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Imported Acquired Immunodeficiency Syndrome–Related Histoplasmosis in Metropolitan France: A Comparison of Pre–Highly Active Anti-Retroviral Therapy and Highly Active Anti-Retroviral Therapy Eras

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Abstract. *Histoplasma capsulatum* var. *capsulatum* infection is rare outside disease-endemic areas. Clinical presentation and outcome of acquired immunodeficiency syndrome–related histoplasmosis are unknown in non-endemic areas with wide access to highly active anti-retroviral therapy (HAART). Retrospective analysis of cases recorded at the French National Reference Center for Mycoses and Antifungals during two decades: pre-HAART (1985–1994) and HAART (1997–2006). Clinical features and outcome of all adults with proven acquired immunodeficiency syndrome–related histoplasmosis were compared between the two periods. One hundred four patients were included (40 during the pre-HAART era and 64 during the HAART era). Diagnosis was established a mean of 62 days after onset of symptoms. One-year overall mortality rates decreased from 53% (pre-HAART era) to 22% (HAART era). Diagnosis during the pre-HAART era and an older age were the only independent factors associated with death. Histoplasmosis is a rare invasive fungal infection outside disease-endemic areas. Its prognosis improved significantly during the HAART era.

INTRODUCTION

Extrapulmonary infection caused by *Histoplasma capsulatum* var. *capsulatum* is an acquired immune deficiency syndrome (AIDS)–defining opportunistic infection.[1] This systemic fungal infection is endemic in certain areas of North and South America, Asia, and Africa.[2] It represented the first manifestation of human immunodeficiency virus (HIV) infection in up to 25% of AIDS patients in highly endemic areas before the availability of highly active anti-retroviral therapy (HAART).[3] AIDS-related histoplasmosis is almost always disseminated and mortality is high in the absence of accurate diagnosis and prompt appropriate antifungal treatment.[3,4] Liposomal amphotericin B has proved superior to deoxycholate amphotericin B in reducing overall mortality and iatrogenic renal failure in the HIV infection context and is the recommended first-line therapy of severe cases.[5,6] Retrospective[7,8] and prospective[9,10] studies from endemic areas have identified various prognostic factors. The impact of HAART on the epidemiology and outcome of histoplasmosis has not been extensively studied, even in endemic areas, and only a limited number of cases of immune reconstitution inflammatory syndrome (IRIS) cases have been reported in AIDS patients.[11]

Disseminated histoplasmosis can also be diagnosed in AIDS patients living in non-endemic area after acute exposure or delayed reactivation of a latent infection providing the patient had previously lived or traveled to a disease-endemic area.[2] Updated data on AIDS-related histoplasmosis in non-endemic areas are lacking. A recent review of the literature identified only 68 cases in Europe published during 1984–2004,[12] and an epidemiologic survey reported 45 cases diagnosed in 10 countries in Europe during 1995–1999.[13]

We thus performed a 10-year (1997–2006) nationwide retrospective study to describe AIDS-related histoplasmosis during the HAART era in metropolitan France, a non-endemic country. We compared these recent cases to those recorded during the pre-HAART era (1985–1994) to investigate the impact of HAART on the epidemiology, clinical manifestations, and prognosis of AIDS-related imported histoplasmosis.

METHODS

Study design. A retrospective study was implemented at the French National Reference Center for Mycoses and Antifungals (NRCMA). All adult cases of AIDS-related *H. capsulatum* infections diagnosed in metropolitan France during January 1, 1985–December 31, 1994 (first period, pre-HAART era) and during January 1, 1997–December 31, 2006 (second period, HAART era) and reported to the NRCMA were reviewed. Additional cases were identified by direct contact with members of the French Mycosis Study Group. Because HAART was not routinely available as standard care during 1995 and 1996 in metropolitan France, cases diagnosed during January 1, 1995–December 31, 1996 were not included.

Inclusion criteria were an age > 18 years, serologically confirmed HIV infection, proven histoplasmosis according to updated 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 Consensus Group definition[14] (i.e., illness consistent with histoplasmosis and positive culture, direct examination, or histopathologic results), and a diagnosis established in metropolitan France. Patients were not eligible when the diagnosis was established in French overseas departments (i.e., French Guiana and French West Indies, regions in which *H. capsulatum* var. *capsulatum* infections are endemic).

