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Review Article

Histoplasmosis in AIDS Patients in Venezuela

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Abstract

Histoplasmosis, caused by *Histoplasma capsulatum*, endemic in Venezuela, is the most frequent AIDS defining disease. It is associated with significant morbidity and mortality in these patients. The aim of this study was to review the demographic data, clinical features, diagnostic methods, treatment and follow-up, of patients with diagnosis of AIDS and histoplasmosis, evaluated at the Medical Mycology Department, Instituto de Medicina Tropical, Universidad Central de Venezuela, from 1994 to 2013. We collected demographic, epidemiologic, and clinical data from each case. Viral load and CD4+ counts were recorded when available. The diagnosis of histoplasmosis was performed by standard methods. Treatment and outcome was also considered. We found a high proportion of co-infection of HIV/AIDS and histoplasmosis, 39.42%, quite similar to other reports. The majority of patients, 149 (68.34%), came from urban environments. 155 had CD4+ counts below 150 cells/mL. Out of these, 16 had previous ART. Adherence could not be established. In 79.8%, histoplasmosis was the AIDS-defining disease. All patients presented with a progressive disseminated disease. It is noteworthy that 9 (4.13%) patients were co-infected with *Paracoccidioides brasiliensis*. Finally, we believe that in our country, and what is more, in any other country in which histoplasmosis is endemic, it is necessary that clinicians consider the diagnosis of this disease, when they evaluate AIDS patients with fever, pulmonary, skin/mucosal, CNS or gastrointestinal manifestations and laboratory alterations such as cytopenias or liver enzyme abnormality. Physicians must be familiar with the uses and limitations of the current diagnostic tests available for fungal diseases.

Keywords: Histoplasmosis; HIV/AIDS; *Histoplasma capsulatum*; Co-infection; Epidemiology; Endemic Mycoses

Introduction

Endemic mycoses have increased their frequency in the last years in our country, due, among other causes, to the rise of immunocompromised patients, especially since the appearance of Human Immunodeficiency Virus (HIV) infection. In the world, the incidence of this association is between 4 and 5%, affecting more frequently individuals with CD4+ counts less than 150 cells/mL [1-3].

Among other endemic mycoses, Histoplasmosis, caused by *Histoplasma capsulatum*, is the most clinically significant fungal disease in Venezuela. It has also been described in the Ohio and Mississippi River valleys of the United States, and in Central America, as well as other countries in South America. Furthermore, it has recently been reported in various African and Asian countries, including China and India [4,5]. Histoplasmosis is an Acquired Immunodeficiency Syndrome (AIDS)-defining disease, associated with significant mor-

bidity and mortality in these patients [2,6]. It is dramatically underdiagnosed, and often confused with other diseases such as tuberculosis and pneumocystosis, causing delay in the diagnosis and treatment [1,6,7]. The absence of a simple, reliable, and affordable diagnostic test has made it difficult to determine the burden of this disease in HIV-infected patients, making histoplasmosis a truly neglected disease. Moreover, most clinicians are not always very thorough in their investigations, often overlooking the diagnosis of histoplasmosis, ultimately resulting in the death of numerous patients [8].

In this sense, there is limited published evidence for the knowledge of the demographic data, clinical features, diagnostic methods, treatment and follow-up, of patients with diagnosis of AIDS and histoplasmosis. In the current study we review the characteristics of these patients, evaluated at the Medical Mycology Department, Instituto de Medicina Tropical, Caracas, Venezuela, during the past two decades.

Patients and methods

We reviewed the medical records for all patients with a diagnosis of AIDS and histoplasmosis, evaluated at the outpatient service at the Medical Mycology Department from 1994 to 2013. We also considered data from patients attended at other hospitals in the Caracas Metropolitan Area (Hospital Universitario de Caracas, Hospital de Niños ''J. M. de Los Rios,'' Hospital Pediátrico Elías Toro, Hospital Perez Carreño, Clínica El Avila, Clìnica Atias, Hospital José Ignacio Baldó) or at outpatient services, whose clinical samples were processed at our laboratory.

We collected demographic, epidemiologic, and clinical data from each case, as available. All patient records revealed appropriate diagnostic investigations for AIDS. Viral load and CD4+ counts were not registered in all cases. Antiretroviral treatment (ART) data was not found in all the records. The diagnosis of histoplasmosis was made by clinical manifestations, radiographic chest findings, and laboratory findings, as well as standard mycologic methods, including Giemsa stain and culture in Sabouraud and Mycosel media. Histologic preparations such as Grocott, periodic acid-Schiff (PAS) and hematoxylin-eosin stains were performed when necessary [9]. Serologic tests (immunodiffusion method) were performed in most cases, as described previously [10,11]. *Histoplasma* antigen urine detection test was not performed, due to lack of availability.

