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Latent Tuberculosis Infection and Isoniazid Preventive Therapy among Human Immunodeficiency Virus positive adults in Southern Nigeria

Bamidele David Ajayi[1], John Omotola Ogunkoya[2], Folake Olubunmi Ajayi[3].

Abstract

Aim/objectives: It was aimed to assess the prevalence of latent TB among HIV+ patients, evaluate the coverage of isoniazid preventive therapy (IPT), the continuous risk of latent tuberculosis infection, and factors associated with the presence of latent Tb in HIV+ patients.

Methods: This is an analytical cross-sectional study of HIV+ patients attending the HIV clinic or admitted not previously treated for TB and did not have clinical and laboratory evidence of active TB and matched HIV-negative population attending our GOC. Data collected with a pre-tested investigator administered questionnaire included the age, sex, height and weight, medical and drug history, and relevant physical examination findings such as body temperature and respiratory rate. Active TB was excluded by history, sputum AFB Z-N staining, or GeneXpert test and chest radiography. Whole blood samples were collected from participants for QuantiFERON TB Gold Plus for quantification of Interferon Gamma Release assay (IGRA) in order to diagnose or exclude latent TB. Data were analyzed using IBM SPSS version 25.0 software at a level of significance of $p < 0.05$. Association between means and qualitative variables was analyzed with student-t-test and Chi-square test

Results: The mean ages of the HIV+ and control groups were 42.69 ± 9.91 and 41.29 ± 9.20 years respectively with no significant statistical difference. 76(95.0%) of HIV+ patients and 74(92.5%) controls had no symptoms of TB and chronic lung disease. 18(22.5%) HIV+ patients and 2(2.5%) controls were exposed to persons with chronic cough (p=<0.001). The prevalence of latent TB among HIV+ patients was 22.50% and 10.0% among controls (p-value=0.001). 8(44.4%) out of 18 with latent TB had prior use of IPT compared with 24 (38.7%) out of 62 without latent TB (p-value =0.67). CD4 count was a significant factor associated with the presence of latent TB among HIV+ persons (p-0.03). Similarly, there was a significant association between viral load and positive IGRA (p<0.001).

Conclusion: Latent TB infection remains significantly higher among HIV+ than HIV-negative patients which may account for the higher incidence of active disease amongst them. Isoniazid preventive therapy coverage was poor amongst HIV+ patients in this study.

Keywords: Human Immunodeficiency Virus, Interferon Gamma Release Assay, Isoniazid Preventive Therapy, Latent Tuberculosis; QuantiFERON TB Gold.

***Corresponding author**
John Omotola Ogunkoya
ORCID-NO: https://orcid.org/0000-0002-8403-9679
Email: ogunkoyaj@babcock.edu.ng;

[1]Dermatology and Infectious Disease Unit, Department of Internal Medicine, University of Benin Teaching Hospital Benin City, Nigeria.
[2]Department of Medicine, Benjamin Carson Senior College of Health and Medical Sciences, Babcock University/ Babcock University Teaching hospital, Ilishan Remo, Nigeria
[3]Nigeria Field Epidemiology and Laboratory Training Program, Federal Capital Territory, Abuja, Nigeria.

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Infection tuberculose latente et thérapie préventive à l'isoniazide parmi les adultes positifs au virus de l'immunodéficience humaine dans le sud du Nigéria

Bamidele David Ajayi[1], John Omotola Ogunkoya[2], Folake Olubunmi Ajayi[3].

Resume

Contexte de l'étude : L'étude visait à évaluer la prévalence de la tuberculose latente chez les patients séropositifs, à évaluer la couverture du traitement préventif à l'isoniazide (TPI), le risque continu d'infection tuberculeuse latente et les facteurs associés à la présence de tuberculose latente chez les patients séropositifs.

Méthode de l'étude : Il s'agit d'une étude analytique transversale de patients séropositifs fréquentant la clinique du VIH ou admis sans traitement antérieur pour la tuberculose et n'ayant pas de preuves cliniques et de laboratoire de tuberculose active et de population séronégative correspondante fréquentant notre GOC. Les données recueillies à l'aide d'un questionnaire administré par l'investigateur pré-test comprenaient l'âge, le sexe, la taille et le poids, les antécédents médicaux et médicamenteux, ainsi que les résultats d'examen physique pertinents tels que la température corporelle et la fréquence respiratoire. La tuberculose active a été exclue par les antécédents, la coloration des BAAR ZN des crachats ou le test GeneXpert et la radiographie pulmonaire. Des échantillons de sang total ont été prélevés sur les participants au test QuantiFERON TB Gold Plus pour la quantification du test de libération d'interféron gamma (TLIG) afin de diagnostiquer ou d'exclure une tuberculose latente. Les données ont été analysées à l'aide du logiciel IBM SPSS version 25.0 à un niveau de signification de $p < 0,05$. L'association entre les moyennes et les variables qualitatives a été analysée avec le test t d'apprenant et le test du chi carré

Résultat de l'étude : Les âges moyens des groupes VIH+ et témoin étaient respectivement de 42,69 ± 9,91 et 41,29 ± 9,20 ans sans différence statistiquement significative. 76 (95,0 %) des patients séropositifs et 74 (92,5 %) des témoins ne présentaient aucun symptôme de tuberculose et de maladie pulmonaire chronique. 18 (22,5 %) patients séropositifs et 2 (2,5 %) témoins ont été exposés à des personnes souffrant de toux chronique (p=<0,001). La prévalence de la TB latente chez les patients séropositifs était de 22,50 % et de 10,0 % chez les témoins (valeur de p = 0,001). 8 (44,4 %) sur 18 atteints de TB latente avaient déjà utilisé l'IPT contre 24 (38,7 %) sur 62 sans TB latente (valeur p = 0,67). Le nombre de Cd4 était un facteur significatif associé à la présence de TB latente chez les personnes séropositives (p-0,03). De même, il y avait une association significative entre la charge virale et un TLIG positif (p<0,001).

