Original Article

Incidence of tuberculosis and immunological profile of TB/HIV co-infected patients in Nigeria

Baba Maiyaki Musa, Babashani Musa, Hamza Muhammed, Nashabaru Ibrahim, Abubakar Garbati Musa[1]

Department of Medicine, Bayero University/Aminu Kano Teaching Hospital, Kano, Nigeria, [1]Section of Infectious Diseases, King Fahad Medical City, Riyadh, Saudi Arabia

Address for correspondence:
Dr. Musa Baba Maiyaki, Department of Medicine, Bayero University/Aminu Kano Teaching Hospital, Kano, Nigeria.
E-mail: babamaiyaki2000@yahoo.co.uk

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Abstract:

BACKGROUND: We obtained estimates of the incidence of tuberculosis (TB) among patients receiving HIV Treatment. We also modeled the relationship between incident TB and change in CD4 count over the follow-up period.

METHODS: We analyzed the incidence of TB over 10 years from initiation of HIV treatment among 345 HIV treatment-naïve persons, who were enrolled in a cohort in Kano, Nigeria. We used Generalized Estimating Equation [GEE] to identify determinants of TB incidence and model the relationship between the occurrences of TB with change in CD4 count over the follow-up period. We created Kaplan-Meier curves stratified by anti-retroviral therapy (ART) treatment failure status to examine the effect of first line ART treatment failure on occurrence of TB.

RESULT: During the 10-year period, 47(13.62%) had TB [incidence was 7.43 per (1,000) person year)]. It is associated with decreasing age (OR = 0.98), female gender (OR = 0.83), being on first line ART other than AZT (OR = 0.87), poor adherence (OR = 1.25), change in ART regimen (OR = 2.3) and ART treatment failure (OR = 1.51). Odds of TB occurrence was also associated with CD4 increment at 10 years (OR = 0.99). Those with TB/HIV co-infection tend to have statistically significant shorter time to failing first line ART regimen compared to those with HIV infection alone.

CONCLUSION: There was high incidence of TB in the studied HIV cohort with a deleterious effect on the outcome of ART treatment. There is need for early TB screening and re-screening among all HIV patients.

Key words:

HIV, incidence, Nigeria, tuberculosis

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Human immunodeficiency virus (HIV) infection and tuberculosis (TB) not only constitute an unresolved public health challenge in sub-Saharan Africa but also in the entire world. The World Health Organization (WHO) estimated that in 2013, 9 million people developed TB and 1.5 million died from the disease globally, a quarter of which occurred in Africa.[1]

The persisting epidemic of TB is facilitated by HIV infection; and it is more pronounced in sub-Saharan countries. Whereas the lifetime risk of an immunocompetent person developing TB is 10-20%; the annual risk in those with HIV is 10%.[2-5] The number of people with the dual infection in Nigeria is increasing, with an estimated 570,000 cases in 2013.[6] With 3.4 million people with HIV in 2013, Nigeria has the second largest burden of HIV infection, globally, even as it has the fourth highest prevalence of TB. In 2012, Nigeria had an estimated incidence of 338 cases of TB per 100,000 population.[7,8]

TB can occur in a person with HIV infection at any level of immunoparesis though the clinical picture varies with the level of immunosuppression. Typically, fibro-cavitatory lung disease is seen in persons with a fairly preserved immune status.[9] This is similar to what is seen in immunocompetent individuals. There is a graded decline in the degree of fibrotic lung changes and tendency to form cavities with decline in CD4 count.[10] Furthermore, there is higher likelihood of smear-negative sputum Acid Fast Bacilli (AFB) test in a person with TB/HIV co-infection compared to someone with TB alone.[11] Moreover, in chest radiography, there is a gradient in the level of lung parenchymal involvement, with upper zone being affected in mild immunoparesis and lower zone being affected in severe immunoparesis. Indeed, a normal chest radiograph may be associated with active TB in a person with HIV infection.[12]

There had been studies in Nigeria addressing the prevalence of TB in persons with HIV, with a prevalence of 10.5-40%.[13,14] Similarly, cross-sectional studies had looked at the determinants

of TB.[15] However, there haven't been cohort studies on incidence of TB and its impact on immunological trend among persons with HIV.

This study was designed to study the incidence of TB, identify. We also assessed the determinants of TB, and modeled the relationship between the occurrences of TB and change in CD4 count over the follow-up period.

Methods

Study design

This is a 10-year retrospective cohort study (March 2004 to April 2014) undertaken at the HIV/AIDS care center located within the premises of Aminu Kano Teaching Hospital, Kano (AKTH), Nigeria. The center was established by Institute of Human Virology, Nigeria (IHVN) with support from the Centers for Disease Control and Prevention and the President's Emergency Plan for AIDS Relief (CDC/PEPFAR). It is the main tertiary referral center for Kano state which has a population of about 15 million. It also receives patients from neighboring states of Jigawa, Katsina, Kaduna and Bauchi. The hospital provides a range of clinical services for both in- and out-patients, including provision of care and treatment for patients infected with TB and HIV/AIDS.

