

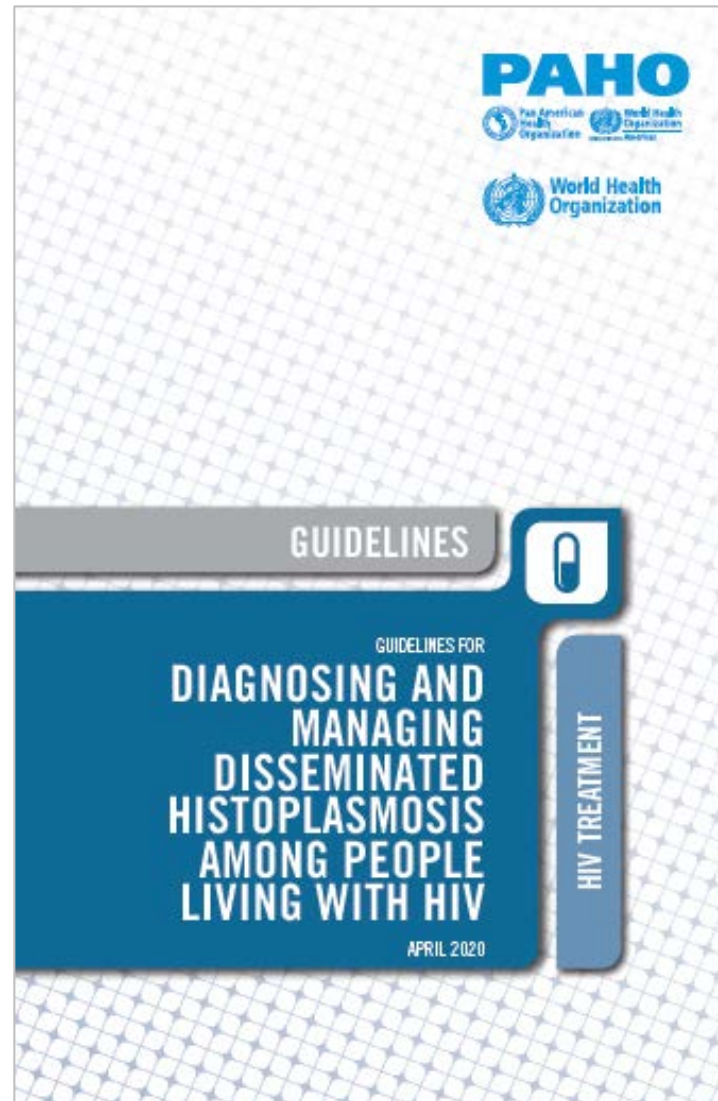


WHO/PAHO Guidelines for Histoplasmosis and HIV

Tom Chiller, MD, MPHTM

Chief, Mycotic Diseases Branch

WHO guidance on Advanced HIV Disease



The Advanced HIV Disease package includes screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions

Background: the burden of histoplasmosis in PLHIV in the Americas

Burden of HIV-associated histoplasmosis compared with tuberculosis in Latin America: a modelling study



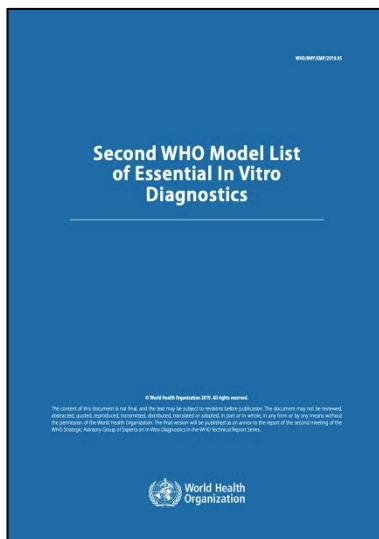
Antoine A Adenis, Audrey Valdes, Claire Crozet, Orion Z McCotter, Gordana Derada, Pierre Couppie, Tom Chiller, Mathieu Nacher



Figure 2: Estimated annual incidence of histoplasmosis cases per 100 people living with HIV in Latin America, 2012

