DISSEMINATED HISTOPLASMOSIS: A COMPARATIVE STUDY BETWEEN PATIENTS WITH ACQUIRED IMMUNODEFICIENCY SYNDROME AND NON-HUMAN IMMUNODEFICIENCY VIRUS–INFECTED INDIVIDUALS

ANGELA M. TOBÓN, CARLOS A. AGUDELO, DAVID S. ROSERO, JUAN E. OCHOA, CATALINA DE BEDOUT, ALEJANDRA ZULUAGA, MYRTHA ARANGO, LUZ E. CANO, JAIME SAMPEDRO, AND ANGELA RESTREPO*

Corporación para Investigaciones Biológicas, Medellín, Colombia; Hospital La María, Medellín, Colombia; Facultad de Medicina, Universidad Pontificia Bolivariana, Medellín, Colombia; Policlínica Villarrobledo, Albacete, Spain; Facultad de Medicina y Escuela de Bacteriología y Laboratorio Clínico, Universidad de Antioquia, Medellín, Colombia

Abstract. We studied 52 patients with disseminated histoplasmosis, 30 with the acquired immunodeficiency syndrome (AIDS) (cohort 1) and 22 not co-infected with the human immunodeficiency virus (cohort 2). Demographic, clinical, laboratory, mycologic findings, as well as antifungal therapy and highly active antiretroviral (HAART), were analyzed. Skin lesions were significantly higher in cohort 1 than in cohort 2 ($P = 0.001$). Anemia, leukopenia, and an elevated erythrocyte sedimentation rate were also more pronounced in cohort 1 than in cohort 2 ($P < 0.001$). *Histoplasma capsulatum* was isolated more often in cohort 1 than in cohort 2 ($P < 0.05$) patients, but antibodies to *H. capsulatum* were detected more frequently in cohort 2 than in cohort 1 ($P < 0.05$). Itraconazole treatment was less effective in cohort 1 than in cohort 2 ($P = 0.012$). In cohort 1 patients, HAART improved response to antifungals when compared with individuals not given HAART ($P = 0.003$), who exhibited higher mortality rates ($P = 0.025$). Cohort 1 patients who were given dual antifungal and anti-retroviral therapies responded as well as the non-HIV patients in cohort 2, who were treated only with itraconazole. These results indicate the need to promote restoration of the immune system in patients with AIDS and histoplasmosis.

INTRODUCTION

Disseminated histoplasmosis (DH) is frequently reported in disease-endemic areas of the Americas, including Colombia.[1–7] Its etiologic agent is the thermally dimorphic fungus *Histoplasma capsulatum* var. *capsulatum*.[1,4] Its habitat is the soil, particularly if enriched with bird and bat excrements.[8] Infection is acquired during aerosol-creating activities around infected foci.[1,3,8] Inhalation of *H. capsulatum* conidia from the environment leads to primary lung infection, the severity of which is related to both number of inhaled propagules and the immune response of the host.[1–4] Control of the infection depends mainly on cellular immunity through the concerted action of CD4 lymphocytes, their cytokines and activated macrophages (TH$_1$ type immunity).[3,4] Thus, certain manifestations of histoplasmosis that attest to the inability of the patient to cope with the fungus, such as disseminated skin lesions, are observed in severely immunosuppressed patients infected with human immunodeficiency virus (HIV).[9–11]

Histoplasmosis encompasses a spectrum of clinical forms with DH being the most severe.[1,4,8] Despite the fact that primary lung infection is frequently followed by spleen and liver invasion, DH refers only to a process of intense fungus multiplication in lungs and in extra-pulmonary organs and body sites.[1–4,9–11] Disseminated histoplasmosis may occur either after recent exposure or upon endogenous reactivation of latent foci.[1,11,12] In fact, HIV-infected individuals who develop DH in areas not endemic for diseases were known to have lived previously in recognized disease-endemic regions.[1,8–10,12] Before the AIDS epidemic, risk factors for DH were immunosuppressive therapies, impaired cellular immunity, hematologic and other type of malignancies, organ transplant and dialysis, as well as extreme ages (children and old persons).[1,12,13] In certain individuals, heavy exposure to infected aerosols may also give rise to DH.[1,3,4,8,9] The above circumstances changed with the advent of the HIV epidemic, which transformed histoplasmosis into a common and severe fungal disease.[8–11] Presently, patients with HIV have their own risk factors, such as low CD4 lymphocyte counts ($< 200/\mu$L), an epidemiologic history of exposure to the fungus, and presence of antibodies to *H. capsulatum* at the time of diagnosis.[13–16]

The present study analyzes two cohorts of DH patients, those with AIDS (cohort 1) and those not infected with HIV (cohort 2). The main objectives were to determine clinical differences, effectiveness of diagnostic methods, results of antifungal therapy in connection with viral co-infection, and influence of highly active antiretroviral therapy (HAART).

