THERAPEUTIC ADVANCES in
*Infectious Disease*

*Case Series*

# Diagnosing disseminated histoplasmosis in advanced HIV/AIDS disease in Cameroon using a point of care lateral flow assay

*Ther Adv Infect Dis*

2022, Vol. 9: 1–5

DOI: 10.1177/20499361221132133



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***Abstract*:** Histoplasmosis is an AIDS-defining opportunistic infection. Disseminated histoplasmosis (DH) can be fatal without early diagnosis and treatment initiation. We present one confirmed and three probable cases of DH in advanced HIV/AIDS disease patients diagnosed using OIDx *Histoplasma* LFA in Yaoundé, Cameroon. Four women with HIV but unknown CD4 count presented with asthenia, weight loss, productive cough, and fever (39°C) as common symptoms for at least 3 weeks. Two of the patients had skin lesions. These included facial papules, macules, and umbilicated vesicles scattered over the trunk and limbs. These were diffuse lesions which were purulent, itching, and papillomatous lesions with a necrotic centre, and one patient had a right forearm ulcer. We performed the *Histoplasma* antigen tests using the OIDx Histo LFA, and they were strongly positive in all four patients. Histopathology in skin biopsy allowed identification of the species as *Histoplasma capsulatum* var *capsulatum* in one patient. In this same patient, *Pseudomonas aeruginosa* and *Proteus mirabilis* were cultured from the forearm ulcer. This patient later commenced antibiotics (Levofloxacin 500 mg) and oral itraconazole (800 mg/day) with immediate improvement. Unfortunately, the other three patients could not access itraconazole, were discharged and lost to follow-up. Early diagnosis and treatment are essential for the management of DH. LFA is a test that can be set up in any setting with limited resource. Access to this can be a major advance in the diagnosis of histoplasmosis in resource-limited settings.

***Keywords:*** disseminated histoplasmosis, HIV/AIDS, lateral flow assay, itraconazole, Cameroon

Received: 8 April 2022; revised manuscript accepted: 25 September 2022.

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## Introduction

Histoplasmosis is an opportunistic fungal infection caused by the dimorphic fungus, *Histoplasma capsulatum*. Human histoplasmosis is caused by *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii*.[1,2] It is an AIDS-defining opportunistic infection.[3] Disseminated histoplasmosis (DH) can be fatal without early diagnosis and treatment initiation [4]. The first local cases of histoplasmosis were published through cases reports, the definitive diagnosis here established through culture and histopathology, and a 100% death rate.[5,6] A burden of 1800 cases of histoplasmosis/year was estimated in Cameroon.[7] Moreover, two prospective studies reported a prevalence of 13% and 26% in 2015 and 2021, respectively.[8,9]

Culture of the organism is still the standard for diagnosis with a 100% specificity, but is slow and often facilities for culture are not available.[6] A new point of care, lateral flow assay (LFA) for urinary *Histoplasma* antigen has recently become available (Miravista, IN), with reported sensitivity of 96% and specificity 90% in highly endemic parts of South America.[10] A similar LFA, the OIDx *Histoplasma* LFA [Optimum Imaging

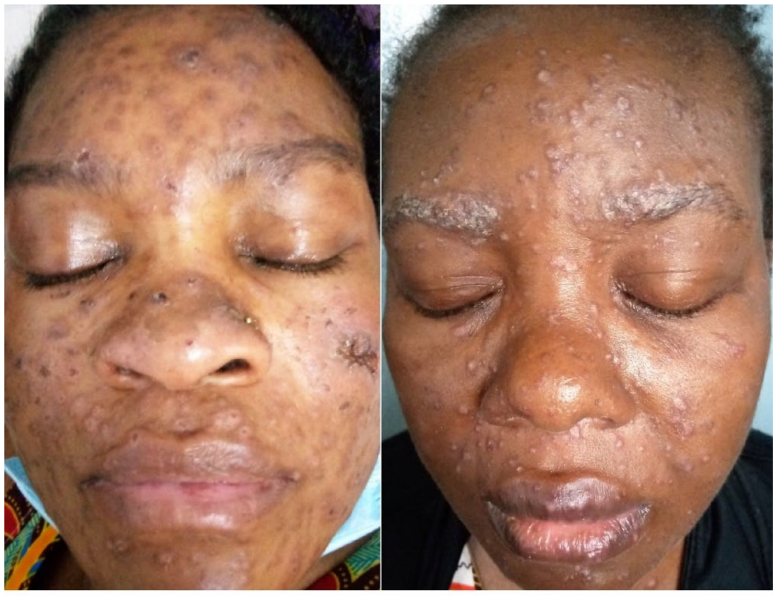


**Figure 1.** Skin lesions showing (a) facial papules and (b) papillomatous lesions.

Diagnostics (OIDx), Scarborough, Maine, US] has become available with a reported in-house performance of 96% sensitivity and 89% specificity.[11] A study in Ghana found a 98% concordance between the OIDx *Histoplasma* LFA and the IMMY *Histoplasma* EIA (Immuno-Mycologics Diagnostics, Oklahoma, U.S), and a 97.3% specificity in urine.[12] The OIDx Histo LFA has the potential to significantly aid diagnosis of DH in parts of the world where culture and molecular methods are not widely available. Based on the Revision and Update of the Consensus Definitions of Invasive Fungal Disease,[13] we present one confirmed cases of DH with skin lesions and three probable cases of DH with and without skin lesions in advanced HIV/AIDS disease patients investigated using OIDx *Histoplasma* LFA in Yaoundé, Cameroon.

