Effectiveness of isoniazid preventive treatment among patients on antiretroviral treatment in Southeast Nigeria: A retrospective cohort study

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Abstract

Introduction: Isoniazid preventive treatment has been shown to reduce the risk of developing tuberculosis (TB) among HIV patients. It is, however, not clear if receiving a 6-month course of isoniazid preventive treatment (IPT) confers additional protection among HIV patients already on ART. We compared the incidence of TB among adult HIV patients on ART who had received IPT for 6 months with those who had not received IPT and identified factors associated with the development of TB to in our operational context. **Methods:** We conducted a retrospective cohort study on adult HIV patients who commenced ART from January 2010 to December 2016. Patients who had a 6-months course of IPT were classified as exposed, while patients who had not received IPT or had not received the complete IPT for six months were classified as unexposed. The outcome measure was the development of TB. We included 324 exposed and 337 unexposed patients' records. We followed them up for a total of 1338.6-person-years of observation with a median follow-up period of 19.8 months. We used a data extraction form to collect data from the patient case notes. Incidence density of developing TB in person-years, incidence rate ratio, Kaplan Meier survival function, and Cox proportionate regression model at 5% significance level were computed. The log-rank ratio was used to compare the equality of the survival function. **Results:** Six hundred and sixty-one patients were recruited for the study with a mean age of 38.5±9.6 years. The incidence of TB among the exposed was 10.6 cases per 1000-person-years of observation and among the unexposed was 16.6 cases per 1000-person-years of observation (incidence rate ratio=0.64, 95%CI: 0.15-1.97). WHO clinical stage 3 and 4 (adjusted hazard ratio [aHR]:4.8, 95% Confidence interval [95%CI]: 1.78-12.94) and poor ART adherence (aHR:3.5, 95%CI: 1.11-11.24) increased risk of development of the TB among the participants. There was no difference in the Kaplan-Meier survival functions between the exposed and unexposed (log-rank test χ^2 =1.58, p=0.209). **Conclusion:** HIV patients on ART who had received a 6-months course of IPT have a lower risk of developing TB compared to those who have not though not statistically significant. Development of TB was also predicted by being in WHO clinical stage 3 and 4 at baseline and having poor adherence to ART. The risk of developing TB remains high among patients on ART. There is a need to consider reviewing isoniazid treatment for patients on AR

Introduction

Co-infection with tuberculosis and Human Immunodeficiency Virus (TB/HIV) is a major public health problem. The co-infection worsens the prognostic outcomes of affected patients compared to outcomes in individuals with only tuberculosis (TB) or HIV infection. People living with HIV are 20-30 times as likely to develop TB compared to those who are not [1,2]. The burden of co-infection is greatest in Africa with prevalence being as high as 30% [3,4]. In Nigeria, the TB/HIV co-infection prevalence of up to 40% has been reported [5–8].

The World Health Organisation (WHO) and the Nigerian national HIV guidelines recommend that HIV positive patients who do not currently have evidence of active tuberculosis infection should be placed on the 6-months course of isoniazid (INH) [9,10]. It has been documented that INH Preventive Treatment (IPT) reduces the risk of developing TB by 33%-67% for up to 48 months in HIV positive patients [9]. This practice has not been generally accepted in the treatment of HIV patients as some physicians doubt its efficacy and fear the possibility of the development of resistance to INH [11]. The resistance to isoniazid in incident cases of TB has been reported in Africa and globally [12]. Development of resistance could worsen TB treatment outcomes [13].

The uptake of the IPT among HIV patients is low in southeastern Nigeria (30%) and many other countries as well though varying from one country to another [14–16]. It has been reported by Yirdaw et al in Ethiopia that the greatest effect of IPT is seen before commencing and at the point of commencing antiretroviral treatment (ART) [17]. Despite the recommendation and the reported efficacy of INH in lowering the risk of developing tuberculosis among HIV patients, there is a need to further explore whether it has a protective effect among HIV patients who are stable on ART. The WHO had recommended a 36-month course of IPT suggesting that 6-month IPT may not be very effective in the prevention of TB infection among people living with HIV in areas of high TB endemicity [18–20]. We compare the incidence of TB among adult HIV patients on ART who had received IPT for 6 months with ART patient who had not received IPT and identified factors associated with the development of TB.

Methods

Study setting

We conducted the study at the Federal Teaching Hospital Abakaliki (FETHA), Ebonyi State, in the southern part of Nigeria. Abakaliki is the administrative headquarters of Ebonyi State. The HIV prevalence in Ebonyi state was estimated at 3.3% in 2010 [21].

