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Disseminated Histoplasmosis; A Threat in Advanced HIV Disease Population in Sub-Saharan Africa?

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Authors' contributions

This work was carried out in collaboration among all authors. Author CEM conceived the article and drafted the initial outline and finalized the manuscript. Author BEE added articles and revised editing English. Author ROO reviewed the manuscript and corrected editing English. All authors read and approved the final manuscript.

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ABSTRACT

Background: Histoplasmosis is a neglected acquired immune deficiency syndrome (AIDS)-defining disease in sub-Saharan African countries, which is commonly misdiagnosed as tuberculosis (TB) due to similar imagery and clinical features; patients usually receive presumptive anti-TB treatment that is considered as anti-TB treatment failure. Patients with advanced human immunodeficiency virus (HIV) disease (AHD), CD4<200/mm^3 or World Health Organisation clinical stage 3 or 4, develop disseminated histoplasmosis (DH) diagnosed at a late stage or at post-mortem, owing to poor clinical suspicion, lack of rapid diagnosis tools to offer rapid and accurate results, and non-availability and accessibility of appropriate antifungal medications. We report 31 cases of DH amongst patients with AHD in sub-Saharan African population from the literature, highlighting the challenging care issue in sub-Saharan Africa.

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Results: Out of 31 reported cases 64.51% (20/31) were caused by *Histoplasma capsulatum* var *capsulatum*, 48.38% (15/31) being immigrants in Europe, Canada and Japan, with 41.93% (13/31) mortality, and 6 cases having no reported outcome. The poor index of suspicion on the part of clinicians; the lack of skilled laboratory personnel and rapid and accurate diagnosis tools of histoplasmosis for a proper detection of either classical or African histoplasmosis coexisting in many sub-Saharan African countries; and the non-availability and accessibility of appropriate antifungal medications were the most challenges in caring DH in advanced HIV disease population in sub-Saharan Africa.
Conclusion: there is a need for prompt and routine screening of advanced HIV disease patients in sub-Saharan Africa for histoplasmosis as an AIDS-defining illness.

Keywords: Advanced HIV disease; AIDS; antifungal medications; disseminated histoplasmosis; histoplasma diagnosis tools; sub-Saharan Africa.

ABBREVIATIONS

≈ : consistent with
ADP : adenopathy
AFB : acid fast bacilli
AH : African histoplasmosis
AHT : arterial hypertension
ALT : alanine aminotransferase
ATB : antibiotic ATF: antifungal treatment
ART : antiretroviral treatment
AST : aspartate aminotransferase
ARDS : acute respiratory distress
cART :conventional
ART CMV : cytomegalovirus
CT : computed tomography
CXR : chest x-rays
GC : general condition
DE : direct examination
DAH : disseminated African histoplasmosis
DIC :disseminated intravascular coagulation
EBV : Epstein Barr virus
F/U : follow-up
GFR : glomerular filtration rate
HAART : highly active
ART Hb : hemoglobin
HMG : hepatomegaly
HSM : hepatosplenomegaly
HVB : hepatitis B virus
HT : hypertension
IRS : immune reconstitution syndrome
LDP : lymphadenopathy
LN : lymph node
NR : non revealed
PLTS : platelets
TSP : total serum protein
SM : splenomegaly
TB : tuberculosis
US : ultrasonography
PBN : bronchopneumopathy
PBS : peripheral blood smear
PCR : polymerase chain reaction
PDH :progressive disseminated histoplasmosis
PTH :parathyroid hormone IRS: immune reconstruction syndrome
RF : renal failure
TMP/SMX :trimethoprim-sulfamethoxazole
VL : viral load
NR : Non-revealed

1. INTRODUCTION

Human histoplasmosis is an invasive mycosis caused by a dimorphic fungus, *Histoplasma capsulatum* (Hc), occurring at an increasing rate with the human immunodeficiency virus (HIV) epidemics with a high death rate in patients. In a study by Adenis et a*l* (2014), the death rates observed in HIV-associated histoplasmosis were 45.3% with 16.8% of early death in French Guiana [1].

Classically, two types are encountered in humans: histoplasmosis due to *Histoplasma capsulatum var. capsulatum* (Hcc), known as classical histoplasmosis, which is endemic in North and Latin America and can also occur worldwide, and African histoplasmosis due to *Histoplasma capsulatum var. duboisii* (Hcd) which is found mainly in Africa. Both types of histoplasmosis coexist in parts of west and central African countries [2].

Patients with advanced HIV disease (PAHD), CD4 <200/mm^3 or World Health Organization (WHO) clinical stage 3 or 4, develop disseminated histoplasmosis (DH), commonly associated with a poor prognosis [3,4]. Despite being classified as an AIDS-defining illness in 1987, and a major cause of death in PAHD, histoplasmosis remains a neglected infection in most African countries, owing to lack of clinical suspicion on the part of practitionners, lack of

skilled laboratory personnel and infrastructure to make diagnosis, and poor availability of antifungal medications [5,6]. Moreover, owing to similarities between histoplasmosis and tuberculosis (TB), most advanced AIDS patients with presumptive TB receive anti-TB treatment even when sputum acid fat bacilli (AFB) and/or GeneXpert is negative; DH is then diagnosed in late stage or at post-mortem. A report by Oladele et al (2017) [7] revealed an 8.7% prevalence of chronic pulmonary aspergillosis in a cohort of patients being managed as smear negative/TB treatment failure. How many of these patients could have had histoplasmosis? A number of PAHD who are lost to follow-up might have died of DH without being diagnosed.

Estimating the true burden of histoplasmosis in sub-Saharan Africa (SSA) is difficult owing to the paucity of data. However, few publications and non-published papers reported its existence in Africa in both HIV negative and positive persons, and in PAHD. Oladele *et al* (2018) reported a total of 470 documented cases of histoplasmosis in Africa based on literature research, in both HIV positive and negative persons, and a total of 32/735 (4.4%) positive histoplasmine skin test in a similar population study in Nigeria [5,8]. Two studies from Cameroon (2015 and 2019) reported respectively 13% [9] and 26%[1] of DH in PAHD. The endemicity of HIV and TB and the existence of histoplasmosis in SSA, necessitates our concern for prompt diagnosis and appropriate management of histoplasmosis. Currently, to the best of our knowledge, most countries in SSA have not included diagnosis and treatment of DH in their HIV package of care for PAHD.

In this study we highlight the challenging care issue of histoplasmosis in PAHD in SSA.

2. METHODOLOGY

A search of literature on DH in HIV-infected Africans preceding 30 September 2020 were performed using African Journals Online (AJOL), Google Scholar, PubMed, Cochrane Library, Africa-Wide: NiPAD, CINAHL (accessed via EBSCO Host) databases, and grey literature to identify all published papers regarding the topic. Articles published in other languages (e.g., French and Italian) were considered if they were cited in any of the databases searched. The main search comprised individual searches using detailed medical subject heading (MeSH) terms for DH, Sub-Saharan Africa (also the names of the 46 African countries designated by UN as sub-Saharan Africa), and HIV/AIDS combined with terms relevant to DH including broad terms such as `diagnosis' and `management'. The Boolean operator `AND' and `OR' were used to combine and narrow the searches. The references in all relevant papers were reviewed for additional publications that may not have been cited elsewhere (`snow balling').

