Human Immunodeficiency Virus and Tuberculosis Coinfection in a Tertiary Hospital in Southern Brazil: Clinical Profile and Outcomes

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ABSTRACT: Worldwide, the convergence of tuberculosis (TB) and human immunodeficiency virus type 1 (HIV-1) infection epidemics is a public health challenge. In Brazil, TB is the leading cause of death by infectious disease in people living with HIV (PLWH). This study aimed to report the clinical, demographic, epidemiological, and laboratory data for TB in PLWH. This cross-sectional study involved a retrospective analysis of data for patients with TB/HIV coinfection who attended from 2006 to 2015 through a review of medical records. A total of 182 patients were identified, of whom 12 were excluded. Patients were divided according to whether they had pulmonary tuberculosis (PTB; n = 48; 28%) or extrapulmonary tuberculosis (EPTB; n = 122; 72%). The diagnosis was laboratory confirmed in 75% of PTB patients and 78.7% of EPTB patients. The overall 1-year mortality rate was 37.6%, being 22.9% in PTB patients and 69% in EPTB patients; 84% of these deaths were TB-related. The CD4+ count and disseminated TB were independent risk factors for death. The frequency of resistance among *Mycobacterium tuberculosis* (MTB) isolates was 14%. TB in PLWH is associated with high morbidity and mortality, and severe immunosuppression is a risk factor for death. Appropriate measures for early TB detection should reduce the case fatality rate in high-burden settings.

KEYWORDS: HIV/AIDS, pulmonary tuberculosis, extrapulmonary tuberculosis, drug resistance, coinfection, fatality rate

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Introduction

Currently, *Mycobacterium tuberculosis* (MTB) and human immunodeficiency virus type 1 (HIV-1) coinfection (TB/HIV) is one of the greatest diagnostic and therapeutic challenges in the care of people living with HIV (PLWH).[1,2] HIV infection is the main known risk factor for the development of tuberculosis (TB).[1] Cellular immunity is essential for TB control, which depends on the activation of CD4+ and CD8+ cells. The subsequent depletion of CD4+ cells directly contributes to the increased risk for TB, via both new infection and reactivation of a latent infection. Moreover, TB accelerates the progression of acquired immunodeficiency syndrome, thereby increasing the mortality rate due to other opportunistic infections.[3] Besides that, TB/HIV management has been a challenger, as it involves complex drugs interactions, overlapping of toxicity, and MTB-associated immune reconstitution inflammatory syndrome (IRIS).[4]

In Brazil, during 2006-2015, the incidence of TB in the general population ranged 30.9-38.7/100 000 persons. However, the incidence varies widely across the country; in 2015, the TB incidence was 18.1 and 17.6/100 000 persons in Parana State and Curitiba city, respectively. Similarly, the frequency of TB in HIV patients was 9.7%, 12.2%, and 21.5% in Brazil, Paraná, and Curitiba, respectively,[5] which reflects different approaches in monitoring PLWH.

Brazil has been offering easy access to HIV testing and universal access to antiretroviral therapy (ART) since 1996. From 2010 onward, screening of and treatment for latent TB infection (LTBI) in PLWH has been strongly recommended. Nonetheless, TB infection has been the most frequent diagnosis in PLWH. Thus far, only a few studies have described the burden of TB coinfection in the country. Seeking to report the impact of coinfected TB/HIV patients treated in a referral center, this study aimed to evaluate the incidence of TB and its consequences among HIV-positive individuals.

Material and Method

Study design and data collection

This was a cross-sectional study with retrospective data collection via a review of the medical records of adult and pediatric patients diagnosed with TB/HIV coinfection during 2006-2015. The Infectious Diseases Division of Hospital de Clínicas-Universidade Federal do Parana (UFPR) is the largest tertiary academic care center of the state of Paraná and a reference to follow-up HIV-positive patients, most of whom live in Curitiba and metropolitan areas. Patients were identified by cross-matching of records of HIV-positive individuals and TB cases identified from two Brazilian databases: Sistema de Informacao sobre Mortalidade de Agravos de (SINAN), The Notifiable Diseases Information

System, and Sistema de Informacao sobre Mortalidade (SIM), The Mortality Information System. It was included PLWH with clinical, radiographic, or laboratory suspicion of TB infection who received TB therapy or patients with TB with a subsequent diagnosis of HIV. Patients were excluded if the records were not located or when there was no clinical or epidemiological or laboratory evidence of TB or HIV infection. The Hospital de Clinicas Universidade Federal do Parana (HC-UFPR) institutional review board approved this study (IRB# 17274713.8.0000.0096), and the need for written consent was waived due to the retrospective nature of this study.