- **Limited reduction in AIDS-related deaths overtime** in LAC (19% between 2010 and 2018) and 1 out of 3 new HIV cases are diagnosed late (initial CD4 cell count <200 cells/mm³) (UNAIDS 2019).
- **Histoplasmosis is a prevalent OIs in PLHIV in the Americas** (up to 15,600 cases and 4,500 deaths per year) with some geographic areas of high endemicity. (Adenis AA et al, Lancet Infect Dis 2018)
- **The burden of histoplasmosis is equivalent or higher than TB** and other disseminated fungal infections among PLHIV in Latin America (Adenis AA et al, Lancet Infect Dis 2018; Calderon EJ et al, Expert Rev Anti Infect Ther, 2013; Rajasingham R et al, Lancet Infect Dis 2017).
- **Co-infection of TB and histoplasmosis is frequent** in PLHIV (8–38%) (Caceres DH et al, J Fungi, 2019; Samayoa B et al, Open Forum Inf Dis 2019)
- **Symptoms of disseminated histoplasmosis are nonspecific** and may be indistinguishable from other OIs (Adenis AA et al, Am J Trop Med Hyg 2014).

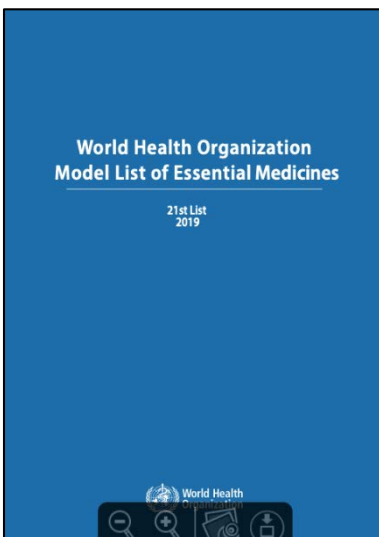
Essential diagnostics and medicines are available



II.b Disease-specific IVDs for use in clinical laboratories <i>continued</i>						
Disease	Diagnostic test	Test purpose	Assay format	Specimen type	WHO prequalified or recommended products	WHO supporting documents
	Histoplasma antigen	To aid in the diagnosis of disseminated histoplasmosis	Immunoassay	Urine	N/A	Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy (2017) https://apps.who.int/iris/handle/10665/255884

https://www.who.int/docs/default-source/nutritionlibrary/complementary-feeding/second-who-model-list-v8-2019.pdf?sfvrsn=6fe86adf_1

Ag-based IVDs for histoplasmosis are accurate, provide rapid confirmation of diagnosis, enables differential diagnosis with other OIs, improves timely optimal treatment, reduces empirical treatment.



6.3 Antifungal medicines	
amphotericin B	Powder for injection: 50 mg in vial (as sodium deoxycholate or liposomal complex).
itraconazole*	Capsule: 100 mg. Oral liquid: 10 mg/mL. * For treatment of chronic pulmonary aspergillosis, histoplasmosis, sporotrichosis, paracoccidioidomycosis, mycoses caused by <i>T. marneffe</i> and chromoblastomycosis; and prophylaxis of histoplasmosis and infections caused by <i>T. marneffe</i> in AIDS patients.

<https://www.who.int/medicines/publications/essentialmedicines/en/>

Guideline development process

- WHO guideline development process
- Guideline Development Group (chair and methodologist)
- PAHO/WHO Secretariat
- PICO questions defined
- Systematic reviews (See Annex)
- GRADE method
- Additional considerations (feasibility, acceptability, sustainability).
- External Review Group
- **4 main recommendations developed**

The following three questions were identified:

1. Is antigen testing versus standard microbiological techniques of diagnosis associated with an increase in the diagnosis of histoplasmosis and a decrease in mortality among people with HIV disease?
2. What are the optimal therapeutic regimens for treating disseminated histoplasmosis in people living with HIV infection?
3. How does HIV or TB therapy need to be modified to ensure successful outcomes for histoplasmosis for people coinfecting with TB, HIV, and *H. capsulatum*?

1. Diagnosis of disseminated histoplasmosis among people living with HIV

1. Among people living with HIV, disseminated histoplasmosis should be diagnosed by detecting circulating *Histoplasma* antigens (*conditional recommendation; low-certainty evidence*).

