Treating progressive disseminated histoplasmosis in people living with HIV (Review)

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**ABSTRACT**

**Background**
Progressive disseminated histoplasmosis (PDH) is a serious fungal infection that affects people living with HIV. The best way to treat the condition is unclear.

**Objectives**
We assessed evidence in three areas of equipoise.

1. **Induction.** To compare efficacy and safety of initial therapy with liposomal amphotericin B versus initial therapy with alternative antifungals.

2. **Maintenance.** To compare efficacy and safety of maintenance therapy with 12 months of oral antifungal treatment with shorter durations of maintenance therapy.

3. **Antiretroviral therapy (ART).** To compare the outcomes of early initiation versus delayed initiation of ART.

**Search methods**
We searched the Cochrane Infectious Diseases Group Specialized Register; Cochrane CENTRAL; MEDLINE (PubMed); Embase (Ovid); Science Citation Index Expanded, Conference Proceedings Citation Index-Science, and BIOSIS Previews (all three in the Web of Science); the WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, and the ISRCTN registry, all up to 20 March 2020.

**Selection criteria**
We evaluated studies assessing the use of liposomal amphotericin B and alternative antifungals for induction therapy; studies assessing the duration of antifungals for maintenance therapy; and studies assessing the timing of ART. We included randomized controlled trials (RCT), single-arm trials, prospective cohort studies, and single-arm cohort studies.

**Data collection and analysis**
Two review authors assessed eligibility and risk of bias, extracted data, and assessed certainty of evidence. We used the Cochrane 'Risk of bias' tool to assess risk of bias in randomized studies, and ROBINS-I tool to assess risk of bias in non-randomized studies. We summarized dichotomous outcomes using risk ratios (RRs), with 95% confidence intervals (CI).
Main results
We identified 17 individual studies. We judged eight studies to be at critical risk of bias, and removed these from the analysis.

1. Induction
We found one RCT which compared liposomal amphotericin B to deoxycholate amphotericin B. Compared to deoxycholate amphotericin B, liposomal amphotericin B may have higher clinical success rates (RR 1.46, 95% CI 1.01 to 2.11; 1 study, 80 participants; low-certainty evidence). Compared to deoxycholate amphotericin B, liposomal amphotericin B has lower rates of nephrotoxicity (RR 0.25, 95% CI 0.09 to 0.67; 1 study, 77 participants; high-certainty evidence). We found very low-certainty evidence to inform comparisons between amphotericin B formulations and azoles for induction therapy.

2. Maintenance
We found no eligible study that compared less than 12 months of oral antifungal treatment to 12 months or greater for maintenance therapy.

For both induction and maintenance, fluconazole performed poorly in comparison to other azoles.

3. ART
We found one study, in which one out of seven participants in the ‘early’ arm and none of the three participants in the ‘late’ arm died.

Authors’ conclusions
Liposomal amphotericin B appears to be a better choice compared to deoxycholate amphotericin B for treating PDH in people with HIV; and fluconazole performed poorly compared to other azoles. Other treatment choices for induction, maintenance, and when to start ART have no evidence, or very low certainty evidence. PDH needs prospective comparative trials to help inform clinical decisions.

PLAIN LANGUAGE SUMMARY
How best to treat progressive disseminated histoplasmosis in people with HIV

What was the aim of this review?
The aim of this Cochrane Review was to investigate some treatment dilemmas with progressive disseminated histoplasmosis in people living with HIV. We collected and analysed all relevant studies to answer this question and found 17 studies.

Key messages
Liposomal amphotericin B may improve clinical success compared to deoxycholate amphotericin B when starting treatment.

Liposomal amphotericin B results in less kidney damage compared to deoxycholate amphotericin B when starting treatment.

We are unsure how long people should stay on treatment after they have successfully completed the starting stage. We are unsure at what time during treatment of the fungal infection it is best to start treatment to fight the HIV virus.

What was studied in this review?
Histoplasmosis is an infection caused by inhaling a fungus called Histoplasma. The most severe form of histoplasmosis is called progressive disseminated histoplasmosis, in which the infection spreads from the lungs to other organs. It is life-threatening for people with advanced HIV.

The treatment of progressive disseminated histoplasmosis starts with ‘induction’, in which medicines are started to rapidly attack the fungus. The next phase is called ‘maintenance’, in which medicines are used to prevent the fungus taking hold again. During treatment of the fungus, antiretroviral medicines are started to fight the HIV virus.

We wanted to find out the best induction treatment, if maintenance could be for less than one year, and when was the best time to start antiretroviral medicines.

What are the main results of the review?
We found 17 studies. We removed eight from the review as they did not include important measurements that might change results. These included how severe the HIV infection was, or if the patients had other infections at the same time.
One study compared two forms of the same medicine for starting treatment of histoplasmosis, liposomal amphotericin B and deoxycholate amphotericin B. It found that the more expensive liposomal form is less likely to cause kidney damage and may have higher clinical success rates than the deoxycholate form.

None of the studies looked at whether maintenance could be less than one year. Two studies looked at antiretroviral medicines, but we do not know when it is best to start them.

How up to date is the review?
We searched for studies that had been published up to 20 March 2020.
### Summary of findings 1. Induction: liposomal amphotericin compared with amphotericin deoxycholate

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

**Patient or 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* (95% CI) | Relative effect (95% CI) | Number of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|-----------------------------------|----------------------------------------|--------------------------|----------------------------------|----------------------------------|----------|
| Assumed risk                      | Corresponding risk                      |                          |                                  |                                  |          |
| dAmB                              | lAmB                                   |                          |                                  |                                  |          |
| **Clinical success**              | 560 per 1000                           | 818 per 1000 (566 to 1000) | RR 1.46 (1.01 to 2.11)           | 80 (1 study)                     | ⊕⊕⊝⊕ ⊝ ⊝ ⊝ ⊝ Low ⁹ | Compared to dAmB, lAmB may have higher clinical success rates. |
| **Death**                         | 125 per 1000                           | 19 per 1000 (3 to 173)   | RR 0.15 (0.02 to 1.38)           | 77 (1 study)                     | ⊕⊕⊕⊕ ⊝ ⊝ ⊝ ⊝ Low ¹⁰ | Treatment with lAmB may result in lower mortality than treatment with dAmB. |
| **Safety outcomes: nephrotoxicity** | 375 per 1000                           | 94 per 1000 (34 to 251) | RR 0.25 (0.09 to 0.67)           | 77 (1 study)                     | ⊕⊕⊕⊕ ⊝ ⊝ ⊝ ⊝ High | Treatment with lAmB resulted in lower rates of nephrotoxicity compared to treatment with dAmB; this was supported by findings of a Cochrane Review which reported moderate-certainty evidence (Botero Aguirre 2015). |
| **Safety outcomes: drug discontinuation** | 83 per 1000                           | 19 per 1000 (2 to 198) | RR 0.23 (0.02 to 2.38)           | 77 (1 study)                     | ⊕⊕⊕⊕ ⊝ ⊝ ⊝ ⊝ Very low ¹¹ | We do not know if treatment with lAmB leads to fewer treatment discontinuations than dAmB. |

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**CI:** confidence interval; dAmB: deoxycholate amphotericin B; lAmB: liposomal amphotericin B; 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.

downgraded two levels for very serious imprecision: the CI met the line of no effect and was based on very few events (73 participants, 1 randomized controlled trial).

downgraded one level for serious risk of bias (due to unclear reporting criteria) and two levels for very serious imprecision (the CIs were wide and crossed the line of no effect).
**BACKGROUND**

**Description of the condition**

Progressive disseminated histoplasmosis (PDH) is an important infectious disease among people living with HIV. PDH is one of the endemic mycoses, meaning a fungal infection localized to a specific region. It is caused by two human pathogens, *Histoplasma capsulatum* var. *capsulatum* (in the Americas) and *Histoplasma capsulatum* var. *duboisii* (in Africa). It causes severe morbidity and carries a risk of mortality of over 60% (Adenis 2014; Cano-Torres 2019). *H capsulatum* var. *capsulatum* has historically been thought of as predominantly affecting the Americas, but there is evidence of a wider global distribution (Baker 2019).