3. RESULTS AND DISCUSSION

Table 1 which is a non-exhaustive case-patients reported in SSA and from Sub-Saharan Africans living in the West [10-31], gives a caricature of histoplasmosis in PAHD.

A total of 31 cases-patients in AHD with CD4 < 50/mm^3.were captured, with 48.38% (15/31) reported in African immigrants in Europe, Canada and Japan, with a mean age of 34.32 and 41.93% (13/31) mortality. It appears in Table 1 that 67.7% (21/31) of classical histoplasmosis (Hcc) were recorded while 32.25% (10/31) of patients were infected with African histoplasmosis (Hcd). It is known that despite HIV epidemic in SSA, Hcd is not commonly described as acquired immunodeficiency syndrome (AIDS) defining illness, most cases being reported from African immigrants. It is also pointed out from Table 1 that in most patients DH revealed a background of advanced AIDS, in late stage with fatal course or at post mortem. These challenges are directly linked to: 1) DH commonly misdiagnosed as TB; 2) DH presenting as a persistent fever of unknown etiology in patients with unknown HIV status, and revealing AHD; 3) DH associated with coinfections; 4) The laboratory tools of diagnosis and lastly; 5) The difficulties of DH care and treatment.

3.1 DH Misdiagnosed as TB

TB is one of the commonest opportunistic infection in SSA, where both TB and HIV infections are highly endemic, and are both considered a cause of death among people living with HIV (PLHIV) [4,32]. Moreover, clinical and imagery similarities between TB and histoplasmosis lead to mistakes in advanced AIDS population, histoplasmosis being misdiagnosed as TB. Consequently, patients experience automatic presumptive anti-TB treatment based only on clinical diagnosis of TB despite being negative for sputum GeneXpert test, and resulting in “anti-TB treatment failure”.

Nine reported case-patients with histoplasmosis were clinically diagnosed and initially and unsuccessfully treated for TB. DH (Classical or African types) was finally detected in late stage and revealed advanced AIDS (case-patients 1, 2, 3, 5,7,14, 26, 27 and 28), with a fatal course of the patient (case-patients 1, 2, 7, and 27), or at postmortem (case-patients 5 and 14). This situation is mainly linked to the ignorance of histoplasmosis by clinician practitionners, the focus of African governments on TB or lack of government engagement that prevents any significant developments with respect to the other major causes of death in AIDS patients, namely histoplasmosis. It is noteworthy that two case-patients late diagnosed for DH were cured (case-patients 26 and 28).

3.2 DH Presenting as a Persistent Fever of Unknown Etiology in Patients with Unknown HIV Status

Symptoms of DH are nonspecific and are often indistinguishable from those of other febrile illnesses like malaria, bacterial pneumonia, or other undiagnosed infections in African countries.

Due to low financial conditions and lack of health insurance schemes in most SSA countries, patients pay from pocket for care that is not covered in the antiretroviral therapy (ART) programs. They are thus exposed to self-medication in cases of fever, without any detection of the disease. This leads to a delay in the diagnosis and treatment of histoplasmosis. As previously reported in French Guiana and in India [33,34], and as shown in Table 1 are 10 case-patients (4, 11, 13, 15, 16, 17, 21, 23, 29 and 30) with unknown HIV status presenting with fever ≥ 1 week that were later discovered to have developed DH revealing a background of advanced AIDS (CD4 < 50/mm^3) at late stage with fatal course. Diagnosis of DH was mainly performed by biopsies of skin lesions, “accidently” by routine peripheral blood film, and at post-mortem. DH should therefore be screened in advanced AIDS patients with prolonged fever [35].

3.3 DH and Co-infections in AHD

3.3.1 DH and TB co-infection

DH and TB co-infection seems more frequent in advanced AIDS patients in Latin American countries with frequencies from 2% to 38% and the same symptoms although several studies tried unsuccessfully to identify clinical patterns discriminating between both infections in a context on AHD [36-38].

Only one documented case-patient has been reported in Table 1 (case-patient 16) presenting with a 1-year history of prolonged fever of unknown origin, weight loss and wasting, and tested positive for HIV; DH and TB revealed advanced AIDS. Unfortunately, the outcome of the patient was not precised.

The co-infection might be under-reported in SSA owing to misdiagnosis, endemicity of TB infection and similarities between both infections. However, Oladele reported in 2018 TB associated histoplasmosis in Africa with frequencies from 8% to 15% [5]. Thus, a high index of suspicion is mandatory in SSA countries, along with availability of accurate tools of diagnosis to disclose the co-infection for accurate treatment.

3.4 DH and Other Co-infections

Other infections and parasites associated with DH are reported on Table 1: cerebral toxoplasmosis, *Fusarium verticillicoïdes*, *Mycobacterium avium*, intestinal *Strongiloides stercoralis*, and disseminated cytomegalovirus infection (Case-patients 8, 11, 12, and 15). They appear as minor condition though death was recorded in patient 8 with cerebral toxoplasmosis and disseminated African histoplasmosis co-infection, due to acute respiratory syndrome and disseminated intravascular coagulation.

3.5 The Laboratory Tools of Diagnosis

Laboratory tests used for the diagnosis of DH in PAHD include mycology culture, histopathology of affected organs, cytology of body fluid or aspirates, and molecular techniques [39-43].

Culture in Sabouraud medium is the gold standard, but takes up to 8 weeks to yield growth of colonies; the method is risky (inhalation of spores) for laboratory personnel and requires a laboratory with biosafety level 3 safety equipment and facilities [39-43].

Histopathology demonstrates the presence of yeast cells in tissue biopsies, but with a risk of misidentification with other pathogens, namely *Candida glabrata*, *Penicillium marneffei, Talaromyces marneffei*, *Pneumocystis jirovecii*, *Toxoplasma gondii*, *Leishmania donovani*, and

Cryptococcus neoformans; the use of special histochemical stains like Periodic Acid Schiff (PAS) and Gomori methenamine silver (GMS) facilitates differentiation between these pathogens by highlighting Hc yeast wall [39-43]. Hc stains poorly with Gram stain and is rarely detected by this modality; Calcofluor white, a fluorescent stain that binds chitin in the cell wall of all fungi is more useful [41]. Meanwhile Hcc yeasts are ovoid, 2-4µ in size, with thin nonrefractile cell walls and a narrow-base budding, predominantly phagocytosed within macrophages and histiocytes, seen in clusters in many organisms but sometimes in extracellular spaces; although Hcd is larger, 6-12µm and easily distinguishable from the more common variety [39-42].].

Cytology of tissue aspirates or fine-needle aspiration and fluids stained with GMS or PAS often show narrow-based budding yeast cells mainly within macrophages [41].

PCR techniques have a sensitivity and specificity for DH, but not yet used routinely [39-43].

Histoplasma antigen detection validated in 2019 and included in the WHO essential diagnostic list has become a leading tool to diagnose histoplasmosis in AHP [43-46] with rapidity and overall sensitivity and specificity of 95%-97%, being more sensitive in urine than in serum, and no need of laboratories with higher levels of biocontainment [6,38,41,42,46].