Inclusion criteria

To be eligible for inclusion, a patient had to be anti-retroviral treatment (ART)-naïve and newly enrolled in HIV care from 2004 to 2007 with minimum of one CD4 lymphocyte count results for each year of follow-up, and the patient should have documentation of clinical evaluation on at least two visits and documentation of baseline CD4 count. Patients gave consent for their de-identified data to be used for research.

Exclusion criteria

We excluded patients less than 18 years and those with prior ART usage. In analyzing incidence of TB, we excluded those with TB at enrollment in care.

Study population

The study population was made up of all HIV-positive, ART-naïve persons enrolled in the AKTH HIV/AIDS care program. The follow-up period was up to April 2014. Selection was based on simple random sampling technique, with the persons enrolled during the time frame constituting the sampling frame.

Exclusion criteria included age less than 18 years, prior exposure to ART and those with chronic medical conditions.

HIV care protocol

Patients evaluated for ART initiation underwent routine medical examination, including screening for TB and other opportunistic infections. For TB screening, subjects had full clinical assessment, sputum smears for acid fast bacilli (AFB) as well as chest radiography. Pre-ART assessment included baseline determination of CD4 count and viral load, liver function and renal function tests. The program also offers diagnosis and treatment of opportunistic infections prior to initiating ART. HIV genotypic resistance testing was offered to those who failed their primary regimen.

HIV testing

HIV infection in AKTH, like other centers spread across the country, is diagnosed based on the WHO and the Nigerian National HIV screening guideline that stipulates usage of a combination of rapid tests that do not require expensive Western Blot confirmation assays. Patients offered care in the center routinely have pre-test and post-test counseling for HIV that assesses their risk (s) of acquisition.

Tuberculosis testing

A diagnosis of TB was established by clinical screening for corresponding signs and symptoms as well as sputum testing by Ziehl-Neelsen technique according to protocol. Often, a chest X-ray or tissue biopsy may be required for diagnosis.

Definition of terms

First line ART refers to combination of medications used in a new patient commencing HIV medication. Second line ART regimen refers to a combination of medications used in patients who failed treatment on first line ART regimen; includes a protease inhibitor (PI). Regimen change denotes substitution of an ART medication with another due to toxicity resulting from usage of initial drug. Regimen switch refers to replacement of first line ART regimen with a second line ART regimen due to treatment failure.

Data collection

A structured datasheet was used to extract data from the medical records of all eligible patients. HIV-seropositive patients enrolled in the AKTH HIV/AIDS care program from March 2004 to April 2007. Follow-up data up to April 2014 was captured. Socio-demographic characteristics, and clinical and laboratory data were extracted into a proforma by trained personnel. This information had been prospectively captured on patient management and monitoring [PMM] forms designed specifically for the program.

Data analysis

Extracted data was entered into a computerized database and analyzed using STATA version 11 (Stata Corporation, College Station, USA). Quantitative variables were summarized using range, mean, and standard error, or median and quartiles, as appropriate. Categorical variables were tabulated using frequencies and percentages. Differences in means were determined by t-test when normally distributed and by Mann-Whitney test when non-parametric. Differences in categorical variables were determined by chi-square test and where necessary with Fisher's exact correction.

TB disease incidence was calculated as the number of new TB episodes per 1,000 person-months (PYM) of follow-up. $P < 0.05$ was considered statistically significant.

Due to the longitudinal nature of the data, we modeled the relationship between the occurrences of TB with change in CD4 count over the follow up period. Several bio-demographic and clinical covariates were considered to address confounding. We used Generalized Estimating Equation [GEE], assuming a binomial distribution. We specified logit link function and adopted independent correlation structures. We used the quasi-likelihood information criterion (QIC) statistics to evaluate fitness.

To examine the effect of first line ART treatment failure on occurrence of TB, we created Kaplan-Meier curves stratified by ART treatment failure status and determined its statistical significance with log-rank test. We used Cox proportional hazards models to estimate the effect of treatment failure on the risk of TB occurrence.

Ethical considerations

We obtained ethical clearance from the ethics committee of AKTH. No real time human study was involved and data was collected from routine care records.

Results

Description of study population

A total of 345 patients were enrolled in the study from among 1,034 persons enrolled in care from 2004 to 2007. Total 59% of them were females, with 200 (66.96%) married and 37% un-employed. The median age at the time of enrollment was 40 years (25th-75th percentile: 35-45 years) with about 32,340 person-months of follow-up. About 60% of the patients lived further than 30 kilometers from the treatment center. At the time of this analysis, the median time on ART was 102 months (25th-75th percentile: 94-105 months) with 91.3%, 5.5% and 3.19% being on ART for at least 60 months, between 13 months and 59 months, and 12 months or less, respectively as shown in Table 1.

Majority of the patients (72.75%) were on zidovudine (AZT)-based first line ART regimens. The median absolute CD4 count at ART initiation was 300 cells/μL with 30.72 % having absolute count less than 200 cells/μL. Although 67.25% self-reported a suboptimal adherence of <95%; only 23.77% had a regimen switch due to immunologic failure [Table 2]. We found 12 (3.48%) people who failed by immunological criteria and who had no documentation of regimen switch.

