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High Mortality and Coinfection in a Prospective Cohort of Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome Patients with Histoplasmosis in Guatemala

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Abstract. Histoplasmosis is one of the most common and deadly opportunistic infections among persons living with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome in Latin America, but due to limited diagnostic capacity in this region, few data on the burden and clinical characteristics of this disease exist. Between 2005 and 2009, we enrolled patients ≥ 18 years of age with suspected histoplasmosis at a hospital-based HIV clinic in Guatemala City. A case of suspected histoplasmosis was defined as a person presenting with at least three of five clinical or radiologic criteria. A confirmed case of histoplasmosis was defined as a person with a positive culture or urine antigen test for *Histoplasma capsulatum*. Demographic and clinical data were also collected and analyzed. Of 263 enrolled as suspected cases of histoplasmosis, 101 (38.4%) were confirmed cases. Median time to diagnosis was 15 days after presentation (interquartile range [IQR] = 5–23). Crude overall mortality was 43.6%; median survival time was 19 days (IQR = 4–69). Mycobacterial infection was diagnosed in 70 (26.6%) cases; 26 (25.7%) histoplasmosis cases were coinfected with mycobacteria. High mortality and short survival time after initial symptoms were observed in patients with histoplasmosis. Mycobacterial coinfection diagnoses were frequent, highlighting the importance of pursuing diagnoses for both diseases.

INTRODUCTION

Histoplasmosis is an infection caused by inhalation of the fungus *Histoplasma capsulatum* from contaminated soil. It is the most prevalent mycosis in Central America, and is challenging to diagnose.[1–5] The clinical presentation of histoplasmosis ranges from asymptomatic infection or mild respiratory illness to severe disseminated disease.[6] Although histoplasmosis can occur among immunocompetent persons, immunocompromised individuals, such as people living with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) (PWAs), are at high risk of developing disseminated disease. In AIDS patients, mortality due to disseminated histoplasmosis may approach 50%, especially in those with severe manifestations.[7] Among those at highest risk, clinical manifestations are nonspecific and similar to those produced by other disseminated infectious diseases,[6] which can delay diagnosis and treatment. These symptoms include malaise, fever, anorexia, and weight loss; physical examination often shows hepatosplenomegaly, lymphadenopathy, pallor, and petechiae, and in some patients, ulcerations and/or nodules of skin and mucous membranes.[6,8,9] These similarities can delay diagnosis and treatment. Guatemala is considered a hyperendemic country for histoplasmosis, with previous surveys showing a 23–81% range of skin test positivity to the histoplasmin skin test antigen.[10] However, reports of clinical disease and outcomes from the country are limited and based mainly on case reports, traveler-associated outbreaks, and one study that evaluated symptoms and risk factors in eight histoplasmosis cases.[1,11,12] In 2005, a new assay for detection of *Histoplasma* antigen in urine was developed and validated in Guatemala.[13] During the assay evaluation, we prospectively enrolled patients who had symptoms consistent with histoplasmosis. Herein, we describe clinical presentation and outcomes of disseminated histoplasmosis in patients attending a large urban HIV clinic in Guatemala.

MATERIALS AND METHODS

Study design and data collection. A prospective cohort study was conducted among patients attending to an HIV clinic (Clínica Familiar "Luis Ángel García"), housed within a large public hospital in Guatemala City, Guatemala. All HIV-positive patients who were ≥ 18 years of age and visited the clinic between February 2005 and March 2009 were eligible for enrollment as suspected cases if they presented with three of five of the following clinical criteria: fever, pancytopenia, weight loss, skin or mucosal lesions indicative of histoplasmosis, or radiological evidence suggestive of histoplasmosis. Informed consent was obtained from all enrolled participants, and clinic personnel performed a baseline questionnaire and laboratory evaluation at the initial visit. Additional clinical data were collected at subsequent clinic follow-up visits. Clinical and demographic data were collected and stored on-site in a Microsoft® Access database (Microsoft Corporation, Redmond, WA) developed for this study.

Case definition. A case of histoplasmosis was defined as a PWA who had a sterile-site clinical specimen positive for *H. capsulatum* by culture, or a urine specimen positive for *Histoplasma*. The diagnosis of histoplasmosis was made based on the recommendations of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.[9] A case of mycobacterial infection was defined as a PWA who had a sterile-site or sputum culture positive for mycobacteria, or microscopic observation of acid-fast bacilli in tissue.