PATIENTS AND METHODS

From 1979 to 2001, the Corporación para Investigaciones Biológicas in Medellín, Colombia established a diagnosis of DH in 62 patients, 52 of whom had prolonged follow-up observations that facilitated evaluation of their final outcome. In the 52 selected DH patients, 30 (57.7%) had AIDS (cohort 1); the remaining 22 were not co-infected with HIV (cohort 2). Databases were prepared that included demographic and clinical information, chest radiographs, as well as general laboratory (blood cell counts, erythrocyte sedimentation rate) and mycologic tests results, the latter corresponding to direct microscopic examinations (Wright stain) from exudates and biopsies (silver methenamine), cultures from the same specimens, and detection of antibodies to *H. capsulatum* (complement fixation and agar gel immunodiffusion tests with histoplasmin).[1,17]

The immune status of those patients in cohort 1 receiving HAART was determined by CD4 lymphocyte counts, both during and in some cases, at the end of antifungal treatment. All patients with DH received antifungal therapy appropriate to the severity of their clinical manifestations and more recently, observing the recommendations of Wheat and others.[11,18] Treatment consisted of amphotericin B, itraconazole,

* Address correspondence to Angela Restrepo, Corporación para Investigaciones Biológicas, Carrera 72A # 78B-141, Medellín, Colombia. E-mail: angelares@geo.net.co

TABLE 1
Clinical manifestations in two cohorts of patients with disseminated histoplasmosis*

Characteristic	Cohorts	
	DH and HIV (n = 30)	DH (n = 22)
Age, years (range)	36.1 (23–59)	33.8 (1–69)
Sex (M:F)	29:1	1.4:1†
Constitutional (asthenia, weight loss, anorexia, fever)	90	86.4
Respiratory (cough, sputum production, shortness of breath)	80	59
Gastrointestinal (nausea, vomiting, diarrhea)	46.6	54.5
Hypertrophied lymph nodes	56.6	31.8
Hepatosplenomegaly	13.3	22.7
Skin lesions	53.3†	9†
Mucosal lesions	40	40.9
Lung auscultation abnormalities (rales, wheezing, rhoncus, hypoventilation)	26.6	50

* Except where indicated, values are percentages.
† P = 0.01.

and in some cases of fluconazole, ketoconazole, or posaconazole given in the context of clinical trials. The outcome of therapy was evaluated according to a scoring system previously reported,[17] in which each of the clinical abnormalities present before therapy and any mycologic findings received an arbitrary score of 2. The sum of all these scores constituted the denominator of a fraction. During treatment (3–5 months) and at the end of therapy, the above abnormalities and mycologic observations were re-evaluated. If they had resolved, each was given the same score of 2 recorded at initiation of treatment; if abnormalities had improved but not resolved, a score of 1 was assigned to each one; if they had not resolved, each received a score of 0. If a patient showed clinical and/or mycologic deterioration, a negative score equivalent to deducting 2 points for each parameter evaluated before therapy was used. These scores were aggregated to form the numerator of the fraction. The resultant equation was calculated and the results expressed as follows: 1) a negative score indicated deterioration of the clinical condition; 2) zero indicated no change in the patient's condition; 3) a positive score indicated minor or major improvement; and 4) a score of 1 indicated complete resolution of all abnormalities observed before therapy.

The data were processed using Excel® (Microsoft, Redmond, WA). Statistical analyses were done using Fisher's exact test. The Student's t-test was used for group comparisons, and the Pearson correlation test was used to evaluate response to antifungal treatment.

Appropriate informed consent was obtained from the patients and the study was reviewed and approved by the Ethics Committee of the Corporación para Investigaciones Biológicas.

RESULTS

The male-to-female ratio was 29:1 in cohort 1 patients and 1.4:1 in cohort 2 patients (P = 0.001). The mean ages for cohorts 1 and 2 were 36.1 years (range = 23–59) and 33.8 years (range = 1–69), respectively, with no statistically significant differences among the cohorts. Cohort 2 included five children less than 10 years of age.

The most frequent clinical manifestations are shown in Table 1. In both cohorts, constitutional symptoms (asthenia, weight loss, anorexia, fever) predominated, being observed in more than 85% of the patients. Additional symptoms such as

TABLE 2
Active co-morbidities reported in patients with disseminated histoplasmosis according to cohort

Co-morbidity	Number of patients with co-morbidities			
	Cohort 1 (n = 30)		Cohort 2 (n = 22)	
	Previous to diagnosis	Simultaneous with diagnosis	Previous to diagnosis	Simultaneous with diagnosis
Malignancy*	3	6	1	0
Mycotic diseases†	2	13	0	0
Bacterial diseases‡	0	4	0	0
Viral diseases§	2	4	0	0
Parasitic diseases¶	2	4	0	0
Diabetes mellitus	0	0	1	1
Malnutrition	0	0	0	3
Adrenal insufficiency	0	0	0	1
Alcoholism	0	0	2	2
Total with co-morbidities	7 (23.3%)#	21 (70%)#	4 (18.2%)	7 (31.8%)

* Kaposi's sarcoma and laryngeal carcinoma.
† Pneumocystosis, candidiasis, and cryptococcosis.
‡ Tuberculosis, salmonellosis, and syphilis.
§ Cytomegalovirus, hepatitis B, and herpes virus.
¶ Toxoplasmosis and cryptosporidiasis.
# Some patients had two or more co-morbidities.