Conclusion : L'infection tuberculeuse latente reste significativement plus élevée chez les patients séropositifs que chez les patients séronégatifs, ce qui peut expliquer l'incidence plus élevée de la maladie active parmi eux. La couverture du traitement préventif à l'isoniazide était faible chez les patients séropositifs de cette étude.

Mots-clés : Virus de l'immunodéficience humaine, test de libération d'interféron gamma, traitement préventif à l'isoniazide, tuberculose latente, QuantiFeron TB Gold

***Corresponding author**
John Omotola Ogunkoya
ORCID-NO: https://orcid.org/0000-0002-8403-9679
Email: ogunkoyaj@babcock.edu.ng;

[1]Dermatology and Infectious Disease Unit, Department of Internal Medicine, University of Benin Teaching Hospital Benin City, Nigeria.
[2]Department of Medicine, Benjamin Carson Senior College of Health and Medical Sciences, Babcock University/ Babcock University Teaching hospital, Ilishan Remo, Nigeria
[3]Nigeria Field Epidemiology and Laboratory Training Program, Federal Capital Territory, Abuja, Nigeria.

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INTRODUCTION

World Health Organization (WHO) defines latent TB as a state of persistent immune response to stimulation by *M. tuberculosis* antigens without evidence of clinically manifested active TB [1]. It's an asymptomatic *M. tuberculosis* infection without clinical, bacteriological, or radiological evidence of active disease [2]. People with latent TB are not sick and cannot spread TB to others [3]. Overall, without treatment, about 5-15% of infected persons will develop TB sometime in their lifetime, and about half of those developing TB will do so within the 1st 2 years of infection. Treatment confers protection and cures on people with latent TB hence diagnosis is important [4].

Globally, about 1.7 billion of the world's population is latently infected with TB and an estimated 10 million of this population had active TB disease in 2017 whilst an estimated 1.2 million were co-infected with HIV [1]. Individuals with latent TB infection represent a vast pool of reservoirs of infection, many of whom will not only progress to active disease but will also serve as the major barrier to global control. Currently, six countries accounted for 60% of cases of active disease including India, Indonesia, China, Nigeria Pakistan, and South Africa [1]. Incidentally, these countries with a high burden of active disease also harbor a large pool of cases of latent tuberculous infections [4,5]. Presently the annual rate of infection ranges from 4.2% in SA and 1.7% in Vietnam to 0.03% in the USA.

A systematic review and meta-analysis study carried out among healthcare workers in the 22 high TB burden countries showed the pooled prevalence of 47% using TST, lowest in Brazil, 37%, and highest in South Africa at 64% [6]. A Nigerian study on the prevalence of TB infection amongst healthcare workers in Akwa-Ibom state showed a prevalence of 24.8% and 45.8% using IGRA and TST tests respectively [7]. It was also found that working in the laboratory, being orderly and work duration of over 10 years was contributory [7].

It has been estimated that one-third of patients infected with HIV are also infected with tuberculosis [8]. Characteristics of Latent Tuberculosis include positive TST or blood interferon-gamma release assay, normal chest x-ray, and negative sputum test, the person is not sick and therefore cannot spread infection but needs treatment to prevent TB disease. However, if exposed and infected by a person with multidrug-resistant TB or extensively resistant TB preventive treatment may not be an option [9]. Latent TB is usually diagnosed using Tuberculin Skin Test (TST) method or Interferon Gamma Release Assay (IGRA) method [9]. Most people that developed the tuberculous disease are initially latently infected but oftentimes diagnosis is not made at this time when treatment is less cumbersome since there are no symptoms. This is a result of the lack of a standard program geared toward routine screening tests in areas of high prevalence [10].

HIV-infected patient has a yearly rate of developing TB of 10-15% and once developed, fatality in HIV/TB co-infection approaches 100% if untreated and there are also higher chances of developing drug-resistant TB with its attendant treatment difficulty [11]. A recent study in Kano by Musa BM et al [12], revealed a 13.6% incidence of tuberculosis disease in the HIV population over a 10-year period despite HAART initiation. Individuals with latent tuberculosis infection represent a reservoir of infection, many of whom will progress to tuberculous disease, especially in the setting of HIV infection [5,6]. Most countries in the endemic area embraced global TB control policies which currently focused on the treatment of active disease, this approach alone without latent TB detection and treatment will not be sufficient to achieve the steep annual reductions in incidence necessary to reach the End TB strategic target of WHO towards TB elimination by 2050 [13].