## Cases

### *History*

Four women with HIV but unknown CD4+ T-cell count were received at the Infectious Disease unit of the Central Hospital Yaoundé and at the emergency unit of the Jamot Hospital Yaoundé presenting with asthenia, weight loss, productive cough and fever (39°C) as common symptoms for at least 3 weeks. Two of the patients had skin lesions. These included facial papules, macules, and umbilicated vesicles scattered over the trunk and limbs (Figure 1). These were diffuse lesions which were purulent, itching, and papillomatous lesions with a necrotic centre. One patient had a right forearm ulcer. Chest X-ray showed a basal reticular heterogeneous opacity in the right lung and abdominal echography showed hepatomegaly in one of the patients. Testing for tuberculosis using sputum stained with auramine and cryptococcosis using cerebrospinal fluid stained with India ink was negative in all of them.

### *Investigations*

We performed the *Histoplasma* antigen tests using the *Histoplasma* antigen LFA (OIDx company, Scarborough, US). They were strongly positive (0.75) in all four patients (Figure 2). Histoplasmosis was later confirmed by skin biopsy and tissue stains with Giemsa [Figure 3(a)] at the hospital laboratory and Gomori-Grocott and periodic acid schiff (PAS) staining [Figure 3(b)] at the Centre Pasteur du Cameroon in one of the patients [Figure 1(a)]. The species was identified as *Histoplasma capsulatum* var *capsulatum*. In this same patient, in addition to *Histoplasma*, *Pseudomonas aeruginosa* and *Proteus mirabilis* were cultured from the forearm abscess.

### *Treatment and follow-up*

*P. aeruginosa* and *P. mirabilis* were treated with antibiotics (Levofloxacin 500 mg) and *Histoplasma capsulatum* var *capsulatum* with oral itraconazole (800 mg daily for 3 months and 400 mg daily for 9 months) immediately after the diagnosis was made. After 1 month of treatment with major improvement, she was discharged, reinitiated on antiretroviral therapy, and returned regularly for wound dressings. The other three patients could not access itraconazole, were discharged and lost to follow-up.

## Discussion

In this report, we describe the first cases of histoplasmosis diagnosed using a point of care LFA in Cameroon. Approximately 10% to 25% of AIDS patients with DH develop skin lesions,[14] and this is usually associated with severe immunosuppression.[15] Skin lesions associated with

histoplasmosis can be polymorphic papules, plaques with or without crusts, pustules, nodules, mucosal ulcers, erosions, punched out ulcers, lesions resembling molluscum contagiosum, acneiform eruptions, erythematosus papules and keratotic plaques, and purpuric.[14,16] It is not known in Cameroon or Africa generally, what proportion of patient develop skin lesions, in our case series, this was 50%.

Fungal diagnostics in most sub-Saharan African countries is difficult due to the lack of assays.[3] Antigen assays have shown good performances in the diagnosis of histoplasmosis in the past.[10,17] These techniques (EIA and LFA) that compensate the lack of laboratory infrastructure and laboratory personnel trained in diagnostic mycology.[18] Culture remains the gold standard with 100% specificity[9] but with a poor sensitivity in case of pulmonary forms of the disease.[19] Skin biopsy is rapid method of arriving at a specific diagnosis of DH. The cells of *H. capsulatum* are visualized in histological sections stained with special stains like PAS or Giemsa. The cells appear as round or oval bodies surrounded by a clear space that was originally interpreted as a capsule, giving rise to the name *H. capsulatum*.[16] Greatly improved detection rates and reduced mortality have been shown with the use of antigen detection or molecular testing.[20] The value of the simple LFA for *Histoplasma* antigen is shown by these cases.

Amphotericin B and itraconazole are the antifungal drugs of choice; fluconazole use is associated with poor clinical response and higher relapse rates.[20–22] However, amphotericin B is unavailable in Cameroon while itraconazole is rare and expensive, therefore inaccessible to patients with limited financial resources. This makes proper treatment and management of DH in AIDS patients difficult and limited. This was the case in our study, only one of the four patients was able to afford itraconazole. There is no established

