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Determinants of TB/HIV coinfection-related deaths audited using the TB death checklist from health facilities in Rwanda

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ABSTRACT

INTRODUCTION: Tuberculosis (TB) remains a public health threat worldwide, mainly affecting countries with low-resource settings, including Rwanda. TB/HIV coinfection increases the severity of TB and has a high of resulting in poor outcomes, such as death. This study aims to investigate the actual causes and factors associated with mortality among TB/HIV coinfected patients in Rwanda, to better understand the profile of deaths in this population.

METHODS: The retrospective study was conducted nationwide in Rwanda between July 2017 and June 2023, collecting information on TB patients who had died. The data were collected from death audit reports submitted to the National TB Program (NTP) after being filled by healthcare providers at the health facilities. To explore associations between HIV status at the time of TB diagnosis and other variables, bivariate analysis was performed. Multivariate analysis was made to find adjusted odds ratios (AOR), 95% confidence intervals and to assess statistical significance with p-values set at < 0.05.

RESULTS: The study examined 1,112 TB death audits. The majority of death audit reports (68.2%) were from men. Among the reported deaths, 70.6% were TB-related. Pulmonary TB smear-negative showed a significantly higher likelihood of being HIV positive (P-value 0.082, aOR 1.97, 95%CI 0.96, 2.12). Individuals who were retreated for TB were likely to be HIV positive compared to the newly diagnosed individuals (P-value <0.007, aOR 2.03, 95%CI 1.22, 3.40). Individuals with severe malnutrition also showed a strong association with TB/HIV coinfection, at P-value 0.002, aOR1.71, 95% CI 1.23, 2.40.

CONCLUSION: Individuals who had prior TB infection and pulmonary TB with smear-negative results showed a higher likelihood of having HIV coinfection, highlighting a need for regular screening by using rapid and accurate TB diagnostic tools, specifically among PLHIV.

Keywords: TB/HIV coinfection, Tuberculosis mortality, HIV-associated TB, Rwanda TB death audits, Smear-negative TB, Malnutrition and TB, TB control in Rwanda

INTRODUCTION

Tuberculosis (TB), though largely preventable and treatable, continues to pose a significant global health challenge, affecting over 10 million people annually [1]. According to the 2023 WHO report,

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the estimated global TB incidence rate was 133 per 100,000 in 2022, with 10.6 million new cases reported, which is the highest since the World Health Organization (WHO) began monitoring TB globally in 1995 [2]. This surge can be attributed in part to disruptions in healthcare services and accessibility due to the COVID-19 pandemic.

HIV coinfection exacerbates the impact of TB, creating a dual burden for affected individuals and increasing the societal cost of TB control [3]. Africa bears a disproportionately high TB burden, and in 2022, the WHO African Region reported 410,000 people with multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB), yet only 40% of these individuals received anti-TB treatment [2].

In 2022, two-thirds of global TB cases were concentrated in eight countries, all categorized as low- and middle-income countries (LMICs). Some regions in Africa and Asia, particularly those that are remote or underserved, face significant barriers to healthcare access. In Africa alone, 2.5 million people contracted TB in 2022, accounting for a quarter of the world's new cases [2]. In 2022, the disease claimed 424,000 lives in the region, representing over 33% of all global TB deaths that year [2,4]. This suggests that TB might be closely linked to poverty, highlighting the critical need for social protection measures to help eradicate the disease [5].

