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GUIDELINES



GUIDELINES FOR
**DIAGNOSING AND
MANAGING
DISSEMINATED
HISTOPLASMOSIS
AMONG PEOPLE
LIVING WITH HIV**

APRIL 2020

HIV TREATMENT

GUIDELINES FOR

DIAGNOSING AND MANAGING DISSEMINATED HISTOPLASMOSIS AMONG PEOPLE LIVING WITH HIV

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Guidelines for Diagnosing and Managing Disseminated Histoplasmosis among People Living with HIV

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ABBREVIATIONS AND ACRONYMS

CD4	CD4 T lymphocyte
CI	confidence interval
ELISA	enzyme-linked immunosorbent assay
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
PAHO	Pan American Health Organization
PICO	population, intervention, comparison, outcome
RR	relative risk
TB	tuberculosis
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Histoplasmosis is a disease caused by the fungus *Histoplasma capsulatum*. This disease is highly endemic in some regions of North America, Central America, and South America and is also reported in certain countries of Asia and Africa. It often affects people with impaired immunity, including people living with HIV, among whom the most frequent clinical presentation is disseminated histoplasmosis. The symptoms of disseminated histoplasmosis are non-specific and may be indistinguishable from those of other infectious diseases, especially disseminated tuberculosis (TB), thus complicating diagnosis and treatment. Histoplasmosis is one of the most frequent opportunistic infections caused by fungal pathogens among people living with HIV in the Americas and may be responsible for 5–15% of AIDS-related deaths every year in this Region.

These guidelines aim to provide recommendations for the diagnosis, treatment, and management of disseminated histoplasmosis in persons living with HIV. Although the burden of disease is concentrated in the Americas, the recommendations contained within these guidelines are applicable globally. These guidelines were produced in accordance with the World Health Organization (WHO) handbook for guideline development. The Guideline Development Group elaborated the final recommendations based on systematic review of scientific literature and critical evaluation of the evidence available using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.

These guidelines are intended for health-care providers, HIV program managers, policy-makers, national treatment advisory boards, and other professionals involved in caring for people who either have or may be at risk of developing disseminated histoplasmosis.

Recommendations

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

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

Disseminated histoplasmosis classification definitions

- Severe or moderately severe histoplasmosis is defined as the presence of at least one sign or symptom involving vital organs: respiratory or circulatory failure, neurological signs, renal failure, coagulation anomalies and a general alteration of the WHO performance status greater than 2, in which the person is confined to a bed or chair more than half of the waking hours and only capable of limited self-care.
- Mild to moderate histoplasmosis is defined as signs and symptoms that do not include the above features defining severe or moderately severe histoplasmosis.

2.1 Induction therapy

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

In settings where liposomal amphotericin B is unavailable, deoxycholate amphotericin B, 0.7–1.0 mg/kg, is recommended for two weeks (conditional recommendation; very-low-certainty evidence). As a good practice for people with renal failure, or at risk of renal injury, measures to prevent or treat toxicity are recommended (subsection 3.5).

Induction therapy should be given for two weeks. Since deoxycholate amphotericin B may be associated with renal toxicity, therapy may need to be shorter than two weeks based on the clinical assessment of how the person responds to treatment. Involvement of the central nervous system may require extending induction therapy or increasing dosage.

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

2.2 Maintenance therapy: itraconazole 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 improved (conditional recommendation, very-low-certainty evidence).

3. Timing of antiretroviral therapy initiation: 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).

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

2. BACKGROUND

Considerable progress has been made in access to HIV testing and treatment globally, with 79% of people living with HIV aware of their status and 62% receiving treatment in 2018. Expanding the testing and treatment of HIV has led to a decline in HIV-associated mortality globally by 33% between 2010 and 2018. Nevertheless, an estimated 770,000 people died from HIV-related illness in 2018 (1). Global progress has been mirrored in Latin America and the Caribbean, where an estimated 79% of people living with HIV knew their status and 61% were receiving treatment in 2018. Despite this progress, the number of people dying from HIV-associated causes declined by only 19% from 2010 to 2018 (41,000 in 2018). Further, more than 30% of the people newly diagnosed with HIV in Latin America and the Caribbean present to care with advanced HIV disease (initial CD4 cell count less than 200 cells/mm³), with little to no progress compared with 2016 (1). For Latin America and the Caribbean to reach the regional target of fewer than 19,000 people dying annually from HIV-related causes, national programs need to enhance their capacity to diagnose HIV earlier, offer antiretroviral therapy with rapid initiation to everyone living with HIV regardless of their immune status and address the most common causes of illness and death among people living with HIV (2).

Globally, leading causes of mortality among adults with advanced HIV disease include tuberculosis (TB), severe bacterial infections, cryptococcal meningitis, toxoplasmosis, and *Pneumocystis jirovecii* pneumonia. Among children, TB, severe bacterial infections, *Pneumocystis jirovecii* pneumonia, diarrheal diseases, malnutrition, and wasting are the leading causes of death (3). In Latin America and the Caribbean, in addition to TB (2), fungal infections are a major contributor to mortality, especially histoplasmosis, cryptococcal meningitis, and *Pneumocystis jirovecii* pneumonia; recent estimates suggest that the burden of histoplasmosis is equivalent in incidence and even higher in deaths compared with TB among people living with HIV in Latin America (4–6).

Histoplasmosis has a high endemicity in certain areas of the Americas (7). Although most frequently diagnosed in the Americas, it is also diagnosed in certain countries of Asia (China, India, Indonesia, Japan, Malaysia, Singapore, Thailand, and Viet Nam) and Africa (Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Gambia, Guinea Bissau, Liberia, Senegal, South Africa, and Uganda) (8). Among people living with HIV, the most frequent clinical presentation of this disease is disseminated histoplasmosis. Symptoms of disseminated histoplasmosis are nonspecific and may be indistinguishable from those of other infectious diseases, especially TB, thus complicating diagnosis and treatment (9). Most histoplasmosis reports come from the Region of the Americas, and each year there are up to 15,600 new cases and 4,500 deaths among people living with HIV (4).

Although recent technological advances have improved the diagnostic accuracy of fungal diseases, these technologies are not yet widely available. Conventional laboratory methods such as culture and histopathology that are used for diagnosing histoplasmosis have several limitations; these include the need for complex laboratory infrastructure (Biosafety Level 3 laboratory), limited laboratory staff with mycology training, delays of several weeks for final diagnosis, and variable diagnostic sensitivity (10). Antibody tests are less sensitive for immunocompromised people, with sensitivity ranging between 38% and 70%, and not usually helpful for diagnosing disseminated histoplasmosis among people living with HIV (10). Although the detection of circulating *Histoplasma* antigens in urine by enzyme-linked immunosorbent assay (ELISA) has proven highly sensitive (95%) for diagnosing disseminated histoplasmosis, testing is hampered by the limited availability of commercial in vitro diagnostic kits and poor local distribution (10). In summary, lack of access to appropriate antifungal therapies, in vitro diagnostics for rapid detection of histoplasmosis and the co-occurrence of other infectious

diseases, especially TB, may affect clinical outcomes and underlie the high mortality of disseminated histoplasmosis among people living with HIV (11, 12).

Recognizing the importance of addressing late HIV diagnosis and deploying differentiated packages of care for people living with HIV with advanced HIV disease, the WHO has recently published guidance documents and recommendations for managing advanced HIV disease and rapidly initiating antiretroviral therapy (3) and updated guidelines for diagnosing, preventing, and managing cryptococcal disease among adults, adolescents, and children living with HIV (13). WHO's consolidated guidelines for managing advanced HIV disease do not include histoplasmosis but acknowledge its higher burden in Latin America. In 2019, WHO's updated Model List of Essential In Vitro Diagnostics included *Histoplasma* antigen testing, and the List of Essential Medicines included new effective antifungal agents (14, 15). Guidelines for managing advanced HIV disease were developed before the availability and inclusion of *Histoplasma* antigen assays and antifungal medicines in the WHO Model List of Essential In Vitro Diagnostics. These new opportunities, together with updated data on the burden of histoplasmosis among people living with HIV, provide the rationale for producing this WHO guidance for diagnosing and managing disseminated histoplasmosis among people living with HIV.

2.1 Objectives

The objectives of these guidelines are to provide updated, evidence-informed recommendations as well as additional clinical and implementation guidance for a public health approach to diagnosing and managing disseminated histoplasmosis and disseminated histoplasmosis and TB coinfection among people living with HIV. The recommendations contained in these guidelines and provision of technical cooperation for their implementation is expected to improve the capacity to diagnose and treat histoplasmosis throughout regions that are endemic for this disease.

2.2 Target audience

The target audience for these guidelines includes HIV program managers, policy-makers, national treatment advisory boards, implementing partners, and health-care professionals providing care for people living with HIV in resource-limited settings, especially in countries with a high burden of histoplasmosis. These guidelines were initially developed for Latin America and the Caribbean. Nevertheless, the recommendations apply globally.

2.3 Guiding principles

The following principles have informed the development of these guidelines:

- The guidelines are based on a public health approach to scaling up the use of antiretroviral therapy along the continuum of HIV prevention, care, and treatment.
- Detecting HIV infection early and rapidly initiating antiretroviral therapy, regardless of CD4 count or immune status ("treat all"), are the most important strategies to reduce the incidence of opportunistic infections.

- Early and rapid diagnosis and prompt initiation of optimal antifungal treatment are essential to improving survival among people living with HIV who have histoplasmosis.
- People should be promptly referred for HIV testing and care after being diagnosed with histoplasmosis to facilitate prompt HIV diagnosis, linkage to care and uptake of antiretroviral therapy.

The implementation of the recommendations in these guidelines should be informed by local context, including HIV epidemiology, the burden of histoplasmosis, the prevalence of other comorbidities, access to laboratory services and availability of specific assays, access to antifungal medicines for treatment, the organization and capacity of the health system, and the anticipated cost-effectiveness.

Annex 1 summarizes the methods for developing these guidelines.