TABLE 3
Comparison of diagnostic methods for disseminated histoplasmosis according to cohort

Tests		Cohort 1 n = 30 (%)	Cohort 2 n = 22 (%)	P
Positive direct test results	Microscopic examination*	13/16 (81.3)	8/14 (57.1)	> 0.05
	Histoplasma capsulatum in culture	26/27 (96.3)	14/19 (73.6)	< 0.05
Positive indirect test results	Agar gel immunodiffusion	11/29 (37.9)	18/22 (81.8)	< 0.05
(serology with histoplasmin)	Complement fixation	13/29 (44.8)	18/22 (81.8)	< 0.05

* Wright stain.

respiratory problems and gastrointestinal alterations were also frequently recorded (59% and 46% in cohorts 1 and 2, respectively), with no significant differences. Physical examination showed enlarged lymph nodes, hepatosplenomegaly, skin and mucosal lesions, as well as lung auscultation abnormalities (Table 1). These signs were not significantly different among the two cohorts, with the exception of skin lesions, which were observed in 16 (53.3%) in cohort 1 and 2 (9%) in cohort 2 (P = 0.001). In 13 of cohort 1 patients (81.2%) skin lesions were widespread (face, thorax, abdomen, and upper limbs) and showed various characteristics (maculopapular, ulcerated, and/or crusted). In contrast, in cohort 2, skin lesions were nodular and less widespread.

Anemia and leukopenia were documented in 72.4% and 62.1% of the patients in cohort 1, and in 15% and 10.5% of the patients in cohort 2 (P < 0.001 for either parameter). No differences were noticed in platelet counts. Erythrocyte sedimentation rates were elevated in all patients in cohort and in 15 patients in cohort 2 (P = 0.001).

Active co-morbidities observed previous to or simultaneous with the diagnosis of histoplasmosis are shown in Table 2. They were present simultaneously with DH in 21 (70%) patients in cohort 1 with a predominance of mycotic diseases (13 of 30 patients), mostly oral candidiasis. In cohort 2, simultaneous co-morbidities were observed in 7 (31.8%) patients, with 6 showing associated conditions indicating immune response alterations (diabetes, malnutrition, and cirrhosis). Active co-morbidities observed before a diagnosis of histoplasmosis were present in 23.3% of the patients in cohort 1 and 18.2% of the patients in cohort 2.

Chest radiographs showed interstitial infiltrates in 63.3% of the patients in cohort 1 and in 45.5% of the patients in cohort 2; alveolar infiltrates were seen in 3.3% of the patients in cohort 1 and in 9.1% of the patients in cohort 2, but no significant differences were observed for either type of infiltrate. Nodules were observed only in cohort 2 (13.6%).

As shown in Table 3, DH was often diagnosed in both cohorts by direct microscopic observation (Wright stain) of *H. capsulatum* yeast cells in clinical specimens, and the fungus was also isolated in culture from these specimens. Significant differences (P < 0.05) were observed only for the latter procedure. In eight patients (four in each cohort), a diagnosis was established by the observation of yeast cells in hematoxylin and eosin- and/or Gomori-stained tissue biopsy specimens. Serologic test results with histoplasmin were significantly more reactive (P < 0.05) in cohort 2 than in cohort 1.

As shown in Figure 1, 11 patients (36.7%) in cohort 1 received HAART. In 10 of them, CD4 cell counts were available at diagnosis, with a mean value of 53 cells/μL (SD = 36.4). The remaining 19 patients did not receive HAART. In five of them, CD4 cell counts were available, with a mean

value of 30 cells/μL (SD = 19.7). No significant differences were observed between these sub-groups. During antifungal therapy (mean = 9 months), the patients who received HAART had higher mean CD4 cell counts (193 cells/μL [SD = 121.4]) than patients who did not receive HAART (6.7 cells/μL [(SD = 4.1]) (P = 0.001).