Of the 345 patients reviewed, 47 (13.62%) had TB, giving an overall TB incidence of 47 per 32,340 person-months, or (17.43 per (1,000) person-year); 95% C. I. (13.10-23.21). When disaggregated by gender, the incident rate in men was 17.56 per (1,000) person-year, 95% C. I. (11.52-27.48); and 17.28 per (1,000) person-year, 95% C. I. (11.88-25.08) in females with an incident rate ratio of 0.86; mid *P* - value (0.49).

There was no statistically significant difference in age between those with TB/HIV co-infection and those without even when age is stratified. Similarly, no differences were seen in gender, marital status, employment status and distance from treatment center. When stratified by immunological status, there were statistically significant differences in CD4 count change at 5 and 6 years. Equally, there were statistically significant differences between the two groups when stratified by occurrence of regimen change and regimen switch. (Regimen change denotes substitution of an ART medication with another due to toxicity resulting from usage of initial drug, while regimen switch implies replacement of first line ART regimen with a second line ART regimen due to treatment failure). However, similar difference were not documented for baseline CD4 count, WHO clinical staging, type of first line regimen and CD4 count change at 10 years [Table 3].

Table 1: Socio-demographic characteristics of HIV positive study participants at AKTH

Characteristics	Frequency (%)
AGE	
18-29	20 (5.80)
30-39	129 (37.39)
40-49	143 (37.39)
50 and above	53 (15.36)
SEX	
Male	140 (40.58)
Female	205 (59.42)
Marital status	
Single	36 (10.43)
Married	231 (66.96)
Divorced	24 (6.96)
Widowed	54 (15.65)
Employment status	
Employed	217 (62.90)
Not employed	128 (37.10)
Distance from treatment center	
<30 kms	137 (39.71)
>30 kms	208 (60.29)

Table 2: Clinical and immunological profile of study participants

Parameters	Sub-types	Frequency (%)
Who clinical stage	I	201 (58.26)
	II	66 (19.13)
	III	70 (20.29)
	IV	8 (2.32)
First line art regimen	ZDV/3TC/NVP or EFV	251 (72.75)
	D4T /3TC/NVP or EFV	22 (6.38)
	TDF/3TC/NVP or EFV	68 (19.71)
	ABC/3TC/NVP or EFV	4 (1.16)
Art duration	<12 months	11 (3.19)
	13-59 months	19 (5.51)
	>60 months	315 (91.30)
CD4 count at enrolment in care	<200	106 (30.72)
	200-349	101 (29.28)
	≥350	138 (40.00)
Bmi at enrolment in care	<18	23 (7.12)
	18-24.9	173 (53.56)
	25-29.9	85 (24.64)
	≥30	42 (12.17)
Adherence level	<95	232 (67.25)
	>95	113 (32.75)
Art regime switch	No switch	211 (75.09)

In the multivariate GEE regression, which included all patients and adjusted for ART duration, occurrence of TB was associated with decrease in age (OR = 0.98, confidence interval 95% C. I. [0.98-0.99], *P* value 0.001), being female, *with females as the reference gender* (OR = 0.83, 95% C. I. [0.72-0.95], *P* value 0.007), weight gain {though marginal difference) (OR = 1.01, 95% C. I. [1.00-1.01], *P* value 0.0001), type of ART regimen (*zidovudine was*

reference ART, OR = 0.87, 95% C. I. [0.81-0.92] *P* value 0.0001), low level of adherence (OR = 1.25, 95% C. I. [1.10-1.42], *P* value 0.001), change of ART regimen (OR = 2.3, 95% C. I. [1.91-2.79], *P* value 0.0001) and treatment failure (OR = 1.51, 95% C. I. [1.27-1.80], *P* value 0.0001). Odds of TB occurrence was also associated with CD4 increment at 6 and 10 years (OR = 1.0, 95% C. I. [0.99-1.00], *P* value 0.0001 and 0.99, 95% C. I. [0.99-1.01], *P* value 0.016) [Table 4].

Compared to patients with CD4 cell counts below 200 cells/μL (in WHO clinical stages I and II), those with CD4 count between 200 and 350 cells/μL had a reduced risk of having TB (OR = 0.78, 95% C. I. [0.56-89] *P* = 0.006).

Those who had been on ART for 13-59 months and those on therapy for more than 60 months had a higher chance of developing TB compared with those on therapy for 12 months or less (OR = 2.39, 95% C. I. [1.23-4.66] and 4.97, 95% C. I. [2.35-6.53]; *P* = 0.000). Longer travel distance from hospital was not significantly associated with increased risk of developing TB (OR= 1.00, 95% C. I. [0.98-1.01] *P* = 0.143) [Table 3].

On 10-year trend analysis, those with TB/HIV co-infection had lower CD4 profile compared to those with HIV alone [Figure 1].

While 76% of all patients retained sensitivity to ART drugs for up to 107 months (8.9 years), 57.9% of those with TB/HIV co-infection remained sensitive up to 120 months, whereas 66.8% of those with only HIV infection remained so, up to 120 months. Kaplan-Meier crude survival curves show that these differences are statistically significant [log rank 0.001] [Figure 2].