A standardized questionnaire was established and data were obtained by reviewing the medical, microbiologic, and pathologic charts in the corresponding centers and by discussion with the clinician/mycologist in charge of the patient whenever needed. The following data were extracted: epidemiologic data (date and place of birth, living area, travel to or residency in disease-endemic areas, time since last travel to these disease-endemic areas), HIV

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infection parameters (date of diagnosis, CD4 cell count, and viral load at the time of histoplasmosis diagnosis, previous opportunistic infections, anti-retroviral therapy) and histoplasmosis characteristics (clinical presentation, diagnostic modalities, antifungal treatment and follow-up up to April 2008).

Data from the pre-HAART cohort were obtained in 1995 by using the same questionnaire and methods and were reported in part in 1996 (Lortholary O and others, Abstract I174, 36th Interscience Conference on Chemotherapy and Antimicrobial Agents, New Orleans, LA, September 15–18, 1996).

Definitions. Histoplasmosis was defined by isolation of *H. capsulatum* from any body site or by visualization of small ovoid (3–4 μm) intracellular yeasts compatible with *H. capsulatum* upon examination of tissue section or fluid pellet in a context compatible with the diagnosis.

Clinical pulmonary signs included cough, dyspnea, sputum, and hemoptysis. Mucocutaneous symptoms were defined as presence of any of skin ulceration, papule, pseudo-molluscum lesions, and/or pharyngeal ulceration. Neurologic signs were defined as presence of any of seizure, motor deficit, coma, meningitis. Histoplasmosis was considered as disseminated if at least two non-contiguous organs were involved.

Previously established criteria of severity were used[7,10] and corresponded to the presence of at least one of the following: hypoalbuminemia (< 35 g/L), disseminated intra-vascular coagulation, lactate dehydrogenase levels > 2 times the upper limit of the reference range, creatinine concentration > 185 μM (2.1 mg/dL), systolic blood pressure < 90 mm of Hg, and hypoxemia (PaO_2 < 60 mm of Hg).

Amphotericin B treatment should have lasted at least 14 days to be considered for analysis. In case of successive therapy with deoxycholate amphotericin B and liposomal amphotericin B, only the formulation that had been received longer was considered for analysis. Maintenance therapy was considered as therapy that started three months after initiation of antifungal treatment. Relapse was defined as new onset of clinical signs with new isolation of *H. capsulatum* on culture or visualization of small ovoid (3–4 μm) intracellular yeasts upon examination of tissue section or fluid pellet. The existence of histoplasmosis-related IRIS was systematically investigated using published criteria (i.e., progression of organ dysfunction or enlargement of pre-existing lesion or exaggerated inflammatory reaction and decrease in plasma HIV viral load by > 1 log copies/mL).[11,15] All IRIS and relapse cases were reviewed and validated by two infectious diseases specialists who were experts in the field. The underlying cause of death was considered to be histoplasmosis in the presence of clinical symptoms related to histoplasmosis and with a positive direct examination result or culture of *H. capsulatum* within one month before death.

Statistical analysis. The current study based on specific missions of the NRCMA has been approved by the appropriate Institutional Review Board. Information was obtained anonymously and entered coded in a secured website (approved by the French commission on personal data and freedom). Statistical analysis was performed by using StataSE10 software (StataCorp, College Station, TX) and R software (http://cran.r-project.org). Distributions of variables were compared by using the chi-square test or Fisher's exact test for categorical variables and the Student's *t*-test for continuous variables.

Overall survival was the time interval between the date of diagnosis and the date of death or last follow-up. Kaplan-Meier estimates were used to describe survival distributions. The log-rank test was used to compare survival distributions. Multivariate analyses were performed by using Cox proportional hazards regression model.

Histoplasmosis-related death probabilities were obtained from crude cumulative incidence estimates, which treated death from other causes as competing risk events. Cumulative incidences of death related to histoplasmosis were compared between subgroups by using the method of Fine and Gray.[16] Multivariate proportional hazards models accounting for death from other causes as a competing risk were fitted by using the same method.