In cohort 1, itraconazole was given at a dose 400 mg/day for 3.4 months (range = 0.5–13 months), with maintenance treatment of 200–400 mg/day for a mean of 28.4 months (range = 1–78 months). Amphotericin B was given for 12.3 days (range = 1–15 days) and other azole compounds were given for 6.9 months. None of the latter two groups of medications were used for maintenance therapy. As shown in Table 4, three of the patients who received HAART were also treated with amphotericin B, seven with itraconazole, and 1 with posaconazole; nine of these patients received itraconazole maintenance therapy. In patients who did not receive HAART, 2 were also treated with amphotericin B, 13 with itraconazole, and 4 with other azole compounds (fluconazole and saperconazole); 7 of these patients received itraconazole maintenance therapy. Therapy with amphotericin B was given to 5 patients (16.7%), itraconazole to 20 patients (66.7%), and ketoconazole, fluconazole or posaconazole to 5 patients (16.7%). Maintenance treatment was given to 16 (53.3%) patients in cohort 1. Six (20%) of 30 patients in cohort 1 died before initiating the second stage of treatment; mean time to death was 3.4 months (range = 2 days to 12 months). Eight (26.6%) patients were lost for follow-up after the initial treatment.

In cohort 2, treatment was continuous. Due to severe illness, an adult patient received amphotericin B initially for 15 days and was then treated with itraconazole. This triazole was given to 13 other patients (59%) as the only medication at doses of 100 (children) to 400 mg/day for a mean of 8.7 months (range = 3–13 months). One child died soon after initiating therapy. The remaining eight patients were treated with other azole-derived compounds such as ketoconazole, saperconazole, or fluconazole.

The scores of the point system evaluation were condensed into two groups (Figure 2): patients responding adequately (complete resolution or major improvement), and patients not responding (minor improvement, worsening, or death). This system was applied during and at the end of therapy. During treatment (three months in cohort 1 and five months in cohort 2), 53.4% of cohort 1 patients showed complete resolution or major improvement. In contrast, 86.4% of cohort 2 patients showed an adequate response (P = 0.012) (Figure 2a). At the end of therapy, the scores indicated complete resolution or major improvement in 66.7% of the patients in cohort 1 versus 95.5% of the patients in cohort 2 (P < 0.05) (Figure 2b).

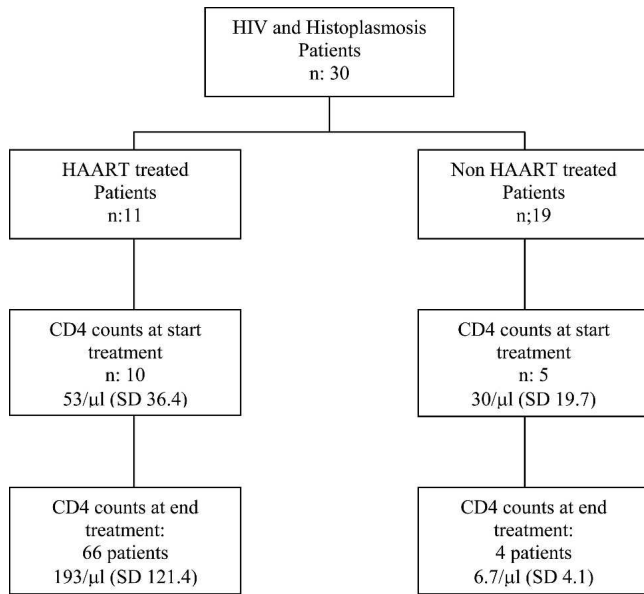As shown in Table 5, there were significant differences in

FIGURE 1. Distribution of highly reactive retroviral therapy (HAART) and CD4 cell counts in patients with disseminated histoplasmosis in cohort 1.

response to antifungal therapy in cohort 1 patients receiving HAART. All of those treated responded, whereas this type of response was lower (47.4%) in the group not receiving antiretroviral therapy ($P = 0.03$). Also, patients treated with HAART responded to antifungals in a manner similar to cohort 2 patients (95.5%); no inadequate responses were observed in this group. Conversely, a significant difference ($P = 0.02$) was found between cohort 2 patients and cohort 1 patients who did not receive HAART. Additionally, 52.6% of those patients who did not receive antiretroviral therapy failed to respond to antifungal treatment, whereas all patients receiving HAART responded ($P = 0.030$). Seven (36.8%) patients who did not receive HAART but failed to respond to antifungal therapy died, six during initial therapy and one during maintenance therapy. Treatment failure or death differed between those treated with HAART and those not receiving HAART, and was significantly higher in the latter group ($P = 0.03$) and also when compared with cohort 2 patients ($P = 0.02$).

