Predictors of the occurrence of tuberculosis in HIV-infected adults during the first six months of antiretroviral therapy in Kisangani, DR Congo

ABSTRACT

Objective: To determine the predictive factors for the occurrence of tuberculosis (TB) in adults infected with the human immunodeficiency virus (HIV) during the first 6 months of antiretroviral therapy (ART) in Kisangani.Methods: A case-control study was carried out during the period from January 1, 2017 to December 31, 2018. Clinical data were collected retrospectively from patients receiving antiretroviral therapy in the city of Kisangani. Of a total of 1,161 HIV-infected patients included in this study, 58 of them developed TB. The diagnosis of tuberculosis was made on the presence of Acid-Alcohol-Resistant Bacile (BAAR) on at least one biological sample or on the basis of a bundle of clinical and paraclinical arguments. This test is done during the first six months of initiating anti retroviral therapy (ART). Predictive factors for the onset of TB in these patients on antiretroviral therapy were identified using logistic regression analysis. Results : After multivariate analysis, the independent factors associated with the onset of TB were: being married (OR = 4.456; 95% CI: 1.061-18.713), residence in the town of Tshopo (OR = 7.04; 95% CI: 1.168-42.47) as well as stages 3 and 4 of AIDS disease (OR = 29 95% CI: 4.563-184.872 and OR = 50.8 95% CI: 3.971 -680.995).

Conclusion: The results found by this study highlight the need for active TB testing in HIV-infected individuals. Particular emphasis should be placed on the category of patients on antiretroviral therapy who have one of the independent factors for the onset of TB.

Keywords: Predictors, Tuberculosis, HIV, Antiretroviral Treatment, Kisangani.

Introduction

In Africa, tuberculosis (TB) has been found to be common in the first six months after initiation of antiretroviral therapy (ART). TB occurring during this period is associated with high mortality [1, 2]. It is the most common opportunistic infection found in people living with HIV (PLHIV) [3]. , approximately 5-40% of patients enrolled in antiretroviral therapy services are diagnosed with TB [2]. In Africa, 10% of adults infected with HIV and started on ART die within the first year, TB being the leading cause of death. [1]. Most studies across Africa predicting factors for the onset of

tuberculosis in HIV-infected adults within the first 6 months of initiating ART demonstrate that the independent factors for onset were: male, married subjects, alcohol consumption, family TB patient, BMI <18.5 and OMS4 clinical stages, low CD4, low hemoglobin starting ART. The protective effect of isoniazid and cotrimozazole prophylaxis is also noted [1, 2, 3, 5,6]. Key interventions recommended to reduce the burden of TB in PLHIV include: intensified screening and treatment of TB, isoniazid preventive therapy, control of TB infection and early initiation of ART [7]. However, to our knowledge, there is no study on the main factors favoring the occurrence of TB in PLWHA in DR Congo in general and in the city of Kisangani in particular. It is in this context that the present study aims to determine the predictive factors for the occurrence of TB in adults infected with HIV during the first 6 months of initiating ART in Kisangani.

Population and Methods

This study was carried out in all general hospitals in the city of Kisangani. These hospitals were chosen because of their high attendance by PLHIV and the presence of medical personnel trained in the management of the human immunodeficiency virus / acquired immunodeficiency syndrome (HIV / AIDS). This is a case-control study during the period from January 1, 2017 to December 31, 2018. The cases are all people living with the human immunodeficiency virus (PLWHA) on ART and who have developed TB within the first 6 months of initiating ART while the controls are PLWHA and who have not developed TB within the first 6 months of initiating ART. It is because of a high frequency of tuberculosis during the said period that we chose the six month period as criteria for inclusion of the cases. In total, all people living with the human immunodeficiency virus (PLHIV) on ART made up the population of our study, that is 1,161 patients. Of these, 58 developed TB within the first 6 months of initiating ART. The diagnosis of tuberculosis was made on the presence of BAAR on at least one biological sample or on the basis of a bundle of clinical and paraclinical arguments. Cohort registers of patients on ART, consultation cards for PLWHIV, treatment cards for HIV and TB were reviewed in order to collect the variables of interest, in this case age, sex the civil status, the municipality of residence, the date of the start of initiation of ART, the clinical stages during the diagnosis of HIV disease, the result of BAAR research. The data collected was grouped and presented through the percentage tables. The data were analyzed using SPSS version 20.0 and Microsoft Office Excel 2007. The data were expressed in the tables. We used percentage calculations, mean, Odd Ratio, nonparametric means comparison test, and univariate and multivariate logistic regression were performed to identify the predictors of TB onset among PLHIV on ART. The statistical significance threshold used was set at 0.05 or 5%. The information