Advantages of Ag-based tests

- High diagnostic accuracy for histoplasmosis among PLHIV
- Commercial kits available (ELISA; POC/LFA in the pipeline)
- Can be performed in laboratories with lower complexity (Biosafety Level 1 and 2)
- Ease of use in resource limited settings
- Use of non-invasive samples (urine)
- Rapid turn-around time
- Reduced time to diagnosis and optimal treatment initiation

2. Induction and maintenance antifungal treatment regimens for disseminated histoplasmosis among people living with HIV

2.1 Induction therapy

2.1.1 Treating severe or moderately severe histoplasmosis among people living with HIV: **liposomal amphotericin B¹**, 3.0 mg/kg daily, for two weeks is recommended (*conditional recommendation; very-low-certainty evidence*).

Alternative regimen: **deoxycholate amphotericin B** (0.7–1.0 mg/kg) for the initial two weeks.

2.1.2 Treating mild to moderate histoplasmosis among people living with HIV: **itraconazole²** 200 mg three times daily for three days and then 200 mg twice daily is recommended (*conditional recommendation, very-low-certainty evidence*).

¹ Compared with deoxycholate amphotericin B, people treated with liposomal amphotericin B had improved clinical success (82% versus 56%), lower mortality (2% versus 13%) and less nephrotoxicity (9% versus 37%). (*Johnson PC et al, Ann Intern Med. 2002; Murray M et al, Cochrane Database Syst Rev 2020*).

² For treating people with less severe disease, fluconazole (800 mg daily for 12 weeks) was less effective than itraconazole (*Wheat et al, Am J Med 1997; Wheat et al, Am J Med 1995*).

2. Induction and maintenance antifungal treatment regimens for disseminated histoplasmosis among people living with HIV

2.2 Maintenance therapy

- **Itraconazole**¹ 200 mg twice daily for 12 months is recommended (*conditional recommendation; very-low-certainty evidence*).
- Less than 12 months of therapy can be considered when the person is clinically stable, receiving antiretroviral therapy, has suppressed viral load, and the immune status has improved² (*conditional recommendation, very-low-certainty evidence*).

¹ Treatment success rates are higher when maintenance therapy is with itraconazole (75%) compared with fluconazole (40%) (Norris S et al, Am J Med 1994; Sharkey-Mathis PK et al J Acquir Immune Defic Syndr 1993)

² Balancing the risk of relapse, drug–drug interactions, and side-effects, clinicians may opt for shorter courses of maintenance therapy (at least six months long), based on response to antiretroviral therapy, immune recovery, clinical resolution of histoplasmosis, and drug–drug interactions.

3. Timing of antiretroviral therapy initiation

3. Antiretroviral therapy should be initiated as soon as possible among people with disseminated histoplasmosis for whom central nervous system involvement is not suspected or proven (*conditional recommendation; very-low-certainty evidence*).

GDG considerations on timing of ART initiation

- IRIS appears to be uncommon among PLHIV with disseminated histoplasmosis following ART (*Melzani A et al, Clin Infect Dis 2020*).
- The evidence of IRIS in early vs. delayed ART initiation is limited and efficacy and safety outcomes unknown (*Zolopa A et al, PLoS One 2009*).
- Antiretroviral therapy should not be delayed for PLHIV diagnosed with disseminated histoplasmosis who are administered antifungal therapy.
- This recommendation only applies to PLHIV without CNS involvement to avoid immune reconstitution syndrome in the central nervous system.

4. TB therapy for people coinfecting with TB, HIV, and histoplasmosis

4. People living with HIV with TB and histoplasmosis coinfection should receive TB therapy according to WHO treatment guidelines (*conditional recommendation; very-low-certainty evidence*).

GDG considerations on management of PLHIV coinfecting with TB and histoplasma

- **Prompt treatment initiation** after diagnosis according to WHO treatment guidelines and preferred regimens.
- **Risk of drug–drug interactions** (rifampicin, certain ARVs) leading to subtherapeutic itraconazole levels, itraconazole drug levels should be monitored, if possible.
- **If histoplasmosis not controlled because of drug-drug interactions:** extend amphotericin B induction; once-weekly courses of amphotericin B; increase itraconazole dose, monitoring blood level and toxicity; use other azoles; replace rifampicin with rifabutin.

