immunodeficiency, as highlighted in the latest WHO guidelines (34). Furthermore, the independent protective effect of cotrimoxazole prophylaxis (aHR 0.70), even after adjustment for CD4 count, suggests its benefit extends beyond Pneumocystis pneumonia prevention, likely mitigating fatal bacterial co-infections and sepsis during the vulnerable early treatment phase, a finding supported by several trials (35–37).

Our study has several practical implications. First, it reinforces the need for systematic screening for EPTB in all HIV infected patients with low CD4 counts, even in the absence of pulmonary symptoms. Second, it highlights the urgent need to strengthen diagnostic capacities for disseminated forms such as TBM and miliary TB, using rapid molecular tests (e.g., GeneXpert Ultra) on extrapulmonary samples (38). Third, the high mortality rate of TBM observed in our study underscores the significance of the current challenges and issues surrounding the therapeutic strategies being tested in the numerous ongoing clinical trials designed to improve the prognosis of this condition (39, 40). And finally, it confirms the lifesaving potential of cotrimoxazole prophylaxis and early ART initiation in EPTB patients.

While observational research is important for studying real-world clinical settings, it often suffers from limitations inherent to its single-center, retrospective design may limit generalizability, and some EPTB cases were presumptively diagnosed, potentially leading to misclassification. Indeed, the results observed at SMIT, a university national HIV reference center in Côte d'Ivoire, cannot be extrapolated to all TB/HIV co-infected patients in the country. Some essential clinical and biological data, such as the presence of other opportunistic infections, serial CD4 counts, or HIV plasma viral load, were not available or were incomplete. The retrospective nature of the study posed another limitation, precluding the assessment of some potential risk factors for mortality. Cause-of-death data were not collected prospectively, which could lead to an underestimation of the number of deaths and misclassification bias. Despite these limitations, this study provides critical evidence that should inform policy at both district and national levels.

Conclusion

EPTB is a frequent and highly lethal condition among HIV-infected patients in Côte d'Ivoire. Tuberculous meningitis, serous membrane TB and miliary TB are the most severe forms, with mortality peaking early after treatment initiation. Cotrimoxazole prophylaxis and higher CD4 counts are strongly associated with improved survival. These findings underscore the urgent need for earlier HIV diagnosis, rapid ART initiation, and strengthened diagnostic and therapeutic support for disseminated EPTB in resource-limited settings.

Abbreviations

aHR : adjusted hazard ratio

ART : Antiretroviral Treatment

CI : Confidence Interval

EPTB Extrapulmonary TB

HIV : Human Immunodeficiency Virus

HR : crude hazard ratio

LAM : lipoarabinomannan assay

PLWH : People living with HIV

TBM Tuberculous meningitis

WHO World Health Organization

Declarations

Ethics approval and consent to participate

This study was a retrospective analysis of routine clinical data collected as part of standard medical care at the Service des Maladies Infectieuses et Tropicales (SMIT) of Treichville University Hospital, Abidjan, Côte d'Ivoire between 2010 and 2019. No intervention was performed and no contact was made with participants. All personal identifiers were removed prior to data extraction. In accordance with Ivoirian national guidelines of the National Ethics Committee for Life Sciences and Health of Côte d'Ivoire (CNESVS), ethical approval and individual informed consent were waived for research using de-identified data without patient contact. Administrative authorization for data access All data were anonymized before analysis. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable

Competing interests

The Authors declare that they have no competing interests.

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None

Author Contribution

NFE and SPE were involved in the conception and study design. Methodology of study was validated by NFE, FB and SPE. Formal analysis was performed by AM & NFE. GAK, DA, CNK, supervised the data collection and helped with data Interpretation. NFE and SPE drafted the initial version of the manuscript. AT, FB and SPE reviewed and edited the final version. All authors critically reviewed the manuscript and read and approved the final version for submission and had final responsibility for the decision to submit for publication.

