Characteristics Indicative of Tuberculosis/HIV Coinfection in a High-Burden Setting: Lessons from 13,802 Incident Tuberculosis Cases in Harare, Zimbabwe

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Abstract. Country-specific interventions targeting high-risk groups are necessary for a global reduction in Tuberculosis (TB)/HIV burden. We analyzed the data of 13,802 TB cases diagnosed in Harare, Zimbabwe, during 2013–2017. Pearson's chi-square tests and multivariate logistic regression models were used to identify patient characteristics significantly associated with TB/HIV coinfection. Of the 13,802 TB cases analyzed, 9,725 (70.5%) were HIV positive. A significantly higher odds of having TB/HIV coinfection diagnosis was found among females, patients aged 25–64 years, previously treated cases, and acid-fast bacillus sputum smear-negative cases. Compared with nondisseminated pulmonary TB, miliary TB (adjusted odds ratio [aOR]: 1.469, 95% CI: 1.071, 2.015) and TB meningitis (aOR: 1.715, 95% CI: 1.074, 2.736) both had a significantly higher odds for TB/HIV coinfection, whereas pleural TB (aOR 0.420, 95% CI: 0.354, 0.497) and all other extrapulmonary TB (EPTB) (aOR: 0.606, 95% CI: 0.516–0.712) were significantly less likely to have TB/HIV coinfection. The risk for TB/HIV coinfection varied significantly by patients' sociodemographic and clinical characteristics in Harare. Our finding that different forms of EPTB have different relationships with HIV coinfection has extended the knowledge base about clinical markers for TB/HIV coinfection which can lead to a greater public health impact on eliminating TB/HIV infection.

INTRODUCTION

Tuberculosis (TB) continues to be a major global burden as one of the leading causes of death for communicable diseases, with 1.5 million deaths in 2018.¹ Because TB is the leading cause of death for people living with HIV, HIV and TB coinfection must be addressed if we are to meet the Sustainable Development Goal of the United Nations to eliminate TB and AIDS by 2030.¹ The need for country-specific TB interventions has been identified as a key strategy in ending TB.²

Zimbabwe, the study site, carries a high burden of TB and TB/HIV coinfection and is currently one of the WHO-defined 30 high-burden countries for TB and TB/HIV coinfection.¹ In 2018, the TB incidence rate for Zimbabwe was estimated to be 210 cases per 100,000 and the TB/HIV coinfection rate was 130 cases per 100,000.¹ A better understanding of the characteristics of cases with TB/HIV coinfection will allow for an improvement in the identification of coinfection, thereby leading to the timely treatment of both diseases and prevention of the spread of disease.

The presentation of TB disease in people living with HIV can make diagnosis difficult for clinicians, with some TB diagnosis occurring postmortem.^{3,4} Previous studies have contributed fundamental knowledge to TB prevention strategies by identifying key TB characteristics for HIV-seropositive and -seronegative patients in some populations.^{5–8} Such knowledge is important, as failure to receive antiretroviral therapy for HIV infection in TB patients is known to be a risk factor for poor health outcomes of TB/HIV-coinfected patients.⁹ With a better understanding of how TB disease disseminates throughout the body of people living with and without HIV, clinicians are able to make timely, accurate diagnosis of the disease. A previous study conducted in Zimbabwe characterized pediatric TB cases with and without HIV infection during 2011–2012. However, the

characteristics of TB/HIV coinfection among adults remain largely unknown.⁶ This cross-sectional study is the first study to include patients of all ages in the characterization of TB cases with and without HIV infection in Zimbabwe and supports the call for country-specific interventions.^{1,2}