RESULTS

Baseline demographic and HIV parameters during the pre-HAART and HAART eras. Among the 104 patients studied (Table 1), 40 were diagnosed during the pre-HAART era (1985–1994) and 64 during the HAART era (1997–2006). In the second period, the proportion of women ($P = 0.04$) and that of patients born in Africa ($P < 0.001$) increased. The proportion of females born in Africa increased from 5% (2 of 40) to 31% (20 of 64; $P = 0.001$). There was a significant change in the mode of HIV transmission with a decrease in the proportion of homosexual or bisexual men and intravenous drug users and an increase in the proportion of heterosexual patients ($P < 0.001$). Histoplasmosis was significantly more

TABLE 1

Demographic and virologic characteristics of 104 HIV-infected patients with imported histoplasmosis, France*

Characteristic	Pre-HAART (1985–1994), n = 40	HAART (1997–2006), n = 64	*P*
Mean (SD) age in years	38 (7)	40 (11)	0.22
Male, no. (%)	31 (78)	37 (58)	0.04
Continent of birth, no. (%)			$< 10^{-3}$
Africa	6 (15)	36 (58)	
United States	15 (38)	18 (29)	
Europe	17 (44)	7 (11)	
Asia	1 (3)	0	
Oceania	0	1 (2)	
HIV characteristics			
Median CD4 cell count (/μL) (IQR, 95% CI)	21 (10–33)	12 (5–30)	0.74
HIV status at the time of histoplasmosis diagnosis, no. (%)			0.02
Histoplasmosis indicating HIV infection	7 (17)	27 (42)	
HIV infection already known	15 (38)	22 (34)	
AIDS already known	19 (45)	15 (23)	
Mode of HIV transmission, no. (%)			0.001
Heterosexual	17 (42)	48 (75)	
Homosexual	12 (32)	3 (5)	
Intravenous drug use	4 (10)	2 (3)	
Transfusion	3 (8)	2 (3)	
Unknown	4 (10)	9 (14)	
Geographic areas of suspected *Histoplasma capsulatum* exposure, no. (%)†‡			
Africa	10 (25)	39 (61)	$< 10^{-3}$
United States	15 (38)	9 (14)	0.008
French Guiana	13 (33)	14 (22)	0.23
French West Indies	8 (20)	6 (9)	0.15
Asia	3 (8)	2 (3)	0.37
Unknown	1 (3)	0	0.39

*HIV = human immunodeficiency virus; HAART = highly active antiretroviral therapy; IQR = interquartile range; CI = confidence interval; AIDS = acquired immunodeficiency syndrome.

†For whom information was available.

‡The same patient may have traveled to several disease-endemic areas.

frequently the initial event leading to the diagnosis of HIV infection during the HAART era. Median CD4+ T cell count was similar during the two periods.

All patients traveled to areas in which histoplasmosis was endemic. Geographic areas of exposure were diverse but mostly in Africa and French Guiana (Table 1). The time interval between the last travel to a disease-endemic area and the diagnosis was known for 93 patients (interval < 1 month [n = 18, 19%], 1 month–1 year [n = 20, 22%], 1–10 years [n = 42, 45%], and > 10 years [n = 13, 14%]). The longest time interval recorded was 15 years.

Characteristics of histoplasmosis at diagnosis. Histoplasmosis was diagnosed nearly two months after the first symptoms in both periods (Table 2). Clinical presentation did not differ during the two periods for more frequent clinical signs (fever, peripheral adenopathies, liver or spleen enlargement, abdominal pain, diarrhea). However, pulmonary symptoms (cough and sputum) were more frequently recorded during the pre-HAART era but the same proportion of patients had an abnormal chest radiograph. The pattern of dermatologic lesions evolved and showed a significant decrease in papules (37% versus 17%; $P = 0.02$). Neurologic symptoms remained scarce. Overall, histoplasmosis was disseminated in 73 (70%) of 104 patients. Biological parameters remained similar and showed only a trend towards decreased hemoglobin levels during the HAART era (9.1 ± 2.2 versus 8.3 ± 1.9 g/dL; $P = 0.07$). Serum alkaline phosphatase levels were increased (> 2× the upper limit of the reference value) in 43% and 39% of patients, respectively ($P > 0.05$) and aspartate aminotransferase levels were increased (> 2× the upper limit of the reference value) in 32% and 55%, respectively ($P = 0.03$).

Clinical severity was assessed only during the second period. Most (n = 41, 64%) patients had at least one of the severity criteria, including hypoalbuminemia (48%), a lactate dehydrogenase level > 2× the upper limit of the reference value (36%), hypotension (14%), disseminated intravascular coagulation (13%), renal insufficiency (11%), and hypoxemia (5%).