Table 1 reports that DH has been diagnosed mostly by direct examination using staining with PAS, GMS, H&E, Mucicarmin, or Giemsa stains, on tissue biopsies or aspirates, or by culture on Sabouraud medium, or medium sometimes not often specified. PCR was performed in only four case-patients (6, 8, 19 living in the West; and 29 at Senegal). Apart from Cameroon where cultures were performed at the Pasteur Institute in a biosafety level 3 safety laboratory, only direct examination were used in other SSA countries. Routine peripheral blood smear also detected DH "accidently" in four cases (12, 21, 23 and 29), the fourth being confirmed by PCR. Stained blood film may detect DH in about 40%, but should not be used in early stages or with low fungal burdens, owing to its low sensitivity [47]. Cultures of buffy coat confirmed DH in one case-patient (case 11). This method commonly used in Latin America could be an alternative in SSA in case a biosafety level 3 safety laboratory is available [6].

Histoplasma antigen detection tools is not yet available in most SSA countries. It was used only in Tanzanian specimens (serum and urine), testing being performed in the USA (Miravista Diagnostics, Indianapolis) [48]. Making this tool widely available and accessible in SSA countries would reduce the burden of histoplasmosis mortality in advanced AIDS patients.

Diagnosing DH and TB co-infection is a challenge in AHP in SSA countries without rapid diagnostic tools. Only one documented case-patient (case 16) has been reported on Table 1. TB testing was performed by culture of sputum while skin biopsy detected *Histoplasma sp.* Direct microscopy is still widely used and provides quick results with strong performance for TB and histoplasmosis, but it seems not appropriated for the diagnosis of histoplasmosis [38,46]. Making *Histoplasma* antigen and TB LAM Ag readily available in SSA countries, will aid quick detection in PLHIV at risk of developing both infections, or presenting with signs and symptoms of TB in advanced AIDS situation.

3.6 DH Care and Treatment

Amphotericin B and itraconazole are both the most effective antifungal fungicidal medications indicated for the first-line treatment of histoplasmosis, and recommended by the Infectious Diseases Society of America (IDSA) for treatment induction while waiting for laboratory confirmation in a patient with a strong suspicion of histoplasmosis [38,40,49,50].

For moderately severe to severe disease, liposomal amphotericin B (3.0 mg/kg daily, 1–2 weeks) is used, then switched to oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily for a total of at least 12 months); deoxycholate amphotericin B (0.7–1.0 mg/kg daily) may be an alternative in patients who are at a low risk for nephrotoxicity [38,49,50].

Itraconazole is indicated for mild to moderate disease (200 mg 3 times daily for 3 days, then twice daily for at least 12 months) treatment monitoring being recommended for 12 months after the end of the therapy to detect early signs of relapse, by checking blood levels of itraconazole and monitoring of *Histoplasma* antigen concentrations on sera or urine [49,50].

Most case-patients treated with these medications in this study were living in the West.

Only case-patients 1 and 2 from Congo were treated with deoxycholate amphotericin B and/or itraconazole, without treatment monitoring, with fatal outcome in patients. These medications are costly and still unavailable in most SSA countries despite itraconazole was added to the WHO list in 2017. Fluconazole which is available in generic is commonly used in high doses as in case-patient 24, from Cameroon.

Treatment of DH and TB co-infection is challenging. Table 1 shows that the treatment-protocol of case-patient 16 was not clearly described and he was finally lost to follow-up; he may have died as did all case-patients treated concomitantly with antifungal treatment and anti-TB treatment.

The WHO released guidelines 2017 (screening, diagnosis and treatment of the most common opportunistic diseases in HIV-infected people) [4] had not indicated the treatment of histoplasmosis and TB co-infection in AIDS persons, thus making it more difficult as the treatment monitoring for both DH and TB is unavailable in SSA. It is known that histoplasmosis medications, amphotericin B and itraconazole, are respectively nephrotoxic and hepatotoxic; itraconazole is also associated with anti-TB treatment drug interactions; rifampicin and rifabutin may decrease itraconazole blood levels leading to treatment and clinical failure [49-52]. Replacing rifampicin with a fluoroquinolone especially moxifloxacin used in the treatment of multidrug resistant and extensively drug-resistant TB, might obviate the drug-drug interaction although extending the treatment for as long as 12-18 months [38,52]. Thus repurposing another fluoroquinolone could be an alternative in SSA countries in case moxifloxacin is not available.

Clinical or biological risk factors for poor prognosis or death in PAHD are well-defined [50,53,54]. They are recorded on Table 2 in 27 case-patients, although not commonly quantified.

According to the Centers for Disease Control and Prevention, the presence of only one risk-factor predicts a poor prognosis or death in patients with advanced AIDS [53].

Table 3 shows outcome of the case-patients. Only 1 risk-factor was found in 8 case-patients, with 4 deaths and 1 healing, outcome not being revealed in 3 patients; ≥ 2 risk factors were found in 19 patients, with 7 deaths and 9 healings, outcome not being indicated in 1 patient, and 2 patients being lost to follow-up who could have died. It is noteworthy that patients are commonly lost to follow-up in SSA countries, owing to the low financial income of patients and/or their relatives that support the treatment cost, and the lack of health insurance schemes; they usually die at a supposed cost-effective native treatment center.

Complications during the treatment course as fever, ascites, peritonitis, immune reconstitution syndrome, renal failure, acute respiratory distress syndrome associated to disseminated intravascular coagulation, and invasive treatment e.g. laparotomy and splenectomy were recorded on Table 1. They are additional challenges in DH cure and treatment, along with clinical presentation mimicking public health infectious disease such as lepra.

DH is a serious infection in patients with AHD, with heterogenic presentation, single algorithms still being difficult to extract. Thus clinical expertise still remains important. Authors from French Guiana recently tried to point out four major “typical’’ proteiform expressions of DH, covering the most frequent situations encountered in this population, each of which leading to search for distinct differential diagnoses [55].

- first situation: patients with a digestive presentation (differential diagnose: intestinal pathogens, endoscopy)
- second situation: patients with fever, general condition impairment but no focal signs (differential diagnose: typical mycobacterial infections)
- third situation: patients with enlarged lymph nodes (differential diagnose: tuberculosis and lymphoma)
- fourth situation: patients with a pulmonary presentation (differential diagnose: tuberculosis, pneumocystosis and bacterial pneumonia)

Screening these situations and risk factors for death in patients could additionally help preventing fatal outcome in DH in AHD population in SSA.