WHO currently recommends isoniazid preventive therapy (IPT) as part of the 3 I's of TB/HIV collaborative services (Isoniazid preventive therapy, Intensified screening, and Infection control for TB) after symptomatic exclusion of active tuberculosis [13]. A practice with a current coverage among the target population of between 1% in Eswatini to 58% in South Africa [14]. This practice has been shown to allow for treatment far in excess of necessary and when considering the problems of additional pill burden, drug toxicity, and drug-drug interactions it would be wise to possess good evidence before embarking on such treatment. Several studies have shown the benefits of IPT mostly in the presence of a positive diagnosis of latent TB infection. However, in a high endemic area of burden, it has been shown that IPT confers short-term protection as observed in several studies [15.16]. The burden of latent tuberculosis in our HIV-infected population is not known thus the determination of the extent and importance of IPT intervention amongst our HIV-infected population cannot be quantified and objective

performance of IPT cannot be made, hence need to assess the level of disease burden to allow for improvement and or review of present practice.

This study aimed to improve the knowledge base and to provide information on the prevalence of latent TB among HIV+ patients, evaluate the coverage of isoniazid preventive therapy, the continuous risk of latent tuberculosis infection, and factors associated with the presence of latent Tb in HIV+ patients.

MATERIALS AND METHODS

Study setting

This study was conducted in the Infectious diseases HIV clinic, the medical wards, and the General Patient Clinic (GPC) of the University of Benin Teaching Hospital (UBTH), Benin City, Edo state Nigeria. The HIV clinic had about 5000 active patients on Highly Active Anti-Retroviral Therapy (HAART) as stated in the UBTH DATA. The facility is a federal government tertiary hospital located in Egor Local Government Area of Edo State. Benin city is the capital and largest city of Edo State and it is situated approximately 40km north of the Benin river and about 320km by road east of Lagos. A state in the south-south geo-political zone of Nigeria rich in rubber plantation and oil with several higher institutions huge trade and rich culture. UBTH serves as a referral center for health facilities in Edo, Delta, Ondo, Ekiti, Kogi, and Bayelsa states.

Study population

The study population was made up of 160 participants which included a study group-consisting of eighty (80) HIV-infected patients and a Control group –consisting of eighty (80) age and gender-matched HIV-negative patients.

Study duration/ study design

The study was conducted over a period of 10 months between February 2018 to November 31, 2018. This is an analytical cross-sectional study of HIV-infected patients attending the HIV clinic or admitted into the wards that have not been treated for TB in the past and who presently do not have clinical and laboratory evidence of active tuberculosis and similarly matched HIV-negative population attending our GPC.

Sampling technique and sample size estimation

A simple random sampling technique was used to select respondents for the HIV seropositive group. The approach was a random assignment. The table of random numbers was used to select 80 participants from the sample frame of 5,000 patients accessing care at the HIV clinic and in a few cases where the selected individual did not meet the inclusion criteria another individual on the list was selected from the table of random sampling numbers. While for HIV un-infected group, 80 participants were randomly recruited from the medical screening clinic. The minimum sample size of 74 for this study was calculated using the formula, SS/ [1 + {(SS - 1)/Pop}], for finite population size and was rounded up to 80 with adjustment for non-response or dropout.

Inclusion Criteria for Study Group: All HIV-infected patients enrolled for care at the hospital HIV clinic and medical wards who were 18 years and above [only adult patients].

Exclusion Criteria for Study Group: This included all patients with clinical, laboratory/imaging diagnosis of active TB, patients with previous or current TB treatment, patients who were less than 18 years of age, and patients with malignancies or on immunosuppressive therapy and diabetes.

Inclusion Criteria for Control Group: Patients who attended the General Patient clinic of UBTH were screened negative for HIV and were 18 years and above.

Exclusion Criteria for Control Group: Patients with positive HIV results or unknown HIV status, patients with clinical, Laboratory/ imaging diagnostic of active TB, patients with previous or current TB treatment, patients with malignancies or on immunosuppressive therapy and diabetes, and patients who were less than 18 years of age were excluded from the study

Data collection tools and methods

Quantitative data collection was done using a structured interviewer-administered questionnaire. The questionnaire was pre-tested using 10 HIV–infected patients and 10 HIV-negative patients attending HIV clinics and General Patient Clinics respectively in UBTH. This was to enhance the comprehensibility, validity, reliability, and sensitivity of the data.

The questionnaire comprised of the following sections;

Section A: Socio-demographic characteristics of all respondents.

Section B: This contained questions on clinical assessments. A detailed medical and drug history which included the history of predisposing factors with relevant physical examination such

as vital signs [temperature, respiratory]. Weight was measured using a bathroom weighing scale and a Height stadiometer was also used to measure the patient's height. BMI was calculated in weight/Kg^2. Laboratory tests such as Packed Cell Volume (PCV) and White Cell Count (WBC) were also done. Active tuberculosis was excluded by history, sputum Acid Fast Bacilli Ziehl-Neelsen (AFB Z-N) staining, or GeneXpert test and chest radiography.