These data indicate that a prognosis of DH is greatly influenced by HIV co-infection, with mortality being higher in

TABLE 4
Treatment of disseminated histoplasmosis in cohort 1 patients according to highly active antiretroviral therapy (HAART)

	Antifungal therapy no. (%)			Maintenance therapy no. (%)
Antiviral therapy (n)	Amphotericin B*	Itraconazole†	Other azoles‡	Itraconazole§
HAART (11)	3 (27.3)	7 (63.6)	1 (9.1)	9 (81.8)
No HAART (19)	2 (10.5)	13 (68.4)	4 (21.1)	7 (36.8)
Total (30)	5 (16.7)	20 (66.7)	5 (16.7)	16 (53.3)

* Mean = 12.3 days, range = 1–15 days.
† Mean = 3.4 months, range = 0.5–13 months.
‡ Ketoconazole, fluconazole, posaconazole.
§ Mean = 28.5 months, range = 1–78 months.

cohort 1 patients than in cohort 2 patients. Additionally, response to antifungal therapy was less in the former group. Prognosis also depended on the immune status of the patient because all DH patients treated with HAART improved, whereas less than 53% of those not receiving this medication responded to antifungal treatment.

DISCUSSION

Sub-clinical infection with *H. capsulatum* is common in persons residing in disease-endemic areas, whereas clinically manifested disease was not, at least not until the onset of AIDS, when HIV-infected individuals were shown to develop rapidly progressive and often fatal histoplasmosis.[1,4,8–10] This was also the case in Colombia where infection, as detected by skin tests, was demonstrated in approximately 12% of the population,[19] with various clinical forms of histoplasmosis, including outbreaks, reported sporadically.[6–8,20] Once AIDS appeared, DH became more apparent, and showed a high morbidity rate.[6]

We conducted a retrospective study of 52 DH patients and divided them in two cohorts, 30 with AIDS and 22 not co-infected with HIV. Patients in cohort 1 were diagnosed from 1988 to 2004, whereas patients in cohort 2 were diagnosed for a longer period (1979–2001). The aim of this comparative study was to detect significant differences between the two cohorts to facilitate early recognition and treatment of DH in HIV-infected patients.

As previously reported in other series,[6,21–23] males predominated (80.7%) in cohort 1 with a male to female ratio of 29:1; in cohort 2, the sex distribution was not so markedly different ($P < 0.05$). Age distribution was similar in the two cohorts (young adults) as reported by others,[15,21,22] but the age range of cohort 2 patients extended from childhood to old age. This indicated that in individuals not infected with HIV, DH may occur at any age,[22–24] whereas in those with AIDS, a rather restricted age range is to be expected.[15,21–23]

We found few significant differences in the clinical manifestations of histoplasmosis among the two cohorts. Fever appeared to be a common symptom (more than 80% of the cases) in both DH patients with AIDS and in those not co-infected with HIV.[9,10,13,21,23] Skin lesions, mostly widespread, predominated (53.3%) in cohort 1 patients and were uncommon in cohort 2 cases ($P = 0.001$). Such lesions were also more frequent (66%) in Brazilian DH patients co-infected with HIV compared with those in North America (7%).[21] In another series of Brazilian patients, skin lesions had an intermediate (47.6%) frequency.[24] No skin lesions were observed in a large multi-center study in the United States of HIV-infected histoplasmosis patients.[13] We observed that cohort 2 patients differed significantly from cohort 1 only in their lower proportion of skin lesions (9%). It is interesting to note that in HIV-infected Latin American patients, the skin constitutes a more important target organ for *H. capsulatum* than in North American patients; however, no explanations for this can be given unless a late diagnosis or inadequate diagnostic facilities were considered.

Gastrointestinal involvement was observed in similar proportions in both cohorts, but was more frequent in Brazilian HIV-infected patients with histoplasmosis than in cases in the