Other clinical aspects addressed in the GL

- Managing IRIS associated with histoplasmosis
- Monitoring the toxicity of amphotericin B treatment
- Monitoring the treatment response
- Diagnostic approach to persistent or recurrent symptoms
- Managing relapse
- Research priority

Acknowledgments

Guideline Development Group

The following individuals contributed to developing this guideline:

John Baddley (Department of Medicine, Division of Infectious Diseases, University of Maryland School of Medicine, Baltimore, Maryland, USA), **Mathieu Nacher** (Centre d'Investigation Clinique, CIC INSERM 1424, Centre Hospitalier de Cayenne, Cayenne, French Guiana), **Alessandro C. Pasqualotto** (Universidade Federal de Ciências da Saúde de Porto Alegre and Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, Brazil), **Ana Belen Arauz** (Hospital Santo Tomas, Panama City, Panama), **Antoine Adenis** (Centre d'Investigation Clinique, CIC INSERM 1424, Centre Hospitalier de Cayenne, Cayenne, French Guiana), **Beatriz L. Gomez** (School of Medicine and Health Sciences, Universidad del Rosario, Bogota, Colombia), **Cristina Elena Canteros** (Mycology Department, INEI, ANLIS "Dr. Carlos G. Malbrán," Buenos Aires, Argentina), **Eduardo Arathoon** (Asociación de Salud Integral, Guatemala City, Guatemala), **Flavio Queiroz Telles** (Departamento de Saúde Coletiva, Universidade Federal do Paraná, Curitiba, Brazil), **Nataly Garcia** (Departamento de Microbiología, Referlab, Caracas, Bolivarian Republic of Venezuela), **Tom Chiller** (Mycotic Diseases Branch, United States Centers for Disease Control and Prevention, Atlanta, GA, USA).

The following individuals contributed to the systematic reviews and supporting evidence:

Diego H. Caceres (Mycotic Diseases Branch, United States Centers for Disease Control and Prevention, Atlanta, GA, USA - Center of Expertise in Mycology Radboudumc/CWZ, Nijmegen, The Netherlands), **Marylou Murray** (Cochrane Infectious Diseases Group, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, United Kingdom), **Paul Garner** (Cochrane Infectious Diseases Group, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, United Kingdom), **Paul Hine** (Cochrane Infectious Diseases Group, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, United Kingdom)

External Review Group

Alexandro Bonifaz (Hospital General de México, "Dr. Eduardo Liceaga", Mexico City, Mexico), **Ana Alastruey** (Servicio de Micología, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain), **Angela Tobon** (Instituto Colombiano de Medicina Tropical, Medellín, Colombia), **Arnaldo Colombo** (Universidade Federal de São Paulo (UNIFESP), São Paulo, SP, Brazil), **Blanca Samayoa** (Asociación de Salud Integral, Guatemala City, Guatemala), **Carol Kauffman** (Division of Infectious Diseases, University of Michigan, Ann Arbor, MI, USA), **Juan Luis Rodriguez-Tudela** (Global Action Fund for Fungal Infections, Geneva, Switzerland), **Mohamed Chakroun** (Infectious Diseases Department, University Hospital of Monastir, Monastir, Tunisia), **Nathan Bahr** (University of Kansas, Kansas City, KS, USA), **Nelesh P. Govender** (National Institute for Communicable Diseases, Johannesburg, South Africa), **Stephen Vreden** (SRCS, Academic Hospital Paramaribo, Paramaribo, Suriname), **Thuy Le** (Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam).

PAHO and WHO staff

Freddy Perez (WHO Regional Office for the Americas) provided overall coordination for the development of this guideline, with the support of **Giovanni Ravasi** (WHO Regional Office for the Americas), **Ludovic Reveiz** (WHO Regional Office for the Americas) and **Nathan Ford** (HIV Department, WHO).