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Laboratory methods. Specimens analyzed included blood, urine, cerebrospinal fluid (CSF), bone marrow, lymphatic nodes, or skin depending on the patient's presentation. Blood and bone marrow were processed by lysis centrifugation and were subsequently cultured using Mycosel™ (BD, Franklin Lakes, NJ), Sabouraud, and Lowenstein–Jensen media to detect fungi and mycobacteria; it was done locally. Urine was tested for *Histoplasma* antigen by enzyme-linked immunosorbent assay (ELISA) at Centers of Disease Control and Prevention (Atlanta, GA).[13,14] Mycobacteria were detected with Ziehl–Nielsen stain or culture, but speciation was only to *Mycobacterium tuberculosis*. All CSF and tissue biopsies were stained with Giemsa, Gram, and Ziehl–Nielsen and were subsequently cultured for bacteria, mycobacteria, and fungi as above. Additionally, CSF samples were evaluated for the presence of *Cryptococcus* spp. by microscopy with India ink stain and/or with the *Cryptococcus* latex agglutination (BIO-RAD; New South Wales, Gladeswille, Australia). Other diagnostic tests included complete blood cell count, liver function tests, and lactate dehydrogenase (LDH).

Statistical analysis. Clinical data were analyzed using SAS 9.3. χ^2, Fischer's exact, and Wilcoxon rank-sum tests were used to perform bivariate analysis, as appropriate. Kaplan–Meier survival analysis was performed to compare mortality among cases and by infection. Factors associated with survival with a significance level of $P < 0.05$ were included in the model.

RESULTS

Etiology of infection. During January 2005–March 2009, 567 patients were evaluated and 387 (68.2%) patients met the inclusion criteria. A total of 263 (67.9%) patients were enrolled, of whom 101 (38.4%) met the case definition for histoplasmosis: 71 (27.0%) had histoplasmosis infection alone, 26 (9.9%) had histoplasmosis and mycobacterial coinfection, and four (1.5%) had histoplasmosis and other coinfections (Table 1). Among the nonhistoplasmosis cases, 38 (14.4%) cases had mycobacterial infections only, six (2.3%) had mycobacterial disease and another coinfection, and 18 (6.8%) had other nonmycobacterial infections and other infections, including cryptococcosis, *Pneumocystis* pneumonia (PCP), and coccidioidomycosis as well as viral, bacterial, and parasitic infections. A total of 100 (38.0%) patients had no identified etiology of infection.

Medical history and clinical presentation. Median age and gender were similar among histoplasmosis cases and nonhistoplasmosis cases (age: 35 years versus 31 years, $P = 0.15$; male gender: 80.2% versus 72.8%, $P = 0.18$; Table 2). At clinical presentation, no symptoms were significantly different between histoplasmosis cases and nonhistoplasmosis cases; however, gastrointestinal (GI) complaints (66.3% in cases versus 73.5% in nonhistoplasmosis cases; $P = 0.22$), pulmonary complaints (62.4% versus 61.7%; $P = 0.92$), and oral or skin lesions were most common. The skin lesions ($N = 70$ patients) were predominantly ulcers (71%), papules (11.4%), and erythema multiforme (10.6%), whereas oral ulcers ($N = 78$ patients) were seen in lips (6.0%), bucal mucosa (5.7%), and tongue (5%).

Of 101 patients receiving a diagnosis of histoplasmosis, 91 (90%) had positive *H. capsulatum* sterile-site cultures, and 62 (61.3%) had positive urine antigen. Laboratory findings are detailed in Table 2. Several laboratory markers were significantly lower in cases than noncases at first visit, including median CD4 T-cell count (25 cells/mm^3, range = 10–57; versus 45, range = 18–98; $P = 0.02$), median white blood cell counts (4,280 cells/μL versus 5,360; $P = 0.01$), platelet count (181×10^3 cells/μL versus 284; $P \leq 0.001$), hemoglobin levels (9.0 g/dL versus 10.0; $P = 0.003$), and hematocrit levels (27.7% versus 29.2%; $P = 0.003$). LDH levels were significantly higher among histoplasmosis cases versus nonhistoplasmosis cases (471 units/L versus 333; $P = 0.002$), as were serum glutamic oxaloacetic transaminase levels (136 units/L versus 68; $P = 0.004$), bilirubin levels (0.6 mg/dL versus 0.5; $P = 0.03$), and alkaline phosphatase (381 units/L versus 303; $P < 0.001$).

Overall, 15 (14.9%) of histoplasmosis cases were receiving antiretroviral therapy (ART) at their initial visit, 69 (68.3%) were on *Pneumocystis jirovecii* (PCP) prophylaxis, and 39 (38.6%) were on antifungal therapy (Table 2).