Discussion

HIV is a major driving force for the persisting TB epidemic in sub-Saharan Africa. Hence there is a strong correlation between increment in the prevalence of HIV and the incidence of TB. In this retrospective cohort study on HIV positive patients, the incidence of TB was 17.43 per (1,000) person-year, with TB occurring in 13.62% of our cohort during the 10-year follow-up period. Like other cohorts in Nigeria and sub-Saharan Africa, the patients were mostly females, largely living far away from the point of care and had been in care for more than 5 years.[16-18]

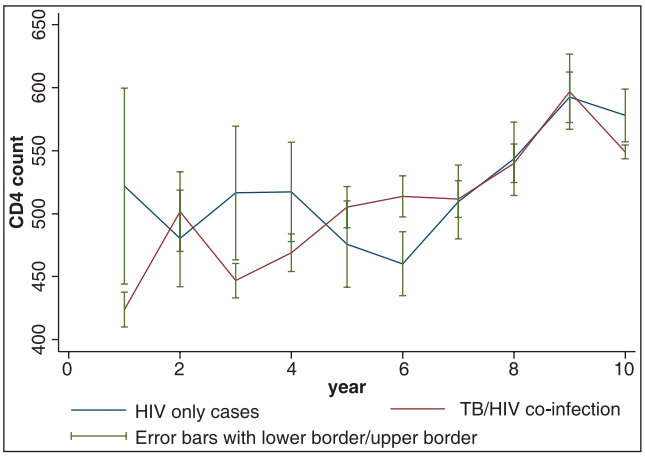

Figure 1: 10 years CD4 count trend disaggregated by presence of TB infection

The incidence of TB (of 17.43 per (1,000) PYR) in our study was higher than 8.7 cases/1,000 PYR reported from Jos, Nigeria.[19] The Jos study evaluated TB after the first year

Table 3: Differences in demographic clinical and immunological characteristics between HIV patients with and without TB infection

Characteristics	TB/HIV (%)	HIV only (%)	*P*-value
AGE*			
18-29	3 (15)	17 (85)	0.588
30-39	17 (13.18)	112 (86.82)	
40-49	17 (11.89)	126 (88.11)	
50 and above	10 (13.62)	43 (86.38)	
Sex*			
Male	19 (13.87)	121 (86.43)	0.557
Female	28 (13.66)	177 (86.34)	
Marital status			
Single	2 (19.44)	29 (80.56)	0.396
Married	28 (12.12)	203 (87.88)	
Divorced	5 (20.83)	19 (79.17)	
Widowed	7 (12.96)	47 (87.04)	
Employment status			
Employed	30 (13.86)	187 (86.18)	0.512
Not employed	17 (13.28)	111(86.72)	
Distance from treatent center			
<30 kms	21 (15.33)	116 (84.67)	0.276
>30 kms	26 (12.50)	182 (87.50)	
Who clinical stage			
I	25 (12.44)	176 (87.56)	0.839
II	10 (15.15)	56 (84.85)	
III	11 (15.71)	59 (84.29)	
IV	1 (12.50)	7 (87.50)	
Nadir cd4 count			
<200	11 (10.38)	95 (89.62)	0.509
200-350	15 (14.85)	86 (85.15)	
>350	21(15.22)	117 (84.78)	
First line art regimen			
ZDV/3TC/NVP or EFV	29 (11.55)	222 (88.45)	0.156
D4T /3TC/NVP or EFV	3 (13.64)	19 (86.36)	
TDF/3TC/NVP or EFV	15 (22.06)	53 (77.94)	
ABC/3TC/NVP or EFV	0 (0.00)	4 (100)	
Regimen change			
Change made	43(18.22)	129 (81.78)	0.025
No change	4 (7.02)	53 (92.98)	
Regimen switch			
Switch made	6 (8.57)	64 (91.43)	0.033
No switch	39 (18.48)	172 (81.52)	
Duration on art			
<12 months	3 (27.27)	8 (72.73)	0.173
13-59 months	4 (21.05)	15 (78.95)	
>60 months	40 (12.70)	275 (87.30)	
‡CD4 count diff at 5 years	19.47 (70.53)*	138.81 (17.01)*	0.0201†
‡CD4 count diff at 6 years	3.87 (62.35)*	147.33 (17.69)*	0.005†
‡CD4 count diff at 10 years	121.70 (45.36)*	182.64 (16.47)*	0.1784†

*standard error † t-test: ‡CD4 difference: Denotes difference between CD4 at stated year and baseline CD4 count

Table 4: Generalized estimation equation analyses of characteristics associated with risk of developing tuberculosis among adult Nigerian patients on an ART program