METHODS

Study population and data collection. The study sample included 13,802 (91.1%) incident TB cases of 15,151 total cases that were diagnosed in Harare, Zimbabwe, and registered in the National TB Registry (NTBR) from 2013 to 2017. Of the 1,349 (9.8%) cases excluded, 1,298 cases were excluded because of unknown HIV results and 51 cases were excluded for not being incident cases. The study cases were diagnosed at Beatrice Road Infectious Diseases Hospital (BRIDH), Wilkins Infectious Diseases Hospital (WIDH), and several other referral clinics in Harare. Tuberculosis cases were diagnosed, in principle, following the WHO-recommended algorithms.^{10,11} However, although there had been an increase in the use of Xpert MTB/RIF over time in Zimbabwe, the routine diagnosis of TB sometimes was carried out using only direct sputum smear microscopy during the study period. GeneXpert MTB/RIF technology was only used for high-risk drug-resistant TB. Patients negative for two acid-fast bacilli sputum smear (AFBSS) tests and those with signs and symptoms suggestive of TB were referred to the medical officer for chest X-ray and clinical diagnosis of TB as per the guidelines of the WHO.^{10,12}

To characterize TB cases with and without HIV coinfection, we retrieved data on the study patients' demographic and clinical characteristics as well as on where the TB diagnosis was made, from the NTBR. The demographic data captured included gender and age. The clinical characteristics included TB treatment history, AFBSS result, site of disease, and HIV status determined routinely at the diagnosis of TB. The data set was de-identified before the data analysis. The data collection protocol was approved by both the University of Michigan Health Science and Behavior Science Institutional Review Board (HSBS-IRB) and the Ethical Committee of the University of Zimbabwe. The

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study was determined unregulated by the University of Michigan HSBS-IRB, given it used de-identified patient data.

Patient classification. To compare the characteristics of patients with and without HIV coinfection, we grouped the study patients by HIV status and then subgrouped the HIV-positive and -negative patients by demographics and other clinical characteristics. The study patients were classified as new or previously treated patients based on the WHO definitions.¹¹

To more thoroughly explore clinical characteristics associated with TB/HIV coinfection, the study patients were also classified based on the site of their disease, using three different classification systems. The first classification system (designated disease classification 1) grouped the study patients into two categories: pulmonary TB (PTB) and extrapulmonary TB (EPTB), following the classification methodology that was commonly used by the WHO in its annual global TB surveillance report.¹¹ In this classification system, PTB also included miliary TB cases and EPTB included all cases whose disease occurred outside their lungs including pleural TB. The second classification system (designated disease classification 2), which grouped the patients into three categories: 1) thoracic TB (TTB), 2) extra-thoracic TB (ETTB), and 3) miliary TB, was explored to search for better clinical markers for TB/HIV coinfection diagnosis, given that the classification system described earlier can potentially misclassify miliary TB occurring outside the lung as PTB, skewing the association in question, especially in a high-TB/HIV coinfection population. For a similar purpose, we explored the usefulness of a third classification system (designated disease classification 3) in the identification of patient characteristics associated with TB/HIV coinfection. This third classification system classified the patients into five categories, including nondisseminated pulmonary TB (NDPTB), miliary TB, pleural TB, TB meningitis, and all other forms of EPTB.

Data analysis. To identify patient characteristics associated with a TB/HIV coinfection diagnosis, we first compared the frequency distributions of patient demographic and clinical characteristics between patient groups with and without HIV infection and tested the association of these characteristics with HIV status using Pearson's chi-square test and bivariate logistic regression. Percent difference between the HIV-positive (HIV+) group and the HIV-negative (HIV-) group and its 95% CI for each characteristic were calculated. To control for potential confounders, we next performed three multivariate logistic regressions to obtain adjusted odds ratios (aORs), based on each of the three classification systems described earlier. For the three models, model fit was assessed using the Pearson goodness-of-fit test, and the variance inflation factor for each model parameter was calculated to check for multicollinearity. Considering the possibility that the covariate effect on HIV infection might differ between patients with and without previous TB treatment, we also performed similar analysis using three multivariate logistic regression models stratified by treatment history (new versus previously treated TB cases). In addition, to examine the potential bias of the study sample, we compared the distribution of patient characteristics between the 13,802 study cases and the 1,349 cases excluded from the study sample using Pearson's chi-square test.