Table 1. A caricature of histoplasmosis in PAHD in sub-Saharan Africans illustrating the challenge care issue: misdiagnosis of histoplasmosis as tuberculosis, lack of accurate diagnosis tools for definite diagnosis of histoplasmosis, lack of effective antifungal medications and treatment monitoring, poor clinical course with complications leading to death

Case-patients (n°)	**country of Origin, Age, sex**	**Past history-Underlying disease**: HIV/AIDS, CD4 count, VL, ART	**Mains findings** (Clinical, Laboratory and/or Radiology)	**Definite Diagnosis of Histoplasmosis**	**Treatment and clinical course**	**Outcome**
			Chandenier et *al*, 1995 [16]			
1	Congo, 26 F	Unknown HIV status, 04 months Pregnancy	Presumptive TB (skin abscesses and large cervical ADP) HIV test positive Yeast ≈ Hcd (pus and biopsy abscesses, stains NR) Others: Pseudomonas from abscess of the lobula of the ear	AH revealing AIDS at late stage misdiagnosed as TB	Amphotericin B (4, 4 g in 6 months), Itraconazole 300 mg/j (duration NR), Poor clinical course: - Remissions and relapse of skin lesions and abscesses. - Febrile ascitis: anti TB and ATF treatment stopped after 1.5 months, AGC, bloody vomiting.	Death
2	Congo, 44 M	Unknown HIV status. presumptive TB (skin lesions, massive weight lost and LDP), unsuccessful anti TB treatment	Skin lesions: ulcerative, and crusty lesions, and molluscum-like growths. HIV test positive. Numerous yeasts ≈ Hcd on skin biopsies (stains NR)	DAH revealing AIDS at late stage misdiagnosed as TB	Ketoconazole 600 mg/dx 2 ½ months Poor clinical course: political crisis, financial distress, closure of the hospital, several lost to follow-up and complications: - Peritonitis, skin involvement; numerous Hcd on pus; Amphotericin B (total dose 3,5g x 11 months Itraconazole 3tablets/d x 3weeks, - Severe abdominal pain, and hematemesis	Death
3	Congo 41 M	Unknown HIV status. Presumptive TB	PGC, SM. Skin lesions: scars of ophthalmic zona; nodules; MC-like lesions; cervical, submental,	DAH revealing AIDS misdiagnosed as	Amphotericin B 1 mg/ kg within 10 days (progressive dose), duration of treatment depending	NR

Case-patients (n°)	country of Origin, Age, sex	Past history-Underlying disease: HIV/AIDS, CD4 count, VL, ART	Mains findings (Clinical, Laboratory and/or Radiology)	Definite Diagnosis of Histoplasmosis	Treatment and clinical course	Outcome
		(fever, 13 kg weight loss in 2-months), unsuccessful anti TB treatment (1month)	axillar and inguinal ADP. CT scan: consolidation and cavitation right pulmonary upper lobe HIV test positive, no AFB on sputum Hb: 5.9 g/dl), PLTS: 64 × 10 9/l TSP: 6.3 g/dl with albumin: 2.5 g/dl and globulins: 3.8 g/dl. AST /ALT 134 IU/137 IU; yeast forms ≈f Hc. (trephine and bone marrow biopsy, bone marrow aspirate)	TB	to clinical condition of the patient	
			Pillay et *al*, 1997 [11]			
4	South Africa 8, F	unknown HIV status, general malaise, fever, respiratory distress (3 weeks)	Fever, LDP, ulcer (left lower leg, tip of the tongue and angle of the mouth). HMG, presumptive pneumonia (*Pneumocystis carinii*) CT scan: consolidation and cavitation of right upper lobe of the lung HIV test positive, TB skin test (-) and no AFB on sputum Hb 5.9 g/dl), PLTS: 64 × 10 9/l, AST /ALT 134 IU/137 IU yeast forms of *Hc* on Trephine bone marrow biopsy and bone marrow aspirate (stains NR):	DH revealing advanced AIDS at late stage (postmortem diagnosis)	Patient died on 2nd day of hospitalization. Postmortem specimens from liver, lungs, lower limbs, skin lesions and LN demonstrated histoplasmosis	Death prior to definite diagnosis

Case-patients (n°)	**country of Origin, Age, sex**	**Past history-Underlying disease**: HIV/AIDS, CD4 count, VL, ART	**Mains findings** (Clinical, Laboratory and/or Radiology)	**Definite Diagnosis of Histoplasmosis**	**Treatment and clinical course**	**Outcome**
			Ouattara et *al*, 1998			
5	Ivory Coast 32, M	AIDS, CD4: 7/mm^3, ART. Presumptive disseminated TB: fever, gradual massive weight loss, and night sweets (1year)	Pallor, T 38°C, HMG, SM, CXR: diffuse and slight infiltrates on both lungs, and massive LDP on left hilum. US of abdomen: HSM, LDP; No AFB on sputum samples; TB skin test (-) yeast cells ≈ Hcc on tissues from autopsy (mediastinal LN, lung, gut, liver and spleen)	DH in advanced AIDS patient misdiagnosed as TB (postmortem diagnosis)	:/	Death prior to definite diagnosis
			Rivasi et *al*, 2001 [13]			
6	Ghana living in Italy for 7 years, 36, M	AIDS, CD4: 352/µl Herpes Zoster, malaria, Candida esophagitis	Fever, significant weight loss skin lesions: wildfire papules, umbilicated and ulcerative lesions, face and upper extremities CXR: nodules infiltrates on right upper lobe. Yeast cells of Hcc (nodule biopsy, H&E, PAS and GMS, and mucicarmin stains), confirmed by PCR testing	DH in advanced AIDS patient	Returned to Ghana prior to definitive results and ATF treatment	NR
			Mosam et *al*, 2006 [14]			
7	South Africa 11, M	Unknown HIV status, 1 year of repeated treatment (NR) for chest infections and	Emaciation, pallor, fever, general LDP, HMG, and acute BPN, hyperpigmented cutaneous plaques and nodules HIV test positive, CD4 not available routinely, Hb: 91 g/L,	DH revealing AIDS at late stage misdiagnosed as TB	Poor clinical course under treatment (2 weeks conventional antibiotic treatment, Presumptive anti TB therapy, IV amphotericin B (1 mg/kg per day)	Death

Case-patients (n°)	**country of Origin, Age, sex**	**Past history-Underlying disease**: HIV/AIDS, CD4 count, VL, ART	**Mains findings** (Clinical, Laboratory and/or Radiology)	**Definite Diagnosis of Histoplasmosis**	**Treatment and clinical course**	**Outcome**
		diarrhoea, 1-month loss of weight, cough, and skin lesions	PLTS 94×10^9 / L. CXR: bronchiectasis and acute pneumonia. No AFB on 3 sputum specimens Yeast cells of Hcc on skin biopsy (PAS and Fontana-Masson stainings)			
			Murata et *al*, 2007 [15]			
8	Ghana, living in Japan for many years, from many European countries 45, M	AIDS, Weight loss (10 kg), herpes-zoster, and headache.	Left facial nerve palsy and atactic gait, Glasgow Coma Scale:15. Isochoric and round pupils. Prompt light reflex and intact ocular movement; right ptosis. Left hemiplegia and pyramidal tract signs. Oral candidiasis. SM. CT: brain mass; MRI contrast-enhancing mass lesion with peripheral edema; Brain biopsy suggestive of cerebral toxoplasmosis. Toxoplasmosis tests positive Hb 13.5 g/dl; PLTS: 27.2 × 104/µl; LDH: 370IU/l; CD4 24/µl and VL10 copies /ml. Yeast-like cells ≈ Hcd on routine PBS confirmed by PCR test	DAH in advanced AIDS patient	Poor clinical course under treatment (itraconazole, 400 mg/d, conventional amphotericin B, 1 mg/kg/d switched to liposomal amphotericin B, 3 mg/kg/d: severe RF)	Death
Loulergue et *al*, 2007 [16						
9	DR Congo, living in	HIV-1, fever of unknown origin,	Fever, left axillary tumefaction 2 inches diameter	AH in advanced	Poor clinical course under treatment (Itraconazole, 400	Death