The diagnostic tools used remained similar during the two periods (Table 3). More than 90% of the patients had a positive histopathologic or direct examination results and approximately 80% had a positive fungal culture. The most frequently contributive clinical specimens were bone marrow (60%), skin or mucosal specimen (39%), blood (36%), and respiratory samples (36%). Positive skin/mucosal samples were slightly more frequent during the pre-HAART era (50% and 31%; $P = 0.06$). There was also a trend towards an increase in the prevalence of positive blood culture (35% and 54%; $P = 0.10$).

Histoplasmosis-related IRIS. Seven (11%) patients diagnosed during the HAART era showed development of IRIS related to histoplasmosis (Table 4). Four of them had been reported elsewhere.[11,17] In two cases, a 51-year old woman treated with HAART and chemotherapy for Kaposi's sarcoma and a 33-year old man who had AIDS-defining toxoplasmosis and onset of HAART three weeks before IRIS, IRIS was the first manifestation of histoplasmosis. Histoplasmosis was the first manifestation of HIV infection for the five other patients. IRIS occurred 1–2 months after diagnosis of histoplasmosis in three patients. Two patients had late-onset IRIS but they had unplanned interruption of HAART, resumed HAART without medical advice 2–3 months before IRIS, and consulted a physician only when IRIS occurred. IRIS was severe in two patients: one had uveitis that finally required enucleation, and one had intestinal obstruction that required colectomy.

Outcome of 104 patients with histoplasmosis. Ninety-five (91%) patients received antifungal drugs for at least 48 hours. Most (64%) patients received one amphotericin B formulation. Forty-seven (45%) patients received deoxycholate amphotericin B, including 38 patients subsequently switched to itraconazole. Twenty (19%) patients were prescribed liposomal amphotericin B, including 15 patients switched

TABLE 2

Baseline characteristics of imported histoplasmosis in 104 HIV-infected patients, France*

Characteristic	Pre-HAART (1985–1994), n = 40	HAART (1997–2006), n = 64	*P*
Clinical presentation			
Time between onset of symptoms and diagnosis (days)	59 (66)	65 (65)	0.66
Fever, no. (%)	35 (88)	54 (84)	0.78
Adenopathy, no. (%)	21 (49)	40 (63)	0.17
Hepatomegaly, no. (%)	19 (48)	27 (43)	0.56
Splenomegaly, no. (%)	14 (36)	28 (44)	0.39
Pulmonary symptoms, no. (%)	24 (60)	22 (34)	0.01
Cough	23 (58)	17 (27)	0.002
Sputum	12 (30)	2 (3)	$< 10^{-3}$
Dyspnea	11 (28)	13 (20)	0.40
Abnormal chest radiograph	25 (61)	33 (52)	0.34
Mucocutaneous symptoms, no. (%)	23 (56)	28 (44)	0.17
Papule	15 (37)	11 (17)	0.02
Oral ulceration	6 (15)	4 (6)	0.18
Skin ulceration	3 (8)	2 (3)	0.37
Abdominal symptoms, no. (%)	16 (40)	23 (36)	0.68
Neurologic symptoms, no. (%)	6 (15)	7 (11)	0.56
Biologic parameters, no. (%)			
Hemoglobin (g/dL)	9.1 (2.2)	8.3 (1.9)	0.07
Leukocytes (10^9/L)	2.9 (1.2)	3.5 (4.4)	0.37
Platelets (10^9/L)	188 (104)	147 (150)	0.14
AST (N× upper reference value)	2.1 (2.1)	3.9 (4.5)	0.04
ALP (N× upper reference value)	3.9 (7.1)	1.8 (1.2)	0.03

*HIV = human immunodeficiency virus; HAART = highly active antiretroviral therapy; AST = aspartate aminotransferase; ALP = alkaline phosphatase.

