

EPIDEMIOLOGICAL CHARACTERISTICS AND CLINICAL OUTCOME OF HIV-RELATED TUBERCULOSIS IN A POPULATION OF TB PATIENTS IN SOUTH-WESTERN NIGERIA

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Tuberculosis (TB) is the second leading cause of death from infectious disease globally with its impact more dramatic in resource limited settings. Individuals with human immunodeficiency virus (HIV) infection who also develop tuberculosis represent a significant challenge to TB control. This study was carried out to determine the prevalence of TB–HIV coinfection and pattern of infection among TB patients. We also compared treatment outcome among coinfecting patients with those not coinfecting.

A six-year retrospective review of records of patients managed at the Tuberculosis Treatment Center of the LAUTECH Teaching Hospital, South-Western Nigeria from January 2009 to December 2014 was carried out.

One hundred and five (26.3%) of the 399 TB patients seen in the study period were coinfecting with HIV. About 10% of the subjects had extrapulmonary tuberculosis. Treatment failure was significantly worse among patients who had both HIV and TB compared with those who had TB only (49.5% vs. 32%, $p = 0.001$). Death rate was also higher in the coinfecting individuals implying a poorer clinical outcome.

High prevalence of TB–HIV coinfection and poor treatment outcome in this group of individuals, though predictable, calls for a more concerted effort in the management of TB–HIV coinfection.

Keywords: tuberculosis, HIV/AIDS, TB–HIV coinfection, extrapulmonary TB, treatment outcome

Introduction

Tuberculosis (TB) has remained a major health problem globally, affecting millions of people every year. It has been ranked as the second leading cause of death from an infectious disease worldwide. The World Health Organization (WHO) in 2014 estimated that there are over 9 million new active cases of tuberculosis resulting in 1.5 million TB deaths per year. Over one quarter of these deaths are found in human immunodeficiency virus (HIV) positive individuals [1].

Tuberculosis and infection with HIV constitute the major burden of infectious diseases in resource-limited regions such as African and Asian countries [2].

When both infections occur in the same individual, this coinfection can result in diagnostic and therapeutic chal-

lenges due to the peculiar clinical picture that is seen with TB–HIV coinfection [2].

Tuberculosis is one of the earliest opportunistic infections seen in HIV-infected individuals and is the leading cause of death in these patients [3]. The prevalence of TB–HIV coinfection globally is about 13% but much higher in African countries which have the highest burden of HIV infections [4, 5].

TB–HIV coinfection has been reported to result in an accelerated course of disease and is also responsible for a disproportionately high number of TB-related deaths [1, 6–8]. A report which revealed the case fatality rate for TB in South Africa to be twice that of Brazil attributed it mainly to the high HIV infection rate in South Africa compared to Brazil, proposing that high death rates are associated with TB–HIV coinfections [4].

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The immune suppression associated with HIV increases the risk of reactivation of latent tuberculosis and rapid progression to active infection. Therefore, areas with high HIV prevalence also have high TB incidence rates [3, 6]. TB–HIV coinfection is prevalent in Africa as the WHO report of 2014 shows that about 80% of the 1.1 million TB patients who were HIV-positive were from the African region [1].

Although pulmonary tuberculosis is the commonest TB manifestation, those who are HIV positive are more likely to have extrapulmonary TB. Extrapulmonary TB is seen in 40–80% of TB–HIV infection but in only 10–20% of patients without coinfection [8, 9].

Furthermore, drug-resistant infections have been seen in TB–HIV coinfections although a direct association is yet to be established [3].

It is therefore evident that HIV-related TB impacts negatively on the efforts to control tuberculosis.

This study was carried out to determine the prevalence of TB–HIV coinfection among those being treated for TB, to compare the pattern of TB in HIV-infected and non-HIV-infected individuals and to observe the trend of coinfection over time. We also wanted to assess the outcome of treatment among the HIV-infected patients.

