The Effect of long term HAART on the incidence of tuberculosis among HIV positive individuals in Addis Ababa, Ethiopia: A Nested Case-Control Study

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Abstract

Background: The introduction of antiretroviral therapy (ART) significantly decreases the incidence of tuberculosis (TB) in Human Immunodeficiency Virus (HIV) positive individuals during their follow-up. However, a considerable proportion is still co-infected with TB after ART initiation. Thus, this study aimed to assess the determinants of TB incidence among HIV-positive individuals during their ART follow-up in Addis Ababa, Ethiopia. Methods: A nested case-control study was conducted among HIV-positive individuals who were enrolled in ART clinics in Addis Ababa, Ethiopia from 2013 up to 2018. Cases were tuberculosis co-infected HIV positive individuals who were taking antiretroviral treatment, while controls were TB free HIV positive individuals who were taking antiretroviral treatment. The cases and controls are matched exactly in age and sex. Data were entered in EpiInfo version 7.1 and analyzed using SPSS version 20. Bivariable and multivariable conditional logistic regression were employed along with 95% CI. A P-value < 0.05 in the multivariable analysis was considered statistically significant. Results: Fifty-seven cases were compared with 114 controls pair-matched exactly in age and sex. Accordingly, previous TB history (X^{2;} 13.790 , P<0.001), baseline functional status (X^{2;} 9.120 , P=0.010), baseline WHO clinical stage $(X^{2}; 10.083, P=0.001)$, baseline hemoglobin value $(X^{2}; 6.985, P=0.008)$, baseline body mass index $(X^{2}; 3.873, P=0.049)$, isoniazid preventive treatment intake status (X^{2;} 8.047 , P=0.005), baseline CD4 value (X^{2;} 12.741 , P<0.001) and length of stay on ART (X 2 ; 53.359 , P < 0.001) were associated with TB infection. Length of stay on ART was found to be the statistically significant determinant of TB infection after ART initiation (aOR=5.925, 95%CI=2.649-13.250). Conclusion: Advanced clinical stages at the baseline, previous TB history, and not taking IPT were associated with TB infection. The long term ART exposure significantly decreases tuberculosis incidence in HIV patients. Screening HIV-positive patients for tuberculosis throughout their ART follow-up would be important early detection and treatment of tuberculosis.

Title Page

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Abstract

Background: The introduction of antiretroviral therapy (ART) significantly decreases the incidence of tuberculosis (TB) in *Human Immunodeficiency Virus* (*HIV*) positive individuals during their follow-up. However, a considerable proportion is still co-infected with TB after ART initiation. Thus, this study aimed to assess the determinants of TB incidence among HIV-positive individuals during their ART follow-up in Addis Ababa, Ethiopia.

Methods: A nested case-control study was conducted among HIV- positive individuals who were enrolled in ART clinics in Addis Ababa, Ethiopia from 2013 up to 2018. Cases were tuberculosis co-infected HIVpositive individuals who were taking antiretroviral treatment, while controls were TB free HIV positive individuals who were taking antiretroviral treatment. The cases and controls are matched exactly in age and sex. Data were entered in EpiInfo version 7.1 and analyzed using SPSS version 20. Bivariable and multivariable conditional logistic regression were employed along with 95% CI. A P-value <0.05 in the multivariable analysis was considered statistically significant.

Results: Fifty-seven cases were compared with 114 controls pair-matched exactly in age and sex. Accordingly, previous TB history (X^{2} ; 13.790 P < 0.001), baseline functional status (X^{2} ; 9.120 P = 0.010), baseline WHO clinical stage (X^{2} ; 10.083 P = 0.001), baseline hemoglobin value (X^{2} ; 6.985 P = 0.008), baseline body mass index (X^{2} ; 3.873 P = 0.049), isoniazid preventive treatment intake status (X^{2} ; 8.047 P = 0.005), baseline CD4 value (X^{2} ; 12.741 P < 0.001) and length of stay on ART (X^{2} ; 53.359 P < 0.001) were associated with TB infection. Length of stay on ART was found to be the statistically significant determinant of TB infection after ART initiation (aOR=5.925, 95%CI=2.649-13.250).

Conclusion: Advanced clinical stages at the baseline, previous TB history, and not taking IPT were associated with TB infection. The long term ART exposure significantly decreases tuberculosis incidence in HIV patients. Screening HIV- positive patients for tuberculosis throughout their ART follow-up would be important early detection and treatment of tuberculosis.