Treatment and outcomes. Median time to diagnosis was 15 days among histoplasmosis cases, compared with 7 days among nonhistoplasmosis cases diagnosed with other infections ($P = 0.23$). Of the 101 histoplasmosis cases, 18 (17.8%) received empiric antifungal therapy prior to definitive diagnosis of histoplasmosis, and 68 (67.3%) were started on antifungal therapy at diagnosis; median time to treatment was 21 days (interquartile range [IQR] = 7–31). Of the histoplasmosis cases who did not receive antifungal therapy and for whom information was available ($N = 21$), almost all cases ($N = 17$, 80%) died before a diagnosis of histoplasmosis was made. ART had been initiated in 15 (14.9%) cases and continued in 53 (53%) cases and 81 (50%) noncases. Detailed data are shown in Table 3.

There was a higher crude mortality in patients with histoplasmosis (43.6% among cases versus 30.8% among nonhistoplasmosis cases; $P = 0.04$), and mortality at 30 days after enrollment was significantly higher among histoplasmosis cases (24.8% versus 9.3%, $P < 0.001$; Figure 1). Median

TABLE 1

Etiology of infection among patients suspected to have histoplasmosis, by patient ($N = 263$ patients) and by disease frequency ($N = 218$ infections)

Etiology of infection, by patient ($N = 263$)	*n* (%)
Histoplasmosis	101 (38.4)
Histoplasmosis alone	71 (27.0)
Histoplasmosis + mycobacterial coinfection	26 (9.9)
Histoplasmosis + other coinfection	4 (1.5)
Mycobacterial disease	70 (26.6)
Mycobacterial alone	38 (14.4)
Mycobacterial + other coinfection	6 (2.3)
Other infection (nonhistoplasmosis, nonmycobacterial)	18 (6.8)
No identified etiology of infection	100 (38.0)
Etiology of infection, by disease frequency ($N = 218$)	*n* (%)
Histoplasmosis	101 (46.3)
Mycobacterial disease	70 (32.1)
Other fungal disease	17 (7.8)
Cryptococcosis	9 (4.1)
Candidiasis	3 (1.4)
Coccidioidomycosis	3 (1.4)
Pneumocystis pneumonia	2 (0.9)
Parasitic disease	8 (3.7)
Bacterial disease	3 (1.4)
Viral disease	2 (0.9)

Parasitic diseases identified include Chagas, *Cryptosporidium*, *Cyclospora*, and *Toxoplasma*. Bacterial diseases include *Klebsiella* and *Shigella*. Viral diseases include hepatitis B and hepatitis C.

TABLE 2
Demographic and clinical characteristics of patients suspected to have histoplasmosis, by etiology of infection identified

	Histoplasmosis (*N* = 101)	No histoplasmosis (*N* = 162)	*P* value
Characteristic	*n* (%)	*n* (%)	
Male	81 (80)	118 (73)	0.18
Median age, years (IQR)	35 (27 - 41)	31 (28–40)	0.15
Prior HIV diagnosis	94 (93)	158 (98)	0.08
Prior AIDS diagnosis	7 (7)	13 (8)	0.74
Previous histoplasmosis infection	5 (5)	2 (1)	0.07
Clinical signs and symptoms at first visit			
GI symptoms	67 (66)	119 (74)	0.22
Pulmonary symptoms	63 (62)	100 (62)	0.92
Oral lesions	27 (27)	51 (32)	0.41
Skin lesions	26 (26)	44 (27)	0.80
Palpable lymph nodes	20 (20)	39 (24)	0.42
Neurologic symptoms	17 (17)	37 (23)	0.24
Fever (> 38.0°F)	25 (25)	40 (25)	0.99
Karnofsky score ≤ 50	28 (28)	29 (18)	0.06
Laboratory markers at first visit (median)			
Median CD4 count (IQR)	25 (10–57)	45 (18–98)	0.02*
WBC (cells/μL)	4,280	5,360	0.01*
Hemoglobin (g/dL)	9.0	10.0	0.003*
Hematocrit (%)	27.7	29.2	0.0032*
Platelet count (10^3/μL)	181	284	< 0.001*
LDH (units/L)	471	333	0.002*
SGOT (AST) (units/L)	136	68	0.004*
SGPT (ALT) (units/L)	48	44	0.14
Bilirubin (mg/dL)	0.6	0.5	0.03*
Alkaline phosphatase (units/L)	381	303	< 0.001*
Medications at first visit			
ART	15 (15)	25 (15)	0.90
PCP prophylaxis	69 (68)	111 (69)	0.97
Antifungal therapy	39 (39)	35 (22)	< 0.001*
Fluconazole	27 (27)	28 (17)	0.07
Amphotericin B	7 (7)	4 (3)	0.08
Itraconazole	5 (5)	4 (3)	0.28