Section C: **Interferon Gamma Release Assay Quantification.**

Whole blood samples were collected from participants for QuantiFERON TB Gold Plus (QFT-plus) testing using QFT-Plus test kits manufactured by Cellestis, Carnegie, Australia. The QFT-Plus assay uses one Millilitre [1mL] of whole blood in four tubes, grey cap containing no antigen, while the green tube is TB Antigen Tube 1 (TB1) and the yellow tube is TB Antigen Tube 2 (TB2). Both tubes contained peptide antigens from the MTB–complex associated antigens, Early Secreted Antigenic Target of 6KDA (ESAT-6), and Culture Filtrate Protein-10 (CFP-10). Whereas the TB1 tube contained peptides from ESAT-6 and CFP-10 that were designed to elicit Cell-Mediated Immune (CMI) responses from Cluster of Differentiation 4 (CD4+) T-helper lymphocytes, the TB2 tube contained an additional set of peptides that targeted to the induction of CMI responses from Cluster of Differentiation 8 (CD8+) cytotoxic T lymphocytes and a purple capped bottle which contained mitogen used to assess the performance of circulating lymphocytes. Samples were incubated at 37°C within 16hours of collection for 16-24 hours; they were then centrifuged, and the plasma was removed and harvested to perform the Enzyme-Linked Immunosorbent Assay (ELISA). The Interferon gamma values for TB-specific antigens were corrected by subtracting the values obtained for the respective negative controls; the test was considered positive for Interferon gamma levels that were above the cut-off test value (0.35 IU/mL). The laboratory work was carried out at the advanced laboratory of UBTH with the support of chemical pathologists. Interpretation of results was done using the manufacturer's software [17].

Data Analysis

Data obtained was entered into IBM SPSS version 25.0 software [SPSS Inc. Ill., Chicago, USA] for analysis. Categorical variables were presented using frequency tables, pie charts, and bar charts as appropriate while Quantitative variables were presented as means and standard deviation. The comparison of means between HIV-positive patients and controls was done using the student t-test while the associations between qualitative variables were tested using the Chi-square test. The strength of the relationship between continuous variables was determined using Spearman's rank correlation analysis. A multivariate logistic regression model was used to predict factors that were associated with latent TB adjusting for possible confounders. All statistical analyses were carried out at a level of significance of $p < 0.05$.

Ethical Consideration: Ethical clearance to conduct this study was sought and obtained from the University of Benin Teaching Hospital Research and Ethical Committee [ADM/E22/VOL.VII/14541]. Informed written and verbal consent was obtained from each respondent before conducting interviews. The confidentiality and privacy of the respondent were respected during the interview. In order to ensure confidentiality, respondents' serial and hospital numbers were used for identification. Respondents were informed of their right to decline participation or to withdraw from the study at any time they wished. Respondents were informed that there will be no penalties or loss of benefits for refusing to participate in the study or withdrawing from it. There was no risk of harm or injury to the participants during and after the conduct of the study.

RESULTS

Socio-demographic characteristics

Table 1 shows the socio-demographic characteristics of HIV-infected patients and controls. The mean age among the HIV group was 42.69 ± 9.91 years, while the mean age for non-HIV-infected persons was 41.29 ± 9.20 years. The majority, 28(35.0%) of the HIV group and 28(35.0%) of controls were within the age range of 31-40 years however no statistically significant difference was observed (p-value-0.11). This study also revealed the majority of HIV-infected patients 57(71.2%) and 54(67.5%) controls as females but no statistically significant difference was found among the gender between the two groups (p-value-0.28. Major occupation among the HIV-infected patients was trading 45(56.2%), while the result showed that the majority 38 (47.5%) of controls were civil servants, this difference in occupations was statistically significant (p-value <0.001). Forty-eight (60.0%) of HIV-infected patients and 46

(57.5%) controls were married this also showed statistically significant difference (p-value-0.003). A large proportion of 63(78.8%) of HIV-infected patients and 78(97.5%) of controls live in urban areas and the differences observed in the pattern of residential area was also statistically significant (p-value < 0.001). More than 54(67.5%) of controls than 37(46.2%) HIV-infected patients were Binis. There was a significant difference in the tribe between HIV-infected patients and controls (p value<0.001). The majority 42(52.5%) of HIV-infected patients had just secondary education while the majority of control 52(65.0%) had tertiary education and this was statistically significant (p value<0.001). There was also a statistically significant difference observed among the two groups in the number of persons living per room and average household size (p-value-0.04 and p value<0.001 respectively).

Medical history of the study population

Table 2 shows the medical history of HIV-positive patients and controls at UBTH Benin city. A large proportion of 76(95.0%) of HIV-infected patients and 74(92.5%) of controls had no medical history of cough. Same results were seen for fever, night sweat, weight loss, and chronic lung disease. More 18(22.5%) of HIV-infected patients than controls 2(2.5%) were exposed to persons with chronic cough and this was statistically significant (p=<0.001). Furthermore, 79(98.8%) of controls and 50(62.5%) of HIV-infected cases reported not having any past medical illness, few 17(21.2%) of the HIV-infected patients reported having fever as a past medical illness. There was a significant difference in past medical illness among HIV-infected patients and controls (p=<0.001).

Anthropometric and laboratory characteristics of the study population

Table 3 shows the physical measurements among HIV-infected patients and controls. HIV-infected patients recorded a lower mean ± SD weight (kg) of 70.61 ± 12.18kg when compared to controls of 74.36 ± 12.97kg. The mean ± SD of height (cm) among HIV-infected patients was 1.63 ± 0.08 cm, while that of controls was 1.68 ± 0.08cm. HIV-infected patients recorded a relatively higher Body Mass Index (BMI) than controls. The mean ± SD of PCV among HIV-infected patients was 35.13 ± 2.77, while that of controls was 37.61 ± 3.18.

Prevalence of latent tuberculosis in HIV-positive and controls

Figure 1 shows the prevalence of latent TB in HIV-infected patients and controls. The prevalence of latent TB among HIV-infected patients was found to be 18 (22.50%) while among controls was 8 (10.0%). The difference was found to be statistically different [p value-0.001].