RESULTS

Characteristics of study patient. Of the 13,802 cases analyzed, 8,724 (63.2%) came from BRIDH. Male patients were the majority, 8,106 (58.7%) (Table 1). Patient age ranged from 0 to 97

years, with the median age being 35 (interquartile range: 16) years. There were 12,653 (91.7%) new TB cases. The HIV-seropositive cases accounted for 70.5% (9,725/13,802) of the study sample. Of the 12,872 cases with AFBSS test results and known ages, 0–14, 25–64, and 65+ age-groups had a greater percentage of AFBSS-negative results than AFBSS-positive results (Figure 1). A majority (82.8%) of cases had non-disseminated TB, whereas the remaining cases had miliary TB (2.6%), pleural TB (6.0%), TB meningitis (1.3%), and all other EPTB (7.4%) (Table 1). The most common form of EPTB was pleural TB, with 40.7% (823/2024) (Figure 2). Data on concurrent pulmonary and extra pulmonary involvement were not available.

Characteristics associated with TB/HIV diagnosis. Pearson's chi-square tests were conducted, and unadjusted odds ratios and *P*-values were reported to identify the differences between HIV-seropositive and HIV-seronegative groups (Table 2). Using three multivariate logistic regression models by three different disease classification systems described earlier,

TABLE 1
Demographic and clinical characteristics of 13,802 tuberculosis (TB) cases diagnosed in Harare, Zimbabwe, during 2013–2017

Variable	Number of cases	Percentage of cases
Age-group (years)*		
0–14	1,191	8.6
15–24	1,473	10.7
25–64	10,621	77.0
65+	501	3.6
Gender		
Male	8,106	58.7
Female	5,696	41.3
Treatment history		
New	12,653	91.7
Previously treated	1,149	8.3
AFBSS result†		
Negative	7,504	58.2
Positive	5,384	41.8
HIV status		
Negative	4,077	29.5
Positive	9,725	70.5
Medical center‡		
BRIDH	8,724	63.2
WIDH	3,000	21.7
Other clinics	2,085	15.1
Disease classification 1§		
PTB with miliary TB	11,778	85.3
EPTB	2,024	14.7
Disease classification 2		
TTB	12,247	88.7
ETTB	1,201	8.7
Miliary TB	354	2.6
Disease classification 3¶		
NDPTB	11,424	82.8
Miliary TB	354	2.6
Pleural TB	823	6.0
TB meningitis	177	1.3
All other EPTB	1,024	7.4

AFBSS = acid-fast bacilli sputum smear; PTB = pulmonary TB.

* Based on 13,786 cases for which age was known.

† Based on 12,888 cases for which AFBSS results were available.

‡ BRIDH = Beatrice Road Infectious Disease Hospital; WIDH = Wilkins Infectious Diseases Hospital; other clinics = other clinics throughout Harare.

§ Disease classification 1 included two categories: PTB and EPTB. PTB: TB in the lungs as well as miliary TB consistent with the disease classification used by the WHO in reporting global TB surveillance results.⁹ EPTB = extrapulmonary TB, including TB in any organ or tissue that is outside the lungs, including the pleura.

|| Disease classification 2 included three categories: TTB, ETTB, and miliary TB. TTB = thoracic TB including all cases with TB that occurred within the thoracic cavity, except for miliary TB; ETTB = extra-thoracic TB, including TB in all the locations outside the thoracic cavity, except for miliary TB.

¶ Disease classification 3 provided a more detailed classification of the disease by placing the study subjects into five categories: nondisseminated pulmonary TB (NDPTB), miliary TB, pleural TB, TB meningitis, and all other EPTB.