3. KEY RECOMMENDATIONS, RATIONALE, AND EVIDENCE SUMMARY

3.1 Diagnosis of disseminated histoplasmosis among people living with HIV

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

3.1.1 Background and rationale

The traditional gold standard for diagnosing histoplasmosis is based on conventional laboratory tests (culture, histopathology, and special stains) (10, 16). However, these assays have important limitations, notably the need for laboratory infrastructure for handling isolates (Biosafety Level 3), the need for laboratory staff with appropriate training and experience, variable analytical performance of the tests and long turnaround time for diagnosis. Several weeks are required to undertake fungal culture, and this can lead to providing empirical treatment while awaiting the results, potentially adding unnecessary toxicity and associated costs to patient care (10, 16). Alternatively, people may die if treatment is delayed while awaiting culture confirmation (17). The Guideline Development Group was confident that this recommendation can be achieved in most countries, although financial and technical support may be needed in some settings to strengthen laboratory capacity to be able to provide adequate and timely testing. The Guideline Development Group also noted the need to strengthen implementation strategies (for example, educational programs) to improve the diagnosis of histoplasmosis (18) (Annex 2).

3.1.2 Systematic review

A systematic review and a meta-analysis compared the diagnostic accuracy of different laboratory approaches for disseminated histoplasmosis among people living with HIV (19). Studies were included for analysis if they demonstrated validation of *Histoplasma* laboratory assays among people living with HIV using culture or histopathological analysis to determine proven cases as defined by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group (20). Meta-analysis found that antigen detection tests have the highest analytical performance for diagnosing disseminated histoplasmosis among people living with HIV (overall sensitivity 95% and specificity 97%). Culture-based assays presented variable analytical performance in diagnosing disseminated histoplasmosis (overall sensitivity of 77% and unknown specificity). Antibody testing had high specificity but low sensitivity, probably because these people are highly immunosuppressed. Molecular testing through DNA detection showed high

diagnostic accuracy (sensitivity 95% and specificity 99%), but the lack of consensus on techniques or procedures and the lack of availability of commercial kits makes implementing these types of assays difficult (19) (Annex 3).

Antigen detection assays were the most accurate method for diagnosing disseminated histoplasmosis among people living with HIV. These types of assays are commercially available as kits, which facilitates transfer of this assay to clinical laboratories. Using commercial assays reduces technical problems related to reproducibility and permits to undertake a better quality control. In addition, antigen testing can be performed in laboratories with lower level biosecurity (Biosafety Level 1 and 2 laboratories). In settings where *Histoplasma* antigen testing has been implemented, the number of diagnosed cases increased significantly, providing further evidence of the higher analytical performance of this type of assay (17, 18, 21, 22). In addition, the relative ease and speed with which these antigen assays can be performed and the use of non-invasive samples has reduced the time to diagnosis and the mortality associated with disseminated histoplasmosis among people living with HIV (17, 18, 21, 22). The main limitation is that commercial kits are only available in ELISA format, and point-of-care testing is needed to further reduce diagnostic delays. Further, assay distribution and costs need to be evaluated in each setting. Annex 4 summarizes the alternative commercially available assays for diagnosing histoplasmosis.

3.1.3 Recommendation

The Guideline Development Group recommends antigen detection assays to diagnose disseminated histoplasmosis among people living with HIV. This recommendation is based on the high diagnostic accuracy of *Histoplasma* antigen testing for these people and is also supported by preference for non-invasive testing and ease of use in resource-limited settings. The recommendation is conditional, since it is based on low-certainty evidence.

This recommendation applies to suspected disseminated histoplasmosis among people living with HIV. In the case of mucocutaneous infections, central nervous system, and pulmonary-only localizations of histoplasmosis may require complementary testing such as serum antibody tests or culture and histopathological analysis of different specimens, including tissue biopsy or body fluids.

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

3.2.1 Disseminated histoplasmosis classification definitions

The categories of disseminated histoplasmosis are defined as follows:

- Severe or moderately severe histoplasmosis is defined as the presence of at least one sign or symptom involving vital organs: respiratory or circulatory failure, neurological signs, renal failure, coagulation anomalies and a general alteration of the WHO performance status greater than 2, in which the person is confined to a bed or chair more than half of the waking hours and only capable of limited self-care.
- Mild to moderate histoplasmosis is defined as signs and symptoms that do not include the above features defining severity.

3.2.2 Induction therapy

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

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

3.2.2.1 Background and rationale

Disseminated histoplasmosis among people living with HIV is a rapidly progressing, life-threatening infection that requires prompt treatment with antifungal medication. The standard treatment, deoxycholate amphotericin B has good treatment success rates (23) but is associated with considerable toxicity, especially infusion-related toxicity, renal failure, electrolyte abnormalities, and anemia (24, 25). The Guideline Development Group considered that not all regimens for treating moderate or severe disseminated histoplasmosis are consistently available in all resource-limited settings. The Guideline Development Group further recognized that there may be concerns about adverse events associated with some of the proposed treatments but was confident that the treatments recommended offer improved safety and tolerability compared with the alternatives; as such, the Guideline Development Group considered that the values and preferences overall favored the proposed interventions. In addition, the Guideline Development Group noted that therapeutic drug monitoring is proposed in some settings; however, the feasibility of implementing therapeutic drug monitoring and some treatment options depends on resource availability (26). However, the absence of therapeutic drug monitoring or of the first-line recommended treatment should not

be a reason to not give treatment for disseminated histoplasmosis, a potentially fatal disease. Acceptability of treatment is a key issue because suboptimal adherence to using an antifungal drug is associated with treatment relapse and mortality among people living with HIV who have disseminated histoplasmosis (27, 28). The Guideline Development Group was confident that key stakeholders are likely to find this recommendation acceptable (Annex 2).

3.2.2.2 Systematic review

The systematic review identified four studies, including one randomized trial, that compared the efficacy of liposomal amphotericin B versus deoxycholate amphotericin B for induction therapy for moderately severe to severe disseminated histoplasmosis among people living with HIV (Annex 5). Compared with deoxycholate amphotericin B, the people treated with liposomal amphotericin B had improved clinical success (82% versus 56%), lower mortality (2% versus 13%) and less nephrotoxicity (9% versus 37%) (24, 29).

For treating people with less severe disease, fluconazole (800 mg daily for 12 weeks) was less effective than itraconazole (200 mg three times a day for three days and then 200 mg twice daily for 12 weeks) (30, 31). Moreover, triazoles all showed lower efficacy than polyenes among more severely ill people. Randomized trials of amphotericin B formulations compared with triazole antifungal agents have not been conducted (32).

3.2.2.3 Recommendations

Treating severe or moderately severe histoplasmosis among people living with HIV

Liposomal amphotericin B, 3.0 mg/kg for two weeks is recommended as the preferred treatment. This recommendation is conditional based on the very-low-certainty evidence (Annex 2).

Induction therapy should be given for two weeks. Because amphotericin B is associated with renal toxicity, the duration of therapy can be shortened based on clinical assessment of how the person responds to treatment.

Involvement of the central nervous system may require extending induction therapy or increasing dosage.

Alternative treatment for severe or moderately severe histoplasmosis among people living with HIV

In resource-limited settings where liposomal amphotericin B is unavailable, deoxycholate amphotericin B (0.7–1.0 mg/kg) should be administered for the initial two weeks. This is a conditional recommendation, based on very-low-certainty evidence because of imprecision and indirectness. For people with renal failure or at risk of renal injury, preventing and monitoring toxicity associated with deoxycholate amphotericin B are recommended (13).

Treating mild to moderate histoplasmosis among people living with HIV

Itraconazole 200 mg twice daily after a loading dose of 200 mg three times daily for three days is recommended. This is a conditional recommendation, based on very low certainty of evidence, because of imprecision and indirectness.

Based on the histoplasmosis treatment guidelines of the Infectious Diseases Society of America, this recommendation can be used for treating HIV-uninfected immunosuppressed individuals for disseminated histoplasmosis (25).

3.2.3 Maintenance therapy

Itraconazole 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 loads, and the immune status has improved (conditional recommendation, very-low-certainty evidence).

3.2.3.1 Background and rationale

After successful induction therapy for disseminated histoplasmosis among people living with HIV, rates of relapse can be as high as 90% among people not receiving maintenance therapy (32). Relapse occurs more frequently 6–18 months after discontinuing induction therapy. Reinfection can occur in regions that are hyperendemic for histoplasmosis (23). Antifungal maintenance therapy is therefore necessary to effectively suppress residual infection and prevent relapse. Treatment success rates are higher when maintenance therapy is with itraconazole (75%) compared with fluconazole (40%) (33, 34), although direct randomized comparisons are lacking. Itraconazole treatment 200 mg twice daily is usually preceded by a loading dose of 200 mg itraconazole thrice daily for three days to achieve steady-state itraconazole concentrations more rapidly (35). The efficacy and duration of such regimens required for people with central nervous system involvement is less clear.

The ideal duration of maintenance therapy has not been established and should be determined based on clinical judgment. Lifelong maintenance antifungal therapy has been recommended in some national guidelines, and relapses were usually associated with poor adherence to therapy, low itraconazole levels or central nervous system infection. Guidelines from the Infectious Diseases Society of America recommend maintenance therapy with azoles for one year (25).

3.2.3.2 Systematic review

The systematic review sought to compare the efficacy and safety of maintenance therapy with 12 months of oral itraconazole with shorter durations of maintenance therapy. The only study to report evidence on this comparison was a retrospective cohort study that compared a group in which maintenance therapy was discontinued (38 participants) with a group in which maintenance therapy was continued (59 participants) (28). The review authors judged the study to be at high risk of bias (29).

3.2.3.3 Recommendation

Itraconazole (200 mg twice daily) for one year is the recommended maintenance therapy. The recommendation is conditional, with very-low-certainty evidence because of imprecision and indirectness. The Guideline Development Group decided that the desirable effects of shortening the maintenance course were moderate and undesirable effects were trivial; there was no important uncertainty of values. The balance of effects was therefore judged to be in favor of the intervention, which was both feasible and acceptable. Itraconazole and dolutegravir, antiretroviral drug used in

combination with two nucleoside reverse-transcriptase inhibitors for WHO-recommended first-line regimens, have no expected drug–drug interactions. Annex 7 presents more information on drug–drug interactions between itraconazole and antiretroviral drugs. The University of Liverpool’s drug interaction charts may also be consulted online at <https://www.hiv-druginteractions.org> (36).