Case-patients (n°)	country of Origin, Age, sex	Past history-Underlying disease: HIV/AIDS, CD4 count, VL, ART	Mains findings (Clinical, Laboratory and/or Radiology)	Definite Diagnosis of Histoplasmosis	Treatment and clinical course	Outcome
	France 37, M	left axillary tumefaction negative for fungus, and TB (Ziehl, PAS, and GMS) (5 months):	CD4 100/mm$^{3.}$ Histology of adenopathy: necrosis and large yeasts, culture ≈ *Histoplasma sp.*	AIDS patient	mg/d x 3 weeks, then 1 year amphotericin B (total dose 1,200 mg), then itraconazole 400 mg/d, lowered to 200 mg/d for 3 years) – HIV-related encephalitis 3 years after despite ART	
10	DR Congo, living in France 41, M	AIDS, CD4 < 50/mm^3, HAART *Pneumocystis jiroveci* pneumonia	Skin nodules, right cervical ADP and a right Bell's palsy numerous yeast cells of Hcd on direct examination of the lymph node (stains NR) Culture ≈ *Histoplasma sp*	AH in advanced AIDS patient	Itraconazole (400 mg/d, no response > 1 month treatment) then conventional amphotericin B (1 mg/kg/d switched to liposomal amphotericin B, 3 mg/kg/d) Severe RF > 8 days treatment switched to itraconazole after 1 month, 400mg/d (long term therapy). Stable condition 11 years later	Recovery
11	DR Congo, living in France since age of 18 months 2, F	unknown HIV status, Fever of unknown origin (duration NR)	Frontal swelling and generalized weakness HIV test positive, CD4 45/mm^3 yeasts of Hcd (skin biopsy, stains NR) Culture ≈ *Histoplasma sp* *E. coli* (pyelonephritis) Radiography: diffuse bone lytic lesions Bone biopsy: large yeasts of Hcd Culture of the buffy coat positive for *Fusarium verticilioïdes.*	DAH revealing advanced AIDS, and *Fusarium verticilioïdes* coinfection	Liposomal amphotericin B, switched after 1 month to Itraconazole (dose NR), then Fluconazole x2 years and 3 months (dose NR)	Recovery
			Débat-Zoguereh et *al*, 2008 [17]			

Case-patients (n°)	**country of Origin, Age, sex**	**Past history-Underlying disease**: HIV/AIDS, CD4 count, VL, ART	**Mains findings** (Clinical, Laboratory and/or Radiology)	**Definite Diagnosis of Histoplasmosis**	**Treatment and clinical course**	**Outcome**
12	Ghana, living in France >18 years 38, M	AIDS, ART (irregular observance) Presumptive CMV colitis (nonspecific ulcerations on colon biopsy, and highly positive pp65 antigenaemia), successful treatment with ganciclovir	Massive cachexia, fever, profuse bloody diarrhea (15 times daily), profuse skin papulonodules, and ulcerations of the gums CT scan: pulmonary interstitial syndrome, HSM CD4: 6 /mm^3, VL17 700 copies/ml (4,25log); Hb 8.3 g/dl, PLTS 18 G/l); LDH 17 962 g/l, ASAT /ALAT: 16 ×N/1.5 ×N, uremia 32 mmol/l and creatininemia 337 mmol/l. PBS. + bone marrow aspirate and stools: yeast cells ≈ Hcc. Culture of same specimens and Hemoculture (standard and Sabouraud medium): *Histoplasma sp* Hemoculture and stool culture: *Mycobacterium avium* complex (MAC).	DH in advanced AIDS patient and *M. avium* coinfection	Liposomal amphotericin B x 14 days (doses adapted to renal clearance), switched to Itraconazole 600 mg/d (doses adapted to plasmatic monitoring) Healing of all signs of DH, although *Histoplasma sp* still detected in bone marrow macrophages	Recovery
			Ndiaye et *al*, 2011 [18]			
13	Senegal 50, M	Unknown HIV status, Fever of unknown origin (duration NR), deterioration of GC, and disseminated skin eruption with oral	Fever (NR), poor GC, papulo-nodules, umbilicated and necrotic skin lesions, and oral involvement (NR) HIV test (+), CD4 4/mm^3 Yeast-bodies of Hcd on biopsy of ulcerative skin lesions (stains NR) Culture: *Histoplasma sp*	DAH revealing advanced AIDS	NR	NR

Case-patients (n°)	**country of Origin, Age, sex**	**Past history-Underlying disease**: HIV/AIDS, CD4 count, VL, ART	**Mains findings** (Clinical, Laboratory and/or Radiology)	**Definite Diagnosis of Histoplasmosis**	**Treatment and clinical course**	**Outcome**
		involvement (01 month)				
			Mandengue et *al*, 2011			
14	Cameroon 34, F	HIV-1 +, ART (irregular observance) Presumptive TB (cough, fever, weight loss, and miliary on x-rays of the lungs, but no AFB on sputum) and 6-months unsuccessful anti TB treatment	T 38.8°C, poor GC, weakness, jaundice, skin eruption (papulo-nodules, pustules, umbilicated, and hemorrhagic crusty lesions), fetid nasal discharge, and vulva ulceration, HSM CD4: 1/mm^3; Hb: 5.4g/dl; PLTS: 7000/mm^3. ASAT/ALAT: 410 /146 IU/L abdominal US: coelio-mesenteric LDP and HSM skin biopsy: Hcc (PAS and GMS stains), culture (Sabouraud medium): *Histoplasma sp*	DH revealing advanced AIDS misdiagnosed as TB (postmortem diagnosis)	/	Death prior to definite diagnosis
			Inojosa et *al*, 2011 [20]			
15	Ghana, living in Italy 30, M	Unknown HIV status Fever, weakness, malaise, and weight loss, HT (Amlopidine 10)	Fever, mild HSM, diffuse small sized LDP, and seborrhoeic like dermatitis with scratching lesions HIV test positive, CD4 17/mm^3, VL 218,000/µl; Creatinine 2.58 mg/dl, urea 69 mg/dl; Hb: 9.1 g/dl, PLTS: 93,000/µl, AST / ALT 299/140 U/L, LDH: 2,782 U/L. Yeast cells of Hcc on bone marrow biopsy (H&E, GMS and PAS) *Strongyloides stercoralis* on	PDH revealing advanced AIDS, associated AHT and intestinal *Strongyloides stercoralis*	Liposomal amphotericin B (3 mg/kg/day, for 9 days), switched to Itraconazole (200 mg bid) Ivermectine (*S. stercoralis*) A month later: no recovery of renal function, HT not under control, CD4 248/mm^3 and undetectable viral load	NR Lost to follow up