The diagnosis of PDH in people living with HIV is usually made based on:

- risk factors for the disease (advanced HIV);
- clinical manifestations consistent with disseminated histoplasmosis, such as fever, fatigue, weight loss, and hepatosplenomegaly;
- histoplasma antigen assays;
- microscopic demonstration or isolation of *Histoplasma* from extrapulmonary sites; due to slow growth, isolation is likely to be too slow to allow diagnosis.

**Description of the intervention**

The current standard of care for PDH is typically based on Infectious Diseases Society of America 2007 guidelines (Wheat 2007). This guideline recommends:

- for moderately severe to severe disease, liposomal amphotericin B (3.0 mg/kg daily for 1 to 2 weeks), followed by oral itraconazole (200 mg 3 times daily for 3 days and then 200 mg twice daily for a total of at least 12 months);
- for mild-to-moderate disease, itraconazole (200 mg 3 times daily for 3 days), and then twice daily for at least 12 months.

Alongside treatment of PDH, HIV is treated with antiretroviral therapy (ART). Commencing ART might rapidly restore immune function. This may cause an excessive inflammatory response known as immune reconstitution inflammatory syndrome (IRIS) (Melzani 2020).

**How the intervention might work**

Azoles inhibit biosynthesis of ergosterol, which is essential in fungal cell membranes. Itraconazole, voriconazole, and posaconazole are thought to be fungicidal for histoplasma, but fluconazole is thought to have fungistatic activity only. Polyenes, such as amphotericin B, bind to fungal membrane sterols and disrupt cell membranes. They are thought to have fungicidal activity. Non-randomized trial data from animal studies suggest that near maximal antifungal activity with amphotericin B occurs within three days, which has led to interest in shorter courses in treatment of other mycoses, such as cryptococcal meningitis (Tenforde 2018).

**Why it is important to do this review**

Currently available guidelines for management of PDH date from 2007. These were designed for use by clinicians in the USA, a high-resource country. The advent of widespread availability of ART internationally has changed treatment paradigms for HIV. In resource-limited settings, there is interest in revisiting the optimal treatment options for PDH. This review summarizes available evidence, and in particular we aimed to understand if new evidence could inform updated international guidelines on PDH.

**OBJECTIVES**

1. Induction. To compare efficacy and safety of initial therapy with liposomal amphotericin B versus initial therapy with alternative antifungals.

2. Maintenance. To compare efficacy and safety of maintenance therapy with 12 months of oral antifungal treatment with shorter durations of maintenance therapy. (Please note, itraconazole is a preferred oral antifungal agent, see results.)

3. Antiretroviral therapy (ART). To compare the outcomes of early initiation of ART versus delayed initiation of ART.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We planned to synthesize the study types in order of priority. At each stage, if we found a sufficient number of studies to allow a high-certainty synthesis, we did not intend to progress further. As we did not find sufficient evidence to allow high-certainty synthesis, our review includes the following study types:

- randomized controlled trials (RCTs);
- quasi-RCTs/non-RCTs;
- prospective cohort studies;
- retrospective cohort studies;
- single arm cohort studies.

We excluded case reports and case series.

**Types of participants**

HIV-positive children, adolescents, and adults with a clinical diagnosis of PDH.

**Types of interventions**

We aimed to make the following comparisons.

| Objective | Intervention | Comparisons |
|-----------|--------------|-------------|
| 1. Induction | Liposomal amphotericin B (3.0 mg/kg daily) for 1–2 weeks | Lipid complex amphotericin B Deoxycholate amphotericin B Other antifungal agents |

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2. Maintenance

Oral antifungal treatment for < 12 months

Oral antifungal treatment for ≥ 12 months

3. ART

Early initiation (within 4 weeks of commencing antifungal therapy)

Delayed initiation (> 4 weeks after starting antifungal treatment)

Types of outcome measures

We collected data on key outcomes, as summarized in the table below.

| Objective | Efficacy outcomes of interest | Safety outcomes of interest |
|-----------|-------------------------------|-----------------------------|
| 1. Induction | Clinical failure at or before study end | Toxicity |
| | Laboratory failure at or before study end | Early discontinuation |
| 2. Maintenance | Relapse of histoplasmosis at 12 months, or other clinically important time points | Toxicity |
| | All-cause mortality at 12 months | Early discontinuation |
| 3. ART | Incidence of immune reconstitution inflammatory syndrome | Toxicity |
| | Viral failure | Early discontinuation |

Where possible, we collected dichotomous and time-to-event data for relevant outcomes. We also collected data on mortality, and severe adverse events, including type and frequency.

Search methods for identification of studies

Electronic searches

We developed our search strategy with the assistance of the Information Specialist, Vittoria Lutje. We searched the following databases on 20 March 2020 using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register; Central Register of Controlled Trials (CENTRAL; 2020, Issue 3, published in the Cochrane Library); MEDLINE (PubMed, from 1966); Embase (Ovid, from 1947); 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 World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/search/en/), ClinicalTrials.gov (clinicaltrials.gov/), and the ISRCTN registry (www.isrctn.com/) to identify ongoing studies.

Searching other resources

We examined reference lists of relevant studies and reviews.

Data collection and analysis

Selection of studies

Two review authors (MM and PH) screened the titles and abstracts of the search results to determine eligibility using Covidence (www.covidence.org/). We did not perform double screening as we prepared the review rapidly to inform a guidelines meeting. We each assessed a random sample of the other author's screening. There were no disagreements. Both review authors screened the full texts of potentially eligible studies, and resolved any disagreement by discussion. At the time of full-text screening, we categorized the studies by study design.

Data extraction and management

One review author (PH) extracted data, and one review author (MM) reviewed all data extraction to ensure accuracy.

Assessment of risk of bias in included studies

For each included study, both review authors performed a risk of bias assessment resolving any disagreements through discussion. We used the Cochrane 'Risk of bias' tool for RCTs. For non-randomized studies, we used the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool. We developed a theoretical target study and assessed each non-randomized study across up to seven domains. Each assessment was discontinued if a domain was deemed to be at critical risk of bias. Each outcome was assessed. We identified relevant confounding factors through investigation of the literature and in discussion with expert clinicians. These a priori factors included severity of disease (histoplasmosis and CD4 count); time to treatment; and, for objectives 2 and 3, adherence to ART/maintenance therapy for histoplasmosis.

Data synthesis

Narrative synthesis

We followed narrative synthesis methodology (Popay 2006). Within this synthesis, we organized findings from included studies to describe patterns across the studies in terms of the:
• direction of effects;
• size of effects.

We calculated 95% confidence intervals (CI) for binomial proportions. We calculated 95% CIs for risk ratios (RR) using Review Manager 5 (Review Manager 2014). Studies assessed as at critical risk of bias were excluded from narrative synthesis.

Quantitative synthesis
We did not identify trials that were sufficiently similar in design or outcomes to allow a meaningful meta-analysis of outcome data. Therefore, we have not performed quantitative synthesis.

Exploring relationships in the data
We planned to explore relationships to consider the factors that might explain any differences in direction and size of effect across the included studies. For data included in narrative synthesis, we explored relationships using textual descriptions of key study elements (see Characteristics of included studies table), groupings and clusters of similar studies, and presentation of findings in tabulated form.

