Antoine ADENIS

Epidemiology of Histoplasmosis in Latin America: Trends and perspectives

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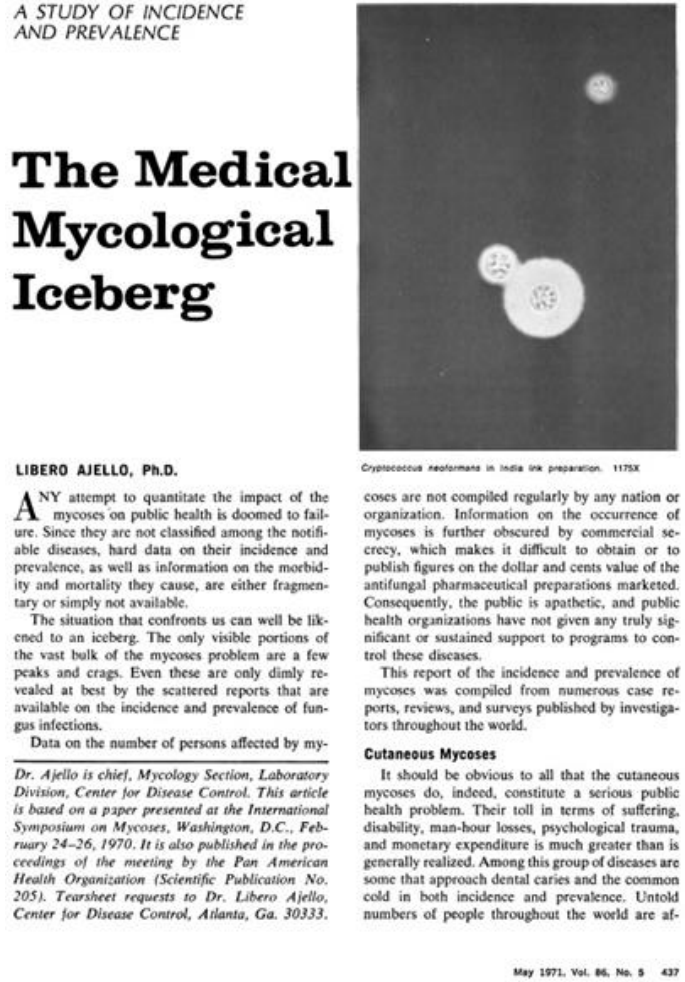
Human fungal infections

 # 1 billion individuals infected each year, with:
11.5 millions potentially letal infections
Accounting for #5% of the global deaths toll yearly

Enormous advances in fungal diagnostics and antifungal drug developments over the past 20 years
➔ most of the world's population has not yet benefited from these advances

Lacking funding, understudied and understimated health issues ➔ high morbidity and mortality levels

Consensus on the « neglected » aspects of medical mycology and human fungal infections



A STUDY OF INCIDENCE AND PREVALENCE

The Medical Mycological Iceberg

Cryptococcus neoformans in India ink preparation. 1175X

LIBERO AJELLO, Ph.D.

ANY attempt to quantitate the impact of the mycoses on public health is doomed to failure. Since they are not classified among the notifiable diseases, hard data on their incidence and prevalence, as well as information on the morbidity and mortality they cause, are either fragmentary or simply not available.

The situation that confronts us can well be likened to an iceberg. The only visible portions of the vast bulk of the mycoses problem are a few peaks and crags. Even these are only dimly revealed at best by the scattered reports that are available on the incidence and prevalence of fungus infections.

Data on the number of persons affected by mycoses are not compiled regularly by any nation or organization. Information on the occurrence of mycoses is further obscured by commercial secrecy, which makes it difficult to obtain or to publish figures on the dollar and cents value of the antifungal pharmaceutical preparations marketed. Consequently, the public is apathetic, and public health organizations have not given any truly significant or sustained support to programs to control these diseases.

This report of the incidence and prevalence of mycoses was compiled from numerous case reports, reviews, and surveys published by investigators throughout the world.

Dr. Ajello is chief, Mycology Section, Laboratory Division, Center for Disease Control. This article is based on a paper presented at the International Symposium on Mycoses, Washington, D.C., February 24–26, 1970. It is also published in the proceedings of the meeting by the Pan American Health Organization (Scientific Publication No. 205). Tearsheet requests to Dr. Libero Ajello, Center for Disease Control, Atlanta, Ga. 30333.

Cutaneous Mycoses

It should be obvious to all that the cutaneous mycoses do, indeed, constitute a serious public health problem. Their toll in terms of suffering, disability, man-hour losses, psychological trauma, and monetary expenditure is much greater than is generally realized. Among this group of diseases are some that approach dental caries and the common cold in both incidence and prevalence. Untold numbers of people throughout the world are af-

May 1971, Vol. 86, No. 5 437

Tudela JLR & al., Lancet Infect Dis 2017

Ajello L., HSMHA Health Rep. 1971

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Classification of human fungal infections

According to the geographic distribution or the bioclimatic ecosystem

Cosmopolitans ⇔ Tropicals or endemics

According to the disease's clinical spectrum

External ⇔ Deep, systemic or disseminated

→ **Common features of deep or invasives fungal infections (IFI):**

- Immunosuppression condition (innate or acquired)
- High levels of severity and case-fatality rates
- Diagnosis uneasy, often misdiagnosed for other diseases
- High index of suspicion and medical skills for the diagnosis and treatment

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Invasive fungal infections and HIV/AIDS infection

Major public health issues

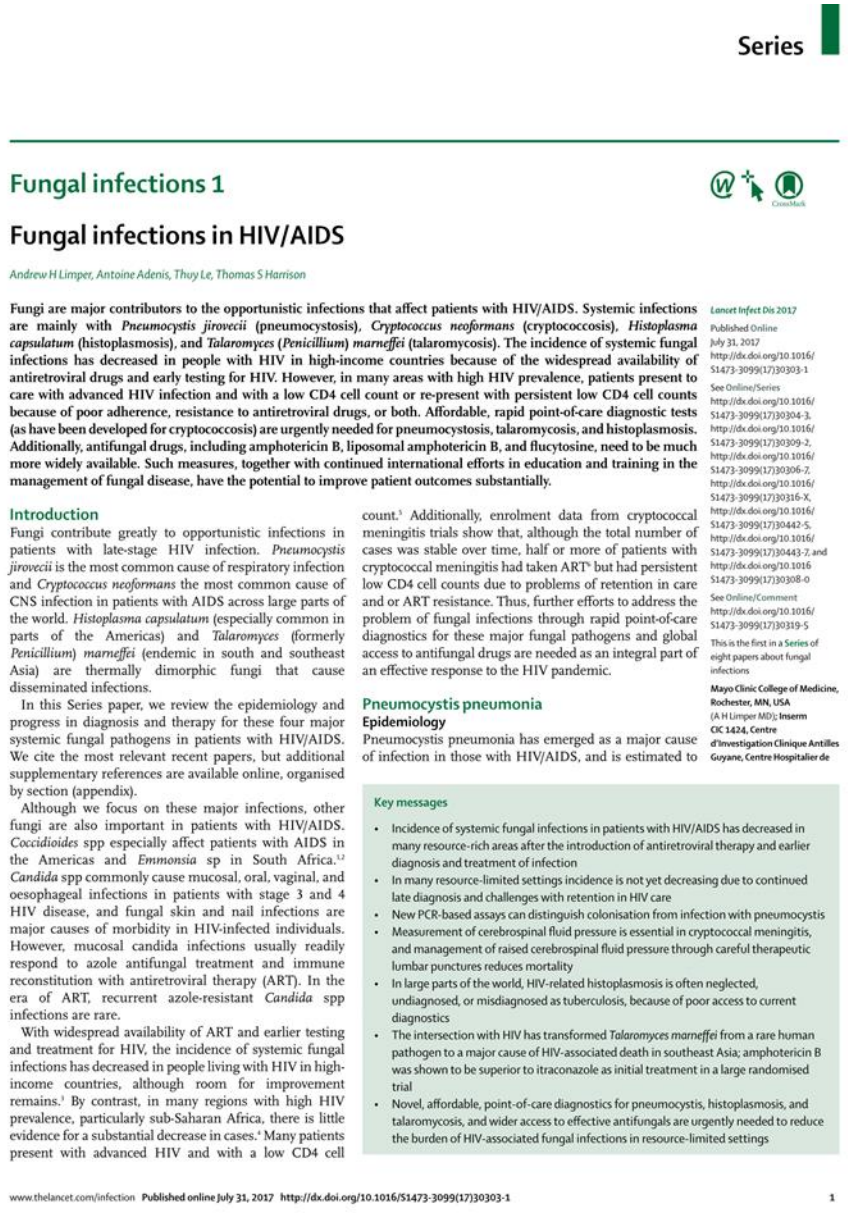
- Frequent
- Numerous avoidable deaths
- Notably in high HIV prevalence levels settings

Progress are required in

- Health practitioners trainings
- Point-of-care diagnostics diffusion/availability
- Effective antifungals diffusion/availability

Major opportunistic infections in advanced HIV disease (AIDS)

- Pneumocystosis
- Cryptococcosis
- Talaromycosis
- Histoplasmosis



Series

Fungal infections 1

Fungal infections in HIV/AIDS

Andrew H Limper, Antoine Adenis, Thuy Le, Thomas S Harrison

Fungi are major contributors to the opportunistic infections that affect patients with HIV/AIDS. Systemic infections are mainly with *Pneumocystis jirovecii* (pneumocystosis), *Cryptococcus neoformans* (cryptococcosis), *Histoplasma capsulatum* (histoplasmosis), and *Talaromyces* (*Penicillium*) *marneffei* (talaromycosis). The incidence of systemic fungal infections has decreased in people with HIV in high-income countries because of the widespread availability of antiretroviral drugs and early testing for HIV. However, in many areas with high HIV prevalence, patients present to care with advanced HIV infection and with a low CD4 cell count or re-present with persistent low CD4 cell counts because of poor adherence, resistance to antiretroviral drugs, or both. Affordable, rapid point-of-care diagnostic tests (as have been developed for cryptococcosis) are urgently needed for pneumocystosis, talaromycosis, and histoplasmosis. Additionally, antifungal drugs, including amphotericin B, liposomal amphotericin B, and flucytosine, need to be much more widely available. Such measures, together with continued international efforts in education and training in the management of fungal disease, have the potential to improve patient outcomes substantially.

Lancet Infect Dis 2017
Published Online July 31, 2017 http://dx.doi.org/10.1016/S1473-3099(17)30303-1
See Online/Series http://dx.doi.org/10.1016/S1473-3099(17)30304-3, http://dx.doi.org/10.1016/S1473-3099(17)30309-2, http://dx.doi.org/10.1016/S1473-3099(17)30306-7, http://dx.doi.org/10.1016/S1473-3099(17)30316-X, http://dx.doi.org/10.1016/S1473-3099(17)30442-5, http://dx.doi.org/10.1016/S1473-3099(17)30443-7, and http://dx.doi.org/10.1016 S1473-3099(17)30308-0
See Online/Comment http://dx.doi.org/10.1016/S1473-3099(17)30319-5
This is the first in a Series of eight papers about fungal infections

Mayo Clinic College of Medicine, Rochester, MN, USA (A H Limper MD); **Inserm CIC 1424, Centre d'Investigation Clinique Antilles Guyane, Centre Hospitalier de**

Introduction

Fungi contribute greatly to opportunistic infections in patients with late-stage HIV infection. *Pneumocystis jirovecii* is the most common cause of respiratory infection and *Cryptococcus neoformans* the most common cause of CNS infection in patients with AIDS across large parts of the world. *Histoplasma capsulatum* (especially common in parts of the Americas) and *Talaromyces* (formerly *Penicillium*) *marneffei* (endemic in south and southeast Asia) are thermally dimorphic fungi that cause disseminated infections.

In this Series paper, we review the epidemiology and progress in diagnosis and therapy for these four major systemic fungal pathogens in patients with HIV/AIDS. We cite the most relevant recent papers, but additional supplementary references are available online, organised by section (appendix).

Although we focus on these major infections, other fungi are also important in patients with HIV/AIDS. *Coccidioides* spp especially affect patients with AIDS in the Americas and *Emmonsia* sp in South Africa.[1,2] *Candida* spp commonly cause mucosal, oral, vaginal, and oesophageal infections in patients with stage 3 and 4 HIV disease, and fungal skin and nail infections are major causes of morbidity in HIV-infected individuals. However, mucosal candida infections usually readily respond to azole antifungal treatment and immune reconstitution with antiretroviral therapy (ART). In the era of ART, recurrent azole-resistant *Candida* spp infections are rare.

With widespread availability of ART and earlier testing and treatment for HIV, the incidence of systemic fungal infections has decreased in people living with HIV in high-income countries, although room for improvement remains.[3] By contrast, in many regions with high HIV prevalence, particularly sub-Saharan Africa, there is little evidence for a substantial decrease in cases.[4] Many patients present with advanced HIV and with a low CD4 cell count.[5] Additionally, enrolment data from cryptococcal meningitis trials show that, although the total number of cases was stable over time, half or more of patients with cryptococcal meningitis had taken ART[6] but had persistent low CD4 cell counts due to problems of retention in care and or ART resistance. Thus, further efforts to address the problem of fungal infections through rapid point-of-care diagnostics for these major fungal pathogens and global access to antifungal drugs are needed as an integral part of an effective response to the HIV pandemic.

Pneumocystis pneumonia

Epidemiology

Pneumocystis pneumonia has emerged as a major cause of infection in those with HIV/AIDS, and is estimated to

Key messages

- Incidence of systemic fungal infections in patients with HIV/AIDS has decreased in many resource-rich areas after the introduction of antiretroviral therapy and earlier diagnosis and treatment of infection
- In many resource-limited settings incidence is not yet decreasing due to continued late diagnosis and challenges with retention in HIV care
- New PCR-based assays can distinguish colonisation from infection with pneumocystis
- Measurement of cerebrospinal fluid pressure is essential in cryptococcal meningitis, and management of raised cerebrospinal fluid pressure through careful therapeutic lumbar punctures reduces mortality
- In large parts of the world, HIV-related histoplasmosis is often neglected, undiagnosed, or misdiagnosed as tuberculosis, because of poor access to current diagnostics
- The intersection with HIV has transformed *Talaromyces marneffei* from a rare human pathogen to a major cause of HIV-associated death in southeast Asia; amphotericin B was shown to be superior to itraconazole as initial treatment in a large randomised trial
- Novel, affordable, point-of-care diagnostics for pneumocystis, histoplasmosis, and talaromycosis, and wider access to effective antifungals are urgently needed to reduce the burden of HIV-associated fungal infections in resource-limited settings

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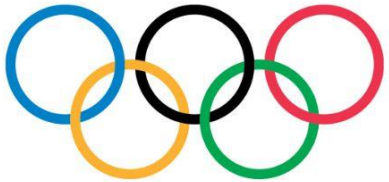
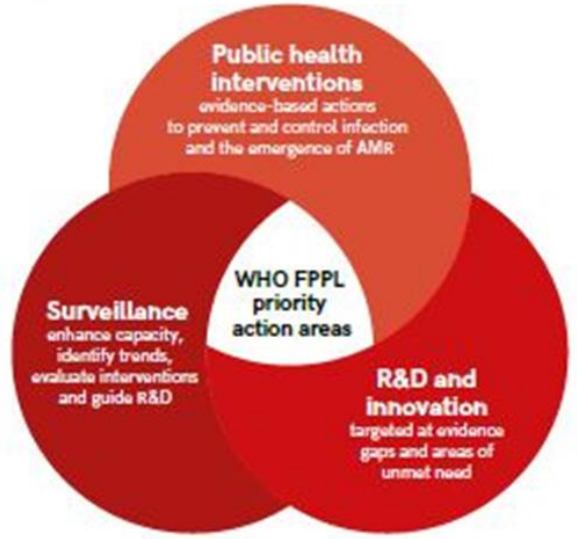
WHO first list of health-threatening fungi (2022)
→ Histoplasma listed among the top priority fungal diseases



WHO fungal priority pathogens list

Critical group	High group	Medium group
Cryptococcus neoformans	*Nakaseomyces glabrata (Candida glabrata)*	*Scedosporium* spp.
Candida auris	*Histoplasma* spp.	*Lomentospora prolificans*
Aspergillus fumigatus	Eumycetoma causative agents	*Coccidioides* spp.
Candida albicans	Mucorales	*Pichia kudriavzeveii (Candida krusei)*
	Fusarium spp.	*Cryptococcus gattii*
	Candida tropicalis	*Talaromyces marneffei*
	Candida parapsilosis	*Pneumocystis jirovecii*
		Paracoccidioides spp.

Fig. 2. Proposed priority areas for action



AMR: antimicrobial resistance; R&D: research and development; WHO FPPL: World Health Organization fungal priority pathogens list.

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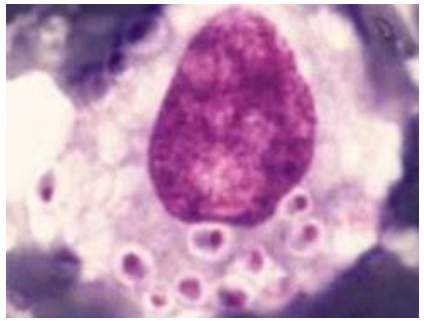
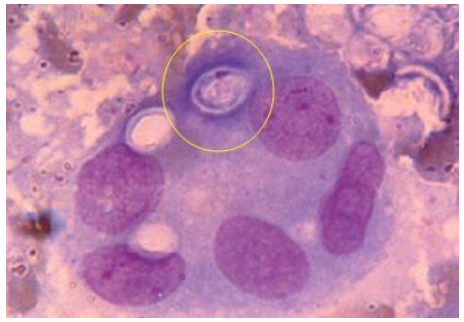
Histoplasma capsulatum: a dimorphic pathogen

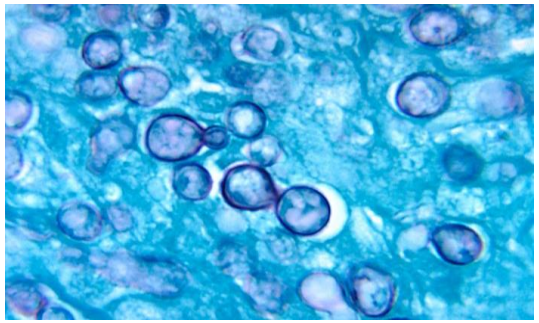
Two Histoplasma varieties are pathogen for humans

Histoplasma capsulatum* var. *capsulatum **« *American* histoplasmosis»**



Histoplasma capsulatum* var. *duboisii **« *African* histoplasmosis »**





Recent knowledge on molecular epidemiology showed geographic and genetic overlap between species, and distribution overlap of human cases…

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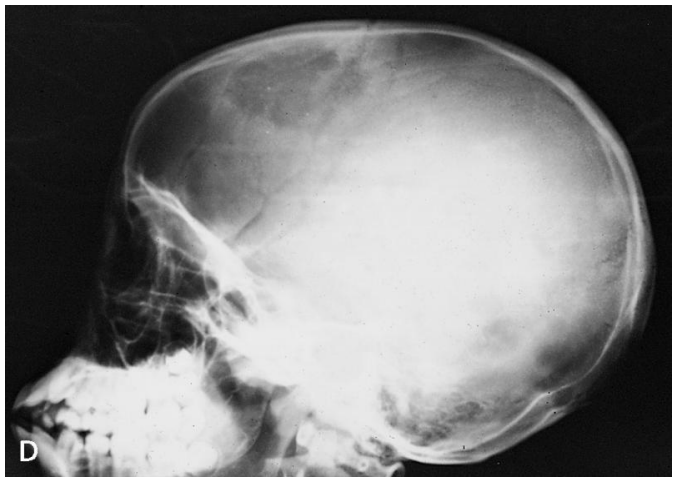
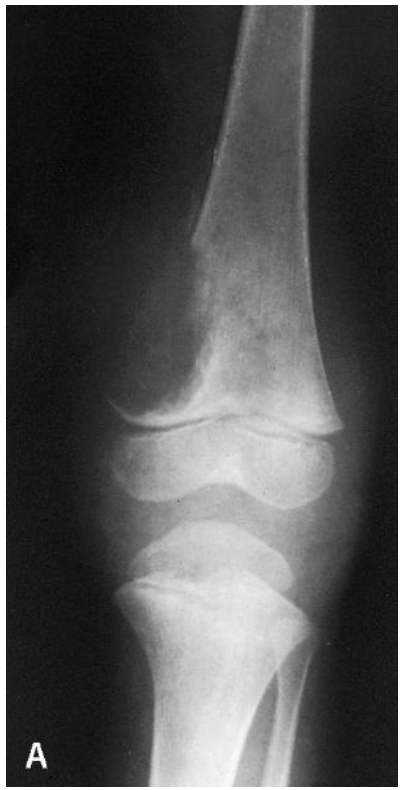
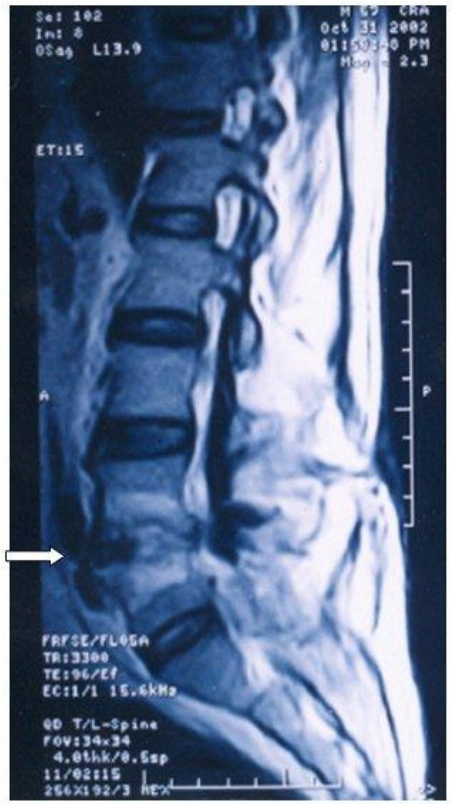
« African Histoplasmosis »

Peculiar phenotypic features in mycology and clinical features upon examination

→ Caseus granuloma in bones, lymphnodes and exophytic cutaneous features







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« African Histoplasmosis »

To date, not considered as an AIDS-defining condition…

Médecine et Santé Tropicales 2018 ; 28 : 255-256

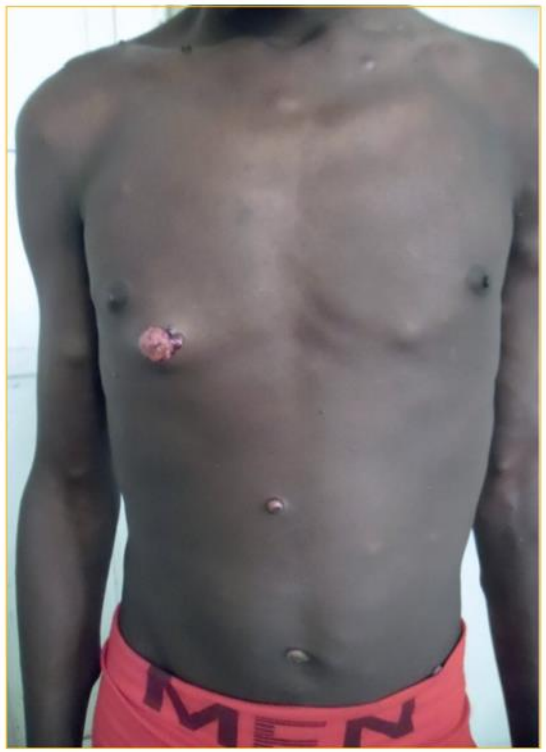
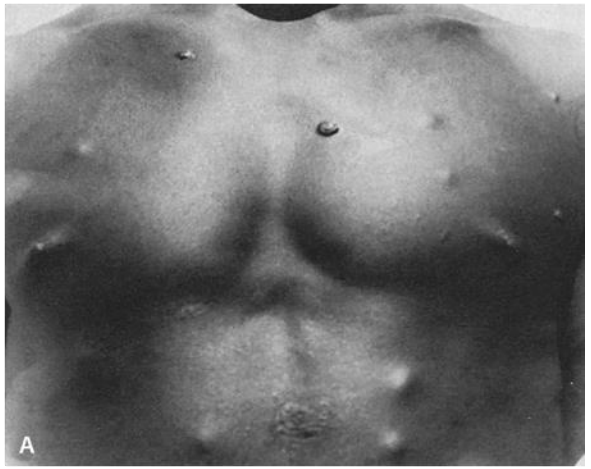


Figure 1. Papule ombiliquée, nodule sous-mammaire charnu et sous-cutané.
Figure 1. *Umbilical papule, fleshy subcutaneous nodule and subcutaneous.*



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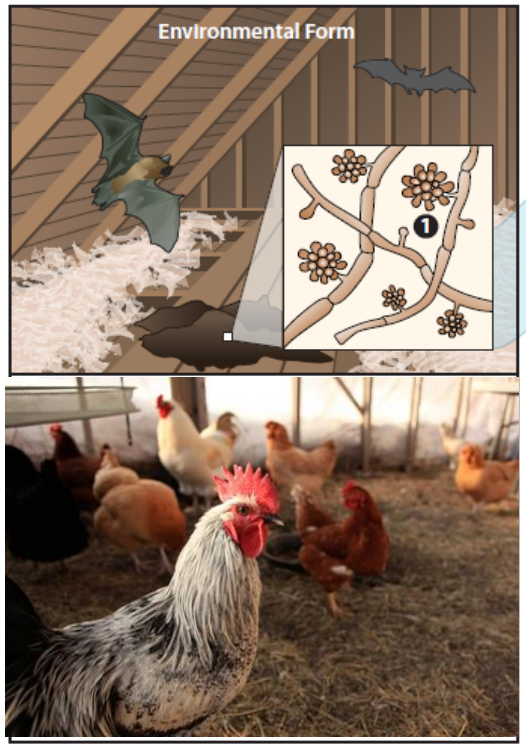
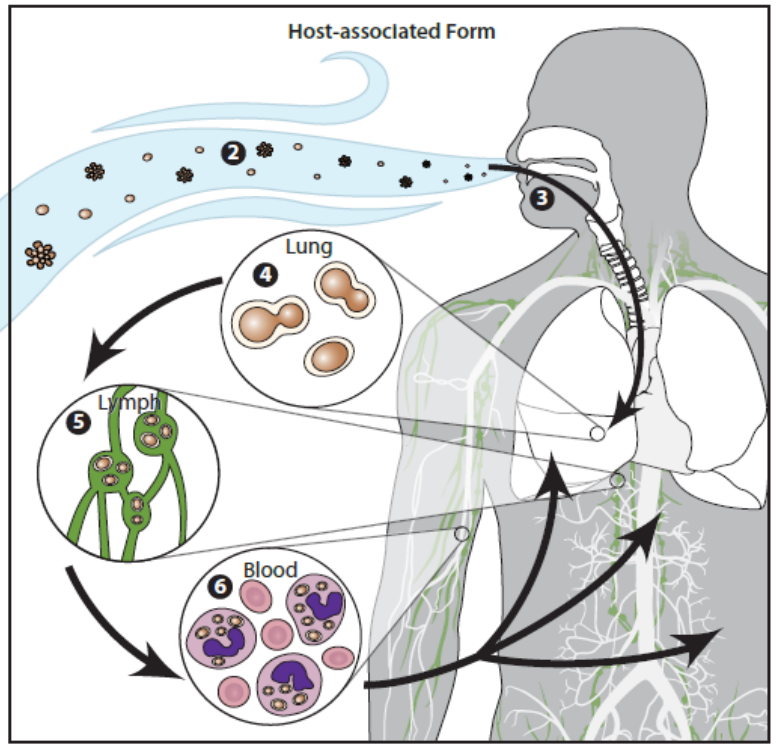
« American Histoplasmosis »

Histoplasmosis is primarly a pulmonary disease

Mostly airborne acquired by inhaling spores from the environment

Airborne >>>>>>>>>> Transplant-derived >>>>>>>>>>>>> Vertical transmission





Source : http://www.cdc.gov/fungal/histoplasmosis/causes.html, 19/11/2013

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Risk factors: environmental and host-related

Occupational activities:
→ **Any activity exposing to dust contaminated with *Histoplasma***
(construction/demolition, agriculture, forestry, hunting industries, archelologists, lab workers etc.)