Rwanda, a small East African country with a population of 14 million, has made remarkable strides in reducing its TB burden [6]. From 2000 to 2023, TB incidence in Rwanda decreased from 96 to 56 cases per 100,000 people, and the mortality rate fluctuated around 5 deaths per 100,000 from 2000 to 2020 [7–9]. In 2023, the mortality rate dropped to 3.2 TB deaths per 100,000, a reduction likely driven by sustained investments in TB control measures [8,10]. Rwanda has had the technical capability to diagnose and treat drug-resistant TB (DR-TB) since 2005, which has contributed significantly to controlling TB-related deaths [11]. Additionally, by adopting global strategies such as Directly Observed Treatment, Short-course (DOTS), and the End TB Strategy, Rwanda has made significant progress in alleviating the TB burden [12,13]. However, with HIV prevalence stabilizing at 3.0%, the country continues to grapple with TB-related deaths, as HIV coinfection complicates TB treatment outcomes [14,15]. While the global target for TB/HIV coinfection is fewer than 10 cases per 100,000 people by 2035, Rwanda's rate remains higher at 12 per 100,000 [10,16]. This underscores the need to critically assess the nature of TB-related deaths and the factors driving them to better inform Rwanda's National TB Program.

In this context, we conducted a comprehensive analysis of death audits from all health facilities in Rwanda between July 2017 and June 2023. The aim was to identify the determinants of TB/HIV coinfection, characterize TB deaths, and explore the potential factors associated with the deaths of TB/HIV coinfected patients, using the TB death audit checklist.

METHODS

Study Design, Setting, and Population

This nationwide retrospective cross-sectional study examined audited TB deaths in Rwanda between July 2017 and June 2023. The study included 48 District Hospitals, 4 Referral Hospitals, and 550 Health Centres.

The study population included all cases of TB-related deaths that were audited using the TB death checklist, regardless of the patient's age or sex. Cases lacking a confirmed cause of death were excluded from the analysis. In Rwanda, all TB cases are electronically reported through the Health Management Information System (HMIS), which captures essential details related to TB care, from diagnosis to treatment outcomes. TB-related deaths are audited by a medical doctor in collaboration with the TB focal point at the health facility where the death occurred, using a standardized, paper-based TB death checklist. Audit reports are submitted to the National TB Program (NTP) for aggregation and monthly analysis. A census sampling was used, where all TB death audit reports received within study period were included.

Data Collection

Data were collected from TB death audit reports filled out by healthcare workers at the originating health facilities. Data were filled in a developed data collection sheet, which recorded socio-demographic characteristics, such as age and sex, and clinical characteristics, including type of TB, TB history, nutritional status, HIV status at the time of TB diagnosis, and cause of death.

TB deaths were categorized into two groups based on the underlying cause of death: TB-related and non-TB-related deaths. Death was classified as TB-related if it met the following criteria: (1) Microbiological or pathological

evidence of TB infection without confirmation of other pathogens cultured from sterile body fluids or aseptically collected tissues; (2) agreement between the reviewing physician and the primary care physician's records or the death certificate regarding the underlying cause of death; and (3) absence of any other cause equally likely to result in death. If any of these criteria were unmet, the death was classified as non-TB-related. Death audit reports that were not reported on standardized checklist were excluded from the study.

Data Analysis

The final dataset was cleaned and analyzed using R Software Version 4.4.0. Descriptive statistics, including frequencies and proportions, were used to summarize socio-demographic characteristics and clinical variables. We conducted bivariate analyses to assess associations between HIV status at the time of TB diagnosis and other relevant variables. Variables that were statistically significant ($p<0.05$) in the bivariate analysis were further evaluated in a multivariate logistic regression model to control for confounding factors. Adjusted odds ratios (AOR) with 95% confidence intervals (CI) were calculated to identify factors associated with TB/HIV coinfected patient deaths.

This was a retrospective study, which did not pose potential risks to the study participants or their families, as it did not involve direct interaction. Patient identifiers were not included in the analysis. The data were anonymized and stored securely to protect patient confidentiality. Relevant information from the paper-based TB death checklist was entered into a secure, password-protected Excel file for further analysis.

RESULTS

We analyzed 1,112 tuberculosis (TB) death audit reports from patients who died between July 2017 and June 2023. This number represents a total of complete death audit reports received at national TB program, from 2,822 TB patients who died within the study period in Rwanda. The majority of the patients were men, accounting for 758 (68.2%) of the cases. The highest proportion of TB death audits, 269 (24.3%), were reported among individuals aged 35-44, while the lowest, 18 (1.6%), were reported in those under 15 years of age (Table 1).