FIGURE 1. Frequency distribution of acid-fast bacillus sputum smear (AFBSS) results among different age-groups of TB cases diagnosed in Harare, Zimbabwe, during 2013–2017 ($N = 12,872$). Black bars represent AFBSS-negative cases; gray bars represent AFBSS-positive cases.

we identified several patient characteristics that are significantly associated with TB/HIV coinfection (Table 3). More specifically, all the three models consistently revealed a significantly increased likelihood for having TB/HIV coinfection among females compared with males, people in the 25–64 age-group compared with people in the age-groups of 0–14 and 15–24 years, patients having a previous TB treatment history compared with the new patients, AFBSS-negative patients compared with AFBSS-positive ones, and patients diagnosed at BRIDH compared with those diagnosed at WIDH.

The disease classification 3 model indicated that patients with miliary TB (aOR: 1.469, 95% CI: 1.071, 2.015) and TB meningitis (aOR: 1.715, 95% CI: 1.074, 2.736) were significantly more likely to have TB/HIV coinfection than those with NDPTB, whereas patients with pleural TB (aOR: 0.420, 95% CI: 0.354, 0.497) and all other EPTB (aOR: 0.606, 95% CI: 0.516, 0.712) were found to be significantly less likely to have TB/HIV coinfection. In addition, the disease classification 2 model indicated that compared with nondisseminated TTB, patients with miliary TB were significantly more likely to have TB/HIV coinfection (aOR: 1.647, 95% CI:

FIGURE 2. Frequency distribution of different forms of extrapulmonary TB (EPTB) among 2,024 EPTB cases diagnosed in Harare, Zimbabwe, during 2013–2017.

TABLE 2

Comparison of demographic and clinical characteristics between HIV-positive and HIV-negative TB cases who were diagnosed in Harare, Zimbabwe, during 2013–2017

	HIV+		HIV–		Unadjusted OR (95% CI)†	P-value§
	(N = 9,725)		(N = 4,077)			
	N	%*	N	%*		
Age-group (years)						
15–24	791	8.1	682	16.8	1.389 (1.191, 1.619)	< 0.0001
25–64	8,213	84.5	2,408	59.2	4.084 (3.612, 4.617)	< 0.0001
65+	169	1.7	332	8.2	0.610 (0.490, 0.758)	< 0.0001
0–14	542	5.6	649	15.9	Ref	
Gender						
Female	4,080	42	1,616	39.6	1.101 (1.022, 1.186)	0.0117
Male	5,645	58.1	2,461	60.4	Ref	
Treatment history						
Previously treated	942	9.7	207	5.1	2.005 (1.717, 2.342)	< .0001
New	8,783	90.3	3,870	94.9	Ref	
AFBSS result¶						
Positive	3,504	37.8	1880	52.1	0.558 (0.516, 0.603)	< 0.0001
Negative	5,776	62.2	1728	47.9	Ref	–
Medical center#						
WIDH	2,084	21.4	916	22.5	0.878 (0.802, 0.962)	0.0051
Other clinics	1,354	13.9	731	17.9	0.711 (0.643, 0.787)	< 0.0001
BRIDH	6,294	64.7	2,430	59.6	Ref	–
Disease classification 1**						
EPTB	1,385	14.2	639	15.7	0.893 (0.807, 0.989)	0.0301
PTB with miliary TB	8,340	85.8	3,438	84.3	Ref	–
Disease classification 2††						
ETTB	862	8.9	339	8.3	1.094 (0.959, 1.248)	0.1806
Miliary TB	300	3.1	54	1.3	2.39 (1.784, 3.201)	< 0.0001
TTB	8,563	88.1	3,684	90.4	Ref	–
Disease classification 3‡‡						
Miliary TB	300	3.1	54	1.3	2.338 (1.745, 3.133)	< 0.0001
TB meningitis	150	1.5	27	0.7	2.338 (1.549, 3.529)	< 0.0001
Pleural TB	523	5.4	300	7.4	0.734 (0.633, 0.850)	< 0.0001
All other EPTB	712	7.3	312	7.7	0.961 (0.836, 1.104)	0.5699
NDPTB	8,040	82.7	3,384	83	Ref	–

AFBSS = acid-fast bacilli sputum smear; PTB = pulmonary TB.