Introduction

Individuals infected with Human Immunodeficiency Virus (HIV) virus are vulnerable to secondary infections including tuberculosis (TB) (1). Compared to the general population, the risk of TB infection is higher in HIV- positive individuals (2, 3) such that people living with HIV have a 10% annual risk of TB infection (1). Based on the world health organization (WHO) estimates, HIV-positive individuals are 19 times more likely to develop active TB disease than people without HIV. Besides, TB is the major cause of death inHIV-positive individuals (4). Both TB and HIV are the major causes of morbidity and mortality globally. According to the 2019 global TB report, about 10 million individuals were infected with TB in 2018 (5). In 2017, among the total TB cases, 9% were HIV positive (6).

Ethiopia is among the countries seriously affected by both infections. The 2019 global tuberculosis report showed that there were an estimated 151 TB cases per 100,000 population in Ethiopia (5). The country is among the TB, TB/HIV, and MDR-TB hig burden countries in the world (5, 6). A recent study conducted in Ethiopia reported that 7.4% of TB patients are co-infected with HIV and 0.8% of HIV patients are infected with active TB (7). Studies conducted in different settings reported that enrollment on highly active antiretroviral therapy (HAART) significantly decreases the incidence of TB infection such that those HIVpatients enrolled on HAART have a lower risk to develop tuberculosis compared to those not taking antiretroviral therapy (ART) (8-12). Studies conducted in Ethiopia also supported this evidence (8, 13-16). However, still considerable proportions of individuals who were enrolled in HAART develop TB in Ethiopia (17, 18). Also, studies showed that the incidence of TB was higher in the early phase of ART initiation (19-24). Thus, we designed a nested case-control study where individuals are matched in age and sex to assess the determinates of TB infection in HIV positive individuals who were taking ART.

Methods

Study setting and period

The study was conducted among seven ART centers found in Addis Ababa, the capital and the most urban city of Ethiopia. Patients who were enrolled in ART clinics from January to December 2013 were included in the study and were followed for five years up to December 2018 retrospectively. Data were collected retrospectively in a period between July and August 2019.

Study design

A matched case-control study was conducted based on data collected in our previous retrospective cohort study published previously (13). For the current study, HIV -positive patients enrolled on HAART were selected based on their tuberculosis co-infection status, and the determinants were assessed retrospectively.

Participants

Based on the tuberculosis infection status, which is the outcome in the current study, HIV-positive patients who were taking ART were categorized into two groups, cases, and controls. Cases were tuberculosis coinfected HIV positive individuals who were taking antiretroviral treatment, while controls were TB free HIV positive individuals who were taking antiretroviral treatment. Every case was matched with two controls exactly matched with age and sex. HIV-positive individuals newly enrolled on HAART from 01 January 2013 to 31 December 2013 who were free from TB were included in the study and were followed retrospectively for five years up to 31 December 2018. Individuals who didn't have baseline data and missed charts were excluded.

Sampling procedure

Among a total of 566 HIV -positive individuals included in our previous study, 476 individuals who were taking ART were selected in the first stage. Then, categorized into two groups, who developed TB and were not infected with TB in their follow-up period. Tuberculosis co-infected HIV patients were categorized as cases and the counterparts were considered as controls. For every case, two controls with an exact match in age and sex were selected systematically. Accordingly, 57 cases were pair-matched with 114 controls. Thus a total sample size of 171 was used in the study.

Variables

The dependent variable was tuberculosis infection and the independent variables were demographic characteristics (marital status, educational status, occupation, address, disclosure status, number of family members, and homeless), behavioral characteristics (smoking, alcohol use, Khat and substance use (Shisha), baseline clinical characteristics (TB treatment history, functional status, WHO clinical stage, CD4 count, hemoglobin (Hgb) level, initial ART regimen type, isoniazid preventive treatment (IPT), co-infection other than TB and body mass index) and length of ART.