Isoniazid Preventive Therapy usage among HIV-positive patients

Table 4 shows the prevalence of latent TB and prior use of IPT among HIV-positive patients. Eight (44.4%) patients out of 18(100%) with latent TB had prior use of IPT compared with 24 (38.7%) out of 62(100%) without latent TB while 3(16.7%) patients with latent TB were still on IPT compare with 4(6.45%) patients without. There was no statistically significant difference observed (p-value =0.67). Figure 2 shows the proportion of HIV-infected patients with latent TB and a history of isoniazid preventive treatment [IPT] usage. The majority of 8 (44.4%) had used IPT at one point or the other while 7 (38.9%) did not have a history of IPT usage. Only 3 (16.7%) were still on IPT.

Laboratory and anthropometric factors among HIV-infected patients with positive and negative IGRA

Table 5 shows that CD4 count was found to be a significant factor associated with the presence of latent TB among HIV-infected persons [p-0.03]. Similarly, a significant association was found between viral load and positive IGRA (p<0.001). This study also revealed a significant difference in the PCV of IGRA-positive and IGRA-negative HIV-infected patients [p-0.001].

Predictive factors for latent TB in HIV-positive population and controls (HIV-negative population)

Table 6 shows a multiple linear regression model to determine factors that predicted latent TB among HIV-negative patients. Factors that predicted latent TB among HIV-negative patients according to this study included weight, height, and body mass index [BMI]. However, when these factors were analyzed in Table 7 for HIV-positive patients none predicted latent TB.

DISCUSSION

The socio-demographic characteristics among respondents in this study revealed that the mean age of HIV-infected patients visiting

UBTH, Benin City was 42.69 ± 9.91 years, while that of the control population was 41.29 ± 9.20 years. These age means reflect the metropolitan nature of the city with most residents in their active young age group. Our results are similar to the findings from a study by Wen Chen Lin *et al (18),* on the prevalence of latent TB infection among persons with and without HIV infection in Taiwan which reported a mean age of 40.4 ± 12.6 years among HIV-infected patients, and 38.9 ± 8.4 years among the control populations. Our age range of 20-71 years was also similar to the age range of 20.1-71.3 years of the Taiwan study (18). Results from this study also revealed no significant difference in age between the case and control populations. The majority of the HIV-infected persons and the control group were females which is a reflection of the higher health-seeking habit seen among females than males. This is similar to results from Mitku AA *et al (19),* who reported more females (72.2%) than males (27.8%) in their study. The female proportion in this study was similar to that of a study by Kizza et al [11], who reported a proportion of 67.8% of females in where prevalence and risk factors for latent tuberculosis in the HIV population were studied respectively.

Forty-eight (60.0%) of HIV-infected patients and 46 (57.5%) controls were married. Awadalla et al (20), also reported the majority (44.0%) of married respondents. A large proportion of HIV-infected patients and controls lived in urban areas this is not unexpected as the study was carried out in a state capital city, a similar study from Ethiopia (21), also revealed majority of respondents lived in urban areas. The majority 42 (52.5%) of HIV-infected patients had just secondary education compared with 52 (65.0%) of controls who had tertiary education. This showed a statistically significant difference in educational status among the two groups ($p<0.001$). Melkamu et al (22), in their study also reported a significant difference in the educational status among the subjects studied in Ethiopia**.** The apparently healthy group was better educated than the HIV-infected group. This implies that education level has an effect on the prevalence of HIV infection. People who are better educated are likely to be more informed about measures necessary to guide against being infected and are also likely to make informed decisions.

There was no significant difference in the body mass index (BMI) status between the two groups. Mean of 26.51 versus 26.23. Even though both are within the overweight range, however, there is a significant statistical difference in weight between the two groups, the lower mean age in HIV infected group compared with HIV negative group was likely due to cytokine dysregulation and metabolic demand of highly active antiretroviral therapy [HAART]. This was demonstrated in the data from the Nutrition for Healthy Living cohort study where a significant proportion of the participants had weight loss despite being on HAART (23).

The prevalence of latent TB among the HIV-infected patients tested using the QFT-Gold Plus at UBTH was 22.5%, this is a reflection of the overall high tuberculosis endemicity of the country most especially in urban areas. The study prevalent rate is higher than 4.6% found by Brock et al (24), in Denmark using Quantiferon-TB Gold In-Tube test kits. However, much higher values of 50.6% were obtained by Karam et al (25), in Senegal using ELISPOT. Though, the Senegal result may be attributed to its high TB endemicity with a 2017 annual incidence rate of 122/per 100,000 populations (4).