Procedures and definitions

Medical records or death certificates were reviewed to collect demographic, clinical, laboratory, and outcome data. The underlying causes of death were categorized as TB-related or not.

TB diagnosis was defined as (1) "Proven" when positive culture or polymerase chain reaction (PCR) results for MTB were obtained; (2) "Probable" when acid-fast bacilli or granulomatous inflammation on smear or tissue biopsy specimens were detected; and (3) "Presumptive" when TB treatment was prescribed based on clinical criteria, that means presence of symptoms (coughing for more than 4 weeks, fever, night sudoresis, and weight loss), and suggestive radiography. For a Probable and Presumptive TB diagnosis, fungal infection or non-tuberculous mycobacteria should be excluded, and there would have to be at least two clinical criteria in association with the radiological criterion, respectively.

Pulmonary tuberculosis (PTB) was defined as the disease compromising only the lungs, and extrapulmonary tuberculosis (EPTB) as the disease affecting any organ except the lungs. The disease was considered disseminated when TB was documented in at least two organ systems (one of which should be the lungs), miliary TB was detected, or *M. tuberculosis* was isolated from blood or bone marrow. Moreover, patients were divided according to the number of sites of TB (1, 2, or ⩾3).

HIV infection was diagnosed by immunological tests that included the combination of screening tests (enzyme-linked immunosorbent assay of third or fourth generation), followed by a complementary test (Western Blot or fast immunoblot). More recently, quantitative molecular tests were used, and the presence of a viral load above 5000 copies/mL was considered positive.

Statistical analysis

Quantitative variables are described as means, standard deviations, medians, and minimum and maximum values. Qualitative variables are described as frequencies and percentages. To compare patients according to outcome (dead or alive), in relation to the quantitative variables, the Student *t*-test for independent samples or the non-parametric Mann-Whitney test was used. The normality of the variables was evaluated using the Kolmogorov-Smirnov test. Qualitative variables were compared using the Fisher exact test or the Chi-square test. To determine the independent contribution of the study variables to death, a logistic regression model was performed. The final multivariate logistic model included only the factors that remained independently and significantly associated with outcome after adjustment for the effects of all other variables.

The Kaplan-Meier curve was fitted to describe the probability of survival according to the last date of evaluation of the patient, and the findings were compared using the log-rank test. This curve was constructed using the date of HIV diagnosis (from the SINAN database) and the date of death (from the SIM database). The level of significance was set at .05. Data were analyzed using the SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, 2011).

Results

A total of 170 patients were eligible for the current analyses, and 12 patients were excluded—5 with *Mycobacterium avium* complex infection, 4 eventually diagnosed with cancer, 2 who were HIV negative, and 1 with missing medical records. The patients were divided into two groups: PTB (48/28%) and EPTB (122/72%). One-hundred (59%) patients had non-disseminated TB, and 70 (41%) had disseminated disease. Overall, 126 (74%) patients had one, 32 (19%) had two, and 12 (7%) had three TB affected sites. The most common EPTB manifestations were miliary disease, central nervous system infection, and ganglionar infection, with 47, 32, 28 cases, respectively. The median CD4+ nadir and baseline counts were 89 and 56 cells/mm^3 and 99 and 81 cells/mm^3 in the PTB and EPTB patients, respectively (Table 1). No significant difference was observed among patients with PTB and EPTB.

Regarding clinical manifestations presented prior to the TB diagnosis, patients reported a median of 75 days of symptoms (interquartile range, IQR: 43-120) of weight loss, 35 days (IQR: 14-120) of sweating, and 30 days (IQR: 15-90) of cough.

At baseline, 123 (72%) patients were known to be HIV-1 positive, 11 (6%) patients were diagnosed with HIV infection after TB, and 36 (22%) patients received a concomitant diagnosis of TB/HIV. A total of 80/123 (65%) patients with a previous HIV infection diagnosis were receiving ART. Furthermore, of those who underwent HIV RNA measurement before or at baseline, 29 (36%) had undetectable viral load upon TB diagnosis.