Balancing the risk of relapse, drug–drug interactions, and side-effects, clinicians may opt for shorter courses (at least six months long) of maintenance therapy. The Guideline Development Group is aware that short maintenance therapy (3–6 months) has been used successfully for people receiving antiretroviral therapy, with suppressed viral loads, and clinically stable with immune recovery. Shortening the duration should be based on how the person responds to antiretroviral therapy with an undetectable viral load, some immune recovery, which can be defined as CD4 cell counts >200 cells/mm³, and clinical resolution of histoplasmosis. People with drug–drug interactions are more likely to benefit from shorter courses of maintenance therapy (28, 37). This conditional shortening of maintenance therapy was judged to be aligned with the values and preferences of people with disseminated histoplasmosis, physicians, and policy-makers (Annex 2). The Guideline Development Group recommendation for shortening maintenance therapy is conditional, with very-low-certainty evidence because of imprecision and indirectness.

Based on the histoplasmosis treatment guidelines of the Infectious Diseases Society of America, this recommendation can be used for treating HIV-uninfected immunosuppressed individuals for disseminated histoplasmosis (25).

3.3 Timing of antiretroviral therapy initiation

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*).

3.3.1 Background and rationale

WHO guidelines recommend initiating antiretroviral therapy within seven days after HIV diagnosis and that people with advanced HIV disease be given priority for assessment and antiretroviral therapy initiation; these guidelines further recommend that antiretroviral therapy initiation should be offered on the same day to people who are ready to start (3). However, people presenting for the first time or those returning to care should undergo evaluation for opportunistic infections, in particular signs and symptoms of TB and cryptococcal meningitis, before antiretroviral therapy initiation is offered. Immediate antiretroviral therapy initiation is contraindicated among people living with HIV who have cryptococcal meningitis because of the increased mortality presumed to be caused by immune reconstitution inflammatory syndrome in the central nervous system, especially in the context of increased intracranial pressure (13, 3). Apart from the above situation, evidence indicates that starting antiretroviral therapy within 14 days of starting treatment for acute opportunistic infections (*Pneumocystis jirovecii* pneumonia, cryptococcal meningitis, and bacterial infections) reduced disease progression and death in individuals with other opportunistic infections (38) (Annex 2).

3.3.2 Systematic review

The systematic review sought to compare the outcomes of early versus delayed initiation of antiretroviral therapy. One randomized clinical trial with 282 participants met the inclusion criteria (39). Only 10 participants had HIV and a presumptive or confirmed diagnosis of disseminated histoplasmosis. By day 30, one of the seven people in the early arm and none of the three people in the late arm died. Based on this limited evidence, the efficacy and safety outcomes of early versus late initiation of antiretroviral therapy are unknown (29).

3.3.3 Recommendation

Antiretroviral therapy should not be delayed for people diagnosed with disseminated histoplasmosis who are administered antifungal therapy. The recommendation is conditional with very-low-certainty evidence. The Guideline Development Group considered that the risk of potential harms was minor. The recommendation was judged feasible and likely to be acceptable, with possible important uncertainty regarding values and preferences and the balance of effects. This recommendation is based on the balance between the substantial risk of dying from another opportunistic infection when delaying antiretroviral therapy and the low incidence of immune reconstitution inflammatory syndrome versus morbidity and mortality associated with immune reconstitution inflammatory syndrome among people living with HIV receiving antiretroviral therapy who have histoplasmosis. Immune reconstitution inflammatory syndrome appears to be uncommon among people with disseminated histoplasmosis following antiretroviral therapy initiation (38).

Most of the literature on immune reconstitution inflammatory syndrome is case reports or small case series, which cannot provide evidence on the incidence of immune reconstitution inflammatory syndrome or the optimal timing of antiretroviral therapy (Annex 2).

This recommendation regarding the timing of antiretroviral therapy only applies to people without central nervous system involvement, to avoid immune reconstitution syndrome in the central nervous system.

3.3.4 Managing immune response inflammatory syndrome associated with histoplasmosis

Immune reconstitution inflammatory syndrome associated with histoplasmosis is unusual, occurring at about 0.74 cases per 1,000 person-years among people living with HIV (38). Typically, immune reconstitution inflammatory syndrome occurs a median of 60 days after initiating antiretroviral therapy. The features of histoplasmosis-associated immune reconstitution inflammatory syndrome are non-specific and resemble disseminated histoplasmosis, with symptoms including fever, weight loss, cough, diarrhea and abdominal pain. Typically, antifungal therapy does not need to be adjusted. The following steps are recommended for managing immune reconstitution inflammatory syndrome associated with histoplasmosis:

- continue antiretroviral therapy; and
- ensure optimal antifungal therapy.

Short-course oral steroid therapy can be considered if there are life-threatening complications despite appropriate treatment of histoplasmosis. In these cases, it has been recommended that 1–2 mg/kg per day of prednisone or the equivalent be given for 1–2 weeks followed by dose-tapering for two weeks.

3.4 TB therapy for people coinfecting with TB, HIV, and histoplasmosis

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

3.4.1 Background and rationale

TB and histoplasmosis coinfection is a challenge because the symptoms are non-specific. Coinfection is frequent although likely underestimated, since clinicians may stop investigation after initial diagnosis and thus fail to see coinfections. Depending on the local epidemiology, this situation may occur frequently among people living with HIV (8–38%), and screening should look for both diagnoses (12). When coinfections are diagnosed, this can lead to complex patient management, with drug–drug interactions that may affect HIV, TB, and histoplasmosis treatment. In particular, rifampicin results in reduced itraconazole levels, potentially leading to ineffective treatment for histoplasmosis (40) (Annex 6).

3.4.2 Systematic review

To address this concern, a systematic review was conducted to assess whether TB therapy should be adjusted for people coinfecting with TB and histoplasmosis. This review found only two studies (including one case report) reporting on treatment outcomes among coinfecting people (40, 41). The rationale for this recommendation therefore relies on the expertise of the Guideline Development Group and considers existing guidance on managing HIV and TB coinfection (Annex 2).

3.4.3 Recommendation

People living with HIV with TB and histoplasmosis coinfection should receive prompt treatment after diagnosis according to WHO treatment guidelines. The recommendation balances the risk for *M. tuberculosis* resistance and the risk of drug–drug interactions (rifampicin and itraconazole), leading to subtherapeutic itraconazole levels and potential ineffective treatment for histoplasmosis. The Guideline Development Group judged that there may be important variability in how much the people with histoplasmosis, physicians, and policy-makers value the main outcome but that the intervention was feasible and acceptable (Annex 2).

This recommendation has several possible resource implications. It is important to review potential antiretroviral therapy options for people with coinfection and to make necessary adjustments as recommended in WHO's consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Because of the potential decrease in itraconazole levels related to some types of antiretroviral therapy, itraconazole drug levels should be monitored if possible (42). When histoplasmosis is not controlled because of interactions with rifampicin and itraconazole, clinicians may consider, depending on local context, extending the duration of amphotericin B induction therapy, once-weekly courses of amphotericin B, increasing the itraconazole dose and monitoring

the blood level and toxicity and considering using other azole drugs (posaconazole, voriconazole, or fluconazole). Finally, clinicians can consider replacing rifampicin with rifabutin.

Treatment may need to be revised for people experiencing toxicity, drug-drug interactions, or for those with resistance profiles requiring protease inhibitors or second-line anti-TB drugs. When possible, antiretroviral resistance genotyping and *M. tuberculosis* drug susceptibility testing may assist clinical decisions. Itraconazole serum level testing may not be available in some areas.

3.5 Preventing, monitoring, and managing histoplasmosis among people living with HIV

3.5.1 Monitoring the toxicity of amphotericin B treatment

- Drug toxicity and side-effects from amphotericin B therapy and drug–drug interactions associated with itraconazole use are important barriers to the successful treatment of people living with HIV who have histoplasmosis, especially in low- and middle-income countries (Annex 5).
- Safe administration of amphotericin B formulations is a priority and may require referral to a center with resources available to manage toxicity.
- Renal function should be evaluated to prevent, monitor, and manage toxicity such as nephrotoxicity, hypokalemia, infusion-related reactions and anemia.
- Renal function should be measured to reduce the risk of kidney damage, including appropriate fluid and electrolyte reposition, in addition to drug infusion (for deoxycholate amphotericin B) over 4–6 hours (43).

3.5.1.1 Background and rationale

Adverse effects of amphotericin B therapy include renal toxicity, anemia, hypokalemia, hypomagnesemia and acute infusion-related reactions. A review of using amphotericin B formulations for treating people living with HIV for histoplasmosis found that nephrotoxicity was common (18%), as was infusion-related toxicity (36%) (24). In a study from Uganda among people with cryptococcal meningitis, proactive fluid and electrolyte management as part of amphotericin-based therapy was associated with improved survival (44).

The most common adverse reactions associated with itraconazole for treating people with histoplasmosis are nausea and vomiting, rash and pedal edema (31, 45). An important limitation to using itraconazole is variable bioavailability, and the guidelines of the Infectious Diseases Society of America recommend monitoring serum itraconazole levels for disseminated histoplasmosis (25). Serum concentrations are useful for determining whether itraconazole is adequately absorbed and may also be helpful in assessing adherence and the impact of drug–drug interactions. Toxicity has been associated with higher serum levels of itraconazole among people with aspergillosis (46).

3.5.2 Monitoring the treatment response

- Clinical response, including resolution of fever, fatigue, and weight changes and other symptoms associated with disease severity (hypotension and hypoxia) should be assessed daily during the initial period of induction therapy (13).
- Itraconazole blood levels, where available, should be monitored after two weeks of therapy. Blood levels of itraconazole between 1 and 2 µg/mL have been recognized as effective. Concentrations higher than 15 µg/mL has been related with development of toxic (42). Lack of capacity for drug monitoring should not be an obstacle to itraconazole treatment.

- The co-occurrence of other opportunistic infections should be evaluated by clinical evaluation and using specific laboratory testing for other opportunistic infections (12, 47).

