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Research Article

Incidence of Active Tuberculosis and Risk Factors in Patients Infected with HIV at the Start of Antiretroviral Treatment in Luanda 2016/2017

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Abstract

Background: In 2017, an estimated 920 000 people living with HIV (PLHIV) have fallen ill with Tuberculosis (TB) worldwide. Angola is one of 20 countries with the highest estimated numbers of incident TB cases among PLHIV. The objective of this study was to assess the incidence and risk factors for active TB among HIV patients during the first 12 months of initial antiretroviral therapy (ART) in Luanda.

Methods: A cohort study with a 12 month, follow-up period was conducted in 267 HIV patients that started ART and that had a negative screening for active TB in 2016. The outcome was the development of active TB during the follow-up period. Questionnaires and review of clinical files were used for data collection. Significance level was set at PV<0.05 for all hypothesis tests. Pearson chi-squared (χ^2) tests, followed by multivariable logistic regression modelling were used to identify factors associated with active TB; we had PPD tuberculin deficiency at national level for perform the Mantoux test.

Results: The incidence of active tuberculosis was 12.0% (32 patients out of the 267 followed during the 12-months period), from which 59,4% (19) were between 30-49 years old, 75% (24) of coinfected developed pulmonary tuberculosis. 65,6% (21) patients coinfected were female. Independent associated factors for active TB were: viral load higher than 10,000 copies [OR = 16.8; 95% CI: 1.7-70; p < 0.001]; and having less than 2 meals per day [OR = 17.2; 95%: 2.1-40; p < 0.01.

Conclusion: The high incidence of tuberculosis in HIV patients makes it urgent to implement strategies that lead to timely identification, treatment, prophylaxis and prevention of TB among HIV patients on ART. Our study reinforces the results of other colleagues in Luanda province that clearly show the urgent need for stringent Isoniazide prophylactic therapy policy implementation and increased coverage among HIV patients with a negative TB screening.

Keywords: TB/HIV Coinfection; Incidence; Risk Factors; Luanda

Abbreviations

AIDS: Acquired Immunodeficiency Syndrome; ART: Antiretroviral Treatment; HIV: Human Immunodeficiency Virus; I: Incidence; INH: Isoniazid; PNCT (do português): National Tuberculosis Control Program; PLHIV: People Living with HIV; TB: Tuberculosis; χ^2: Pearson Chi-squared Tests

Introduction

In Angola, according to the report of the National Tuberculosis Control Program (PNCT) 2016, it said that, throughout their lives, 5% of HIV-negative individuals can develop active TB. people with HIV and in countries with high TB rates, the risk of reactivating latent TB to active TB is 15%, due to the immunosuppression that

causes HIV. TB is an opportunistic disease most common in the course of HIV infection and a high risk factor for people with HIV to more rapidly develop AIDS, and increased mortality due to TB/HIV co-infection [1].

Across the country in 2016, 27,579 cases of TB in all its forms were tested for HIV, corresponding to 45% of the total registered cases, and of these 10% were co-infected with TB/HIV. Among new BK (+) cases, 12,150 TB patients (49%) were tested for HIV, of whom 11% were HIV positive [1].

In the province of Luanda, 43% of TB patients were tested for HIV screening, and of these 13% were co-infected with TB/HIV, in 2015, 41% of TB patients were tested for HIV screening and 14.3% were positive [1]. It is estimated that between 30 and 50% of all new TB cases detected are associated with HIV and 40% of AIDS deaths are due to TB [2].

we conduct this study to determine the incidence of tuberculosis and assess its association with risk factors in HIV-infected patients in Luanda, 2016/2017.

Methodology

We conducted a cohort study, with 12 month follow-up in patients infected with HIV that started ART and who were not coinfected with tuberculosis, to know the incidence of tuberculosis and risk factors in HIV-infected patients starting Anti-Retroviral Treatment (ART) in Luanda, in the period of 2016/2017.

were included all HIV-infected patients that were not infected with tuberculosis during the last quarter of 2016. we exclude all patients under 14 years of age, pregnant patients, patients with TB and patients suspected of tuberculosis, we obtained a sample of 267 patients that underwent a questionnaire and monthly screening for TB.