Assessing the certainty of our conclusions
We planned to present adapted GRADE tables to summarize the certainty of our findings for each outcome. As we did not find good evidence to answer all objectives, we presented a GRADE table for outcomes relevant to 'Objective 1. Induction' detailing certainty of findings. We could not include any studies to answer 'Objective 2. Maintenance', so presented a narrative summary of indirect evidence in the body of the review only. We presented an additional summary table for 'Objective 3. ART'.

RESULTS
Description of studies

Results of the search
We retrieved 1259 results from our electronic search. After title and abstract screening, we identified 206 reports for full-text screening. Following full-text screening, we identified 16 individual studies which were relevant to the review. These included:
• two RCTs (ACTG-A5164, 2009; Johnson 2002);
• four single arm trials (ACTG084, 1992; ACTG120, 1992; ACTG174, 1994; McKinsey 1989);
• four prospective cohort studies (Baddley 2008; Couppié 2004; Goldman 2004; Ramdial 2002);
• six retrospective cohort studies (Luckett 2015; Mootsikapun 2006; Myint 2014; Negroni 2017; Norris 1994; Pietrobon 2004).

We have shown the results of our search in Figure 1.
We found one additional unpublished retrospective cohort study via correspondence with authors (Melzani 2020).

Therefore, there were 17 individual studies. We excluded eight of these studies from analysis as we assessed them to be at critical risk of bias using ROBINS-I methodology (Table 1). We listed these below.

**Included studies**

1. **Induction**

   From our search, the studies that gave information about relevant outcomes for induction therapies included:
   - one RCT (Johnson 2002);
   - two single arm trials (ACTG120, 1992; ACTG174, 1994);
   - one retrospective cohort study (Luckett 2015).

The following studies were excluded from narrative synthesis as they were at critical risk of bias using ROBINS-I methodology:
   - one single arm trial (McKinsey 1989);
   - two prospective cohort studies (Couppié 2004; Ramdial 2002).

2. **Maintenance**

   From our search, the studies that gave information about relevant outcomes for maintenance therapies included:
   - three single arm trials (ACTG084, 1992; ACTG120, 1992; ACTG174, 1994);
   - one prospective cohort study (Goldman 2004);
   - one retrospective cohort study (Mootsikapun 2006).

The following studies were excluded from narrative synthesis as they were at critical risk of bias using ROBINS-I methodology:
• one single arm trial (McKinsey 1989);
• one prospective cohort study (Baddley 2008);
• four retrospective cohort studies (Myint 2014; Negroni 2017; Norris 1994; Pietrobon 2004).

3. ART
We found one RCT which helped inform decisions regarding ART (ACTG-A5164, 2009). We included Melzani 2020 in a narrative synthesis as it provided evidence of baseline risk, but could not directly inform the objective.

Excluded studies
We excluded 186 studies (including an RCT, single arm trials, prospective cohort studies, and retrospective cohort studies) after full-text review. In the majority of cases, we were unable to extract relevant data from the study reports. We reported reasons for exclusion for a sample of 34 references in the Characteristics of excluded studies table.

Risk of bias in included studies
For the two randomized studies, risk of bias was low (Johnson 2002 shown in Table 2; ACTG-A5164, 2009 shown in Table 3). These are summarized in Figure 2.
### Figure 2: Risk of bias summary: review authors’ judgements about each risk of bias item for each included randomized study.

| Study                | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias): All outcomes | Blinding of outcome assessment (detection bias): All outcomes | Incomplete outcome data (attrition bias): All outcomes | Selective reporting (reporting bias) |
|----------------------|---------------------------------------------|----------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------|--------------------------------------------------------|----------------------------------|
| ACTG084, 1992        | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| ACTG120, 1992        | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| ACTG174, 1994        | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| ACTG-A5164, 2009     | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
| Baddley 2008         | +                                           | +                                     |                                                                         |                                                              |                                                        |                                  |
For the remaining 15 non-randomized studies, we assessed eight to be at critical risk of bias using ROBINS-I, and excluded these from synthesis as described above (Table 1). The remaining seven non-randomized studies were at serious risk of bias using ROBINS-I (Table 4). One study was at critical risk of bias for the relapse outcome, and serious risk of bias for the mortality outcome (Pietrobon 2004). We excluded this study from synthesis as the mortality outcome did not sufficiently inform the objective.

Risk of bias was low in both included randomized studies (Table 2; Table 3; Figure 2). Eight non-randomized studies were at critical risk of bias and eight at serious risk of bias overall using ROBINS-I. Details on assessment by outcome are provided in Table 1 and Table 4. Detailed domain assessments are available in Appendix 2.

Effects of interventions
See: Summary of findings 1 Induction: liposomal amphotericin compared with amphotericin deoxycholate

1. Induction therapy for progressive disseminated histoplasmosis

**Liposomal amphotericin B compared to deoxycholate amphotericin B**

One RCT compared liposomal amphotericin B and deoxycholate amphotericin B (Johnson 2002). There was greater treatment success with liposomal amphotericin B compared to deoxycholate amphotericin B (RR 1.46, 95% CI 1.01 to 2.11; 1 trial, 80 participants; Analysis 1.1). There were three deaths in the deoxycholate amphotericin B arm and one death in the liposomal amphotericin B arm (RR 0.15, 95% CI 0.02 to 1.38; 1 trial, 77 participants; Analysis 1.2). There were lower rates of nephrotoxicity (defined as creatinine greater than twice the upper limit of normal) with liposomal amphotericin B than with deoxycholate amphotericin B (RR 0.25, 95% CI 0.09 to 0.67; 1 trial, 77 participants; Analysis 1.3). The authors did not report other safety data, including frequencies of commonly reported toxicities such as anaemia.

**Liposomal amphotericin B compared to other antifungals**

No RCTs compared liposomal amphotericin B to other antifungals.

One retrospective cohort study compared all forms of amphotericin B to triazole therapy (including itraconazole, posaconazole, and voriconazole) (Luckett 2015). Treatment success for triazoles was 83% (95% CI 62% to 95%). The report did not disaggregate data by disease severity, but reported that across the study (which included people who were immunocompromised for reasons other than HIV infection), frequency of triazole failure was similar among people with severe infection compared with those with mild-to-moderate infection.

**Deoxycholate amphotericin B compared to other antifungals**

No study compared deoxycholate amphotericin B to other antifungals.

**Treatment success rates for other antifungals**

In the absence of comparative studies, we reported treatment success rates for antifungal agents (see ‘Narrative results table 1’).
### Narrative results: table 1: induction therapy