3.5.3 Diagnostic approach to persistent or recurrent symptoms

About 25% of the people with disseminated histoplasmosis have persistent or recurrent symptoms. Persistent symptoms may be caused by failure of induction or maintenance therapy (inadequate dose or duration) or concomitant infection, such as TB (12, 24, 47). Recurrent symptoms, reappearing after symptoms initially resolve, may occur from inadequate doses of maintenance therapy (drug level and drug interactions), failure of adherence, other concomitant illness, and immune reconstitution inflammatory syndrome (25).

It is important to review treatment history to determine whether drug regimen, dosing, or duration of therapy have contributed to treatment failure. Adherence to therapy, itraconazole drug levels, and potential drug interactions should be investigated.

- Review patient adherence.
- Perform relevant investigations for other concomitant illnesses such as TB, especially among people with CD4 cells counts <200 cells/mm³.
- Consider paradoxical immune reconstitution inflammatory syndrome among people who have started antiretroviral therapy.
- Monitor progress by using *Histoplasma* antigen testing following treatment initiation (25, 48).
- Ensure appropriate drug levels, as necessary (42).

3.5.4 Managing relapse

In case of persistent or recurrent symptoms related to disseminated histoplasmosis, induction therapy should be restarted. It is important to ensure adherence to therapy and appropriate dose, drug levels, and duration.

Good practice statements

- Measure *Histoplasma* urinary antigen and perform other complementary laboratory tests, such as culture (25, 48).
- Restart induction or maintenance therapy (see subsection 3.2).
- Prevent, manage, and monitor for drug toxicity.
- Ensure appropriate drug levels, as necessary (42).

4. IMPLEMENTATION CONSIDERATIONS

Implementation challenges include: (1) access to rapid diagnostics; (2) access to optimal antifungal medicines; and (3) educating and training health-care providers.

4.1 Access to rapid diagnostics

Since early diagnosis and timely treatment initiation are key to improving mortality from histoplasmosis, countries need to give priority to access to high-quality in vitro diagnostics for rapid detection of *Histoplasma* antigen (17, 18, 21, 22). The WHO Model List of Essential In Vitro Diagnostics recently included immunoassays for *Histoplasma* antigen detection for implementation in clinical laboratory settings (14). Lateral flow assay-based rapid diagnostic tests for *Histoplasma* antigen will soon be available and provide additional opportunities to rapidly diagnose histoplasmosis at the point of care (49). Price negotiation and pooled procurement mechanisms should be used to improve access, especially for countries highly endemic for histoplasmosis. For Latin America and the Caribbean, the Pan American Health Organization (PAHO) Regional Revolving Fund for Strategic Public Health Supplies is one source of potential support. Implementing this recommendation implies taking appropriate steps to guarantee adequate availability of antigen testing in health facilities managing advanced HIV disease. Kit distribution and costs should be monitored to ensure that tests are accessible.

4.2 Access to optimal antifungal medicines

The WHO Model List of Essential Medicines (15) includes optimal antifungal medicines for treating people with histoplasmosis (conventional and liposomal amphotericin B and itraconazole). Nevertheless, these drugs are not widely available in many of the countries with a high burden of histoplasmosis, and the cost of treatment is extremely high, especially for liposomal amphotericin B. Barriers to accessing antifungal medications for treating histoplasmosis may be overcome by:

- increasing advocacy for drug price reduction, expanding the coverage of global access price initiatives, both in terms of scope (such as including histoplasmosis in the current access price of liposomal amphotericin B for leishmaniasis and cryptococcal meningitis) and eligible countries and promoting generic production, especially for amphotericin B;
- carrying out quality assurance of available generic formulations;
- ensuring national registration of all antifungal drugs and including them in national essential medicine lists based on the WHO Model List of Essential Medicines;
- procuring medicines through joint regional procurement mechanisms such as the PAHO Strategic Fund;
- ensuring adequate supply chains at the national level; and
- developing proper drug forecasting and monitoring systems.

4.3 Educating and training health-care providers

Health-care providers need to have a low threshold for suspecting histoplasmosis among people living with HIV with advanced HIV disease and be trained in differential diagnoses with TB and other systemic fungal infections. Greater efforts need to be made to educate health-care providers and to provide policy guidance at the national level on managing histoplasmosis among people living with HIV. Effectively implementing guidelines also requires supportive supervision systems and prescribing decision-making aids.

4.4 Disseminating, adapting, and implementing the guidelines

These guidelines are available as a web-based product for dissemination and supported by peer-reviewed publications of the systematic reviews on which these recommendations are based. Although these guidelines were initially developed with a focus for the Americas, the recommendations in these guidelines apply globally, and as such will be integrated in the next edition of the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. These consolidated guidelines are planned to be reviewed and updated every 2–3 years.

WHO and PAHO will work closely with national health ministries and implementing partners to plan for rapidly disseminating, adapting, and implementing the recommendations. Key steps in dissemination include: presenting the recommendations at international conferences, workshops to support country adaptation, rapidly developing adaptation tools to assist countries in setting priorities among limited resources to facilitate full implementation over time, and carrying out briefings and joint planning for dissemination with international and national implementing partners. The policy uptake of the recommendations in national guidelines will be evaluated regularly.

4.5 Research needs

The following research questions emerge from the Guideline Development Group discussions and the evidence reviews:

- What is the antigen detection performance outside the context of advanced HIV disease?
- Among people with advanced HIV disease, can *Histoplasma* antigen detection be used as a screening approach for histoplasmosis?
- Can antigen detection performance be increased by designing new antibodies through significant support in developing basic science on *Histoplasma capsulatum*?
- Will a *Histoplasma* interferon-gamma release assay be useful to screen for latent histoplasmosis in advanced HIV disease, prevent histoplasmosis-associated immune reconstitution inflammatory syndrome and help to reduce the time to antiretroviral therapy initiation among people recently diagnosed with HIV?
- Can antigen detection screening studies inform about the true burden of histoplasmosis from a global perspective?
- Will recently developed *Histoplasma* antigen detection by lateral flow become the standard diagnostic method for disseminated histoplasmosis among hospitalized people with histoplasmosis, as an outpatient screening tool or both?

- How can the specific impact of antigen detection on the incidence and mortality trends of HIV-associated histoplasmosis be evaluated compared with conventional practices for diagnosing histoplasmosis and the future development of more molecular biology assays?
- What are the best definitions for severity of disease among people with histoplasmosis?
- Among people with a clinical and immune response to therapy, can maintenance antifungal therapy be safely discontinued earlier than 12 months?
- Do people with central nervous system involvement have a higher incidence of *Histoplasma*-related immune reconstitution inflammatory syndrome and associated mortality? In relation to this, what is the optimal time to start antiretroviral therapy?
- When will *Histoplasma* antigen detection and liposomal amphotericin B be affordable to people with histoplasmosis in low- and middle-income countries?
- What are the outcomes of treating TB and histoplasmosis coinfection?
- What is the impact of genetic varieties of *Histoplasma* on the epidemiology and treatment response to histoplasmosis?
- What are the alternative antifungal drugs or alternative treatment stewardship in the pipeline that might help increase the efficacy and decrease the secondary effects and toxicity of the recommended therapy?

The optimal dose of liposomal amphotericin B has not been determined for people living with HIV who have disseminated histoplasmosis. Based on the experience with leishmaniasis, and more recently with cryptococcosis, high doses of liposomal amphotericin B given for short periods (including as a single dose) may work as well as standard (3 mg/kg) doses given for two weeks. A randomized multicenter Phase 2 clinical trial (NCT04059770) is planned to evaluate the activity of three regimens of liposomal amphotericin B in Brazil, for disseminated histoplasmosis in hospitalized adults living with HIV: (1) 10 mg/kg single dose; (2) 10 mg/kg on day one followed by 5 mg/kg on day three; and (3) 3 mg/kg for two weeks. All induction regimens will be followed by itraconazole at 400 mg/day for one year. The study is estimated to be completed in October 2021. The incidence of immune reconstitution inflammatory syndrome should be quantified prospectively, and its severity should be described.

ANNEX 1. METHODS FOR DEVELOPING THE GUIDELINES

PAHO/WHO, advised by external experts, convened a guideline process to formulate guidelines on diagnosing and managing progressive disseminated histoplasmosis among people living with HIV. From May 2018 to October 2019, three groups worked to establish the key questions, analyze the evidence, and develop the guidance: (1) the WHO Steering Group, consisting of WHO experts; (2) the independent Guideline Development Group; and (3) the External Review Group. The Guideline Development Group and the External Review Group comprised experts with a wide variety of experience and knowledge in histoplasmosis and HIV. Gender, equity, human rights, and community perspectives were considered based on the expertise of the Guideline Development Group. The External Review Group members were sought from countries across WHO regions to ensure that diverse perspectives were included. The Guideline Development Group formulated all recommendations by using the GRADE approach.

Guideline Development Group meeting

The Guideline Development Group formulated guidelines on diagnosing and managing disseminated histoplasmosis among people living with HIV based on their knowledge of the optimal approach to diagnosing and managing histoplasmosis, using as reference the systemic reviews that were undertaken and considering the constraints of resource-limited settings. The Guideline Development Group had bi-monthly teleconferences between June 2018 and February 2019 and a face-to-face meeting in March 2019. The systematic reviews and supportive evidence, including values and preferences, acceptability, feasibility, and cost, were presented to the Guideline Development Group. Evidence-to-decision-making tables were prepared in accordance with the GRADE process and presented to the Guideline Development Group. A methodologist supported the formulation of the recommendations and facilitated discussions. The Guideline Development Group made decisions through a consensus process; all decisions were unanimous and voting was not required. Following the face-to-face meeting in March, the Guideline Development Group held subsequent discussions by videoconference on May 31, June 26, July 31 and August 28, 2019 to review draft versions of this publication.

Peer review

The draft guidelines were circulated for review to members of the Guideline Development Group and the External Review Group. The Guideline Development Group reviewed the comments and incorporated them into the final document with due consideration of any conflicts of interest of External Review Group members.