Data regarding treatment was reviewed in some patients, as well as follow-up and outcome (death or the most recently recorded clinical visit). Results are presented in tables with a descriptive analysis. The cases were clinically classified, according to the classical definition [12-14]. Criteria for evaluating the responses to antifungal drugs and defining outcomes are uncertain, but depend on the individual clinical form and the response capacity of the patient (host) as well as on mycological factors [2,15,16]. Unequivocally improved clinical manifestations, negative control test results in mycologic examinations (such as serologic tests, stains, cultures), improvement of chest radiographs, and normalization of laboratory findings were taken into account when considering the success or failure of the outcome.

Results

From 553 patients with diagnosis of histoplasmosis evaluated in our Department, we found 218 (39.42%) medical records with diagnosis of histoplasmosis and AIDS, in the study period. Data was not complete in all cases.

Demographic Data

From these 218 cases, 181 (83.03%) were male and 37 (16.97%) were female. Ages ranged between 5 and 74 years, with a median of 34.96 years.

We found that 149 (68.34%) patients came from urban areas. The rest came from rural areas all over the country. Demographic data is summarized in Table 1.

As expected, the majority of patients were deeply immunocompromised at the moment of diagnosis, 92 of 155 available results, had CD4+ counts less than 150 cells/mL and high viral loads (Table 1). In 16 of these 92 patients, we found previous ART. 76 patients were naïve, and in the rest of 218 patients, the data was not found. In 174 (79.8%) cases, histoplasmosis was the AIDS-defining disease.

The other risk factors, such as occupation, alcohol and smoking habits, were not relevant in these patients (Table 1).

Table 1. Demographic characteristics, viral load and CD4+ cell count in AIDS patients with histoplasmosis.

Demographic Data	No. of Patients (%)*
Age	34.96 (range 5-74)
Gender	F 37 (16.97) M 181 (83.03)
Residing in	
Urban area	149 (68.34)
Rural area	40 (18.34)
Not available	29 (13.30)
Alcoholic	64 (29.35)
Smoker	58 (26.60)
Occupation known	152 (69.72)
Office	33 (15.13)
Housewife	20 (9.17)
Agriculture	7 (3.21)
Construction	23 (10.55)

Chauffeur	11 (5.04)
Other	58 (26.60)
Occupation undisclosed	66 (30.27)
Median Viral load copies/mL (range) n=65/218	298,983 (<50 - >2.500.000)
Median CD4+ cell count, cells/mL (range) n=155/218	79.67 (0-772)
CD4+ < 150 cells/mL n=155/218	92 (59.35)

*Percentages may exceed 100% due to rounding. Some patients had more than 1 factor

Clinical Data

All patients presented progressive disseminated disease. The most frequently observed clinical manifestations were fever, in 186 (85.32%) patients; cough, 137 (62.84%); weight loss, 104 (47.70%); dyspnea, 95 (43.57%); sputum production 93 (42.66%); headache, 52 (23.85%); diarrhea, 42 (19.26%); anorexia, 27 (12.38%); abdominal pain, 20 (9.17%); vomiting, 16 (7.34%) and chest pain, 2 (0.92%) (Table 2).

Table 2. Clinical manifestations in AIDS patients with histoplasmosis.

Symptom	No. of Patients*	(%)
Fever	186	85.32
Cough	137	62.84
Weight loss	104	47.70
Dispnea	95	43.57
Sputum production	93	42.66
Headache	52	23.85
Diarrea	42	19.26
Anorexia	27	12.38
Abdominal pain	20	9.17
Vomiting	16	7.34
Chest pain	2	0.92

*Some of the patients had more than one symptom

The following organ involvement was observed: 137 (62.84%) lung, 110 (50.46%) cases involving bone marrow, 94 (43.12%) liver and/or spleen, 94 (43.12%) lymph nodes, 65 (29.82%) skin, 33 (15.13%) mucosa; 14 (6.42%) central nervous system (CNS), 8(3.67%) bone and joint, 3(1.38%) pleura. Other rare clinical findings included 2 adrenal gland, 1 pericardium, 1 esophagus, 1 ileum, 1 colon and 1 larynx (Table 3).