FETHA is a tertiary level hospital that provides comprehensive HIV/AIDS care including HIV testing and counselling (HTC), Adult and Paediatric ART and prevention of mother-to-child transmission of HIV (PMTCT). The HIV/TB services in the hospital are fully integrated – patients who are receiving TB care are routinely screened for HIV, and those receiving HIV care are screened routinely for TB before commencing HIV antiretroviral treatment. The hospital provides free sputum acid-fast bacilli (AFB) testing, Gene Xpert testing, and free tuberculosis and HIV treatment in accordance with the national treatment guidelines [22]. According to the national HIV treatment guidelines [10], all patients who test positive for HIV are screened for TB using the symptomatology screening checklist. Those who have affirmative answers (suspected to have TB) to any of the screening questions are further investigated for TB using sputum AFB examination, chest x-ray and Gene Xpert testing. Patients who test positive for any of these three tests (sputum AFB, chest X-ray and Gene Xpert) are commenced on the standard 6-month TB treatment using the directly observed short course (DOTS) strategy. The clinical screening for TB is repeated at every clinic visit. All the patients who developed TB were commenced on the first line anti-TB regimen (Isoniazid, rifampicin, Pyrazinamide and Ethambutol) based on the national guideline. HIV patients who do not have evidence of active TB are expected to receive a 6-month course of INH [9,10]. More than 3000 patients were receiving ART at FETHA by the end of 2016.

Study design

We conducted a retrospective cohort study on adult patients living with HIV who had been on ART at FETHA. It was an open cohort in which patients entered and exited the cohort at different time periods. We used routinely collected HIV program

data obtained from the ART register and patients case notes.

Study population

The study population were adult patients living with HIV who were on ART. We used records for patients who commenced ART from January 2010 to December 2016 at FETHA.

Inclusion criteria

All HIV positive patients aged 18 years and above, determined not to have active TB disease at time of ART commencement were included.

Exclusion criteria

All patients who had been diagnosed with TB or treated for TB before ART commencement, and those with unknown TB status at commencement were excluded from the study. We also excluded patients without records of follow-up visits after the beginning of ART, and those who were transferred in with incomplete records.

Exposure ascertainment

We defined the exposure as having received a complete 6-month course of IPT while on ART. Therefore, the control (unexposed) group comprised those who had not received IPT at all while on ART or who failed to complete the 6 months of IPT.

Study outcome

The main outcome of interest was defined as HIV infected patient on ART who was diagnosed of active TB disease over the period of follow up.

Study variables

We collected data on body mass index, functional status, CD4 count, adherence to ART, HIV disclosure status, adherence to INH. Additionally, data on socio-demographic characteristics including level of education, marital status, age, sex, occupational status, and place of residence for both the exposed and unexposed were extracted.

Sample Size

We estimated the minimum sample size for the study using the formula [23]

$$n = \frac{1}{(1-f)} \times \left[\frac{2 \times (Z_\alpha + Z_\beta)^2 \times p \times (1-p)}{(p_0 - p_1)^2} \right]$$

$$p = \frac{p_0 + p_1}{2}$$

where p_0 (13.6%) represented the proportion of the HIV patients who are on ART alone and are expected to have TB [24], p_1 (6.8%) represented the proportion of the HIV patients who are on ART and IPT and are expected to have TB, this proportion was assumed because the authors expected a 50% reduction in this group. Z_β (0.84) represented the standard normal deviate corresponding to a power of 80%. Z_α (1.96) represents standard normal deviate corresponding to 5% level of significance, and f (15%) represents the proportion of study subjects who are expected to leave the study for reasons other than developing TB based on the best retention estimate of 85% [25]. A sample size of 327 was estimated for each group after finite population correction.

Sampling technique

We used systematic random sampling to select the records to include in the study. The sampling interval was obtained by dividing the number of the patients receiving ART in the hospital as at end of 2016 (3000) with the total sample size (684). Using the hospital ART register, every fourth patient record that was commenced on ART was selected to participate in the study until the desired sample size for each group was achieved. We selected the first record by balloting the first four patients records that were commenced ART in January 2010 in the hospital.

Data collection

We retrieved data from the patients' case file using the data extraction forms. The data retrieved included socio-demographics (sex, age, level of education, occupational status, marital status and place of residence) and clinical characteristics (date of HIV confirmation, date of commencement of ART, WHO clinical stage, weight and height at

baseline, functional status – working, ambulatory or bedridden, baseline CD4 count, baseline haemoglobin level, HIV disclosure status, ART adherence). We also retrieved information on the date of commencement of INH, date completed INH, adherence to INH, ART regimen type – first line or second line at the end of the study or at the point of censorship. Information on whether the patient had ART treatment failure at any point in the course of follow-up; exposure status; outcome status and person-time contributed to follow up were also retrieved.