Determining the magnitude of TB–HIV coinfection and associated factors will aid in assessing the HIV-related burden of tuberculosis and the need for targeted control measures.

Materials and methods

Study site and design

The study was carried out at the Tuberculosis Treatment Center of the Ladoko Akintola University of Technology (LAUTECH) Teaching Hospital Osogbo, Osun state. This center, located in a tertiary health care institution in South-Western Nigeria, is a referral center for the management of TB and provides care for patient from various parts of the state.

This study was a six-year retrospective review of records of all patients seen at the center from January 2009 to December 2014.

Patient selection

Patients who presented with cough lasting for 2 weeks or more were clinically suspected of having TB. This was followed by laboratory and radiological investigations. Laboratory investigation for TB was by sputum smear for acid-fast bacilli (AFB). Patients had three sputum samples taken for detection of AFB by microscopy. Those who had at least one smear positive for AFB were categorized as smear-positive pulmonary TB (PTB). All patients also had chest X-ray to detect radiological changes of PTB. Extrapulmonary tuberculosis included tuberculosis of organs

other than the lungs, such as the abdomen, genitourinary tract, lymph nodes, skin, bones, joints, and meninges. A diagnosis of extrapulmonary tuberculosis was made based on clinical findings suggestive of TB, radiology, cytology, and/or tissue histology. Patients were treated using the directly observed treatment short course (DOTS) regimen of at least 6 months of anti-TB drugs which consists of 2 months of rifampicin, isoniazid, pyrazinamide, and ethambutol followed by 4 months of rifampicin and isoniazid. All patients at the clinic had testing for HIV. Blood samples that were reactive after an initial rapid test screening had confirmatory testing done by Western blot. Patients with TB–HIV coinfection were either those being managed for TB in whom HIV infection was detected or patients already being managed for HIV infection who were subsequently diagnosed with TB and seen at the center. All HIV-positive individuals in this cohort were placed on antiretroviral therapy (ART), in addition to anti-TB drugs, following the national guidelines which recommend zidovudine or tenofovir plus lamivudine (or emtricitabine) plus efavirenz. Timing of initiation of ART was between 2 weeks following commencement of anti-TB and the end of the intensive phase of anti-TB treatment (8 weeks). This timing was individualized based on the patients CD4 count and the severity of illness.

Demographic and clinical information were retrieved from patients' records using a standardized questionnaire.

Data analysis

Data analysis was performed using the SPSS version 20 software. Quantitative variables were summarized using range, mean, and standard deviation, or frequency tables and percentages were used for categorical variables. The Chi-squared test was used to test for association between categorical tables. The level of significance was set at $p \leq 0.05$.

Ethics statement

Approval for the study was obtained from the Ethics Committee of LAUTECH Teaching Hospital, Osogbo, Nigeria.

Results

Demographic characteristics

Three hundred and ninety nine persons with tuberculosis were seen during the study period.

The age range was 5–90 years with a mean age of 39 (± 15.7) years. The mean age of both coinfecting people and those with TB only was comparable (38.9 and 39.0 years, respectively); the age groups 30–39 and 40–49 had the highest rate of coinfection (*Table 1*).

Table 1. Demographic characteristics of patients

Characteristics	HIV Status		Total	χ^2	<i>p</i> value
	Positive	Negative			
Age group (years)				11.37	0.044
>20	3 (9.7%)	28 (90.3%)	31 (7.8%)		
20–29	17 (21.2%)	63 (78.8%)	80 (20.1%)		
30–39	40 (33.1%)	81 (66.9%)	121 (30.3%)		
40–49	24 (33.3%)	48 (66.7%)	72 (18.0%)		
50–59	11 (25.0%)	33 (75.0%)	44 (11.0%)		
≥60	10 (19.6%)	41 (80.4%)	51 (12.8%)		
Total	105 (26.3%)	294 (73.7%)	399 (100.0%)		
Sex				3.25	0.07
Male	40 (22.0%)	142 (78.0%)	182 (45.6%)		
Female	65 (30.0%)	152 (70.0%)	217 (54.4%)		
Total	105 (26.3%)	294 (73.7%)	399 (100.0%)		

The overall sex distribution was 182 (45.6%) men and 217 (54.4%) women. Twenty two percent of the male TB patients were coinfecting while this was the case in 30% of the female patients (*Table 1*).

