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## OCCURRENCE OF CONFECTION BY HISTOPLASMOSIS AND TUBERCULOSIS IN PATIENTS LIVING WITH HIV: STUDY IN A REFERENCE UNIT IN THE STATE OF GOIÁS

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*Marcela Diniz Rassi Rincon*

*Taiguara Fraga Guimarães*

*Roberta Abrão Pacheco Rodrigues*

*Cassia Silva de Miranda Godoy*

*Renata de Bastos Ascenço Soares*

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## INTRODUCTION

Histoplasmosis is an endemic mycosis caused by *Histoplasma capsulatum* and was first described by Samuel Darling<sup>1</sup>. This disease is widely distributed in the Americas, with high prevalence rates in the central and southern regions of the United States, along the Mississippi and Ohio river valleys; Mexico; Honduras; Guatemala; Nicaragua; Panama; the Caribbean islands; Venezuela; Colombia; Peru; Brazil; Argentina and Uruguay. Some cases have also been described in Africa and Asia, mainly in Thailand, Malaysia, Indonesia, India and Vietnam. And rare cases have been described on the European continent, with the exception of Italy. Epidemiologically speaking, it is important to point out that in Brazil, rare cases of histoplasmosis had been described before the 1980s, since the vast majority of cases were diagnosed after the discovery of Acquired Human Immunodeficiency Syndrome, as a result of this mycosis being an opportunistic disease that suffered major increases in incidence after the discovery of AIDS<sup>1,2</sup>. It should be noted that this mycosis can affect both immunocompetent and immunosuppressed individuals<sup>3</sup>.

Hundreds of thousands of people are infected with *H. capsulatum* every year in North and Central America<sup>6</sup> and this data shows the importance of this mycosis in these regions, since in addition to spending a lot of money on medical care, patients also have to pay for treatment, which can burden the health system.

In this sense, Brazil's large territory, difficult access to health centers and lack of epidemiological studies make it difficult to quantify cases of histoplasmosis<sup>4,5</sup>. The main studies describing the prevalence of histoplasmosis in Brazil were carried out in large urban centers, which have great differences in climate, environment and urban development<sup>7,8</sup>. The studies published on the subject have data mainly on the prevalence of the states of Rio

Grande do Sul, Minas Gerais; the Amazon region and the cities of Rio de Janeiro, Fortaleza, Uberaba and Uberlândia<sup>7,8,9,10,11</sup>. A study carried out in Minas Gerais revealed that 17% of the 417 miners studied were positive for histoplasmin<sup>12</sup>. In contrast, in a study carried out in the Amazon region, histoplasmin positivity rates ranged from 27 to 43%<sup>13</sup>. Thus, little data is available on histoplasmosis cases in the state of Goiás. In this sense, it is coherent to analyze the incidence of histoplasmosis in patients co-infected with HIV and tuberculosis.

Furthermore, it is important to note that AIDS can be a determining factor in histoplasma infection, since the individual becomes immunosuppressed, favoring infection by the fungus. This fact is more evident in developing countries, since the difficulty of access to treatment favors the occurrence of opportunistic diseases<sup>14</sup>. In addition, it is worth noting that opportunistic infections do not only occur with fungi, but also with bacteria, such as *Mycobacterium tuberculosis*, which leads opportunistic infections in these patients, as well as having a high incidence and often leading to death<sup>14</sup>. As far as tuberculosis is concerned, this disease is also a serious health problem, given that it has a large number of infected individuals and there is a continuity in its incidence with significant rates of death complications and deaths<sup>14</sup>.

This brings us to a scenario in which the occurrence of tuberculosis and histoplasmosis in patients co-infected with HIV, although possible and incident, has not been studied in Brazil. And when these diseases occur simultaneously, there is a loss of treatment, diagnosis and patient progression, which is a direct consequence of drug interaction<sup>15,16</sup>. In summary, interaction occurs when treatment is carried out with rifampicin, itraconazole and antiretroviral therapies, especially when non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors (PIs) are prescribed simultaneously<sup>17,18</sup>.

A study carried out in Colombia states that little data is available on the co-infection of TB and histoplasmosis in AIDS patients<sup>19</sup>. In French Guiana, a co-infection rate of 8% was reported. Therefore, an analysis was carried out from 1992 to 2011 to describe a little more about this existing co-infection and the difficulties of treatment, as well as its outcomes<sup>19</sup>. And this study found 14 cases of TB and histoplasmosis in HIV co-infected patients, predominantly males, two of whom failed treatment and 01 of the 14 patients died in the eighth month of treatment with anti-TB drugs which included rifampicin and had previously received amphotericin B and then treatment with itraconazole. In these three patients, it was likely that the interaction between itraconazole and rifampicin resulted in undetectable azole levels, which contributed to treatment failure<sup>17,18,19</sup>.