Presence of TB	ODDS ratio	Standard error	*P* > z	95% CI	
				Lower limit	Upper limit
Duration of treatment (in months)	1.00	0.00	0.000	1.00	1.01
Age in years	0.98	0.00	0.000	0.98	0.99
Sex (Reference: Male)	0.83	0.06	0.007	0.72	0.95
Marital status (Reference: Single)	1.03	0.04	0.454	0.96	1.11
Occupation (Reference: Unemployed)	1.12	0.07	0.081	0.99	1.27
Weight (in kg)	1.01	0.00	0.000	1.00	1.01
Initial CD4 count (cells/μL)	1.00	0.00	0.844	.99	1.00
Type of regimen (Reference: Regimen AZT-based)	0.87	0.03	0.000	.81	0.92
Adherence level (Reference: >95% adherence)	1.25	0.08	0.001	1.10	1.42
Regimen change (Reference: Regimen change occurred)	2.30	0.22	0.000	1.91	2.79
Failure (Reference: treatment failure occurred)	1.51	0.13	0.000	1.27	1.80
CD4 count difference at 5 yrs	1.00	0.00	0.528	0.99	1.00
CD4 count difference at 6 yrs	1.00	0.00	0.000	0.99	1.00
CD4 count difference at 7 yrs	0.99	0.00	0.729	0.99	1.00
CD4 count difference at 10 yrs	0.99	0.00	0.016	0.99	1.01
Distance from hospital (Reference: <30 km)	1.09	0.069	0.143	.96	1.24
Time on treatment category					
Reference: 13-59 months	2.43	0.518	0.000	1.60	3.69
>60 months	5.05	1.76	0.000	2.54	10.03

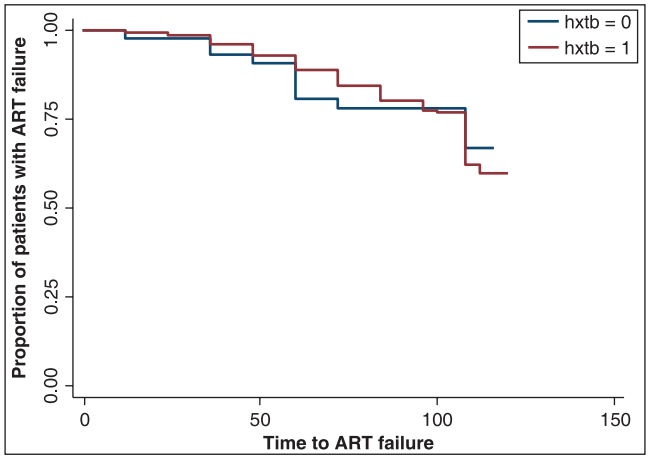

Figure 2: Kaplan-Meier curves of time to ART failure stratified by presence of TB in a cohort of patients on ART

of ART and found the incidence of TB is highest in the first year of ART. Our finding is also higher than that of studies in Ethiopia (0.33/1,000 PYR), Israel (6.9 cases/1,000 PYR), Denmark (8.2 cases/1,000 PYR) and incidence from combined cohorts of patients in Europe and North America (4.7 cases/1,000 PYR).[20-24] Such findings are not unexpected, considering Nigeria has a high burden of HIV and TB compared to the aforementioned countries. Furthermore, interventions aimed at curbing HIV and TB in these countries had been more successful than in Nigeria. The incidence density of TB disease among persons infected with HIV in this study was however, lower than 54 /1,000 PYR reported from 8 Médecins Sans Frontières (MSF) HIV programs in SSA.[24] Perhaps it may be due to the differences in TB index of suspicion and rigor of screening between the two programs. Overall there is a consistent pattern between the occurrence of muted burden of TB in persons living with HIV and those countries with effective intensive TB case finding and early treatment interventions.

TB can emerge in the early stages of HIV infection and indeed in all stages of the disease. While immunocompetent persons may have a relatively reduced risk of TB infection, the risk remarkably increases after HIV infection. In a South African cohort of gold miners, the risk of TB increased one year following HIV infection.[25] Whereas the risk of TB decreases in patients on potent ART, it immediately increases in the event of the failure of ART medication. Overall, it is pertinent to note that while ART allows immune reconstitution in a person with HIV, the risk of TB in them is still more than that of the general population.[26-28]

Our study found those with CD4 count of 200-350 cells/μL had a lower occurrence of TB compared to those with count < 200 cells/μL. Similarly, in a meta-analysis to assess the protective effect of ART on the emergence of TB, a 65% reduction in the incidence of TB was seen across all CD4 cell counts. More so, reduction of 57% was shown in patients with CD4 counts of > 350 cells/μL, but above all the highest influence was seen in persons with CD4 counts of <200 cells/μL, in whom a decline in TB incidence of 84% was seen.[29]

There was slow but sustained increase in CD4 count over the study period in our cohort. In spite of the overall CD4 count increment in the cohort, there was a statistically significant higher increment in those without active TB disease [Figure 1]. Other studies have also suggested that those with TB have suboptimal immune recovery.[30]

The baseline mechanism leading to poor immune response among patients with TB is not fully understood. However, it is thought to be due to a complex immune cascade. It is seen

that excessive T-cell destruction persist in spite of virologic suppression. Perhaps TB/HIV co-infection might reduce T helper cell restoration through intensifi cation of the HIVinduced immune activation with resultant extensive apoptosis of both HIV-infected and uninfected lymphocytes. Another reason might be due to reduced adherence to ART during TB" treatment because of high pill burden and side effects.[31]

It is worthwhile to assess risk factors for developing TB in persons with HIV infection; however, a comprehensive strategy focusing on major risk factors of TB is essential to achieve the 'Stop TB' partnership targets.[32,33]

While there are several studies in SSA assessing the risk of tuberculosis in the community, only few had looked at it among persons with HIV.[34-37]

In our study, the likelihood of TB occurrence was associated with CD4 change at 6 and 10 years. Likewise, the need for change in ART and switch from a failing regimen to a new viable ART option are associated with developing TB. In our cohort, immunological failure starts setting in mostly around the 5th-6th year on ART, thus the observed association may be due to immunological failure. Conversely, a change in regimen may have been necessitated by intolerable side effects or patients' preference, both of which can affect adherence and ultimately compromise ART potency.