Manaus declaration

Current Fungal Infection Reports

<https://doi.org/10.1007/s12281-019-00365-3>

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

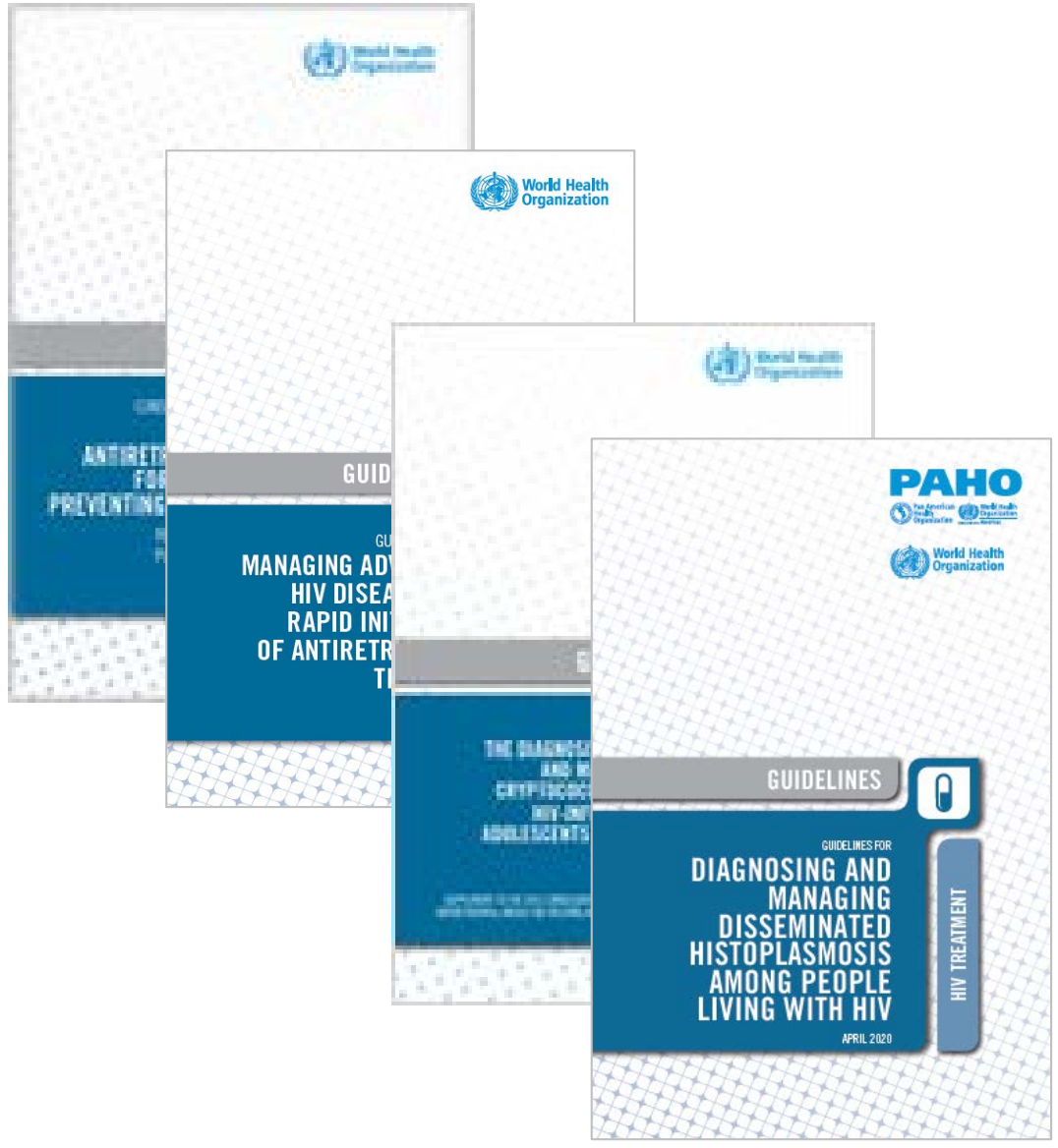


The Manaus Declaration: Current Situation of Histoplasmosis in the Americas, Report of the II Regional Meeting of the International Histoplasmosis Advocacy Group

Diego H. Caceres¹ • Antoine Adenis² • João Vicente Braga de Souza³ • Beatriz L. Gomez⁴ • Katia Santana Cruz⁵ • Alessandro C. Pasqualotto⁶ • Giovanni Ravasi⁷ • Freddy Perez⁷ • Tom Chiller¹ • Marcus Vinicius Guimaraes de Lacerda^{8,9} • Mathieu Nacher³ • The International Histoplasmosis Advocacy Group (iHAG)

100 by 25 target: 100% of countries in the Americas with access to rapid testing for histoplasmosis (antigen or molecular testing) and itraconazole and lipid formulations of amphotericin B by 2025.





Thank you