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Disseminated histoplasmosis in people living with HIV in Lao PDR

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Background

Histoplasma capsulatum is a dimorphic fungus that is commonly found in the environment. It has a global distribution and is particularly associated with exposure to caves and bat guano.

In Southeast Asia, studies have demonstrated high levels of exposure to *Histoplasma* – although no data has been published for Lao PDR.

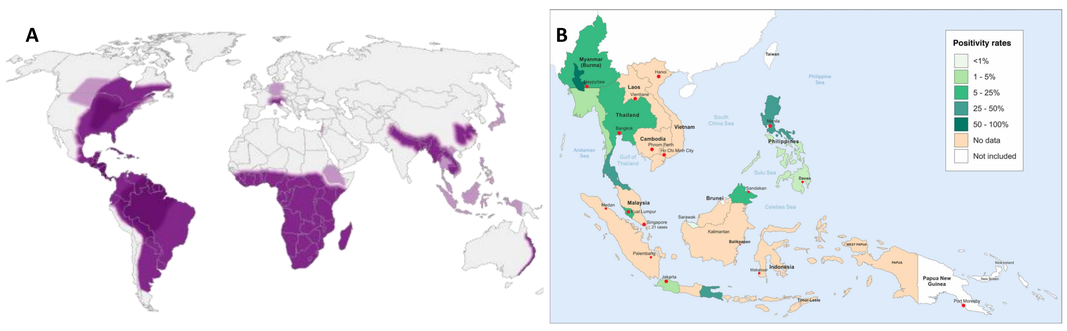

Fig 1. A: Global distribution of *Histoplasma* (www.cdc.gov). **B:** Prevalence of *Histoplasma* exposure in Southeast Asia determined by histoplasmin sensitivity (Baker e*t al*., 2019).

The majority of infections are asymptomatic and self-resolving. Symptomatic presentations are usually respiratory – including acute pulmonary and chronic cavitary forms. However, disseminated histoplasmosis is the most severe presentation, and most commonly occurs in immunocompromised patients, such as patients living with HIV. A CD4 count of <150 cells/mm^3 is a particular risk factor. Even when treated, mortality is 21-53%. UNAIDS data estimates that 17,000 people are living with HIV in Laos, and anecdotal reports suggest incidence is increasing.

Diagnosis of histoplasmosis is difficult. Culture is slow and insensitive, and is complicated because *H. capsulatum* is an ACDP group 3 pathogen. Histopathology and PCR are other diagnostic strategies, but are not widely available. Antigen detection in blood or urine using well established assays is reliable, but may require sophisticated laboratory infrastructure.

Methodology

This work was nested within a study investigating the prevalence of visceral leishmaniasis in Lao PDR (Roberts *et al*., 2025). Consecutive adult patients (>15 years) newly diagnosed with HIV infection at two hospitals (Setthathirath and Mahosot Hospitals, Vientiane, Laos) were invited to participate in the study.

Study procedures:

1) A standardised form was completed to collect demographic, clinical and laboratory features.
2) Urine (preferably an early morning sample to increase sensitivity) was collected and used in the OIDx *Histoplasma* urinary antigen lateral flow assay (Fig 2).
3) An EDTA blood sample was collected, and separated into buffy coat and plasma. At the end of the study, plasma was shipped on dry ice to MiraVista Diagnostics, Indianapolis, USA, and tested for *Histoplasma* antigen using a quantitative EIA assay.

Fig 2: *Histoplasma* urinary antigen lateral flow test – positive control.

Patients testing positive by urinary antigen were further assessed by an ID or HIV physician, and offered treatment as per current WHO guidelines.

References & Acknowledgements:
The *Histoplasma* antigen lateral flow tests used in this study were provided free of charge by Optimum Diagnostics, USA.
Baker *et al*. (2019) *Emerg Microbes Infect* **8**, 1139-1145. Edwards *et al*. (2023) *Diagn Microbiol Infect Dis* **106**, 115952. Kang *et al*. (2023) *OFID*, **10**, ofad472. Medina *et al*. (2021) *Microorganisms* **9**, 2596. Ocansey *et al*. (2022) *OFID*, **9**, ofac277. Roberts et al., (2025) *Trop Med Health*, **53**, 101.