Poor ART treatment adherence is associated with high probability of both virologic and immunological failure. It is known that TB has a higher likelihood of occurring with decline in immunological status.[16] This study found poor treatment adherence to be a risk factor for active TB.

This analysis found a relationship between risk of occurrence of TB and age. While no age is exempt from the risk of acquiring TB, people of younger age are often more outgoing and thus more likely to have contact with a person with TB. Older persons may perhaps be more willing to adhere to ART medications, and thus achieve faster immune stability. Nevertheless, older persons might have a premature immune aging.[38] In line with this, higher incidence of TB was seen in a cohort of HIV positive patients above 50 years of age in USA and Europe.[39]

The finding of our study of an association between female gender with a lower risk of developing TB/HIV co-infection is consistent with other studies that have suggested that men have a higher risk of developing TB at all immunological levels, and during ART treatment.[35,36,40] This may be due to attitudinal gender differences in adherence to ART or innate genetic variability in response to ART.

In this study, weight gain was found to be a risk factor for manifesting TB. This may be explained by the renewed ability of the immune system to mount a resistance against the presence of pathogenic TB, which is described as immune reconstitution syndrome (IRIS). Weight gain while on ART therapy correlates with improvement in immunologic status.[41,42] TB may be masked on account of weakened cellular immunity, and thus with improvement in immunity some patients may manifest with TB as a form of immune reconstitution syndrome.[43]

In our cohort, ART options remained potent for a fairly long duration among all patients. In all, 76% of all studied patients remained with a viable first line ART for 108 months (9 years). However, occurrence of TB was associated with earlier time to treatment failure, with a statistically significant difference in time to ART failure between the two groups [Figure 2]. *In vitro* studies had shown that tuberculosis facilitates the capability of HIV to replicate by enhancing the survival of CD4 T lymphocytes and macrophages harboring latent HIV.[44] Furthermore, in patients with HIV, the occurrence of TB can also lessen CD4 lymphocyte count.[45] The emergence of tuberculosis in persons with HIV accelerates the intense release of pro-inflammatory cytokines, which activate lymphocyte and macrophages.[46] This manifests clinically as treatment failure. Being a signpost for deteriorating immunological status, the emergence of TB often predates manifestation of treatment failure.[46]

We have tried to analyze data from a programmatic cohort, as opposed to a "classical cohort" that has regular periods of follow-up. This challenge was addressed by using GEE analysis, which takes this variation into cognizance. The accuracy of this study was limited by the use of CD4 count alone to define failure. This had become necessary because viral load was available only to patients fulfilling some set of eligibility criteria. Perhaps treatment failure would have been earlier detected if viral load were routinely used as monitoring tool for all patients on treatment. Furthermore, we took a pragmatic decision to do retrospective study, since the intent for the study was taken long after the treatment program had commenced.

Conclusion

The finding of high incidence of TB in this HIV cohort and its deleterious effect on ART treatment outcome alludes to the need for early continued TB screening among all HIV patients. This should be backed up with intensified screening among high risk groups. Furthermore, HIV and TB services and programs should be integrated not only to create synergy between the programs, but also to improve efficiency of the services delivered.

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References

1. World Health Organization: Global Tuberculosis Report 2014. [homepage on the Internet]. Geneva, Switzerland: WHO; 2014. Available from: http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf?ua=1 [Last accessed on 2015 Jan 27].
2. Meya DB, McAdam KP. The TB pandemic: An old problem seeking new solutions. J Intern Med 2007;261:309-29.
3. Girardi E, Raviglione MC, Antonucci G, Godfrey-Faussett P, Ippolito G. Impact of the HIV epidemic on the spread of other diseases: The case of tuberculosis. AIDS 2000;14: S47-56.