AIDS = acquired immune deficiency syndrome; ALT = alanine transaminase ART = antiretroviral therapy; AST = aspartate transaminase; GI = gastrointestinal; HIV = human immunodeficiency virus; IQR = interquartile range; LDH = lactate dehydrogenase; PCP = *Pneumocystis* pneumonia; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell.
* Significant at $P < 0.05$.

survival time was lower for histoplasmosis cases (19 days [range = 4–69] versus 61.5 [27–105]; $P < 0.001$). In comparing survival among patients with histoplasmosis versus patients with other diagnosed infections, median survival was significantly shorter among patients with histoplasmosis, even for those with histoplasmosis and mycobacterial infection. ($P = 0.01$; Figure 2.). Histoplasmosis patients also had lower CD4 cell counts (median = 32; IQR = 15–59) than non-histoplasmosis patients (median = 45; IQR = 18–98), whereas patients with both histoplasmosis and mycobacterial infections had lowest CD4 counts (median = 19; IQR = 6–51).

DISCUSSION

Disseminated histoplasmosis remains an important and deadly opportunistic infection among PWAs. Although Guatemala is a hyperendemic area for histoplasmosis, laboratory detection is limited, and this disease remains

TABLE 3
Treatment and outcomes

Treatment and outcomes	Histoplasmosis (*N* = 101) *n* (%)	No histoplasmosis (*N* = 162) *n* (%)	*P* value
Empiric antifungal therapy	18 (18)	21 (13)	< 0.001*
Received antifungal therapy	68 (67)	63 (40)	< 0.001*
Fluconazole	36 (36)	45 (28)	0.18
Amphotericin B	30 (30)	19 (12)	< 0.001*
Itraconazole	43 (43)	18 (11)	< 0.001*
On ART after diagnosis	53 (53)	81 (50)	0.70
Outcome			
Median days to diagnosis (IQR)	15 (5–23)	7 (1–21)	0.23
Median days to antifungal treatment (IQR)	21 (7–31)	24 (7–33)	0.95
Crude mortality	44 (44)	50 (31)	0.04
30-day mortality	25 (25)	15 (10)	< 0.001*
Median days survival (IQR)	19 (4–69)	61.5 (27–105)	< 0.001*

ART = antiretroviral therapy; IQR = interquartile range.
* Significant at $P < 0.05$.

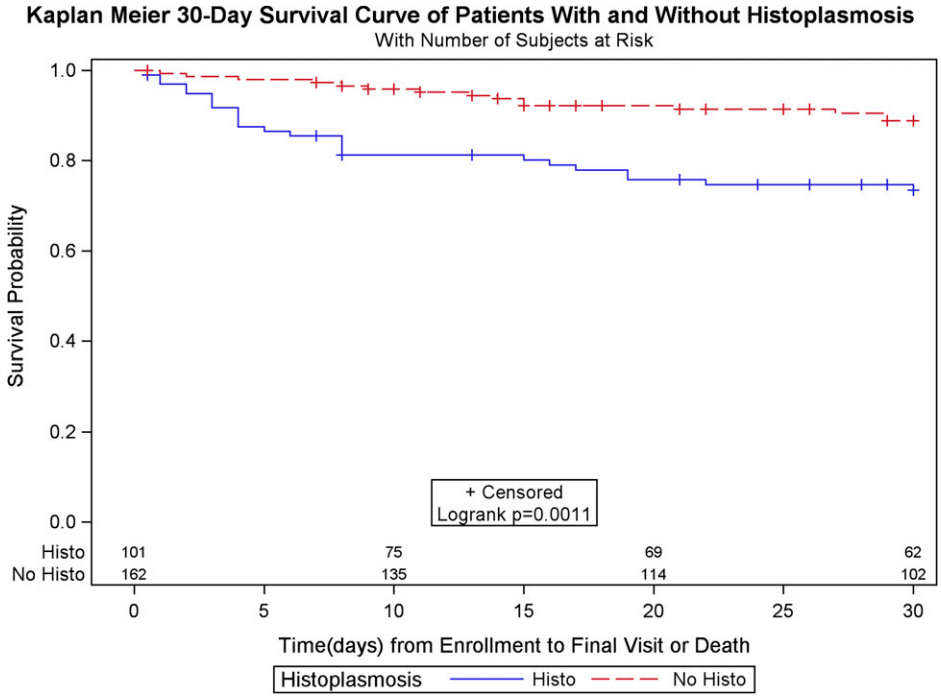

FIGURE 1. Kaplan–Meier survival curve of histoplasmosis cases vs. patients without histoplasmosis.