A database was created in EpiInfo statistical software (version 7.2.0.1), where the collected data were digitized. A descriptive analysis was performed on sociodemographic data (gender, age, marital status, education level and occupation) by calculating frequencies and chi-square to determine whether there is statistical significance in this group of variables; the standard deviation and the mean of the age variable were also calculated.

The incidence (I) of TB was defined as the number of TB cases that occur per 100 patients/year after starting ART. It was calculated using the following formula: I = number of diagnosed TB cases during follow-up/ Sample *100.

To analyze the association between the outcome and each of the risk factors of interest, a bivariate analysis was performed, with the objective of calculating the relative risk, followed by a multivariate analysis to study the independent effects of each factor, through the use of logistic regression, using a confidence interval of 95% (CI 95%), and a value of p = <0.05.

The present study had the "Positive" opinion of the ethics committee of the Ministry of Health; process nº: 23/2017. A verbal consent was obtained from the participants, respecting the decision to participate and there was confidentiality.

Results

The incidence of tuberculosis was 11.9% (95% CI = 8.3 - 16.5) in 100 HIV patients starting ART, 9.3% with pulmonary TB and 2.6% with extrapulmonary TB (Peripheral lymph node 2.2%; Bone 0.4%).

Graph 1: Distribution of HIV patients that developed active tuberculosis during the 12 months of follow-up.

	HIV patients on ART		
Variables	**With TB n = 32 (%)**	**WithoutTB n = 235 %**	**PV**
Sex:			0,07
Female	21 (65,6)	164 (69,8)	
Male	11 (34,4)	71 (30,2)	
Age group:			
14-29	8 (25,0)	43 (18,3)	0,3
30-49	19 (59,4)	155 (66,0)	
≥50	5 (15,6)	37 (15,7)	
Age average:	38,7 ± 11,0	39 ± 10,9	
Marital status:			
Married/marital	10 (31,2)	107 (45,5)	
Divorced/Separated	3 (9,4)	21 (9)	0,2
Not married	14 (43,8)	91 (38,7)	
Widower	5 (15,6)	16 (6,8)	
School level:			
Primary school	12 (37,5)	45 (19,2)	0,1
Secondary education	18 (56,3)	165 (70,2)	
University education	1 (3,1)	15 (6,4)	
Illiterate	1 (3,1)	10 (4,2)	

Table 1: Distribution of patients according to sociodemographic characteristics.

Risk factor	With TB n = 32 (%)	Without TB n = 235 (%)	Total n = 267 (%)
Alcoholic habits:			
Yes	9 (28,1)	3 (1,3)	12 (4,5)
No	23 (71,9)	232 (98,7)	255 (95,5)
≤ 2 daily meals:			
Yes	19 (59,4)	26 (11,1)	45 (16,9)
No	13 (40,6)	209 (88,9)	222 (83,1)
Smokers:			
Yes	2 (6,2)	1 (0,4)	3 (1,1)
No	30 (93,8)	234 (99,6)	264 (98,9)
Illicit drug user:			
Yes	0 (00)	1 (0,4)	1 (0,4)
No	32 (100)	234 (99,6)	174 (99,6)
Night work:			
Yes	2 (6,5)	3 (1,3)	5 (1,9)
No	29 (93,5)	230 (98,7)	259 (98,1)
Work more than 44 Hours/ week: Yes	4 (28,1)	43 (18,3)	52 (19,5)
No	23 (71,88)	192 (81,7)	215 (80,5)

Table 2: Distribution of lifestyle factors associated with the risk of developing active tuberculosis in HIV-infected patients.