Prevalence and clinical outcome

One hundred and five of the 399 patients were HIV positive giving a TB–HIV coinfection prevalence of 26.3%. The annual prevalence of coinfection was 28.3%, 35.2%, 19.4%, 19%, 18.6%, and 34.6% for the first, second, third,

fourth, fifth, and sixth years, respectively. The trend of TB–HIV coinfection in the six-year period showed an annual fluctuation in the prevalence of coinfection. There was an initial rise in prevalence followed by a remarkable drop in subsequent years, and then a rise in the latter period (*Fig. 1*). This trend was statistically significant (*Table 2*).

Table 3 shows the sites of TB infection. Overall, there were 38 (9.5%) extrapulmonary and 361 (90.5%) pulmonary infections. About 6% of patients with TB and HIV infection had extrapulmonary tuberculosis compared to 10.9% in individuals with TB only. This difference was not significant ($p = 0.12$).

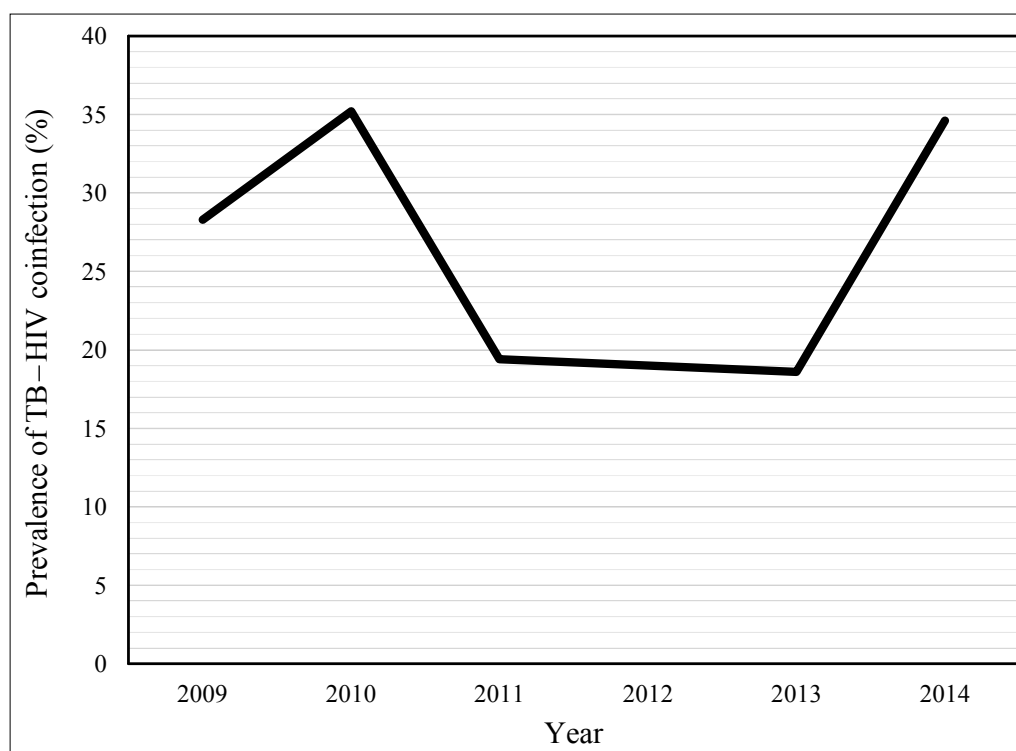
**Fig. 1.** Trend in the prevalence of TB–HIV coinfection