Case-patients (n°)	country of Origin, Age, sex	Past history-Underlying disease: HIV/AIDS, CD4 count, VL, ART	Mains findings (Clinical, Laboratory and/or Radiology)	Definite Diagnosis of Histoplasmosis	Treatment and clinical course	Outcome
			stools			
16	Liberia, living in Italy for 8 years 32, M	Unknown HIV status, Fever, weight loss (5 kg) and wasting (1year)	Hard palatal ulcer, HSM and generalized LDP HIV test positive, CD4 11/mm^3, Hb 8.8 g/dl, PLTS 74,000/µl); LDH 1,041 U/L CT scan: osteolytic hard palate, interstitial micro nodules in both lung; right pleural thickening; SM, coarse casting retro-peritoneal ADP, multiple LNs at mesenteric root, and pelvic peritoneal effusion. *Mycobacterium tuberculosis* on sputum (culture) yeast cells of Hcc (biopsy of the bottom of the palatal ulcer, Grocott staining), culture : *Histoplasma sp*	PDH revealing advanced AIDS and TB co-infection	Liposomal Amphotericin B lipid (5 mg/kg/d) for 3 ½ months, switched to fluconazole 400 mg Initiation of healing (CD4 102/mm^3 (12%) and undetectable viral load	NR Lost to follow-up
17	Ivory Coast, living in Italy 40, F	Unknown HIV status Nausea, vomit, and fever of unknown origin (1week)	T: 39°C), Tachycardia (rate NR) HIV test (+), CD4: 2/mm^3, VL:7.580.000/µL; Creatinine: 18.7 mg/dL; urea: 125 mg/dl, GFR: 3 ml/min/1.73 mq; inorganic phosphorus 8.6 mg/dL, PTH 226 pg/mL; uricaemia 13.2 mg/dL, Hb: 5.6 g/dl, PLTS: 365,000/µL, LDH: 2,208 U/l. CMV disseminated infection	PDH in advanced AIDS patient associated Stage 5 renal failure, and disseminated CMV co-infection	Hemodialysis treatment x several weeks, Erythropoietin, Gancyclovir, HAART, Liposomal amphotericin B adjusted to renal failure and Itraconazole oral solution	NR

Case-patients (n°)	**country of Origin, Age, sex**	**Past history-Underlying disease**: HIV/AIDS, CD4 count, VL, ART	**Mains findings** (Clinical, Laboratory and/or Radiology)	**Definite Diagnosis of Histoplasmosis**	**Treatment and clinical course**	**Outcome**
			US : increased-sized kidneys with increased echogenicity Hcc on bone marrow biopsy (Grocott stain)			
18	Senegal, living in Italy for 23 years 47, M	HIV1, HAART (poor observance) *Pneumocystis pneumonia* (Cotrimoxazole), fever, cough, dyspnea, dysphagia, and wasting syndrome (2 weeks)	Severe oro-pharyngeal candidiasis, and diffuse pruritic papulonodules skin eruption CD4 2/µl (1%); Hb 12.1 g/dL; AST/ ALT: 610 /142IU/L; LDH 249 U/L, CT scan: interstitial micronodular lesions widespread in both lungs Yeast cells ≈ Hcc on bone marrow biopsy (PAS and GMS) Stool examination: rhabditiform larvae (*Strongyloides stercoralis* infection);	DH in advanced AIDS patient associated intestinal *Strongyloides stercoralis* infection	Ivermectine (*S. stercoralis*) Pneumocystis prophylaxis HAART Liposomal amphotericin B (5 mg/kg x 3 weeks) switched to oral solution itraconazole (dose NR). Satisfactory clinical course : CD4 138/mm^3	Recovery
			Borges-Costa et *al*, 2011 [21]			
19	Congo, living in Portugal 55, M	HIV-1 + Fever, weight loss, diarrhoea and disseminated non-pruritic maculopapular rash (3 months)	Palpable LN and HSM CD4: 28 cells/mm^3; anemia and leukopenia (NR); high hepatic enzymes rate (NR) Yeast cells of Hcc on skin biopsy (PAS stain), confirmed by PCR and DNA sequentiation	PDH in advanced AIDS patient	Amphotericin B (total dose NR)	Death
			Dawood H, 2011 [22]			
20	South Africa 32, M	HIV , Intermittent fever and rigors, increased abdominal	Fever (39.8° C) and rigors, left flank pain, increase in abdominal circumference, pallor and generalized LDP, SM and HM	DH in advanced HIV disease complicated with	HAART, Amphotericin B (1 mg/kg per d) for 14 d switched to followed Itraconazole 200 mg 2x/d.	Recovery

Case-patients (n°)	country of Origin, Age, sex	Past history-Underlying disease: HIV/AIDS, CD4 count, VL, ART	Mains findings (Clinical, Laboratory and/or Radiology)	Definite Diagnosis of Histoplasmosis	Treatment and clinical course	Outcome
		circumference (> 3 months) and gradual weight loss (6, 10 kg)	CD4 20/mm^3, viral load <400 copies/mL, Hb 6.6 g/dL, PLTS173 x 109/L, Abdominal US: LPD, HSM, Characteristic of histoplasmosis (NR) on bone marrow aspirate and trephine, and liver biopsy No AFB on bone marrow and trephine and liver biopsy	IRS	Severe clinical course: : Renal impairment, hypokalemia, and thrombophlebitis, IRS, splenic abscess (splenic rupture on US); laparotomy, planectomy and a wedge liver biopsy (H&E staining) : yeast of Hcc, 10 d amphotericin B, switched to itraconazole 200 mg twice daily	
			Mandengue et *al*, 2012			
21	Cameroon 25, F	unknown HIV status, persistent fever, weight loss >10 kg, fatigue and weakness, unsuccessful antipyretic and antimalarial medications (self-medication, 1month)	Fever (38.5°C), fatigue, weight loss, distended and tender abdomen, HM; difficulties with attention without focal neurological deficit. HIV test positive, CD4 7/mm^3 Hb 7.3 g/dL; AST/ALT: 352/59 IU/L. Routine PBS: yeast of Hcc-Culture (Sabouraud medium): *Histoplasma sp.*	DH revealing advanced AIDS at terminal phase (postmortem diagnosis)	/	Death prior to definite diagnosis
			Scarlata et al, 2012 [24]			
22	Ghana, living in Italy for 2 years, no trip to his native country 36, M	AIDS, CD4 17/mm^3, VL27 copies, ART	Fever, catarrhal cough, diffuse skin lesions: erythematous umbilicated or ulcerated papulo-nodules, and pustules, deep circle line of the fore head mimicking lepra; HSM, and generalized LDP. Anemia and leucopenia (NR),	DH in advanced AIDS patient mimicking lepra	Liposomal amphotericin B, 5 mg/kg /d switched to Itraconazole 200 mg /8h the first 3 days, then 200mg/12h. Satisfactory clinical course: CD4 34/mm^3, healing of skin lesions of the face, sclerotic and atrophic scars	Recovery