Results

229 patients were enrolled. The majority of participants were male (72%), with a median age of 29 years (IQR 24-36). 11% of patients tested positive for *Histoplasma* urinary antigen, and 7% had a positive serum antigen. 6 patients (2.6%) were positive in both assays.

		Mahosot	Setthathirath	Total
Urinary antigen	Positive	6	20	26
	Negative	73	130	203
	% Positive	**8%**	**13%**	**11%**
Serum antigen	Positive	7	9	16
	Negative	72	141	213
	% Positive	**9%**	**6%**	**7%**

Table 1. Numbers of patients testing positive by each assay separated by hospital.

	Urine antigen		Serum antigen	
	Urine OR	Urine p	Serum OR	Serum p
Outpatient	0.2 (0.1 - 0.4)	<0.01	0.1 (0.0 - 0.2)	<0.01
Age	1 (1.0 - 1.1)	0.03		
Height	1.1 (1.0 - 1.1)	0.04		
Fever			11.9 (3.3 - 43.2)	<0.01
Night sweats	3.2 (1.2 - 8.0)	0.03	10.1 (3.5 - 30.0)	<0.01
Arthralgia			4.7 (1.4 - 16.6)	0.03
Nausea			16.2 (3.0 - 88.0)	0.01
Active TB	6.5 (1.4 - 30.7)	0.03		
Sputum			6.6 (2.3 - 19.0)	<0.01
Temp			4.2 (2.0 - 8.7)	<0.01
Pulse			1.1 (1.0 - 1.1)	<0.01
Systolic BP			0.9 (0.9 - 1.0)	<0.01
Pale			7.4 (2.4 - 22.9)	<0.01
Splenomegaly	16.8 (1.5 - 191.7)	0.04		
Hepatomegaly			35.2 (5.9 - 211.5)	<0.01
Abdomen tender	6.5 (1.4 - 30.7)	0.03		
Weight loss			6.6 (2.3 - 19.1)	<0.01
HCT	0.9 (0.8 - 1.0)	<0.01	0.8 (0.7 - 1.0)	<0.01
Hb	0.8 (0.6 - 1.0)	0.01	0.6 (0.4 - 0.9)	<0.01

Table 2. Demographic and clinical features that were significantly associated with a positive antigen test. OR = Odds Ratio (95% confidence interval). P was calculated using Fishers exact test for categorical variables, and Mann-Whitney U test for continuous variables.

Factors significantly associated with a positive antigen test are shown in Table 2. Night sweats and low haemoglobin were associated with both positive urinary antigen and serum antigen.

Correlation between the two assays was not optimal, with a Cohen's kappa coefficient = 0.228 ('fair agreement').

15/26 patients with a positive urinary antigen test received treatment for histoplasmosis. Only 1 patient with a positive urinary antigen test died during the follow-up period; they were receiving amphotericin.

Discussion

- Positive urinary and serum *Histoplasma* antigen was a common finding in this cohort – more common than in similar cohorts in Trinidad (6.5%; Edwards *et al*., 2023) and Ghana (4.7%; Ocansey *et al*., 2022). If this represents disseminated histoplasmosis in this cohort, this is concerning. In Guatemala, disseminated histoplasmosis is a more common cause of death than TB in people living with HIV (Medina *et al*., 2021).
- The importance of these results is emphasized by the World Health Organization's recent categorization of *Histoplasma* spp. in the "high" group of fungal pathogens for research, development and public health action.
- A variety of clinical variables were associated with a positive antigen test, including night sweats and low haemoglobin. The poor correlation between the two assays needs to be investigated further.
- Exposure to environmental fungi may be higher in rural communities in Southeast Asia, and the cross-reactivity with important local fungi such as *Talaromyces* needs to be investigated. Therefore, further validation of *Histoplasma* antigen assays is required in our population.
- Liposomal amphotericin B is used for the initial treatment of severe infection, but is not available in Laos, even though it is superior to non-liposomal formulations (Kang *et al*., 2023). Itraconazole, which is required for many months, is typically available.

Conclusions

Disseminated histoplasmosis is common in patients who are newly diagnosed with HIV infection. Treatment is available and is effective in reducing mortality.

A possible diagnosis of histoplasma must be considered more widely. Diagnostic tests and first-line treatments must be made readily available.

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