Recreational activities: visiting caves, spelunking, chicken coop etc.

Underlying condition or therapy with an impact on immunity (non specific and cellular)
(CD4 count level <200, COPD, diabetes, malignancies, corticosteroids, biotherapy etc.)

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Independant predictors of first episode in PLHIV

Table 2. Independent predictors of a first episode of disseminated histoplasmosis in a cohort of HIV-infected patients in French Guiana: 1996–2008.

Variable	Incidence rate (per 100 person-years)	Crude hazard ratio	Adjusted hazard ratio* (95% CI)	*P*
Age (years)				
18–30	0.9	1	1	
31–40	2.1	2.7 (1.5–4.6)	1 (0.5–1.9)	0.9
41–60	1.4	1.8 (1–3.2)	0.8 (0.4–1.6)	0.6
61-max	1.2	1.5 (0.7–3.7)	0.9 (0.3–2.6)	0.8
Sex				
Men	2.1	1.4 (1.2–1.7)	1.4 (1.1–1.7)	0.004
Women	1			
CD4 count (per mm3)				
[0–50[	11.8	118.8 (29–485)	47.2 (5.8–380)	<0.001
[50–200[	2.4	23.8 (5.7–98.6)	16.9 (2.2–128)	0.006
[200–350[	0.6	6.1 (1.4–27)	7.1 (0.9–55)	0.06
[350–500[	0.1	1.1 (0.1–7.8)	1.8 (0.16–20)	0.6
[500-max]	0.1	1	1	
CD4 nadir <50/mm3				
Yes	4.7	2.1 (1.1–3.9)	1.9 (1–3.6)	0.05
No	0.6			
CD8 count in the lowest quartile (<643 per mm3)				
Yes	3.5	1.9 (1.3–2.7)	1.8 (1.2–2.9)	0.008
No	0.7			
Antiretroviral treatment				
Yes	0.7	0.4 (0.2–0.5)	0.2 (0.1–0.4)	<0.001
No	2.4			
First six months of antiretroviral treatment				
Yes	11.1	2.8 (2–4)	2.4 (1.1–5)	0.01
No	2.3	0.7 (0.5–0.9)	0.5 (0.2–0.9)	0.03
No treatment	3.9	1		
History of herpes				
Yes	17.1	10.3 (5.7–18.6)	6.4 (3.1–13.2)	<0.001
No	1.4			
History of Pneumocystosis				
Yes	8.7	4.3 (1.8–10.6)	0.1 (0.0–0.5)	0.003
No	1.4			

*Cox multiple model in HIV positive patients with first episode of disseminated histoplasmosis as failure event. Model with 1404 subjects and 94 single failures.
doi:10.1371/journal.pntd.0002638.t002

Nacher & al., PlosNTDs, 2014

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Independant predictors of deaths in PLHIV

Table 4. Predictors of death within 6 months in HIV infected patients with disseminated histoplasmosis in French Guiana: 1996–2008.

Variables	Crude hazard ratio (95% CI)	Adjusted hazard ratio* (95% CI)	*P*
Male gender	1.9 (1.3–2.7)	1.9 (1.2–3)	0.005
Antiretroviral treatment	0.1 (0.0–0.5)	0.2 (0.0–0.5)	0.003
CD8 count in the lowest quartile (<643 per mm3)	9.6 (4–22.6)	4.3 (1.1–7.5)	0.002
CD4<50 per mm3	30 (13–67)	14.6 (5.7–37)	<0.001

*Cox model in HIV positive patients with disseminated histoplasmosis with death at 6 months as failure event adjusted for sex, antiretroviral treatment, CD4 count (below 50/mm3 or not) and CD8 count (below first quartile or not). Oral fluconazole or cotrimoxazole were not significantly linked to outcome, and thus removed from the final model with 156 subjects and 28 failures.

doi:10.1371/journal.pntd.0002638.t004

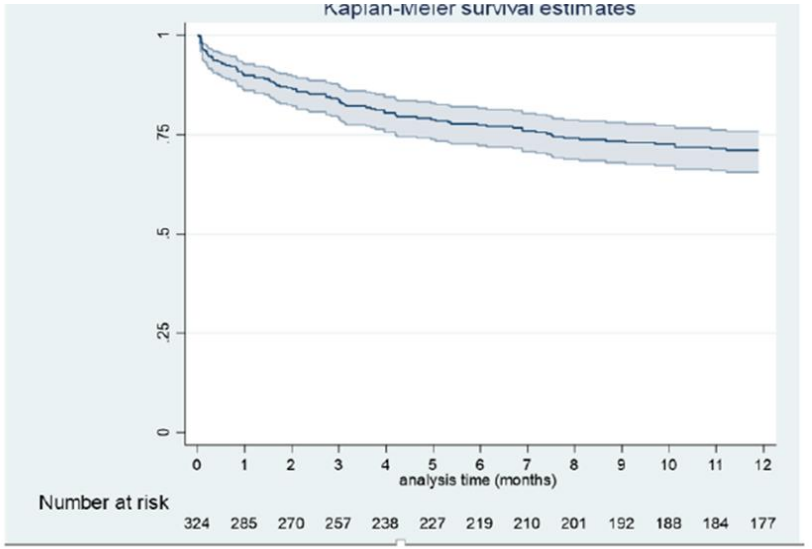

Figure 1. Survival curves for the first 12 months for HIV-associated disseminated histoplasmosis in French Guiana.

Nacher & al., PlosNTDs, 2014

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Wide spectrum of populations at-risk for histoplasmosis

General population
→ children/elderly, workers at-risk, transplant donors, travelers to endemic areas

Primary / Monogenic Immunodeficiencies

Autoimmune diseases

Solid organ and hematopietic cell transplant recipients

People receiving immunosuppressive therapy (Corticosteroids, TNF-α blocker, etc.)

People living with HIV/AIDS (PLHIV)

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Wide spectrum of clinical features and disease burden depending on the level of exposure and the patient's underlying condition

« Immunocompetent »

Clinical profil and outcome

- **Asymptomatic (>90%)**
- **Flu-like syndrome**
- Disseminated, severe (large incoulum, infants)
- Chronic with potential severe sequellae (elderly)
- Mortality (rare)

Diagnosis most often fortuitous

- Isolated pulmonary nodule
- Serology +/- PCR

Treatment

- **Self-limited disease is the rule**
- Oral or IV according to severity

« Immunosuppressed »

Clincal profil and outcome

- **Disseminated (#90%), CD4<200**
- Acute pulmonary
- **Severe (10-20%)** (Hemophagocytosis)
- **Mortality (<10-70%)**

Diagnosis*

- Direct & culture (tissues/fluids)
- Antigen detection +/- PCR

Treatment**

- Non severe (Itraconazole)
- Moderate to severe (Lip. Ampho. B)

* Gold standard relies on conventional methods according to EORTC/MSG criteria (Donnelly, CID, 2020)
** IDSA Guidelines (Wheat, CID, 2007)

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Latest histoplasmosis case definition

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium

Histoplasmosis case definition:

- **Proven:** Positive histopathology or culture.
  - Serology and molecular testing not applicable
- **Probable:** Negative histopathology or culture, with environmental exposure to the fungus, a compatible clinical illness, and positive antigen test.
- **Possible:** not applicable

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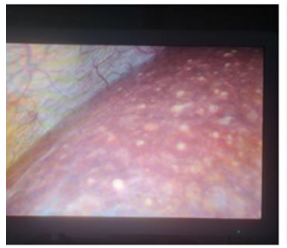
Proven histoplasmosis
Conventional mycology as the reference for the diagnosis

Out of blood culture, diagnosis relies on conventional fungal direct examination and culture of samples issued from invasive procedures

BSL level 3 facilities

Median time to culture = 2 weeks [1-6]



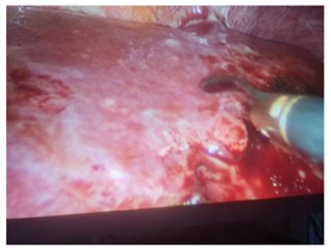
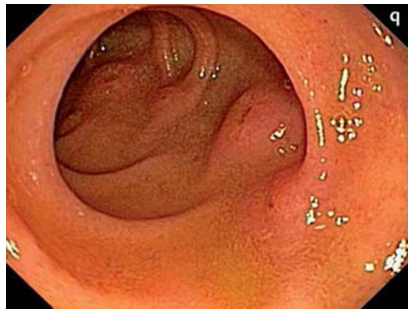
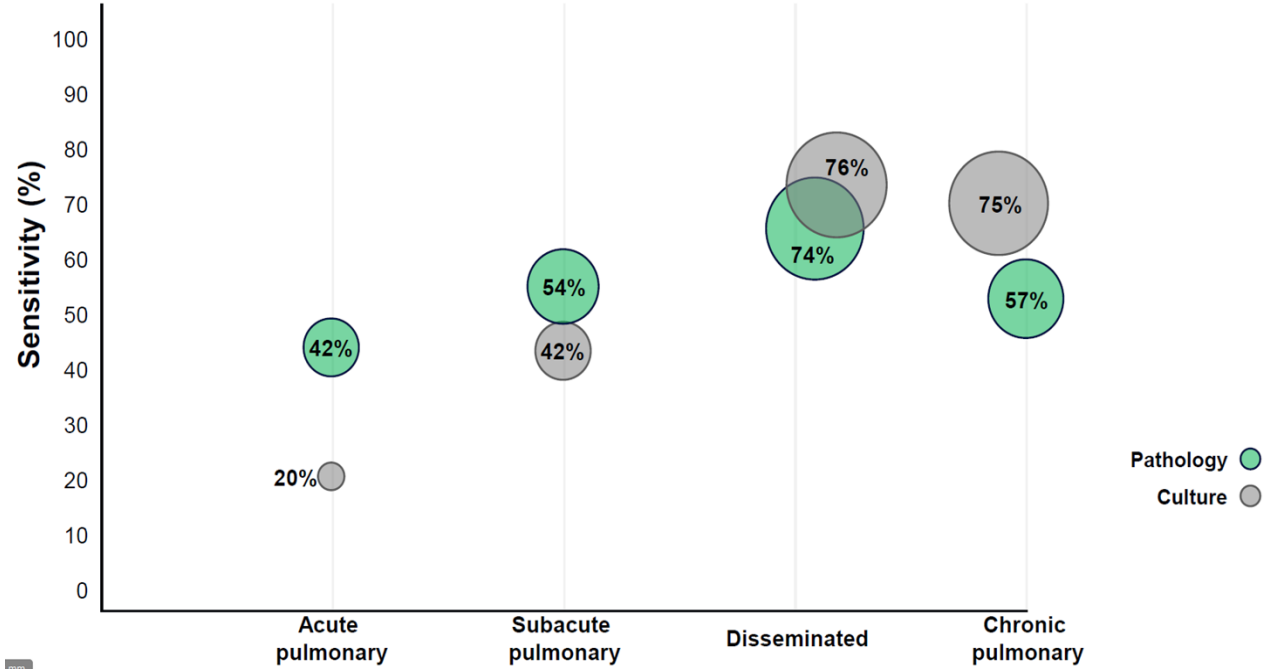


Figure 2. Laparoscopic view (2× magnification) of liver appearance and biopsy sampling of liver tissue that is infiltrated by small yellowish nodules.



Sensitivity of the "Gold standards" for histoplasmosis



Hage et all. Semin Respir Crit Care Med. 2015 Oct;36(5):729-45.

Source: In approval with D. Caceres

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Probable histoplasmosis
Antigen detection and molecular biology on the rise

Antibody detection systems
- Immunodiffusion

meridian BIOSCIENCE

Microbiologics Gibson Bioscience

- Immunodiffusion
- Complement fixation

IMMY

Antigen detection systems
- Ag EIA and Ag LFA

IMMY MiraVista DIAGNOSTICS Rapid Fungal Testing. Accurate Results.

OIDx

- (1–3)-β-D-glucan

Fungitell (1→3)-β-D-Glucan Assay

FUJIFILM Value from Innovation

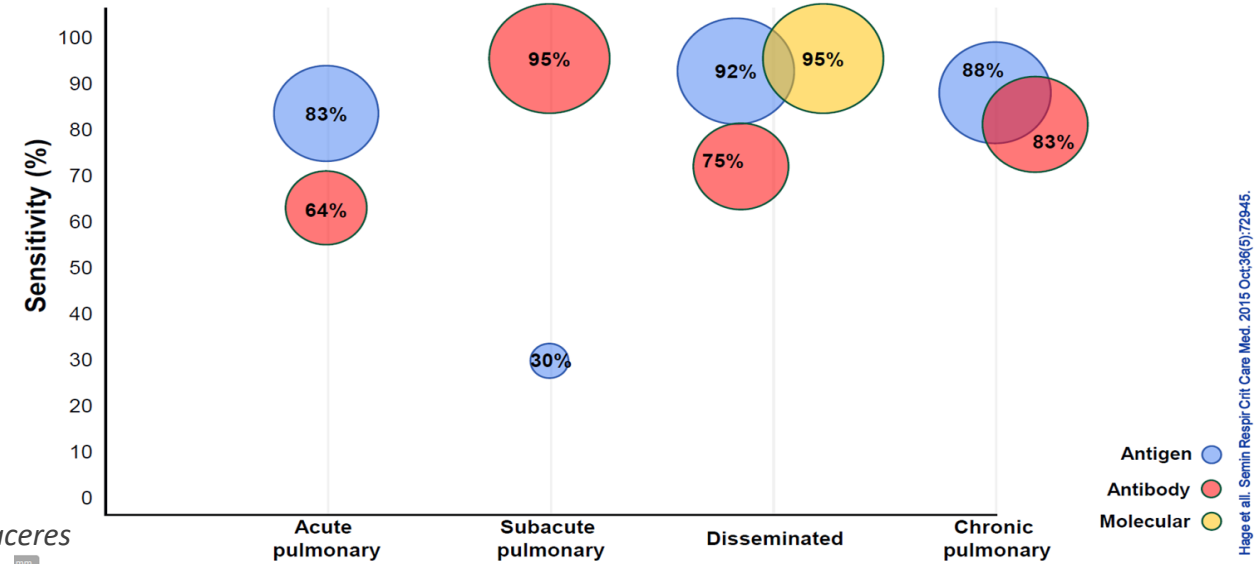
DNA detection systems
- AccuProbe: Nucleic acid hybridization tests for culture identification

HOLOGIC

Company	ELISA (sensitivity / accuracy)	LFA (sensitivity / accuracy)
IMMY	Sensitivity: 98% Accuracy: 97% Ref. 1	No available
MiraVista DIAGNOSTICS Rapid Fungal Testing. Accurate Results.	Sensitivity: 96% Accuracy: 82% Ref. 2 In house, no available as commercial kit	Sensitivity: 96% Accuracy: 96% Ref. 2
OIDx	Sensitivity: 92% Accuracy:51% Ref. 3	Kit available. No data of validation studies

1. IMMY: https://pubmed.ncbi.nlm.nih.gov/29563205/ 2. Miravista: https://pubmed.ncbi.nlm.nih.gov/34682221/
3. OIDx: https://pubmed.ncbi.nlm.nih.gov/34802111/

Sensitivity of the "mycological evidence" for histoplasmosis



Hage et all. Semin Respir Crit Care Med. 2015 Oct;36(5):72945.

Source: In approval with D. Caceres

First description of histoplasmosis

« ..in a case that appeared to be a miliary tuberculosis .. »

APRIL 28, 1906. *PROTOZOON INFECTION—DARLING.* 1283

Clinical Notes, New Instruments, Etc.

A PROTOZOÖN GENERAL INFECTION PRODUCING PSEUDOTUBERCLES IN THE LUNGS AND FOCAL NECROSES IN THE LIVER, SPLEEN AND LYMPHNODES.

SAMUEL T. DARLING, M.D.
Pathologist, Ancon Hospital.
ANCON, CANAL ZONE, ISTHMUS OF PANAMA.

On Dec. 7, 1905, while examining smears from the lungs, spleen and bone marrow in a case that appeared to be miliary tuberculosis of the lungs, I found enormous numbers of small bodies generally oval or round. Most of them were intracellular in alveolar epithelial cells, while others appeared to be free in the plasma of the spleen and rib marrow. Tubercle bacilli were absent. The following is an account of the case:

Patient.—C. D., negro from Martinique, aged ..., occupation carpenter; address, ..., a village in the Canal Zone.

History.—The patient had been a resident of the zone three months. While in Martinique he had suffered from some mental disturbance. His present illness dates from Sept. 15, 1905, when he complained of fever and vomiting.

Condition on Admission to Hospital.—On entering Ancon Hospital Dec. 5, 1905, he was mildly delirious and incoherent. Lungs were clear; abdomen was scaph... larged.

Blood: Negative for malarial parasite...
Hemoglobin: 60 per cent. (Dare's).
Feces: Negative.
Temperature: On admission, Dec. 5... pulse 120; Dec. 6, 8 a. m., 95, pulse 96; 4...

circular ulcers from 2 to 4 mm. in diameter in the cecum and ileum.

The mesenteric lymphnodes and those at the hilum of spleen were enlarged and pale.

Bacteriologic Examination.—Spleen smears were negative for malarial parasites or pigment. Oval and round bodies were free in the plasma.

In rib bone marrow smears there were traces of intracellular malarial pigment. A number of bodies similar to those in the spleen were seen.

In lung smears tubercle bacilli were absent.

There were myriads of intracellular and extracellular bodies similar to those found in the spleen and the marrow.

A moist coverslip preparation from intestinal ulcers showed motile ameba.

Anatomic Diagnosis.—Acute miliary tuberculosis, pulmonary type. Tuberculous lymphadenitis, peribronchial. Chronic interstitial splenitis. Atrophic cirrhosis. Chronic interstitial nephritis, slight. Lymphadenitis, mesenteric. Chronic leptomeningitis. Edema of pia-arachnoid. Ulcerative enterocolitis. Amebiasis. General infection by protozoön.

APPEARANCE OF THE PARASITE IN SMEARS.

Lung: This specimen was stained by carbolfuchsin and Gabbet's methylen blue, overstained with polychrome methylen blue, and washed with eosin.

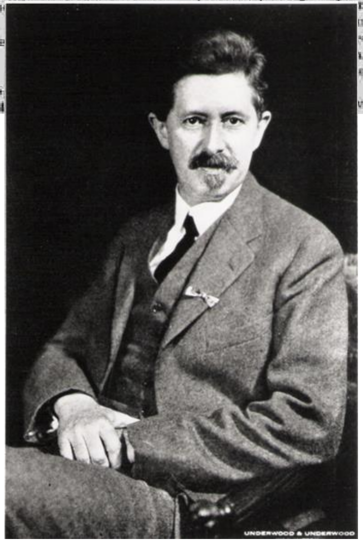
The polychrome blue was prepared as follows:

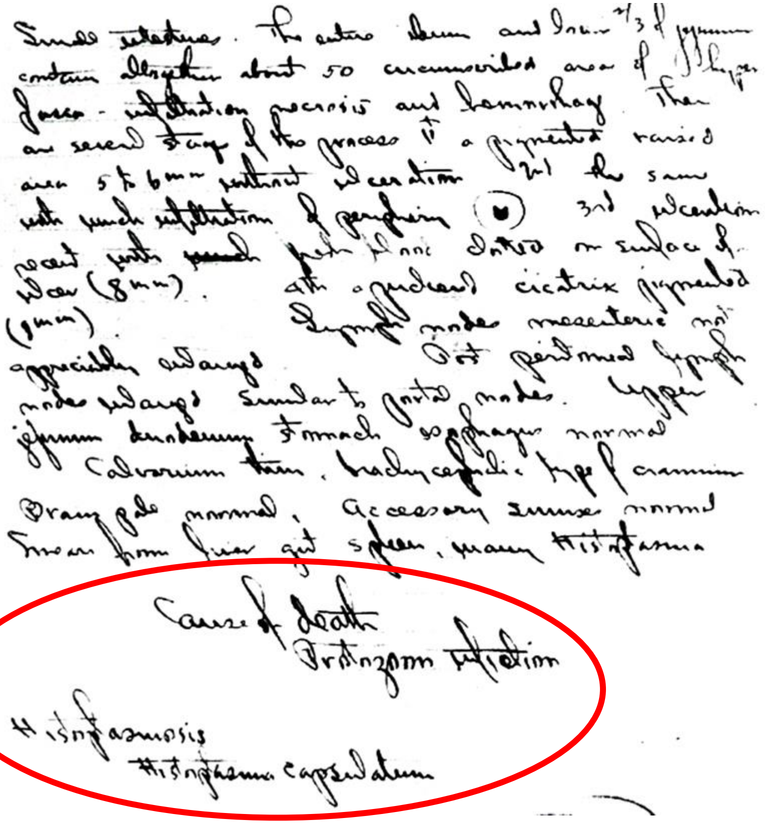
Methylen blue, pure, medic, Grüb	g.	1.
Sodium carbonate, pure	g.	.5
Distilled water	g.	100.

This was placed in thermostat one week, and kept at room ... months.

...ue was removed by washing the smear ...oholic solution of eosin (.5 per cent. in ...lcohol) one second and distilled water a ...e internal structure of the parasite showed ...