Case-patients (n°)	country of Origin, Age, sex	Past history-Underlying disease: HIV/AIDS, CD4 count, VL, ART	Mains findings (Clinical, Laboratory and/or Radiology)	Definite Diagnosis of Histoplasmosis	Treatment and clinical course	Outcome
			and slight increased liver enzymes (NR), Mantoux test negative. CXR and CT: nodules disseminated on both lungs, hyperplasia and nodular infiltrates of the hila. MRI of the brain: hyperactivity and evidence of enhancement Skin and nasal mucosa biopsies (stains NR): Yeast cells of *Hc.*			
			de Hoog et *al*, 2014 [25]			
23	Ghana, living in Netherlands for 8 years 27, M	Unknown HIV status Fever (39.3 °C), persistent cough and night sweats, bloody sputum and weight loss (20 kg) (3 weeks)	Multiple small sized LN (submandibular and inguinal). HIV test positive, CD4 = 0, and VL: 5 million copies/ml. Hb 4.7 mmol/l, LDH 2967 U/l Routine blood smear and LN biopsy (GMS stain): yeast figures of *H. capsulatum*	DH revealing advanced AIDS and detected on peripheral blood smear	Liposomal amphotericin B 5 mg/kg x two weeks, switched to Itraconazole 200 mg twice/d, HAART after two weeks Gradual improvement, Job and daily activities resumed after two months	Recovery
			Mandengue et *al*, 2015 [9]			
24	Cameroon 38, M	HIV1+, ART (irregular observance) Cough, fever, weight loss and weakness, ineffective ATB treatments (>1month)	Weight 53 kg. Skin lesions (face and forearms): squamous papulo-nodules, and papulo-pustules; nasal and genital ulcerations. Hb: 5.7 g/dl, PLTS: 3/mm^3, CD4=3/mm^3 ; Syphilis test negative; no AFB on sputum Skin biopsy (PAS and GMS	DAH in advanced AIDS patient	HAART, Fluconazole 1600 mg/d (4 times) interrupted after 1 m (unaffordable for the patient); Satisfactory clinical course: healing of fever, cough and skin lesions, weight 59kg, Hb: 12 g/dL, PLTS 435 000/mm^3 and CD4 289/mm^3	Recovery

Case-patients (n°)	country of Origin, Age, sex	Past history-Underlying disease: HIV/AIDS, CD4 count, VL, ART	Mains findings (Clinical, Laboratory and/or Radiology)	Definite Diagnosis of Histoplasmosis	Treatment and clinical course	Outcome
			stains): yeast like organisms of Hcd			
			Murphy et *al*, 2015 [27]			
25	South Africa 36, M	AIDS, CD4: 14/mm^3, ART. Oral candidiasis (fluconazole 200mg/d) Presumptive CNS toxoplasmosis (high dose cotrimoxazole) Skin lesions (4weeks), Altered mental status and vomiting (1 week)	Fever (NR), skin lesions (chin and chest): flesh-colored nodules, erosions on forehead, disorientation US of Abdomen: LDP and HSM. CSF: normal pressure, chemistry, and cells count Skin biopsy (stains NR): yeast-like of Hcc	PDH in advanced AIDS patient involving skin and CNS (postmortem diagnosis)	Rapid deterioration of GC within 24h of admission with hypotension and worsening of mental status	Death
26	South Africa 35, M	Unknown HIV status, presumptive TB, polyadenitis, anti TB treatment (4 months) Pruritic skin ulcerations (2 months)	Skin lesions (face, legs, and hands): ulcerated nodules, ulcer of the tongue, and destruction of the nasal septum and nostrils. Oral candidiasis, HIV test positive, CD4 14/mm^3 Skin biopsy (Gram stain): yeast of Hcd, Culture: *H c*.	AH revealing advanced AIDS misdiagnosed as TB and	HAART Itraconazole (200 mg twice /d) x 1 year, then switched to fluconazole 200 mg twice/d Healing of cutaneous lesions within 9 months	Recovery
27	South Africa 45, M	AIDS, CD4: 29 cells/mm^3 Epigastric pain, vomit, and bloody	Cervical LDP, HSM US of Abdomen: LDP on left para aortic and splenic hilar, multiple splenic hypo densities,	DH in advanced AIDS patient misdiagnosed as	Empiric anti TB therapy and HAART, then Amphotericin B for 14 days (dose NR), then h oral Fuconazole 800 mg/d for 30	Death

Case-patients (n°)	country of Origin, Age, sex	Past history-Underlying disease: HIV/AIDS, CD4 count, VL, ART	Mains findings (Clinical, Laboratory and/or Radiology)	Definite Diagnosis of Histoplasmosis	Treatment and clinical course	Outcome
		diarrhea; perforated duodenum ulcer on endoscopy; histoplasmosis on biopsy (5years prior)	and a solid mass in the hepatic flexure of the colon. Colonoscopy: 1.5 cm deep ulcer, hypertrophic edges in the hepatic flexure Biopsies (ulcers of the colon, cervical LN, stains NR): numerous yeast cells ≈ histoplasmosis	TB	days (maintenance therapy) Poor clinical course: sepsis, reportedly *Acinetobacter baumannii* bacteremia	
			Nalwanga & Henning, 2016 [28]			
28	Uganda 29, F	AIDS, CD4:34 /µl, VL: 199,994 copies/ml, second line ART (irregular observance), TMP/SMX (prophylaxis) Presumptive extra pulmonary TB (4 kg Weight loss (46 to 42 kg), abdominal pain, diarrhea, vomiting, and evening fevers) (1 months), unsuccessful anti TB therapy (good observance):	Evening fevers, generalized weakness, abdominal pain, diarrhea, vomiting. Skin lesions (face): hyperpigmented non-itchy and dome-shaped nodules HM Albumin level 35.5 g/L. US of the abdomen: LDP. Skin biopsy (stains NR) ≈ *H capsulatum infection* (NR)	DH misdiagnosed as TB, in advanced AIDS patient	Anti TB treatment (04 months). ATF treatment: amphotericin B (0.7 mg/kg, 14 d), switched to fluconazole (400 mg x 2 /d, then a maintenance therapy. 400 mg once daily). Resolution of skin lesions and LDP	Recovery

Case-patients (n°)	country of Origin, Age, sex	Past history-Underlying disease: HIV/AIDS, CD4 count, VL, ART	Mains findings (Clinical, Laboratory and/or Radiology)	Definite Diagnosis of Histoplasmosis	Treatment and clinical course	Outcome
		continuing weight loss (about 15%)				
			Dieng et al, 2017 [29]			
29	Senegal 25, M	Unknown HIV status, spontaneous epistaxis of limited abundance, persistent fever, and a progressive poor GC (3 weeks)	Fever (40.3°C), pallor of conjunctiva, petechiae on nasal cavities, multiple bilateral cervical and axillar firm and painless LN. Typical signs of oropharyngeal candidiasis. HIV test positive, CD4: 3/mm^3, Hb: 7.9 g/dL, ASAT/ ALAT: 17x N /3.6 x N. Thin blood smear for malaria: yeast cells ≈ Hcc, confirmed by PCR (DNA amplification from the blood of the thin smear (rDNA)	DH revealing advanced HIV disease at late stage (postmortem diagnosis)	Worsen of patient GC, with multiple organs failure	Death prior to definite diagnosis
			Zanotti et al, 2018 [30]			
30	Ivory Coast, living in Italy 19, F	unknown HIV status, persistent fever	Fever (38.8°C), severe asthenia, chills, and tachycardia (110 bpm), mono-lateral tonsillar hypertrophy and submandibular LDP. HIV test positive, CD4 19 cell/µL and VL:1,787,000 cp/mL; Hb 8.7 g/dL, PLTS 80,000/µL); LDH 5,201 U/L, EBV-DNA 1,297 cp/mL, CMV-DNA 266 cp/mL, and HBV-DNA >700,000,000 UI/mL Stool test: blood	PDH revealing HIV advanced disease with CMV & HVB co-infections	Liposomal Amphotericin B switched to Itraconazole after 03 weeks of induction therapy, and cART (tenofovir/emtricitabine + dolutegravir). Poor clinical course: poor observance of both ART and ATF therapy; pregnancy: internal abortion complicated by sepsis choc (wide spectrum ATB therapy, many blood transfusions and mechanical ventilation, fever, pancytopenia), and skin	Recovery