Comment [C1]: - State the study design very clearly whether it is matched case control (or) unmatched case control. And if it is matched CC, describe age-matched (or) age & sex matched etc. accordingly.
- Mention the sampling clearly. I have noticed that the ratio of cases and control is 1:3 (3 controls per 1 case). But you failed to mention it. Your sample size is 232 (58 cases and 174 controls). You need to describe it very clearly. (For example: 232 participants (58 cases and 174 controls) were included in this study. Whenever one case was recruited into the study, three control were selected randomly from the study population simultaneously.) or something like that!!!

collected from each PLWHIV file was completely confidential and remains forever disclosed.

They were only used for research purposes after obtaining the authorization of the health authorities of the province of Tshopo before carrying out this study.

Results

A number of factors have been studied for their potential association with the onset of TB in people on ART on ART within the first six months of initiating ART.

1. Age and occurrence of TB in PLWHA on ART

Age was not associated with the occurrence of tuberculosis in PLWHA on ARVs.(See table I).

2. Sex and occurrence of TB in people on ART

In the univariate analysis, it turns out that the male sex is associated with the onset of TB (OR = 1.8 95% CI: 1.01-3.36 p = 0.036). (See table I). During the multivariate analysis, the male sex was not associated with the occurrence of TB (see Table II).

3. Marital status and the occurrence of TB in PLWHA on ART

The marital status of the married couple is associated with the occurrence of TB (OR = 3.7 95% CI: 1.005-13.5 p = 0.049). (See table I and II).

4. Clinical stages of AIDS and the onset of TB in PLWHA on ART

Stages 3 and 4 are associated with the occurrence of TB in PLWHA (OR = 17 95% CI: 3.3-90.5 p = 0.001 and OR = 25 95% CI: 2.3-275, 4 p = 0.009 respectively). (See table I and II).

5. Residence and occurrence of TB in PLWHA on ART

Considering Table I and II, residence in Tshopo commune is associated with the occurrence of TB (OR = 7 95% CI: 1.08-42.5 p = 0.033) while residence in Makiso commune appears protective (OR = 0.2 95% CI: 0.08-0.59 p = 0.003).

In Table II, we present the results of the univariate and multivariate analyzes by logistic regression of the various factors whose difference was significant between the cases and the controls. In the univariate analysis, the results showed that the male sex (OR = 1.8; 95% CI: 1.01-3.36), being married (OR = 3.7; CI at 95%: 1,005-13,5), residence at the commune TSHOPO (OR = 7; 95% CI: 1.08-42.5), stages 3 and 4 of the AIDS disease (OR = 17; IC 95%: 3.3-90.5 and OR = 25; 95% CI: 2.3-275.4 respectively) were associated with the occurrence of tuberculosis in PLWHA. (See table I and II). We then did the multivariate logistic regression analysis of the variables that were found to be predictors of TB occurrence in PLWHA on ART in the univariate analysis in order to determine the best predictors or independent determinants of occurrence of tuberculosis in PLWHA. (See table II).After the multivariate analysis, being married (OR = 4.456; 95% CI: 1.061-18.713), residence in the Tshopo commune (OR = 7.04; 95% CI: 1.168-42.47), stages 3 and 4 of AIDS disease (OR = 29 95% CI: 4.563-184.872 and OR = 50.8 95% CI: 3.971-680.995) were the best predictors of the occurrence of tuberculosis in PVV.(See table II). Male sex was not associated with the occurrence of TB in the multivariate analysis (see Table II).

Discussion

1. Age and occurrence of TB in people on ART

In our study, age was not associated with the onset of tuberculosis in PLWHA on ARVs (see Table I). This resembles the result of Panella et al. in Burkina Faso, in 2014, DANIEL W.G et al. in Tanzania, in 2018; PECK R. N et al. in Tanzania in 2012 where they found that age was not associated with the onset of tuberculosis [2,4,7].

Other shares ABGRALL et al. In France, in 1997-2008 had found that the age group varying between 15 and 46 years with an average of 39.7 ± 11.2 years was associated with the occurrence of TB in During the first six months of initiating ART, TB presents itself as a disease that mainly affects young adults. [9].