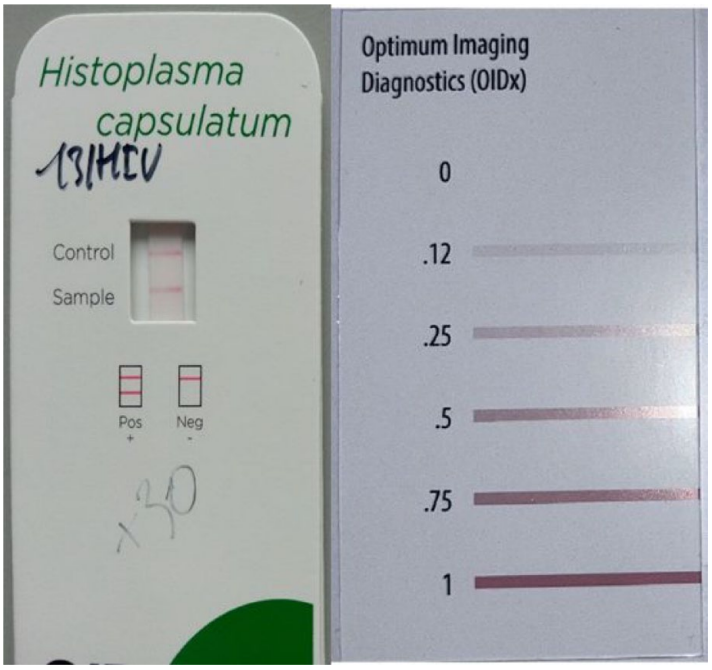


**Figure 2.** Highly positive Histoplasma LFA.

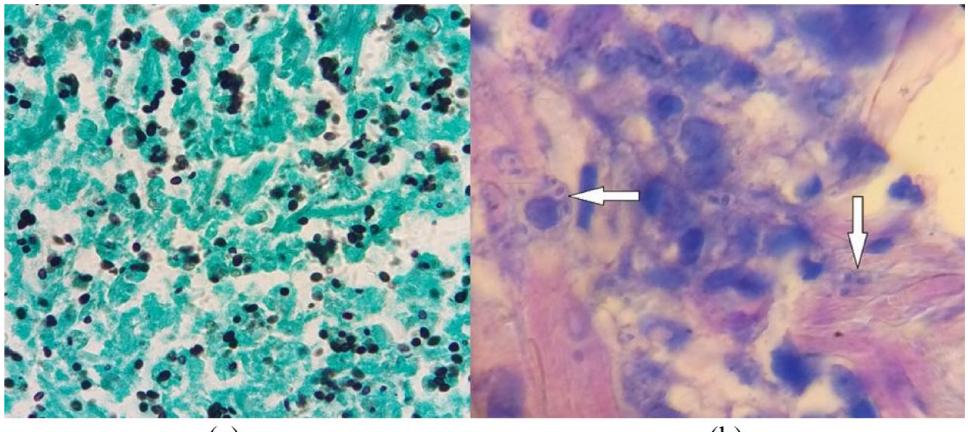


**Figure 3.** Skin biopsy showing *Histoplasma* cells: (a) Gomori-Grocott stain at ×40. *H. capsulatum* appears as small spherical or ovoid yeasts, (b) Giemsa satin at ×40 and showing pseudo-encapsulated yeast consistent with *Histoplasma capsulatum*.

protocol for the management of DH (sometimes presenting with skin lesions) in Cameroon, but the Pan-American Health Organization has issued guidelines.[23] Depending on the severity of the infection and the person's immunity, treat severe disease with liposomal amphotericin B 3 mg/kg (or conventional amphotericin B, 0.7–1 mg/kg) for 14 days and mild to moderate disease with itraconazole (loading doses then 200 mg twice daily). This is followed by 12 months of itraconazole as maintenance therapy.[23] It is usually too costly for patients in sub-Saharan Africa. Although oral itraconazole is usually used for mild to moderate disease,[17,23] it was shown to be effective in our patient with a severe condition, at a high dose to overcome any potential absorption issues, which are well recognized in AIDS. Both amphotericin B and itraconazole need to be made available for patients with DH in AIDS in Cameroon.

## Conclusion

Early diagnosis and treatment are essential for the management of DH. The gold standard for diagnosis, culture is invasive, expensive, and slow. LFA is a test that can be set up in any setting with limited resource. Access to this can potentially be a major advance in the diagnosis of histoplasmosis in resource-limited settings. Large-scale, prospective study of using this test in high-risk populations is required.

## Declarations

### *Ethics approval and consent to participate*

Ethical clearance for this study was obtained from the Centre Region Ethics Committee for Human Health Research (CRERSH-Ce) (N1275/CRERSHC/2021).

### *Consent for publication*

Written informed consent was obtained from the patients for publication of this case series and accompanying images.

### *Author contributions*

**Marius Paulin Ngouanom Kuate:** Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

**Hermine Abessolo Abessolo:** Investigation; Writing – review & editing.

**David W. Denning:** Conceptualization; Funding acquisition; Project administration; Writing – review & editing.

**Neil R. Stone:** Data curation; Validation; Writing – review & editing.

**Roland Ndip Ndip:** Supervision; Writing – review & editing.

### *Acknowledgements*

The authors wish to thank Geoff Piasio and Optimum Imaging Diagnostics (OIDx) company for providing test reagents used in this study. Our gratitude also goes to the Military Health Research Centre (CRESAR) and the Chief of the Centre Colonel Dr Julius Nwobegahay for allowing us to use their Microbiology Laboratory for sample analysis.

### *Funding*

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Fungal Infection Trust (FIT) through a small grant and the American Society of Tropical Medicine and Hygiene (ASTMH) through an ACGH research support award.

### *Competing interests*

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### *Availability of data and materials*

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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