This study showed that HIV-infected patients with high viral load are more likely to have latent tuberculosis than those with low viral load [p-0.021]. A similar study by Bunjun et al (26), reported high HIV viral replication as an independent risk factor for tuberculosis infection and progression. This study also revealed no significant relationship between prior IPT use and latent TB among HIV-infected patients [p-0.67, OR-1.23(0.47-3.24)]. This is in contrast to a similar prospective study by Golub et al (27), who reported that isoniazid preventive therapy significantly reduced tuberculosis risk among HIV-infected patients. Whether IPT provides long-term protection against tuberculosis in HIV-infected individuals has been questioned, as trials in Africa suggest that people with HIV are only protected from tuberculosis while receiving isoniazid and that the protection is diminished once the drug is stopped (28). In an individually randomized clinical trial in Cape Town (29), it was reported that there was a more gradual increase in tuberculosis rates after one year of cessation of IPT. Also, a recent study in South Africa by Houben et al (30), concluded that current preventive therapies, including isoniazid, are not sufficient to cure latent tuberculosis in most people with HIV, thus leading to high tuberculosis rates upon cessation of IPT. The fact that this study showed no relationship between IPT and the presence of latent TB may not be unconnected to the fact that the study was carried out in a TB high endemic area [Nigeria's TB

annual incidence rate in 2017 stated by WHO to be 219/100,000 population] where there is continuous exposure and the attendant high risk of reinfection

This study revealed the prevalence of latent TB in HIV-infected patients and matched controls. The majority of 72.50% of HIV-infected patients and 83.80% of controls tested negative for latent TB, while more than 22.50% of HIV-infected patients than controls 10.0% tested positive for latent TB. These results showed that the prevalence of latent TB is high in our environment but higher in the HIV-infected population because of poor handling of tuberculosis infection among this population due to defective immune systems. However, the overall rate is not unrelated to the high tuberculosis endemic situation of the country where there is high tuberculosis incidence rate with an ever-available large pool of active cases allowing for easy transmission A study by Wen-Chen Lin et al (18), reported high cases of latent TB 28.6% using QuantiFERON Gold In-Tube [QFT-GIT] among HIV-uninfected persons compare with 7% among HIV-infected. This is surprising because TB is an opportunistic infection, and it is expected to be common among people who have an already compromised immune system, which is the case of an HIV-infected person. However, this may not be unconnected with the fact that different generations of Quantiferon test kits were used while this study used the fourth generation of Quantiferon test kits which is more sensitive than the older version used in the previous study, also when the immune system is severely compromised response to immune stimulation may be higher suppressed.

The present study also showed that factors that predicted latent TB among HIV-negative patients included weight, height, and BMI while weight inversely predicted latent TB among HIV- positive patients. A study carried out by Kizza et al (11), reported ages >25 years and marital status to be predictive of latent TB among normal individuals. They further demonstrated that the risk of LTBI is higher among those who are employed and students in the general population. Melkamu et al (22), also reported BMI to be independently associated with latent TB among HIV-negative patients in their study. These are contrary to the factors identified to predict latent TB among HIV-positive patients viz, being an artisan, living in urban centers, history of contact with a person having a chronic cough, reducing CD4 count, and increasing viral load. Mitku AA et al (19), similarly reported a CD4 count of ≤200 cell/µl to predict latent TB among HIV-positive patients. However, when the predictive factors reported from either group were analyzed for the study population none of these factors predicted commonly for both groups, this showed that the various predictors were group dependent.

CONCLUSION

Latent tuberculosis infection remains significantly higher among HIV-positive patients than HIV-negative patients attending UBTH, 22.5% versus 10.0% which may readily account for the higher incidence of active disease amongst them. Weight was found to be an inverse predictor of latent Tb among HIV-positive patients. Isoniazid preventive therapy coverage was found to be poor amongst HIV-infected patients in this study.

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Authors consideration: BDA participated in the conception and design of the study, definition of intellectual content, literature search, data acquisition, data analysis, drafting, editing and review of the manuscript for sound intellectual content. JOO participated in the conception and design of the study, definition of intellectual content, literature search, data acquisition, data analysis, drafting, editing and review of the manuscript for sound intellectual content. FOA participated in the design of the study, definition of intellectual content, literature search, data acquisition, data analysis, drafting, editing and review of the manuscript for sound intellectual content. All the authors approved the final version of the manuscript. All authors also agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table 1: Socio-demographic Characteristics of the Study Population

Socio-demographic Characteristics	HIV positive n = 80	Controls n = 80	p-value
Age (years)			
=20	0 (0.0%)	1 (1.1%)	0.11
21-30	9 (11.2%)	10 (12.5%)	
31-40	28 (35.0%)	28 (35.0%)	
41-50	23 (28.8%)	22 (27.5%)	
51-60	17 (21.2%)	16 (20.0%)	
61-70	3 (3.8%)	2 (2.5%)	
>70	0 (0.0%)	1 (1.3%)	
Mean ± SD	**42.69 ± 9.91**	**41.29 ± 9.20**	
Sex			
Male	23 (28.8%)	26 (32.5%)	0.28
Female	57 (71.2%)	54 (67.5%)	
Occupation			
Trader	45 (56.2%)	15 (18.8%)	<0.001**
Unemployed	5 (6.2%)	19 (23.8%)	
Civil servant	17 (21.3%)	38 (47.5%)	
Artisan	12 (15.0%)	6 (7.5%)	
Farmer	1 (1.2%)	2 (2.5%)	
Marital Status			
Married	48 (60.0%)	46 (57.5%)	0.003*
Single	13 (16.2%)	29 (36.2%)	
Others [divorced, separated, widow]	19 (23.8%)	5 (6.3%)	
Residence			
Rural	17 (21.3%)	2 (2.5%)	<0.001**
Urban	63 (78.8%)	78 (97.5%)	
Housing Unit			
Single room [face me I face you]	35 (43.8%)	35 (43.8%)	0.36
Self-contained	45 (56.2%)	45 (56.2%)	
Religion			
Christianity	78 (97.5%)	78 (97.5%)	1.00
Islam	2 (2.5%)	2 (2.5%)	
Tribe			
Bini	37 (46.2%)	54 (67.5%)	<0.001**
Ibo	22 (27.5%)	8 (10.0%)	
Urhobo	10 (12.5%)	5 (6.2%)	
Others [Yoruba and Hausa]	11 (13.8%)	13 (16.3%)	
Educational Status			
Primary	13 (16.2%)	1 (1.2%)	<0.001**
Secondary	42 (52.5%)	27 (33.8%)	
Tertiary	24 (30.0%)	52 (65.0%)	
No formal education	1 (1.2%)	0 (0.0%)	
No. of person per room (Mean ± SD)	2.06 ± 0.93	1.96 ± 0.72	0.04*
Household size (Mean ± SD)	8.00 ± 4.48	9.05 ± 6.72	<0.001**