2. Sex and occurrence of TB in people on ART

In our study, it turns out that male patients had an increased risk of developing TB (OR = 1.8 95% CI: 1.01-3.36 p = 0.036) (see Table I). Several studies have had a similar result, including an Ethiopian study by Panela et al. in 2014 (RR: 1.48, CI: 95%: 1.02-2.14), de Brennan et al. , Gupta et al. In South Africa in 2013 (RR: 1.2 95% CI: 1.1-1.2),

a Mexican study by Martin –Echevarria et al. in 2014 also that of Dar es Salaam in Tanzania by Liu et al. in 2015 predicting males to be at greatest risk of developing TB within the first six months of initiating ART. TB presents itself as a disease that predominantly affects males. On the one hand, social behavior and hormonal differences between the susceptibility of men and women to developed TB have been suggested as a possible explanation for the prevalence of TB in adult men. On the other hand, the difference in Gender in the susceptibility to develop TB is clinically important because it has been shown that male patients have a higher risk of mortality [Gupta, A 2012, Panela, P 2014; ABGRALL 2008, Echevarria, E. M. 2014.]. [3, 5, 10,13].

3. Marital status and the occurrence of TB in people on ART

The results of our study showed that marriage is associated with the onset of TB (OR = 3.7 95% CI: 1.005-13.5 p = 0.049) (See Table I and II). already reported in other countries, like that made by Yihun et al. in Burkina Faso assigning a very high risk to married patients. Indeed, it is difficult to establish with certainty the link between TB and marriage. However, we think it shows in the idea that those who marry and stay united have the advantage of being infected because of the importance of promiscuity with the spouse living in the same house. [6]. Studies in The Gambia and Guinea Bissau have reported contrary results where divorced and widowed patients were at higher risk of developing TB within the first six months of initiating ART. Marriage has a negative effect on the transmission of TB, in that those who marry have better health because of the positive psychological and social impact [3].

4. Clinical stages of AIDS and occurrence of TB in people on ART

In our study, we found that stages 3 and 4 are associated with the onset of TB in PVV (OR = 17 95% CI: 3.3-90.5 p = 0.001 and OR = 25 95% CI %: 2.3-275.4 p = 0.009 respectively) (See Table II) .This study is in agreement with several other studies, for example, in 2015 by Lawn et al. in South Africa reported that patients who had started ART at clinical stages 3 and 4 of WHO were 3.6 times more likely to have TB. [14] another study in Ethiopia by Melkanu et al. Found that the development of active TB was significantly higher in patients who were in WHO clinical stages 3 and 4 compared to those in clinical stages 1 and 2 (OR = 2.29,; p = 0.003) [4]. Also similar to those found by Panela et al. in Burkina-Faso and Abgrall et al. in France who have shown that the risk was higher in stage IV patients (RR: 6, 41, 95% CI: 2.86-14.38) [5, 10]. This could

be explained by the that once patients reach an advanced stage, the immune defense capacity will be minimal, which would expose them to TB infection. It should also be mentioned that TB is one of the criteria for defining AIDS to classify patients in the WHO clinical classification. Where they came from in the advanced stages of AIDS. This shows the importance of implementing the innovation of algorithms for active tuberculosis research among PLHIV as advocated by the NLP.

5. Residence and occurrence of TB in people on ART

It is difficult to establish with certainty the link between TB and residence in the municipality of Tshopo. However, we think it shows in the idea that those who live in the Tshopo commune have the advantage of contaminating themselves because of the importance of crowded living conditions.

Conclusion

The predictive factors for the onset of tuberculosis in people on ART are: being married, living in Tshopo Municipality, clinical stages 3 and 4 of AIDS disease. Our results underscore the need for active tuberculosis research among PLHIV in African cohorts. special emphasis will be placed on the category of patients mentioned above, that is to say those with one of the factors independent of the occurrence of TB on ART