...viform or round, and is surrounded by a





Source : Darling S.T., Journal of the American Medical Association, 1906

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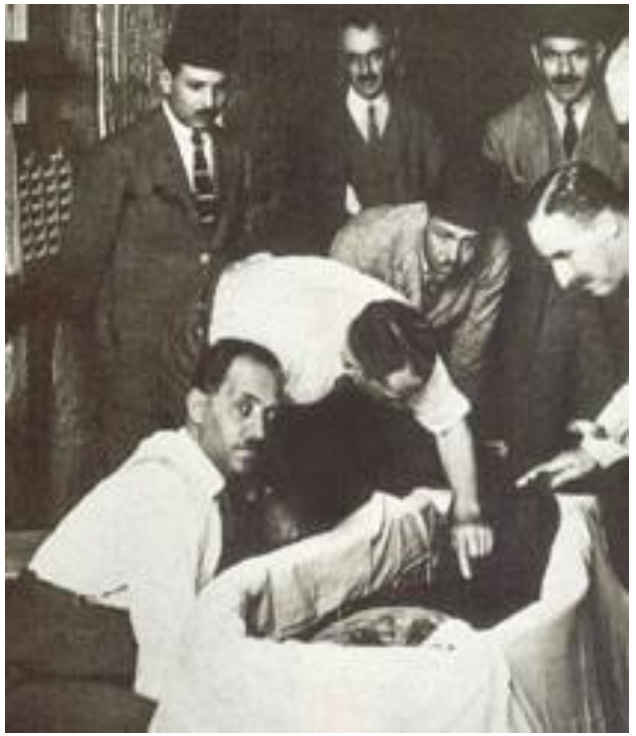
Histoplasmosis as a « mysterious killer »
« The pharaoh's curse »… A controversial theory



***Sir Howard Carter*, 1922**
Discovery of the Tutankhamun tomb

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From a rare uniformly fatal disease in childs & elderly to an ubiquitous mostly non fatal disease

Public Health Reports

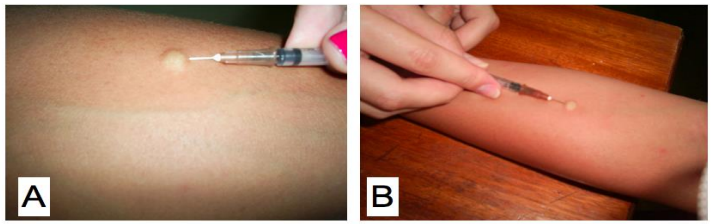
Vol. 63 • MARCH 5, 1948 • *No. 10**

Printed With the Approval of the Bureau of the Budget as Required by Rule 42 of the Joint Committee on Printing

A REPORT ON TEN PROVED CASES OF HISTOPLASMOSIS [1]

By IVAN L. BUNNELL, *Senior Assistant Surgeon, and* MICHAEL L. FURCOLOW, *Surgeon, United States Public Health Service*

Histoplasmosis has been considered a rare, uniformly fatal disease. Only 74 cases had been reported by January 1945 (*1*) and at the present time the total number of cases reported is less than 100. The true prevalence of the disease is unknown, but it is suspected that the disease in some form occurs more frequently than the number of reported cases would indicate; a mild, nonfatal form of histoplasmosis may be widely prevalent (*2, 3*). Furthermore, whenever intensive search for the disease has been made, a marked increase in the number of reported cases has resulted. This occurred in Ann Arbor (*1*), Nashville (*4*), and is now true in Kansas City.



Public Health Reports

Vol. 64 • JULY 15, 1949 • *No. 28*

Isolation of *Histoplasma capsulatum* From Soil

By C. W. EMMONS*

Another mycosis which appears to be noncontagious, sporadic, and world-wide in distribution is histoplasmosis. Whether one speaks of proved histoplasmosis which, so far as is definitely known, is relatively rare and almost always fatal, or of a hypothetic mild form of the disease associated with pulmonary calcification, the source of the infectious agent and the mode of human infection have been unknown. Histoplasmosis has been recently shown to occur in wild rats in Virginia (*Rattus norvegicus*) (*8*) and in Georgia (*R. norvegicus* and *R. rattus*) (*9*), and in the skunk (*Spilogale putorius*) (*9*). A total of 24 rats with histoplasmosis have now been collected in Virginia (*6*). No association between infected animals and histoplasmosis in man has been found in this area to date, and the relationship of rodent to human infection remains obscure. Indeed, the very limited extent of the lesions and the apparent chronicity of the disease in naturally infected rats in which histopathologic studies were made do not suggest any mode of transfer directly from rats to man (*7*). The character-

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High levels of human exposure described worldwide

→ *asymptomatic or pauci symptomatic cases, few deaths*

THE AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGIENE
Vol. 20, No. 2

Printed in U.S.A.

WORLDWIDE PATTERN OF SKIN SENSITIVITY TO HISTOPLASMIN

PHYLLIS Q. EDWARDS AND ELIZABETH L. BILLINGS
Tuberculosis Branch, Center for Disease Control, U.S. Public Health Service, Atlanta, Georgia 30333

FIGURE 1. Worldwide pattern of histoplasmin sensitivity in human populations.

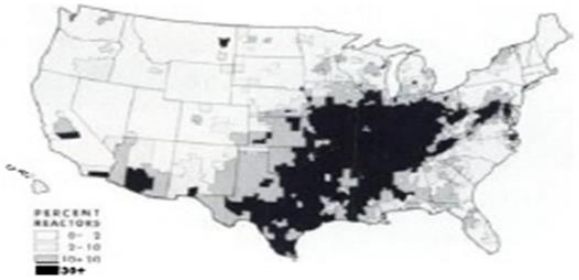

FIGURE 2. Histoplasmin sensitivity in U.S. Navy recruits, 1958–1964, by county of lifelong residence.

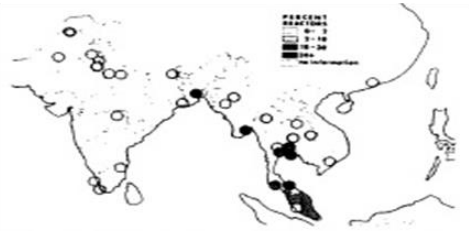

FIGURE 7. Histoplasmin sensitivity in southeast Asia

FIGURE 3. Histoplasmin sensitivity in Central and South America.

children living in the western side of a particular city than in the eastern side. Soil samples were collected from all over the city. *H. capsulatum* was isolated from only one of several hundred samples, and that one positive soil was from the eastern side, the low prevalence side, of town. Suppose the positive sample had been from the high prevalence side of town, as might have been expected; would it have been thought that the point source of infection had been found?

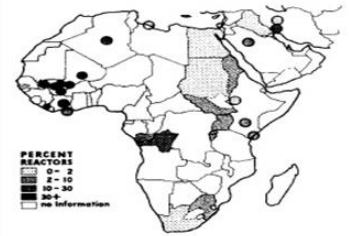

FIGURE 4. Histoplasmin sensitivity in Africa

FIGURE 5. Histoplasmin sensitivity in Europe

Where do the vast numbers who become infected but do not develop clinical disease get their infections? A number of possibilities are represented schematically in Figure 8. Each block could represent several square miles. The shaded spots represent areas where the soil contains the fungus. Two of the blocks depict the extremes in a broad range of possibilities, from no fungus whatever—A, to soil literally carpeted with it—F. Blocks B, C, D, and E show different numbers of foci, varying in size and in the pattern of coverage. Whether the people who live in each block are likely to become infected could well

FIGURE 6. Histoplasmin sensitivity in Italy

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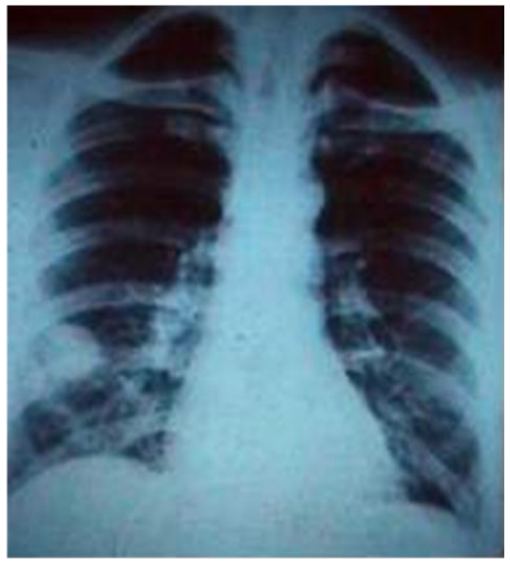
And then came the HIV/AIDS pandemic…

→ From outbreaks in the gen. pop. to histoplasmosis recognized as an AIDS-defining condition in its extrapulmonary form (1987)



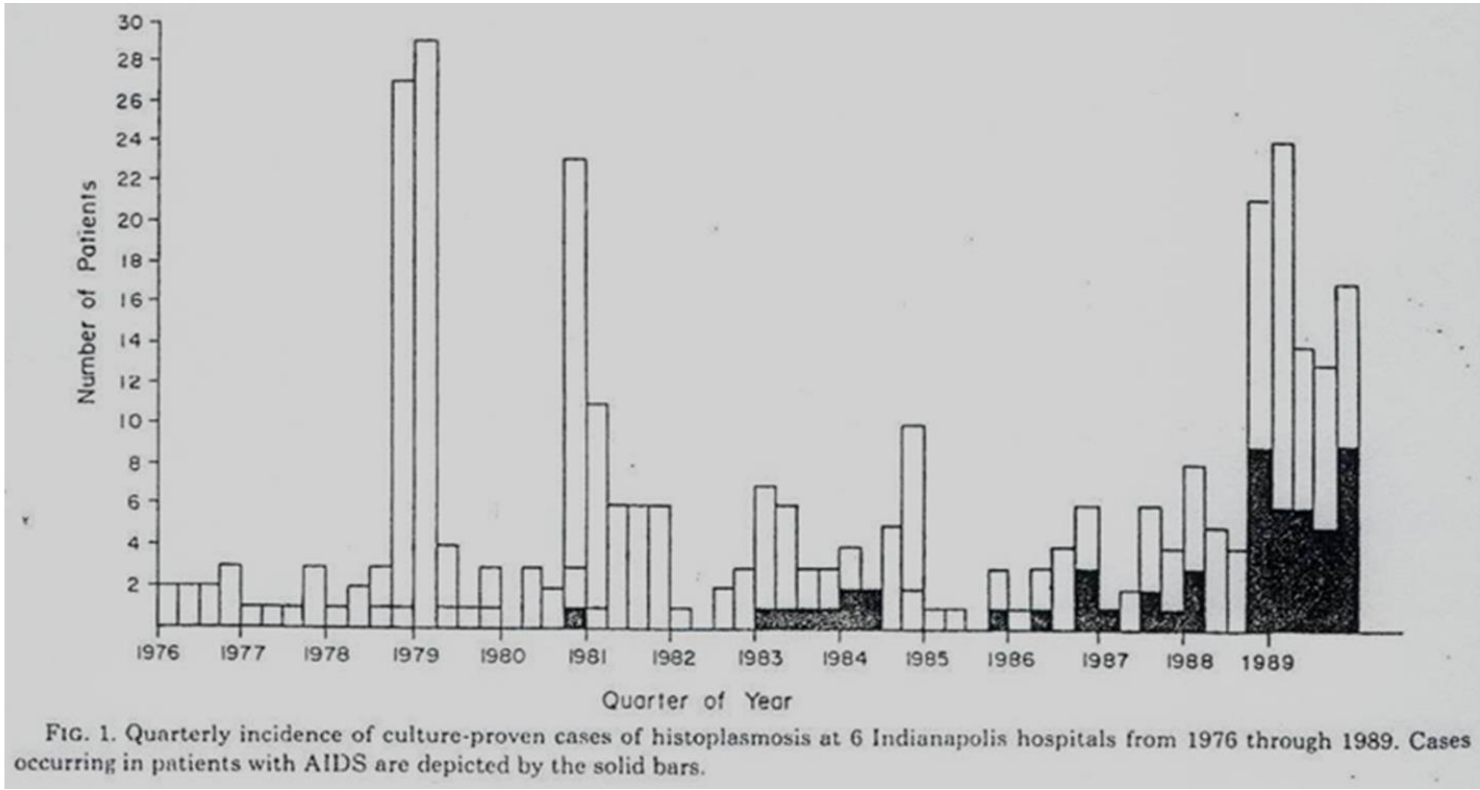


FIG. 1. Quarterly incidence of culture-proven cases of histoplasmosis at 6 Indianapolis hospitals from 1976 through 1989. Cases occurring in patients with AIDS are depicted by the solid bars.

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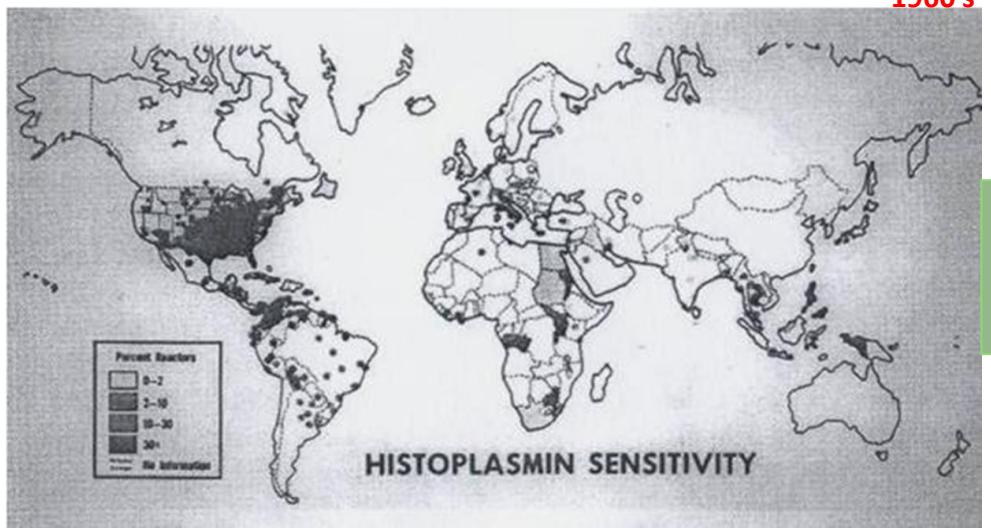
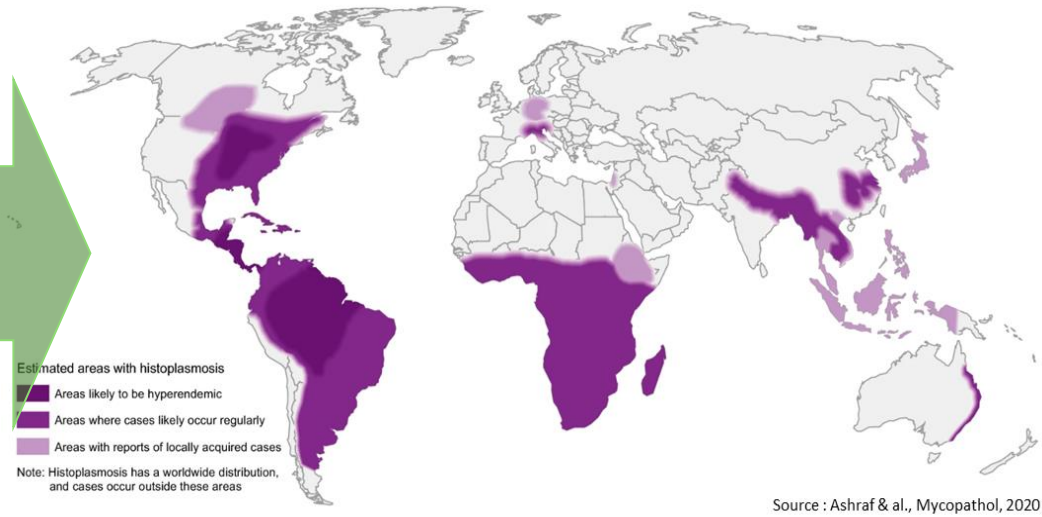
« Classics » on the burden of disease

1960's



2020's



Source : Ashraf & al., Mycopathol, 2020

1st respiratory fungal infection worldwide

Up to 90% of children exposed at 15 years of age in endemic areas

>20% of the USA population exposed during their lifetime

5% of the world population exposed

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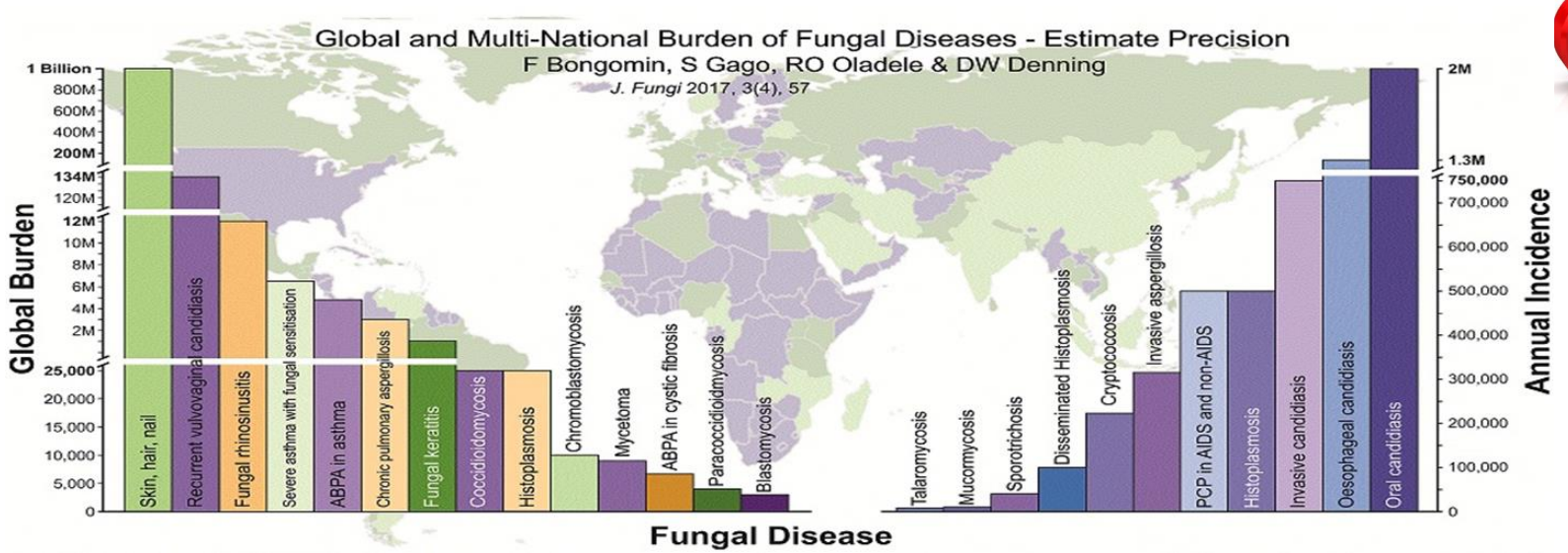
To date, the global burden remains unknown



500,000 new cases/y with 100,000 cases in PLHIV and 80,000 deaths

25,000 new cases/y in the USA

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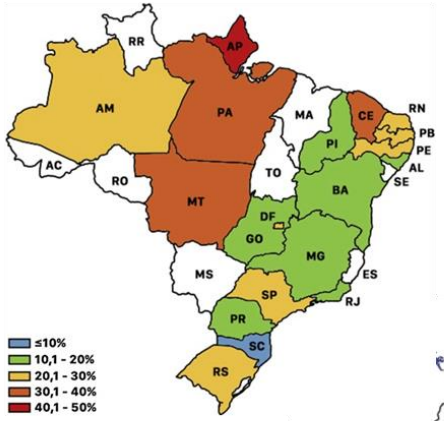
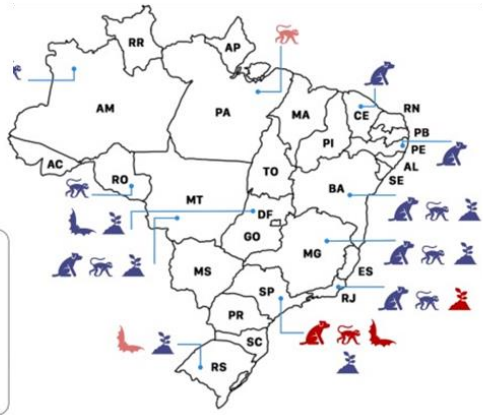
One health and wildlife exposure tell us more on the probable ubiquitous exposure of humans and its evolutions

The occurrence of histoplasmosis in Brazil: A systematic review

Marcos de Abreu Almeida[a], Fernando Almeida-Silva[a], Allan Jefferson Guimarães[b], Rodrigo Almeida-Paes[a], Rosely Maria Zancopé-Oliveira[a,*]

[a] Laboratório de Micologia, Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, RJ, Brazil
[b] Departamento de Microbiologia e Parasitologia, Universidade Federal Fluminense, Niterói, RJ, Brazil



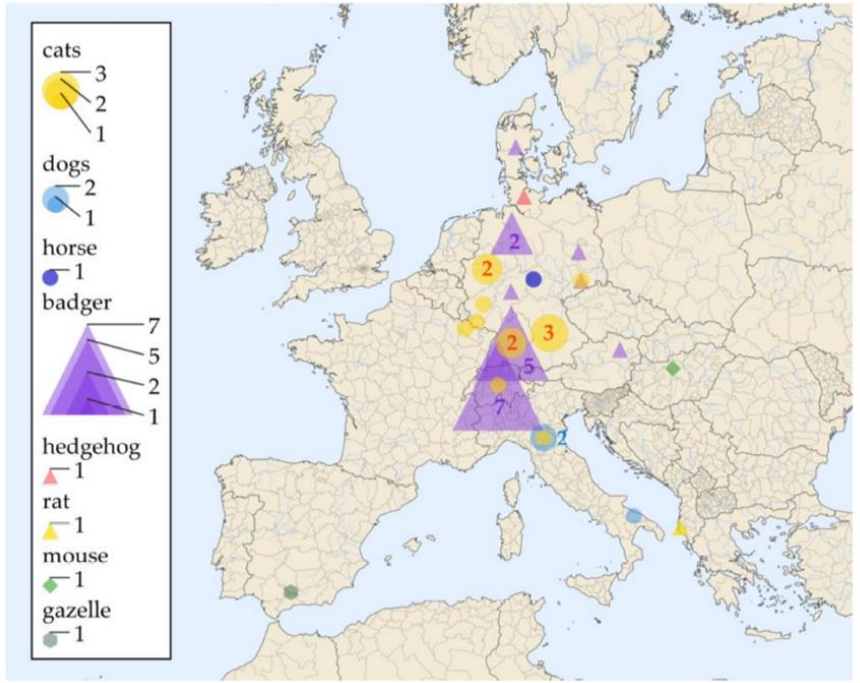


Animal Histoplasmosis in Europe: Review of the Literature and Molecular Typing of the Etiological Agents

2022

Dunja Wilmes [1,*], Ursula Mayer [2], Peter Wohlsein [3], Michael Suntz [4], Jasmin Gerkrath [1], Christoph Schulze [5], Ina Holst [6], Wolf von Bomhard [7] and Volker Rickerts [1]

Autochthonous histoplasmosis in animals in Central Europe



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Distribution shift in areas of endemicity with the global warming

Mapping *Histoplasma capsulatum* Exposure, United States

Amelia W. Maiga, Stephen Deppen, Beth Koontz Scaffidi, John Baddley, Melinda C. Aldrich, Robert S. Dittus, Eric L. Grogan

Integrating Public Health Surveillance and Environmental Data to Model Presence of *Histoplasma* in the United States

Staci A. Hepler,[a] *Kimberly A. Kaufeld,*[b] *Kaitlin Benedict,*[c] *Mitsuru Toda,*[c] *Brendan R. Jackson,*[c] *Xiaonan Liu,*[a] *and David Kline*[d]

Combine satellite imagery integrating land cover use (70%), distance to water (20%), and soil pH (10%)

Preferred soil environments for *Histoplasma* have migrated into the upper Missouri River basin

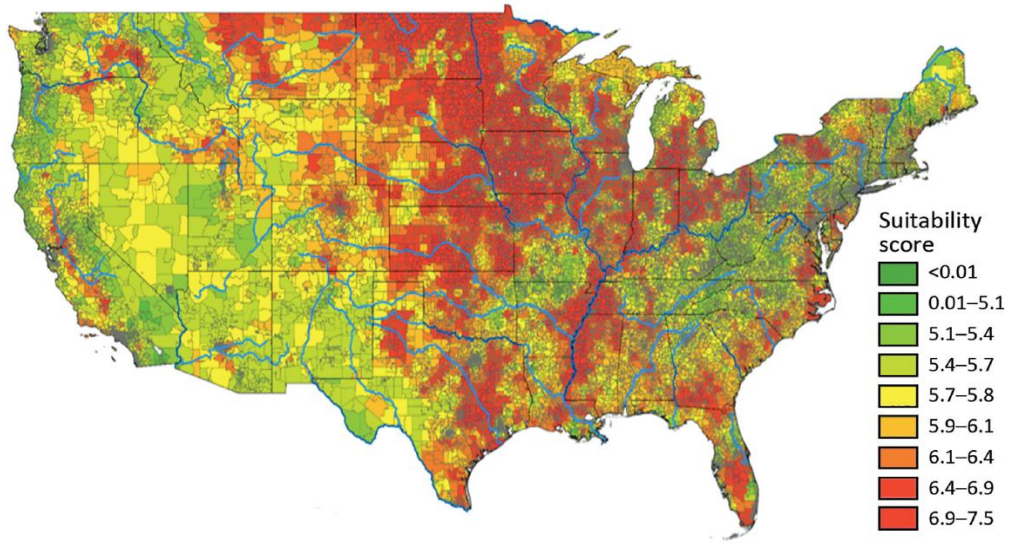
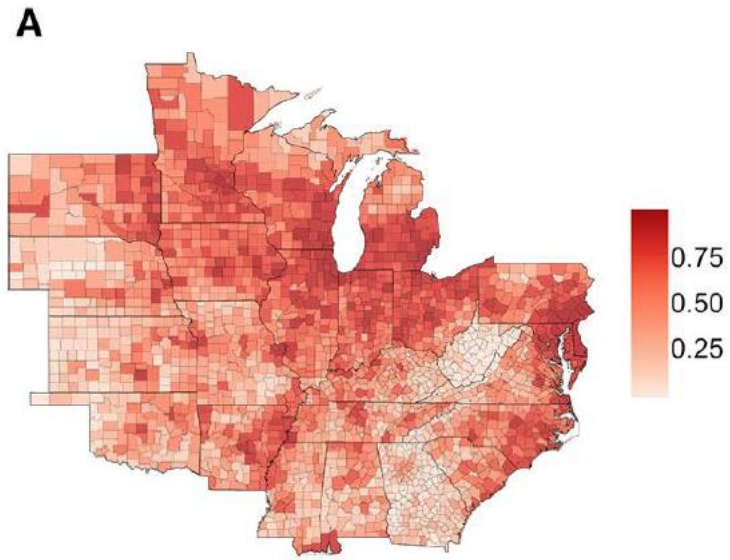


Figure 1. Mean *Histoplasma* site suitability score by US ZIP code. Red reflects greater histoplasmosis suitability; green reflects less suitability. The weighted mean score (Table) was calculated for each ZIP code. Data for geographic regions west of the Rocky Mountains are considered insufficient because of limited surface water data.