Table 3. Organ involvement in AIDS patients with histoplasmosis.

Organ Involvement	No. of Patients*	(%)
Lung	137	62.84
Bone marrow	110	50.46
Liver/spleen	94	43.12
Lymph nodes	94	43.12
Skin	65	29.82
Mucosa	33	15.13
CNS	14	6.42
Bone and Joint	8	3.67
Pleura	3	1.38
Adrenal gland	2	0.92
Pericardium	1	0.46
Esophagus	1	0.46
Ileum	1	0.46
Colon	1	0.46
Larynx	1	0.46

*Some of the patients had more than one affected organ

Pulmonary Manifestations

We observed that 137 (62.84%) patients had pulmonary manifestations of the disease. These patients presented with cough 137 (62.84%), dyspnea 95 (43.57%), sputum production 93 (42.66%), and chest pain 2 (0.92%) (Table 2)

Gastrointestinal manifestations

These manifestations were present in 65 (29.82%) patients. Of these, 42 (19.26%) had diarrhea, 20 (9.17%) abdominal pain and 16 (7.34%) vomiting (Table 2).

Cutaneous and Mucosal Manifestations

Skin lesions were documented in 65 (29.82%) cases, and corroborated at our Department by specimen smears and biopsies stained with giemsa and grocott, respectively.

Thirty-three (15.13%) of the 218 patients had mucosal lesions (Table 3); including two palate lesions, one nasal septum perforation, one postseptal cellulitis as complication of sinusitis and 2 mouth ulcers were described. In all of them, diagnosis was established by giemsa stain of skin lesions and mucosal samples, which showed intracellular ovoid yeasts, 2–5 μm in diameter, compatible with *Histoplasma* sp.

Central Nervous System

In 14 patients, we found CNS involvement (Table 3). This was corroborated by performing Giemsa stain in cerebrospinal fluid (CSF). One of our patients had palpebral ptosis, 1 mental status change, 1 behavioral change, 1 hemiparesia, 2 had seizures,

6 complained of headache. The most significant case had fever, cough, cutaneus lesions, vomiting, diarrhea, knee arthritis, and meningoencephalitis signs. In two patients, only fever was described, no other data was available. One of the above mentioned patients had also positive criptococcal latex and india ink. Unfortunately only 2 computed tomography images were reported, both suggestive of cerebral toxoplasmosis. CSF cultures in all of these patients were negative.

Associated comorbidity

Among the associated comorbidity, the most frequent were: 52 (23.95%) candidiasis, 9 (4.13%) paracoccidioidomycosis, 8 (3.67%) tuberculosis (Table 4).

Table 4. Associated comorbidity in AIDS patients with histoplasmosis.

Comorbidity	Nº patients	%
Candidiasis	52	23.95
Paracoccidioidomycosis	9	4.13
Tuberculosis	8	3.67
Hepatitis B	5	2.29
Syphilis	5	2.29
Hepatitis C	4	1.83
Toxoplasmosis	3	1.37
Malignant diseases	3	1.37
CMV retinitis	3	1.37
Kaposi`s sarcoma	2	0.92
Herpes zoster	1	0.46
Coccidioidomycosis	1	0.46
Aspergilosis	1	0.46
Cryptococcosis	1	0.46
Leishmaniasis	1	0.46

*Some of the patients had more than one comorbidity

Laboratory Findings

All clinical laboratory findings were available for 171 patients. Of these, 38 (22.22%) had pancytopenia (low hemoglobin, low white blood cell count, and low platelet count). 88 (51.46%) leukopenia, 76 (44.44%) had anemia, 57 (33.33%) had thrombocytopenia, 20 (11.70%) had eosinophilia without any other underlying disease, and 80 (46.78%) had a high erythrocyte sedimentation rate. 88 (51.46%) patients had lactate dehydrogenase (LDH) over 400 mg/dL, of which, 56 (32.74%) were over 600 mg/dL.

Chest Radiographs

Chest radiographs were available in 89 (43.7%) of the 218 cases. In 65 of these (74.02%), radiographic analysis revealed diffuse infiltrates in a miliary reticulonodular opacity pattern in both lungs (interstitial pneumonitis pattern); 15 (16.85%) cases were described as normal. Other pulmonary findings were 3 condensation images, 4 paracardiac/hiliar images, 1 cavitation, and 1 chronic obstructive pulmonary disease. All but 3 of these patients had clinical or microbiologic evidence of lung involvement.