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Data Availability

The datasets supporting the conclusions of this article are available upon request to the corresponding author

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Figures

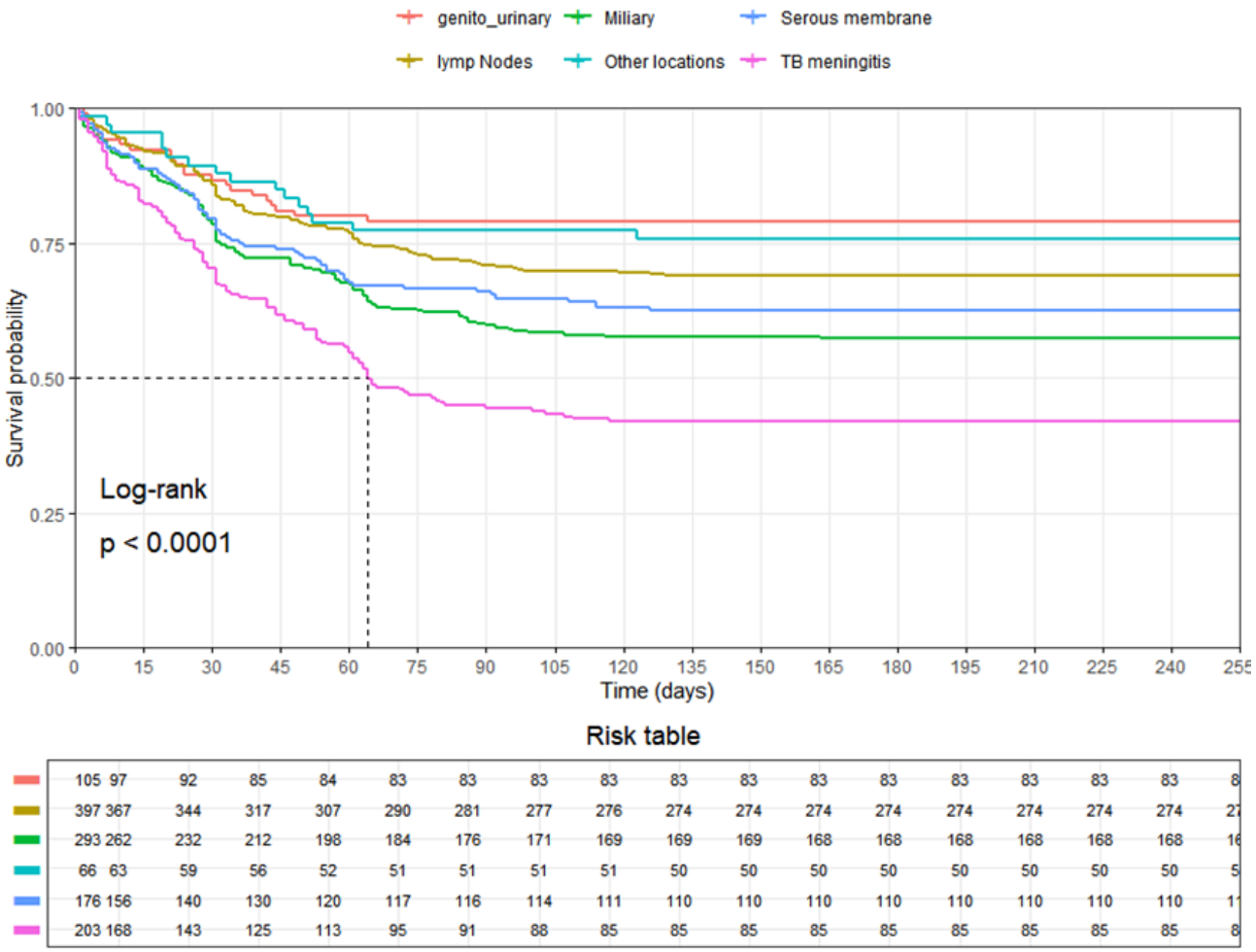


Figure 1

Kaplan-Meier survival estimates according to the sites of extrapulmonary tuberculosis in the cohort, N=1240