Case-patients (n°)	country of Origin, Age, sex	Past history-Underlying disease: HIV/AIDS, CD4 count, VL, ART	Mains findings (Clinical, Laboratory and/or Radiology)	Definite Diagnosis of Histoplasmosis	Treatment and clinical course	Outcome
			Biopsies of bone marrow, gut, lateral-cervical lymph node and tonsils (H&E, GMS, and PAS): yeast cells ≈ histoplasmosis (type NR), Culture of bone marrow aspirate (medium NR) : *Hc*		lesions suggestive to histoplasmosis reactivation. Progressive improvement of her condition after fully adherence with cART and histoplasmosis prophylaxis	
			Zhang & Sander, 2019 [31]			
31	Zimbabwe, living in Canada for 7 years 58, F	HIV (30years), ART (7 years, failure treatment), weight loss, decline general cognitive function (1 year), skin rash (cephalo-caudally), fever, night sweats, headaches, cough and dyspnea (3 months)	Skin lesions (face, trunk, and extremities): diffuse infiltrated, scaly, verrucous, hyperpigmented plaques on the face (leonine facie), non-blanching, violaceous-to-brown papules and plaques of varying size with bleachable halo, erythematous patches. CD4 1 cell/µL VL 5.28 log copies/ml No AFB on sputum sample. CT scan of the trunk: calcified granulomata in upper lobes of both lungs, bulky mesenteric and retroperitoneal LDP MRI scan of the brain: a small lesion within the right parietal lobe. Skin lesions biopsy (H&E, PAS, GMS, and Giemsa stains): numerous yeast-like organisms ≈	DH in patient with advanced HIV disease mimicking lepra	Liposomal amphotericin B (2 weeks, dose NR), switched to Itraconazole 200 mg PO BID for a planned 12-months course. Response to antifungal treatment assessed by serial serum *Histoplasma* antigen titers	Recovery

Case-patients (n°)	**country of Origin, Age, sex**	**Past history-Underlying disease**: HIV/AIDS, CD4 count, VL, ART	**Mains findings** (Clinical, Laboratory and/or Radiology)	**Definite Diagnosis of Histoplasmosis**	**Treatment and clinical course**	**Outcome**
			Hcc. Culture of skin, bone marrow and retroperitoneal LN biopsies, and blood: *H. capsulatum*.			

Table 2. Risk factors for death in advanced HIV disease population

Case-Patients (N°)	Clinical signs							Laboratory abnormalities							Outcome
	Fever > 39°C	Weight loss > 5%	Systolic BP < 90mmHg	Diarrhea	Respiratory insufficiency	Neurology involvolm.	Renal failure	PLTS < 100000/mm^3	Hb < 8.0 g/dl	Albumin<3, 5g/dl	urea 2 x Nl upper limit	Creat > 1,5 mg/dl	AST > 2,5 x Nl upper limit	LDH > 2 x normal	
2		weight loss													Death
3	Fever	Weight loss						64×10^9/L	5.9	2.5			134 IU		NR
4	Fever				respiratory distress			64×10^9/L	5.9				134 IU		Death
5		Weight loss													Death
6	Hyper pyrexia	weight loss													NR
7	Fever	weight loss						94×10□ / L							Death
8		weight loss (10kg)				Neurology involv		27.2 × 10^4/µl						370 IU/l	Death
9	Fever														Death
11	Fever														Recovery
12	Fever	massive cachexia		profuse bloody diarrhea (15x daily)				18 G/l	8,3 g/dl,		32 mmol/l	337 mol/l	16xNl	17 962 IU/l,	Recovery
13	Fever														NR
14	Fever	weight loss						7000/mm^3	5,4 g/dl				410 IU/L		Death

15	Fever	weight loss	arterial hypertension				93,000/µl	9.1 g/dl		69 mg/dl	2.58 mg/dl	299 IU/L	2,782 U/L	Lost to follow-up
16	Fever	weight loss (5 kg)					74,000/µl	8.8 g/dl					1,041 U/L	Lost to follow-up
17						Stage 5 renal failure	365 000/µl	5,6 g/dl	2.1 g/dl	125 mg/dl	18.7 mg/d		2,208 IU/L	Recovery
18	Fever											610 IU/L	249 U/L	Recovery
19	Fever	weight loss		diarrhoea			Anaemia					elevated hepatic enzymes		Death
20	Fever (39.8° C)	Weight loss (10 kg /6 months)					173 x 109/L	6.6 g/dl						Recovery
21	Fever (38,5°C)	weight loss >10 kg	80/50 mmHg					7.3 g/dL				352 IU/L		Death
22	Fever													Recovery
23	Fever 39.3°C	weight loss (20 kg)						4.7 mmol/l					2967 U/l.	Recovery
24	Fever	weight loss					3/mm^3	5.7 g/dl						Recovery
25	Fever				Altered mental status									Death
27				Bloody diarrhea										Death
28	Fever	weight loss(15%)		Diarrhea					35.5g/L					Recovery

29	Fever (40.3°C)	7.9 g/dL	17xN	Death
30	Fever (38.8°C)	8.7 g/Dl	5,201 U/L	Recovery

Table 3. Outcome of patients related to the presence of risk factors in advanced AIDS case-patients

Number of Risk-factors /Patients	Number of patients	Outcome			
		Death	Recovery	Lost to follow-up	NR
1	8	4	1	/	3
≥ 2	19	7	9	2	1
Total	27	11	10	2	4

4. CONCLUSION

DH is a serious threat in AHD population in SSA countries that urgently need to be addressed, based on a continued engagement of:

- The clinicians; their training would increase the high index of suspicion on histoplasmosis and particularly in AIDS population, and help educating PLHIV on risk factors associated with histoplasmosis
- The Governments; they should make all the WHO recommended tools of diagnostic and antifungal drugs available, along with antifungal treatment monitoring.
- The Pharmaceutical companies: they could reduce the cost of rapid diagnostic tools for detection of histoplasmosis and make effective antifungal drugs available in generic form and at low cost.
- The National and Pan African Working Group : with epidemiological studies data will be generated to determine the burden of DH in SSA

Ongoing actions including continuing national and pan African seminaries, workshops and multicentric published studies, involving clinicians and laboratory technicians, Governments and international organizations (WHO, NGO, International Scientific societies) would raise interest on histoplasmosis in sub-Saharan Africa.

CONSENT

It's not applicable.

ETHICAL APPOVAL

It's not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX

[1] Kuate Ngouanom Marius. Master Degree study, 2019, University of Buea (South West Region of Cameroon)
Title: Prevalence And Risk Factors For *Histoplasma Capsulatum* Infection Amongst Hiv Patients Attending The Buea Regional Hospital Using The Optimum Imaging Diagnostics (Oidx) Histoplasma Antigen EIA.

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