The same Colombian study concluded that patients with histoplasmosis and TB co-infection had advanced HIV infection with an average CD4 count of 70 cells/mL, and the majority of these patients (71%) were on antiretroviral treatment. Thus, they were at great risk of infection with intracellular pathogens such as TB and histoplasmosis. In addition, significant therapeutic failures with itraconazole in AIDS patients who had co-infection with histoplasmosis and TB have been reported<sup>16,21,22,23</sup>.

It is important to point out that, despite the drug interaction that occurs in the treatment of these diseases that appear in HIV-positive patients, there are several treatment alternatives that may be able to avoid this interaction, but most of them are not acceptable. An example of this is rifabutin, which could be used instead of rifampicin, but it also decreases the serum concentration of itraconazole<sup>24</sup> and is not available in many of the countries where these infections occur. In addition, the literature shows that amphotericin B can

be used instead of itraconazole, but there are concerns about adverse effects and the need for parenteral administration. Another drug that could be used is posaconazole, which has few cytochrome P450 interactions when compared to other azoles and is therefore an attractive alternative. Another option that may be superior to any of the above is replacing rifampicin with moxifloxacin and this was the option studied in the Colombian study, which found no treatment failures in patients who were treated in this way. The study concluded that the use of moxifloxacin instead of rifampicin produces satisfactory results.

Regarding alternative drugs, moxifloxacin is an antibiotic used to treat infections caused by various types of bacteria. It works by killing these bacteria by interfering with the enzymes that control the bacteria's cell proliferation. It should not be used together with anti-psychotics, erythromycin or in patients with cirrhosis or low heart rate. Posaconazole is used for fungal infections and is slowly absorbed and eliminated, with extensive penetration into peripheral tissues and no circulating metabolites.

In view of the fact that TB and histoplasmosis occur in HIV-positive patients, it is necessary to study both the incidence and alternative forms of treatment so that the outcome of the disease is positive. In addition, it is important to look for alternative therapies for dual infection due to the drug interaction that occurs between rifampicin and itraconazole. Therefore, there was a need to analyze the incidence of histoplasmosis and tuberculosis in HIV-positive patients in the state of Goiás, and the lack of publications on the subject makes this study new, interesting and relevant, contributing to the construction of medical knowledge on the epidemiology of these co-infections and to medical education in Brazil.

## OBJECTIVES

**General objective:** To analyze the epidemiology of tuberculosis and histoplasmosis in HIV-positive patients in the state of Goiás.

### SPECIFIC OBJECTIVES:

- To measure the incidence of co-infection of tuberculosis and histoplasmosis in HIV-positive patients over a 5-year period;
- To highlight the difficulties in treating tuberculosis and histoplasmosis in HIV co-infected patients;
- To analyze the evolution (outcome and survival) of histoplasmosis and tuberculosis in HIV-positive patients;
- To describe the clinical-epidemiological and laboratory aspects of associated tuberculosis in patients undergoing therapeutic follow-up for disseminated histoplasmosis and HIV/AIDS;

## MATERIALS AND METHODS

*Population and study site:* the study population was made up of patients diagnosed with HIV/AIDS co-infected with tuberculosis and histoplasmosis in the last five years (2012-2016) treated at the Dr. Anuar Auad State Hospital for Tropical Diseases HDT/HAA. The HDT is a unit of the Goiás State Health Department, which is part of the Brazilian Unified Health System. Patients are referred to this hospital for treatment of infectious diseases, including patients with tuberculosis and histoplasmosis who require hospitalization.

## INCLUSION CRITERIA

### Tuberculosis/Disseminated histoplasmosis/HIV/AIDS

In this work plan, the diagnosis of tuberculosis and histoplasmosis as a co-infection was established when both infections were diagnosed during the same hospital admission; histoplasmosis cases that were diagnosed during tuberculosis treatment, or tuberculosis cases that were diagnosed during histoplasmosis treatment. The inclusion criteria for human immunodeficiency virus (HIV/AIDS) infection were in accordance with those adopted by the Ministry of Health\*

\*(Ministry of Health. Health Surveillance Secretariat. National STD and AIDS Program. Criteria for defining AIDS cases in adults and children. Ministry of Health, Health Surveillance Secretariat, National STD and AIDS Program. Brasília, 2000).