Acid-fast bacilli smear, mycobacterial culture, real-time PCR, as well as histopathological examination, when feasible, were performed. The EPTB group showed a high frequency of positive results from pulmonary samples. Overall, laboratory diagnoses confirmed TB infection in 75% and 78.7% of cases in the PTB and EPTB groups, respectively (Table 2). Radiographic findings suggestive of TB were frequently observed in both groups. However, among 37 patients with normal chest radiographs, 7 (19%) presented positive bacilloscopy, culture, or PCR results for MTB.

Patients were treated according to Brazilian guidelines—three-drug (after 2009, ethambutol was added) intensive phase for 2 months, followed by 4 months of dual therapy in

Table 1. Clinical and epidemiological characteristics of HIV/Tuberculosis co-infected patients, southern Brazil, 2006-2015 (n = 170).

FEATURES	PULMONARY TB (N = 48)	EXTRAPULMONARY TB (N = 122)	ALL CASES (N = 170)	*P* VALUE
Median age (IQR)	28 (22-38)	32 (26-37)	31 (25-37)	**.254**
Male sex	30 (62)	85 (70)	115 (68)	**.37**
Educational status, years of study (%)				
<5	13 (27)	19 (15)	32 (19)	**.112**
5-11	22 (46)	77 (63)	99 (58)	
>11	4 (8)	8 (7)	12 (7)	
Unknown	9 (19)	18 (15)	27 (16)	
HIV risk factor				
Heterosexual	10 (21)	20 (16)	30 (18)	N/A
MSM	7 (15)	16 (13)	23 (13)	N/A
IDU	14 (29)	23 (20)	37 (22)	N/A
Other	4 (8)	6 (4)	10 (6)	N/A
Unknown	13 (27)	57 (47)	70 (41)	N/A
Chronic viral hepatitis (HCV, HBV)	9 (24)	20 (21)	29 (22)	**.817**
CD4+ count baseline, median (IQR)	99 (34-266)	81 (38-173)	89.5 (38-207)	**.219**
CD4+ count nadir, median, (IQR)	89 (17-207)	56.5 (22-120)	61 (21-143)	
HIV-1 viral load, $\log_{10}$, (IQR)	4.7 (1.8-6.1)	5 (4.3-5.7)	4.9 (4.2-5.7)	N/A
ART use	22 (46)	58 (48)	80 (47)	**.446**
2 NRTI + 1 NNRTI	6 (27)	38 (66)	44 (55)	**.0027**
2 NRTI + 1 PI	16 (73)	20 (34)	36 (45)	

Abbreviations: TB, tuberculosis; HIV, human immunodeficiency virus; IQR, interquartile range; MSM, Men who have sex with men; IDU, intravenous drug user; HCV, hepatitis C virus; HBV, hepatitis B virus; ART, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitor.

continuation phase. In the case of tuberculous meningitis, this period was extended to 7 months.[6] Adverse events related to the TB treatment were recorded in 25% of cases, and a switch to standard therapy was required in 40% of these cases. TB resistance was detected in 10/69 (14%) MTB isolates. Eight of these isolates were obtained from patients first diagnosed with MTB infection (3 with resistance to rifampicin and isoniazid; 3 with resistance to rifampicin, isoniazid, and ethambutol; 1 with resistance to isoniazid; and 1 with resistance to streptomycin). In two cases, the patients relapsed and had EPTB (one isolate demonstrated resistance to isoniazid and rifampicin, and the second one showed resistance to streptomycin).

In the first year, after the coinfection diagnosis, 64 (37.6%) patients died. TB was the underlying cause of death in 52 (84%) cases. The Kaplan-Meier estimates of survival after TB diagnosis stratified by PTB and EPTB infection are shown in Figure 1.

PTB patients were significantly less likely to die during the follow-up period than EPTB patients (log-rank test $P = .005$). In the unadjusted analysis, EPTB, multiple infection sites, disseminated TB, and CD4+ counts were significantly associated with death. In the adjusted analysis, only disseminated TB, lower nadir, and baseline CD4+ counts maintained an association with this outcome (Table 3).