Diagnostic methods

Tuberculosis diagnosis was based on Ethiopian tuberculosis and leprosy control guidelines (25), such that TB is defined as any clinical, histological, and or microbiological diagnosis. Microbiologically, different technologies are used to rule out TB. Among them, smear microscopy, mycobacterial culture, and Xpert MTB/RIF assay were used. Histological diagnostic methods such as chest radiography, ultrasound, and pathological examination were also used to rule out TB. Besides, a clinician decision based on strong clinical evidence was also used. Among the 57 cases, 31 were diagnosed with extrapulmonary TB, while the remaining 26 were diagnosed with pulmonary TB. Several combinations of diagnostic methods were used to rule out TB. Accordingly, 24, 23, 8, and 2 TB cases were confirmed by chest radiography, histological examination, microbiological diagnostic methods, and strong clinical evidence respectively.

Operational definitions

Cases: Cases were HIV-positive individuals who developed tuberculosis infection during their ART followup. **Controls:** Controls were HIV-positive individuals who were not infected with tuberculosis during their ART follow-up.

Matching: Matching in the current study is defined as an exact age and sex match of cases and controls, such that two controls were exactly matched in age and sex with one case. Individual pair matching was used.

Disclosure Status: If there is anyone else who knows the HIV status of the patient it is defined as disclosed.

User : Any level of alcohol use, smoking, Khat use, and Shisha use were operationalized as a user.

Functional status: It is the condition of the patient at the time of enrollment in ART clinic categorized as to whether working (able to perform usual work), ambulatory (able to perform the activity of daily living), or bedridden functional status (not able to perform the activity of daily living).

Isoniazid preventive treatment completion: Taking the complete prophylaxis, such that a dose of 300mg/day isoniazid for six months.

Data management and quality control

Data were collected by trained data collectors who had previous experience of data collection in a health care setting. The data extraction form was pre-tested on the five percent of the sample size and updated accordingly. All patients included in the previous study who developed TB after ART initiation were included in the cases list, and *HIV* patients exactly matched in age and sex with cases who did not develop TB during their ART follow-up period were included in the controls list. Among all patients with TB co-infection, those with a pair-matched with controls were selected in the final as cases. Controls were selected systematically using simple random sampling, such that among the available list of controls, two controls for each case were selected systematically.

Data processing and analysis

We exported the data entered into Epi Info 7 to IBM SPSS Statistics version 20 for statistical analysis. Descriptive summary measures were used to characterize demographic, behavioral, and baseline clinical characteristics of study participants. Conditional logistic regression analysis was performed to identify determinants of tuberculosis infection among HIV patients during their ART follow-up. The bi-variable analysis was performed and those variables with a *P-value* < 0.25 in the bi-variable analysis were entered into the multivariable analysis to identify the independent determinants. The odds ratio and their 95%CI were determined, and those with a *P-value* < 0.05 were considered as a statistically significant association.

Ethical considerations

Ethical clearance was obtained from St. Paul's Hospital Millennium Medical College, Addis Ababa City Administration Health Bureau, and St. Peter Specialized Hospital. A letter of permission was sent to all participating facilities and permission was obtained from these facilities. A written permission letter was sent to each selected health facility. Also, confidentiality was maintained by using unique identification codes rather than patient names and identifications. A unique study identification number was used in the entire process rather than patient identifiers.

Results

Demographic and behavioral characteristics

Among 566 HIV -positive individuals enrolled and included in the final analysis of our previous retrospective cohort study, 476 individuals were taking ART during their follow-up period. Of those who were taking the ART drugs, 61 developed TB in their follow-up period and the remaining 415 were not co-infected with TB by the end of the study period. For the current study, we got two exact age and sex matches or controls for each 57 TB co-infected HIV -positive individuals who were taking ART. Thus, we compared those 57 cases with 114 controls to assess the determinants of tuberculosis infection while taking ART

(Figure 1).

The comparably higher proportion of study participants from both the cases (20, 35.1%) and the control group (52, 45.6%) is married. Regarding the educational status, more than half of the cases (30, 53.1%) and a half from the controls (57, 50%) either not had formal education or were at the primary level. Likewise, 61.1% (35) of the cases and 57.0% (65) of the controls did not have work. About 77.9% (33) among the cases and 81.6% (93) had 1-3 family members. Besides, less than half percent of both among the cases and the controls were using tobacco, alcohol, soft drugs like Khat, and hard drugs like Shisha

(Table 1).