We calculated the person-time of observation each participant contributed to the study in months. The person-time contributed for the exposed participant was the number of months of observation from the end of the 6-month IPT to the end of the study or until the participant exited the study for any reason or developed the outcome of interest (TB), whichever came first. Whereas, for the unexposed participant, the person-time contributed was measured in months from the time of commencement of ART to the end of the study or until the participant exited the study or developed TB. The person-time contributed by each participant was computed and summed for IPT and non IPT.

Data management

We analysed socio-demographic and clinical characteristics of the patients and presented as frequencies and proportions. We compared the socio-demographic and clinical characteristics between IPT and non-IPT patients using the Chi-squared test, at a p-value of 0.05 to check for comparability of the groups. We calculated the incidence density of TB (in person-years) for IPT and non IPT patients. We also compared the incidence rate ratio of developing TB among IPT and non IPT patients and their corresponding 95% confidence interval estimated. We stratified the incidence rate ratio by age, occupation, clinical stage, and adherence to ART treatment to assess for effect modification. We performed the Cox proportional hazard regression analysis to identify risk factors for developing TB. We plotted the Kaplan Meier survival curve for the exposure and outcome status and the log-rank test to determine the equality of survivor functions.

Ethical considerations

We obtained ethical approval from the Research and Ethics Committee of FETHA (approval number 04/04/2017-19/4/2017). We kept the data in a password protected computer and access was granted to only investigators. We ensured participant's anonymity throughout the study and did not collect personal identifying information such as name, phone number, and address.

Results

Sociodemographic characteristics

In total, 324 patients were enrolled in the exposed group while 337 were enrolled in the unexposed group. The mean age of the participants was 38.5 ± 9.6 years {exposed (39.8 ± 9.6years), unexposed (37.2 ± 9.3years)}. Among those who had received IPT, 39.8% (129/324) were males, 44.8% (145/324) had not attained more than primary education, 52.2% (169/324) were employed, and 64.8% (210/324) were married. On the other hand, among those who had not received INH prophylaxis, 33.8% (114/337) were males, 39.5% (133/337) had not attained more than primary education, 43.9% (148/337) were employed while 56.7% (191/337) were married (Table 1). The distribution of the level of education (p=0.169), sex (p=0.111) and place of residence (p=0.314) were comparable in both groups. However, occupational status (p=0.034) and marital status (p=0.032) were significantly different between the two groups. Participants who had received IPT were more likely to be employed and to be currently married, compared to those who had not received IPT. Similarly, those who had received IPT were more likely to have disclosed their HIV status, compared to those who had not received IPT (p=0.011).

Baseline clinical characteristics

At baseline, 92% (641/661) of the patients had early HIV disease (WHO clinical stages 1 and 2). Among those who received IPT, 94.1% (305/324) were in WHO clinical stage 1 and 2, 91.4% (296/324) were on first line regimen, and 39.2% (127/324) had CD4 count ≤ 200cells/ml at baseline, while among those who had not received IPT 91.7% (309/337) were in WHO clinical stage 1 and 2, 94.7 (319/337) were on

first line regimen, and 46.5% (154/331) had CD4 count ≤200cells/ml at baseline. The baseline clinical characteristics of patients were comparable between the exposed and unexposed groups (Table 2). Among the participants who had received IPT, 95.7% (311/324) had good adherence to IPT.

Incidence of tuberculosis

In all, 334 IPT and 337 non-IPT participants were followed up for a total of 1342.6 person-years of observation. The median follow-up period was 19.8months (exposed: 10.2 months, unexposed: 33.3 months). The exposed groups were followed up for a total of 378.4person-years of observation, while the unexposed groups were followed up for a total period of 964.2 person-years of observation. The incidence of TB was 10.6 cases per 1000 person-years of observation among those receiving IPT, and 16.6 cases per 1000 person-years of observation among those who were not on IPT. Patients who received IPT had a 36% reduced risk of developing TB compared to those who did not. (Table 3). The incidence of TB at different levels of IPT exposure showed that those how had received incomplete IPT had higher risk of TB infection compared to those who had not received IPT at all (Figure 1).

The TB incidence rate ratio was not modified by age, occupation, clinical stage and adherence to treatment to after stratified analysis. The Kaplan Meier survival curve showed the rate of developing TB among the ART patient who received and those who had not received INH (Figure 2). The log-rank test for equality of survivor function showed that there was no significant difference in the survival function in both groups (log-rank test χ2 =1.58, p=0.209).