4. Sutherland I. Recent studies in the epidemiology of tuberculosis, based on the risk of being infected with tubercle bacilli. Adv Tuberc Res 1976;19:1-63.
5. Vynnycky E, Fine PE. The natural history of tuberculosis: The implications of age-dependent risks of disease and the role of re-infection. Epidemiol Infect 1997;119:183-201.
6. World Health Organization: Country profile: Nigeria. Tuberculosis Profile. [homepage on the Internet]. Geneva, Switzerland: WHO; 2014. Cited 21st February, 2015. https://extranet.who.int/sree/Reports?op=Replet&name=/WHO_HQ_Reports/G2/PROD/EXT/TBCountryProfile&ISO2=NG&outtype=PDF.
7. World Health Organization. Global tuberculosis control: Surveillance, planning, financing, WHO report 2013. [homepage on the Internet]. Geneva: World Health Organization; 2013. Available from: http://www.who.int/tb/publications /global_report/gtbr13_annex_2_country_profiles.pdf [Last accessed on 2014 May 20].
8. Federal Ministry of Health. National HIV/Syphillissero-prevalence sentinel survey among pregnant women attending antenatal clinics (2010). [homepage on the Internet]. Federal Ministry of Health, Abuja. Nigeria. Available from: http://www.nigeria-aids.org/documents/2010_National%20HIV%20Sero %20Prevalence%20Sentinel%20Survey.pdf [Last accessed on 2015 Jan 27].
9. Habib AG, Keshinro IB, Gebi UI, Olatunde BO, Onyemelukwe GC, Kangave D. Clinical presentation of HIV-infection in northern Nigeria and its relationship to CD4 + T-cell counts. Niger Med Pract 1998;35:3-8.
10. Sester M, Giehl C, McNerney R, Kampmann B, Walzl G, Cuchí P, *et al*. European Network for global cooperation in the field of AIDS and TB (EUCO-Net). Challenges and perspectives for improved management of HIV/Mycobacterium tuberculosis co-infection. Eur Respir J 2010;36:1242-7.
11. Getahon H, Gunneberg C, Granich R, Nunn P. HIV infection-associated tuberculosis: The epidemiology and the response. Clin Infect Dis 2010;50:S201-7.
12. Cain KP, McCarthy KD, Heilig CM, Monkongdee P, Tasaneeyapan T, Kanara N, *et al*. An algorithm for tuberculosis screening and diagnosis in people with HIV. N Engl J Med 2010;362:707-16.
13. Awoyemi OB, Ige OM, Onadeko BO. Prevalence of active pulmonary tuberculosis in human immunodeficiency virus seropositive adult patients in University College Hospital, Ibadan, Nigeria. Afr J Med Med Sci 2002;31:329-32.
14. Salami AK, Katibi IA. Human immunodeficiency virus associated tuberculosis: Pattern and trend in the University of Ilorin Teaching Hospital. Afr J Med Med Sci 2006;35:457-60.
15. Iliyasu Z, Babashani M. Prevalence and predictors of tuberculosis coinfection among HIV-seropositive patients attending the Aminu Kano Teaching Hospital, Northern Nigeria. J Epidemiol 2009;19:81-7.
16. Charurat M, Oyegunle M, Benjamin R, Habib A, Eze E, Ele P, *et al*. Patient retention and adherence to antiretrovirals in a large antiretroviral therapy program in Nigeria: A longitudinal analysis for risk factors. PLoS One 2010;5:e10584.
17. Geng EH, Glidden DV, Bwana MB, Musinguzi N, Emenyonu N, Muyindike W, *et al*. Retention in care and connection to care among HIV-infected patients on antiretroviral therapy in Africa: Estimation via a sampling-based approach. PLoS One 2011;6:e21797.
18. Auld AF, Ekra KA, Shiraishi RW, Tuho MZ, Kouakou JS, Mohamed F, *et al*. Temporal trends in treatment outcomes for HIV-1 and HIV-2-infected adults enrolled in Coˆte d'Ivoire's national antiretroviral therapy program. PLoS One 2014;9:e98183.
19. Akanbi MO, Achenbach CJ, Feinglass J, Taiwo B, Onu A, Pho MT, *et al*. Tuberculosis after one year of combination antiretroviral therapy in Nigeria: A retrospective cohort study. AIDS Res Hum Retroviruses 2013;29:931-7.
20. Mor Z, Lidji M, Cedar N, Grotto I, Chemtob D. Tuberculosis incidence in HIV/AIDS patients in Israel, 1983-2010. PLoS One 2013;8:e79691.
21. Girardi E, Sabin CA, d'Arminio Monforte A, Hogg B, Phillips AN, Gill MJ, *et al*. Antiretroviral Therapy Cohort Collaboration. Incidence of Tuberculosis among HIV-infected patients receiving highly active antiretroviral therapy in Europe and North America. Clin Infect Dis 2005;41:1772-82.
22. Kassa A, Teka A, Shewaamare A, Jerene D. Incidence of tuberculosis and early mortality in a large cohort of HIV infected patients receiving antiretroviral therapy in a tertiary hospital in Addis Ababa, Ethiopia. Trans R Soc Trop Med Hyg 2012;106:363-70.
23. Taarnhoj GA, Engsig FB, Ravn P, Johansen IS, Larsen CS, Røge B, *et al*. Incidence, risk factors and mortality of tuberculosis in Danish HIV patients 1995-2007. BMC Pulm Med 2011;11:26.
24. Nicholas S, Sabapathy K, Ferreyra C, Varaine F, Pujades-Rodríguez M. AIDS Working Group of Médecins Sans Frontières. Incidence of tuberculosis in HIV-infected patients before and after starting combined antiretroviral therapy in 8 sub-Saharan African HIV programs. J Acquir Immune Defic Syndr 2011;57:311-8.
25. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. J Infect Dis 2005;191:150-8.
26. Moore D, Liechty C, Ekwaru P, Were W, Mwima G, Solberg P, *et al*. Prevalence, incidence and mortality associated with tuberculosis in HIV-infected patients initiating antiretroviral therapy in rural Uganda. AIDS 2007;21:713-9.
27. Van Rie A, Westreich D, Sanne I. Tuberculosis in patients receiving antiretroviral treatment: Incidence, risk factors, and prevention strategies. J Acquir Immune Defic Syndr 2011;56:349-55.
28. Gupta A, Wood R, Kaplan R, Bekker LG, Lawn SD. Tuberculosis incidence rates during 8 years of follow-up of an antiretroviral treatment cohort in South Africa: Comparison with rates in the community. PLoS One 2012;7:e34156.
29. Suthar AB, Lawn SD, del Amo J, Getahun H, Dye C, Sculier D, *et al*. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: A systematic review and meta-analysis. PLoS Med 2012;9:e1001270.
30. Assefa A, Gelaw B, Getnet G, Yitayew G. The effect of incident tuberculosis on immunological response of HIV patients on highly active anti-retroviral therapy at the university of Gondar hospital, northwest Ethiopia: A retrospective follow-up study. BMC Infect Dis 2014;14:468.
31. Hermans SM, Kiragga AN, Schaefer P, Kambugu A, Hoepelman AI, Manabe YC. Incident tuberculosis during antiretroviral therapy contributes to suboptimal immune reconstitution in a large urban HIV clinic in sub-Saharan Africa. PLoS One 2010;5:e10527.
32. Lonnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: The role of risk factors and social determinants. Soc Sci Med 2009;68:2240-6.
33. Dye C, Maher D, Weil D, Espinal M, Raviglione M. Targets for global tuberculosis control. Int J Tuberc Lung Dis 2006;10:460-2.
34. Gustafson P, Gomes VF, Vieira CS, Rabna P, Seng R, Johansson P, *et al*. Tuberculosis in Bissau: Incidence and risk factors in an urban community in sub-Saharan Africa. Int J Epidemiol 2004;33:163-72.
35. Lienhardt C, Fielding K, Sillah JS, Bah B, Gustafson P, Warndorff D, *et al*. Investigation of the risk factors for tuberculosis: A case-control study in three countries in West Africa. Int J Epidemiol 2005;34:914-23.
36. Hill PC, Jackson-Sillah D, Donkor SA, Otu J, Adegbola RA, Lienhardt C. Risk factors for pulmonary tuberculosis: A clinic-based case control study in The Gambia. BMC Public Health 2006;6:156.
37. Grant AD, Bansi L, Ainsworth J, Anderson J, Delpech V, Easterbrook P, *et al*. United Kingdom Collaborative HIV Cohort Study Group. Tuberculosis among people with HIV infection in the United Kingdom: Opportunities for prevention? AIDS 2009;23:2507-15.