underrecognized. This report describes one of the largest cohorts of histoplasmosis patients in Latin America, and is the first study to describe histoplasmosis presentation, coinfection, and outcomes among PWAs in Guatemala.[10]

Histoplasmosis was diagnosed in 101 (38.4%) of the enrolled patients, and mycobacteria infection in 70 (26.6%). Mycobacterial infection was also the most frequent coinfection in patients with histoplasmosis, with 26 (9.9%) patients. This finding is similar to other reports in some Latin American countries where mycobacterial coinfection was reported in 8–15% of patients with histoplasmosis.[15] Other nonmycobacterial infections, including cryptococcosis, PCP, and coccidioidomycosis as well as viral, bacterial, and parasitic infections were also identified, which has been well described among patients with low CD4 cell counts.

Patients coinfected with *Histoplasma* and *Mycobacterium* had better survival rates than those infected with *Histoplasma*

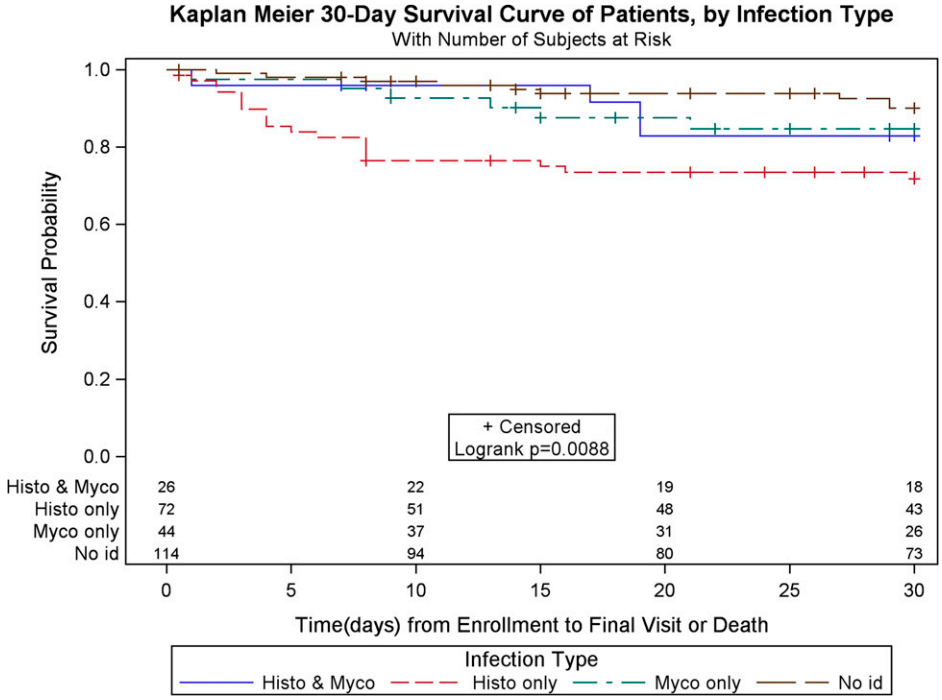

FIGURE 2. Kaplan–Meier 30-day survival curve, by infection type.

alone; yet median CD4 counts were lower among patients with both infections (19 versus 32) (Figure 2). A possible explanation for this finding could be that *M. tuberculosis* regulates the production of several cytokines.[16,17] The control of tuberculosis by the host defenses involves a balance between pro-inflammatory and anti-inflammatory responses. Among these, tumor necrosis factor (TNF)-α, interleukin-12, and interferon (IFN)-γ are key to control the dissemination and severity of histoplasmosis.[16–18] In patients with active tuberculosis, T cells secreting IFN-γ and TNF-α are frequent.[17] On the other hand, the inhibition of TNF-α exacerbates histoplasmosis in mice.[18] We hypothesize that in patients with HIV coinfected with *M. tuberculosis* and *Histoplasma*, the active *M. tuberculosis* infection and its effects on the increased production of TNF-α and IFN-γ acts as a semiprotective mechanism against histoplasmosis, a mechanism that is absent in HIV patients infected with *Histoplasma* alone. Further evidence is required to test this hypothesis. Treatment of these coinfected patients presents special challenges. Rifampin, a first-line drug for treatment of mycobacterial infections, induces cytochrome P450 enzymes that metabolize azoles, effectively reducing azole serum concentrations by more than half, while increasing rifampin concentrations when the two are coadministered.[19,20] Thus, rifampin and itraconazole cannot be administered together,[21] moxifloxacin, a first-line fluoroquinolone used to treat rifamycin-resistant tuberculosis, does not interact with itraconazole,[22] and may be an effective replacement for rifampicin in coinfected patients,[15] but is cost-prohibitive in resource-limited settings.