Discussion

TB has been considered one of the main diseases that compromise individuals with HIV infection. In this cases series, we recorded a high fatality rate among HIV/TB coinfected patients, which was directly related to the high percentage of EPTB, disseminated TB, and severe immunosuppression, as demonstrated by the low CD4+ counts. According to Brazilian and other international guidelines,[6,7] TB therapy and ART was promptly initiated; however, the mortality rate has remained high in the first few months following TB diagnosis, emphasizing the importance of immune recovery to control the disease.[8]

Table 2. Laboratory findings related to the diagnosis of tuberculosis in patients with pulmonary (P) and extrapulmonary (EP) disease.

LABORATORY FINDINGS	PTB (N = 48) (%)	EPTB (N = 122) (%)	*P* VALUE
Acid-fast bacilli sputum			
Positive	30 (68)	34 (38)	**.002**
Negative	14 (31)	55 (62)	
Other sites[a]			
Positive	2 (22)[b]	34 (38)	.479
Negative	7 (78)	55 (62)	
Cerebrospinal fluid			
Positive	0	0	N/A
Negative	10 (100)	52 (100)	
Culture sputum			
Positive	16 (57)	23 (32)	**.039**
Negative	12 (43)	23 (32)	
Other sites[a]			
Positive	0	42 (39)	N/A
Negative	23 (100)	65 (61)	
Cerebrospinal fluid			
Positive	0	8 (14)	
Negative	9 (100)	49 (86)	N/A
Blood culture			
Positive	0	9 (18)	N/A
Negative	6 (100)	40 (82)	
PCR MTB			
Positive	4 (50)	26 (50)	N/A
Negative	4 (50)	26 (50)	
Histopathology examination			
Probable[c]	1 (100)	49 (96)	N/A
Negative	0	2 (4)	

Values in bold are statistically significant.
Abbreviations: PCR, polymerase chain reaction; MTB, *Mycobacterium tuberculosis*; TB, tuberculosis; PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis.
[a]Tissue specimens, aspirates of sterile fluids, bone marrow aspirate.
[b]Bronchoalveolar lavage fluid.
[c]Presence of granulomas suggestive of mycobacterial disease or visualization of acid-fast bacilli.

Demographic and epidemiological findings, such as higher prevalence in young men, low education level, and drugs users, reflect the profile of high-risk populations for HIV infection and TB in Brazil.[5] The time of symptom onset has also been shown to be a factor associated with mortality.[9] In this study, most patients presented with weight loss, sweating, and cough for months before the hospitalization. This delay in diagnosis could have contributed to fatal outcomes observed in this cohort of patients.

Despite most patients were previously diagnosed with HIV infection, and only 35% were in ART use, and of these, 41% had detectable viral loads, which increase the risk for MTB disease.[10,11] It is important to note, we evaluated cases during 2006-2015, wherein ART use followed distinct guidelines based on CD4+ counts. After 2013, ART was prescribed at earlier stages of the disease, when cell immunity was still preserved. Only 2016, the 90-90-90 target launched by UNAIDS in 2014,[12] which emphasizes viral suppression among PLWH, has been applied in Brazil.

