# Histoplasmosis in Advanced HIV Disease (ADH) - A Multi-Center Prospective Diagnostic Validation Study

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## BACKGROUND

- Histoplasmosis is a common invasive mycosis among patients with advanced HIV disease (AHD) in the Americas but its burden in Southeast Asia is unknown due to the lack of Histoplasma antigen (HAg) assays and fungal cultures.
- We report results of a multi-center prospective diagnostic validation study of the IMMY Clarus Histoplasma GM enzyme immunoassay (HAg EIA) in hospitalized patients with AHD in Vietnam.

## METHODS

**Study population:** 901 hospitalized patients with **AHD (CD4 count ≤ 100 cells/µL OR WHO stage III or IV disease).**

- Aged ≥ 18 years
- Not on ART, on ART ≤ 3 months, OR on ART > 12 months
- Not on effective antifungal therapy for systemic mycoses

Urine *Histoplasma* antigen (HAg): using the IMMY HAg EIA

Fungal blood culture: using the Myco/F Lytic bottle (incubated x 6 weeks)

Conventional microscopy, cultures, and histopathology as clinically indicated

**Follow up:** weekly over first month, then monthly over 6 months

**Case definitions:**

- **Proven histoplasmosis**: was defined as a compatible clinical syndrome and culture-confirmed disease
- **Probable histoplasmosis:** was defined as a compatible clinical syndrome plus resolution (or declining) of HAg levels on antifungal therapy

**Treatment:** All Hag (+) patients with a compatible syndrome received antifungal therapy without waiting for culture results

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1. Disseminated histoplasmosis accounts for 3.0% of hospitalized patients with AHD in Vietnam.
2. The IMMY *Histoplasma* EIA has an excellent diagnostic performance: sensitivity 100%, specificity 99.2%, accuracy 99.9%, PPV 79.4%, and NPV 100% in screening for histoplasmosis in patients with AHD.
3. High mortality (29.6%) despite antifungal therapy highlights the need of earlier screening of *Histoplasma* antigen in patients with AHD

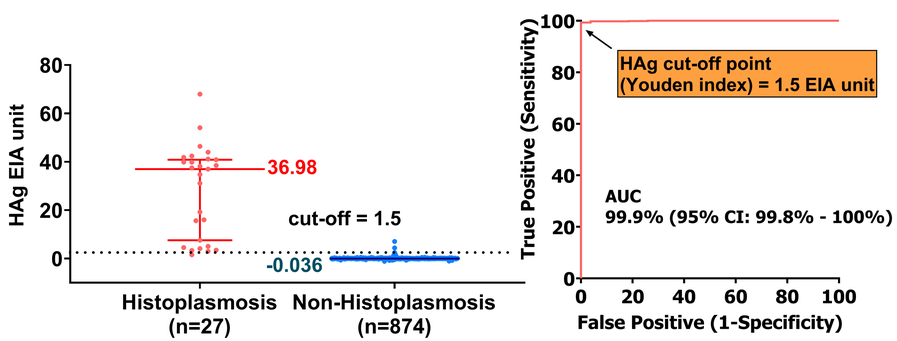
## RESULTS

- 901 patients were enrolled between Feb 2021 and July 2023. Follow up was completed by Jan 2024. 82.9% were men. Median age was 36 (IQR: 29-44)

**Table 1. Characteristics of 27 participants with histoplasmosis**

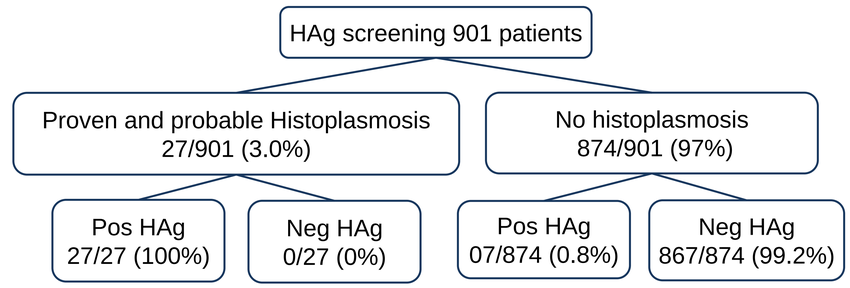
| Characteristics | |
|---|---|
| Median CD4 count (IQR) – cells/µL | 17 (7.5 – 28.5) |
| Specimens positive for *H. capsulatum* cultures – n (%) | |
| *Blood culture* | 12 (44.4%) |
| *Bone marrow culture* | 11 (40.7%) |
| *Skin lesion culture* | 1 (3.7%) |
| Time to culture positivity (Mean ± SD) – days | |
| *Blood cultures (n=11)* | 15.5 ± 7.5 |
| *Bone marrow cultures (n=8)* | 11.5 ± 5.8 |
| Mortality over 6 month – n (%) | 08 (29.6%) |

**Figure 1. Diagnostic performance of the IMMY Histoplasma GM EIA**




## RESULTS

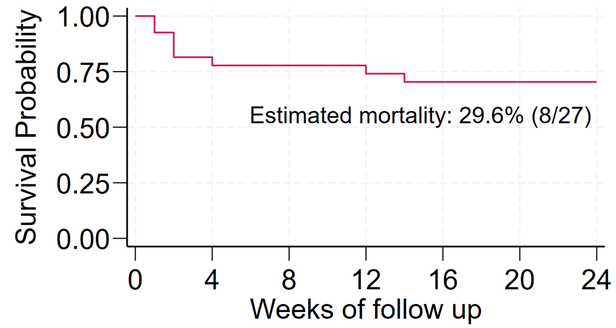
**Figure 2. Histoplasma antigen screening results**




| | Value | 95% CI | | Value | 95% CI |
|---|---|---|---|---|---|
| **Sensitivity:** | **100%** | 87.2% – 100% | **Specificity:** | **99.2%** | 98.4% - 99.7% |
| **PPV:** | **79.4%** | 64.8% - 89.0% | **NPV:** | **100%** | 99.6% - 100% |

***Abbreviations***: **HAg**: Histoplasma antigen; **PPV:** Positive Predictive Value; **NPV:** Negative Predictive Value

**Figure 3: Survival estimates of patients with proven and probable histoplasmosis on antifungal therapy over 24 weeks**




## CONCLUSIONS

- The IMMY *Histoplasma* GM EIA has an excellent diagnostic performance in screening for histoplasmosis in hospitalized patients with AHD in Vietnam.
- The high mortality despite antifungal therapy highlights the need to investigate the utility of *Histoplasma* antigen screening in asymptomatic patients with AHD.

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