Cox proportional model of incident tuberculosis

The clinical stage of the disease, ART adherence, receipt of isoniazid prophylaxis, participants' occupational and marital status were the potential predictors included in the model. However, only the clinical stage of the disease and adherence to ART significantly predicted the development of TB. Patients with advance stage of the disease – stage 3 and 4 (adjusted hazard ratio {aHR}: 4.8, 95%CI: 1.79-12.99) and poor adherence to ART (aHR: 3.5, 95%CI: 1.11-11.24) were more likely to develop TB (p=0.032), (Table 4).

Discussion

We set out to compare the incidence of TB among patients on ART who received and those who had not received IPT among patient who were on ART from 2010 to 2016. Our study found that ART patients who received the 6-month course IPT had a reduced risk of developing TB, although the risk reduction was not statistically significant. Clinical disease severity and adherence to ART treatment independently predicted the development of TB.

The incidence of TB among the participants who received IPT was high compared findings of earlier study in Nigeria [26]. This could be due to the high level of endemicity of TB in Nigeria. The high incidence of TB could also be due to the relatively low period of follow-up among the exposed. It has been documented that the incidence of TB is usually high in the first few years following commencement of ART [24,27]. The incidence of TB in this study was much lower compared to the incidence of 2.3 cases of TB per 100 person-years reported among a similar group of patients in South Africa [28].

The incidence of TB among HIV patients on ART who had not received the IPT was also high for the population who are already on ART. The TB incidence in our study may not be unrelated to the endemicity of TB in the population. The TB incidence in our study was similar to the incidence of 17.43 per 1000 person-year reported in Kano, Nigeria, among HIV patients [24]. The similarity between the TB incidence reported in our study and that reported in Kano, Nigeria could be due to the similarity in the hospital settings. Both hospitals were referral centres and thus had a greater likelihood of receiving more HIV patients compared to other hospitals. However, the TB incidence reported in our study was much higher than that reported in Jos, Nigeria [27].

The six-month course of isoniazid independently lowers the incidence of TB by 36% among HIV patients on ART. The lowering of incidence of TB by INH in this study is comparable to findings in a double-blind placebo-controlled study in South Africa among HIV patients on ART which reported a 37% reduction in the incidence of tuberculosis [26]. The rate of developing tuberculosis among the exposed compared to the unexposed was not significantly lower. Our study population were

patients who were already on ART. Being on ART substantially reduce the risk of TB among HIV patients. The lack of statistical significance in the rate of development of TB in both groups could have been related to the time of observation. The period of observation was much lower for those who had received INH prophylaxis compared to those who had not. However, the result could also indicate that 6-month isoniazid may not confer any additional protection against TB on HIV patients who had been on ART with possible viral suppression, considering high proportion of patients with good adherence among those who received IPT.

The lack of additional protection observed supports the growing debate that probably a 6-month course of isoniazid may not be the best offer for patients who are already on ART, compared with those yet to commence ART in areas with high TB endemicity. It has been poised that a 36-month course of isoniazid preventive treatment offers more benefit to HIV patients in TB endemic settings than a 6-months course [19,29]. Among HIV patients who are yet to commence ART (pre-ART), the benefit of IPT in reducing the incidence of TB is unequivocal but among those who are already on ART, there has been varying results [30]. Some authors did not differentiate between these two distinct populations in their report so the result reported may have been clouded by effect observed in one group. Recently, WHO updated its recommendation on IPT, recommending the use of a 36-months course of IPT among HIV patients in resource-poor high endemicity settings [20]. The study setting in our case has of high TB endemicity and is resource-constrained hence may need to adopt the new recommendation.

Patients who were in an advanced stage of HIV at baseline and those who had poor adherence to their antiretroviral treatment were at greatest risk of developing TB. The relationship between advanced HIV disease and the development of TB is probably due to severe immunosuppression associated with the advance HIV infection. Tuberculosis infection is also one of the opportunistic infections observed at this stage of HIV infection. On the other hand, the relationship of TB with poor adherence ART is probably due to the loss of the protective effect the ART. Poor adherence often leads to treatment failure leading to the inability of the ART to fully suppress the virus, and one of the manifestations of

opportunistic infections is TB. The relationship between TB, advanced HIV and poor adherence to ART are in keeping with other studies [26,31,32]. Patients with advanced HIV disease at baseline and those with poor adherence to ART should be identified early and ensure they are placed on IPT to protect them from developing active TB.

We recommend that HIV program managers should optimise the patients' adherence to ART, and efforts should be made to quickly identify and respond to those that are having adherence challenges to low their risk of developing TB. The current guideline of test and treat should be strengthened to avoid deterioration of the patient WHO clinical stage. Those identified at an advanced stage of the disease should be specifically targeted for intervention to low their risk of developing TB. The Federal Ministry of Health, National AIDS Control Agency and National TB and Leprosy Control Program should consider reviewing the recommendation on the 6 months to of IPT to 36 months for Nigeria.