A distribution shift to Northern USA

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Time to revise common concepts

Histoplasmosis-Associated Hospitalizations in the United States, 2001–2012

Kaitlin Benedict,[1] Gordana Derado,[2] and Rajal K. Mody[1]

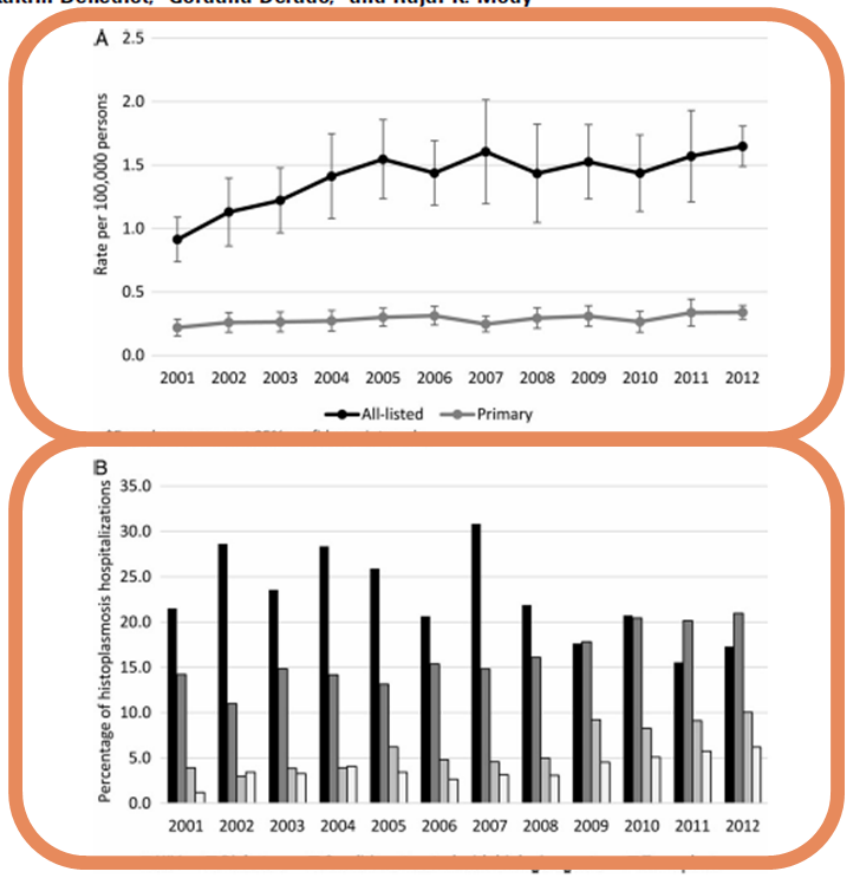

Figure 1. (A) Annual rates of all-listed and primary histoplasmosis-associated hospitalizations per 100 000 persons (*) and (B) percentage of all-listed histoplasmosis-associated hospitalizations with selected comorbidities, United States, 2001–2012. Abbreviation: HIV, human immunodeficiency virus.

Curr Trop Med Rep (2015) 2:70–80
DOI 10.1007/s40475-015-0044-0

TROPICAL MYCOSIS (D BOULWARE, SECTION EDITOR)

Histoplasmosis Infections Worldwide: Thinking Outside of the Ohio River Valley

Nathan C. Bahr[1,2] · Spinello Antinori[3] · L. Joseph Wheat[4] · George A. Sarosi[2,5]

Revising Conventional Wisdom About Histoplasmosis in the United States

Kaitlin Benedict, Mitsuru Toda, and Brendan R. Jackson
Mycotic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

1. **Histo disease burden relative to other dimorphics**
2. **Restricted areas of endemicity in the USA**
3. **Mandatory association with bird or bat droppings**

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What about histoplasmosis in Latin America?

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Histoplasma in soil and populations widely exposed

Publication N° 367 Juillet 1955 XVI° Année

ARCHIVES DE L'INSTITUT PASTEUR DE LA GUYANE FRANÇAISE ET DE L'ININI

L'histoplasmose de S. T. Darling (III)
Isolement de « H. capsulatum » à partir du sol en Guyane Française

par H. Floch et J. André

Mycopathologia
DOI 10.1007/s11046-012-9550-y

Histoplasma capsulatum in Cayenne, French Guiana

Olivier Moquet · Denis Blanchet · Stéphane Simon · Vincent Veron · Myriam Michel · Christine Aznar

2012

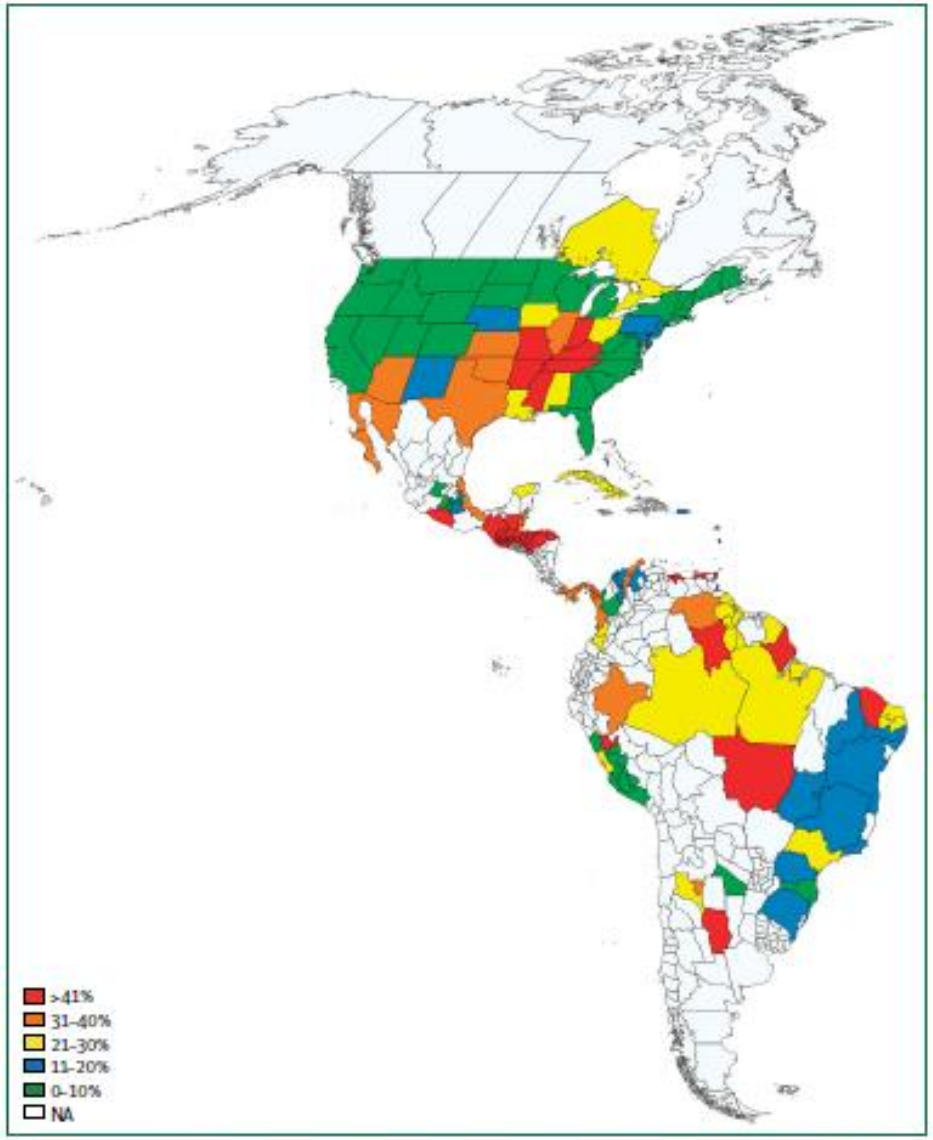

Figure 2: Frequency of positive intradermal reactions against histoplasmin in the Americas and the Caribbean
Data obtained from a review of 95 studies in 19 countries from 1949 to 2009.

F. Queiroz-Telles & al., LID, 2017

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HIV care and treatment remain challenging in Latin America
→ High % of late HIV diagnosis

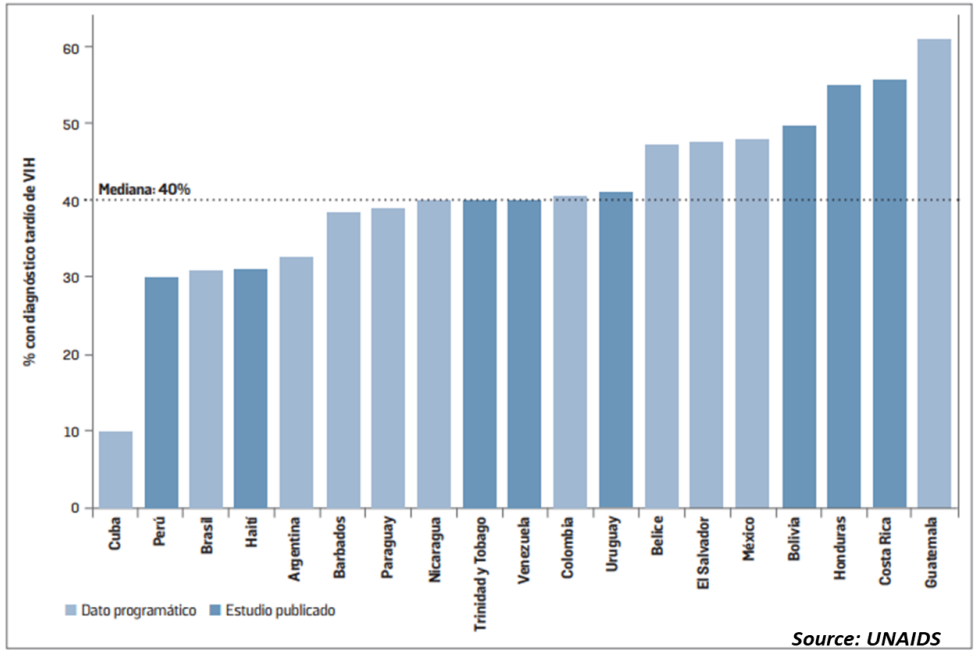
The HIV care continuum in Latin America: challenges and opportunities

Alicia Piñeirúa, Juan Sierra-Madero, Pedro Cahn, Rafael Napoleón Guevara Palmero, Ernesto Martínez Buitrago, Benjamin Young, Carlos Del Rio

Combination antiretroviral therapy (ART), also known as highly active antiretroviral therapy, provides clinical and immunological benefits for people living with HIV and is an effective strategy to prevent HIV transmission at the individual level. Early initiation of ART as part of a test and treat approach might decrease HIV transmission at the population level, but to do so the HIV continuum of care, from diagnosis to viral suppression, should be optimised. Access to ART has improved greatly in Latin America, and about 600 000 people are on treatment. However, health-care systems are deficient in different stages of the HIV continuum of care, and in some cases only a small proportion of individuals achieve the desired outcome of virological suppression. At present, data for most Latin American countries are not sufficient to build reliable metrics. Available data and estimates show that many people living with HIV in Latin America are unaware of their status, are diagnosed late, and enter into care late. Stigma, administrative barriers, and economic limitations seem to be important determinants of late diagnosis and failure to be linked to and retained in care. Policy makers need reliable data to optimise the HIV care continuum and improve individual-based and population-based outcomes of ART in Latin America.

Lancet Infect Dis 2015; 15: 833-39

Hubert Department of Global Health, Rollins School of Public Health of Emory University, Atlanta, GA, USA (A Piñeirúa MD, Prof C Del Rio MD); Instituto Nacional de Ciencias Medicas y Nutricion 'Salvador Zubiran', Tlalpan, Mexico (A Piñeirúa, J Sierra-Madero MD); Juan A Fernandez Hospital, Fundación Huésped, Buenos Aires, Argentina (P Cahn MD); Department of Infectious



Source: UNAIDS

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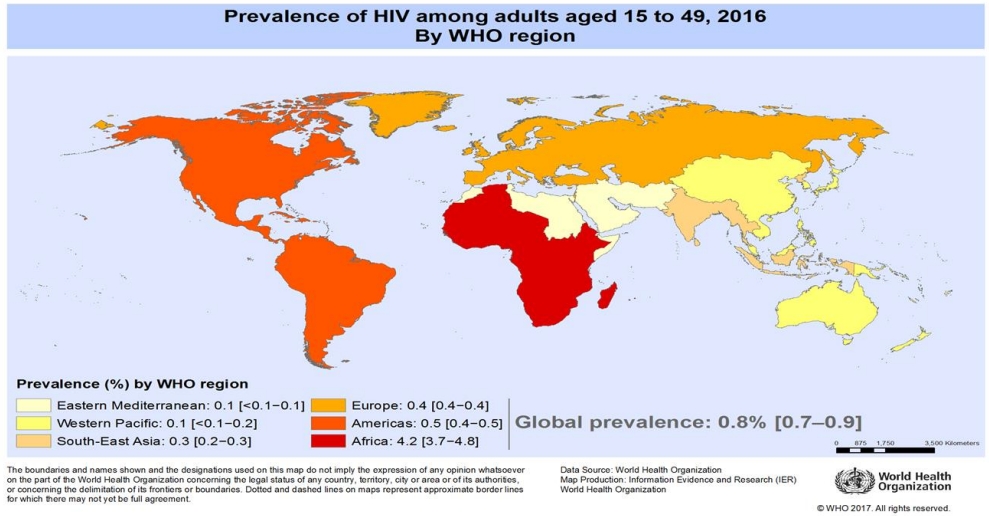
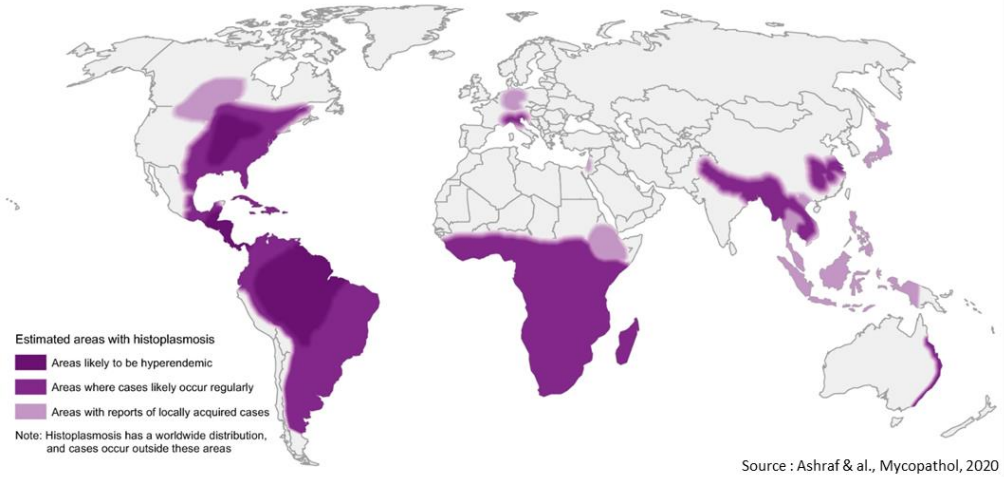
Histoplasmosis and HIV hotspots overlap in Latin America





Source : Ashraf & al., Mycopathol, 2020

People living with HIV/AIDS represent the population at-risk with the highest incidence levels & case-fatality rates from histoplasmosis

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Areas of expertise reporting numerous symptomatic cases of histoplasmosis …. from a lab-based approach

Rev Iberoam Micol. (2013);30(1):39–46

Revista Iberoamericana de Micología

www.elsevier.es/reviberoammicol

Original

Las micosis en Venezuela: casuística de los Grupos de Trabajo en Micología (1984-2010)

Dilia Martínez Méndez [a,*], Rosaura Hernández Valles [a], Primavera Alvarado [b] y Mireya Mendoza [b]

[a] Laboratorio de Microbiología, Programa de Medicina, Ciencias de la Salud, Universidad Nacional Experimental Francisco de Miranda, Coro, Falcón, Venezuela
[b] Laboratorio de Micología, Instituto de Biomedicina, Caracas, Venezuela

623 histo case = 33% of #2000 IFI

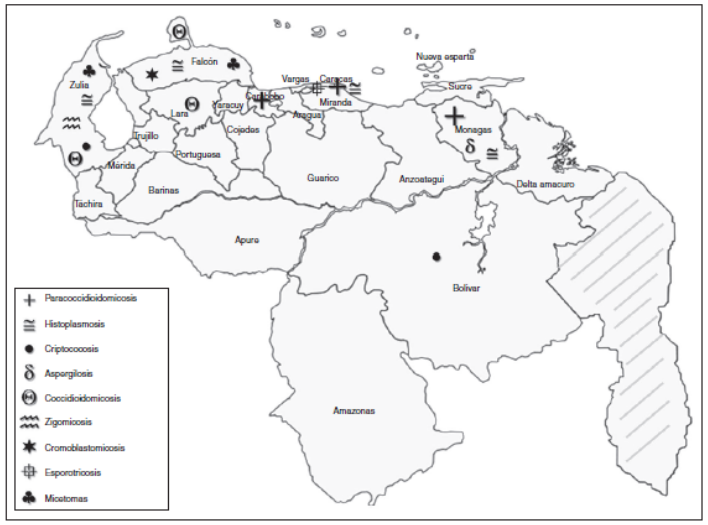


Figura 1. Distribución geográfica de los casos más frecuentes de micosis profundas. GTMV 1984-2010.

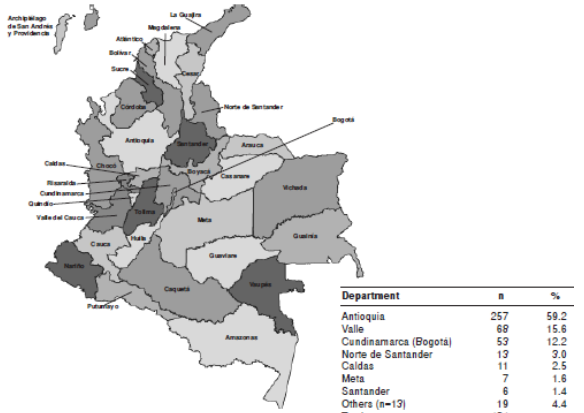
Biomédica 2011;31:344-56

ARTÍCULO ORIGINAL

Histoplasmosis: results of the Colombian National Survey, 1992-2008

Myrtha Arango[1,2], Elizabeth Castañeda[3], Clara Inés Agudelo[3], Catalina De Bedout[2], Carlos Andrés Agudelo[2,4], Angela Tobón[2,5], Melva Linares[3], Yorlady Valencia[2], Ángela Restrepo[2], The Colombian Histoplasmosis Study Group[7]

434 histo cases with 70% among PLHIV



Department	n	%
Antioquia	257	59.2
Valle	68	15.6
Cundinamarca (Bogotá)	53	12.2
Norte de Santander	13	3.0
Caldas	11	2.5
Meta	7	1.6
Santander	6	1.4
Others (n=13)	19	4.4
Total	434	

Figure 1. Histoplasmosis, number and percentage of cases by Department

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And high case-fatality rates accross various settings

Disseminated Histoplasmosis in Patients with AIDS in Panama: A Review of 104 Cases

Maria Eugenia Gutierrez,[1] Alfredo Canton,[1] Nestor Sosa,[1] Esther Puga,[1] and Leyda Talavera[2]

[1]Department of Infectious Diseases and [2]Microbiology Laboratory, Mycology Branch, Arnulfo Arias Madrid Hospital, Panama City, Panama

We identified the incidence and primary clinical characteristics of histoplasmosis in patients with acquired immunodeficiency syndrome (AIDS) in our hospital. Disseminated histoplasmosis is a common and severe disease among patients with AIDS in Panama and should be suspected for patients with a CD4 cell count of <100 cells/μL, fever, respiratory symptoms, weight loss, and diarrhea.

High Mortality and Coinfection in a Prospective Cohort of Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome Patients with Histoplasmosis in Guatemala

Blanca Samayoa,[1,2]* Monika Roy,[3] Angela Ahlquist Cleveland,[3] Narda Medina,[1] Dalia Lau-Bonilla,[1] Christina M. Scheel,[3] Beatriz L. Gomez,[4,5] Tom Chiller,[3] and Eduardo Arathoon[1]

Clinical and laboratory features of disseminated histoplasmosis in HIV patients from Brazil

Elizabeth F. Daher[1], Geraldo B. Silva Jr[1], Fernando A. S. Barros[1], Christianne F. V. Takeda[2], Rosa M. S. Mota[3], Marúsia T. Ferreira[1], Soraya A. Oliveira[1], Julieta C. Martins[1], Sônia M.H.A. Araújo[1] and Oswaldo A. Gutiérrez-Adrianzén[1]

Case-fatality rates range between 10%-60%

Table 5 Geographic differences regarding mortality, presence of cutaneous lesions, and association with concomitant tuberculosis during disseminated histoplasmosis in patients with HIV infection

			Patients (*n*)	Study period	Amphotericin B (%)	Total death rate (%)	Skin lesions (%)	Associated tuberculosis (%)
US	Indiana	Wheat *et al.* [11]	72	1980–1989	95	23[a]	1	4
	Indiana	Wheat *et al.* [40]	155	1988–1995	30	13	1	ND
	Multicentric	Hajjeh *et al.* [41]	92	1996–1999	64	12	4[b]	ND
	Multicentric	Johnson *et al.* [31]	73[c]	1995–1999	100	16[d]	7	ND
Central America	Panama	Gutierrez *et al.* [46•]	104	1997–2003	96	12	17	15
South America	Colombia	Tobon *et al.* [47•]	30	1988–2004	17	23	53	ND
	French Guiana	Couppié *et al.* [42]	87[e]	1994–2002	27	26	7	13
	Brazil	Karimi *et al.* [48]	29	1993–1996	57	39	66	ND
	Brazil	Unis *et al.* [49]	70	1977–2002	56	39	44	7
	Brazil	De Francesco Daher *et al.* [43••]	164	1995–2004	>50	32	ND	ND
	Argentina	Négroni *et al.* [50]	27	Before 1992	19	30	93	15
	Argentina	Pietrobon *et al.* [51]	16	1993–2000	100	19	75[b]	19

Source : Couppié P. et al., *Curr. Op. Inf. Dis.*, 2006

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Knowledge on histo-HIV in Latin America

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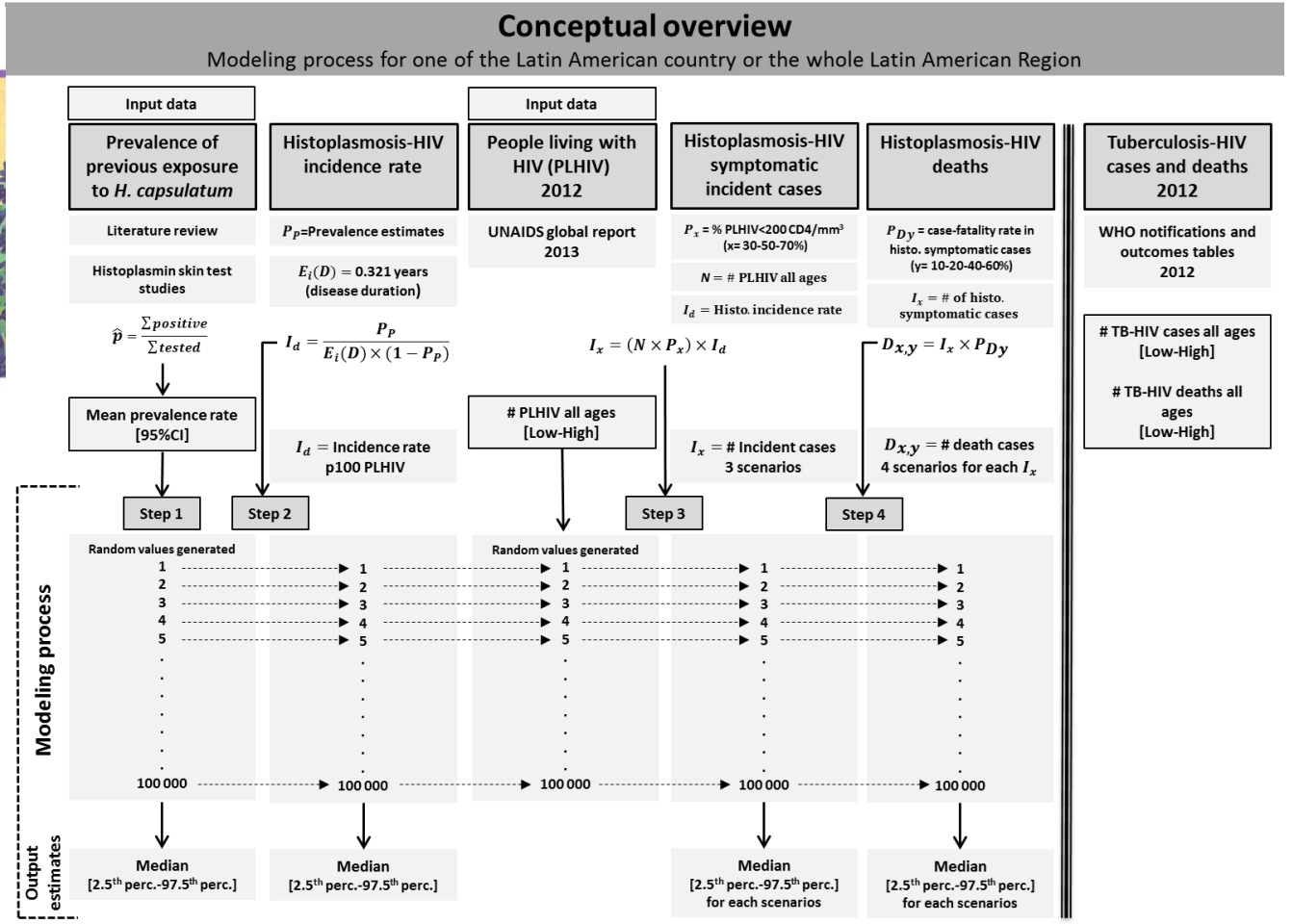
Attempt in modeling incidence and deaths estimates