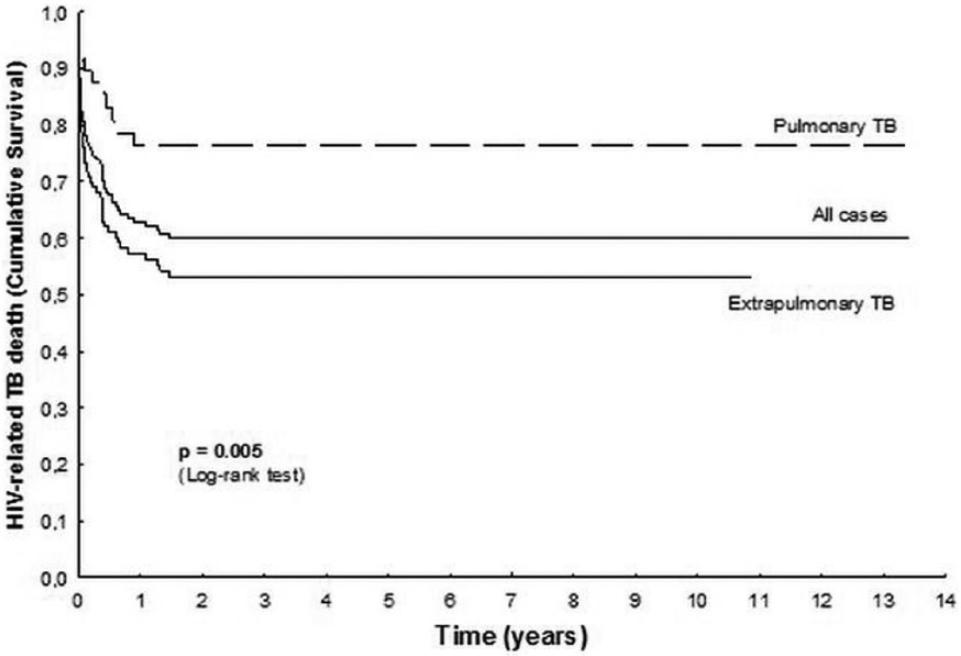

Figure 1. Time from tuberculosis (TB) diagnosis to death in human immunodeficiency virus (HIV) infection patients with pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB).

Table 3. Risk factors associated with mortality in patients with HIV/TB coinfection.

FEATURES	NONSURVIVORS, N = 64 (%)	SURVIVORS, N = 106 (%)	*P* VALUE	
			UNADJUSTED	ADJUSTED
Sex (M/F)	44/20 (69/31)	71/35 (67/33)	.866	.947
Age, years (median, IQR)	36.5 (31-41)	34.5 (28-42)	.229	.304
Time of symptoms (days)				
0-30	14	24	.634	
31-120	14	20		
>120	5	13		
Tuberculosis				
Pulmonary	11 (17)	37 (35)	.014	.068
Extrapulmonary	53 (83)	69 (65)		
Affected sites				
1	36 (56)	77 (73)	**.042**	.350
2	15 (24)	20 (19)		
3	13 (20)	9 (8)		
CNS-TB				
Yes	17 (27)	15 (14)	.067	.142
No	47 (73)	91 (86)		
Intolerance to tuberculostatics				
Yes	8 (12)	17 (16)	.610	.156
No	18 (28)	50 (47)		
Unknown	38 (60)	39 (37)		

(Continued)

Table 3. (Continued)

FEATURES	NONSURVIVORS, N = 64 (%)	SURVIVORS, N = 106 (%)	*P* VALUE	
			UNADJUSTED	ADJUSTED
Regimen with Rifampicin				
Yes	47	92	.415	
No	3	3		
Unknown	14	11		
CD4+ nadir (cells/mm^3)	42 (16-131.5)	70 (24-144)	.154	**.040**
Current CD4+ count (cells/mm^3)	55 (18.5-128)	100 (47-256)	**.003**	**.024**
Baseline median HIV-1				
RNA in Log_{10} (IQR)	5.1 (4.3-5.6)	4.3 (2.2-5.2)	**.006**	.506
ART use				
Yes	23	57	**.003**	
No	36	43		
Unknown	5	6		
Patients with ART appropriate[a]				
Yes	6	26	.202	
No	8	13		
Disseminated TB	41 (53.9)	35 (46.1)	**.001**	**.005**

Values in bold are statistically significant.
Abbreviations: CNS-TB, central nervous system tuberculosis; IQR, interquartile range; HIV-1, human immunodeficiency virus type 1; ART, antiretroviral therapy.
ART appropriate: ART were modified considering TB drug interactions.

ART use was significantly associated with fatality rates, being less frequently reported among those evolved to death. No difference was observed between ART appropriate, that is, non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) were modified considering TB drug interactions and mortality. Nonetheless, the low number of patients evaluated may have influenced this analysis. ART adherence and previous links to health assistance were not evaluated in this group, but this analysis should be carried out to identify the weaknesses in PLWH care.

Some factors could have contributed to delay the TB diagnosis, as most patients required hospitalization and were in advanced stages of the disease, among these can be cited: (1) the frequency of paucibacillary TB in immunocompromised patients, which requires more complex investigations; (2) nonsuspicion of TB infection by health professionals; and (3) limited access to health care.