Mycologic Diagnosis

All 218 patients had confirmed diagnosis of histoplasmosis by at least one of the aforementioned diagnostic methods. Results of the mycologic tests are summarized in Table 5. Giemsa stain was performed in 53 different clinical specimens, such as mucosal biopsies, sputum, lymph nodes, blood cultures, broncoalveolar lavage, CSF, tongue tissue, bone marrow, and purulent secretions. In all positive samples (52/53) intracellular yeasts compatible with *Histoplasma* species were found, including 3 peripheral blood and 15 bone marrow smears. *H. capsulatum* was isolated in 77 (79.38%) of 97 cultivated specimens. Immunodiffusion test was performed in 123 patients; 89 (72.35%) resulted positive for *H. capsulatum*. In all hematoxylin-eosin, PAS, and Grocott stains of 88 tissue biopsies received (skin, liver, lung, larynx, pleura, ileum, and esophagus); intracellular yeasts compatible with *Histoplasma* species were found.

Table 5. Mycologic diagnosis in AIDS patients with histoplasmosis.

Diagnostic method	No of patients* (%)	
	Positive	Negative
Wright/Giemsa	52/53 (98.11)	1/53 (1.88)
Culture	77/97 (79.38)	20/97 (20.62)
Serology	89/123 (72.35)	34/123 (27.64)
Biopsy† (HE, PAS, Grocott)	88/88 (100)	

Abbreviations: HE = hematoxylin-eosin, PAS = periodic acid-Schiff.
*Some patients had more than 1 diagnostic method.
†Only positive biopsies were received to corroborate diagnosis. Negative samples were discarded in the pathology lab.

Treatment and Outcome

From the 218 total patients, treatment was recorded in 168 (77.06%). Of these, 139 (63.76%) received only amphotericin B (AMB) at a dose of 1 mg/kg per day up to 2g accumulated dose or more if the improvement was slow. Six of the 168 (2.75%) patients received itraconazole (ITC) at a mean dosage of 7-11 mg/kg per day orally, in variable periods of 3 to 12

months, depending on the individual response and the toxic effects of the medication. Finally, 16 of the 168 (31.9%) patients received AMB at the same dose, until improvement, followed by ITC for the aforementioned period. (Table 6)

The outcome was recorded in 120 (55.04%) patients. From these, 109 (90.83%) improved with antifungal treatment. Exceptions are 11 (9.16%) patients who died: 4 from the AMB group; 4 from the AMB + ITC group; 1 who received fluconazole and 2 patients with unknown treatment. From the 120, 20 (16.66%) relapsed, including 3 patients who had 2 relapses.

Table 6. Treatment in AIDS patients with histoplasmosis.

Treatment	N° of patients	%
Amphotericin B	139	63.76
Itraconazole	6	2.75
Ampho+itra	16	7.34
Other (Fluco/Keto)*	7	3.21
NA**	50	22.93
Total	218	100

* (Fluco/Keto): Fluconazole/Ketoconazole

**NA: not available

Discussion

Histoplasmosis is one of the most prevalent endemic mycoses, caused by *Histoplasma capsulatum*. With the advent of the HIV epidemic, it has become, in many countries, a common and severe fungal disease. [4,5,13,17].

In Venezuela, prevalence of HIV/AIDS, reported in 2014 by the Ministry of Health, was 0.56% in the general population, reaching up to 5% in high risk patients, especially men who have sex with men (MSM) [18].

In our data, we found a high proportion of co-infection of HIV/AIDS and histoplasmosis, 39.42%, quite similar to other reports. Although data regarding this issue is scarce, it is evident that in recent years the association of histoplasmosis and HIV/AIDS in endemic areas has become very important [4-6,8,14,19-21]. In this sense, in our country, Garcia et al in 1989 and Merheb et al, in 1991, found in autopsy protocols, 52% and 74,4% respectively, of co-infection with HIV and *Histoplasma* sp. [22,23]. Later, Dos-Santos et al, in 2006, reported 75.4% of this co-infection, also in autopsy protocols [24]. Again, Mata et al, in 2008, found that from 158 histoplasmosis patients, 53 (33.5%) had AIDS [16]. Such studies remain as current as ever.

We have no data on prevalence of histoplasmosis in AIDS patients in our laboratory, due to the fact that most of them are sent for diagnosis of fungal disease. In our patients, all had diagnosis of histoplasmosis, candidiasis (23.95%) was the most frequent co-infection, followed by paracoccidioidomycosis (4.13%) and tuberculosis (3.67%). Other studies in the Venezuelan literature are not reliable due to lack of diagnosis of the disease, most reported as wasting syndrome and suspected pneumocystosis. This situation is also reported in other countries, such as the French Guiana [25].