Provide with robust estimates to guide public health decision



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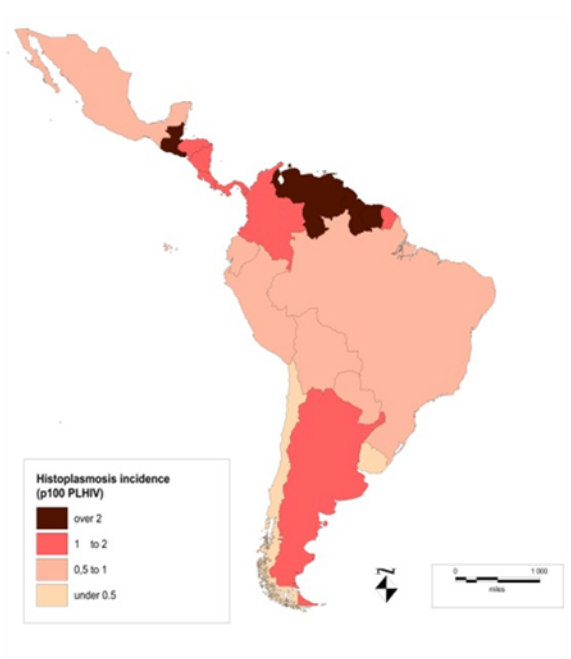
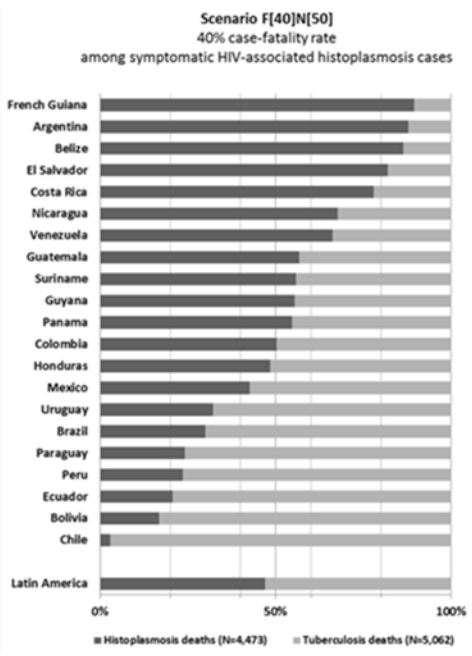
Estimates showed similar and even greater numbers of cases and deaths of histo-HIV as of TB-HIV

Prevalence of gen. pop. exposure>30% and 1.5p100 PLHIV annual incidence

1/2 countries with symptomatic histo cases >or = TB cases

2/3 countries with histo deaths > or = TB deaths (conservative 40% case-fatality rate)





A. Adenis & al., Lancet ID, 2018

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HIV-associated histoplasmosis as the 1st AIDS-defining condition in Latin America

Disseminated histoplasmosis in Central and South America, the invisible elephant: the lethal blind spot of international health organizations

The neglected histoplasmosis in Latin America Group

Since the onset of the HIV epidemic, there have been convergent reports suggesting that disseminated histoplasmosis is one of the major AIDS-defining infections and a major killer of HIV-infected patients. However, most hospitals still have no way of diagnosing the disease, and often lack the best treatments for the disease, and confuse it for tuberculosis. There is thus a double tragedy, with clinicians failing to diagnose what is killing their patients, and public health authorities failing to tackle one of the major burdens of disease. There are an estimated 1 600 000 HIV patients in the Americas. If we apply the incidence rate of 1.5 per 100 person-years measured in French Guiana, this suggests there are 24 000 histoplasmosis cases in the Americas per year. The historical death rate of 40% of deaths in histoplasmosis would mean there are 9600 deaths per year. This is much higher than the annual number of malaria deaths in Latin America and comparable to the number of deaths from HIV-associated tuberculosis. Yet, 34 years after the description of AIDS, the strategic priorities of international organizations or most AIDS programmes still do not reflect this staggering burden.

AIDS 2015, **29**:000–000

Keywords: burden, disseminated histoplasmosis, HIV, international organizations, mortality

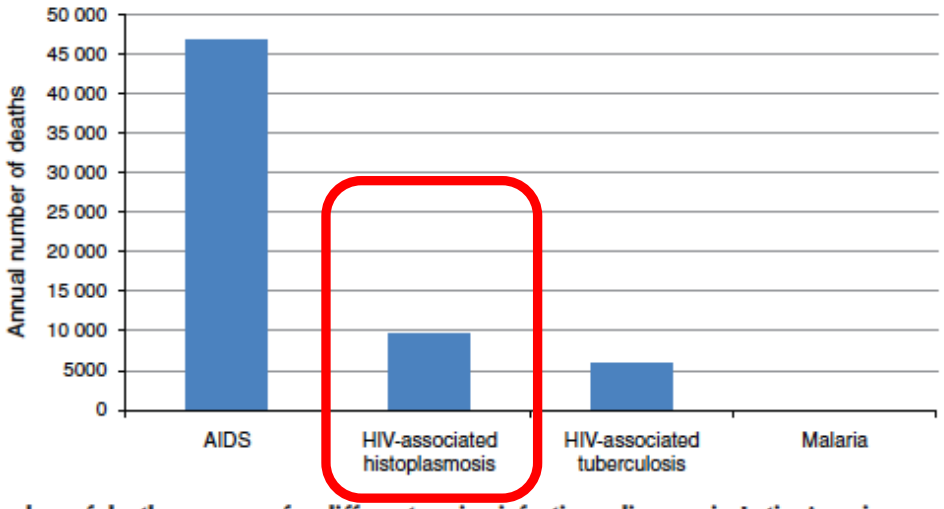

Fig. 1. Estimated number of deaths per year for different major infectious diseases in Latin America.

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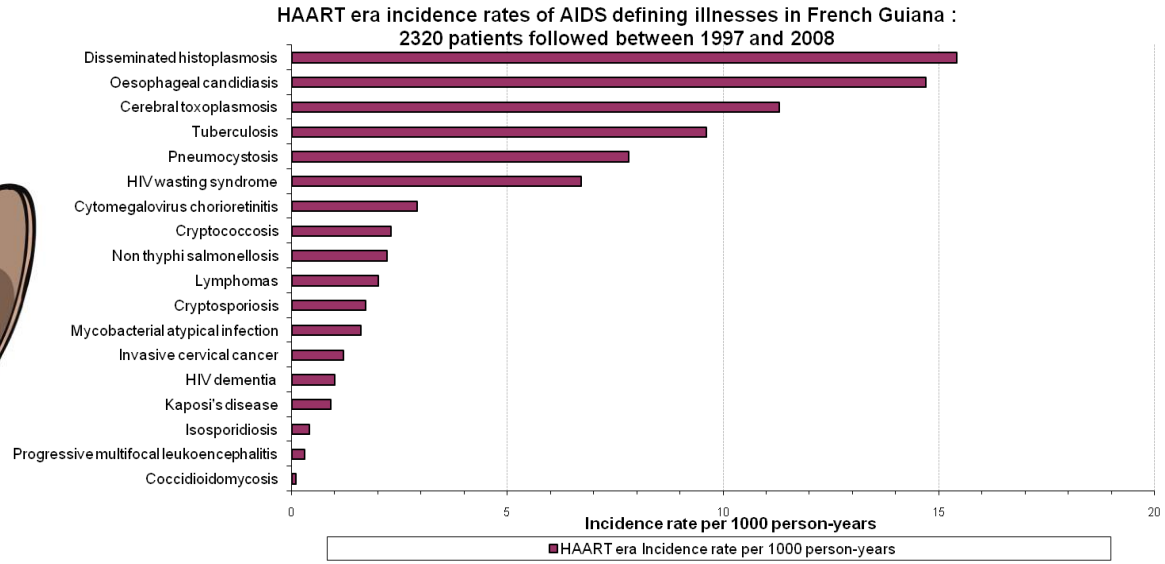
Estimates concordant with « observed » trends in the french guiana PLHIV cohort

What is « Amazonian AIDS » ? Framing the question was crucial !

Am. J. Trop. Med. Hyg., 84(2), 2011, pp. 239–240
doi:10.4269/ajtmh.2011.10-0251

Short Report: What Is AIDS in the Amazon and the Guianas? Establishing the Burden of Disseminated Histoplasmosis

Mathieu Nacher,* Antoine Adenis, Leila Adriouch, Julie Dufour, Emmanuelle Papot, Matthieu Hanf, Vincent Vantilcke, Mélanie Calvez, Christine Aznar, Bernard Carme, and Pierre Couppié

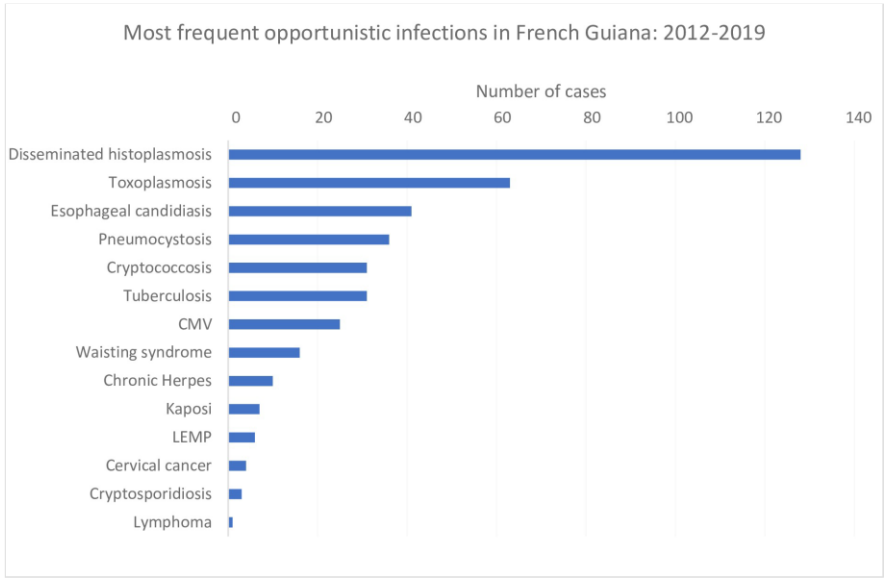


PLOS ONE

RESEARCH ARTICLE

What is AIDS in the Amazon and the Guianas in the 90-90-90 era?

Mathieu Nacher[1,2,3]*, Antoine Adenis[1,2], Basma Guarmit[2], Aude Lucarelli[4], Denis Blanchet[5], Magalie Demar[3,5,6], Felix Djossou[7], Philippe Abboud[7], Loïc Epelboin[7], Pierre Couppié[3,8]



HIV-associated histoplasmosis incidence 15.4/1000 person-years PLHIV

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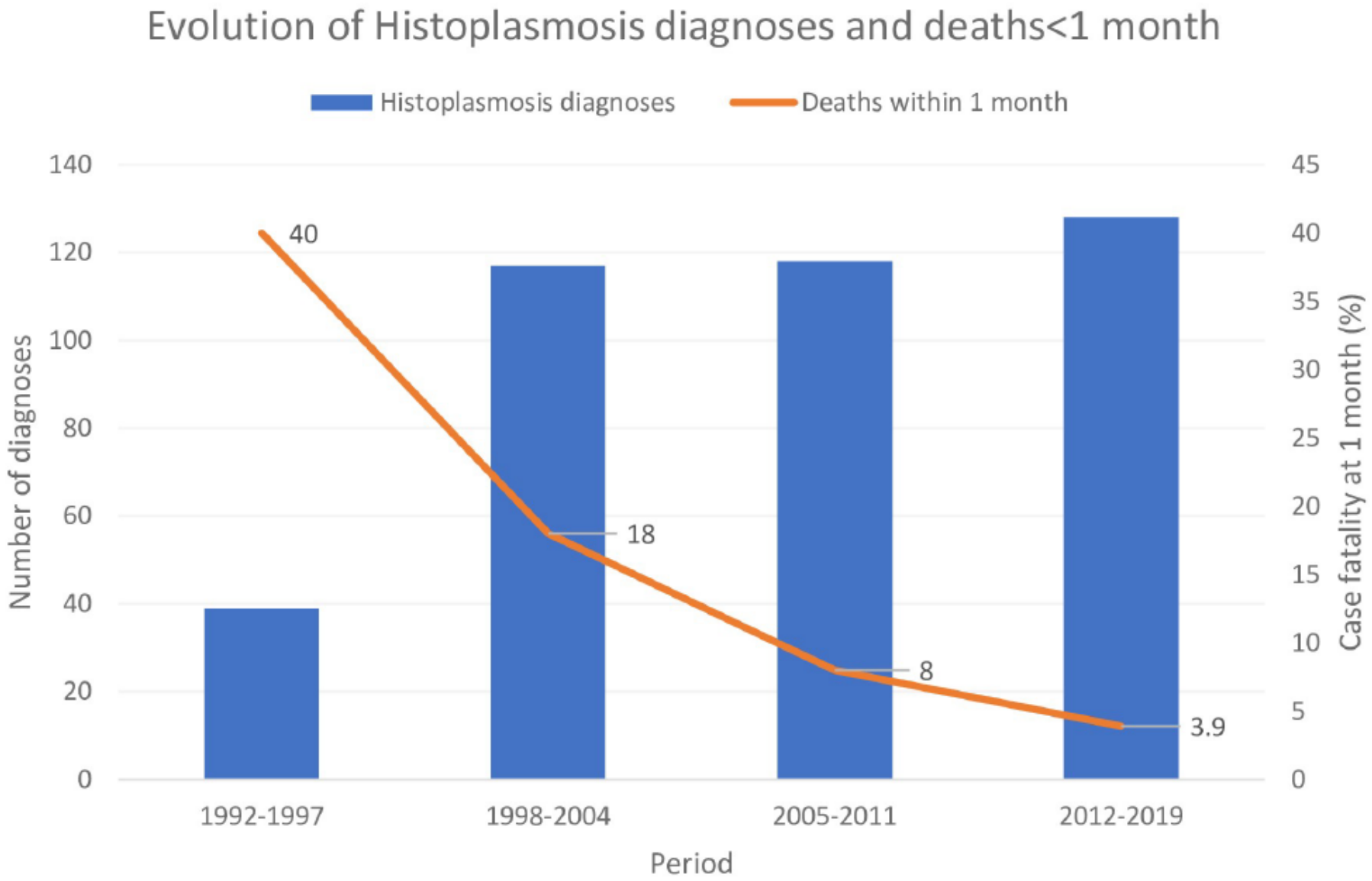
High incidence and decrease case-fatality rates over time



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Developments in *Histoplasma* antignen detection allowed prevalence estimates in various populations

Systematic Review of Prevalence of *Histoplasma* Antigenuria in Persons with HIV in Latin America and Africa

Preethiya Sekar, Gila Hale, Jane Gakuru, David B. Meya, David R. Boulware, Jayne Ellis, Elizabeth Nalintya, Nathan C. Bahr, Radha Rajasingham

Figure 2. Country-level *Histoplasma* antigenuria prevalence in systematic review of prevalence of *Histoplasma* antigenuria in persons with HIV in Latin America and Africa. Asterisks denote countries with studies that were done in advanced HIV populations, whereas solid colors denote countries with studies of participants with HIV screened for histoplasmosis irrespective of CD4 count.

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Various prevalence levels according to sub-populations at-risk and their outcomes

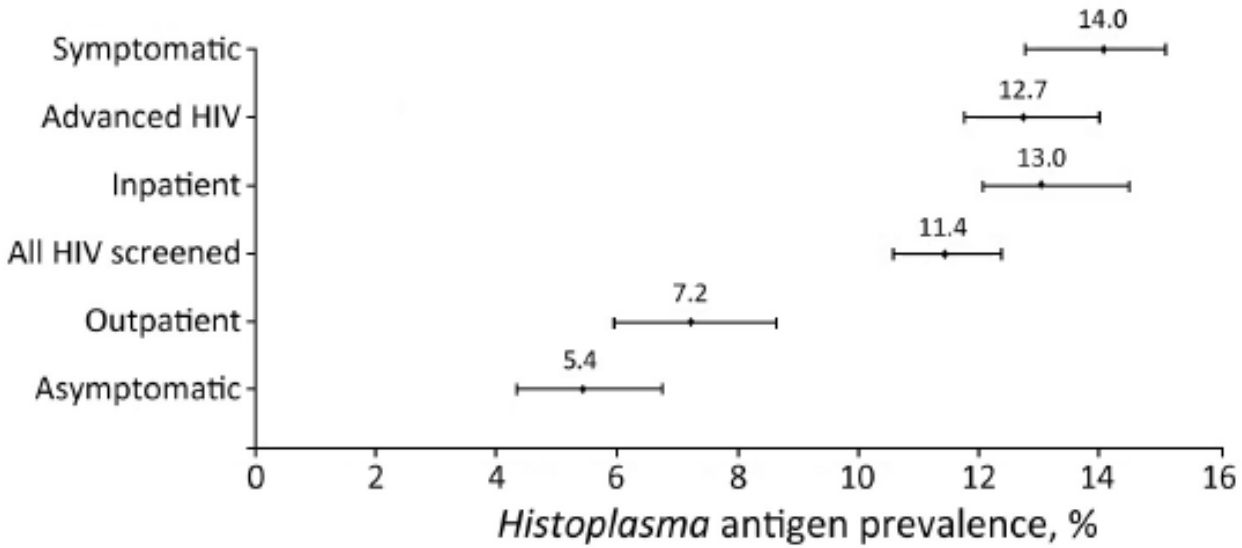

Figure 3. Forest plot of *Histoplasma* antigen prevalence among subgroups of interest in systematic review of prevalence of *Histoplasma* antigenuria in persons with HIV in Latin America and Africa. Error bars indicate 95% CIs.

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 30, No. 8, August 2024 1527

Rising issue of *Histoplasma* Ag + asymptomatic individuals who will not declare any symptomatic disease overtime and not dying in the absence of appropriate antifungal therapy ….

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Simple things have high impact

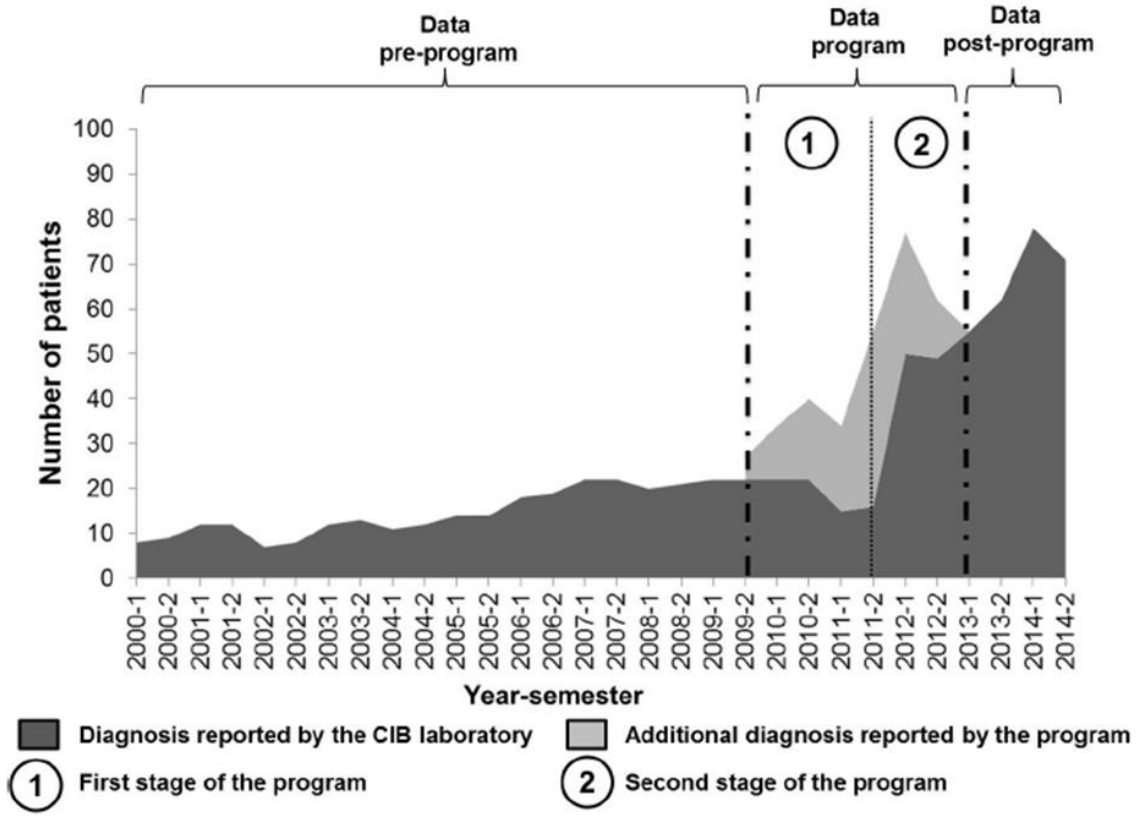
→ Lab-centralized screening program using *Histoplasma* antigen detection

Am. J. Trop. Med. Hyg., 93(3), 2015, pp. 662–667
doi:10.4269/ajtmh.15-0108

Implementation of a Training Course Increased the Diagnosis of Histoplasmosis in Colombia

Diego H. Caceres, Alejandra Zuluaga, Karen Arango-Bustamante, Catalina de Bedout, Ángela Maria Tobón, Ángela Restrepo, Beatriz L. Gómez, Luz Elena Cano, and Ángel González*

Medical and Experimental Mycology Group, Corporación para Investigaciones Biológicas (CIB), Medellín, Colombia; School of Medicine and Health Sciences, Universidad del Rosario, Bogota, Colombia; School of Microbiology, Universidad de Antioquia, Medellín, Colombia; Basic and Applied Microbiology Research Group (MICROBA), School of Microbiology, Universidad de Antioquia, Medellín, Colombia

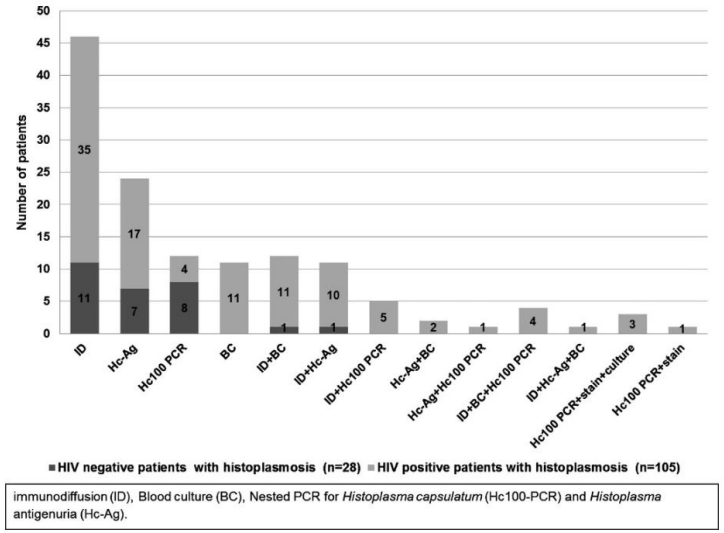


133/768 (17%) of histoplasmosis among clinically suspected cases

38 proven and 95 probable cases

↑↑ from 27 to 44 new cases/year

400% increase of histo incidence



immunodiffusion (ID), Blood culture (BC), Nested PCR for *Histoplasma capsulatum* (Hc100-PCR) and *Histoplasma* antigenuria (Hc-Ag).