* Column percentage.

† CI = confidence interval.

§ P-value from Pearson's chi-square test of equal proportions.

|| Based on 13,786 cases for which age was known.

¶ Based on 12,888 cases for which AFBSS results were available.

BRIDH = Beatrice Road Infectious Disease Hospital; WIDH = Wilkins Infectious Diseases Hospital; other clinics = other clinics throughout Harare.

** Disease classification 1 included two categories: PTB and EPTB. PTB = TB in the lungs as well as miliary TB consistent with the disease classification used by the WHO in reporting global TB surveillance results.⁹ EPTB = extrapulmonary TB, including TB in any organ or tissue that is outside the lungs, including the pleura.

†† Disease classification 2 included three categories: TTB, ETTB, and miliary TB. TTB = thoracic TB including all cases with TB that occurred within the thoracic cavity, except for miliary TB; ETTB = extra-thoracic TB, including TB in all the locations outside the thoracic cavity, except for miliary TB.

‡‡ Disease classification 3 provided a more detailed classification of the disease by placing the study subjects into five categories: nondisseminated pulmonary TB (NDPTB), miliary TB, pleural TB, TB meningitis, and all other EPTB.

1.202, 2.255); by contrast, patients with ETTB in addition to pleural TB, but not miliary TB, were less likely to have TB/HIV coinfection. With disease classification 1, PTB with miliary TB was found to be associated with a higher risk of TB/HIV coinfection than EPTB. The associations described earlier were similar to those found in the stratified analyses for the new (incident) case group that accounted for 92% of the study sample (Supplemental Table 1). However, the results of the stratified analyses for the previously treated group (Supplemental Table 2) showed that because of the low frequency of the previously treated cases, especially in the miliary TB subcategory, the odds ratios could not be reliably estimated and that there might not be enough statistical power to study the differences between different disease types in the previously treated group.

DISCUSSION

We explored major demographic and clinical characteristics that were significantly, differentially distributed among HIV-

positive and -negative TB cases in Harare, Zimbabwe, to identify patient characteristics associated with TB/HIV coinfection. As the first study to include patients of all ages in the characterization of TB cases with and without HIV infection in Zimbabwe, our study found that approximately 70% of the study patients were coinfecting with HIV, which is similar to the WHO report that 72% of TB cases in Africa were HIV coinfecting.¹³ It is concerning to have such a high frequency of HIV coinfection in any population, given that HIV is the leading cause of death for people with TB disease.¹³

All three models (Table 3) consistently showed a significantly increased odds for having TB/HIV coinfection for people aged 25–64 years compared with the 0–14 and 15–24 age-groups. In 2012, the 25–64 age-group accounted for 42% of the general population of Harare, but this age-group accounted for 77% of TB cases in our study sample.¹⁴ Tuberculosis has disproportionately affected the most productive age-group of the population in Harare, Zimbabwe. This can have significant implications for families and society.^{15,16} Although TB treatment is free in Zimbabwe, the total cost related to seeking TB treatment, such

TABLE 3

Results of multivariate logistic regression analyses to identify patient characteristics associated with having TB/HIV coinfection diagnosis using three different models* based on three different disease classifications ($N = 12,827$)†