Our study is not without its limitations. The evidence was largely in the patient's folders. Those who received IPT for less than six months were classified as unexposed. The amount of isoniazid received could have affected the difference between the exposed and unexposed. The diagnosis of tuberculosis was made prior to the commencement of the study and selection of participants into the study was based on the documentation in the medical records. This could have resulted into underreporting the incidence of tuberculosis due to poor or incomplete documentation, missing records. Relying on TB diagnosis of others, some of which might have been clinically diagnosed, might also have shown different incidence compared to the gold standard of having a confirmatory diagnosis of TB. To minimise this, the study team visited the Tuberculosis Treatment Unit and reconciled their data with what we found at the HIV clinic.

Conclusion

The incidence rate of TB among HIV patients who had received IPT was 10.6 per 1000-person-year of observation, while that among HIV patients who had not received isoniazid preventive treatment the incidence was 16.6 per 1000-person-year of observation. The risk of developing tuberculosis was

found not to be significantly lower among those who had received isoniazid preventive treatment compared to those who had not and that the development of TB was predicted by advanced HIV and poor adherence to ART.

Competing interests

The authors have no conflict of interest to declare.

Authors´ contributions

CDU: conceptualization, methodology, data curation, project administration, validation, data analysis, original draft, review and final approval; BS: methodology, supervision, data analysis, review and final approval; PN: review and final approval; MSB: review and final approval; PN: review and final approval; LB: review and final approval; AAU: review and final approval; OIF: supervision, review and final approval.

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Tables and figures

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References

1. Kwan C, Ernst JD. HIV and tuberculosis: A deadly human syndemic. Clinical Microbiology Reviews.2011;24(2):351–376. https://doi.org/10.1128/CMR.00042-10

2. Lönnroth K, Castro KG, Chakaya JM, Chauhan LS, Floyd K, Glaziou P, *et al.* Tuberculosis control and elimination 2010–50: cure, care, and social development. Lancet. 2010;375(9728): 1814–1829. https://doi.org/10.1016/S0140-6736(10)60483-7

3. Denegetu AW, Dolamo BL. Tuberculosis case finding and isoniazid preventive therapy among people living with HIV at public health facilities of Addis Ababa, Ethiopia: a cross-sectional facility based study. BMC Public Health. 2014;14: 52. https://doi.org/10.1186/1471-2458-14-52

4. Gao J, Zheng P, Fu H. Prevalence of TB/HIV co-infection in countries except China: a systematic review and meta-analysis. PLoS One. 2013;8(5):e64915. https://doi.org/10.1371/journal.pone.0064915

5. Pennap G, Makpa S, Ogbu S. Sero-prevalence of HIV infection among tuberculosis patients in a rural tuberculosis referral clinic in northern Nigeria. Pan Afr Med J. 2010;5: 22.

6. Daniel OJ, Adedeji Adejumo O, Abdur-Razzaq HA, Ngozi Adejumo E, Salako AA. Public-private mix for TB and TB-HIV care in Lagos, Nigeria. Int J Tuberc Lung Dis. 2013;17(9): 1195–1198. https://doi.org/10.5588/ijtld.12.0759

7. Ifebunandu NA, Ukwaja KN, Obi SN. Treatment outcome of HIV-associated tuberculosis in a resource-poor setting. Trop Doct.2012;42(2):74–76. https://doi.org/10.1258/td.2011.110421

8. 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(2): 81–87. https://doi.org/10.2188/jea.JE20080026

9. Malhotra B. Guidelines for intensified tuberculosis case-finding and isoniazid preventative therapy for people living with HIV in resource-constrained settings. World Health Organization. Geneva, Switzerland. 2011.

10. Federal Ministry of Health, Nigeria. National Guidelines for HIV Prevention Treatment and Care. Federal Ministry of Health, Nigeria. 2016. Accessed July 2018.

11. Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. Emerg Infect Dis. 2006;12(5):744–51. https://doi.org/10.3201/eid1205.050681

12. Jenkins HE, Zignol M, Cohen T. Quantifying the burden and trends of isoniazid resistant tuberculosis, 1994-2009. PLoS One. Public Library of Science; 2011;6(7): e22927. https://doi.org/10.1371/journal.pone.0022927

13. van der Heijden YF, Karim F, Mufamadi G, Zako L, Chinappa T, Shepherd BE, et al. Isoniazid-monoresistant tuberculosis is associated with poor treatment outcomes in Durban, South Africa. Int J Tuberc Lung Dis. 2017;21(6):670–676. https://doi.org/10.5588/ijtld.16.0843