Risk Factors	With TB n = 32 (%)	Without TB n = 235 (%)	Total n = 267 (%)
WHO classification:			
I/II	2 (6,2)	195 (82,9)	197 (73,8)
III/IV	30 (93,9)	40 (17,1)	70 (26,2)
LTCD4:			
<250	22 (68,8)	72 (30,6)	94 (35,2)
≥250	10 (31,2)	163 (69,4)	174 (64,8)
Viral charge; copies/ mm^3:			
<10.000	5 (15,6)	169 (71,9)	174 (65,1)
≥10.000	27 (84,4)	66 (28,1)	93 (34,8)
Constant contact with TB patient:			
Yes	24 (75,0)	27 (11,5)	51 (19,1)
Não	8 (25,0)	208 (88,5)	216 (80,9)
Low BMI:			
Yes	25 (78,1)	51 (21,7)	76 (28,5)
No	7 (21,9)	184 (78,3)	191 (71,5)
TB history:			
Yes	4 (12,5)	1 (0,4)	5 (1,9)
No	28 (87,5)	234 (99,6)	262 (98,1)
No isoniazid prophylaxis			
Yes	15 (46,9)	13 (5,5)	28(10,5)
No	17 (53,1)	222 (94,5)	239(89,5)
Pneumonia history:			
Yes	2 (6,2)	1 (0,4)	3 (1,1)
No	30 (93,8)	234 (99,6)	264 (98,9)

Table 3: Distribution of clinical/laboratory factors associated with the risk of developing active tuberculosis in HIV-infected patients.

Risk factor	RR	IC 95%	VP
Alcohol consumer	8,3	5,0 - 13,8	<0.001
≤ 2 Meals daily	7,2	3,8 - 13,5	<0.001
Smokers	5,9	2,4 - 13,9	0.03
Illicit drug user	0,0	_____	0.80
Night shifts	3,5	1,2 - 11	0.10
Work more than 46 hours/ week	1,7	0,8 - 3,4	0.08

Table 4: Bivariate statistical analysis of lifestyle factors associated with the risk of developing active tuberculosis in HIV-infected patients.

Risk factors	RR	IC 95%	VP
WHO stage: III,IV	42,5	10,3 - 172	<0,001
Constant contact with TB patient	12,7	6,1 - 26,6	<0,001
Viral load greater than 10,000 copies	10,1	4,0 - 25,4	<0,001
Low BMI	8,9	4,1 - 19,9	<0,001
TB history	7,5	4,3 - 13,1	<0,001
No isoniazid prophylaxis	7,5	4,2 - 13,4	<0,001
Pneumonia history	5,8	2,5 - 13,9	0,02
LTCD4 <250	4,0	2,0 - 8,2	<0,001

Table 5: Bivariate statistical analysis of clinical/laboratory factors associated with the risk of developing active tuberculosis in HIV-infected patients.

Risk Factors	Bivariate analysis		Multivariate analysis		
	RR	IC 95%	ORa	IC 95%	VP
Viral charge; ≥10 mil copies/ mm^3	10,1	4,0 - 25,4	16,8	1,7-170	<0,001
≤ 2 daily meals	7,2	3,8 - 13,5	17,2	2,1-140	0,008

Table 6: Multivariate statistical analysis of factors associated with the risk of developing active tuberculosis in HIV-infected patients.

Discussion

Regarding the outcome found, 59.4% of the coinfected population is between 30 and 49 years old, with an average of 38.7 years, the values recorded follow the national standard, demonstrating a predominance of involvement in the age group active of life, which corroborates with publications that describe that approximately 80% of tuberculosis cases affect this fringe of the population [1-5], it is assumed that at this stage of life the person is more exposed due to the greater contact with other individuals and lifestyle where permissibility and promiscuity are greater, increasing exposure to tuberculosis. According to 2016 data from the PNCT, a total of 13.3% were reported in children under 15 years of age and 86.7% in over 15 years of age in Luanda, which implies that the adult population is more susceptible to developing active tuberculosis.

The level of education combined with the low economic level in many literatures show association with the incidence of tuberculosis, since TB usually affects people with less education, with more disadvantaged incomes and poverty, this conditions have a great influence for an individual to develop active tuberculosis, other authors [6,7,10] observed a growing trend in the presence of tuberculosis among AIDS cases, as the level of schooling of the cases decreases. In the present study, sociodemographic factors did not constitute a significant risk for the development of active tuberculosis.