TABLE 3

Tools for diagnosis of histosplasmosis in 104 HIV-infected patients with imported histoplasmosis, France*

Tools	Pre-HAART (1985–1994), n = 40	HAART (1997–2006), n = 64	*P*
Diagnostic tools, no. (%)			
Histopathology or direct examination	38 (95)	60 (94)	1
Positive *Histoplasma capsulatum* culture	31 (78)	52 (81)	0.80
Blood	11 (35)	27 (54)	0.11
Respiratory specimen	12 (30)	20 (31)	0.89
Skin or mucosal specimen	20 (50)	20 (31)	0.06
Bone marrow	22 (55)	42 (66)	0.28
Lymph node	7 (18)	18 (28)	0.35
Gastrointestinal tract	8 (20)	8 (13)	0.57
Liver	5 (13)	2 (3)	0.10
Cerebrospinal fluid	0	2 (3)	0.52
Detection of antibodies against *H. capsulatum*	3 (8)	1 (2)	0.16

*HIV = human immunodeficiency virus; HAART = highly active antiretroviral therapy.

TABLE 4
Clinical, virologic, and outcome data in seven patients with histoplasmosis-related IRIS, France*

			Baseline‡			IRIS		
Patient no.	Age, y/sex	Time interval, months†	CD4 cells/μL	Viral load (copies/mL)	Manifestation	CD4 cells/μL	Viral load (copies/mL)	Manifestation
1	51/F	0	25	350,000	None	144	< 50	Peripheral necrotic adenopathies
2§	33/M§	0	13	250,000	None	59	150	Hemophagocytic syndrome
3§	57/M§	1	55	> 500,000	Pulmonary involvement	436	< 200	Intestinal obstruction caused by granulomatous colitis
4§	20/F§	2	4	196,000	Papule and hepatomegaly	108	25,000	Arthritis, uveitis
5	29/F	43¶	92	3,328,000	Meningitis	113	68,000	Aseptic meningitis
6	51/M	2	14	1,000,000	Splenomegaly and peripheral adenopathies	180	< 50	Rash
7§	36/M§	35¶	2	290,000	Hepatosplenomegaly and peripheral adenopathies	106	< 50	Peripheral necrotic adenopathies

* IRIS = immune reconstitution inflammatory syndrome.
† Time interval is the period between diagnosis of histoplasmosis and IRIS.
‡ Baseline was diagnosis of acquired immunodeficiency syndrome (AIDS). AIDS was detected by histoplasmosis for all patients except patients 1 and 2 for whom IRIS was the first manifestation of histoplasmosis. Patient 1 was treated with chemotherapy and highly active anti-retroviral therapy (HAART) for Kaposi's sarcoma. Histoplasmosis-related adenopathy appeared three months after onset of HAART, when chemotherapy was stopped. Patient 2 had AIDS-defining toxoplasmosis and onset of HAART three weeks before IRIS.
§ These patients have been reported.[11,17]
¶ These two patients had an unplanned interruption of HAART and became compliant again 2 months before IRIS. No immunovirologic data were available during HAART interruption.

to itraconazole. Itraconazole was the only antifungal drug prescribed to 25 (24%) patients. Voriconazole or fluconazole use was exceptional (one patient each). Five (5%) patients who died less than 48 hours after diagnosis did not receive an antifungal drug. No information related to treatment was available for the remaining four patients.

Median follow-up was 31.5 months (range = 0–120 months) and 41 deaths were observed. Overall mortality rate was 39% in the entire cohort. Mortality rate was higher in the pre-HAART era (hazard ratio [HR] = 0.25, 95% confidence interval [CI] = 0.13–0.48; $P < 0.001$) (Figure 1). Death was related to histoplasmosis in 21 (51%) patients. All related deaths were observed before one year. The histoplasmosis-related mortality rate was higher during pre-HAART era than during the HAART era (HR = 0.30, 95% CI = 0.12–0.74, $P = 0.009$). Two (5%) patients relapsed during the pre-HAART era, and 4(6%) relapsed during the HAART era.