Table 1: Demographic characteristics of individuals with selected TB death audit reports

Characteristics	N[1] = 1,112
Age Group	
<5	18 (1.6%)
5-14	19 (1.7%)
15-24	72 (6.5%)
25-34	196 (17.7%)
35-44	269 (24.3%)
45-54	174 (15.7%)
55-64	171 (15.4%)
>=65	190 (17.1%)
Gender	
Women	354 (31.8%)
Men	758 (68.2%)

[1] *n (%)*

Table 2: Clinical characteristics of individuals with reported TB death audit reports

Characteristic	N = 1,112[1]
Type of TB	
EPTB	357 (32.1%)
PTB-	185 (16.6%)
PTB+	570 (51.3%)
TB History	
New	1,031 (92.7%)
Retreatment	81 (7.3%)
Nutritional status	
Normal	409 (36.8%)
Moderate malnutrition	367 (33.1%)
Severe malnutrition	334 (30.1%)
HIV Status	
Negative	705 (63.4%)
Positive	407 (36.6%)
Cause of Death	
Tuberculosis	785 (70.6%)
Other opportunistic infections	72 (6.5%)
Other medical causes	244 (21.9%)
Other causes	11 (1.0%)

[1] *n (%)*

Clinical characteristics of individuals with reported TB death audit reports

Among the audited TB death cases, 785 (70.6%) were classified as TB-related deaths. Pulmonary TB smear-negative (PTB-) was the most common

Table 3: Bivariate analysis of factors associated with TB/HIV coinfection among individuals with TB death audits

Characteristics	Negative (N[1] = 705)	Positive (N[1] = 407)	p-value[2]
Age Group			<0.001
<5	11 (1.6%)	7 (1.7%)	
5-14	14 (2.0%)	5 (1.2%)	
15-24	43 (6.1%)	29 (7.1%)	
25-34	109 (15.5%)	87 (21.4%)	
35-44	140 (19.9%)	129 (31.8%)	
45-54	86 (12.2%)	88 (21.7%)	
55-64	122 (17.4%)	49 (12.1%)	
>=65	178 (25.3%)	12 (3.0%)	
Gender			0.024
Women	207 (29.4%)	147 (36.1%)	
Men	498 (70.6%)	260 (63.9%)	
Type of TB			0.007
PTB+	363 (51.5%)	207 (50.9%)	
PTB-	100 (14.2%)	85 (20.9%)	
EPTB	242 (34.3%)	115 (28.3%)	
TB treatment history			0.018
New	664 (94.2%)	367 (90.2%)	
Retreatment	41 (5.8%)	40 (9.8%)	
Nutrition category			0.017
Normal	279 (39.6%)	130 (32.1%)	
Moderate malnutrition	232 (32.9%)	135 (33.3%)	
Severe malnutrition	194 (27.5%)	140 (34.6%)	

[1](%), [2]Pearson's Chi-squared test

form, reported in 570 (51.3%) of the cases, while pulmonary TB smear-positive (PTB+) accounted for 185 (16.6%) of the deaths. Extrapulmonary TB (EPTB) was recorded in 357 (32.1%) cases. Most of the deaths occurred among new TB cases, with 1,031 (92.7%) patients being newly diagnosed.

Nutritional status varied across the cases, with only 409 (36.8%) of the patients reported to have a normal nutritional status, while 334 (30.1%) suffered from severe malnutrition. Among HIV-positive individuals, 262 (65.0%) were receiving antiretroviral therapy (ART) at the time of TB diagnosis. However, of those with a recorded CD4 count, 112 (54.6%) had a severely compromised immune system with CD4 counts below 200 (Table 2).