	Model 1		Model 2		Model 3	
	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age-group (years)						
15–24	1.102 (0.903, 1.345)	0.3379	1.114 (0.913, 1.359)	0.2868	1.173 (0.959, 1.433)	0.1197
25–64	3.177 (2.669, 3.782)	< 0.0001	3.178 (2.670, 3.783)	< 0.0001	3.384 (2.837, 4.036)	< 0.0001
65+	0.402 (0.312, 0.519)	< 0.0001	0.409 (0.317, 0.526)	< 0.0001	0.435 (0.337, 0.562)	< 0.0001
0–14	Ref	–	Ref	–	Ref	–
Gender						
Female	1.245 (1.146, 1.354)	< 0.0001	1.240 (1.141, 1.348)	< 0.0001	1.243 (1.144, 1.352)	< 0.0001
Male	Ref	–	Ref	–	Ref	–
Treatment history						
Previously treated	1.733 (1.471, 2.043)	< 0.0001	1.783 (1.514, 2.100)	< 0.0001	1.729 (1.467, 2.038)	< 0.0001
New	Ref	–	Ref	–	Ref	–
AFBSS result‡						
Positive	0.458 (0.416, 0.505)	< 0.0001	0.526 (0.479, 0.578)	< 0.0001	0.466 (0.422, 0.513)	< 0.0001
Negative	Ref	–	Ref	–	Ref	–
Medical center§						
WIDH	0.805 (0.729, 0.890)	< 0.0001	0.825 (0.747, 0.912)	0.0002	0.801 (0.724, 0.886)	< 0.0001
Other clinics	0.823 (0.732, 0.925)	0.0011	0.834 (0.742, 0.937)	0.0023	0.819 (0.729, 0.922)	0.0009
BRIDH	Ref	–	Ref	–	Ref	–
Disease classification 1						
EPTB	0.547 (0.484, 0.618)	< 0.0001	–	–	–	–
PTB with miliary TB	Ref	–	–	–	–	–
Disease classification 2						
ETT	–	–	0.773 (0.665, 0.900)	0.0009	–	–
Miliary TB	–	–	1.647 (1.202, 2.255)	0.0019	–	–
TTB	–	–	Ref	–	–	–
Disease classification 3						
Miliary TB	–	–	–	–	1.469 (1.071, 2.015)	0.0171
TB meningitis	–	–	–	–	1.715 (1.074, 2.736)	0.0237
Pleural TB	–	–	–	–	0.420 (0.354, 0.497)	< 0.0001
All other EPTB	–	–	–	–	0.606 (0.516, 0.712)	< 0.0001
NDPTB	–	–	–	–	Ref	–

AFBSS = acid-fast bacilli sputum smear; PTB = pulmonary TB.

* All the three multivariate regression models included basic demographic variables and all the clinical variables available to this study, except for the disease classification variables that were unique to each model. Model 1 was based on disease classification 1 that included two categories: PTB and EPTB. PTB = TB in the lungs as well as miliary TB consistent with the disease classification used by the WHO in reporting global TB surveillance results; EPTB = extrapulmonary TB, including TB in any organ or tissue that is outside the lungs, including the pleura. Model 2 was based on disease classification 2 that included three categories: TTB, ETT, and miliary TB. TTB = thoracic TB, including all cases with TB that occurred within the thoracic cavity, except for miliary TB; ETT = extra-thoracic TB, including TB in all the locations outside the thoracic cavity, except for miliary TB. Model 3 was based on disease classification 3 that provided a more detailed classification of the disease by placing the study subjects into five categories: nondisseminated pulmonary TB (NDPTB), miliary TB, pleural TB, TB meningitis, and all other EPTB.

† Based on the 12,872 observations with complete data for all variables analyzed.

‡ AFBSS (acid-fast bacilli sputum smear) result.

§ BRIDH = Beatrice Road Infectious Disease Hospital; WIDH = Wilkins Infectious Diseases Hospital; other clinics = other clinics throughout Harare.

as transportation and food, for a patient can be 58% of their reported annual income, which may affect willingness to seek timely treatment.¹⁶ Untreated cases of the most active, productive group in the society can contribute to the transmission of TB in the population, negatively impacting the TB epidemic in Harare, Zimbabwe. An elevated risk of TB/HIV coinfection in children aged 5 years and older was also reported by an earlier study conducted in Harare, Zimbabwe.⁶ This unchanged risk raises a concern about the lack of progress in reducing TB/HIV coinfection in older children especially because older children in Harare have a high burden of undiagnosed HIV.^{17,18} Age-specific public health interventions for TB/HIV prevention are necessary to limit future TB/HIV coinfection.