Declarations of interest

All external contributors to the guidelines, including members of the Guideline Development Group, External Peer Review Group, systematic reviewers and contributors to the supporting evidence completed a WHO declaration of interests form in accordance with WHO policy (50). The steering committee of the WHO/PAHO Guideline Steering Group collected and reviewed a brief biography of each Guideline Development Group member before the first meeting of the Guideline Development Group. No objections were received concerning the members of the Guideline Development Group. At the start of the guideline development meeting, all conflicts of interest identified and the management plan for any conflicts of interest were shared with the meeting participants. Of the members of the Guideline Development Group, one received diagnostic kits from commercial companies at no cost (no relation

with the diagnostic kits or interventions included in this guideline), one received a research grant to conduct clinical trials (no medication or interventions related to the content in this guideline) and two had received a grant to attend conferences (by a private company but with no links to any intervention included in this guideline). No conflicts of interest warranted exclusion from the discussion of specific recommendations. To ensure consistency, the WHO/PAHO Guideline Steering Group applied the criteria for assessing the severity of conflict of interests in the WHO handbook for guideline development (50). All contributors were requested to promptly notify WHO/PAHO if any of the disclosed information changed during the course of this work.

The responsible technical officer reviewed the declaration of interest forms from members of the External Review Group in accordance with WHO guideline development policy, and the results were shared with the Guideline Steering Group. Any conflicts of interest identified were considered when interpreting comments from External Review Group members during the external review process (51).

All declaration of interest forms are in electronic file at the PAHO Communicable Diseases and Environmental Determinants of Health Department and will be maintained for 10 years.

Methods for appraising evidence

The Guideline Steering Group formulated PICO (population, intervention, comparison, and outcome) questions to guide the systematic reviews used in developing these guidelines (52). The following three questions were identified.

- Among people with HIV disease, 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 living with HIV infection with disseminated histoplasmosis, what are the optimal therapeutic regimens depending on the disease severity and the level of country resources?
- How does HIV or TB therapy need to be modified to obtain successful outcomes for histoplasmosis for people coinfecting with TB, HIV, and *H. capsulatum*?

A list of potential outcomes of interest for each question was circulated to all members of the Guideline Development Group, and members provided comments to rank the importance of these outcomes to inform decision-making.

Retrieving, summarizing, and presenting the evidence: quantitative evidence synthesis and evidence for recommendations

The External Review Group developed protocols for questions 1, 2, and 3 identifying studies, appraising the risk of bias, and summarizing the research using standard methods. Annexes 3, 5, and 6 summarize these reviews.

To inform the development of these guidelines, evidence was retrieved from three systematic reviews on:

(1) histoplasmosis diagnosis outcomes using antigen testing compared with standard microbiological techniques of diagnosis at local and reference hospitals;

(2) efficacy (clinical success and death) and safety (nephrotoxicity and drug discontinuation) of initial therapy for severe or moderately severe progressive disseminated histoplasmosis using amphotericin B versus alternative antifungal treatments among people living with HIV with moderately severe or severe progressive disseminated histoplasmosis in low- and middle-income countries; and

(3) how HIV or TB therapy needs to be modified to obtain successful outcomes for people coinfecting with TB, HIV, and *Histoplasma capsulatum*.

To examine feasibility and health system considerations, acceptability, financial and economic considerations, and human rights and equity issues, structured searches were conducted in PubMed, LILACS and Health Systems Evidence (January 2009 to March 1, 2019). The identified studies were considered during the GRADE evidence-to-decision framework process.

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method was used to rate the certainty of the evidence and determine the strength of the recommendations (53). The strength of a recommendation reflects the degree to which the Guideline Development Group is confident that the desirable effects (potential benefits) of the recommendation outweigh the undesirable effects (potential harm). The desirable effects may include beneficial health outcomes (such as reduced morbidity and mortality), reduction of the burden on the individual and/or health services and potential cost savings. Undesirable effects include those affecting individuals, families, communities or health services. Additional considerations include the resource use and cost implications of implementing the recommendations and clinical outcomes (such as drug resistance and drug toxicity). The Guideline Development Group considered the values and preferences of patients, physicians, and decision-makers. The composition of the panel included physicians, laboratory specialists, and ministry executives. The perspective of patients and families was represented by a Guideline Development Group member who collaborates with a nongovernmental organization that defends the views of patients and families to medical institutions. In addition, before the Manaus meeting, a systematic search was performed in PubMed including the terms histoplasmosis OR histoplasma AND patient preference, OR values, OR choices, OR expectation, OR attitude, OR point of view, OR acceptance*, OR user perspective, OR equity, OR human rights. Of 102 references screened, 11 were retained because they would help to inform the recommendation process.

The strength of a recommendation can be either strong or conditional

A strong recommendation (for or against) is one for which there is confidence that the desirable effects of adhering to the recommendation clearly outweigh the undesirable effects.

A conditional recommendation (for or against) is one for which the certainty of the evidence may be low or may apply only to specific groups or settings.

The Guideline Development Group formulated recommendations based on the certainty of the evidence, the balance between benefits and harm, values and preferences (including patients, health-care workers, and policymakers), resource implications and acceptability and feasibility. The Guideline Development Group assessed these through discussion among the members. The evidence-to-decision framework was used to approach each PICO question.

Equity and human rights

Throughout the development of this guideline and the GRADE evidence-to-decision framework process, each recommendation was assessed based on how it could potentially affect human rights and equity. Overall, the Guideline Development Group was confident that improving access to the interventions recommended by these guidelines would not reduce equity or human rights. People living with HIV and/or TB from groups that are marginalized or stigmatized have poor access to health services. Access to a point-of-care diagnostic test for histoplasmosis can improve the diagnosis and management of people with histoplasmosis and contribute to overcoming some of the obstacles to access among these populations.

Regional meeting on histoplasmosis in the Americas

A Regional Meeting of the International Histoplasmosis Advocacy Group (iHAG) was held in Manaus, Brazil, on March 22–24, 2019. More than 100 participants from 24 countries (21 from the Americas) attended the three-day meeting to discuss surveillance, diagnosis and treatment in Latin America. It was reported that 65% of countries had rapid testing for histoplasmosis in at least one laboratory for routine diagnosis. More than 90% of countries reported the availability of itraconazole and amphotericin B deoxycholate, but access to liposomal amphotericin B was limited (61%). Only two countries (Nicaragua and the United States) include histoplasmosis in their surveillance systems, with limited reporting in the United States (reportable in fewer than 15 states).

A regional SWOT analysis (strengths, weaknesses, opportunities, and threats) was conducted, focusing on three main topics: (1) access to diagnostic tests, with a focus on in vitro tests for rapid diagnosis, (2) access to specific antifungal therapy, and (3) surveillance of HIV-associated histoplasmosis (focusing on morbidity and mortality) (54). The main challenges and opportunities identified were as follows.

Challenges

Diagnosis

- A *Histoplasma* enzyme immunoassay kit is not registered in most countries.
- A *Histoplasma* enzyme immunoassay is available in a few scattered and highly specialized reference laboratories.
- Point-of-care testing is not commercially available.
- Validation studies outside the context of people with advanced HIV are lacking.

Treatment

- Amphotericin B and itraconazole are licensed but unavailable or not prescribed.
- Evidence of safety and efficacy is limited (few and old clinical trials).
- Clinical trials of alternative antifungal drugs are lacking.
- Evidence is lacking in specific populations (TB, pregnancy, liver or renal diseases, and children).

Surveillance

- Health-care practitioners and public health authorities lack awareness and education.
- Histoplasmosis is not a reportable disease. The burden of disease not fully known.
- Histoplasmosis is not integrated into national or international HIV and TB programs.

Opportunities

Diagnosis

- *Histoplasma* point-of-care test (lateral flow assay) being developed.
- PAHO/WHO to facilitate registration of new diagnostic kits.
- PAHO/WHO price control and engage industry.
- Development of a laboratory quality assurance program.

Treatment

- PAHO/WHO price control and engagement of industry.
- PAHO/WHO increasing access to liposomal amphotericin B.
- Collaboration with the pharmaceutical industry to increase access to new antifungal agents and management strategies.

Surveillance

- Screening studies in populations with varying risk of histoplasmosis.
- Evaluate how new tests affect incidence and mortality.
- Develop an electronic standard case report system.
- Returning travelers or immigrants from known endemic areas diagnosed in high-income countries may help in reporting information from endemic areas.
- Assessment of the environmental risk for histoplasmosis (work, industry, agriculture, and tourism).
- Merging with other programs (TB, HIV, and neglected tropical diseases) within the framework of the PAHO/WHO strategic plan.
- Develop advocacy, training, and education programs.

ANNEX 2 . SUMMARY OF JUDGMENTS ON POPULATION, INTERVENTION, COMPARISON, AND OUTCOME (PICO) QUESTIONS

	PICO 1	PICO 2A	PICO 2B	PICO 2C	PICO 3
Problem	Favors this option	Yes	Probably no	Yes	Yes
Desirable effects	Favors this option	Moderate	Moderate	Don't know	Moderate
Undesirable effects	Favors this option	Trivial	Trivial	Small	Large
Values	Favors this option	No important uncertainty or variability	No important uncertainty or variability	Possibly important uncertainty or variability	Possibly important uncertainty or variability
Balance of effects	Favors this option	Probably favors the intervention	Probably favors the intervention	Don't know	Probably favors the intervention
Acceptability	Favors this option	Yes	Yes	Probably yes	Yes
Feasibility	Favors this option	Yes	Yes	Yes	Yes
Certainty of the evidence	–	Low	No included studies	No included studies	Very low
Certainty of the evidence of test accuracy	Probably favors this option	–	–	–	–
Certainty of the evidence of test's effects	Probably favors this option	–	–	–	–
Certainty of the evidence of management's effects	Probably favors this option	–	–	–	–
Certainty of the evidence of the test result and management	Probably favors this option	–	–	–	–
Cost-effectiveness	Probably favors this option	–	–	–	–
Certainty of effects	Neither favors this or other options	–	–	–	–
Test accuracy	Favors this option	–	–	–	–

–: does not apply; PICO: population, intervention, comparison, and outcome. **PICO 1.** Among people with HIV disease, is antigen testing versus standard microbiological techniques of diagnosis associated with an increase in the diagnosis of histoplasmosis and a decrease in mortality? **PICO 2A.** Does liposomal amphotericin B as initial therapy for severe or moderately severe progressive disseminated histoplasmosis have better efficacy and safety than alternative antifungal treatments? **PICO 2B.** Is there a difference in histoplasmosis relapse rate between less than 12 months or more than 12 months of oral antifungal maintenance therapy for progressive disseminated histoplasmosis among people living with HIV? **PICO 2C.** Is early antiretroviral therapy (less than two weeks) preferable to deferred antiretroviral therapy (two weeks or more) among people living with HIV who have progressive disseminated histoplasmosis? **PICO 3.** How does HIV or TB therapy need to be modified to obtain successful outcomes for people coinfecting with TB, HIV, and *H. capsulatum*?