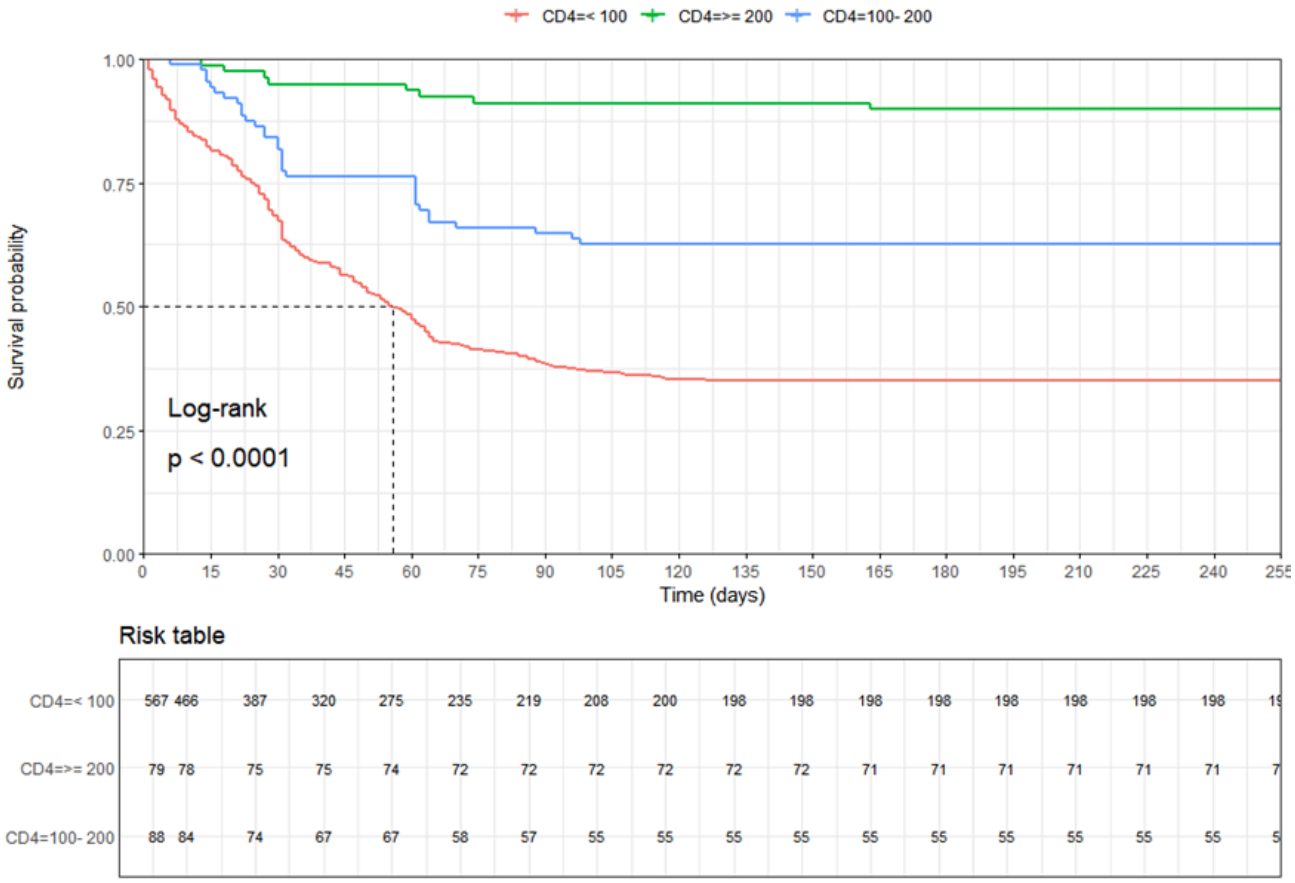
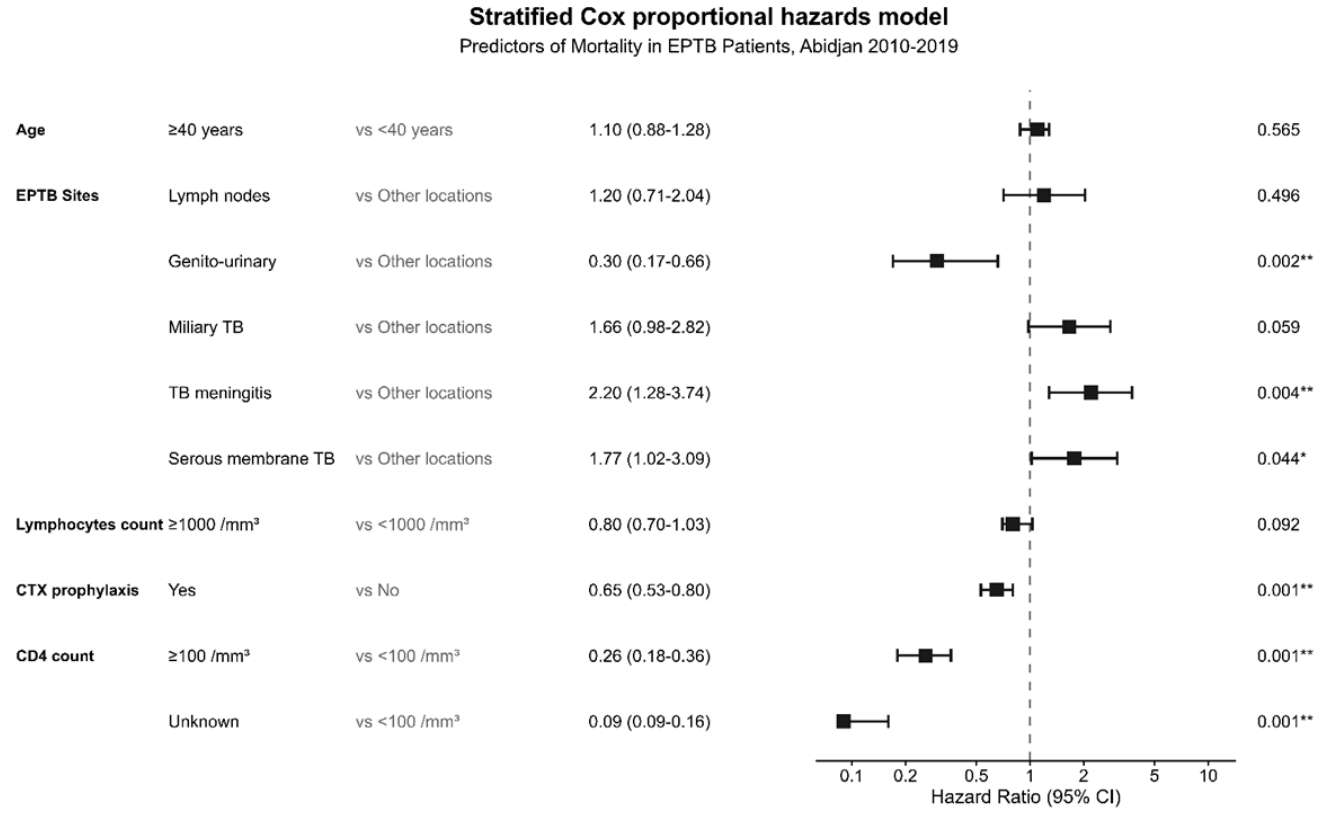


Figure 2

Kaplan-Meier survival estimates according to the CD4 cell counts range in the cohort, N=649



* p < 0.05; ** p < 0.01; *** p < 0.001

Figure 3

Forest plot for stratified cox proportional hazards model of factors associated with overall survival (OS) of EPTB patients, N=1240

Notes: EPTB, extrapulmonary tuberculosis; **HR,** Hazard Ratio**; TB,** tuberculosis, **Serous membrane (***pleural effusion n=62; peritoneal n=62; pericarditis n=52***); Other locations**: *Cutaneous (n=1); Breast (n=3); Bones and joints (n =12); Multifocal (50)*