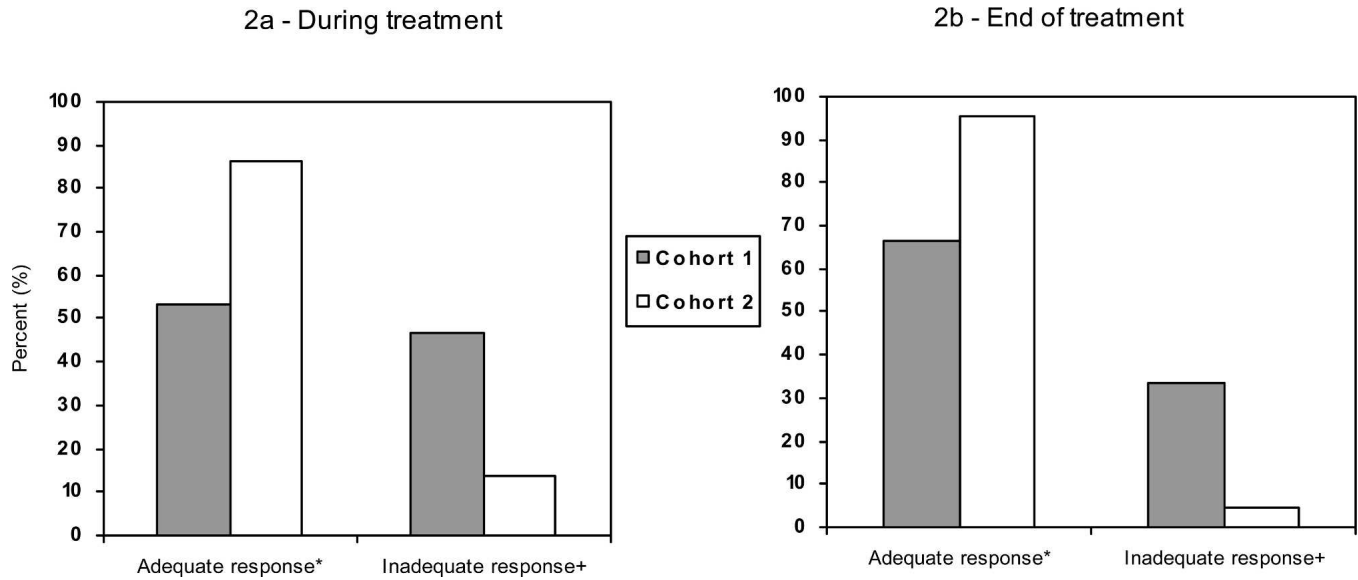## 2a - During treatment

2b - End of treatment

FIGURE 2.   Antifungal treatment of disseminated histoplasmosis according to human immunodeficiency virus status: results of the point system evaluation. *Adequate response = resolution or major improvement; +Inadequate response = minor improvement, worsening, or death.

United States,[21] a finding that has been confirmed in different series.[13,22] The frequency of abdominal problems was similar in this study (46.6%) and in those of Hajjeh and others (24%)[13] and Karimi and others (33%).[21]

Other differential findings were observed for lung lesions, with significantly more interstitial infiltrates observed in cohort 1 (63.3%). Interstitial infiltrates were also observed in half of the patients reported by Hajjeh and others,[13] in 63% of the Brazilian patients studied by Karimi and others,[21] and in 53.3% of French Guyana patients.[16] This involvement suggests the existence of a primary lung infection that was not noticed.[1,13]

Anemia and leukopenia were the most common hematologic abnormalities and differed significantly between cohorts 1 and 2 ($P < 0.001$ for either parameter). Sedimentation rates were elevated in all cohort 1 patients but only in half of cohort 2 patients ($P = 0.001$). These results should considered when HIV infection in a patient with histoplasmosis is suspected.

Although DH can be diagnosed by observation of *H. capsulatum* yeast cells in clinical specimens, isolation of the fungus in culture varied in the two cohorts, with nearly all (96.3%) patients in cohort 1 showing positive results, but only 73.6% in cohort 2 ($P < 0.05$). Conversely, detection of antibodies in sera by either immunodiffusion or complement fixation was significantly lower in cohort 1 patients than in cohort 2 patients ($P < 0.05$). These findings have been previously demonstrated by Wheat[9,12] and by Karimi and others in the Brazilian cohort.[21]

The number of CD4 lymphocytes in cohort 1 patients was low (30–53 cells/μL) in those receiving HAART and in those not receiving HAART, suggesting that histoplasmosis occurs when the immune response is markedly impaired, as demonstrated by McKinsey and others, who found that the annual incidence of histoplasmosis in AIDS patients increases when CD4 lymphocyte counts are less than 50 cells/μL.[14] This finding has also been reported in patients in the United States.[13,23]

In our patients HAART significantly increased CD4 lymphocyte counts (to more than 150/μL), but most importantly, improved the response to antifungal therapy, as shown by the fact that all patients thus treated achieved complete resolution or major improvement of their pre-therapy abnormalities in a manner similar to those patients not co-infected with HIV (cohort 2). In contrast, patients not receiving HAART did not respond as well ($P = 0.003$) to antifungal treatment. Despite the fact that antiretrovirals are known to improve defense mechanisms, thus allowing AIDS patients to overcome opportunistic infections,[25] their positive influence in histoplasmosis has been recognized only recently, as shown by one case report from the Phillipines,[26] and by a series of cases from Argentina,[27] which indicate that HAART immune restoration effectively cooperates with antifungal therapy in controlling the mycosis.

Due to its retrospective character, this study had several limitations, among them lack of information on CD4 lymphocyte counts in the HIV-infected population both before and

TABLE 5

Effect of highly active antiretroviral therapy (HAART) on the efficacy of antimycotic therapy in patients with disseminated histoplasmosis in cohort 1: comparison with cohort 2 patients

| | Cohort 1 (n = 30) | | | Cohort 2 (n = 22) | | |
Outcome	HAART n = 11 (%)	No HAART n = 19 (%)	P HAART vs. no HAART		P vs. HAART	P vs. no HAART
Complete resolution or major improvement	11 (100)	9 (47.4)	0.03	21 (95.5)	> 0.05	0.02
Minor improvement, worsening, or death	0	10* (52.6)	0.03	1 (4.5)	> 0.05	0.02