There is an increased risk of TB in endemic areas for HIV patients soon after contamination, while the immune system responsible for the defense of the organism is still conserved, there will be greater resistance to the bacillus. This is where isoniazid (INH) is introduced as a prophylactic treatment against active tuberculosis. According to the WHO, it is estimated that in regions with a high prevalence of TB, the risk of reactivating latent TB to active TB is 15% [12].

Of the 267 patients, 32 (11.9%) developed active tuberculosis. Some authors [12] found that the incidence of TB was doubled in the first year after HIV infection and four times higher in the two following years; others state that the chance of reactivation of tuberculosis latency increases on average 29-fold in an HIV-infected patient.

Studies carried out in areas with high TB prevalence in developing countries also show a higher incidence among the population with HIV [3] in contrast to what was found in industrialized countries, where the prevalence of co-infection is much lower [22,23].

If there is a greater capacity to monitor and respond to public health problems in developed countries, on the other hand, the greatest public health problems are found in developing countries, with a weak response capacity, deficient technology, weak diagnostic competence and human resources, and this is a reality found in the province of Luanda.

The incidence of TB in the province of Luanda was 119.2 x 100,000 inhabitants, this population was tested for HIV in 2016 and 13.3% are co-infected [1], which is not far from the results found in the present study, which was 11,9 in 100 patients per year, high figures when compared to some authors from the Africa

southern region that showed in their studies that the incidence of co-infection in sub-Saharan Africa is 0.9 to 7.8 in 100 patients per year [15], and 10.9 cases in 100 patients per year in South Africa [16].

Among the clinical forms of the cases of tuberculosis associated with HIV found in this study, it was observed that there is a predominance of the pulmonary form, with a higher incidence of 9.3 in 100 patients per year, this is the most frequent form of tuberculosis in Luanda. second report of the PNCT [1], which had a significant difference in relation to the extrapulmonary forms in patients with HIV.

Some authors [17,18] in their findings show that the extrapulmonary form is more frequent in individuals with LTCD4 lower than 100/ʯL. Among the extrapulmonary forms, the lymph node was the most frequent, which corroborates other literature, for the degree of immunosuppression of the studied group [17,19].

Early diagnosis of active tuberculosis in individuals with HIV reduces the proliferation time of Mycobacterium tuberculosis, even when hosted in a weakened organism, if an early treatment is successful, it reduces the probability of formation of pulmonary cavitations, which is the most effective way of propagating the bacillus, in addition to representing greater severity for the patient. Early treatment of TB cases in HIV patients increases the chances of survival, this is possible with the institution of early diagnosis and specific treatment, because when there is already a spread of the disease, the risk of death increases even when antituberculostatic drugs are used, the treatment of latent tuberculosis in HIV patients significantly prevents the development of TB in this group of individuals, but the lack of diagnostic reagents contributes to late identification and favors the development of active tuberculosis.

Effective diagnosis and treatment are part of the National recommendations for the treatment of latent infection in patients with HIV. Monotherapy with INH is recommended in regimen between 6 and 9 months, the daily intake should be decided based on a relationship between adherence, risk of adverse reactions and efficacy. This treatment is still a very recent indication in Luanda, there are no local studies on the future consequences of this procedure, as treatment with INH requires laboratory control due to its risk of hepatotoxicity, metabolic acidosis and peripheral neuropathy.[21] On the other hand, this new indication for chemoprophylaxis led us to some challenges to implement it, both for the physician (due to the lack of familiarity with the new norms, and the lack of tests to control liver function) and the patient (by difficulty of adhering to the treatment for a long period and the amount of medication to be taken daily).

In the present study, TB prophylaxis was indicated in 28 patients (10.5%) based on medical reports, of these 15 developed active tuberculosis, the justification for so many cases in patients on chemoprophylaxis is that 14 of these were already in the WHO stage III/IV. A late and untimely visit to health services may be at the origin of these cases of co-infection, because the later the therapeutic intervention begins, the less are the chances of combating opportunistic infections, in the face of immunosuppression.

The lifestyle of some patients can become a determining factor for the development of active tuberculosis. If he has alcohol or tobacco use, these factors are significantly associated with TB.