ANNEX 3 . SYSTEMATIC REVIEW PICO 1: PERFORMANCE OF DIAGNOSTIC ASSAYS

Objectives

To evaluate the analytical performance of laboratory assays for diagnosing progressive disseminated histoplasmosis among people living with HIV.

Methods

Search methods

Databases: Medline (Ovid), Embase (Ovid), CAB Abstracts (Ovid), Global Health (Ovid), Scopus, the Cochrane Library, PubMed Central, and LILACS.

Run date: February 20, 2019 for the terms histoplasmosis, HIV, and terms for the diagnostics assays evaluated, including their synonyms, in the title, abstract, keywords, or subject headings. A broader search was also conducted in the same databases for histoplasmosis and HIV, and a diagnostic methods search filter was adapted from the McMaster Health Information Research Unit's recommended search hedges. Searches were limited to the studies published in English, Spanish, and Portuguese.

Types of studies: systematic review

Studies related to validating *Histoplasma* laboratory assays. Studies were excluded if they did not focus on human application or were primarily case reports, clinical studies, environmental or epidemiological studies, or literature reviews with no validation component.

For studies related to validating laboratory assays for diagnosing histoplasmosis, we excluded studies of people without HIV, concordance studies, and studies without a clear number of people tested. To maintain the accuracy of the study, references were not included in the analysis if culture or histopathological analyses were not included to determine proven cases.

Statistical analysis and data synthesis: meta-analysis

Data from selected studies were extracted to reconstructed 2 by 2 tables. Meta-analysis was performed using STATA's `metandi` and `metan` commands. Data were summarized using meta-analysis forest plot and hierarchical summary receiver operating characteristic (HSROC) curves.

Main results

Histoplasma antigen assays were determined to be the most accurate method for diagnosing progressive disseminated histoplasmosis in advanced HIV. Molecular assays appear promising for accurately diagnosing histoplasmosis, but consensus on the exact techniques is needed. Cultures showed variable sensitivity related to sample type and laboratory handling. Antibody assays presented high specificity but low sensitivity (19).

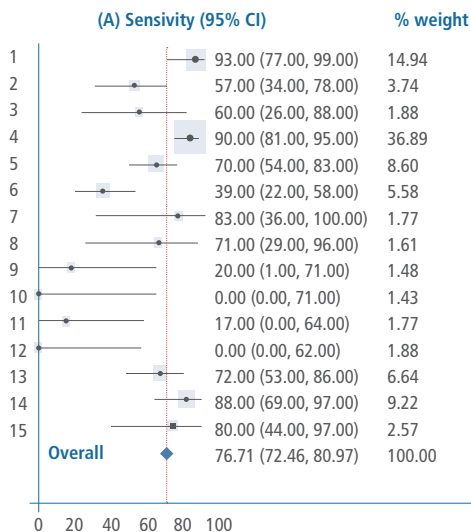
Authors' conclusions

The results of the meta-analysis showed that laboratory assays based on detecting circulating *Histoplasma* antigen demonstrated the best analytical performance. Since there is very-low-certainty evidence, we recommend further prospective research.

Analytical performance of assays

Figure 1. Meta-analysis of the sensitivity for the culture assay's analytical performance

Culture: sensitivity 77% (no data for specificity calculation)



Study summary (reference):

- Messina F, Argentina, blood culture [lysis centrifugation] (16)
- Oliveira F, Brazil, blood culture [lysis centrifugation] (17)
- Unis G, Brazil, conventional fungal media, respiratory samples (18)
- Bianchi M, Argentina, blood culture [lysis centrifugation] (19)
- Arechavala A, Argentina, conventional fungal media, multiple type samples (20)
- Zarabi C, USA, conventional fungal media, multiple type samples (21)*
- Zarabi C, USA, conventional fungal media, blood (21)*
- Zarabi C, USA, conventional fungal media, bone marrow (21)*
- Zarabi C, USA, conventional fungal media, tissue (21)*
- Zarabi C, USA, conventional fungal media, sputum (21)*
- Zarabi C, USA, conventional fungal media, lower respiratory samples (21)*
- Zarabi C, USA, conventional fungal media, body fluids (21)*
- Nightingale S, USA, conventional fungal media, blood (22)*
- Nightingale S, USA, conventional fungal media, blood + smear (22)*
- Nightingale S, USA, conventional fungal media, bone marrow (22)*

(* , +) Data extracted from the same study

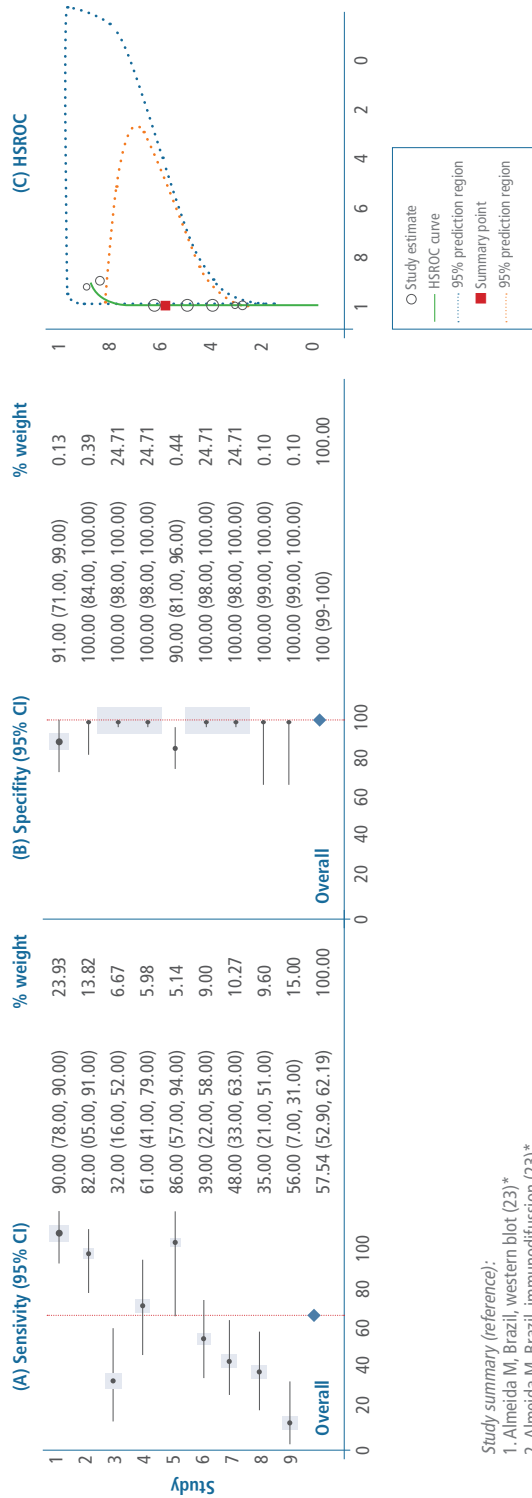
■ Study weight

◆ Overall 95% confidence interval (95% CI)

Source: Caceres et al. *J. Fungi* 2019, 5(3), 76 (19).

Figure 2. Meta-analysis of the antibody detection assay's analytical performance: (A) sensitivity, (B) specificity, and (C) Hierarchical summary receiver operating characteristic (HSROC)

Antibody detection assays: sensitivity 58% and specificity 100%



(* , +, -, £, ¢) Data extracted from the same study

■ Study weight

◆ Overall 95% confidence interval (95% CI)

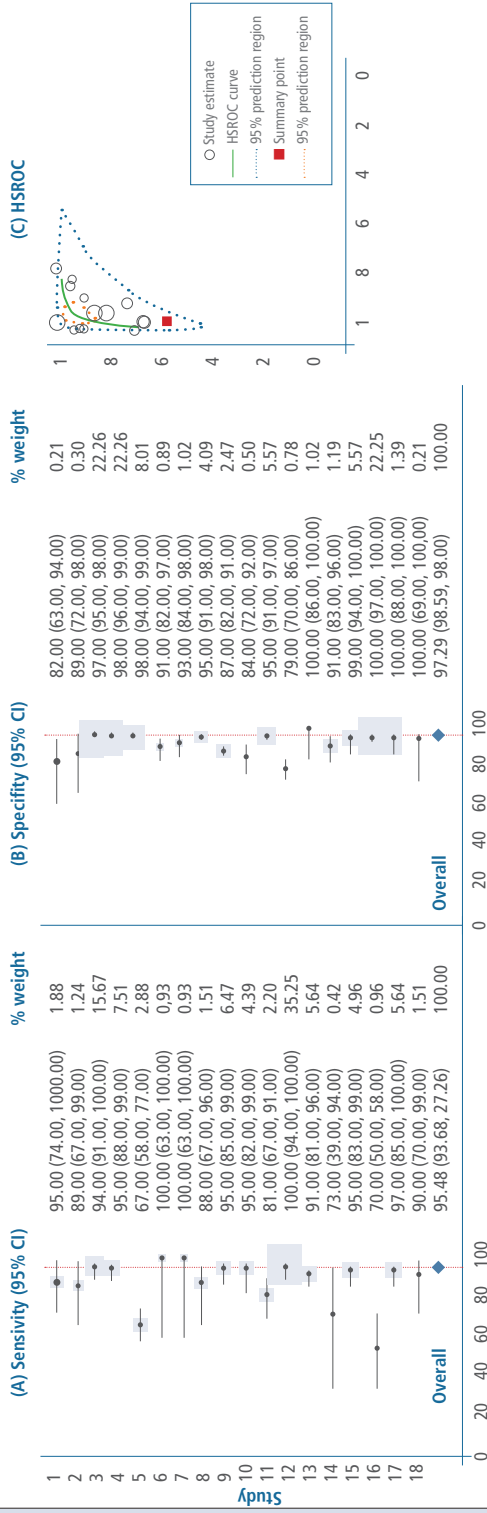
Source: Caceres et al. *J. Fungi* 2019, 5(3), 76 (19).