* There were 7 (36.8%) deaths in this group.

after therapy. Additionally, variations in treatment modalities during the course of the study interfered with a more precise evaluation of the clinical responses, especially in the DH patients co-infected with HIV, whose treatment is currently defined by expert guidelines.[18] However, the extended period of the study (1979–2001) did not alter the way in which diagnosis was established in our laboratory since newer modalities (e.g., antigenemia) have not been used regularly in our institution and have been previously used only for standardization purposes, not for diagnosis.[28]

This study shows that the prognosis of DH is greatly influenced by co-infection with HIV since response rates to antifungal treatment were lower in co-infected patients. Nonetheless, HAART appears to improve this unfavorable condition by restoring the immune response so that even in the presence of AIDS, antifungal therapy can be successful. Therefore, it is mandatory to suspect mycosis as early as possible and initiate antifungal and antiretroviral therapies promptly to improve the prognosis of DH patients co-infected with HIV.

Authors' addresses: Angela M. Tobón, Catalina de Bedout, Alejandra Zuluaga, and Angela Restrepo, Corporación para Investigaciones Biológicas, Carrera 72A # 78B-141, Medellín, Colombia and Hospital La Maria, Medellín, Colombia, Fax: 57-4-441-0855, E-mails: atobon@cib.org.co, cbedout@cib.org.co, azuluaga@cib.org.co, and angelares@geo.net.co. Carlos A. Agudelo and Juan E. Ochoa, Universidad Pontificia Bolivariana, Calle 78B # 72A-109, Medellín, Colombia, Fax: 57-4-257-2428, E-mails: carlosaguedelo@yahoo.com and clio@geo.net.co. David S. Rosero, Policlínica Villarrobledo, c/o Senda Molinera 02600, Villarrobledo, Albacete, Spain, Fax: 34-96-714-5959, E-mail: roserocuesta@hotmail.com. Myrtha Arango, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia and Corporación para Investigaciones Biológicas, Carrera 72A # 78B-141, Medellín, Colombia, Fax: 57-4-441-0855, E-mail: myrtaa@geo.net.co. Luz E. Cano, Escuela de Bacteriología, Universidad de Antioquia, Medellín, Colombia and Corporación para Investigaciones Biológicas, Carrera 72A # 78B-141, Medellín, Colombia, Fax: 57-4-441-0855, E-mail: lcano@cib.org.co. Jaime Sampedro, Hospital La María, Calle 92 EE # 67-61, Medellín, Colombia, Fax 57-4-237-1963.

Reprint requests: Angela Restrepo, Corporación para Investigaciones Biológicas, Carrera 72A # 78B-141, Medellín, Colombia.