Clinical characteristics of study participants

We extracted baseline clinical data and analyzed it descriptively for both cases and controls. Nearly a quarter (24.6%, 14) of the cases were either on ambulatory or bedridden functional status during enrollment, however, this happens for about eight percent of the controls (7.9%, 9). 84.2% (48) among the cases and 97.4% (111) of the controls were categorized under either WHO clinical stage I or II. The majority among the cases (68.4%, 39) had a baseline CD4 count <200 cells/µl, while the majority of the controls (60.5%, 69) had a baseline CD4 count >200 cells/µl. Besides, 19.3% (11) of the cases and 6.1% (7) of the controls were anemic at the time of enrollment. Likewise, 42.1% (24) of the cases and 27.2% (31) of the controls were under nutritional status at the baseline. About 21.1% (12) of the cases had a history of previous TB infection, while this is true for 3.5% (4) of the controls. About 15.8% (9) of the cases 36.8% (42) of the controls took the complete isoniazid preventive treatment. In the end, more than half of the cases (52.6%, 30) cases took ART less than a year before they develop TB, however, 71.1% (81) of the controls took the ART for more than 36 months (Table 2).

The median CD4 count among the cases and the controls were 145.00 (IQR, 80-245) and 224.50 (IQR, 123.75-288.00) respectively. The median Hgb value among the cases and the controls were 12.4 (IQR, 10.5-13.95) and 13.85 (IQR=12.70-15.00) respectively. The median length of stay on ART was 8.57 (2.89-34.97) and 53.67 (33.00-60.36) months, respectively

(Table 3).

Association of clinical and behavioral factors with tuberculosis infection

We performed a chi-square test to assess the association of demographic, behavioral, and clinical factors with tuberculosis infection. Among all the variables assessed in the current study, statistically, significant differences were observed among cases and controls based on previous TB history (P < 0.001), baseline functional status (P=0.010), baseline WHO clinical stage (P=0.001), baseline Hgb value (P=0.008), baseline BMI (P=0.049), IPT intake (P=0.005), baseline CD4 value (P<0.001) and duration of taking ART (P<0.001) (Table 2)

Determinants of tuberculosis infection

Bi-variable analysis

We performed bi-variable conditional logistic regression to assess the crude odds ratio. In the bi-variable analysis eight variables give a P-value < 0.25. The variables were previous tuberculosis infection history, baseline functional status, baseline WHO clinical stage, baseline Hgb value, baseline BMI, IPT intake, baseline CD4 value, and months of ART intake. Based on the crude data, all these variables except baseline BMI had a statistically significant association with TB infection among HIV patients who were taking ART. The crude odds ratio and the confidence interval for the variables is as follows, previous tuberculosis infection history (cOR; 2.744, 95%CI;1.454-5.180), baseline functional status (ambulatory, cOR; 3.243, 95%CI;1.269-8.288, bedridden, cOR; 4.00, 95%CI; 0.363-44.133), baseline WHO clinical stage (cOR; 8.293, 95%CI;1.27-38.693), baseline Hgb value (cOR; 1.857, 95%CI;1.125-3.064), IPT intake (cOR; 3.415, 95%CI; 1.437-8.118), baseline CD4 value(cOR; 1.796, 95%CI; 1.273-2.54) and months of ART intake (<12 Months, cOR; 28.391, 95%CI;7.705-104.6, 13-36 Months, cOR; 3.876, 95%CI; 1.416-10.609) (Table 4).

Multi-variable analysis

All the eight variables with a *P-value* < 0.25 in the bi-variable conditional logistic regression were analyzed using a multivariable conditional logistic regression model to identify the independent determinants of tuberculosis infection among *HIV* positives while enrolled on HAART. Among all these variables, a statistically significant association was found between length of stay in ART and tuberculosis infection. Accordingly, *HIV* -positive individuals who were taking anti-retroviral drugs less than 12 months had about six times the odds to develop tuberculosis infection compared to those taking ART drugs for more than 36 months (aOR=5.925, 95%CI=2.649-13.250) (Table 4).

Discussion

In this study, we assessed the demographic, behavioral, and baseline clinical determinants of tuberculosis infection among HIV-positive individuals during their ART follow-up. From our previous retrospective cohort study, we performed a nested case-control study where the cases and controls were pair-matched exactly in age and sex. The main objective was to assess the effect of long-term ART on decreasing the incidence of tuberculosis infection. Accordingly, the finding supports our hypothesis, such that long-term exposure to ART significantly decreases the incidence of TB among HIV patients during their follow-up.