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Scaling-up the FungiRED initiative (Guatemala)

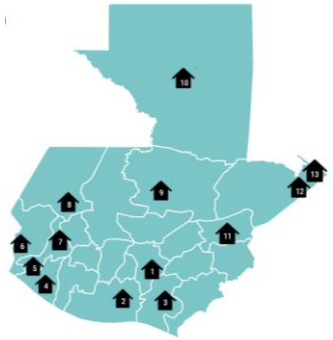
« Reducing HIV-related deaths through rapid diagnosis of fungal infections and an improvement in the attention »

Alliance

gaffi

Asociación de Salud Integral

FUNGIRed™



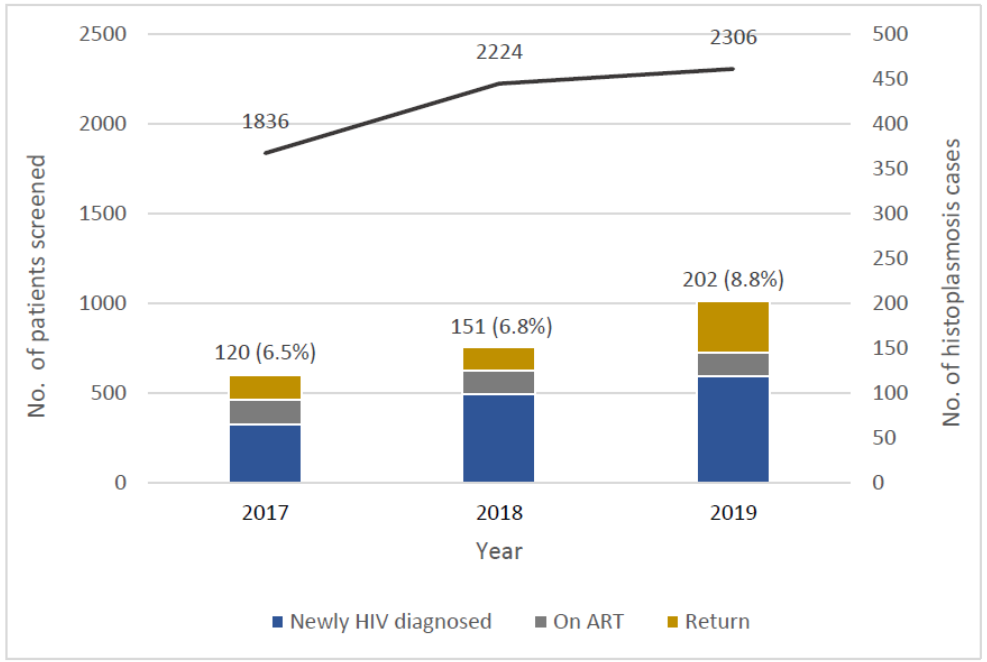


Figure 1. Annual screening patient numbers and histoplasmosis cases detected in the OI program

Screening program based on a lab diagnostic hub (TB, histo, crypto..)

Offers continuum of care (patients), education & training (health practitioners)

6460 screened

Histo incidence in AHD 11.9%

15% of histo cases with CD4>350/mm3

Histo & TB 57%

M6 Deaths ↓↓

32% (2017) to 21% (2019)

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What would be missed if screening was done only in patients with CD4 count <200?

At least half of histoplasmosis cases would have been missed !

CD4 range	Histoplasmosis		Cryptococcosis		Mycobacterium		Coinfection	
	n	%	n	%	n	%	n	%
100-200	8	12.9	13	27.7	17	19.3	3	14.3
201-350	7	11.3	4	8.5	12	13.6	1	4.8
≥350	2	3.2	4	8.5	14	15.9	-	-
Total	17	27.4	21	44.7	43	48.9	4	19.0

% Missing OIs diagnosed estimates	14.5%	17%	29.5%	4.8%

CD4 counts missing values: n=630

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High frequencies of HIV-associated tuberculosis and histoplasmosis coinfection in Latin America

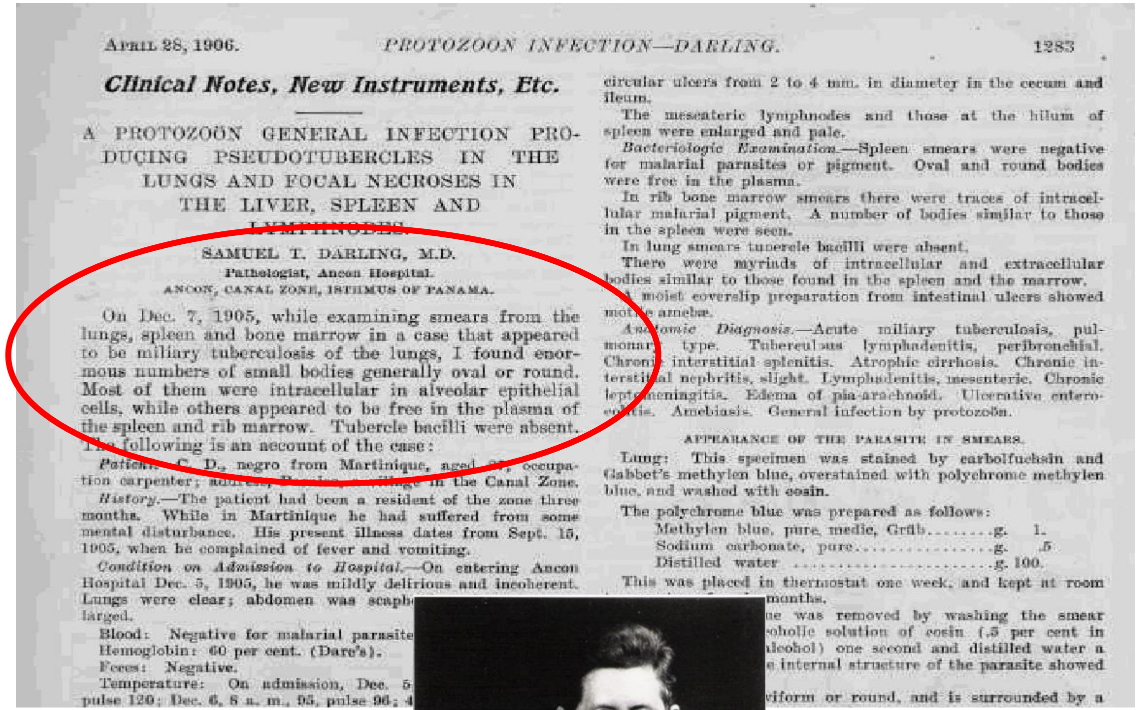
A nightmare for clinicians because of drug-drug interactions notably…

Reference	Study period	Country	% (# TB and # histoplasmosis)	Comments
López AG, et al [17]	2009–2014	Argentina	9% (16/171)	Histoplasmosis patients median CD4 T cell: 29 cells/mm^3
Boigues B, et al [18]	2011–2016	Brazil	26% (6/23)	Histoplasmosis patients median CD4 T cell: 19 cells/mm^3
Falci DR, et al [19]	2016–2018	Brazil	15% (19/123)	Multicenter study, 11 Brazilian cities.CD4 T cell: 39 cells/mm^3
Caceres DH, et al [20]	2008–2011	Colombia	35% (16/45)	Histoplasmosis patients median CD4 T cell: 30 cells/mm^3
Velásquez G, et al [25]	1998–2004	Colombia	16% (7/44)	Histoplasmosis patients median CD4 T cell: 30 cells/mm^3
Huber FN, et al [21]	1982–2007	French Guiana	8% (16/200)	Histoplasmosis patients median CD4 T cell: 63 cells/mm^3
Samayoa B, et al [22]	2005–2009	Guatemala	26% (26/101)	Histoplasmosis patients median CD4 T cell: 25 cells/mm^3
Caceres DH, et al [26]	2017	Panama	38% (18/48)	Diagnosed by *Histoplasma* antigen and lateral flow lipoarabinomannan assays
Pérez G, et al [23]	1996–2014	Peru	11% (3/23)	Histoplasmosis patients median CD4 T cell: 30 cells/mm^3
Mata SC, et al [24]	2000–2005	Venezuela	2% (1/53)	Histoplasmosis/TB co-occurrence including non-HIV patients was 5%

Figure 1. Reports of cohorts of people with histoplasmosis and advanced HIV: frequency of tuberculosis (TB) co-occurrence.

A historical confusion between histo and tuberculosis

« ..in a case that appeared to be a miliary tuberculosis .. »



APRIL 28, 1906. *PROTOZOON INFECTION—DARLING.* 1283

Clinical Notes, New Instruments, Etc.

A PROTOZOÖN GENERAL INFECTION PRODUCING PSEUDOTUBERCLES IN THE LUNGS AND FOCAL NECROSES IN THE LIVER, SPLEEN AND LYMPHNODES.

SAMUEL T. DARLING, M.D.
Pathologist, Ancon Hospital.
ANCON, CANAL ZONE, ISTHMUS OF PANAMA.

On Dec. 7, 1905, while examining smears from the lungs, spleen and bone marrow in a case that appeared to be miliary tuberculosis of the lungs, I found enormous numbers of small bodies generally oval or round. Most of them were intracellular in alveolar epithelial cells, while others appeared to be free in the plasma of the spleen and rib marrow. Tubercle bacilli were absent. The following is an account of the case:

Patient.—C. D., negro from Martinique, aged ..., occupation carpenter; address, ..., a village in the Canal Zone.

History.—The patient had been a resident of the zone three months. While in Martinique he had suffered from some mental disturbance. His present illness dates from Sept. 15, 1905, when he complained of fever and vomiting.

Condition on Admission to Hospital.—On entering Ancon Hospital Dec. 5, 1905, he was mildly delirious and incoherent. Lungs were clear; abdomen was scaph... larged.

Blood: Negative for malarial parasite...
Hemoglobin: 60 per cent. (Dare's).
Feces: Negative.
Temperature: On admission, Dec. 5... pulse 120; Dec. 6, 8 a. m., 95, pulse 96; 4...

circular ulcers from 2 to 4 mm. in diameter in the cecum and ileum.

The mesenteric lymphnodes and those at the hilum of spleen were enlarged and pale.

Bacteriologic Examination.—Spleen smears were negative for malarial parasites or pigment. Oval and round bodies were free in the plasma.

In rib bone marrow smears there were traces of intracellular malarial pigment. A number of bodies similar to those in the spleen were seen.

In lung smears tubercle bacilli were absent.

There were myriads of intracellular and extracellular bodies similar to those found in the spleen and the marrow.

A moist coverslip preparation from intestinal ulcers showed motile ameba.

Anatomic Diagnosis.—Acute miliary tuberculosis, pulmonary type. Tuberculous lymphadenitis, peribronchial. Chronic interstitial splenitis. Atrophic cirrhosis. Chronic interstitial nephritis, slight. Lymphadenitis, mesenteric. Chronic leptomeningitis. Edema of pia-arachnoid. Ulcerative enterocolitis. Amebiasis. General infection by protozoön.

APPEARANCE OF THE PARASITE IN SMEARS.

Lung: This specimen was stained by carbolfuchsin and Gabbet's methylen blue, overstained with polychrome methylen blue, and washed with eosin.

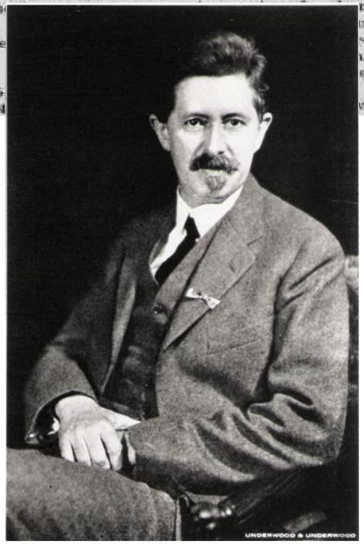
The polychrome blue was prepared as follows:

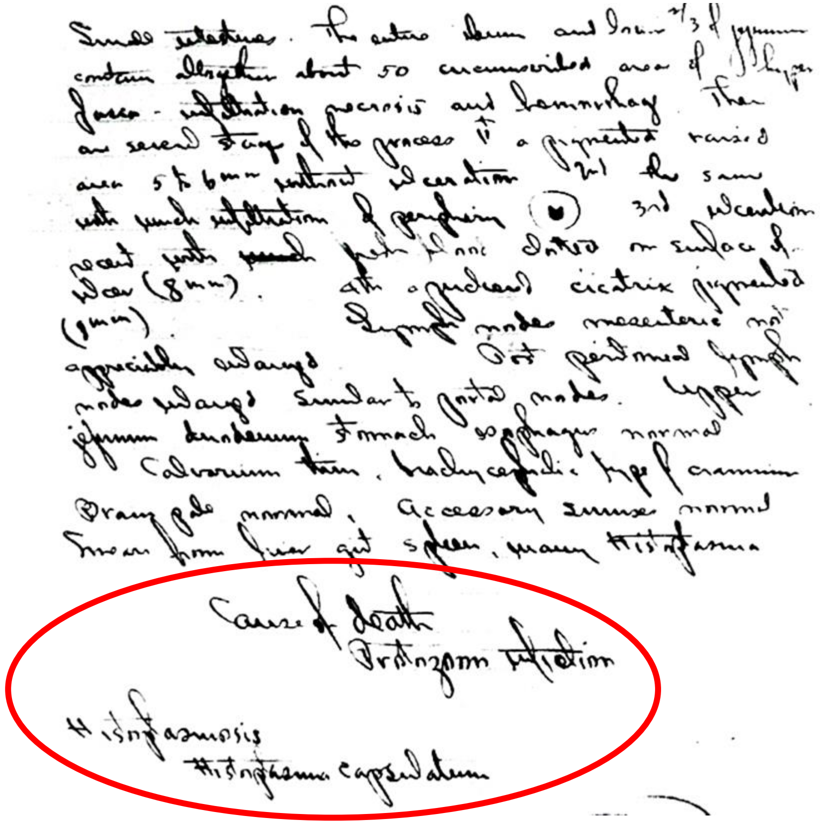
Methylen blue, pure, medic, Grüb	g.	1.
Sodium carbonate, pure	g.	.5
Distilled water	g.	100.

This was placed in thermostat one week, and kept at room ... months.

...ne was removed by washing the smear ...oholic solution of eosin (.5 per cent in ...lcohol) one second and distilled water a ...e internal structure of the parasite showed

...viform or round, and is surrounded by a





Source : Darling S.T., Journal of the American Medical Association, 1906

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Issues in the differential diagnosis documented for decades

HISTOPLASMOSIS AS A PROBLEM IN TUBERCULOSIS SANATORIUMS THROUGHOUT THE UNITED STATES

KENNETH WALLS, PH.D., M. L. FURCOLOW, M.D., AND P. H. LEHAN, M.D.
KANSAS CITY, KAN.

SEROLOGIC surveys for histoplasmosis have now been completed in 22 tuberculosis sanatoriums located in 15 states extending from New York on the east to Arizona on the west. Most of the sanatoriums included in the study are located in the histoplasmosis belt of central United States.

Lesson of the Week

Sporadic disseminated histoplasmosis simulating miliary tuberculosis

P TONG, W C TAN, M PANG

Disseminated histoplasmosis may closely resemble miliary tuberculosis in its clinical presentation.[1] In an area where infection with *Mycobacterium tuberculosis* is common the diagnosis of disseminated histoplasmosis may therefore be delayed or missed.

Acute disseminated histoplasmosis resembles miliary tuberculosis. This may be overlooked in an urban area endemic for tuberculosis

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High % of suspected TB-HIV cases that are in fact Histo-HIV cases

Revista da Sociedade Brasileira de Medicina Tropical 37(6):463-468, nov-dez, 2004

ARTIGO/ARTICLE

Histoplasmose disseminada no Rio Grande do Sul

Disseminated histoplasmosis in Rio Grande do Sul

Gisela Unis[1], Flávio de Mattos Oliveira[1]
e Luiz Carlos Severo[1]

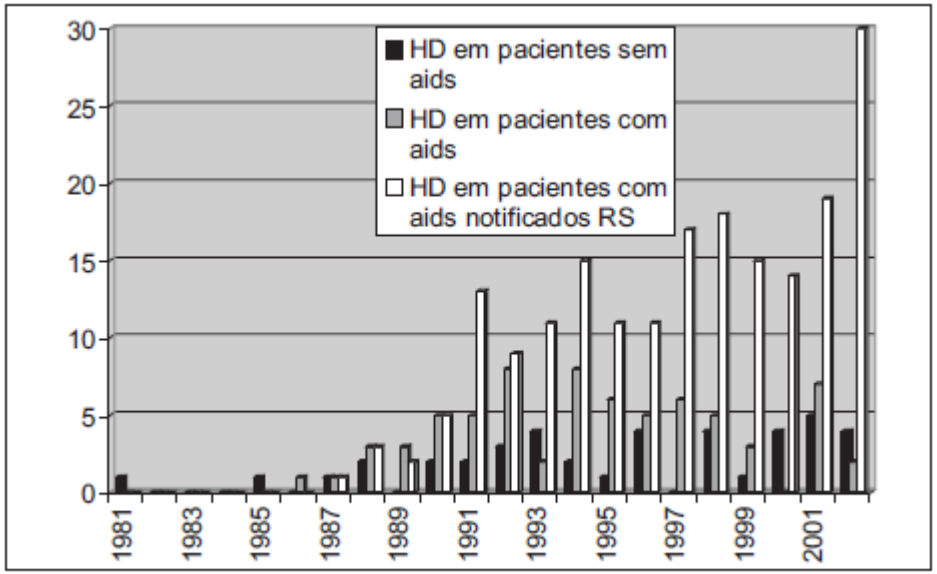

Figura 1 - Comparação dos casos de histoplasmose disseminada desta série com os notificados no Rio Grande do Sul.

111 histoplasmosis cases culture confirmed (63% with HIV)

Presumptive anti-TB therapy

17% (non-VIH)

27% (VIH+)

Fig. 4 — The patient by his chicken house were he contracted histoplasmosis

Source : Severo L.C., Rev. Inst. Med. Trop., 1986

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Unawareness of reference centers across Latin America and the Caribbean

POSTER NUMBER 833

2015

Culture-negative TB is associated with increased mortality in HIV-infected persons

Timothy R. Sterling,[1] Cathy Jenkins,[1] Karu Jayathilake,[1] Eduardo Gotuzzo,[2] Valdilea Veloso,[3] Claudia Cortes,[4] Denis Padgett,[5] Brenda Crabtree Ramirez,[6] Bryan E. Shepherd,[1] Catherine McGowan,[1] and the CCASAnet Region of IeDEA

1. Vanderbilt University, Nashville, TN 2. Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru 3. Instituto Nacional de Infectologia Evandro Chagas, Fundacao Oswaldo Cruz, Rio de Janeiro, Brasil 4. Fundación Arriarán, University of Chile, Santiago, Chile 5. Hospital Escuela and Instituto Hondureño de Seguridad Social, Tegucigalpa, Honduras 6. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

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Nashville, TN USA
Tel: 615 322-2035
Fax: 615 343-6160
E-mail: timothy.sterling@vanderbilt.edu

CCASAnet
Caribbean, Central and South America Network for HIV Epidemiology Research

IeDEA
International epidemiologic Databases to Evaluate AIDS

Background

- In settings where cultures are routinely obtained, ~20% of TB is culture-negative
- Rates of culture-negative TB are higher in resource-limited settings, due in part to less frequent use of acid-fast bacilli (AFB) cultures
- AFB smear-negative TB is associated with increased mortality in HIV+ persons; there are few data on mortality risk in culture-negative TB

Methods

Study design: observational cohort study
Study population: HIV+ persons treated for TB at or after their first clinic visit at sites in Argentina, Brazil, Chile, Honduras, Mexico, and Peru from 2000-2013. Excluded if date of TB treatment relative to HAART initiation was unknown.
TB treatment: 2 months of INH, rifampin, pyrazinamide +/- ethambutol followed by continuation phase treatment: INH + rifampin
TB diagnosis date = date of TB treatment initiation
TB recurrence = new TB diagnosis > 180 days after initial TB episode
TB endpoints validated by medical record review
Statistical analysis: Kaplan-Meier curves and Cox proportional hazards models of time to death from TB diagnosis. Cox models were stratified by study site. Multiple imputation performed for missing data in the multivariable Cox model.

Results

Table 1. Characteristics of the study population.

Characteristic	N	Median or count	(IQR) or percent
Median age	772	36	(30-43)
Male sex	772	583	76%
Study site	772		
Argentina		85	11%
Brazil		255	33%
Chile		62	8%
Honduras		28	4%
Mexico		26	3%
Peru		316	41%
Site of TB disease	772		
Any pulmonary		536	69%
Any extrapulmonary		399	52%
Median CD4 at TB Diagnosis	625	100	(45-228)
AFB smear	654		
Positive		312	48%
Negative		342	52%
AFB culture	536		
Positive		332	62%
Negative		204	38%
TB diagnosis relative to HAART	772		
Never on HAART		50	6%
HAART stopped before TB		14	2%
HAART concurrent with TB Rx		627	81%
HAART started after TB Rx		81	10%

Total TB patients	1,586
+ treated with standard therapy	1,308
+ TB diagnosed at/after 1st visit	884
+ TB treatment relative to HAART start known	772
Isoniazid resistance:	26/276 (9%)
Rifampin resistance:	19/276 (7%)

Table 2. Mortality rates according to culture and smear status.

Characteristic	Negative	Positive	P
Culture	44/204 (22%)	45/332 (14%)	0.02
Smear	56/342 (16%)	56/312 (18%)	0.67

Figure 1. Kaplan-Meier curve of time to death according to AFB culture status.

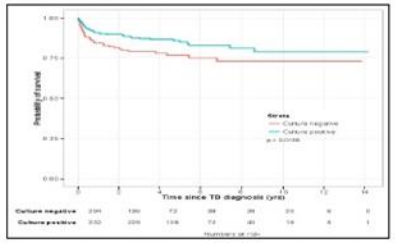
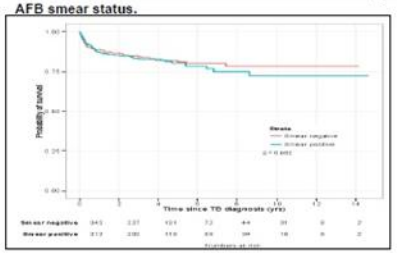


Figure 2. Kaplan-Meier curve of time to death according to AFB smear status.



There were 17 episodes of recurrent TB occurring > 180 days after initiation of TB treatment; recurrence tended to occur more frequently in culture-negative compared to culture-positive persons (log-rank P = 0.10)

Table 3. Risk Factors for Death Among TB Patients. Cox proportional hazards models.

Characteristic	Univariate			Multivariable		
Study population	HR	95% CI	P value	aHR	95% CI	P value
TB culture positive	1.0			1.0		
TB culture negative	1.67	1.10, 2.5	0.017	1.79	1.23, 2.63	0.002
CD4 at TB diagnosis			<0.001			<0.001
50	3.69	2.01, 6.76		4.05	2.14, 7.68	
100	2.78	1.51, 5.12		3.16	1.71, 5.85	
200	1.74	1.03, 2.92		1.97	1.20, 3.24	
350 (ref)	1.00			1.00		
500	0.60	0.32, 1.14		0.51	0.28, 0.94	
TB Dx relative to HAART			<0.001			<0.001
Never on HAART (ref)	1.00			1.00		
HAART stopped before TB	0.38	0.14, 1.00		0.23	0.08, 0.63	
HAART concurrent with TB	0.18	0.11, 0.30		0.13	0.08, 0.23	
HAART started after TB Rx	0.20	0.11, 0.39		0.19	0.09, 0.40	
Age at TB diagnosis			0.71			0.18
25	0.90	0.60, 1.35		0.84	0.55, 1.29	
30	0.95	0.80, 1.13		0.92	0.76, 1.10	
35 (ref)	1.00			1.00		
40	1.04	0.95, 1.14		1.09	0.99, 1.20	
50	1.09	0.78, 1.54		1.30	0.92, 1.84	
Site of TB			0.59			0.79
Pulmonary only	1.00			1.00		
Any extrapulmonary TB	0.84	0.59, 1.18		0.93	0.65, 1.33	
Unknown	0.88	0.22, 3.60		1.46	0.34, 6.32	

Limitations

Information on cause of death was not available.

There were no data on drug resistance in culture-negative TB cases.

Conclusions

In this large, multi-center cohort study, culture-negative TB was associated with a 79% increased hazard of death compared to persons with culture-confirmed TB.

These findings raise the possibility that persons diagnosed with culture-negative TB may not have had TB, and died of other causes.

This underscores the importance of accurate TB diagnosis in HIV + persons.

References

- Getahun H. Lancet 2007;369:2042-9.
- Banda H. Int J Tuberc Lung Dis 2000;4:968-74

CCASAnet Sites, Investigators, and Funding

Fundacion Huesped, Buenos Aires, Argentina: O Sued, C Cesar, V Fink, P Cahn. Instituto Nacional de Infectologia Evandro Chagas, Rio de Janeiro, Brazil: V Veloso, B Grinsztejn. University of Chile School of Medicine, Santiago, Chile: C Cortes, M Wolff. Les Centres GHESKIO, Port-au-Prince, Haiti: A Marcelin, V Rouzier, W Pape. Instituto Hondureño de Seguridad Social y Hospital Escuela, Tegucigalpa, Honduras: A Mallhot, D Padgett. Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico: B Crabtree Ramirez, J Sierra Madero. Universidad Peruana Cayetano Heredia, Lima, Peru: D Hoces, E Gotuzzo. NIAID/DAIDS, Bethesda, United States: M Bacon. Vanderbilt University, Nashville: C McGowan, S Duda, P Rebeiro, F Wehbe, B Shepherd, T Sterling.
Funded by US NIH/NIAID grant U01 AI069923.

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80% increase in deaths hazard among patients with a culture negative TB

Conclusions

In this large, multi-center cohort study, culture-negative TB was associated with a 79% increased hazard of death compared to persons with culture-confirmed TB.

These findings raise the possibility that persons diagnosed with culture-negative TB may not have had TB, and died of other causes.

This underscores the importance of accurate TB diagnosis in HIV + persons.

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Funded by US NIH/NIAID grant U01 AI069923.

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Even in French Guiana we may have missed histo cases among suspected TB cases !

Nacher *et al. BMC Res Notes* (2020) 13:209
https://doi.org/10.1186/s13104-020-05054-w

BMC Research Notes

RESEARCH NOTE Open Access

HIV patients dying on anti-tuberculosis treatment: are undiagnosed infections still a problem in French Guiana?

Mathieu Nacher[1,2*], Antoine Adenis[1], Philippe Abboud[3], Felix Djossou[2,3], Magalie Demar[4,5], Loïc Epelboin[3] and Pierre Couppié[2,6]

<u>From 1992 to 2009</u>
347 patients on anti-TB therapy → 28% proven TB (97cases)
199 patients on antifungals → 71% proven histo (141 cases)

Anti-TB therapy associated with 2 fold greater risk of dying (aHR) = 2.44 (95%CI 1.65-3.60))

If antigen detection had been available, may we found more histo cases and avoided unnecessary TB therapy thereby preventing deaths???