****-significant at p<0.001; *-Significant at p<0.05.**

Table 2: Medical history of the study population

Medical History	HIV-Infected patients n = 80	Controls n = 80	p-value
Cough			
Yes	4 (5.0%)	6 (7.5%)	0.51
No	76 (95.0%)	74 (92.5%)	
Fever			
Yes	7 (8.8%)	13 (16.2%)	0.15
No	73 (91.2%)	67 (83.8%)	
Night sweat			
Yes	1 (1.2%)	0 (0.0%)	0.32
No	79 (98.8%)	80 (100.0%)	
Weight Loss			
Yes	3 (3.8%)	0 (0.0%)	0.08
No	77 (97.2%)	80 (100.0%)	
Contact with person having Cough			
Yes	18 (22.5%)	2 (2.5%)	<0.001**
No	62 (77.5%)	78 (97.5%)	
Chronic Lung Disease			
Yes	0 (0.0%)	0 (0.0%)	-
No	80 (100.0%)	80 (100.0%)	
Past medical illness			
None	50 (62.5%)	79 (98.8%)	<0.001**
Fever	17 (21.2%)	0 (0.0%)	
ZDV Anemia	1 (1.2%)	0 (0.0%)	
Fever + rash	1 (1.2%)	0 (0.0%)	
EFV Psychosis	1 (1.2%)	0 (0.0%)	
Gastroenteritis	2 (2.5%)	0 (0.0%)	
Anemia	1 (1.2%)	0 (0.0%)	
Cataract	1 (1.2%)	0 (0.0%)	
RTA	2 (2.5%)	0 (0.0%)	
Burns	1 (1.2%)	0 (0.0%)	
CVA	1 (1.2%)	0 (0.0%)	
UTI	1 (1.2%)	0 (0.0%)	
Ectopic	1 (1.2%)	0 (0.0%)	
Appendicitis	0 (0.0%)	1 (1.2%)	
Smoking			
Yes	1 (1.2%)	1 (1.2%)	1.00
No	79 (98.8%)	79 (98.8%)	

****-significant at p<0.001**

Table 3: Anthropometric and Laboratory Characteristics of Study Population

Physical	HIV-positive Mean ± SD	Controls Mean ± SD	*t-test*	*p-value*
Weight (kg)	70.61 ± 12.18	74.36 ± 12.97	1.34	0.25
Height (cm)	1.63 ± 0.08	1.68 ± 0.08	0.00	0.96
BMI	26.52 ± 3.93	26.23 ± 3.62	0.35	0.55
PCV	35.13 ± 2.77	37.61 ± 3.18	1.67	0.19
WBC	3.98 ± 0.68	4.67 ± 3.80	1.39	0.24

Table 4 Isoniazid Preventive Therapy usage among HIV-positive patients.

Latent TB	Prior IPT		p-value	OR (95% CI)
	Yes	No		
Positive	8 (44.4%)	7 (38.9%)		
Negative	24 (38.7%)	34 (54.8%)	0.67	1.23 (0.47-3.24)

Table 5: Laboratory and anthropometric factors among HIV-infected patients with Positive and Negative IGRA

Laboratory and Physical factors	Latent TB		*t-test*	p-value
	IGRA-positive Mean ± SD	IGRA-negative Mean ± SD		
CD4 count at diagnosis	187.18 ± 90.03	291.29 ± 185.56	6.45	0.007*
CD4 count now	231.89 ± 110.93	635.69 ± 357.01	7.81	0.03*
Viral load	11338.00 ± 1212.21	52.06 ± 42.81	4.57	<0.001**
Weight (kg)	67.11 ± 10.94	72.96 ± 11.99	23.33	0.61
Height (m)	1.61 ± 0.07	1.64 ± 0.07	0.26	0.99
BMI	26.01 ± 3.84	26.97 ± 3.84	0.00	0.48
PCV	34.25 ± 3.49	35.49 ± 2.19	0.50	0.001*
WBC	3.90 ± 0.63	4.03 ± 0.74	11.83	0.72

****-significant at p<0.001; *-significant at p<0.05**

Table 6: Linear Regression analysis for latent TB in HIV-negative population

Model	Unstandardized coefficient		Standardized Coefficient	Significance	
	B	Stand error	Beta	t-value	p-value
Constant	-12.02	6.31		-1.90	0.61
Weight	-0.09	0.04	-3.64	-2.01	0.04*
Height	7.80	3.67	2.05	2.12	0.03*
BMI	0.26	0.12	3.09	2.12	0.03*
PCV	0.01	0.01	0.14	1.09	0.28
WBC	0.00	0.00	0.05	0.40	0.69
Age	-0.00	0.00	-1.31	-1.31	0.19