Other authors [24] state that if smokers stop smoking, the risk of death from tuberculosis decreases significantly, when compared to those who continue to smoke, which implies that when policies are created to reduce the population of smokers, there will be a decrease in tuberculosis-related mortality. A prospective study conducted in rural China in 2017 [25] highlighted the assumption that smoking is an independent risk factor for tuberculosis infection, especially in elderly smokers, in addition to demonstrating a direct correlation between smoking history (pack-years) and the risk of latent tuberculosis.

Authors [21] reported that alcohol consumption was associated with an increased risk of tuberculosis when accompanied by smoking, which is another risk factor for the development of active tuberculosis. These factors can also lead to loss of appetite and gradual deterioration of nutritional status.

The meal is the most viable way for the body to find essential nutrients for its metabolic activities and subsistence, when the patient's nutritional status is compromised, it also has a great influence on the patient's immune status, which can cause a reduction in body mass index, therefore, the addition of food supplements should be included in the set of medications to be taken, and there is also a need to carry out routine HIV consultations

at the same time as nutrition consultations, in order to assess the anthropometric characteristics, control the patient's daily diet patient, control of lipodystrophy and other dietary guidelines are fundamental aspects for controlling the patient's condition.

After analyzing the factors associated with the risk of developing active TB, we performed a multivariate analysis of them, using the logistic regression model, and showed a statistically significant association with the following factors: Viral load greater than 10,000 copies/mm^3 and taking <2 Meals daily.

Deficient and insufficient nutrient intake was also a predisposing factor for the development of active tuberculosis. There is a close relationship between them, which is a reason for the reactivation of the bacillus in a state of latency [26,27]. Body mass depends a lot on the content of nutrients ingested, a regulated and balanced diet can be a protective factor against chronic diseases, as they will gain greater resistance muscle and systemic resistance. As in this study, other studies [3,28] also found confirmation that eating disorders and, consequently, weight loss are relevant factors related to TB.

The increase in viral load implies a mass destruction of LTCD4 cells, as it is inside them that the virus carry out their replication, and often as a nonspecific response, the cells undergo apoptosis, thus reducing the carrier's immune system. The test-treat strategy, which is a strategy of initiating therapy soon after a positive HIV diagnosis. The quantification of the viral load in the systemic circulation is of paramount importance because it allows us to monitor the disease, the lack and rare availability of diagnostic means often contributes to the delay of patients to their consultations, causing the medication to be not taken in a timely manner, the accompanying doctor is left with an inconclusive diagnosis when the patient is often does not bring all the results of the laboratory tests that were requested to the routine consultation, contributing to a late and not timely action.

The increase in the frequency of active tuberculosis in people with HIV/AIDS has established an obvious burden on the Health Services, showing the existing deficiencies in both Control Programs (TB/HIV), and has presented challenges to Health Professionals in the diagnosis and treatment of these diseases.

Conclusion

The high incidence of tuberculosis in HIV patients makes it urgent to implement strategies that lead to timely identification, treatment, prophylaxis and prevention of TB among HIV patients on ART. Our study reinforces the results of other colleagues in Angola that clearly show the urgent need for stringent Isoniazide prophylactic therapy policy implementation and increased coverage among HIV patients with a negative TB screening.

HIV/TB coinfection has become a pathology of high social complexity, the actions to be implemented for its elimination is not solely the responsibility of the Ministry of Health and its bodies, but depends on an intersectoral (Multiministry) partnership and management, such as : Ministry of Education (insertion of the subject of education for health as a curricular), the Ministry of Urbanism and Housing, and Ministry of Territory Administration (with investment in the areas of housing, and organization of the new neighborhoods that emerge from in order to create a healthy environment, improve sanitation, and the practical implementation of the actions of community agents), Ministry of Transport (so that people can move comfortably and in conditions of required sanitation), Ministry of Agriculture and Rural Development, and Ministry of Commerce (to ensure sufficient, rich and healthy food) and others. The inability of sectoral partnerships frustrates the great goals and objectives of the Ministry of Health and the programs for both pathologies.

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Conflict of Interest

We declare that they have no conflict of interest.

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