| Study          | Method | Participants | Interventions                                      | Primary outcome(s) | Setting | Disease severity | Overall risk of bias | Narrative of efficacy findings (95% CIs) | Narrative of safety findings |
|----------------|--------|--------------|---------------------------------------------------|--------------------|---------|------------------|----------------------|------------------------------------------|-------------------------------|
| ACTG120, 1992  | Single arm trial | 59 with PDH | ITRA 300 mg BD for 3 days then 200 mg BD for 12 weeks | "Response to therapy" | USA     | Mild to moderate | Serious              | Clinical success: 50/59 participants 85% (73% to 93%) | 2/59 participants withdrew due to adverse events, and responded to AmB. |
| ACTG174, 1994  | Single arm trial | 49 with PDH | Initial protocol FCN 1200 mg, then 600 mg OD for 8 weeks | "Treatment response" | USA     | Mild to moderate | Serious              | Clinical success: 36/49 participants. 74% (59% to 85%) | 2 discontinuations due to toxicity, unclear if induction or maintenance. |
|                |        |              | Revised protocol FCN 1200 mg, then 80 mg OD for 8 weeks |                    |         |                  |                      |                                          |                               |
| Johnson 2002   | RCT    | 81 with PDH  | IAmB (55 participants) dAmB (26 participants) | Efficacy: "Clinical success" Safety: early discontinuation | USA     | Moderate to severe | Low                  | Clinical success: IAmB: 82% (69% to 91%) 45/55 participants. dAmB: 56% (37% to 76%) 14/25 participants. RR 1.46 (1.01 to 2.11) | Early discontinuation: 1/53 (2%) with IAmB vs 2/24 (8%) with dAmB RR 0.23 (95% CI 0.02 to 2.38) Nephrotoxicity: 5/53 (9%) with IAmB vs 9/24 (37%) with dAmB RR 0.25 (95% CI 0.09 to 0.67) Of note, authors did not report specific data in re- |
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| Author(s) | Study Type | Country | Number of Participants | Treatments | Outcomes |
|-----------|------------|---------|------------------------|-------------|----------|
| Luckett 2015 | Retrospective cohort study | USA | 56 with HIV and PDH | ITRA/VORI/POSA AmB | Death (90-day histoplasmosis-related), Triazole failure |
|           |            |         |                        |             | Mild to severe, Serious |
|           |            |         |                        |             | Death |

- **dAmB:** 3/24 (13%)
- **RR:** 0.15 (0.02 to 1.38)
- No safety issues reported.

AmB: amphotericin B; BD: twice daily; CI: confidence interval; dAmB: deoxycholate amphotericin B; FCN: fluconazole; ITRA: itraconazole; IAmB: liposomal amphotericin B; n: number of participants; OD: once daily; PDH: progressive disseminated histoplasmosis; PO SA: posaconazole; RCT: randomized controlled trial; RR: risk ratio; VORI: voriconazole.

Relation to other commonly recognized adverse effects, including anaemia.

5/56 participants.
- Not reported by treatment regimen.

**Clinical success:**
- Triazole induction successful in 20/24 participants
- 83% (62% to 95%)
2. Maintenance therapy

Less than 12 months of oral itraconazole compared to 12 months or greater of oral itraconazole

No included study compared less than 12 months of oral itraconazole and 12 months or greater of oral itraconazole.

Continuation of antifungals versus discontinuation of antifungals

This result is summarized in Table 5.

One prospective single-arm cohort study followed a cohort of participants who discontinued antifungal therapy after at least 12 months, providing the participant had received at least six months of ART and had achieved a CD4 count of 150 cells/µL or greater (Goldman 2004). There were no relapses in 32 participants who discontinued therapy after 12 months.

Treatment success rates for modalities of maintenance therapies

'Narrative results table 2' indicates crude treatment success rates for different maintenance therapies used in studies.

Itraconazole

Two single arm trials reported low relapse rates of approximately 0.5% with itraconazole (ACTG084, 1992; ACTG120, 1992).

Fluconazole

One single arm trial was discontinued early due to higher relapse rates (11/36 participants; 30%, 95% CI 16% to 48%) (ACTG174, 1994). This trial used 400 mg doses of fluconazole after induction with fluconazole.
### Narrative results table 2: maintenance therapy

| Study | Method | Participants | Interventions | Primary outcomes | Setting | Disease severity | Overall risk of bias | Narrative of efficacy findings | Narrative of safety findings |
|-------|--------|--------------|---------------|------------------|---------|------------------|----------------------|------------------------------|-------------------------------|
| **Studies assessing discontinuation of oral antifungals** |
| Goldman 2004 | Prospective cohort study (single arm) | 32 | Discontinuation after > 12 months of ITRA/FCN/AmB | Relapse after 1 year | USA | ≥ 6 months of ART. CD4 count < 150 cells/μL | Serious | No relapses after 12 months of discontinuation of antifungal therapy. | No safety issues reported. |
| **Studies reporting outcomes of maintenance therapy regimens** |
| ACTG084, 1992 | Single arm trial | 42 (after dAmB induction) | ITRA 200 mg BD; continuous | Relapse | USA | No ART | Serious | Relapse: 2/42 participants (0.5%, 95% CI 0.05% to 16%) | Treatment discontinuation in 1/42 participants |
| | | | | Death | | | | Median follow-up 98 weeks | Severe or life-threatening adverse events in 37/42 participants; attributed mainly to HIV infection, opportunistic infections, and adverse effects of other medications. |
| ACTG120, 1992 | Single arm trial | 46 (of 59 enrolled) | ITRA 200 mg (26 participants) | Relapse | USA | No ART | Serious | Relapse: 2/46 participants (0.4%, 95% CI 0.05% to 14%) | Treatment discontinuation in 8/46 participants. |
| | | | | | | | | Median follow-up 87 weeks | 24/46 participants enrolled known to have died, including discontinuations; pre-ART. |
A CTG174, Single arm trial
1994
PDH: progressive disseminated histoplasmosis
FCN: fluconazole
USA
Am B: amphotericin B; ART: antiretroviral therapy; BD: twice daily; dAm B: deoxycholate amphotericin B; ITRA: itraconazole; n: number of participants; PDH: progressive disseminated histoplasmosis.

Relapse:

1/136 participants (30%, 95% CI 16% to 48%)
2 discontinuations due to toxicity, unclear if induction or maintenance.

Mild to severe
No ART
Serious:

11/36 participants (30%, 95% CI 16% to 48%)
2 discontinuations due to toxicity, unclear if induction or maintenance.

Relapse:

49 with PDH, 36 entered maintenance therapy
Median duration 30 weeks (early termination of study)
Relapse:
3. ART initiation

One trial compared early ART initiation to late ART initiation in people with coexisting opportunistic infections (ACTG-A5164, 2009). There were 10/282 participants with a presumptive or confirmed diagnosis of histoplasmosis. No diagnostic criteria were given for histoplasmosis. One participant with histoplasmosis in each trial arm developed IRIS. Both survived. One out of seven participants in the early ART died by day 30. None of the three participants with histoplasmosis in the delayed group died by day 30. This result is summarized in ‘Narrative results table 3’ and Table 6.

One additional study reported crude incidence rates of histoplasma IRIS including paradoxical IRIS (flare-up of a previously treated histoplasmosis) (Melzani 2020). This indicated an overall incidence rate of 0.74 cases per 1000 person-years. This study does not directly answer the objective of early versus deferred ART, but provides an indication of baseline risk.
### Narrative results table 3: antiretroviral initiation

| Study         | Method | Participants | Interventions | Outcomes | Setting          | Disease severity | Overall risk of bias | Narrative of findings                                                                 |
|---------------|--------|--------------|---------------|----------|------------------|------------------|---------------------|---------------------------------------------------------------------------------------|
| ACTG-A5164, 2009 | RCT    | 282, AIDS-related opportunistic infections | Early ART (n 7) Deferred ART (n 3) | Primary: composite endpoint of death and HIV viral load. Safety: IRIS; lab adverse events Grades 2–4; clinical adverse events Grades 2–4. | USA, South Africa | Baseline median CD4 count 29 (IQR 10–55) cells/μL | Low | 1/7 participants with histoplasmosis died in the early ART group. 0/3 participants with histoplasmosis died in the deferred ART group. 1/3 people with histoplasmosis in deferred ART arm developed histoplasma IRIS (day 47). IRIS aetiology: hepatitis C. Survived. 1/7 people with histoplasmosis in early ART arm developed hepatitis C IRIS (day 14). IRIS aetiology: histoplasmosis. Survived. |

ART: antiretroviral therapy; IQR: interquartile range; IRIS: immune reconstitution inflammatory syndrome.
DISCUSSION

Summary of main results
For 'Objective 1. Induction' comparing liposomal amphotericin B to other antifungals, four studies met the inclusion criteria: one RCT with 81 participants and three non-randomized studies with 164 participants. We judged all three non-randomized studies at serious risk of bias. Compared to deoxycholate amphotericin B, liposomal amphotericin B may have higher clinical success rates (low-certainty evidence), and has lower rates of nephrotoxicity (high-certainty evidence). We do not know if all amphotericin B formulations are more effective than azoles for the induction phase of management (very low-certainty evidence).