14. Kufa T, Chihota VN, Charalambous S, Churchyard GJ. Isoniazid preventive therapy use among patients on antiretroviral therapy: a missed opportunity [Short communication]. Int J Tuberc Lung Dis. 2014;18(3): 312–3. https://doi.org/10.5588/ijtld.13.0505

15. Onuka O, Uloaku E-U, Andrew U, Kelechukwu N, Eno A, Damaris O, et al. Use of Isoniazid Preventive Therapy on HIV/AIDS Patient in a Tertiary Health Facility South Eastern Nigeria. Sci J Public Heal. 2015;3(2): 265–268. https://doi.org/10.11648/j.sjph.20150302.26

16. Omesa E, Kathure I, Masini E, Mulwa M, Maritim A, Owiti P, et al. Uptake of isoniazid preventive therapy and its associated factors among HIV positive patients in an urban health centre, Kenya. East Afr Med J. 2016;93(10): S47-54.

17. Yirdaw KD, Jerene D, Gashu Z, Edginton ME, Kumar AM V, Letamo Y, et al. Beneficial effect of isoniazid preventive therapy and antiretroviral therapy on the incidence of tuberculosis in people living with HIV in Ethiopia. PLoS One. 2014;9(8):e104557. https://doi.org/10.1371/journal.pone.0104557

18. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med. 2011;365: 11–20. https://doi.org/10.1056/NEJMoa1005136

19. Swaminathan S, Menon PA, Gopalan N, Perumal V, Santhanakrishnan RK, Ramachandran R, et al. Efficacy of a six-month versus a 36-month regimen for prevention of tuberculosis in HIV-infected persons in India: a randomized clinical trial. PLoS One. 2012;7(12): e47400. https://doi.org/10.1371/journal.pone.0047400

20. Matteelli A. Recommendation on 36 months isoniazid preventive therapy to adults and adolescents living with HIV in resource-constrained and high TB- and HIV-prevalence settings: 2015 update. WHO. 2015.

21. Bashorun A, Nguku P, Kawu I, Ngige E, Ogundiran A, Sabitu K, et al. A description of HIV prevalence trends in Nigeria from 2001 to 2010: what is the progress, where is the problem? Pan Afr Med J. African Field Epidemiology Network;2014;18(Suppl1):3. https://doi.org/10.11604/pamj.supp.2014.18.1.4608

22. Federal Ministry of Health, Nigeria. National Tuberculosis, Leprosy and Buruli Ulcer Management and Control Guidelines. 6th ed. Federal Ministry of Health, Nigeria. 2015. https://doi.org/10.4103/2321-9157.186353

23. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian J Psychol Med. 2013;35(2):121–6. https://doi.org/10.4103/0253-7176.116232

24. Musa BM, Musa B, Muhammed H, Ibrahim N, Musa AG. Incidence of tuberculosis and immunological profile of TB/HIV co-infected patients in Nigeria. Ann Thorac Med. 2015;10(3):185–92. https://doi.org/10.4103/1817-1737.160838

25. Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. PLoS Med. 2007;4(10):e298. https://doi.org/10.1111/j.1365-3156.2010.02508.x

26. Pathmanathan I, Dokubo EK, Shiraishi RW, Agolory SG, Auld AF, Onotu D, et al. Incidence and predictors of tuberculosis among HIV-infected adults after initiation of antiretroviral therapy in Nigeria, 2004-2012. PLoS One. 2017;12(3):e0173309. https://doi.org/10.1371/journal.pone.017330

27. 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(6): 931–937. https://doi.org/10.1089/aid.2012.0231

28. Rangaka MX, Wilkinson RJ, Boulle A, Glynn JR, Fielding K, van Cutsem G, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. Lancet. 2014;384(9944):682–690. https://doi.org/10.1016/S0140-6736(14)60162-8

29. Samandari T, Agizew TB, Nyirenda S, Tedla Z, Sibanda T, Shang N, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet. 2011;377(9777): 1588–1598. https://doi.org/10.1016/S0140-6736(11)60204-3

30. Assebe LF, Reda HL, Wubeneh AD, Lerebo WT, Lambert SM. The effect of isoniazid preventive therapy on incidence of tuberculosis among HIV-infected clients under pre-ART care, Jimma, Ethiopia: a retrospective cohort study. BMC Public Health. 2015;15:346. https://doi.org/10.1186/s12889-015-1719-0

31. Ahmed A, Mekonnen D, Shiferaw AM, Belayneh F, Yenit MK. Incidence and determinants of tuberculosis infection among adult patients with HIV attending HIV care in north-east Ethiopia: a retrospective cohort study. BMJ Open. 2018;8(2): e016961. https://doi.org/10.1136/bmjopen-2017-016961