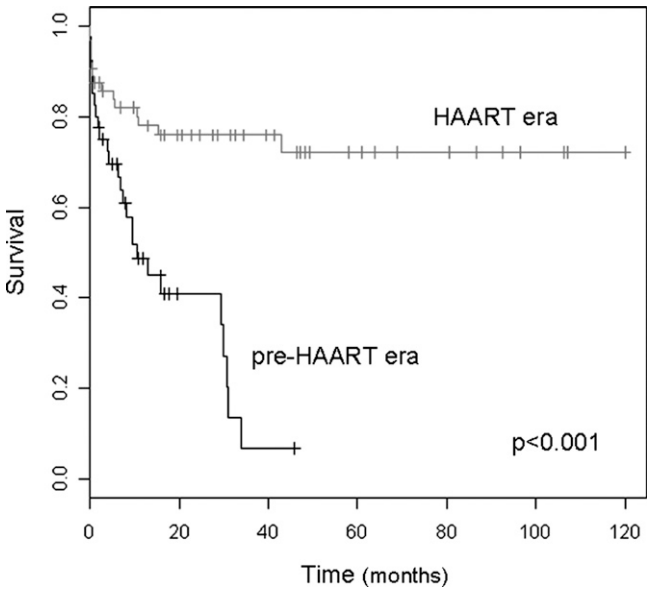

FIGURE 1. Overall survival curves of acquired immunodeficiency syndrome–associated histoplasmosis patients during pre–highly active anti-retroviral therapy (HAART) and HAART periods, France.

Factors associated with mortality. Overall mortality and histoplasmosis-related mortality were significantly associated with arterial hypotension (HR = 2.38, 95% CI =1.05–5.38, $P = 0.037$ and HR = 10.49, 95% CI = 2.59–42.45, $P < 0.001$, respectively) by univariate analysis (Table 5). Pulmonary involvement, dyspnea, cutaneous involvement, platelet count, and hemoglobin level were not associated with overall or histoplasmosis-related mortality (Table 6). There was a trend towards lower mortality among patients treated with liposomal amphotericin B (HR = 0.63, 95% CI = 0.25–1.58, $P = 0.38$) or itraconazole alone (HR = 0.54, 95% CI = 0.21–1.34, $P = 0.18$) than among those treated with deoxycholate amphotericin B.

Age and diagnosis during the HAART era were independently associated with overall mortality (HR = 1.72 per 10-years increase, 95% CI = 1.17–2.54, $P = 0.006$ and HR = 0.19, 95% CI = 0.01–0.39, $P < 0.001$, respectively) and histoplasmosis-related mortality (HR = 2.16 per 10-years increase, 95% CI = 1.10–4.22, $P = 0.025$, and HR = 0.22, 95% CI = 0.08–0.61, $P = 0.04$, respectively) by multivariate analysis.

DISCUSSION

We analyzed 104 cases of proven AIDS-related histoplasmosis in metropolitan France. This study represents the largest reported cohort from a non-endemic area.[12] Histoplasmosis caused by *H. capsulatum* is a rare, invasive, fungal infection in France, and diagnosis is frequently delayed. All patients had traveled to a disease-endemic area, including 14% for more than 10 years before given a diagnosis of histoplasmosis, and all were strongly immunocompromised (median CD4 cell count = 15 cells/μL).

Comparison of our data concerning patients from a non-endemic area with those related to patients from North, Central, and South America is summarized in Table 5. Our patients were characterized by a high frequency of extrapulmonary lesions (skin, adenopathy, hepatomegaly, splenomegaly). This finding could reflect a high fungal burden, a hypothesis strengthened by the high mortality rate (60%) recorded in our study during the pre-HAART era, and potentially explained by delayed diagnosis caused in part by lack of awareness of clinicians in France. An alternative hypothesis to explain the differences in clinical patterns between patients

TABLE 5
Comparison of AIDS-related histoplasmosis cases from disease-endemic areas with 104 cases from France, a non-endemic area*

Area	Period	No.	Age, years	Men, %	CD4 cell count/μL	HAART, %	AIDS defining, %	Clinical features, %						
								Fever	Adp	HM, SM	Skin	Pulm	Abdo	Neuro
Indiana, USA	1981–1989	72	NA	NA	NA	0	69	96	17	26, 13	1	53	3	18
United States	1996–1999	92	39	89	25	35	> 50	88	NA	NA	NA	55	33	16
Colombia	1979–2001	30	36	97	45	37	ND	90	57	13	53	80	47	NA
Panama	1997–2003	104	37	85	65	11	68	92	19	42	17	64	50	NA
French Guiana	1982–2007	200	40	68	34	8	78	89	46	33 19	12	35	47	15
Brazil	1995–2004	164	34	80	104	18	ND	95	3	34,29	10	75	61	17
France†	1985–1994	40	38	78	32	0	17	88	49	48, 36	56	60	40	15
France†	1997–2006	64	40	58	28	23	42	84	63	43, 44	44	34	36	11