Bivariate Analysis of Factors Associated with TB/HIV Coinfection

We explored the relationship between HIV status and various categorical variables, including age, gender, TB treatment history, type of TB, and nutritional status in a bivariate analysis (Table 3). Age was significantly associated with HIV-positive status (p<0.001), with the 35-44 age group having the highest proportion of HIV-positive patients. Gender was also significantly associated with HIV status (p<0.024), with men comprising 63.9% of the HIV-positive cases. TB treatment history was associated with HIV-positive status (p<0.018), with 90.2% of HIV-positive individuals being newly notified TB cases. Nutritional status showed a significant association with HIV (p=0.017), where 67.9% of HIV-positive patients had either severe or moderate malnutrition. Finally, the type of TB also demonstrated a significant association with HIV status (p<0.007), with 50.9% of HIV-positive individuals having bacteriologically confirmed TB, 28.3% having extrapulmonary TB, and 20.9%

Table 4. Multivariate analysis of factors associated with TB/HIV coinfection among individuals with TB death audits

Characteristics	OR[1]	95% CI[2]	p-value
Age group			
25-34	—	—	
<5	0.53	0.18, 1.46	0.2
5-14	0.27	0.08, 0.77	0.020
15-24	0.75	0.42, 1.32	0.3
35-44	1.09	0.75, 1.60	0.6
45-54	1.15	0.75, 1.75	0.5
55-64	0.44	0.28, 0.68	<0.001
>=65	0.07	0.03, 0.13	<0.001
Gender			
Women	—	—	
Men	0.69	0.51, 0.91	0.010
Type of TB			
PTB+	—	—	
EPTB	1.03	0.76, 1.41	0.8
PTB-	1.97	1.35, 2.89	<0.001
TB treatment history			
New	—	—	
Retreatment	2.03	1.22, 3.40	0.007
Nutrition category			
Normal	—	—	
Moderate malnutrition	1.28	0.93, 1.76	0.13
Severe malnutrition	1.71	1.23, 2.40	0.002

[1]OR = Odds Ratio, [2]CI = Confidence Interval, p<0.05: Statistically significant

having clinically confirmed TB.

Multivariate analysis of factors associated with TB/HIV coinfection

A multivariate regression analysis was conducted to assess the relationship between HIV status and factors such as age group, gender, TB treatment history, nutritional status, and type of TB (Table 4). The analysis revealed that individuals aged 5-14 years (p=0.020, aOR 0.27, CI 0.08-0.77), 55-64 years (p<0.001, aOR 0.44, CI 0.28-0.68), and 65+ years (p<0.001, aOR 0.07, CI 0.03-0.13) were significantly less likely to be HIV-positive compared to younger adults. Although men made up the majority of HIV-positive cases, they were less likely to be HIV-positive than women (p=0.010, aOR 0.69, CI 0.51-0.91). Patients with pulmonary TB smear-negative (PTB-) were more likely to be HIV-positive compared to those with smear-positive TB (PTB+) (p=0.082, aOR 1.97, CI 0.96-2.12). Retreated TB cases were significantly more likely to be HIV-positive than newly diagnosed TB cases (p<0.007, aOR 2.03, CI 1.22-3.40). Additionally, severe malnutrition was strongly associated with HIV-positive status (p=0.002, aOR 1.71, CI 1.23-2.40), with individuals in this category showing a higher likelihood of being coinfected with HIV and TB.

DISCUSSION

The study revealed many significant factors associated with TB/HIV coinfection-related deaths in Rwanda. This study could provide useful insights into how to improve TB control efforts, especially for HIV-positive patients.