In this study we found that the majority of patients, 149 (68.34%), came from urban environments, especially the Caracas Metropolitan Area [16]. In previous years, this disease was considered to be found mainly in rural areas, related to agricultural occupations and low socioeconomic status [26]. However, *H. capsulatum* has been isolated from soil of the urban area of Caracas [27], and relevant environmental modifications or conditions have occurred recently in this city, such as landslides caused by heavy rainfall, large construction sites for the subway system of Caracas, and urban condominium development. Moreover, many bird and bat species live in this valley, and are in contact with the human population, due to habitat penetration by human invasion of the geographical areas surrounding the city [13,17]. It is well known that there is a strong association between the presence of bird and bat guano and *H. capsulatum*. In fact, the first isolation of the organism from an environmental source was from an area adjacent to a chicken house [28]. For these reasons, soil is enriched with bird or bat droppings which may enhance the growth of *H. capsulatum*. Consequently, construction or demolition disturbs such soil or nesting areas, which may create volatilization of a high burden of *H. capsulatum* conidia in the air, that are transported easily throughout the valley of Caracas, where constant steady wind is frequently present [16]. Therefore, there is environmental contamination which allows colonization of a large number of persons.

Most individuals are infected during childhood, caused by exogenous exposure. Later in life, predisposing factors, such as AIDS or other immunosupressing conditions can occur, and infection becomes symptomatic. For such patients, it is not possible to ascertain whether the disease is due to a new infection or the reactivation of an old one [29].

From our patients, 155 had CD4+ counts below 150 cells/mL. From these, 16 had previous ART. Adherence could not be established in these patients. Non-adherence to therapy is related to occurrence of histoplasmosis relapses [2].

We consider relevant that most of our patients were naïve to ART at the time of diagnosis of histoplasmosis, probably due to delayed diagnosis of HIV infection. In our country, although ART access has improved in the recent years, our patients are still not aware of the importance of early start of treatment, adherence and regular medical control. To this day, many patients are diagnosed with HIV when opportunistic infections are already present, and CD4+ counts are low. In our case, from the available data collected, at least in 79.8%, histoplasmosis was the AIDS-defining disease.

Ideally, ART must be started before immunocompromise oc-

curs in HIV-infected persons. This reverses the immune defect, reducing the likelihood of development of histoplasmosis and other opportunistic infections. Patients on ART have less risk of developing disseminated histoplasmosis, even at low CD4+ counts. Interestingly, there have been reports of otherwise untreated histoplasmosis in persons with AIDS, improving with ART alone [2,4,30].

Related to clinical manifestations, in this cohort, similar to other authors findings [31-33], all patients, presented with a progressive disseminated disease, with nonspecific signs and symptoms, as seen in many other opportunistic infections complicating the course of HIV/AIDS. As described in published reviews, fever, cough and weight loss were the most common symptoms, occurring in a large number of cases. Dyspnea, sputum production and gastrointestinal manifestations were also important [2,4,16-19,29,34,35].

In relation to organ involvement, a high proportion of our patients presented with pulmonary manifestations, hepatosplenomegaly, adenomegaly, skin and mucosal lesions, CNS, bone and joint and gastrointestinal tract compromise. In fact, any organ can be involved in the disease, due to hematogenous dissemination throughout the reticuloendothelial system, via parasitized macrophages. In this sense, AIDS has helped redefine the spectrum of illness seen with disseminated histoplasmosis [29,33-37]. On the other hand, physical examination is frequently unrevealing, except for these systemic manifestations of the disease. In a study carried out by Dos Santos et al [24], they found, in 71 autopsies performed in patients with AIDS, that 53 had histoplasmosis findings, compromising several organs, such as lung, liver, spleen, lymph nodes, adrenal glands, bone marrow and gastrointestinal tract, among others. This constitutes the best evidence of the disseminated condition of the disease, causing different manifestations [19,23,24,32,38].

From the available laboratory data, leukopenia was the most relevant finding (51.46%), followed by anemia (44.44%) and thrombocytopenia (33.33%). Only 22.22% had pancytopenia. It is noteworthy that 11.70% had eosinophilia, without any other underlying disease; we do not have an explanation for this. 46.78% had a high erythrocyte sedimentation rate and 32.74% patients had LDH over 600 mg/dL. Routine laboratory test results are frequently nonspecific, although it is well known that many reviews describe anemia, leukopenia, and thrombocytopenia. All of these cytopenias, and the increase of LDH twice the normal value, are frequently seen in patients with AIDS and histoplasmosis, and have been associated with bad prognosis [8,17,19,32,39,40].