Table 2. Prevalence of TB–HIV coinfection

Year	Coinfected		Total	χ^2	<i>p</i> value
	Yes	No			
				11.13	0.049
2009	17 (28.3%)	43 (71.7%)	60 (15.0%)		
2010	25 (35.2%)	466 (4.8%)	71 (17.8%)		
2011	12 (19.4%)	50 (80.6%)	62 (15.5%)		
2012	8 (19.0%)	34 (81.0%)	42 (10.5%)		
2013	16 (18.6%)	70 (81.4%)	86 (21.6%)		
2014	27 (34.6%)	51 (65.4%)	78 (19.5%)		
Total	105 (26.3%)	294 (73.7%)	399 (100.0%)		

Table 3. Tuberculosis site

Site	Coinfected		Total	χ^2	<i>p</i> value
	Yes	No			
				2.4	0.121
Extrapulmonary	6 (5.7%)	32 (10.9%)	38 (9.5%)		
Pulmonary	99 (94.3%)	262 (89.1%)	361 (90.5%)		
Total	105 (26.3%)	294 (73.7%)	399 (100.0%)		

Table 4. Clinical outcome of TB of patients

Treatment outcome	Coinfected		Total	χ^2	<i>p</i> value
	Yes	No			
				10.96	0.001
Cured	34 (32.4%)	144 (49.0%)	178 (44.6%)		
Not cured	52 (49.5%)	95 (32.3%)	147 (36.8%)		
Defaulted	0 (0.0%)	12 (4.1%)	12 (3.0%)		
Died	14 (13.3%)	16 (5.4%)	30 (7.5%)		
Transferred out	5 (4.8%)	27 (9.2%)	32 (8.0%)		
Total	105 (26.3%)	294 (73.7%)	399 (100.0%)		

The different outcomes of treatment following 6 months of standard therapy are as presented in *Table 4*. Overall, 325 (81.4%) patients completed the treatment course. The remaining 74 patients had either died in the course of treatment, been transferred to another facility for treatment, with subsequent loss of information regarding the outcome of treatment, or were lost to follow-up as a result of treatment default. Thirteen percent of the HIV-positive patients died in the course of treatment compared to 5.4% in the HIV negative ($p = 0.04$).

Among patients who completed the anti-TB drug regimen, treatment failure rates for the HIV positive and HIV negative TB patients were 60.5% and 39.7%, respectively ($p = 0.001$) (*Table 4*).

Discussion

This study found the prevalence of HIV infection among TB patients to be 26.3% as 105 of the 399 TB patients were also HIV positive. This rate is quite high considering

a global prevalence which has been estimated at 13% [1]. The African region, sub-Saharan Africa in particular, is noted for a high prevalence of tuberculosis. Although their finding was not as high as ours, studies such as that from Ethiopia reported TB–HIV coinfection rates of 18–21% [10]. It is also noteworthy that the coinfection rate from this study is much higher than reports from several studies within this region and in related regions [11–14]. These studies were however carried out several years earlier, some over a decade ago. This might suggest a steady rise in the prevalence TB–HIV coinfection in this environment and, thus, deserves further investigation.

It is interesting to note a significant fluctuation in the prevalence of TB–HIV infection over time. We found a high coinfection prevalence of 35% in the second year and then a significant drop to about 19% the following year. This drop was sustained for 3 years and thereafter followed by a sharp double rise in the last year of study. A consideration of the annual trend in the rates of HIV infection during the period of our study would have shed more light on the impact of HIV prevalence on that of TB–

HIV coinfection rates. In sub-Saharan Africa, the rise in the number of TB cases has been attributed mainly to HIV infection; therefore, fluctuations in HIV prevalence will have an impact on TB rates and control [4].

The age distribution showed the peak age of TB–HIV infection to be of 30–49 years. This is comparable to findings of several other studies where the peak age of coinfection ranged from 31–40 to 41–50 [12, 15, 16, 17]. In contrast, a lower age group was reported by Thanh et al. [18].