Area	Period	No.	AIDS-defining, %	Mortality, % (follow-up, months)	Relapse	Mean for diagnosis, %		
						Blood culture	Histology	Urinary/blood antigen detection
Indiana, USA	1981–1989	72	69	22 (NA)	18 (NA)	90 (19)	NA	97, 83
United States	1996–1999	92	> 50	12 (3)	NA	71 (51)	NA	96, 85
Colombia	1979–2001	30	ND	20 (12)	NA	96	81	NA
Panama	1997–2003	104	68	10 (1)	6 (NA)	NA (68)	34	NA
French Guiana	1982–2007	200	78	31 (6)	NA	NA (8)	NA	NA
Brazil	1995–2004	164	ND	32 (NA)	NA	48 (NA)	81	NA
France†	1985–1994	40	17	53 (12)	5	78 (35)	95	NA
France†	1997–2006	64	42	22 (12)	6	81 (54)	94	NA

*HAART = highly active anti-retroviral therapy; AIDS = acquired immunodeficiency syndrome; Adp = adenopathy; HM = hepatomegaly; SM = splenomegaly; Pulm = pulmonary symptoms; Abdo = abdominal symptoms; Neuro = neurologic symptoms; NA = not available.
†This study.

from different areas could be the implication of different, area-restricted *H. capsulatum* isolates.[18] This hypothesis could not be further explored in our study because of lack of storage of the clinical isolates.

Histoplasmosis caused by *H. capsulatum* is more frequent in AIDS patients than histoplasmosis caused by *H. capsulatum* var. *duboisii*. Less than 20 cases of AIDS-related *H. duboisii* histoplasmosis have been reported in the literature.[19] The two variants infect patients who have poor immunologic status. Skin lesions and adenopathies are common during both diseases. However, patients infected with *H. duboisii* have less hepatosplenomegaly and pulmonary involvement than patients infected with *H. capsulatum* (Table 7). Bone lesions appear to be suggestive of *H. duboisii* infection. The mortality rate is probably higher in *H. capsulatum* patients (39% for the *H. capsulatum* patients in this study and 24% for *H. duboisii* patients in published studies).

One-year overall mortality significantly decreased from 53% during the pre-HAART era to 22% during the HAART era among AIDS-related histoplasmosis patients from metropolitan France. Although clinical features of histoplasmosis were similar during the two periods, some significant changes occurred and could be in part responsible for improvement in survival: modification of HIV infection epidemiology in France, availability of liposomal amphotericin, and widespread use of HAART.

The typical AIDS-related histoplasmosis patient during the pre-HAART era was a homosexual/bisexual male from Europe with previously defined AIDS and one or several prior opportunistic infections. However, heterosexual women from

TABLE 6
Univariate analysis of factors associated with overall mortality and histoplasmosis-related mortality, France*

Factor	Overall mortality			Histoplasmosis-related mortality		
	HR	95% CI	*P*	HR	95% CI	*P*
Demographic						
Male sex	1.50	0.75–2.99	0.25	1.07	0.43–2.63	0.89
Age (10-year increase)	1.36	0.97–1.90	0.08	1.69	1.01–2.84	0.05
Continent of birth: Africa	0.40	0.20–0.82	0.01	0.30	0.10–0.88	0.03
Diagnosis during HAART-era	0.25	0.13–0.48	< 0.001	0.30	0.12–0.74	0.009
HIV status at the time of histoplasmosis diagnosis						
AIDS already known	1.67	0.77–3.62	0.20	1.16	0.42–3.15	0.78
HIV infection already known	1.28	0.58–2.83	0.55	0.74	0.25–2.20	0.59
Mode of HIV transmission						
Heterosexual	0.55	0.30–1.02	0.06	0.60	0.26–1.41	0.24
Clinical characteristics						
Hypotension	2.38	1.05–5.38	0.04	10.49	2.59–42.44	0.001
Pulmonary symptoms	1.43	0.77–2-64	0.25	1.72	0.73–4.05	0.21
Dyspnea	1.27	0.64–2.53	0.50	1.33	0.52–3.38	0.55
Papule	1.61	0.84–3.08	0.15	0.87	0.33–2.31	0.78
Biologic parameters						
Platelet count (50×10^9/L increase)	1.17	0.91–1.52	0.23	1.06	0.84–1.34	0.61
Hemoglobin (g/dL)	0.90	0.76–1.06	0.20	0.49	0.15–1.58	0.23

*HZ = hazard ratio; CI = confidence interval; HAART = highly active anti-retroviral therapy; AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.