At the time of presentation, over 23% of patients in this study had symptoms consistent with histoplasmosis, and more than one-third of these patients died. These findings are consistent with those in Brazil and French Guiana, where most studies on histoplasmosis in Latin America have been performed.[1,3,23,24] In French Guiana in the post–highly active ART (HAART) era, histoplasmosis was the most commonly diagnosed AIDS-defining illness, with an incidence of 15.4/1,000 person years.[24] Disseminated histoplasmosis has been estimated to occur in 2–5% of PWAs who live in endemic regions.[1]

Clinical features of AIDS-associated histoplasmosis in this cohort were similar to those published elsewhere in Latin America, where fever, pulmonary and GI symptoms are most frequent.[7,25] A high prevalence of mucosal and skin involvement has been described throughout Latin America and has been attributed to the possible greater virulence of the South American species[26–29] as well to delayed diagnosis.[3,29] The prevalence of skin lesions in our cohort was greater than in the United States (1–7%) but less than what has been reported in South America (53–93%).[3] Our study found no statistically significant differences in clinical symptoms or signs that might aid in distinguishing *Histoplasma* infections from other diseases; since nonspecific symptoms such as malaise and cough can be confused with tuberculosis, bacterial pneumonia, and other febrile illnesses, clinical diagnosis remains challenging.[3,15]

Laboratory abnormalities, including pancytopenia, elevated LDH, and cholestatic hepatitis have been previously described as possible predictors of disease and mortality.[30–32] We found similar laboratory abnormalities in our bivariate analyses but were unable to evaluate them further in multivariate modeling due to limitations in the data. However, combining clinical data and laboratory markers could be useful in developing a score as a mortality predictor.

Many patients received antifungal therapy if there was clinical suspicion of disease. In patients with histoplasmosis who did not receive initial antifungal therapy and for whom information was available, almost all cases had died before the diagnosis was made. This finding highlights the need for rapid diagnosis to improve treatment management and outcomes. Additionally, at follow-up visits, some patients with histoplasmosis were started on empiric antifungal treatment before diagnosis in response to clinical improvement or because clinicians had excluded other infections such as tuberculosis.

Mortality rates among immunocompromised individuals reported in other South American studies are similar to that found in our study (19–39%)[3,27,33,34] and are higher than rates reported in the United States[35–38] except in circumstances where PWAs are diagnosed late or are not receiving HAART.[7,38] Compared with patients diagnosed with mycobacterial and other opportunistic infections, patients with histoplasmosis had a shorter median survival time, and time to diagnosis neared time to death in many instances. These findings highlight both a need to use faster diagnostic methods and to have a low threshold for empiric treatment of immunocompromised individuals with symptoms and signs consistent with histoplasmosis.

This study is subject to several limitations. Data were not uniformly available for each patient, and histoplasmosis diagnosis using the ELISA assay could not be performed in real time, which could have improved the outcome of some of the patients.

In spite of these limitations, this study provides the first data in Guatemala to describe *Histoplasma* and *Mycobacterium* coinfections and outcomes among PWAs. Rapid and accurate diagnostics for both histoplasmosis and mycobacterial infections are essential, since their symptoms are similar and often indistinguishable. To facilitate earlier diagnosis of histoplasmosis, we suggest consideration of a screening algorithm that includes antibody detection in serum, antigen detection in urine, polymerase chain reaction in blood or pulmonary samples, and fungal culture for pulmonary and blood samples. In parallel, tests for *M. tuberculosis* could be carried out to complement the differential diagnosis. In addition, early presumptive treatments could help to improve patient's survival.

Although histoplasmosis mortality is currently high in many developing countries, a urine *Histoplasma* antigen assay that is accessible and available throughout Latin America has the potential to drastically improve patient outcomes.

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