Study summary (reference):

1. Almeida M, Brazil, western blot (23)*
2. Almeida M, Brazil, immunodiffusion (23)*
3. Caceres DH, Colombia, complement fixation (24)*
4. Caceres DH, Colombia, immunodiffusion (24)*
5. Guimaraes A, Brazil, ELISA (25)
6. Scheel CM, Guatemala, complement fixation (26)£
7. Scheel CM, Guatemala, immunodiffusion (26)£
8. Negroni R, Argentina, counterimmunoelectrophoresis (27)¢
9. Negroni R, Argentina, complement fixation (27)¢

Figure 3. Meta-analysis of the antigen detection assay's analytical performance: (A) sensitivity, (B) specificity, (C) Hierarchical summary receiver operating characteristic (HSROC)

Antigen detection assays: sensitivity 95% and specificity 97%



Study summary (reference):

1. Caceres DH, Colombia quantitative LFA, serum (29)*
2. Caceres DH, Colombia quantitative LFA, serum (29)*
3. Caceres DH-Samayoa B, Colombia-Guatemala quantitative ELISA, urine (28)*
4. Caceres DH-Samayoa B, Colombia-Guatemala semi-quantitative ELISA, urine (28)*
5. Torres P, Mexico, semi-quantitative ELISA, urine (30)
6. Hoffman E, Brazil, semi-quantitative ELISA, urine (31)E

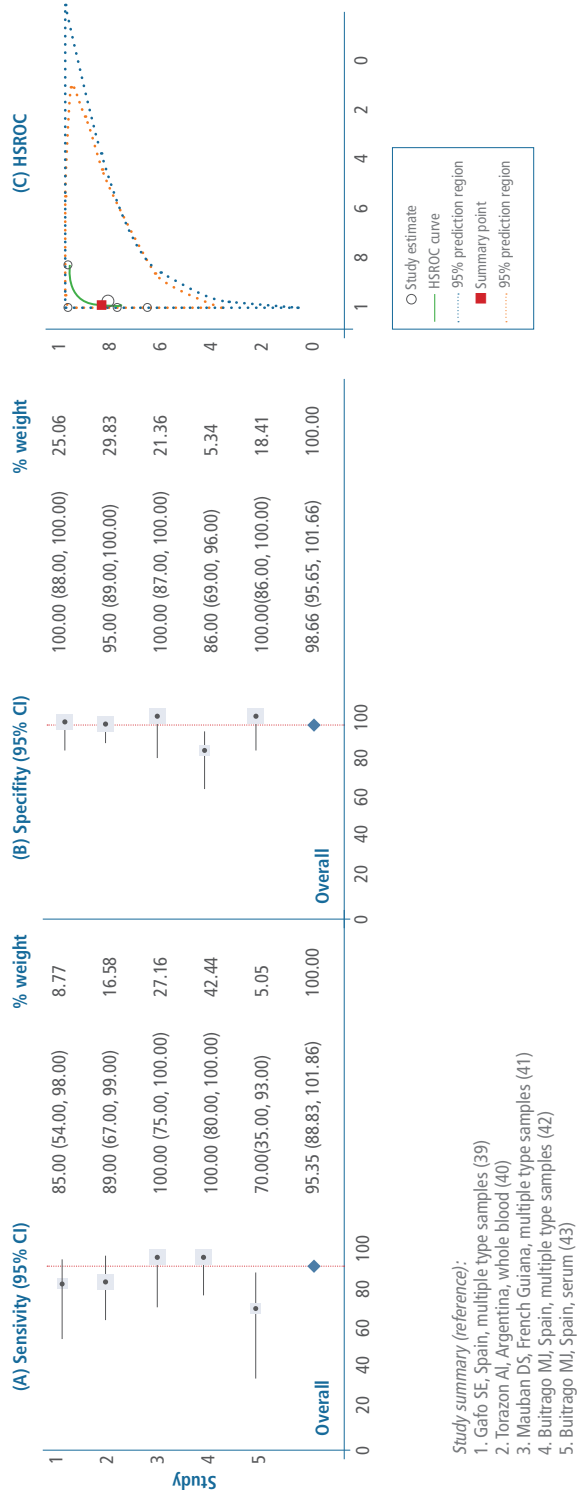
7. Hoffman E, Brazil, quantitative ELISA, urine (31)E
8. Caceres CH, Colombia, quantitative ELISA, urine (24)
9. Hage C, USA quantitative ELISA, urine (32)
10. Swartzentruber S, USA, quantitative ELISA, serum (33)
11. Scheed C, Guatemala, quantitative ELISA, urine (26)
12. Connolly P, USA, quantitative ELISA, urine (34)E
13. Connolly P, USA, quantitative ELISA, serum (34)E
14. Gomez, Colombia, quantitative ELISA, serum (35)
15. Durkin Mh, USA, semi-quantitative ELISA, urine (36)

16. Wheat LJ, USA, radioimmunoassay, bronchoalveolar lavage (37)
17. Wheat LJ, USA, radioimmunoassay, urine (38)
18. Wheat LJ, USA, radioimmunoassay, serum (38)

(* , +, E, t,) Data extracted from the same study
 ■ Study weight
 ◆ Overall 95% confidence interval (95% CI)
 Source: Caceres et al. *J. Fungi* 2019, 5(3), 76 (19).

Figure 4. Meta-analysis of DNA detection (molecular) tests analytical performance: (A) sensitivity, (B) specificity, and (C) Hierarchical summary receiver operating characteristic (HSROC)

DNA detection assays (molecular): sensitivity 95% and specificity 99%



Study estimate

HSROC curve

95% prediction region

Summary point

95% prediction region

Study estimate

HSROC curve

95% prediction region

Summary point

95% prediction region

ANNEX 4 . DIAGNOSTIC TESTS FOR HISTOPLASMOSIS

Company/product	Antigen
IMMY/Clarus Histoplasma GM Enzyme Immunoassay (Ref. HGM201)	Commercial: CE label. Detection of antigens in urine. Research use only in the United States. United States Food and Drug Administration clearance underway. https://www.immy.com/hgm
MiraVista/Polyclonal Ab ELISA (CPT code: 87385)	In-house: Indianapolis, IN, USA. Detection of antigens in urine, sera, and other body fluids. In the process of commercialization. https://miravistalabs.com/medical-fungal-infection-testing/antigen-detection/histoplasma-quantitative-eia-test
Molecular	
HOLOGIC/AccuProbe <i>Histoplasma capsulatum</i> culture identification test (Ref. 102910)	In situ hybridization assay for identification of <i>H. capsulatum</i> isolated from culture
Culture	
Abbott/ISOLATOR™ (Ref. 50C7)	Commercial: Lysis centrifugation system https://www.alere.com/en/home/product-details/isolator-10ml-microbial-tubes.html
BD/BACTEC™ Myco/F Lytic (Ref. 442288)	Commercial: CE label. Lysis system, automatic incubation system http://legacy.bd.com/ds/technicalCenter/inserts/PP162JAA(05).pdf
Antibody	
IMMY/Immunodiffusion Fungal Antibody Test Kit (Ref. ID1001)	Commercial: CE label http://www.immy.com/products/immunodiffusion-reagents-and-plates/#1473453177095-9d6fbd00-fc50
Meridian/Immunodiffusion reagents (Ref. 100201 and 100601)	Commercial: approved by the United States Food and Drug Administration https://www.meridianbioscience.com/human-condition/other/fungals/histoplasma-antigen-for-fungal-immunodiffusion
IMMY/Complement Fixation Reagents (Ref. H10150, H20110, H30150 and H40110)	Commercial: CE and in vitro diagnostic label http://www.immy.com/complement-fixation-reagents/#1473453809831-e685dea0-e154
IMMY. LA-Histoplasma (Ref. HL1001)	Commercial: approved by the United States Food and Drug Administration and CE label. https://www.immy.com/latex
Gibson Bioscience. Fungal serology.	Commercial: The ATCC Licensed Derivative Emblem. http://www.gibsonbioscience.com/GB-Products/Fungal-Serology/

ANNEX 5 . SYSTEMATIC REVIEW PICO 2: HISTOPLASMOSIS TREATMENT

Abstract

Background

Disseminated histoplasmosis is a serious fungal infection affecting people with advanced HIV. The optimal treatment regimens are unclear.

Objectives

Objective 1 – induction: to compare the efficacy and safety of initial therapy with liposomal amphotericin B versus initial therapy with alternative antifungal agents.

Objective 2 – maintenance: to compare the efficacy and safety of maintenance therapy with 12 months of oral antifungal treatment versus shorter durations.

Objective 3 – antiretroviral therapy: to compare the outcomes of early versus delayed initiation of antiretroviral therapy.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register; Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library; MEDLINE (PubMed, from 1966 to the present); Embase (OVID, from 1947 to the present); Science Citation Index Expanded (SCI-EXPANDED, from 1900), Conference Proceedings Citation Index-Science (CPCI-S, from 1900), and BIOSIS Previews (from 1926). We also searched the WHO International Clinical Trials Registry Platform (<http://www.who.int/ictrp/search/en>), ClinicalTrials.gov, and the ISRCTN registry (www.isrctn.com) to identify ongoing studies.

Selection criteria

We evaluated studies assessing the use of liposomal amphotericin B and alternative antifungal agents for induction therapy; studies assessing the duration of antifungal agents for maintenance therapy; and studies assessing the timing of antiretroviral therapy. We included randomized controlled trials, single-arm trials, prospective cohort studies, and single-arm cohort studies.