TABLE 7
Comparison between AIDS-related imported *Histoplasma capsulatum* and *H. duboisii* histoplasmosis, France*

Characteristic	*H. capsulatum*, pre-HAART era	*H. capsulatum*, HAART era	*H. duboisii*
No.	40	64	17
Mean age (years)	38	40	34
No. men	78	58	71
Clinical features, %			
Fever	88	84	58
Adenopathy	49	63	53
Hepatosplenomegaly	48 (HM), 36 (SM)	43 (HM), 44 (SM)	12
Pulmonary symptoms	60	34	0
Skin	56	44	59
Bone	0	0	18
Abdominal	40	36	12
Diagnosis tools, %			
Direct examination	95	94	100
Culture	78	81	64
Blood culture	35	54	12
Outcome, %			
Death	53	22	24
Relapse	5	3	12

*AIDS = acquired immunodeficiency syndrome; HAART = highly active antiretroviral therapy; HM = hepatomegaly; SM = splenomegaly. Data for *H. duboisii*-infected patients are from Loulergue and others.[19]

Africa without a known history of AIDS were more frequently seen during the HAART era. The data support the conclusion that physicians should no longer assume that histoplasmosis is caused by *H. duboisii* in all cases originating in Africa.

During the HAART era, 31% of patients were treated with liposomal amphotericin, a drug that was not previously available, which explains why only deoxycholate amphotericin B and/or itraconazole were prescribed during the first period. Because liposomal amphotericin was more effective than deoxycholate amphotericin B in reducing overall mortality after two weeks of treatment in a randomized controlled trial,[5] it was anticipated that short-term (two weeks) survival would improve during the second period. This prediction was not observed. The design of our study (a cohort study and not a therapeutic trial), and therefore the lack of standardization preclude any definitive conclusions. Finally, all patients in the second period who survived more than two weeks after diagnosis of histoplasmosis received HAART.

Treatment with HAART was started 1–3 months after onset of histoplasmosis. However, the impact of HAART on outcome of AIDS-related histoplasmosis has not been established.[20] Our data suggest that HAART had a major impact in decreasing overall mortality in AIDS patients with histoplasmosis.

Such a positive impact of HAART on late mortality has already been established for other opportunistic infections such as those with *Pneumocystis jirovecii*, cryptococcosis, or tuberculosis in industrialized countries.[21–24] A significant decrease in early mortality had not been reported for any other opportunistic infections.[21]

Patient age and the period of diagnosis were the only independent prognostic factors identified in our study. Hypoalbuminemia, disseminated intravascular coagulation, increased lactate dehydrogenase levels, renal failure, hypotension, and hypoxemia have been reported as prognostic factors[7,10] but were not identified in our study because of the small size of the cohort and the reduced number of deaths.

Immune reconstitution inflammatory syndrome occurred in 11% of the patients during the HAART era. This incidence is similar to that identified for cryptococcosis[25] and lower than that for tuberculosis (40%) in AIDS patients who never received HAART.[26] All histoplasmosis-related IRIS patients had a dramatic increase in CD4 cell count and a decrease in HIV viral load, similar to *Mycobacterium tuberculosis*-related IRIS patients.[26] Severe forms requiring surgery were diagnosed in two patients. Interestingly, IRIS was the first manifestation of histoplasmosis in two patients. Such a finding is consistent with those of a retrospective study that reported that HIV patients living in French Guiana had an increased risk of histoplasmosis during the first two months after beginning HAART.[27] The IRIS cases occurred in three of the patients more than two months after the beginning of HAART. However, two patients had an unplanned interruption of HAART and became compliant again two months before IRIS, and IRIS occurred in one patient shortly after the interruption of chemotherapy for Kaposi's sarcoma.

In conclusion, overall survival after AIDS-related histoplasmosis increased in metropolitan France, a non-endemic area, during the HAART era. Because most patients came from Africa, *H. capsulatum* histoplasmosis should no longer be considered as American histoplasmosis, but must be considered in every febrile severely immunocompromised HIV-infected patient who had already traveled to a disease-endemic area. Immune reconstitution inflammatory syndrome occurred after HAART in up to 11% of patients and may be an indicator of histoplasmosis.

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