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In *Histoplasma* endemic area, first think histoplasmosis and treat first with antifungals may save lives !

OPEN ACCESS Freely available online

PLOS | NEGLECTED TROPICAL DISEASES

Viewpoints

Histoplasmosis or Tuberculosis in HIV-Infected Patients in the Amazon: What Should Be Treated First?

Mathieu Nacher[1,2]*, Antoine Adenis[1,2], Emilie Sambourg[2,3], Florence Huber[4], Philippe Abboud[2,5], Loïc Epelboin[2,5], Emilie Mosnier[5,6], Vincent Vantilcke[7], Julie Dufour[2,3], Félix Djossou[2,5], Magalie Demar[2,8], Pierre Couppié[2,3]

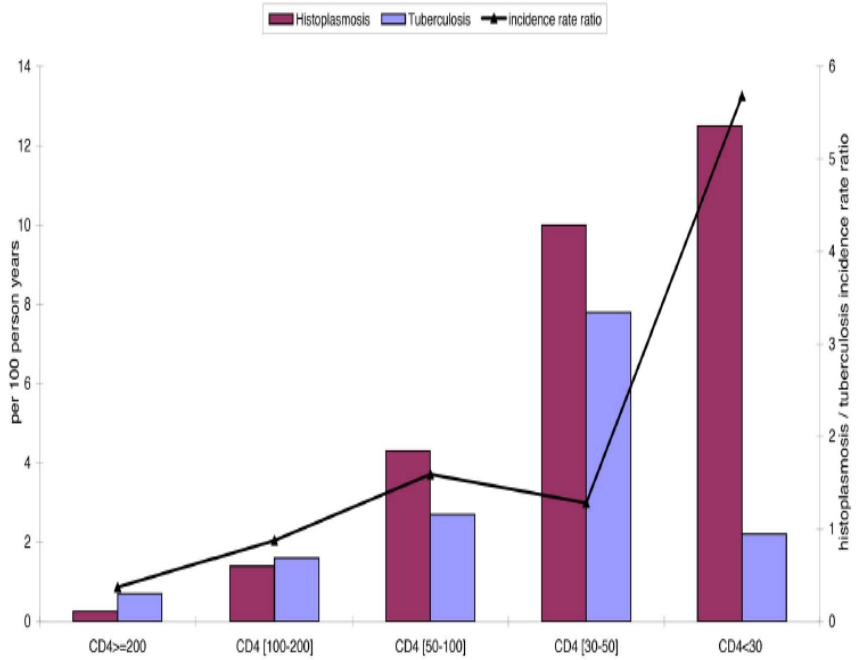

Figure 1. Shows the incidence rate for tuberculosis and histoplasmosis for different CD4 strata.
doi:10.1371/journal.pntd.0003290.g001

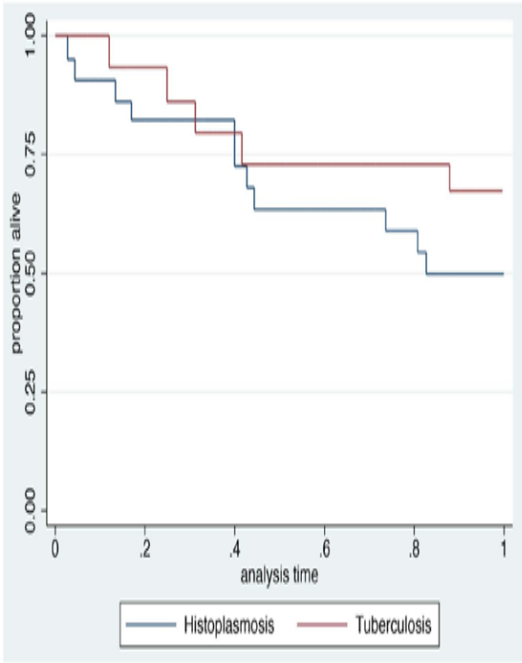

Figure 2. Shows the incidence of death during the first year afer histoplasmosis or tuberculosis among patients with CD4 counts less than 200.
doi:10.1371/journal.pntd.0003290.g002

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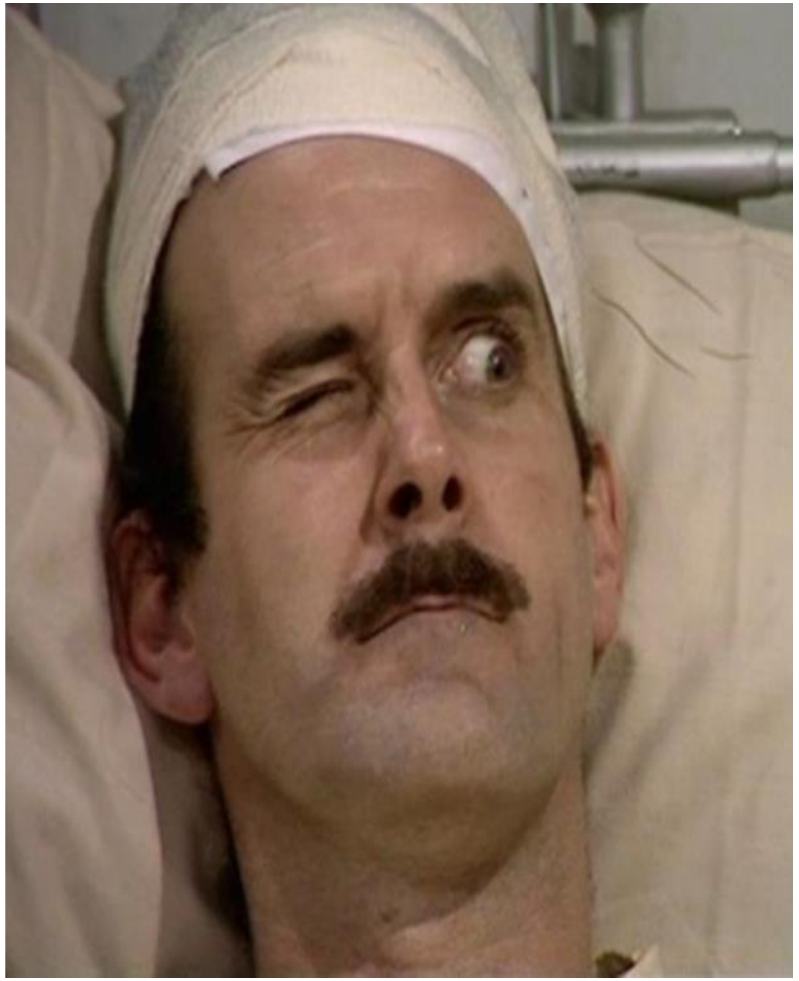
We call for a switch from the classical « TB-like syndrome » to the « Histo-like syndrome » for clinicians in endemic areas for the two diseases !



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Looking for tuberculosis, finding histoplasmosis !

Prevalence of Histoplasmosis and Molecular Characterization of *Histoplasma* species in Patients with Presumptive Pulmonary Tuberculosis in Calabar, Nigeria

Bassey E. Ekeng,[1,2] Rita O. Oladele,[1,3] Ubleni E. Emanghe,[2] Ernest A. Ochang,[2] and Tatfeng Y. Mirabeau[4]

2022

Urine *Histoplasma* Ag detection and sputum PCR in participants with presumptive diagnosis of pulmonary TB between April 2020 and March 2021

Overall prevalence 12.7%

Prevalence among TB confirmed 7.4%

Prevalence among TB unconfirmed 16.8%

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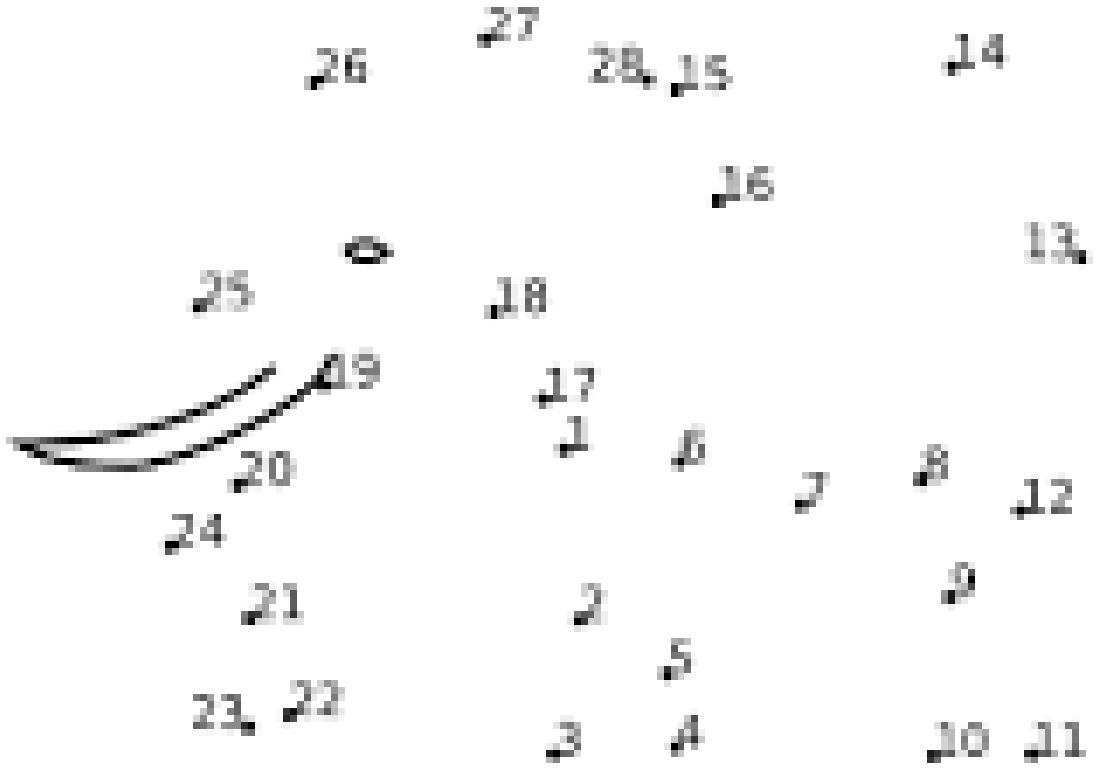
Invisible burden of HIV-associated histoplasmosis in Latin America



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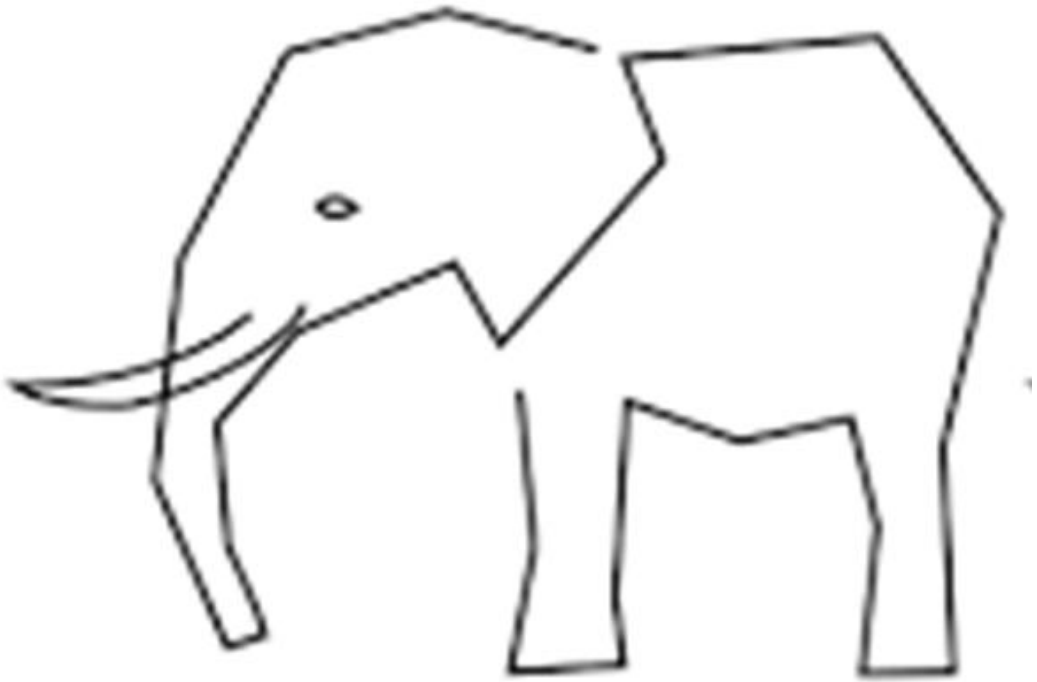
Launching an initiative in order to connect the dots and better see the magnitude of the problem



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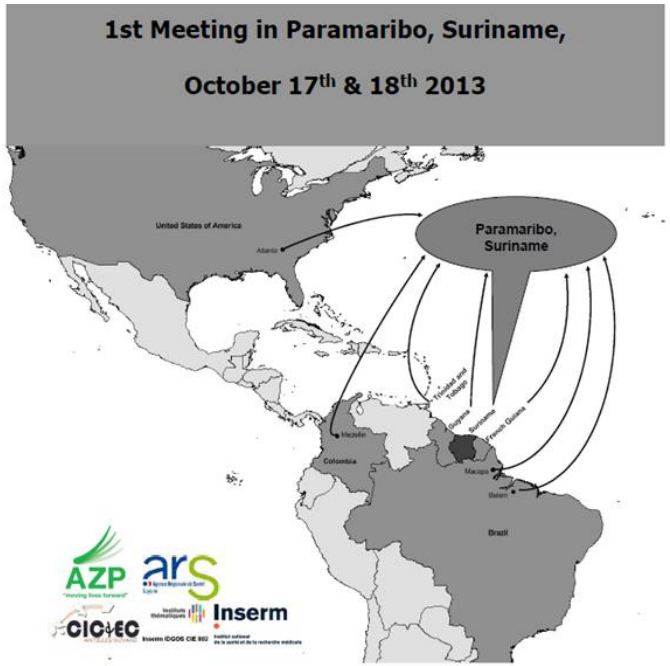
Aim: reducing AIDS-related deaths by decreasing histo-HIV case-fatality rates



Pan American Health Organization
Regional Office of the World Health Organization

Technical Cooperation Among Countries
Suriname – Guyana – French Guiana

Title:

Control of Histoplasmosis in the Guiana Shield

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Strong statement in 2013
Histoplasmosis in Latin America is a « neglected killer »

OPEN ACCESS Freely available online

PLOS | NEGLECTED TROPICAL DISEASES

Editorial

Disseminated Histoplasmosis in HIV-Infected Patients in South America: A Neglected Killer Continues on Its Rampage

Mathieu Nacher[1,2]*, Antoine Adenis[1,2], Sigrid Mc Donald[3], Margarete Do Socorro Mendonca Gomes[4], Shanti Singh[5], Ivina Lopes Lima[4], Rosilene Malcher Leite[4], Sandra Hermelijn[3], Merril Wongsokarijo[6], Marja Van Eer[7], Silvia Marques Da Silva[8], Maurimelia Mesquita Da Costa[8], Marizette Silva[9], Maria Calvacante[9], Terezinha do Menino Jesus Silva Leitao[10], Beatriz L. Gómez[11], Angela Restrepo[11], Angela Tobon[11], Cristina E. Canteros[12], Christine Aznar[2], Denis Blanchet[2], Vincent Vantilcke[13], Cyrille Vautrin[13], Rachida Boukhari[13], Tom Chiller[14], Christina Scheel[14], Angela Ahlquist[14], Monika Roy[14], Olivier Lortholary[15,16], Bernard Carme[1,2], Pierre Couppié[2], Stephen Vreden[3]

1 Centre d'Investigation Clinique Epidémiologie Clinique Antilles Guyane (Inserm/DGOS CIE 802), Centre Hospitalier de Cayenne, Cayenne, French Guiana, France, **2** Epidemiologie Parasitoses et Mycoses Tropicales, EA 3593, Université Antilles Guyane, Cayenne, French Guiana, **3** Academisch Ziekenhuis Paramaribo Hospital, Paramaribo, Suriname, **4** Laboratório Central de Saúde Pública do Amapá, Macapa, Brazil, **5** National AIDS Program, Georgetown, Guyana, **6** Public Health Central Laboratory of Suriname, Paramaribo, Suriname, **7** Diakonessenhuis Hospital, Paramaribo, Suriname, **8** Instituto Evandro Chagas, Belém, Brazil, **9** Hospital de Clinicas Dr. Alberto Lima, Macapa, Brazil, **10** Universidade Federal do Ceara, Faculdade de Medicina, Departamento de Saude Comunitaria, Fortaleza, Ceara, Brazil, **11** Corporación para Investigaciones Biológicas, Medellín, Colombia, **12** INEI-ANLIS "Dr. Carlos G. Malbrán," Buenos Aires, Argentina, **13** Centre Hospitalier de l'Ouest Guyanais, Saint Laurent du Maroni, French Guiana, France, **14** Mycotic Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America, **15** Institut Pasteur, National Reference Center for Mycoses and Antifungals, Molecular Mycology Unit, Paris, France, **16** CNRS URA3012, Paris, France

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Advocacy, networking and capacity building

International Histoplasmosis Advocay Group (iHAG) started in 2013 and endorsed the Manaus declaration in 2019

Volume 22, Number 9—September 2016

Conference Summary

Proceedings of First Histoplasmosis in the Americas and the Caribbean Meeting, Paramaribo, Suriname, December 4–6, 2015

Mathieu Nacher and Antoine Adenis
Author affiliations: Centre d'Investigation Clinique Antilles Guyane, INSERM 1424, Centre Hospitalier Andrée Rosemon, Cayenne, French Guiana; EA3593 Ecosystèmes Amazoniens et Pathologie Tropicale, Université de Guyane, Cayenne

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Conference Summary

80 2020

80 2020

Current Fungal Infection Reports
https://doi.org/10.1007/s12281-019-00365-3

EPIDEMIOLOGY OF FUNGAL INFECTIONS (T CHILLER AND J BADDLEY, SECTION EDITORS)

Check for updates

The Manaus Declaration: Current Situation of Histoplasmosis in the Americas, Report of the II Regional Meeting of the International Histoplasmosis Advocacy Group

Diego H. Caceres[1] · Antoine Adenis[2] · João Vicente Braga de Souza[3] · Beatriz L. Gomez[4] · Katia Santana Cruz[5] · Alessandro C. Pasqualotto[6] · Giovanni Ravasi[7] · Freddy Perez[7] · Tom Chiller[1] · Marcus Vinicius Guimarares de Lacerda[8,9] · Mathieu Nacher[3] · The International Histoplasmosis Advocacy Group (iHAG)

100 by 2025

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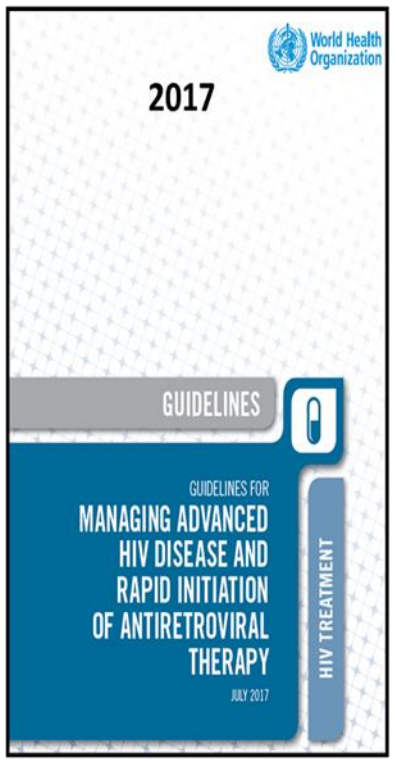
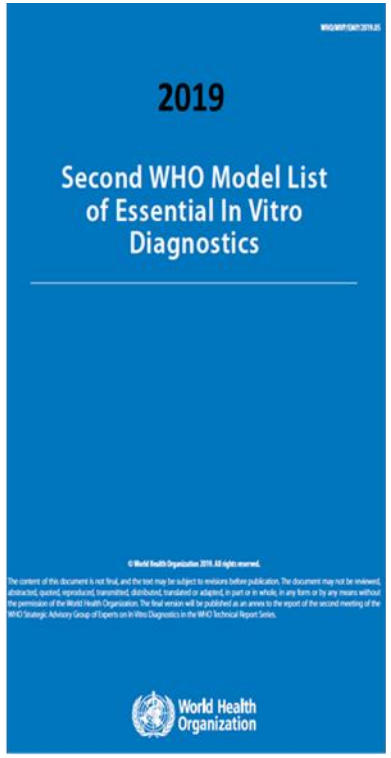
Steps toward international recognition on the public health issue represented by HIV-associated histoplasmosis

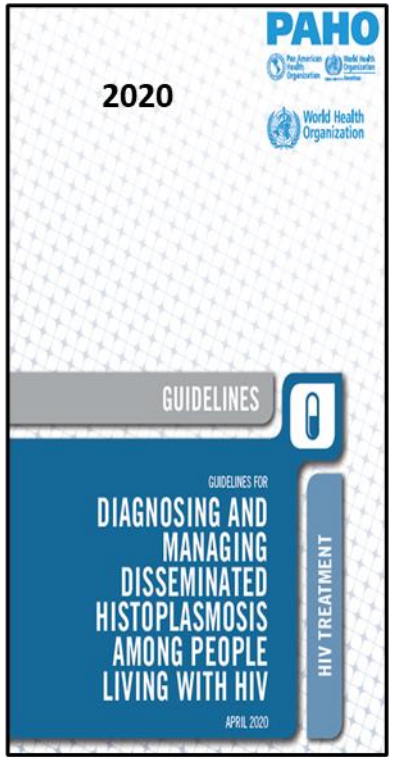


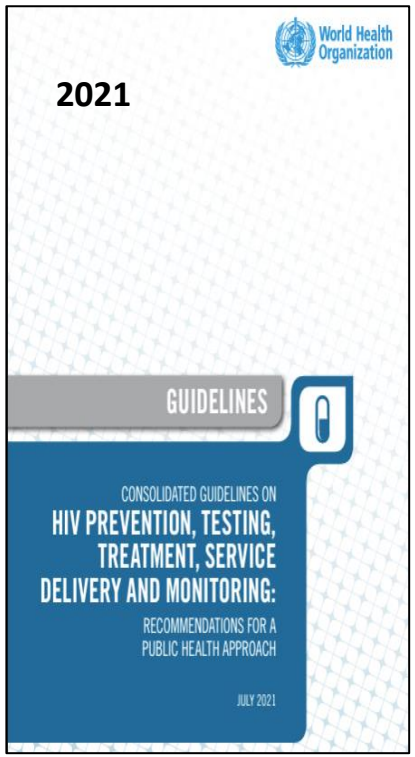
Mention of Histo

Mention of Itraconazole



Mention of Histo Ag detection





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WHO Guidelines for the diagnosis and treatment of histoplasmosis in persons with advanced HIV disease

Advocating for *Histoplasma* antigen detection developments and diffusion

World Health Organization

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Cochrane

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Histoplasma antigen screening among people with advanced HIV is a cost-effective strategy

→ could avert 17% of AIDS-related deaths in Latin America

PLOS GLOBAL PUBLIC HEALTH

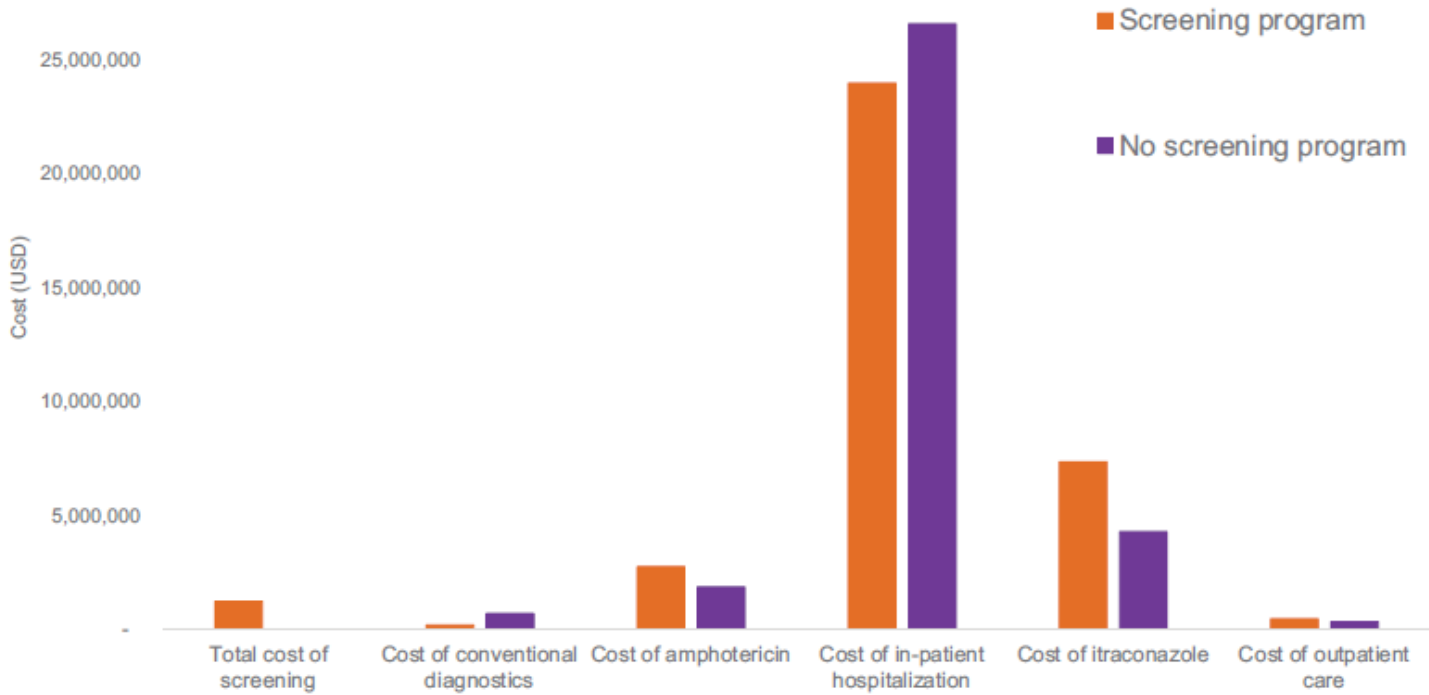
RESEARCH ARTICLE

Cost-effectiveness evaluation of routine histoplasmosis screening among people living with advanced HIV disease in Latin America and the Caribbean

Citation: Rajasingham R, Medina N, Mousquer GT, Caceres DH, Jordan A, Nacher M, et al. (2023) Cost-effectiveness evaluation of routine histoplasmosis screening among people living with advanced HIV disease in Latin America and the Caribbean. PLOS Glob Public Health 3(8): e0001861. https://doi.org/10.1371/journal.pgph.0001861

Table 3. Cost-effectiveness results of *Histoplasma* antigen screening.