For gender, we found the male-to-female (M:F) ratio of TB cases to be approximately 1.42:1, which is consistent with the WHO Zimbabwe national TB profile but differs greatly from the 0.93:1 (M:F) of the Harare population in 2012.^{1,19} Higher M:F for TB cases than M:F for the general Harare population may indicate that males were disproportionately affected by TB in the study population. The gender difference in TB incidence has been found to be about 2:1 in previous studies conducted in Nigeria,²⁰ San Francisco, the United States,²¹ whereas the WHO reported the global M:F of TB as 1:7 for 2018.¹

From the three multivariate logistic regression models, we consistently found that females had a significantly elevated odds ratio for TB/HIV coinfection compared with males. Previous studies have reported gender disparities in other countries^{22–25}; an increased risk for females was found in Nigeria²⁰ and Ghana.²⁶ However, this was the first study to report the elevated risk for women in Harare, Zimbabwe. It was particularly intriguing that the female gender and TB/HIV coinfection association was neither found in a previous study conducted in the pediatric TB population in Harare⁶ nor in an early study conducted in a different region of Zimbabwe.²⁷ Further research on the gender disparities of TB/HIV coinfection in Harare is needed to better understand why women are at an increased risk of coinfection compared with men, although men carry the largest burden of TB disease.

Cases with a previous history of TB treatment made up a small percent (approximately 9%) of TB cases in the study sample but were found to be associated with having TB/HIV coinfection diagnosis in the current study, which is consistent with previous studies.^{28,29} The driving forces for the association may be the high risk of TB disease progression for people living with HIV infection³⁰ and the risk of TB drug resistance for previously

treated cases due to ineffective treatment.³¹ The high risk of HIV infection for previously treated TB cases has negative implications for preventing TB/HIV coinfection, as cases become more difficult to treat and a source of TB/HIV.

To identify the best clinical markers for the identification of cases with TB/HIV coinfection, we used three different disease classification systems described earlier, taking advantage of the unique strength of our large sample size. Previous studies have found EPTB and ETTB to be positively associated with TB/HIV coinfection.^{32–35} However, this study observed the opposite with both PTB and TTB being associated with TB/HIV coinfection. Our analysis based on disease classification 3 has generated data useful for understanding these discrepancies in findings from different studies. As described earlier, our study has shown that not all types of EPTB or ETTB were significantly positively associated with TB/HIV coinfection. For example,

TABLE 4
Comparison of distribution of demographic and clinical characteristics between the study sample (with HIV testing results) and excluded cases (without HIV testing results)

	Study sample, (N = 13,802)		TB cases excluded, (N = 1,349)		P-value†
	N	%*	N	%*	
Age-group (years)‡					
0–14	1,191	8.6	230	17.1	< 0.0001
15–24	1,473	10.7	167	12.4	0.0621
25–64	10,621	77	874	64.9	< 0.0001
65+	501	3.6	76	5.6	0.0003
Gender					
Male	8,106	58.7	828	61.4	0.0631
Female	5,696	41.3	521	38.6	0.0631
Treatment history					
New	12,653	91.7	1,213	89.9	0.0308
Previously treated	1,149	8.3	136	10.1	0.0308
AFBSS result§					
Negative	7,504	58.2	538	45	< 0.0001
Positive	5,384	41.8	657	55	< 0.0001
Medical center					
BRIDH	8,755	63.2	802	61.8	0.0042
WIDH	3,011	21.7	171	13.2	< 0.0001
Other clinics	2,087	15.1	325	25	< 0.0001
Disease classification 1¶					
PTB with miliary TB	11,778	85.3	1,186	87.9	0.0112
EPTB	2,024	14.7	163	12.1	0.0112
Disease classification 2#					
TTB	12,247	88.7	1,232	91.3	0.391
ETTB	1,201	8.7	84	6.2	0.0022
Miliary TB	354	2.6	33	2.5	0.8626
Disease classification 3**					
NDPTB	11,424	82.8	1,153	85.5	0.0131
Miliary TB	354	2.6	33	2.5	0.8626
Pleural TB	823	6	79	5.9	0.9221
TB meningitis	177	1.3	4	0.3	0.0023
All other EPTB	1,024	7.4	80	5.9	0.0508

AFBSS = acid-fast bacilli sputum smear; PTB = pulmonary TB.