The WHO global report indicates that more TB cases and deaths occur among men compared to women [1, 19]. However, our study found more women than men with tuberculosis. The prevalence of coinfection was also higher in women than men. This unusual finding was however not statistically significant ($p = 0.07$).

Atypical presentations such as extrapulmonary TB and sputum smear-negative TB and atypical radiologic manifestations have been said to hamper the diagnosis of TB, thus, affecting the prompt treatment and control of the infection. [5]. In this study, the total proportion of extrapulmonary disease was less than 10%, with an even smaller proportion in coinfecting persons. This contrasts with the reported much higher prevalence of extrapulmonary TB in HIV-related infections compared to infections in HIV-negative individuals [8, 9]. Another study reports a similar contrasting picture in which, even though the prevalence of extrapulmonary TB was 11–38%, it was higher in areas with the lowest HIV prevalence [10]. This picture is very likely to be an underestimate of true events as diagnostic facilities which aid the detection of atypical presentations of tuberculosis, such as extrapulmonary infections and smear-negative test, are not readily available in resource limited settings like ours. This challenge will even be more pronounced in HIV-positive patients who are more likely to harbor such atypical presentations.

We also did not record any concomitant pulmonary and extrapulmonary infection as reported by some studies [8, 9, 15].

A generally high rate of treatment failure was observed in this study group. This is highly unsatisfactory as it is almost impossible to control TB if such a situation persists. A similarly high treatment failure rate was reported by Jibrin et al. in the Northern part of the country [20]. Our study showed a significantly higher rate of treatment failure among the HIV-positive individuals when compared to their noninfected counterparts. Similar findings have been reported by Perriens et al. [21].

Although Mycobacteria strains were not characterized, patients displaying treatment failure had most likely been infected by multidrug-resistant strains. This is in keeping with the reports suggesting that HIV–TB coinfection might be seen alongside multidrug-resistant TB [3]. Drug-resistant TB is becoming a significant challenge to the control of the infection worldwide especially in HIV-positive patients [22]. Although multidrug-resistant tuberculosis is not as common in Africa as it is in Asia and some other parts of this world, it is certainly emerging [4]. Testing for drug resistance was not available as at time of data collec-

tion, such investigation would have been of immense benefit in detecting the cause of treatment failure in patients and is strongly advocated. This is important also in view of the highly infectious potential of HIV-positive patients with drug-resistant infections [23].

We were also able to demonstrate the rapid progression and shortened survival that has been described in HIV-related TB [6, 7, 24]. Our study showed that the death rate in coinfecting individuals was more than two times that of those who were not coinfecting. The high death rate in this population of patients is also probably related to the fact that those who develop TB are more immunosuppressed and have other comorbidities as well, leading to a rapid clinical deterioration.

Our study was limited by the design of the study which did not give us the opportunity to explore all desired epidemiological and clinical factors associated with HIV-related TB.

Conclusion

We conclude that the high prevalence of TB–HIV coinfection and poor treatment outcome in this group of individuals, though predictable, calls for a more concerted effort in the management of TB–HIV coinfection. Interventions should be targeted at treating the immunosuppression associated with HIV which promotes development of active TB. Also a more aggressive screening for TB especially in HIV-positive individuals and subsequent treatment of those infected should be pursued.

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Authors' contribution

O.A.O. and A.S.A. conceived and designed the study. A.S.A. and O.B.M. wrote the protocol and managed the literature search. R.A.O., A.S.A., O.A.O., and O.J.A. managed the acquisition of data. O.A.O., O.B.M., and A.S.A. performed analysis and interpretation of data. A.S.A., R.A.O., and O.J.A. wrote the first draft of the article. O.B.M. and O.A.O. made critical revisions to the draft. All authors read, edited, and approved the final article.

Conflict of interest

The authors declare no conflict of interest.

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