	Cost (USD)	*Incremental Cost*	*Effectiveness (life years)*	*Incremental effectiveness*	*ICER (Cost/LYS)*
No Histoplasma antigen screening	$33,763,183	--	423,567	--	--
Histoplasma antigen screening	$35,975,763	$2,212,580	507,886	84,319	$26



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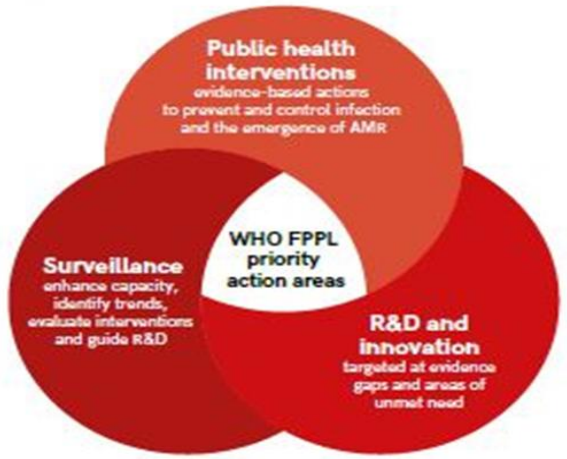
iHAG initiative is nowadays fully endorsed by WHO and in future global guidelines

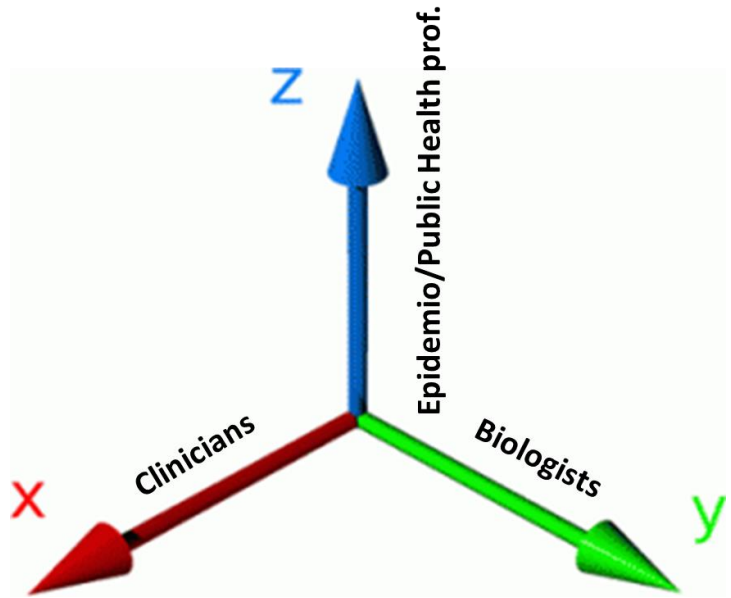
Table 3. WHO fungal priority pathogens list

Critical group	High group	Medium group
Cryptococcus neoformans	*Nakaseomyces glabrata (Candida glabrata)*	*Scedosporium* spp.
Candida auris	*Histoplasma* spp.	*Lomentospora prolificans*
Aspergillus fumigatus	Eumycetoma causative agents	*Coccidioides* spp.
Candida albicans	Mucorales	*Pichia kudriavzevii (Candida krusei)*
	Fusarium spp.	*Cryptococcus gattii*
	Candida tropicalis	*Talaromyces marneffei*
	Candida parapsilosis	*Pneumocystis jirovecii*
		Paracoccidioides spp.

Fig. 2. Proposed priority areas for action



AMR: antimicrobial resistance; R&D: research and development; WHO FPPL: World Health Organization fungal priority pathogens list.



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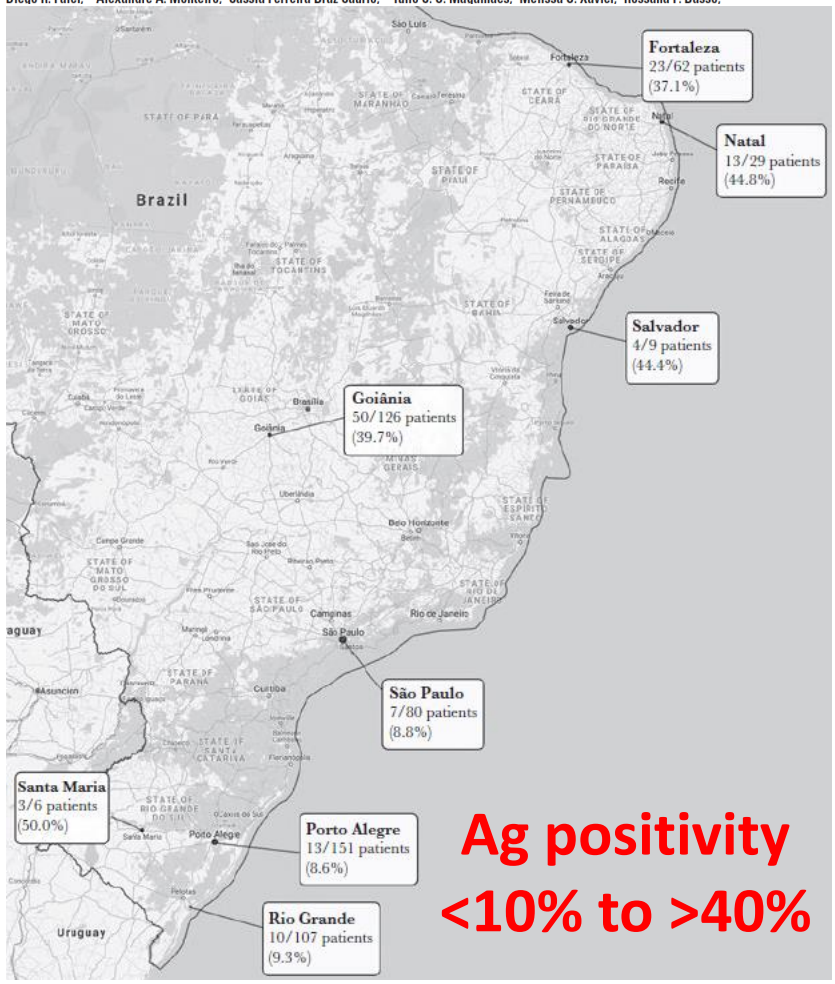
The « Porto Alegre » brazilian experts initiative

Histoplasmosis, An Underdiagnosed Disease Affecting People Living With HIV/AIDS in Brazil: Results of a Multicenter Prospective Cohort Study Using Both Classical Mycology Tests and *Histoplasma* Urine Antigen Detection

Diego R. Falci,[1,2] Alexandre A. Monteiro,[3] Cassia Ferreira Braz Caurio,[3,4] Tulio C. O. Magalhães,[1] Melissa O. Xavier,[5] Rossana P. Basso,[5]



Ag positivity <10% to >40%

The "Histoplasmosis Porto Alegre manifesto"—Addressing disseminated histoplasmosis in AIDS

Citation: Pasqualotto AC, Queiroz-Telles F, Chebabo A, Leitao TMJS, Falci DR, Xavier MO, et al. (2023) The "Histoplasmosis Porto Alegre manifesto"—Addressing disseminated histoplasmosis in AIDS. PLoS Negl Trop Dis 17(1): e0010960. https://doi.org/10.1371/journal.pntd.0010960

Alessandro C. Pasqualotto[1]*, Flavio Queiroz-Telles[2], Alberto Chebabo[3], Terezinha M. J.

Box 1. Main needs related to histoplasmosis in Brazil

- Histoplasmosis is endemic in Brazil; therefore, proper disease awareness is needed, particularly in high-risk patients such as those with advanced HIV disease.
- Early diagnosis of disseminated histoplasmosis (DH) requires access to *Histoplasma* antigen detection.
- All patients with DH should have access to liposomal amphotericin B.

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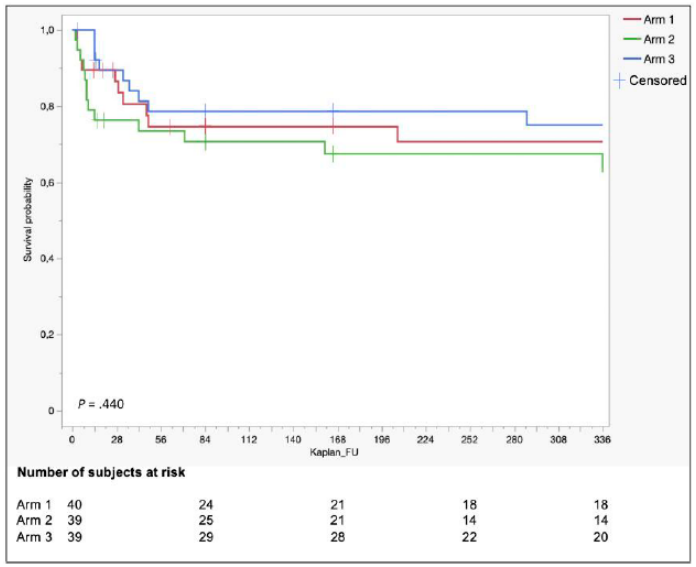
Revisiting antifungal therapy strategy on a phase II trial

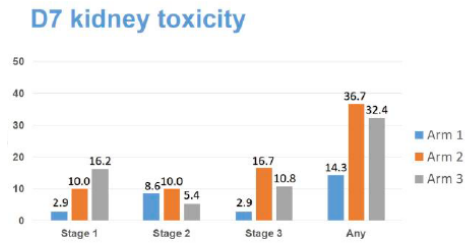
Clinical Infectious Diseases

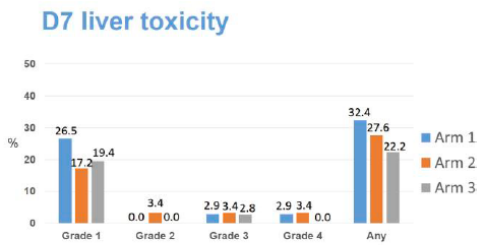
MAJOR ARTICLE

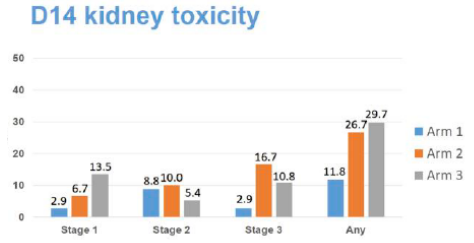
Single High Dose of Liposomal Amphotericin B in Human Immunodeficiency Virus/AIDS-Related Disseminated Histoplasmosis: A Randomized Trial

Alessandro C. Pasqualotto,[1,2] Daiane Dalla Lana,[1] Cassia S. M. Godoy,[3,4] Terezinha do Menino Jesus Silva Leitão,[5,6] Monica B. Bay,[7,8] Lisandra Serra Damasceno,[5,6] Renata B. A. Soares,[3,4] Roger Kist,[2] Larissa R. Silva,[1] Denusa Wiltgen,[1,2] Marineide Melo,[9] Taiguara F. Guimarães,[3] Marilia R. Guimarães,[10] Hareton T. Vechi,[7] Jacó R. L. de Mesquita,[5] Gloria Regina de G. Monteiro,[7,8] Antoine Adenis,[11] Nathan C. Bahr,[12] Andrej Spec,[13] David R. Boulware,[14] Dennis Israelski,[15] Tom Chiller,[16] and Diego R. Falci[17,18]









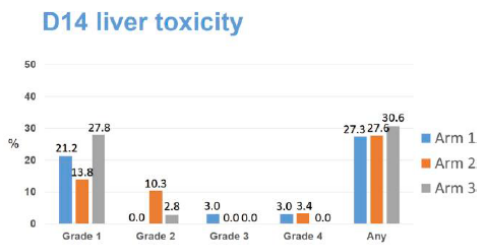


Figure 2. Cumulative survival per study arm. Arm 1 received single (10 mg/kg) high dose of liposomal amphotericin B (n = 40). Arm 2 received 10 mg/kg on day 1, followed by 5 mg/kg on day 3 (n = 39). Arm 3 is the control group (3 mg/kg of liposomal amphotericin B for 2 weeks) (n = 39).

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Moving up to a phase III clinical trial

NIH National Library of Medicine
National Center for Biotechnology Information

PRS Login

ClinicalTrials.gov

NOT YET RECRUITING

Efficacy and Safety of High-dose Liposomal Amphotericin B for Disseminated Histoplasmosis in AIDS

ClinicalTrials.gov ID NCT05814432

Sponsor Federal University of Health Science of Porto Alegre

Information provided by Alessandro Pasqualotto, Federal University of Health Science of Porto Alegre (Responsible Party)

Last Update Posted 2024-09-27

Study Overview

Brief Summary

Phase III trial evaluating the safety and efficacy of a single high dose (10 mg/kg) of liposomal amphotericin B for disseminated histoplasmosis in AIDS patients, in comparison to standard therapy (3 mg/kg of liposomal amphotericin B for two weeks) (INDUCTION trial).

Detailed Description

Histoplasmosis is a serious endemic mycosis that may disseminate in immunocompromised patients. The disease in endemic in the American continent, particularly Brazil. Patients with advanced HIV infection are susceptible to disseminated histoplasmosis, an AIDS-defining illness. According to international guidelines, induction therapy for disseminated histoplasmosis involves the use of liposomal amphotericin B for two weeks, but access to this medication is limited in several regions of the globe. A phase II trial showed promising results with the use of a single high dose of liposomal amphotericin B in this context. Here we propose a phase III study aimed to evaluate non-inferiority of induction therapy with liposomal amphotericin B for disseminated histoplasmosis in AIDS, comparing 10 mg/kg (interventional arm) versus 3 mg/kg for two weeks (standard therapy) regarding two-week mortality and superiority in a Desirability of Outcome Ranking (DOOR). Induction therapy will be followed by oral itraconazole for one year for all patients. A Data Safety Monitoring Board (DSMB) will be established with the aim of defining whether the study needs to be stopped early for efficacy or harm to the study participants. The group will meet every 12 months to review the study data.

Study Start (Estimated)
2024-11-01

Primary Completion (Estimated)
2025-11-28

Study Completion (Estimated)
2026-11-28

Enrollment (Estimated)
279

Study Type
Interventional

Phase
Phase 3

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Scaling-up an AHD package of care (BRAZIL 2022 & Argentina 2024?)

« Advanced AIDS fast track » notably with Histoplasma urinary antigen detection (LFA) and a mandatory surveillance system of incident cases

MINISTÉRIO DA SAÚDE
Secretaria de Vigilância em Saúde
Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis

CIRCUITO RÁPIDO DA AIDS AVANÇADA

Fluxogramas

Brasília – DF
2022

	Atenção primária (APS) Unidades Básicas de Saúde	Atenção secundária Serviço de Assistência Especializada (SAE) Hospital-Dia; Urgência/Emergência	Atenção terciária Hospitais
Diagnóstico e monitoramento do HIV/aids	Diagnóstico de HIV/aids		
	CD4 convencional BD ou Rápido Abbott Pima		
	CD4 imunocromatográfico rápido VISITECT		
	Carga viral do HIV		
Diagnóstico de infecções oportunistas (IO)		LF-LAM (tuberculose)	
	LF-LAM (tuberculose)		
		Teste rápido molecular para tuberculose (TRM-TB) (fluidos e tecidos)	
	Baciloscopia, cultura para micobactérias		
	Radiografia de tórax		
		Biópsia e histopatológico	
		LF-CrAg (amostra sanguínea)	
		LF-CrAg (amostra líquor) - Hospital-Dia	
		Antígeno urinário para histoplasmose	

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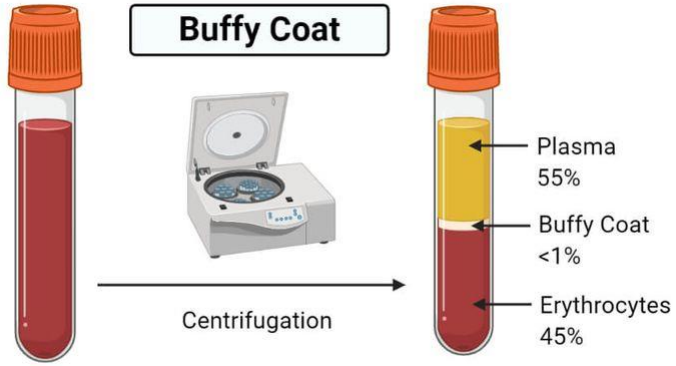
Initiative facing implementation issues & challenges

1. Company unable to produce and distribute enough test



2. Effective access to Liposomal Amphotericin B remains challenging

J Antimicrob Chemother 2024; **79**: 2598–2606
https://doi.org/10.1093/jac/dkae264 Advance Access publication 29 July 2024

Journal of Antimicrobial Chemotherapy

A multicentre study of amphotericin B treatment for histoplasmosis: assessing mortality rates and adverse events

William Kazunori Sekiguchi[1], Vítor Falcão de Oliveira[1], Francelise Bridi Cavassin[2], Mariane Taborda[1], Adriana Satie Gonçalves Kono Magri[1], Isabela Carvalho Leme Vieira da Cruz[1], Jose Ernesto Vidal[1,3], Diego Rodrigues Falci[4], Cássia Silva de Miranda Godoy[5], Renata de Bastos Ascenço Soares[5], Carla Sakuma de Oliveira[6], Ana Verena Almeida Mendes[7], Giovanni Luís Breda[8], Caroline Martins Rego[3], Maíra Araujo Félix[3], Paula Pacheco Katopodis[9], Julia Raquel da Silva do Ó[9], Mirela Pereira Lima Abrão[10], João Luiz Baú-Carneiro[11], Talita Teles Teixeira Pereira[7], Flávio Queiroz-Telles[8,12] and Marcello Mihailenko Chaves Magri[1]*

75% D-AMB, 20% ABLC (Abelcet), 5% L-AMB

Use of D-AMB as a factor associated with death
aOR 4.93 (1.40–22.4)

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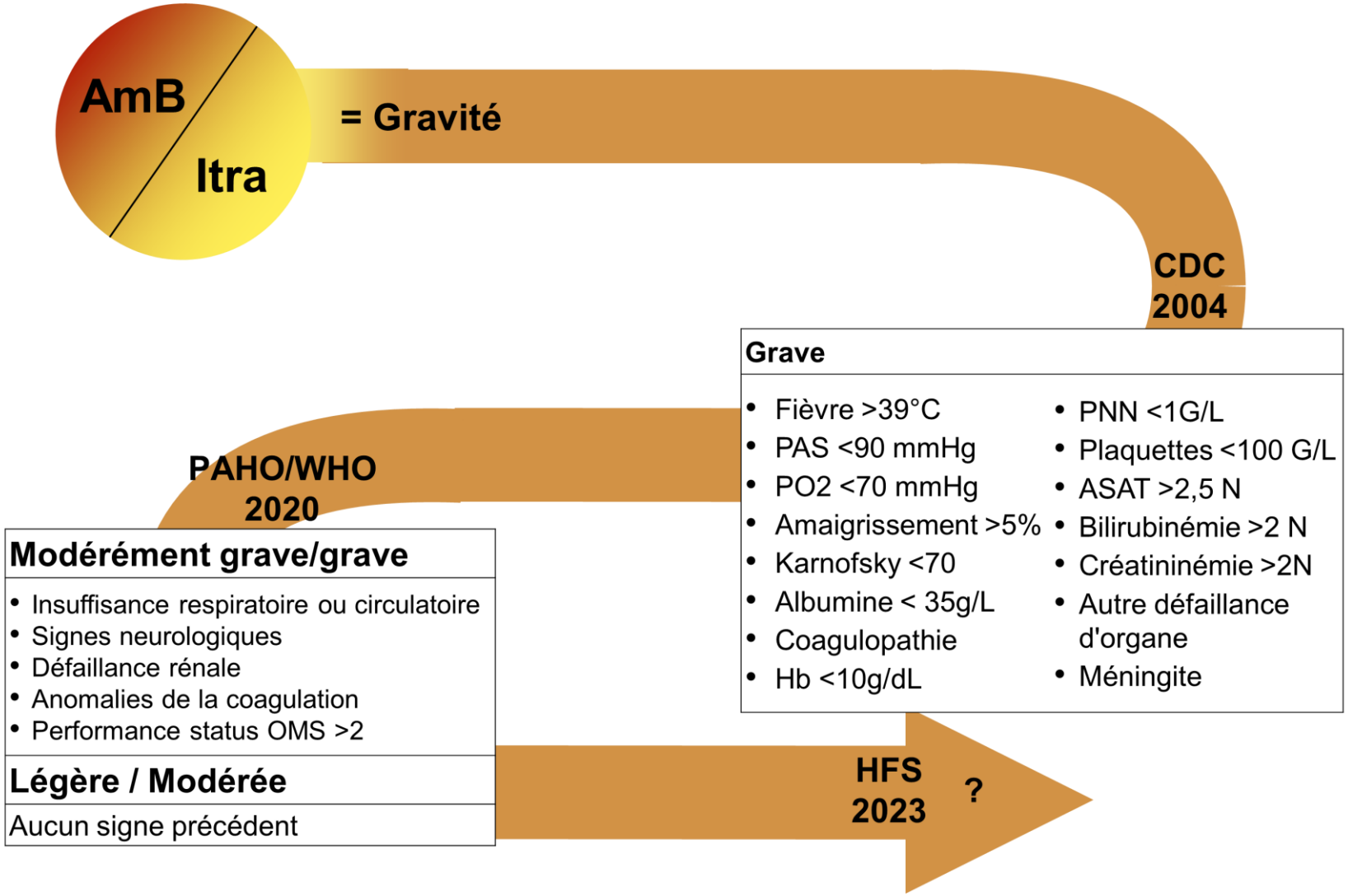
Needs regarding a robust severity case-definition to help inform clinical decision-making



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Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Development of a case fatality prognostic score for HIV-associated histoplasmosis

Ugo Françoise[1,*], Mathieu Nacher[1,2], Morgane Bourne-watrin[3], Loïc Epelboin[2,4], Camille Thorey[5], Magalie Demar[2,6], Jean-François Carod[7], Félix Djossou[2,4], Pierre Couppié[2,3], Antoine Adenis[1,2]

Histoplasmosis case-Fatality Score

Prognostic of death at 30 days of treatment of disseminated histoplasmosis in patients living with HIV

Clinical criteria
- ☐ WHO Performance status ≥3
- ☐ Altered mental status
- ☐ Dyspnea

Radiological criterion
- ☐ Interstitial lung pattern on thoracic X-ray

Biological criteria
- ☐ CRP ≥75 mg/L

Cytopenia
- ○ No cytopenia
- ○ One cytopenia (Hb <9 g/dL OR platelet <100 000 /mL)
- ○ Two cytopenia (Hb <9 g/dL AND platelet <100 000/mL)

SCORE ME

CALCUL

?

A HFS <5 is associated with a risk of death < 5% after 30 days of antifungal therapy → Induction treatment with itraconazole can be considered

A HFS ≥5 is associated with a risk if death ≥33% after 30 days of antifungal therapy → Induction treatment with liposomal amphotericin B is recommended

https://cicec-antilles-guyane.org/hfs/

From Françoise al., IJID, 2023

Development of simple prognostic score

-> External validation ongoing across LATAM

15 research teams
10 countries

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As a conclusion on histoplasmosis nowadays

Global burden remains mostly unknown & probably expanding

Misdiagnosis for tuberculosis remains an issue but also represents an opportunity to raise awareness and reduced AIDS-related deaths

Toolbox (diagnostic & therapeutic) are expanding but their stewardships together with the industry R&D remain insufficient

Initiatives (sometimes transdisciplinary) increased knowledge, showed a rise in incidence and helped tackle mortality

Costs studies are mandatory to support these initiatives

TB + HIV

Histoplasmosis

WARNING

YOU MAY BE IN A BLIND SPOT

ars Agence Régionale de Santé Guyane

Spilf

Centre Hospitalier Cayenne

CARBU

MALINGUY

Université de Guyane

PRÉFET DE LA RÉGION GUYANE
Liberté
Égalité
Fraternité

First think histoplasmosis

And

Look for it

Screen if you can

Or

Treat empirically