For 'Objective 2. Maintenance', comparing less than 12 months of oral antifungal treatment to greater than 12 months, no studies met the inclusion criteria.

For both objectives 1 and 2, fluconazole performed poorly in comparison to other azoles in the single-arm trial which studied this (ACTG174, 1994). No further trials were done as there was no longer sufficient equipoise to justify this.

'Objective 3: ART' sought to compare early and delayed initiation of ART. One RCT with 282 participants met the inclusion criteria. Only 10 participants had coexisting HIV and a presumptive or confirmed diagnosis of PDH. By day 30, one of seven participants in the 'early' arm and none of the three participants in the 'late' arm died. We do not know the efficacy and safety outcomes of early versus late initiation of ART (very low-certainty evidence).

Overall completeness and applicability of evidence
The overall evidence was limited; therefore, we were unable to address all the objectives of our review. Most studies were in the USA and such findings may not be generalizable to low-resource settings as availability of liposomal amphotericin B and management of HIV may differ. This affects the external validity of our review. There is insufficient evidence to be confident that azoles and other formulations of amphotericin are as effective and safe as liposomal amphotericin B in the induction phase of the management of PDH in people living with HIV. Clinical practice may be governed by availability. Current clinical practice would indicate that shorter courses of maintenance therapy may be acceptable; however, there is insufficient evidence available to corroborate or refute this practice. There is insufficient evidence to be confident of the safety of discontinuation of maintenance therapy before 12 months or the timing of ART. Overall, clinical practice tends to favour early ART in most situations. The low rates of IRIS in the single RCT do not present a signal that this practice is unsafe; however, there is insufficient evidence to confirm this. It seems that people in resource-limited settings are doing what they are able to do.

Certainty of the evidence
Overall, the certainty of the evidence for most outcomes was low or very low. Non-randomized study designs predominate in this area of research, many of which were critically compromised by uncontrolled confounding. For the comparison of liposomal amphotericin B to deoxycholate amphotericin B for induction therapy, there was high-certainty evidence of lower rates of nephrotoxicity (RR 0.25, 95% CI 0.09 to 0.67; 1 study, 77 participants). Evidence for clinical success for this comparison was of low certainty due to very serious imprecision indicating that further research is very likely to have an important impact on our confidence in the estimate of effect (RR 1.46, 95% CI 1.01 to 2.11; 1 study, 80 participants). For maintenance regimens, all six studies were of a non-randomized design, at serious risk of bias, and they could only provide low-certainty evidence.

Potential biases in the review process
To minimize the effect of all domains of bias in the non-randomized studies we presented only those at serious risk of bias. There is little evidence available from populations outside the USA.

Agreements and disagreements with other studies or reviews
Liposomal amphotericin B has previously been found to be significantly safer than conventional amphotericin B with respect to renal toxicity in PDH. One systematic review published in 2015 studying any invasive fungal infections reported an effect size of RR 0.49 (95% CI 0.40 to 0.59; 12 studies, 2298 participants; Botero Aguirre 2015).

There is insufficient evidence to confidently challenge or concur with current clinical guidelines on duration of maintenance therapy (Wheat 2007).

One systematic review that investigated the effects of early versus late ART in participants with coexisting HIV and cryptococcal meningitis found the RR for development of IRIS to be 3.56 (95% CI 0.51 to 25.02, 2 RCTs). The authors graded this evidence as very-low certainty due to imprecision, risk of bias, and indirectness indicating that they had little confidence in the effect estimate. This is consistent with the certainty of our findings for this outcome although the effect size of our included study was considerably smaller (RR 0.43, 95% CI 0.04 to 4.82; 1 study, 10 participants). This study also concluded that the risk of death appeared to be higher with early ART, leading to World Health Organization recommendations that treatment should be deferred for four to six weeks (Eshun-Wilson 2018).

AUTHORS' CONCLUSIONS

Implications for practice
Liposomal amphotericin B appears to be a better choice compared to deoxycholate amphotericin B for treating progressive disseminated histoplasmosis in people with HIV. Fluconazole appears unsuitable for induction or maintenance.

Implications for research
As there is very low-certainty evidence to inform other treatment choices, we recommend further prospective research. A priority question is whether in people with a clinical and immunological response to therapy, maintenance antifungal therapy can be safely discontinued earlier than 12 months. A further question is when is the optimal time to start ART, and in what circumstances the risk of IRIS may be higher? The high and varying costs of appropriate oral antifungal agents make these questions more pertinent.

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Best health.
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Library
Cochrane
Treatting progressive disseminated histoplasmosis in people living with HIV (Review)

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Characteristics of included studies [ordered by study ID]

### ACTG-A5164, 2009

| Study characteristics | RCT |
|-----------------------|-----|
| **Methods**           |     |
| **Participants**      | 282 people with AIDS-related OIs (TB excluded), 85% male |
|                       | 78 African-American; 91 Hispanic; 18 from South Africa |
|                       | 10 with HIV + PDH |
241 ART-naive at study entry

Interventions

Early ART (< 14 days, median 12 days)
Deferred ART (≥ 28 days, median 45 days) after start of OI treatment

Outcomes

Primary: composite: 3 ordered categories:
- death/AIDS progression
- no progression HIV VL ≥ 50 copies/mL
- no progression HIV VL < 50 copies/mL

For ALL participants there was no statistically significant difference in the composite outcome between early and deferred ART groups.

Secondary: AIDS progression/death; CD4 count at 24/48 weeks; HIV VL < 50% at 48 weeks, safety parameters including IRIS.

Death/AIDS progression in ALL participants

Favours early treatment

Deaths in people with histoplasmosis in early ART group: 1/7
Deaths in people with histoplasmosis in deferred ART group: 0/3

Safety: IRIS; lab adverse events Grades 2–4; clinical adverse events Grades 2–4

Age

Median 38 years

Setting

USA including Puerto Rico, ZAF

Disease severity

Median CD4+ T cell count 29 cells/μL

Notes

NCT00055120, ACTG A5164

Risk of bias

| Bias                                      | Authors' judgement | Support for judgement                                                                 |
|-------------------------------------------|--------------------|---------------------------------------------------------------------------------------|
| Random sequence generation (selection bias) | Low risk           | Random sequence generated by central computer using permuted blocks within Strata. Neither block size nor treatment assignments to other sites were public. |
| Allocation concealment (selection bias)   | Unclear risk       | No details provided in protocol or included study.                                     |
| Blinding of participants and personnel (performance bias) All outcomes | High risk          | Protocol stated that for arm B (deferred ART), no study-provided drugs were to be provided initially, hence blinding of participants and personnel was not possible. |
| Blinding of outcome assessment (detection bias) All outcomes | Low risk           | Primary outcome was a composite endpoint of survival and VL. Detection bias was unlikely. |
| Incomplete outcome data (attrition bias) All outcomes | Low risk           | Equal numbers withdrew without primary endpoint data in each study arm. Details provided. |
Selective reporting (reporting bias)  Low risk  Reported outcomes were consistent with protocol.

ACTG084, 1992

Study characteristics

Methods  Single arm trial

Participants  42 (after dAmB induction) participants enrolled; 1 excluded after enrolment as diagnosis not confirmed.