### EXCLUSION CRITERIA:

Age  $\leq$  18

- Pregnancy, lactation, belonging to an indigenous tribe, having medical records with incomplete information;
- All patients with histoplasmosis who died before the end of treatment were considered in this study\*\*.
- All TB patients who died before the end of treatment were considered in this study\*\*.
- Immediate causes of death recorded on death Certificates of cardiopulmonary arrest (CPA) or as multiple organ failure were analyzed as undefined causes\*\*.

\*\* Ministry of Health. The Death Certificate: a necessary and important document. 3rd ed, Brasília, 2009.

## VARIABLES TO BE ANALYZED:

A univariate analysis was carried out for the clinical epidemiological criteria (95%CI). The total number of patients and the incidence rate of histoplasmosis and tuberculosis were used to calculate the number of incident cases at the Hospital de Doenças Tropicais Dr. Anuar Auad.

In addition, the following variables were also analyzed: age, gender, year of diagnosis, origin, use of illicit drugs, smoking, method of diagnosis of the confections, treatment of tuberculosis and histoplasmosis, presence of pulmonary symptoms, use of ART and evolution of the case.

## DATA COLLECTION:

The data was collected through the online system GAL GOIÁS, which provides the results of laboratory tests carried out in the last five years; PEP-MV through the analysis of electronic medical records and physical medical records requested from the DEAM of the referral unit.

## RESULTS

With regard to the sample of patients with HIV, TB and histoplasmosis co-infection at the referral unit and during the period under analysis, 13 people were diagnosed with co-infection in the last 5 years. With regard to gender: 03 were female and 10 were male. Thus, there is a higher prevalence among males, with 76.9% of patients being male and 23.07% female.

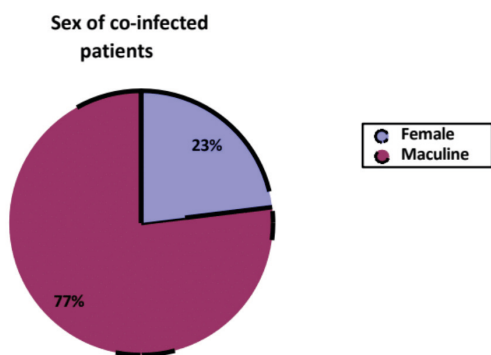


Figure 1. Analysis of the prevalence of co-infection of HIV, TB and histoplasmosis in females and males, in the years 2012-2017, in a reference unit in Goiás.

With regard to age group, the most prevalent age group was 30 to 40 years old, with 07 patients (53.84%), followed by 40 to 50 years old with 04 patients (30.76%) and 20 to 30 years and 60 to 70 years with 01 patient each.

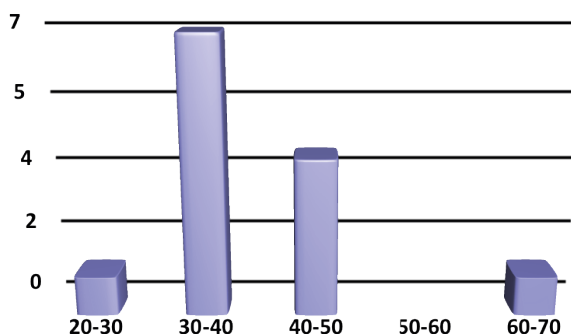


Figure 2. Analysis of the prevalence of HIV, TB and histoplasmosis co-infection by age group, in the years 2012-2017, in a reference unit in Goiás.

Regarding the year of diagnosis of co-infection, 05 patients were diagnosed in 2017 (38.46%), 03 in 2016 (23.07%) and 05 in 2015 (38.46%). There were no patients who met all the sample inclusion criteria proposed by the study in 2014, 2013 and 2012.

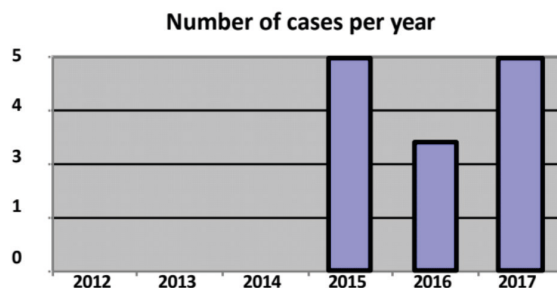


Figure 3. Analysis of the prevalence of HIV, TB and histoplasmosis co-infection by year, from 2012-2017, in a reference unit in Goiás.

The results obtained from the analysis of where the patients came from were: 06 patients from Goiânia, 02 patients from Aparecida de Goiânia, 01 patient from Luziânia, 01 patient from Jaraguá, 01 patient from Senador Canedo and 01 patient from Campo Grande.