Data collection and analysis

Two review authors assessed eligibility and the risk of bias, extracted data and assessed the certainty of evidence. We used the ROBINS-I tool to assess the risk of bias in non-randomized studies. We summarized dichotomous outcomes using relative risks (RR).

Main results

We identified 17 individual studies, 10 of which could inform our review objectives. We found one randomized controlled trial that compared liposomal amphotericin B to deoxycholate amphotericin B. Compared with deoxycholate amphotericin B, liposomal amphotericin B may have higher clinical success rates (RR 1.46, 95% confidence interval (CI) 1.01–2.11, 80 participants, one study, low-certainty evidence) and lower rates of nephrotoxicity (RR 0.25, 95% CI 0.09–0.67, 77 participants, one study, high-certainty evidence) (29).

We found very-low-certainty evidence to inform comparisons between amphotericin B formulations and azoles for induction therapy.

We found very-low-certainty evidence to inform whether early versus deferred antiretroviral therapy is preferable in disseminated histoplasmosis.

Authors' conclusions

Liposomal amphotericin B appears to be preferable to deoxycholate amphotericin B for treating people living with HIV for disseminated histoplasmosis in areas where it is available. Since there is very-low-certainty evidence to inform other treatment choices, we recommend further prospective research.



Liposomal amphotericin compared with amphotericin deoxycholate for induction therapy of progressive disseminated histoplasmosis

Population: adults with HIV and progressive disseminated histoplasmosis

Settings: endemic areas

Intervention: induction therapy with liposomal amphotericin B

Comparison: amphotericin B deoxycholate

Outcomes	Illustrative comparative risks ^a (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Amphotericin B deoxycholate	Liposomal amphotericin B				
Clinical success	560 per 1,000	818 per 1,000 (566 to 1000)	RR 1.46 (1.01–2.11)	80 (one study)	⊕⊕⊕⊕ LOW Due to imprecision ^c	Liposomal amphotericin B may have higher clinical success rates than amphotericin B deoxycholate.
Death	125 per 1,000	19 per 1,000 (3 to 173)	RR 0.15 (0.02–1.38)	77 (one study)	⊕⊕⊕⊕ LOW Due to imprecision ^d	Treatment with liposomal amphotericin B may result in lower mortality than treatment with amphotericin B deoxycholate.
Safety outcomes: nephrotoxicity	375 per 1,000	94 per 1,000 (34 to 251)	RR 0.25 (0.09–0.67)	77 (one study)	⊕⊕⊕⊕ ⊕⊕⊕⊕ HIGH	Treatment with liposomal amphotericin B results in lower rates of nephrotoxicity than treatment with amphotericin B deoxycholate; this is supported by the findings of a Cochrane review that reports moderate-certainty evidence. ^b
Safety outcomes: drug discontinuation	83 per 1,000	19 per 1,000 (2 to 198)	RR 0.23 (0.02–2.38)	77 (one study)	⊕⊕⊕⊕ ⊕⊕⊕⊕ VERY LOW Due to imprecision and risk of bias ^e	We do not know whether treatment with liposomal amphotericin B leads to fewer treatment discontinuations than amphotericin B deoxycholate.

^aThe basis for the assumed risk (such as the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

^bBotero Aguirre JP, Restrepo Hamid AIM. Amphotericin B deoxycholate versus liposomal amphotericin B: effects on kidney function. Cochrane Database Syst Rev 2015;(1):CD010481.

CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: we are very uncertain about the estimate.

^cDowngraded by 2 for very serious imprecision: the confidence interval meets the line of no effect and is based on very few events (73 participants, one

randomized controlled trial).

^dDowngraded by 2 for very serious imprecision: the confidence intervals are wide and cross the line of no effect.

^eDowngraded by 1 for serious risk of bias (due to unclear reporting criteria) and 2 for very serious imprecision (the confidence intervals are wide and cross the line of no effect).

ANNEX 6 . SYSTEMATIC REVIEW PICO 3: HISTOPLASMOSIS AND TB COINFECTION

Objectives

To evaluate the safety of available treatment strategies for TB and histoplasmosis coinfection among people living with HIV.

The evidence base is limited, and we therefore adapted our objectives to the following:

- to describe recognized drug–drug interactions between first-line therapies for histoplasmosis, TB, and HIV; and
- to describe clinical approaches to TB, histoplasmosis, and HIV infection

Methods

Criteria for considering studies for this review

Types of studies

- Randomized controlled trials
- Quasi-randomized controlled trials and non-randomized controlled trials
- Prospective cohort studies, including single-arm cohort studies
- Retrospective cohort studies, including single-arm cohort studies
- Case series
- Case reports

Types of participants

Children, adolescents, and adults living with HIV with coexisting progressive disseminated histoplasmosis and TB.

Types of interventions

- Itraconazole with rifampicin-based anti-TB regimen
- Itraconazole with non-rifampicin-based anti-TB regimen

Types of outcome measures

Primary outcomes

- All-cause mortality
- Treatment failure of HIV
- Treatment failure of TB
- Treatment failure of histoplasmosis

Secondary outcomes

- Serious adverse events
- Duration of hospital stay

Methods

We developed our search strategy with the assistance of Vittoria Lutje, Information Specialist. We searched the following: Cochrane Infectious Diseases Group Specialized Register; Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; MEDLINE (PubMed, from 1966 to present); EMBASE (OVID, from 1947 to present); Science Citation Index Expanded (SCI-EXPANDED, from 1900), Conference Proceedings Citation Index-Science (CPCI-S, from 1900), and BIOSIS Previews (from 1926), all three using the Web of Science platform. We also searched the WHO International Clinical Trials Registry Platform (<http://www.who.int/ictrp/search/en>), ClinicalTrials.gov, and the ISRCTN registry (www.isrctn.com) to identify ongoing studies.

One reviewer (Marylou Murray) selected studies from the search results and extracted data.

We do not present GRADE evidence profiles, since all the evidence presented is of very low certainty due to the design of the contributing studies.

Results

Results of the search

We found only two studies that could directly inform the PICO. In addition, we report anticipated drug–drug interactions from established databases, but this does not represent a pharmacokinetic review.

Effects of interventions

One retrospective cohort study (41) compared outcomes for different treatment strategies for comorbid disseminated histoplasmosis and people with both TB and HIV. The authors do not comment on antiretroviral drug choices.

One case report (40) indicated outcomes for a single person treated with rifampicin and itraconazole.

One person in ACTG120 receiving rifampicin for *Mycobacterium avium-intracellulare* – undetectable itraconazole levels, died.

These are summarized in the following table:

Study	Strategy	Number of people		Outcomes
Agudelo et al. (41)	Itraconazole + RHZE	At initiation n = 10	After switch n = 7	Loss to follow-up: 1/7 Detectable itraconazole levels: 0/3 measured Treatment success: 4/6 Death: 1/6 Relapse (TB + progressive disseminated histoplasmosis): 1/6
	Itraconazole + quinolone + HZE	At initiation n = 4	After switch n = 7	Loss to follow-up: 1/7 Detectable itraconazole levels: 2/2 measured Treatment success: 4/5 (one switched from RHZE to quinolone HZE because of clinical failure)
Drayton et al. (40)	Itraconazole + RHZE	1		Undetectable serum itraconazole levels during rifampicin administration. Discontinuation of R led to improvement in progressive disseminated histoplasmosis.

ANNEX 7 . DRUG–DRUG INTERACTIONS: RIFAMYCINS OR ANTIFUNGAL DRUGS VERSUS ANTIRETROVIRAL DRUGS

	Nucleoside reverse-transcriptase inhibitors				Integrase strand-transfer inhibitors			Non-nucleoside reverse-transcriptase inhibitors			Protease inhibitors	
	TDF	FTC	3TC	AZT	ABC	DTG	RAL	EFV	NVP	LPV/r	ATV/r	
Rifampicin	No interaction expected	No interaction expected	No interaction expected	Potential interaction: rifampicin reduces AZT levels	Potential weak interaction	Rifampicin reduces DTG levels; dose adjustment recommended.	Rifampicin reduces RAL levels dose adjustment recommended	Reduces EFV levels; no dose adjustment recommended	Coadministration is contraindicated due to decreased NVP concentrations	Rifampicin decreases LPV/r levels. Dose adjustment possible but associated with toxicity.	Coadministration is contraindicated. Rifampicin decreases ATV/r levels.	
Rifabutin	No interaction expected	No interaction expected	No interaction expected	No interaction expected	No interaction expected	No interaction expected	No interaction expected	Reduces rifabutin levels; increased rifabutin dose recommended	NVP increases rifabutin levels. Some people may experience toxicity	LPV/r increases rifabutin levels. Reduced dose rifabutin and monitoring recommended.	ATV/r increases rifabutin levels. Reduced dose rifabutin and monitoring recommended.	
Amphotericin B	Potential interaction: caution due to nephrotoxicity	No interaction expected	No interaction expected	Potential interaction: monitor for toxicity	No interaction expected	No interaction expected	No interaction expected	No interaction expected	No interaction expected	No interaction expected	No interaction expected	
Fluconazole	No interaction expected	No interaction expected	No interaction expected	Potential interaction: monitor for toxicity	No interaction expected	No interaction expected	No interaction expected	No interaction expected	Potential interaction: FCN increases NVP levels	No interaction expected	No interaction expected	
Itraconazole	Potential interaction, but clinically significant effect unlikely	No interaction expected	No interaction expected	No interaction expected	No interaction expected	No interaction expected	No interaction expected	Reduces itraconazole levels; no dose recommendation can be made.	Reduces itraconazole levels; dosing recommendations differ	Increases itraconazole levels	Increases itraconazole and ATV/r levels	

	Amphotericin B	Fluconazole	
Rifampicin	No interaction expected	Rifampicin reduces levels of fluconazole	Rifampicin leads to subtherapeutic levels of itraconazole
Rifabutin	No interaction expected	Fluconazole increases levels of rifabutin: monitoring recommended	Rifabutin may decrease levels of itraconazole; itraconazole may increase levels of rifabutin; monitoring recommended.

Sources: <http://www.hiv-druginteractions.org> and <http://new.antifungalinteractions.com>.

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