32. Kibret KT, Yalew AW, Belaineh BG, Asres MM. Determinant factors associated with occurrence of tuberculosis among adult people living with HIV after antiretroviral treatment initiation in Addis Ababa, Ethiopia: a case control study. PLoS One. 2013;8(5): e64488. https://doi.org/10.1371/journal.pone.0064488

Table 1: Socio-demographic characteristics of study participants on ART, Abakaliki Nigeria, 2010-2016			
Variable	Exposed n=324 (%)	Unexposed n=337 (%)	p-value^
Age group (years)			
15 – 34	101 (31.2)	137 (40.7)	0.01
≥ 35	223 (68.8)	200 (59.3)	
Mean age ± SD	39.8 ± 9.6	37.2 ± 9.3	<0.01*
Sex			
Male	129 (39.8)	114 (33.8)	0.11
Female	195 (60.2)	223 (66.2)	
Education			
Primary education or less	145 (44.8)	133 (39.5)	0.17
Secondary education or more	179 (55.2)	204 (60.5)	
Occupation Status			
Employed	169 (52.2)	148 (43.9)	0.03
Unemployed	155 (47.8)	189 (56.1)	
Marital status			
Married	210 (64.8)	191 (56.7)	0.03
Not in a union#	114 (53.2)	146 (43.3)	
Place of Residence			
Within Abakaliki	179 (55.2)	173 (51.3)	0.31
Outside Abakaliki	145 (44.8)	164 (48.7)	
* value based on Student t test statistics (difference of two means) #combined single, divorced, separated; ^values were based on Chi Square statistics;			

Table 2: Baseline clinical characteristics of the study participants on ART, Abakaliki Nigeria, 2010 - 2016

Variable	Exposed n =324 (%)	Unexposed n =337 (%)	p-value**
WHO stage			
1&2	305 (94.1)	309 (91.3)	0.22
3&4	19 (5.9)	28 (8.3)	
ART regimen			
First Line	296 (91.4)	319 (94.7)	0.10
Second line	28 (8.6)	18 (5.3)	
BMI*			
<18 kg/m^2	34 (10.5)	40 (12.5)	0.57
=>18kg/m^2	289 (89.5)	295 (87.5)	
Functional status*			
Working	281 (86.7)	285 (84.9)	0.48
Not working	43 (13.3)	51 (15.1)	
CD4 count*			
<=200 cells/ml	127 (38.0)	154 (45.7)	0.06
> 201 cells/ml	197 (62.0)	177 (54.3)	
Disclosure status			
Disclosed	278 (85.8)	262 (77.7)	0.01
Did not disclosure	46 (14.2)	73 (22.3)	
Disclosed to			
Family member	137 (42.3)	158 (46.9)	0.23
Spouse	153 (47.2)	97 (28.8)	<0.01
Others^	8 (2.5)	13 (3.9)	0.35
Study endpoint			

Completed follow up	308 (95.1)	272 (80.7)	<0.01
Had TB	4 (1.2)	16 (4.7)	
Lost to follow up	9 (2.8)	47 (14.0)	
Died	0 (0)	2 (0.6)	
Transferred out	3 (0.9)	0 (0)	
*These variables had some missing fields, the valid total was used as denominators **the values were based on Chi squared statistics ^Others (friends / spiritual leader)			

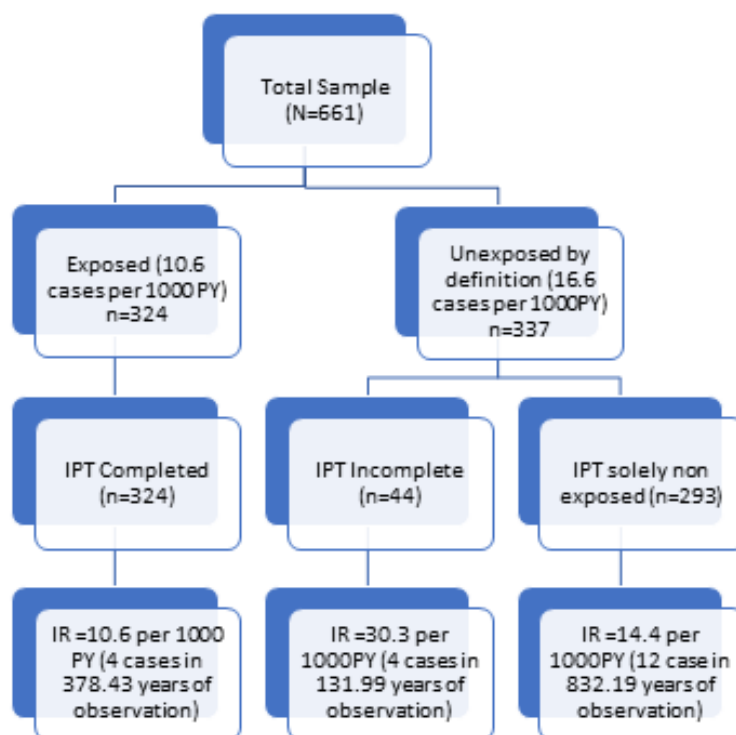**Table 3:** Incidence of tuberculosis among the exposed and unexposed patients