Interventions  ITRA 200 mg BD for prevention of relapse (maintenance)

Outcomes  Relapse (clinical evaluation)
            Death
            Follow-up 109 weeks (range 4–134 weeks)

Age  Mean 33 (range 16–50) years

Setting  USA

Disease severity  Not stated

Notes  2/42 participants relapsed

ACTG120, 1992

Study characteristics

Methods  Single arm trial

Participants  59 people with PDH in induction phase
            46 people in maintenance phase
            96% male
            65% white and non-Hispanic people
            Diagnosis based on clinical findings and laboratory evidence, including stains of tissues or body fluids, positive cultures, or detection of Histoplasma capsulatum antigen in blood or urine.
            People receiving rifampicin therapy were excluded.
            Participants were allowed to receive amphotericin 1.5 mg/kg prior to induction with ITRA.

Interventions  Induction phase: ITRA 300 mg BD for 3 days then 200 mg BD for 12 weeks

            Maintenance phase: ITRA dose reduced to 200 mg OD if induction serum levels were at least 4 µg/mL at week 8 or 200 mg BD if blood concentrations were lower.

Outcomes  Death
**ACTG120, 1992 (Continued)**

Response to therapy: defined as resolution of clinical signs and symptoms of histoplasmosis.

Adverse events.

| Age       | Mean 33 (range 16–68) years |
|-----------|-----------------------------|
| Setting   | USA                         |
| Disease severity | People with severe disease excluded. Defined as PO$_2$ < 60 mmHg, SBP < 90 mmHg, or CNS histoplasmosis |
| Notes | Response to therapy: 50/59 induction phase. Of 9 failures, 2 died; 6 responded to AmB; 1 lost to follow-up. Relapse of histoplasmosis infection: 2/46 participants at median follow-up of 87 weeks. 1 due to poor adherence and 1 to concurrent use of rifampicin. Toxicity: 5/46 participants discontinued treatment Mortality: 24/46 (included participants who discontinued treatment before death). Median survival time from start of maintenance estimated at 79 weeks. 1-year survival rate estimated at 73%. |

**ACTG174, 1994**

**Study characteristics**

| Methods   | Single arm trial |
|-----------|------------------|
| Participants | 49 people with PDH according to the revised protocol |
| Interventions | Induction: FCN 1200 mg on first day, then 600 mg OD for 8 weeks Maintenance: FCN 200 mg OD for ≥ 1 year Following revision of protocol due to high failure rate (10/20) Induction: FCN 1600 mg on first day, then 800 mg OD for 12 weeks Maintenance: 400 mg OD for 1 year |
| Outcomes | "Treatment response" Induction: 36/49 (73.5%) participants responded at 12 weeks; 28 of these had resolution of signs/symptoms and negative cultures; 8 had clinical response but cultures missing/not done 7/49 failed treatment: 1 died histoplasmosis and pneumocystis around day 3 Maintenance: 11/36 participants relapsed. Median time on maintenance was 30 weeks. 10/11 had blood cultures, 8/10 were positive 1/36 participants withdrew due to drug toxicity |
| Age       | Mean 36 (range not stated) years |
| Setting   | USA                           |
| Disease severity | Mild to moderate |
### ACTG174, 1994 (Continued)

**Notes**  
Study terminated early due to relatively high relapse rate (compared to earlier ITRA trial)

### Baddley 2008

**Study characteristics**

| Methods          | Prospective cohort study |
|------------------|--------------------------|
| Participants     | 46, 43 people with PDH   |
| Interventions    | ITRA (dosing not stated) (32/41 participants)  
dAmB (22/41 participants)  
IAmB (7/41 participants) |
| Outcomes         | All-cause mortality at 3 months postdiagnosis of histoplasmosis |
| Age              | Mean 38 (range not stated) years |
| Setting          | USA                       |
| Disease severity | Mild to severe            |
| Notes            | All-cause mortality at 3 months postdiagnosis of histoplasmosis was 18/46 participants.  
Mortality data not reported by treatment regimen. |

### Couppié 2004

**Study characteristics**

| Methods          | Prospective cohort study |
|------------------|--------------------------|
| Participants     | 82 people with PDH       |
| Interventions    | ITRA 400 mg OD (60 participants)  
AmB 0.7 mg/kg/day (22 participants) |
| Outcomes         | Mortality                |
| Age              | Mean 38 (range 19–68) years |
| Setting          | GUF                      |
| Disease severity | Mild to severe           |
| Notes            | Early death: defined as death within 30 days of initiation of antifungal treatment  
Severe histoplasmosis: 12/15 participants died; dAmB 8/12, ITRA 4/12  
Non-severe histoplasmosis: 6/67 participants died; dAmB 2/6, ITRA 4/6 |
Coupïé 2004 (Continued)  
First episode histoplasmosis; histoplasmosis confirmed by ≥ 1/3 methods; HIV confirmed; on antifungal treatment for histoplasmosis; > 15 years  
17% receiving ART. Severe histoplasmosis was defined as either shock that required treatment with vasopressors or respiratory failure that required mechanical ventilation.

Goldman 2004  
**Study characteristics**

| Methods       | Prospective cohort study |
|---------------|--------------------------|
| Participants  | 32 people living with HIV with documented histoplasmosis and ≥ 12 months of antifungal maintenance therapy  
97% male |
| Interventions | Discontinuation of antifungal therapy for PDH |
| Outcomes      | Relapse after 1 year: 0/32 |
| Age           | Mean 40 (range 22–68) years |
| Setting       | USA |
| Disease severity | Median CD4 count at baseline 289 cells/m³ |

Notes  
Aim: to assess the safety of stopping maintenance therapy for disseminated histoplasmosis among people living with HIV after response to ART.  
At study entry, participants discontinued maintenance therapy for disseminated histoplasmosis.  
The median duration of antifungal maintenance therapy before study enrolment was 34 months.  
Median follow-up 24 months

Johnson 2002  
**Study characteristics**

| Methods       | RCT |
|---------------|----|
| Participants  | 81 people with PDH, 88% male  
52% African American, 15% Hispanic |
| Interventions | lAmB (55 participants)  
dAmB (26 participants) |
| Outcomes      | **Efficacy**: “Clinical success” *(defined as a maximum daily temperature < 37.8 °C for 72 hours; no increase in severity of signs, symptoms, or laboratory abnormalities attributable to histoplasmosis; and the resolution of ≥ 1 of the signs or symptoms of histoplasmosis that qualified the patient for enrolment in the trial).*  
73 participants evaluated for efficacy in ITT analysis |
Clinical success in 45/51 IAmB vs 14/22 dAmB

**Safety:** early discontinuation

77 participants evaluated for safety in ITT analysis

Early discontinuation: 1/53 (2%) IAmB vs 2/24 (8%) dAmB

Nephrotoxicity: 5/53 (9%) IAmB vs 9/24 (37%) dAmB

**Death:** 1/53 (2%) IAmB (Staphylococcus aureus) vs 3/24 (12%) dAmB (progression of histoplasmosis)

| Age                  | Mean 33 (range 16–68) years |
|----------------------|-----------------------------|
| Setting              | USA                         |
| Disease severity     | Moderate to severe          |
| Notes                |                             |

**Risk of bias**

| Bias                                      | Authors' judgement | Support for judgement |
|-------------------------------------------|--------------------|-----------------------|
| Random sequence generation (selection bias) | Unclear risk       | Authors reported randomization in blocks. Details of method of randomization not provided. |
| Allocation concealment (selection bias)   | Low risk           | Closed envelopes.     |
| Blinding of participants and personnel (performance bias) | Low risk | Authors reported that participants received the intervention and comparator by intravenous infusion "in a blinded fashion". It is possible that both participants and personnel were blinded. |
| Blinding of outcome assessment (detection bias) | Low risk | Clinical and mycological outcomes were predetermined. These included objective components including temperature and laboratory findings. |
| Incomplete outcome data (attrition bias)  | Low risk           | Reasons reported for missing data. Proportion of data missing from each group was similar. |
| Selective reporting (reporting bias)      | Low risk           | No protocol cited; however, reported outcomes were consistent with trial aims. |