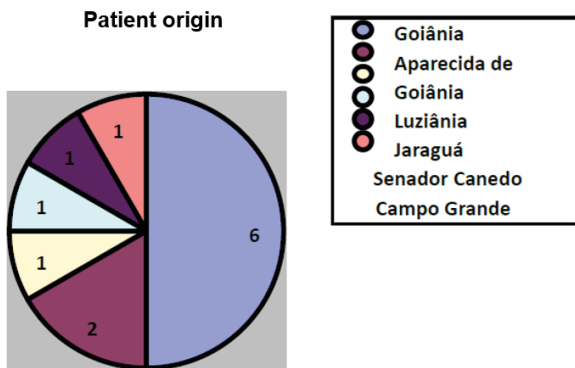


Figure 4 - Analysis of the prevalence of HIV, TB and histoplasmosis co-infection by year, from 2012-2017, in a reference unit in Goiás.

Regarding the use of illicit drugs, 04 patients are/have been illicit drug users, 05 denied using them and 04 did not provide any information.

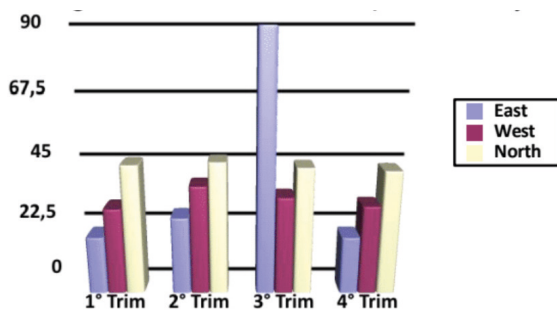


Figure 5 - Analysis of the prevalence of illicit drug use in patients with co-infection of HIV, TB and histoplasmosis, in the years 2012-2017, in a reference unit in Goiás.

Smoking was present in 05 patients (38%) and 08 patients (62%) reported not using tobacco.

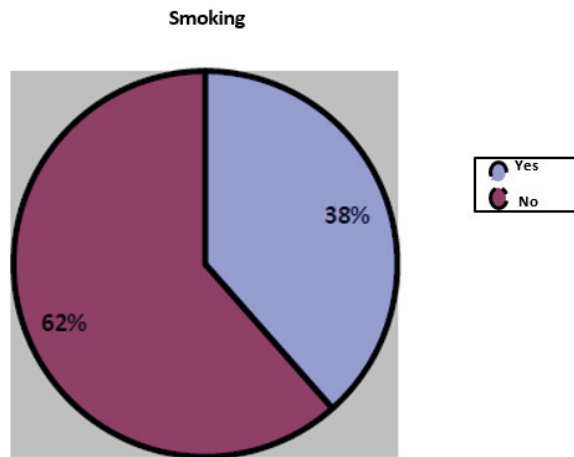


Figure 6. Analysis of the prevalence of smoking in patients with co-infection of HIV, TB and histoplasmosis, in the years 2012-2017, in a reference unit in Goiás.

The methods used to diagnose histoplasmosis were: biopsy, tracheal secretion culture and fungal culture. Of these, 11 were diagnosed by fungal culture (84.61%), 1 by tracheal aspirate (7.69%) and 1 by biopsy (7.69%).

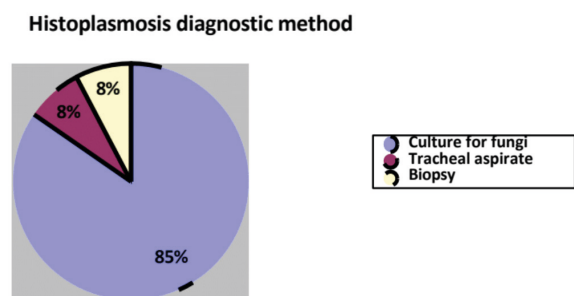


Figure 7. Analysis of the method of diagnosis of histoplasmosis in patients with co-infection of HIV, TB and histoplasmosis, in the years 2012-2017, in a reference unit in Goiás.

Still on the subject of diagnostic methods, the most commonly used method for diagnosing tuberculosis was blood culture, which was performed and tested positive in 09 patients (69.23%), 02 patients were diagnosed by PCR (15.38%), 01 by blood culture sputum (7.69%) and 01 by biopsy (7.69%).