***-significant at p<0.05**

Table 7: Linear Regression Analysis for Latent TB in HIV-Positive Patients

Model	Unstandardized coefficient		Standardized Coefficient	Significance
	B	Stand error	Beta	p-value
Constant	5.69	4.29		1.87
Weight	0.19	0.53	0.62	0.52
Height	-2.14	2.56	-0.42	0.41
BMI	-0.07	0.08	-0.68	0.39
PCV	-0.01	0.01	-0.13	0.14
WBC	-0.01	0.01	-0.04	0.64
Age	0.01	0.03	0.04	0.65

***-significant at p<0.05**

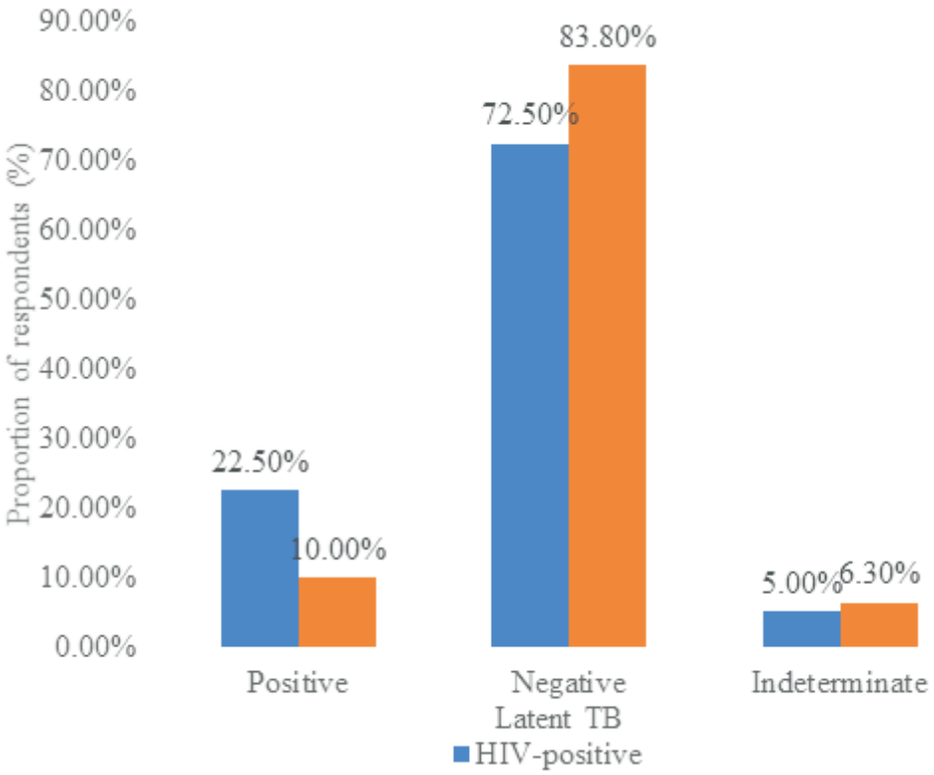

Figure 1: Prevalence of latent TB in the HIV-positive and Controls using IGRA

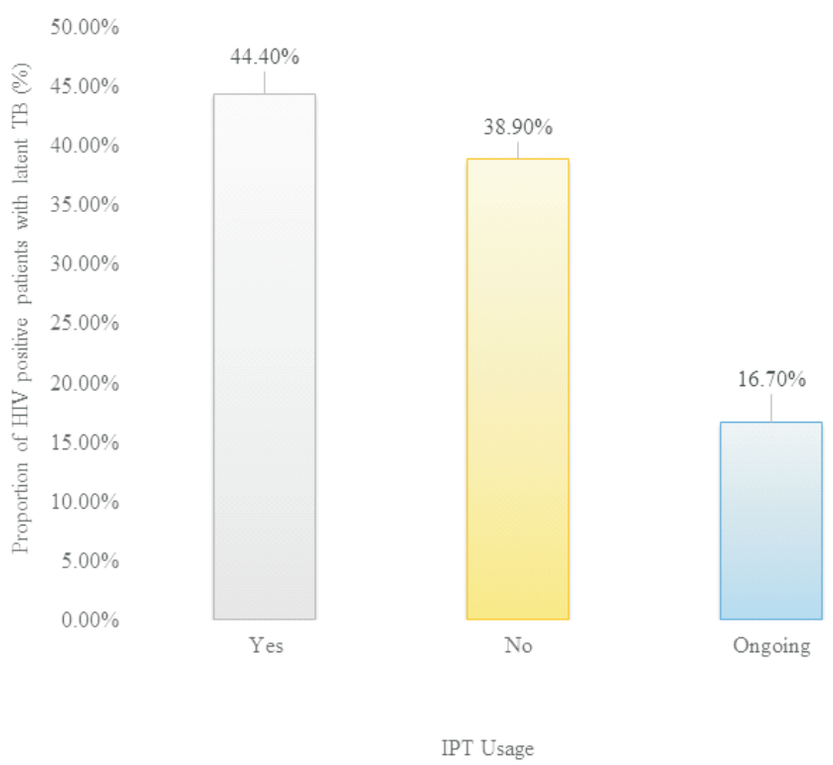

Figure 2: Distribution of IPT among HIV-infected patients with latent TB