38. Martin J, Volberding P. HIV and premature aging: A field still in its infancy. Ann Intern Med 2010;153:477-9.
39. del Amo J, Moreno S, Bucher HC, Furrer H, Logan R, Sterne J, *et al.* HIV-CAUSAL Collaboration. Impact of antiretroviral therapy on tuberculosis incidence among HIV-positive patients in high-income countries. Clin Infect Dis 2012;54:1364-72.
40. Lienhardt C, Fielding K, Sillah J, Tunkara A, Donkor S, Manneh K, *et al*. Risk factors for tuberculosis infection in sub-Saharan Africa: A contact study in The Gambia. Am J Respir Crit Care Med 2003;168:448-55.
41. Phillips, AN, Pillay D, Miners AH, Bennett DE, Gilks CF, Lundgren, JD. Outcomes from monitoring of patients on antiretroviral therapy in resource-limited settings with viral load, CD4 cell count, or clinical observation alone: A computer simulation model. Lancet 2008;371:1443-51.
42. Okechukwu AA, Okechukwu OI. Clinical correlate of tuberculosis in HIV co-infected children at the University of Abuja Teaching Hospital, Gwagwalada, Nigeria. Niger J Clin Pract 2011;14:206-11.
43. Meintjes G, Lawn SD, Scano F, Maartens G, French MA, Worodria W, *et al*. International Network for the Study of HIV-associated IRIS. Tuberculosis-associated immune reconstitution inflammatory syndrome: Case definitions for use in resource-limited settings. Lancet Infect Dis 2008;8:516-23.
44. Del Amo J, Malin AS, Pozniak A, De Cock KM. Does tuberculosis accelerate the progression of HIV disease? Evidence from basic science and epidemiology. AIDS 1999;13:1151-8.
45. Canaday DH, Wu M, Lu S, Aung H, Peters P, Baseke J, *et al*. Induction of HIV type 1 expression correlates with T cell responsiveness to mycobacteria in patients coinfected with HIV type 1 and Mycobacterium tuberculosis. AIDS Res Hum Retroviruses 2009;25:213-6.
46. Badri M, Ehrlich R, Wood R, Pulerwitz T, Maartens G. Association between tuberculosis and HIV disease progression in a high tuberculosis prevalence area. Int J Tuberc Lung Dis 2001;5:225-32.

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