	Tuberculosis (Yes)	Tuberculosis (No)	PY	IR (per 1000PY)	IR ratio
Exposed to INH	4	320	378.4	10.6	0.64 (0.15-1.97)
Unexposed to INH	16	321	964.2	16.6	
PY= Person year of observation INH=Isoniazid IR= Incidence Rate					

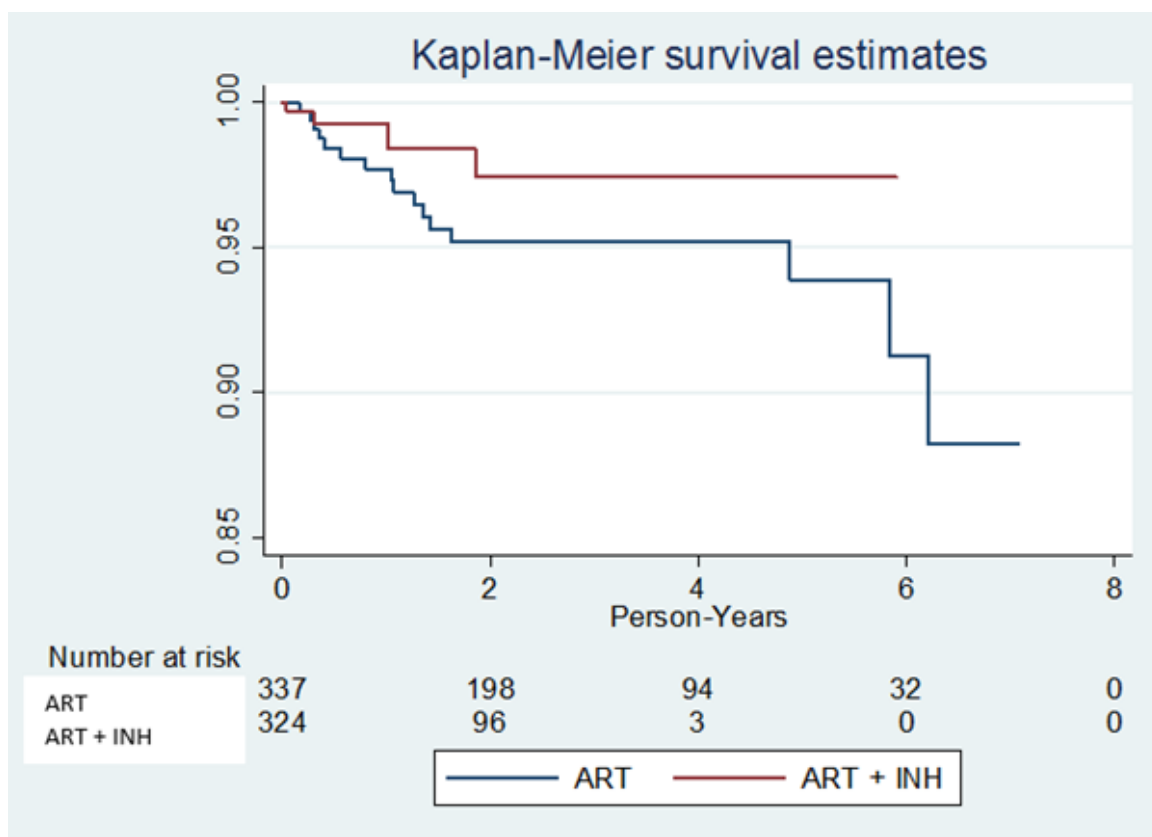**Table 4:** Hazard ratio of possible predictors for developing tuberculosis

Potential predictor	aHR	95% CI	p-value
WHO stage (stage 3&4/ stage 1&2)	4.8	1.8 - 12.9	0.002
Exposure status (unexposed/exposed)	1.9	0.6 – 5.9	0.254
ART adherence (poor/good)	3.5	1.1 – 11.2	0.032
Occupation (unemployed/employed)	1.6	0.6 – 3.9	0.339
Marital status (not in a union/married)	1.2	0.5 – 3.0	0.652
aHR= adjusted hazard ratio CI = confidence interval			

Figure 1: Incidence of TB across the different levels of IPT exposure

Figure 2: Kaplan-Meier survival estimates for exposed and unexposed participants