* Column percentage.

† P-value from Pearson's chi-square test of equal proportions.

‡ Based on 13,786 cases for which age was known.

§ Based on 12,888 cases for which AFBSS results were available.

|| BRIDH = Beatrice Road Infectious Disease Hospital; WIDH = Wilkins Infectious Diseases Hospital; other clinics = other clinics throughout Harare.

¶ Disease classification 1 included two categories: PTB and EPTB. PTB: TB in the lungs as well as miliary TB consistent with the disease classification used by the WHO in reporting global TB surveillance results.⁹ EPTB = extrapulmonary TB, including TB in any organ or tissue that is outside the lungs, including the pleura.

Disease classification 2 included three categories: TTB, ETTB, and miliary TB. TTB = thoracic TB, including all cases with TB that occurred within the thoracic cavity, except for miliary TB; ETTB = extra-thoracic TB, including TB in all the locations outside the thoracic cavity, except for miliary TB.

** Disease classification 3 provided a more detailed classification of the disease by placing the study subjects into five categories: nondisseminated pulmonary TB (NDPTB), miliary TB, pleural TB, TB meningitis, and all other EPTB.

although miliary TB and TB meningitis were significantly more likely to be associated with TB/HIV coinfection, pleural TB and all other EPTB were significantly less likely to be associated with HIV coinfection than NDPTB. This variation, along with the potential difference in the frequency of each specific form of EPTB or ETTB among different populations, may contribute to the discrepancies in findings from different studies that were conducted in different geographic regions of the world. In previous studies that found EPTB to be associated with HIV infection, pleural TB accounted for 18%³³ and 21%³⁴ of total EPTB cases in their study populations. However, in our study sample, the proportion of pleural TB among all EPTB cases was as high as 41% (823/2,024), twice those reported by previous studies. As such, when we grouped pleural TB into EPTB in our disease classification 1 model, as grouped in previous studies, following the WHO's definition,¹¹ the previously reported association between EPTB and TB/HIV coinfection diminished.

Patients without laboratory-confirmed TB diagnosed clinically were treated for TB. With the high HIV prevalence in our study setting, diagnosis of TB in the absence of universal Xpert MTB/RIF could have resulted in false TB patients being treated or true paucibacillary TB patients not able to be diagnosed with sputum smear microscopy.³⁶ Another limitation was the absence of routine CD4 results to assess the level of immunosuppression, which can affect TB presentation.^{37,38} Another limitation of the study was missing HIV coinfection data for 8.6% of the incident TB cases in the NTBR. The differential distribution of demographic and clinical characteristics between cases included and excluded cases due to the lack of HIV infection diagnosis suggests a bias in the study sample (Table 4). Given that it is the policy in Zimbabwe to test all TB cases for HIV infection, we believe that it is most likely that the HIV data missing in this study were at random (i.e., the chance of missing do not differ conditionally on all observed variables). In this scenario, based on the results in our main analysis, multivariate logistic regression should be unbiased.

To summarize, from analyzing 13,802 incident TB cases in Harare, Zimbabwe, we have identified key demographic and clinical characteristics associated with TB/HIV coinfection. Particularly important is our finding of significantly varied associations between TB/HIV coinfection and different types of EPTB, as it extended the knowledge base about clinical characteristics of TB patients with HIV coinfection. The new knowledge generated from the current study can help address the need for and challenge in timely identifying and treating TB/HIV-coinfected individuals. Timely diagnosis and treatment of TB among HIV-infected individuals can contribute to the reduction of death among HIV-coinfected TB patients and the reduction of TB transmission in these patients' communities, thereby contributing to the effort of global TB elimination and ending the HIV epidemic.

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