Individuals with prior TB infections were significantly more likely to be HIV-positive, highlighting people living with HIV (PLHIV)'s increased susceptibility to TB re-infection or reactivation of latent TB. This aligns with research from other regions, such as the United Kingdom, where HIV-infected persons have shown greater sensitivity to tuberculosis reactivation [17,18], likely due to impaired immune systems [18]. Similarly, in sub-Saharan Africa, the dual burden of TB/HIV has been reported, with HIV-positive patients more prone to TB recurrence [19]. This emphasizes the importance of routine TB screening among PLHIV to detect and treat TB at an early stage, hence avoiding serious outcomes such as death. According to studies conducted in South Africa and Uganda, routine TB screening at HIV clinics reduces the incidence of active TB among patients [20]. This emphasizes that Rwanda's National TB Program should increase its emphasis on TB screening in HIV care settings, utilizing both clinical and advanced diagnostic techniques. This screening can help in the early detection and treatment of latent tuberculosis infections (LTBI) in HIV-positive patients and may significantly reduce the likelihood of progression to active illness [21].

Another important finding was the association between severe malnutrition and TB/HIV co-infection. Malnutrition significantly increases the risk of TB-related mortality, consistent with earlier research on the negative impact of malnutrition on immunological function and the progression of TB and HIV [19,22]. Malnutrition can further weaken the immune system; hence, it is vital to incorporate nutritional support into TB and HIV care programs. This could enhance treatment outcomes and lower mortality rates, especially in low-resource settings where malnutrition and infectious illnesses frequently interact [23]. HIV infection can reduce appetite and affect nutrient absorption through the digestive system, exacerbating malnutrition [22]. These findings agree with a study conducted in the Democratic Republic of Congo, which found a high rate of poor nutrition status among TB/HIV co-infected participants, with a higher risk of mortality [24].

Evidence from global TB control programs supports the notion that addressing nutritional deficiencies can improve the efficacy of TB treatment, particularly in HIV-positive patients [25]. Increasing efforts to address malnutrition during TB care will help to improve its treatment outcomes, which could reduce the burden. This also calls for innovative approaches, such as community-based nutrition support services to accompany medical treatments for TB/HIV coinfected individuals.

The study also found that women were more likely than men to be HIV-positive, which could explain Rwanda's higher HIV prevalence among women (3.7%) than men (2.2%). This contrasts findings in Zimbabwe, where there were no significant gender differences in TB/HIV coinfection rates, which might be attributed to disparities in HIV prevalence among the general population [26,27]. However, our observation is supported by regional data that show higher HIV prevalence among women, particularly in sub-Saharan Africa, where social, economic, and cultural factors contribute to increased vulnerability [28]. Women are more vulnerable to HIV, which suggests that gender-specific interventions, such as expanding access to HIV prevention and treatment facilities for women, could help reduce TB/HIV coinfection rates [10]. Moreover, gender-responsive interventions, such as increased access to reproductive health care and HIV prevention for women, could help reduce the prevalence of TB/HIV coinfection in this population. Integrating family planning with TB/HIV programs could be a new method to address both high HIV prevalence and TB susceptibility in women.

Individuals clinically diagnosed with TB (smear-negative results) were more likely to be HIV-positive. This is consistent with the idea that HIV-positive persons generally have lower bacterial loads, which might contribute to smear-negative results [29]. While WHO recommends a combination of symptoms (cough, fever, weight loss, and night sweats) for a clinical diagnosis of smear-negative pulmonary TB, a study conducted in Vietnam showed limited predictivity of TB infection among PLVHIV, missing 54% of cases [30]. Concurrently, a study conducted in Uganda found that it is ineffective to initiate empirical TB treatment for PLVIH who have presumptive pulmonary TB with no bacteriological confirmation [31]. Advanced diagnostic technologies, such as GeneXpert Ultra, can effectively diagnose smear-negative tuberculosis in PLHIV. Expanding access to such diagnostic techniques can boost tuberculosis detection rates and lead to earlier, more effective treatments.