### TB diagnostic method

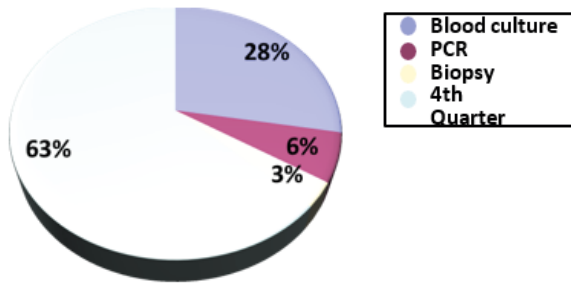


Figure 8. Analysis of the method of diagnosis of tuberculosis in patients with co-infection of HIV, TB and histoplasmosis, in the years 2012-2017, in a reference unit in Goiás.

With regard to the form of tuberculosis, 06 patients were infected with *M. tuberculosis* (46.15%), 06 with *non-tuberculous M. tuberculosis* (46.15%) and 01 with *M. avium* (7.69%).

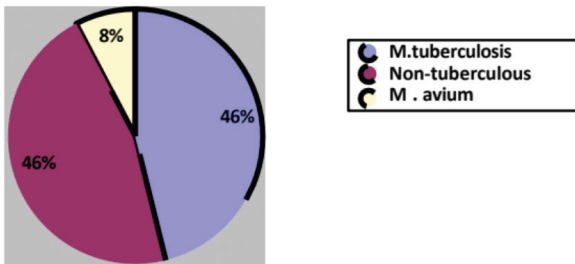


Figure 9. Analysis of the form of tuberculosis in patients with co-infection of HIV, TB and histoplasmosis, in the years 2012-2017, in a reference unit in Goiás.

With regard to the use of amphotericin B, 12 of the 13 patients used amphotericin B, and all of them used the medication for a further 10 days. Among the patients who were using amphotericin B, 2 of them stopped and, after a few days, started using the liposomal form. With regard to the use of ART, 10 of the 13 patients were regularly using ART at the time of diagnosis of co-infection.

Another factor analyzed was the presence of pulmonary symptoms (cough, fever, hemoptysis, chest pain, dyspnea). All the patients reported a cough, with 4 reporting a dry cough and 9 reporting a productive cou-

gh. Fever was present in 7 of the 13 patients. Hemoptysis was reported by only 3 patients. Dyspnea was reported by 6 patients and chest pain by 1 patient.

Finally, with regard to progress, 10 of the 13 patients were discharged from hospital with resolution of the disease and treatment of the co-infections and 3 of the 13 patients died during treatment.

## DISCUSSION

The WHO has pointed to advances in the treatment of tuberculosis and this has led to a significant reduction in mortality and incidence of the disease between the 1990s and 2015. Thus, it is believed that these advances in treatment have been responsible for the reduction in the incidence of tuberculosis co-infection in HIV-positive patients with histoplasmosis. In addition, many advances have been made in HIV treatment in recent years, and access to treatment and health facilities has improved, which has been responsible for the reduction in the incidence of opportunistic diseases. Thus, the incidence of 13 cases in 5 years is part of this context.

It is important to point out that there is a predominance of males, adults in the 30-50 age group, showing and agreeing with other national studies that co-infection occurs mainly in the economically active group. This can be explained by the greater exposure to activities carried out at this stage of life. However, the factors that determine the predominant incidence in men are still not completely clear and several hypotheses may be related, such as self-care with health, delay in seeking a health unit when symptoms start. Other socio-economic variables are being analyzed and could contribute to explaining the higher incidence in men and in this age group.

With regard to the clinical form of the disease presented, the predominance of pulmonary tuberculosis can be explained

by its high infectivity, due to the pathogen's predisposition for the lung parenchyma. This is precisely why respiratory problems are among the most frequent complications in HIV-infected people.

## CONCLUSION

When analyzing the epidemiology of the incidence of co-infection of tuberculosis and histoplasmosis in HIV-positive patients over a 5-year period in a reference unit in the state of Goiás, the total number of cases in the period was 13, distributed mainly between the years 2017, 2016 and 2015.

Still on this epidemiological analysis, the clinical-epidemiological and laboratory aspects of associated tuberculosis in patients

with disseminated histoplasmosis and HIV/Aids, it is important to emphasize that rapid diagnosis is extremely important, changing habits and adherence to treatment are related to treatment success.

The evolution (outcome and survival) of histoplasmosis and tuberculosis in HIV-positive patients is linked to the speed of diagnosis and the start of treatment; the three patients who had a delay in diagnosis and a delay in seeking treatment were not treated health unit ended up dying. On the other hand, patients who sought a health unit quickly, did not evade treatment and took the appropriate therapeutic measures, progressed to hospital discharge and cure of the coinfections.

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