In our previous retrospective study (13), we were able to assess and compare the incidence of tuberculosis infection among HIV patients who were taking ART with those who did not take ART. The findings showed that taking ART significantly decreases the incidence of tuberculosis (10). However, still, a considerable proportion (12.8%, 61) of HIV -positive individuals was infected with TB after ART initiation.

Based on the chi-squared test, TB co-infection among HIV patients after HAART initiation was associated with previous TB history, baseline functional status, baseline WHO clinical stage, baseline Hgb value, baseline BMI, IPT intake, baseline CD4 value, and duration of taking ART. In support of the present study finding, the association of TB infection with previous TB infection history was reported previously (26, 27). The recurrence of TB among the previously treated HIV-positive individuals might be due to the reinfection in a high TB setting like the current study setting (28). Being on the advanced clinical stages such as WHO stage III/IV, lower CD4 count (<200 cells/ μ l), undernutrition (BMI<18.5 Kg/m²), and bedridden functional status at the time of ART enrollment to ART was repeatedly reported to be associated with TB infection among HIV patients(10, 16, 29-31). The advanced clinical stages might be occurred due to the late diagnosis or late healthcare-seeking behavior of study participants (32, 33). These advanced clinical stages at the baseline might lead HIV patients susceptible to subsequent infections including tuberculosis. The other associated factor with TB in the current study is IPT intake status. As reported in previous studies, not taking the complete IPT prophylaxis is a risk factor for TB infection in HIV patients (16, 30, 31, 34). WHO recommends HIV positive individuals take a complete dose of IPT, such that a dose of 300mg isoniazid per day for six months (35).

To look at the strength of association and to identify the independent determinants of TB co-infection among HIV patients during their ART follow-up period, we performed both bi-variable and multi-variable conditional logistic regression analysis. Based on the multivariable analysis, long-term exposure to ART decreases the odds of tuberculosis infection in HIV-positive individuals (36), and the reverse is true. Those HIV positives who took ART for less than 12 months had about six times the odds to be infected with TB compared to those taken for more than 36 months. In support of this study, a higher incidence of TB in the early phase of HAART initiation is reported previously in different settings (37). This higher TB incidence in this stage might have several explanations. First, the advanced clinical stages such as low level of CD4 count at the time of ART initiation might be one factor. Secondly, TB-associated immune-inflammatory immune response (IRIS) might be the other factor (38). To the end, this study has important limitations, including the small sample size and the nature of the retrospective data as it was extracted from patient registries. Besides, the incomplete records were excluded due to the absence of baseline data in the original retrospective cohort study, where we selected cases and controls that might introduce selection bias.

Conclusion

A considerable proportion of individuals were infected with tuberculosis after the initiation of HAART. Baseline immunological and clinical profiles such as WHO stage III/IV, anemia, undernutrition, lower CD4 count and bedridden and ambulatory functional status, previous TB history, and not taking IPT were associated with TB infection. Most of the TB cases occurred among patients who were taking ART for less than a year and the independent determinant of TB infection was the length of stay on HAART. However, the long duration of ART exposure significantly decreases tuberculosis incidence. Screening, *HIV*- positive patients for tuberculosis throughout their ART follow-up would be important.

Abbreviations

ART Antiretroviral Therapy

BMI Body Mass Index

Hgb Hemoglobin

HAART Highly Active Antiretroviral Therapy

HIV Human Immunodeficiency Virus

IPT Isoniazid Preventive Treatment

MDR-TB Multi Drug Resistant

TB Tuberculosis

WHO World Health Organization

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Authors' contribution

AA and AY conceptualized and designed the study. AA, MG, BZ, and ZWB participated in the data collection. AA and ZWB performed the analysis and wrote the original draft. All the authors read and approved the final version of the manuscript.

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Availability of data and materials

The data is available upon request with the corresponding author.

Ethics approval and consent to participate

The study obtained ethical clearance from St. Paul's Hospital Millennium Medical College, Addis Ababa City Administration Health Bureau, and St. Peter Specialized Hospital. Since it is a study based on a review of patient registries, consent was not applicable. Besides, any patient identifier was not used in the entire process to keep confidentiality.

Consent for publication

Not applicable.

Competing interests

The authors have declared that no competing interests exist.

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