Regarding TB diagnosis, most patients had "proven diagnosis," either by conventional microbiological methods such as bacterioscopy and culture, or molecular methods. Positive bacilloscopy findings were even obtained in patients without radiographic images suggestive of TB. Previous reports indicate that 8%-20% of patients with CD4+ cell counts <200 cells/mm^3 may present chest radiographs without alterations.[2,13] More sensitive methods for lung assessment, such as computed tomography, may serve as a valuable tool for the analysis of immunosuppressed patients.[14]

TB resistance was detected in 14% of cases, lower than that in Europe and Asia[15] and similar to previous Brazilian reports.[9,16] MTB resistance to anti-TB drugs is an emerging challenge, and per the Brazilian guidelines implemented since 2011, MTB culture and drug susceptibility testing have been carried out routinely for coinfected patients.[6] However, access to liquid culture media, which presents better results, is still limited to public health laboratories.

Worldwide, around 20% of TB isolates, are globally estimated to be resistant to at least one major drug (first-line or second-line), with approximately 10% resistant to isoniazid,[17] and most of these occurs in TB/HIV coinfection.[18] The WHO estimates that 3.5% of new cases and 20.5% of cases of retreatment involve multidrug-resistant TB,[18–21] and interruption of this transmission critical.[20]

Concerning ART and anti-TB drugs interactions, around 25% of patients presented TB drug intolerance, and in 40% of these patients needed changes in treatment. In addition, HIV

patients usually present the lowest adherence rates for TB treatment due to drug side effects and social.[21,22] Thus, it should be recommended directly observed therapy for these individuals.[23]

Overall, a high lethality rate was observed, and it is possible that some cases identified as PTB had a disseminated disease. Previously, Podlekareva et al[15] reported a 1-year mortality rate of 85% in coinfected patients due to HIV infection-related complications and identified low CD4+ counts and disseminated TB as independent variables. Besides that, some epidemiological data observed in coinfected patients have been a matter of concern in our region; as in 2013 at Curitiba city, the mortality rate and incidence of HIV coinfection were 16.4% and 19%, respectively,[22] higher than that observed in Latin America (11%).[15]

Analyzing the survival curve, a greater survival rate was observed in non-disseminated TB patients. However, in both groups, the mortality rates were higher in the first months of TB diagnosis, after which there was a tendency for a plateau, probably reflecting a gradative immunological recovery, emphasizing the need for earlier ART initiation.

PLWH are particularly vulnerable to progression from LTBI to active disease, and in Brazil, the TB guidelines recommend to perform tuberculin skin test annual in HIV+ patients, and a positive result is indicative for treatment. However, there are several limitations to the currently available immunodiagnostic tests and their ability to predict TB in immunocompromised patients.[24] Thus, in countries with high TB burden, such as Brazil, an assessment of the impact of universal LTBI treatment on PLWH should be undertaken. TB and HIV are important global health threats and represent a novel pathogenic scenario globally; coinfections are associated with high mortality, and the immunological mechanisms produced by infectious cofactors, which impact on the magnitude of disease pathology, have still been under evaluation. MTB induces macrophage activation, and production of proinflammatory cytokines, which could enhance replication of HIV-1. As well as, HIV infection can induce accelerated growth of MTB.[4] Thus, the combat of this coinfection would involve an effective combined approach to develop vaccines and new treatments, for which further studies on the pathogenic mechanisms of these diseases still need to be undertaken.[4]

This study involves some limitations due to its retrospective nature: (1) patients were attended by distinct professionals in different settings in the hospital, which resulted in a non-uniform clinical investigation; (2) some clinical data in the medical records were missing; (3) some patients admitted to the hospital had severe disease and rapidly progressed to death, not allowing adequate time for a laboratory investigation; (4) the implementation of MTB molecular diagnosis occurred in 2010; therefore, many patients did not undergo this test; and (5) there were changes in clinical protocols for TB and HIV treatment during the study period. Despite these limitations, this report allowed the evaluation of the impact of TB on PLWH survival, showing worrying fatality data, which are of concern to the public health.

Studies to perform a critical analysis of TB/HIV coinfection impact are scarce in Brazil and these results reflect the need to improve PLWH care. It is necessary to integrate the services of care of PLWH in order to rapidly and effectively expand the diagnosis of TB. In addition, it is important that all health professionals are prepared to identify suspected TB, perform prompt diagnosis, and start early therapy to reduce the mortality rates.

Author Contributions

Conceived, designed and analysed data: SMR, FT. Reviewed medical records: JCFB, CELR, ACB and NLSS. Write manuscript: SMR and FT. All authors read and aproved final version of the manuscript.

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