REFERENCES

1. Wheat LJ, Kaufman CA, 2003. Histoplasmosis. *Infect Dis Clin North Am 17:* 1–19.
2. Kleiman MB, 2004. Histoplasmosis. Feigin RD, Cherry JD, Demmler GJ, Kaplan SL, eds. *Textbook of Pediatric Infectious Diseases.* Philadelphia: W. B. Saunders, 2607–2629.
3. Deepe GS, 2005. *Histoplasma capsulatum.* Mandell GL, Bennet JE, Dolin R, eds. *Principles and Practice of Infectious Diseases.* Sixth edition. Philadelphia: Churchill Livingstone, 2718–2733.
4. Kaufman CA, 2003. Histoplasmosis. Dismukes WE, Pappas PG, Sobel JD, eds. *Clinical Mycology.* New York: Oxford University Press, 285–298.
5. Tobón A, Franco L, Correa AL, Bedoya F, Ortega J, Soto M, 1997. Histoplasmosis en el adulto. *Acta Med Colombiana 22:* 277–284.
6. Arango M, Bedout C, Tobón AM, Restrepo A, Torrado E, Castañeda E, Sierra P, González GA, Panesso R, Cárdenas J, Estrada S, Jaramillo E, and the Colombian histoplasmosis study Group, 2000. Histoplasmosis en Colombia: Estudio interinstitucional. *Informe Quincenal Epidemiol Nacional 5:* 119–123.
7. Jiménez R, Urán M, De Bedout C, Arango M, Tobón AM, Cano LE, Restrepo A, 2002. Brote de histoplasmosis aguda en un grupo familiar: Identificación de la fuente de infección. *Biomedica 22:* 155–159.
8. Cano M, Hajjeh RA, 2001. The epidemiology of histoplasmosis: a review. *Semin Respir Infect 16:* 109–188.
9. Wheat J, 1996. Histoplasmosis in the acquired immunodeficiency syndrome. *Curr Top Med Mycol 7:* 7–18.
10. Hajjeh RA, 1995. Disseminated histoplasmosis in people infected with human in immunodeficiency virus. *Clin Infect Dis 21:* 108–110.
11. Wheat LJ, Connolly-Stringfield PA, Baker RL, Curfman MD, Eads ME, Israel KS, Norris SA, Douglas FW, Zeckel ML, 1990. Disseminated histoplasmosis in the acquired immunodeficiency syndrome: clinical findings, diagnosis and treatment, and a review of the literature. *Medicine (Baltimore) 69:* 361–374.
12. Wheat LJ, 2003. Current diagnosis of histoplasmosis. *Trends Microbiol 11:* 488–495.
13. Hajjeh RA, Pappas PG, Henderson HD, Lancaster DM, Bamberger KJ, Skahan MA, Phelan,1 G. Cloud M, Holloway, Kauffman CA, Wheat LJ, the National Institute of Allergy and Infectious Diseases Mycoses Study Group, 2001. Multicenter case-control study of risk factors for histoplasmosis in human immunodeficiency virus-infected people. *Clin Infect Dis 32:* 1215–1220.
14. McKinsey DS, Spiegel RA, Hutwagner L, 1997. Prospective study of histoplasmosis in patients infected with human immunodeficiency virus: incidence, risk factors and pathophysiology. *Clin Infect Dis 24:* 1195–1203.
15. Wheat LJ, Chetchotisakd P, Williams B, Connolly P, Shutt K, Hajjeh R, 2000. Factors associated with severe manifestations of histoplasmosis in AIDS. *Clin Infect Dis 30:* 877–881.
16. Couppie P, Sobesky M, Aznar C, Bichat S, Clyti E, Bissuel F, El Guedj M, Alvarez F, Demar M, Louvel D, Pradinaud R, Carme B, 2004. Histoplasmosis and acquired immunodeficiency syndrome: a study of prognostic factors. *Clin Infect Dis 38:* 134–138.
17. Restrepo A, Gómez I, Cano LE, Arango MD, Gutiérrez F, Sanin A, Robledo MA, 1983. Post-therapy status of paracoccidioidomycosis patients treated with ketoconazole. *Am J Med 74:* 53–57.
18. Wheat J, Sarosi G, McKinsey D, Hamill R, Bradsher R, Johnson P, Loyd J, Kaufman C, 2000. Practice guidelines for the management of patients with histoplasmosis. *Clin Infect Dis 30:* 688–695.
19. Restrepo A, Robledo M, Ospina S, Restrepo M, Correa A, 1968. Distribution of paracoccidiodin sensitivity in Colombia. *Am J Trop Med Hyg 17:* 25–37.
20. Ordoñéz N, Tobón A, Arango M, de Bedout C, Gómez B, Castañeda E, Restrepo A, 1997. Brotes de histoplasmosis registrados en el área andina colombiana. *Biomedica 17:* 105–111.
21. Karimi K, Wheat J, Connolly P, Cloud G, Hajjeh R, Wheat E, Alves K, Lacaz CS, Keath E, 2002. Differences in histoplasmosis in patients with acquired immunodeficiency syndrome in the United States and Brazil. *J Infect Dis 186:* 1655–1660.
22. Pietrobon D, Negro-Marquínez L, Kilstein J, Galíndez J, Greca A, Battagliotti C, 2004. Histoplasmosis diseminada y sida en un hospital argentino: manifestaciones clínicas, diagnóstico y tratamiento. *Enferm Infecc Microbiol Clin 22:* 156–159.
23. Mandell WA, Goldberg DM, Neu HC, 1986. Histoplasmosis in patients with the acquired immune deficiency syndrome. *Am J Med 81:* 974–978.
24. Severo LC, Oliveira FM, Irion K, Porto NS, Londero AT, 2001. Histoplasmosis in Rio Grande do Sul, Brazil: a 21-year experience. *Rev Inst Med Trop Sao Paulo 43:* 183–187
25. Aberg JA, 2001. Reconstitution of immunity against opportunis-

tic infections in the era of potent antiretroviral therapy. Volberding PA, Jacobson MA, eds. *AIDS Clinical Review 2000/2001*. New York: Marcel Dekker, 115–138.

26. Sun HY, Chen MY, Hsieh SM, Hung CC, Chang SC, 2004. Successful discontinuation of secondary prophylaxis for histoplasmosis after highly active antiretroviral therapy. *J Formos Med Assoc 103:* 546–548.

27. Negroni R, Helou SH, López-Daneri G, Robles AM, Arechevala

AI, Bianchi MH, 2004. Interruption of antifungal secondary prophylaxis in AIDS-related histoplasmosis. *Rev Iberoam Micol 21:* 75–78.

28. Gomez BL, Figueroa JI, Hamilton AJ, Diez S, Rojas M, Tobon A, Restrepo A, Hay RJ, 1999. Detection of the 70-kilodalton *Histoplasma capsulatum* antigen in serum of histoplasmosis patients: correlation between antigenemia and therapy during follow-up. *J Clin Microbiol 37:* 675–680.