**Luckett 2015**

**Study characteristics**

| Methods                  | Retrospective cohort study |
|--------------------------|----------------------------|
| Participants             | 56 people with HIV and PDH |
| Interventions            | ITRA/VORI/POSA (24 participants) |
|                          | AmB (32 participants)      |
**Luckett 2015 (Continued)**

| Outcomes | Overall and histoplasmosis-related mortality, relapse, and treatment failure |
|----------|--------------------------------------------------------------------------|
| Age      | Mean 42 (range 26–74) years                                              |
| Setting  | USA                                                                      |
| Disease severity | Mild to severe                                           |
| Notes   | Death not reported by treatment regimen                               |
|         | Triazole failure: 4/24 participants                                    |

**McKinsey 1989**

**Study characteristics**

| Methods   | Single arm trial (pilot)                                                |
|-----------|-------------------------------------------------------------------------|
| Participants | 22 people with PDH; 17 received maintenance treatment                   |
|           | 95% male                                                                |

| Interventions | Induction: all received dAmB 0.5–1.0 mg/kg (22 participants) |
|               | Initial intensive/maintenance:                                        |
|               | Group 1                                                                 |
|               | dAmB 1 g (7 participants) then weekly infusions 50–80 mg to 2000 mg cumulatively then indefinite twice weekly infusions of 50–80 mg |
|               | Group 2                                                                 |
|               | dAmB 2g (9 participants) then weekly infusions of 80 mg                |
|               | dAmB 2g (1 participant) course then ketoconazole.                       |

| Outcomes | Induction: dAmB < 1 g, 5 participants: 2 participants died before treatment; 1 died early in treatment; 2 died from other causes. |
|          | dAmB > 1 g, 17 participants: 13 survived → maintenance phase dAmB; 1 survived → maintenance ketoconazole; 1 died histoplasmosis relapse; 2 died from other causes. |
|          | Initial intensive/maintenance:                                        |
|          | Group 1:                                                               |
|          | 6/7 survived at study end without clinical or laboratory evidence of relapse; 1/7 died of unrelated cause. |
|          | Group 2:                                                               |
|          | 7/9 survived at study end; 1 died of histoplasmosis relapse; 1/9 died of unrelated cause. |
|          | Median follow-up 14 months (range 2–23 months)                         |

| Age      | Mean 35 (range 22–57) years                                           |
| Setting  | USA                                                                     |
### McKinsey 1989 (Continued)

| Disease severity | Not stated |
|------------------|------------|
| Notes            | Findings suggested that, although immediate treatment of histoplasmosis in people living with HIV favoured higher dose of dAmB, during the remainder of induction there appeared to be little difference between 1 g and 2 g regimens. |

### Melzani 2020

**Study characteristics**

| Methods          | Retrospective cohort study |
|------------------|----------------------------|
| Participants     | People living with HIV within a cohort formed from 3 major hospitals in French Guiana from 1 January 1997 to 30 September 2017. |
| Interventions    | ART initiation |
| Outcomes         | IRIS cases were classified as: 1. certain, case-definition fulfilled; 2. probable, relevant case with ≥ 1 case-definition criteria missing; or 3. non-IRIS, data missing, or not sufficient to conclude. |
| Age              | Mean 40.5 (SD 7.0) years |
| Setting          | GUF |
| Disease severity | Not stated, IAmB used as proxy indicator for severe histoplasmosis. |
| Notes            | All episodes of histoplasmosis within 6 months of ART initiation. |

### Mootsikapun 2006

**Study characteristics**

| Methods          | Retrospective cohort study |
|------------------|----------------------------|
| Participants     | 68 participants; 32 with PDH, 36 with penicilliosis |
|                  | 29 with HIV + PDH |
| Interventions    | AmB 0.7 mg/kg/day for 30 participants with PDH, duration not specified |
|                  | ITRA 400 mg/day for 3 months; 200 mg/day thereafter for 27/32 participants with PDH |
| Outcomes         | Death: 3/32 participants |
|                  | Relapse: 0/27 participants (median follow-up 9.5 months) |
| Age              | 33 (SD 7) years |
| Setting          | THA |
| Disease severity | Not stated |
| Notes            | Outcomes not disaggregated by HIV status. |
### Myint 2014

**Study characteristics**

| Methods  | Retrospective cohort study |
|----------|----------------------------|
| Participants | 97 people with PDH |
|            | 38/97 participants in discontinued group (ITRA < 1 year) (A) |
|            | 59/97 participants in continued group (ITRA > 1 year) (B) |
| Interventions | ITRA for < 1 year |
|              | ITRA for > 1 year |
| Outcomes    | Relapse |
| Age         | Mean: 37 years in group A, 40 years in group B (range not stated) |
| Setting     | USA |
| Disease severity | Mild to severe |
| Notes       | Relapsed: 0/38 participants in group A; 21/59 participants in group B. |
|            | Relapse defined as clinical and laboratory confirmation > 3 months after initial therapy. |
|            | Adherence to antifungal and ART was determined by the physicians’ assessment and HIV RNA levels. |
|            | Adherence: 87% in group A vs 39% in group B; P ≤ 0.0001 |
|            | Follow-up: median 49 (range 12–170) months |

### Negroni 2017

**Study characteristics**

| Methods  | Retrospective cohort study |
|----------|----------------------------|
| Participants | 26 people with PDH who were followed up after discharge (from 80 hospitalized participants) |
| Interventions | ITRA 200 mg OD (20 participants) |
|              | dAmB twice/week (6 participants) |
|              | Duration: until CD4 count > 150 cells/μL |
| Outcomes    | Not stated |
| Age         | Mean 36 (range 18–60) years |
| Setting     | ARG |
| Disease severity | Not stated |
| Notes       |                             |
### Norris 1994

**Study characteristics**

| Methods   | Retrospective cohort study |
|-----------|----------------------------|
| Participants | 82 people with PDH         |
| Interventions | FCN at physician determined doses |
| Outcomes   | Relapse                    |
| Age        | Not stated                 |
| Setting    | USA                        |
| Disease severity | Not stated                 |

Notes: Norris 1994

### Pietrobon 2004

**Study characteristics**

| Methods   | Retrospective cohort study |
|-----------|----------------------------|
| Participants | 16 people with PDH. 14 men |
| Interventions | AmB 1 mg/kg/day up to 1 g followed by oral itraconazole 400 mg/day or FCN 200 mg/day |
| Outcomes   | Death, clinical relapse    |
| Age        | Mean 28 (range 20–36) years |
| Setting    | Argentina                  |
| Disease severity | Baseline CD4 count < 50 cells/µL (11 participants) |

Notes: Pietrobon 2004

### Ramdial 2002

**Study characteristics**

| Methods   | Prospective cohort study |
|-----------|----------------------------|
| Participants | 14 people living with HIV with disseminated cutaneous histoplasmosis |
| Interventions | ITRA 200 mg BD (4 participants) |
|             | AmB 0.5–1 mg/kg/day (7 participants) |
| Outcomes   | Death                      |

Notes: Ramdial 2002
Clinical success

Age
Mean 28 (range 3–41) years

Setting
ZAF

Disease severity
Not stated

Notes
Follow-up: 32 months
Death: 5/14; 3 died before treatment started; 1 died day 1 in ITRA group; 1 died day 2 in AmB group
Clinical success: 9/14
Induction: 6/9 ITRA; 3/9 dAmB
Maintenance: 7/9 ITRA; 2/9 dAmB

AmB: amphotericin B; ART: antiretroviral therapy; BD: twice daily; CNS: central nervous system; dAmB: deoxycholate amphotericin B; FCN: fluconazole; IRIS: immune reconstitution inflammatory syndrome; ITRA: itraconazole; ITT: intention to treat; lAmB: liposomal amphotericin B; OD: once daily; OI: opportunistic infection; PDH: progressive disseminated histoplasmosis; PO2: partial pressure of oxygen; POSA: posaconazole; RCT: randomized controlled trial; RNA: ribonucleic acid; SBP: systolic blood pressure; SD: standard deviation; TB: tuberculosis; VL: viral load; VORI: voriconazole.