In our study, the factors we reported to be associated with TB death have potential confounders, which can to lead to an overestimation

of the associations we found. Indeed, while we revealed that HIV-positive individuals were likely to have TB reactivation, and found a strong association between TB and HIV coinfection, previous studies reported that people with lower socio-economic status have higher risks of being infected with TB, as they are more likely to work in high-incidence settings with poor ventilation [32,33]. Consequently, as severe malnutrition and TB/HIV co-infection are mostly reported in people who face economic hardship, their association with TB deaths might be influenced by their poor living conditions. Similarly, people with lower socioeconomic status have poor care-seeking behaviours due to limited access to health information, leading to delays in diagnosis and worse treatment outcomes. Moreover, the limited availability of sensitive screening and diagnostic tools in lower levels of the health system, such Chest-X Ray and CT-Scan [34], can cause individuals with low socio-economic status not to have early access to quality diagnosis, leading to higher risks of TB death.

This study emphasized on the need for targeted interventions in TB and HIV care, particularly those aimed at enhancing diagnostic accuracy, treating malnutrition, and providing gender-specific treatment. These measures may help reduce TB/HIV coinfection-related fatalities and contribute to the goal of eradicating tuberculosis as a public health threat. A holistic approach could address the multiple vulnerabilities of TB/HIV co-infected patients, especially in areas with high incidences of malnutrition and food instability. Previous research supports the effectiveness of integrating dietary therapy with TB/HIV treatment, as malnourished patients have lower drug absorption and immunological recovery [22,35]. Implementing such integrated care approaches in Rwanda's communities could enhance patient outcomes and minimize TB/HIV-related mortality.

Strengthening community-based tuberculosis and HIV surveillance systems to improve early detection and treatment adherence is essential. Community health workers (CHWs) have successfully improved TB case detection and monitoring in low-resource settings [36,37]. Thus, leveraging Rwanda's existing CHW network to provide home-based tests and follow-ups for TB/HIV patients has the potential to improve treatment adherence and outcomes, particularly in remote areas with limited healthcare access. Moreover, since the TB national program in Rwanda started a new validation technique of incorporating an electronic checklist into the eTB system for reporting TB death audits [38], continuing this practice will improve the completeness of the data and facilitate their accessibility for accurate evidence-based interventions.

Study limitations

This study has a few limitations that should be noted. First, it relied on TB death audits from health facilities, which may have resulted in underreporting because some deaths were not collected or audited, particularly in distant locations. TB death audits are verified by medical doctors before being reported, which can lead to underreporting, as health centers have to wait for their regular visits, which is not the challenge for the hospitals because they have their own medical doctors. Since hospitals are likely to treat patients with advanced stages of disease and comorbidities, those patients might have been overrepresented compared with patients attending health centers. The retrospective methodology restricted the investigation to existing records, which may include insufficient or inaccurate data, such as missing or incomplete clinical information. Moreover, using paper-based checklists for death audits may result in human mistake or inconsistency in reporting. Finally, the study did not take into consideration other potential confounding factors, such as socioeconomic position or access to healthcare, which could affect TB/HIV coinfection outcomes. Despite these limitations, the use of data from a large network of health facilities throughout Rwanda reinforces the study's findings.

CONCLUSION

Prior TB infection, severe malnutrition, and smear-negative pulmonary TB were found as key risk factors for TB/HIV co-infection deaths. These findings highlight the necessity of including nutritional support in TB care, enhancing diagnostic capacities, and developing gender-responsive and community-based interventions. Increasing community health education can promote care-seeking behaviours, as people are aware of how early diagnosis can lead to good treatment outcomes among TB infected individuals. This can also enhance diet preparation practices, as individuals will be aware of possible options to prepare balanced diets, avoiding malnutrition-

associated TB deaths. Moreover, involving community members in the implementation of infection prevention and control measures in the living areas and workplaces will reduce the burden on those who live in asylums and work in crowded places. By tackling factors associated with TB/HIV co-infection deaths and promote health within the community, Rwanda can make considerable achievements toward lowering TB/HIV-related mortality and reaching its TB elimination targets.

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