Pulmonary manifestations were observed in 62.84% of patients. Chest radiograph data was available only in 43.7% of them. The majority of images showed a diffuse reticulonodular picture; 16.85% were described as normal, similar to reports from other authors, from the revised literature [17,19, 40,41]. Dos Santos et al, demonstrated pulmonary involvement in 20,3% of 120 autopsies from AIDS patients [24].

Among the associated comorbidity, it is noteworthy that 9 (4.13%) patients were co-infected with *Paracoccidioides brasiliensis*, demonstrated by direct examination, serology and/or culture. The association between histoplasmosis and paracoccidioidomycosis has been described previously in the literature [24,42]. The aforementioned conditions that predispose patients to histoplasmosis are probably the same to paracoccidioidomycosis. It has been proposed that both fungi probably share the same habitat [42].

Related to mycological diagnosis, we found, in 53 Giemsa stains performed, that 98.11% were positive, including 4 skin samples, 3 peripheral blood and 15 bone marrow smears. Biopsy slides stained with Grocott, evaluated in our laboratory, were all positive, including 15 skin samples. Direct microscopic examination of clinical specimens, stained with Giemsa and Grocott, may facilitate the rapid diagnosis of patients with histoplasmosis. Due to thorough search and review of the slides stained especially for fungi, carried out by well trained personnel, small yeast-like fungi of *Histoplasma* species can be found in the majority of examined specimens, even though scarce in the tissues. In some cases it was the first result given to the patients, which allowed them to be treated successfully in a short time, as suggested elsewhere [16,19].

Cultures yielded *Histoplasma capsulatum* in 79.38% of cases. Culture has always been the confirmation method for the diagnosis of histoplasmosis. Fungal growth is slow, requiring up to 4 weeks, sometimes causing delay in the diagnosis, while awaiting the results, which may lead to a fatal outcome in more severe cases [16,43].

With respect to serology, we obtained 72.35 % positive results by immunodifussion test, which is similar to other reports [16,19,29,43]. Serologic responses in AIDS patients can be weakly positive, especially in late-stage disease, because antibody production might be impaired [32]. Nevertheless, despite the immunosuppressed state of AIDS patients, positivity of this method can be obtained. This could be explained by the suggestion that much of the disease results from endogenous reactivation of a previous histoplasmosis infection, rather than from acute symptomatic disease, as was discussed above [16,43,44].

All the methods described for the diagnosis of histoplasmosis have their percentage of false negatives. Therefore, it is convenient to use several diagnostic methods, to improve the possibility of obtaining a correct diagnosis [16,43].

Treatment was recorded in 77.06% of the study patients. Of these, 63.76% received only AMB. 2.75% received ITC. Final-

ly, 7.34% patients received AMB, followed by ITC. AMB is recommended for AIDS patients, who require hospitalization. In the current study, we observed that patients treated with AMB alone or in combination with ITC, had a very good outcome. ITC is the drug of choice for treating histoplasmosis when the patients are not severely ill or have CNS involvement. We do not recommend fluconazole because of its lower efficacy for the treatment of histoplasmosis [16, 36,45,46].

Several limitations of this study require consideration. Data is not complete because this is a retrospective study and there is a significant amount of missing information within clinical records. HIV RNA, and CD4+ cell counts were not obtained with consistency or at regular intervals and record review may not accurately describe the clinical status of the patient. Additionally, we do not know the reasons for relapses and/or death.

Finally, we believe that in our country, and what is more, in any other country in which histoplasmosis is endemic, clinicians should consider the diagnosis of this disease, when they evaluate AIDS patients with fever, pulmonary, skin/mucosal, CNS or gastrointestinal manifestations and laboratory alterations such as cytopenias or liver enzyme abnormality. Although excellent laboratory methods are available, in many cases diagnosis is overlooked or delayed because histoplasmosis is not considered.

Clinicians need to be aware of non-specific signs and symptoms in AIDS patients; in doing so, they must make the most of the epidemiological clues or leads available to them, such as activities or occupations that could expose the patient to sites contaminated with bat or bird droppings, including constructions and large soil removals. Furthermore, physicians must be familiar with the uses and limitations of the current diagnostic tests available for fungal diseases [43].

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