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Tableau I: **Comparison of the socio-demographic characteristics of cases and controls of HIV-TB co-infection**

variables	Case, N =58 (%)	Control, N = 174(%)	~~OR (IC 95%)~~	P-value
Age				
15-24	1(1,7%)	11(6,3%)	0,2(0,03-2,9)	0,199
25-34	14(24,14%)	38(21,84%)	0,2(0,2-4,2)	0,0339
35-44	24(41,38%)	70(40,2%)	0,3(0,02-4,5)	0,363
45-54	15(25,9%)	34(19,5%)	0,7(0,21-2,2)	0,405
≥55	4(6,8%)	8(4,6%)	2,8(0,28-26,6)	0,382
Sex				
Male	**30 (51,7%)**	**64 (36,8%)**	**1,8(1,01-3,36)**	**0,036**
Female	28 (48,3%)	110 (63,2%)	0,7(0,5-0,9)	0,036
Marital status				
Married	**32 (55,2%)**	**84 (48,3%)**	**3,7(1,005-13,5)**	**0,049**
Single	22(37,9%)	51(29,3)	1,2(0,6-2,3)	0,564
Divorced	3(5,2%)	24(13,8%)	0,2(0,02-1,4)	0,098
Widower	1(1,7%)	15(8,6%)	0,1(0,18-1,2)	0,069
Residence				
Makiso	7 (12,1%)	52 (29,9%)	0,2(0,08-0,59)	0,003
Tshopo	**18 (31%)**	**30 (17,2%)**	**7(1,08-42,5)**	**0,033**
Kabondo	19 (32,8%)	50 (28,7%)	1,2(0,2-6,7)	0,805
Mangobo	8 (13,8%)	15 (8,6%)	0,28(0,06-1,4)	0,118
Lubunga	4 (6,9%)	15 (8,6%)	0,4(0,08-1,99)	0,268
Kisangani	2 (3,4%)	12 (6,9%)	0,3(0,06-1,8)	0,186

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-Delete OR (IC 95%)

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Comment [C3]: Analyse to see if 'age' distribution is different between cases and controls using chi-square test and show its p-value !

Comment [C4]: Use chi-square test to see if 'sex' distribution is different between cases and controls and show its p-value !

Comment [C5]: Use chi-square test to see if 'marital status' is different between cases and controls and show its p-value !

Comment [C6]: Use chi-square test to see if 'residence' is different between cases and controls and show its p-value !

Tableau II : Predictors of TB onset in PLWA on ART: univariate and multivariate analysis

Variables	CasN=58(%)	Control , N=174 (%)	OR brute (IC à 95%)	OR ajusté (IC à 95%)	P – value
Sex					
Male	30 (51,7%)	64 (36,8%)	1,8 (1,01-3,36)	0,5 (0,257-1,033)	0,062
Female	28 (48,3%)	110 (63,2%)	1	1	
Marital status					
Married	32 (55,2%)	84 (48,3%)	3,7 (1,005-13,5)	4,5 (1,06-18,7)	0,041
Single	22 (37,9%)	51 (29,3%)	1,2 (0,6-2,3)	1,3 (0,635-2,829)	0,389
Divorced	3 (5,2)	24 (13,8)	0,2 (0,02-1,4)	0,13 (0,014-1,225)	0,075
Widower	1 (1,7%)	15 (8,6%)	1	1	
Residence					
MAKISO	7 (12,1%)	52 (29,9%)	0,2 (0,08-0,059)	0,7 (0,122-4,536)	0,750
TSHOPO	18 (31)	30 (17,2)	7 (1,08-42,5)	7,04 (1,168-42,47)	0,033
KABONDO	19 (32,8%)	50 (28,7%)	1,2 (0,2-6,7)	0,2(0,044-1,357)	0,101
MANGOBO	8 (13,8%)	15 (8,6%)	0,28 (0,06-1,4)	0,47(0,103-2,163)	0,333
LUBUNGA	4 (6,9)	15 (8,6)	0,4 (0,08-1,99)	0,35 (0,047-2,617)	0,307
KISANGANI	2 (3,4)	12 (6,9)	1	1	

Comment [C7]: Whose p-value ; OR brute or OR ajusté ?

Variables	CasN=58(%)	Control , N=174 (%)	OR brute (IC à 95%)	OR ajusté (IC à 95%)	P – value
CLINICAL STAGES					
STAGES 1	1 (1,7%)	20 (11,5%)	1	1	
STAGES 2	3 (5,2)	56 (32,2)	0,09 (0,01-0,7)	0,069 (0,008-0,578)	0,014
STAGES 3	49 (84,5%)	94 (54%)	17 (3,3-90,5)	29 (4,56-184,87)	0,000
STAGES 4	5 (8,6%)	4 (2,3%)	25 (2,3-275,4)	50,8 (3,79-680,995)	0,003

Comment [C7]: Whose p-value ; OR brute or OR ajusté ?