Characteristics of excluded studies [ordered by study ID]

| Study               | Reason for exclusion                                                                                   |
|---------------------|--------------------------------------------------------------------------------------------------------|
| Assi 2007           | Retrospective cohort study, unable to extract data to inform our objectives.                           |
| Borges 1997         | Retrospective cohort study, only 9 participants received antifungal therapy.                          |
| Boulougoura 2019    | Conference abstract reporting incidence                                                               |
| Brilhante 2012      | Retrospective cohort study, unable to extract data to inform our objectives: authors indicated high failure rate with AmB, but did not elaborate on formulation, or upon disease severity. |
| Casariego 1997      | Retrospective cohort study, unable to extract data to inform our objectives: authors stated similar efficacy for ITRA and AmB, but no numerators or denominators given. |
| Chaiwarith 2013     | Randomized controlled trial. Unable to extract data to inform our objectives. Authors reported 2 participants with histoplasmosis in secondary prophylaxis group but no details given on their medication type or duration. |
| Crabtree-Ramirez 2016 | Prospective cohort study, unable to extract data specific to PDH to inform our objectives.          |
| Cunha 2007          | Retrospective cohort study, unable to extract data to inform our objectives: authors stated that 3 participants were treated with oral ITRA, and switched to AmB due to poor response. |
| Damasceno 2013      | Retrospective cohort study. Authors did not report drug doses, course durations, or disease severity. |
| Damasceno-Esoura 2020 | Retrospective cohort study. Reports percentages of patients treated with different approaches, but not outcomes. |
| Dismukes 1992       | Prospective trial, included only 1 participant with HIV and histoplasmosis.                           |
| Study                  | Reason for exclusion                                                                 |
|-----------------------|--------------------------------------------------------------------------------------|
| Falci 2015            | Retrospective cohort study of haematological toxicities associated with AmB formulation. Unable to extract data specific to HIV and PDH. |
| Gerber 1995           | Retrospective cohort study. Unable to extract data to inform our objectives as authors did not report HIV subgroup outcomes. |
| Gopalakrishnan 2012   | Retrospective cohort study, only included 4 participants with PDH and HIV. Unable to extract data to inform our objectives as authors did not report HIV subgroup outcomes. |
| Gutierrez 2005        | Retrospective cohort study. Authors did not report drug doses, course durations, or disease severity. |
| Huber 2008            | Retrospective cohort study. Authors did not report outcomes by type of therapy.       |
| Karimi 2002           | Retrospective cohort study. Authors did not report outcomes by drug doses, course durations, or disease severity. |
| Lopez Daneri 2016     | Retrospective cohort study. Authors did not report outcomes by drug doses, course durations, or disease severity. |
| Mata-Essayag 2008     | Retrospective cohort study. Authors were able to collect data on treatment in only 72/158 participants. |
| McKinsey 1996         | Single arm trial of FCN for histoplasmosis. People with HIV were excluded.            |
| Meng 2016             | Retrospective cohort study. Conference abstract only, unable to extract data to inform our objectives. |
| Messina 2018          | Retrospective cohort study. Authors did not report outcomes by treatment regimen.     |
| Mora 2008             | Retrospective cohort study. Authors did not report outcomes by treatment regimen.     |
| Nacher 2014           | Prospective cohort study. Authors did not report outcomes by treatment regimen.       |
| Negroni 1997          | Retrospective cohort study. Authors did not report outcomes by treatment regimen.     |
| Negroni 2004          | Retrospective cohort study reporting on discontinuation of secondary prophylaxis after restoration of CD4 count. Authors did not report treatment durations, therefore, unable to include. |
| Nightingale 1990      | Retrospective cohort study, reporting survival following a stated regimen of AmB in the pre-ART era. Unable to extract outcomes to inform our objectives. |
| Salzman 1988          | Retrospective cohort study. Details on treatment regimens for PDH not provided. Details on HIV status not reported. Participants were described as at risk of AIDS. |
| Samayoa 2017          | Prospective cohort study. Authors did not report outcomes by treatment regimen.       |
| Santos 1998           | Retrospective cohort study. Authors reported good initial response to treatment but no data provided on follow-up. 1 person with histoplasmosis. |
| Silva 2017            | Retrospective cohort study. Authors did not report outcomes by treatment regimen.     |
| Subramanian 2005      | Retrospective cohort study, included only 4 participants with HIV and PDH.            |
| Thompson 2016         | Single arm prospective trial of isavuconazole. Included 4 participants with PDH. They did not appear to have HIV/AIDS. |
| Study       | Reason for exclusion                                                                 |
|------------|---------------------------------------------------------------------------------------|
| Tobon 2005 | Retrospective cohort study. Authors did not report outcomes by treatment regimen.     |
| Wheat 1992 | Retrospective cohort study. Outcome was surrogate marker rather than clinical response.|
| Wheat 2018 | Retrospective cohort study. Outcome data not available for HIV subgroup, or by treatment arm. Reported similar mortality between induction therapy with azoles and induction therapy with AmB formulations. |

AmB: amphotericin B; ART: antiretroviral therapy; FCN: fluconazole; ITRA: itraconazole; PDH: progressive disseminated histoplasmosis.

**Characteristics of studies awaiting classification** [ordered by study ID]

| NCT00002159 |
|--------------|
| Methods      | Randomized open comparative multicentre study                                      |
| Participants | People with blastomycosis or histoplasmosis                                        |
| Interventions| Intravenous itraconazole vs amphotericin B                                          |
| Outcomes     | Not reported                                                                         |
| Notes        | Information sought unsuccessfully from databases, registries, citation searching, and clinical experts. |

**Characteristics of ongoing studies** [ordered by study ID]

| Pasqualotto 2019 |
|------------------|
| Study name       | Randomized Trial of Liposomal Amphotericin B for Histoplasmosis in AIDS Patients     |
| Methods          | Prospective randomized non-comparative multicenter open label trial of induction therapy with LAmB for DH in AIDS patients |
| Participants     | The sample size planned is 99 patients of both sexes, older than 18 years             |
| Interventions    | three study arms:                                                                   |
|                  | (i) single IV dose of 10 mg/kg of L-AmB;                                             |
|                  | (ii) single IV dose of 10 mg/kg of L-AmB on day 1, followed by 5 mg/kg of L-AmB on day 3; |
|                  | (iii) IV dose of 3 mg/kg of L-AmB for 2 weeks.                                        |
| Outcomes         | Primary Outcome Measures                                                             |
|                  | 1. Clinical response                                                                 |
|                  | 2. Weight stability                                                                  |
|                  | 3. Blood Pressure                                                                    |
|                  | 4. Blood oxygen level                                                                |
| Starting date    | Not yet recruiting                                                                   |
| Contact information | Alessandro C. Pasqualotto. acpasqualotto@hotmail.com                                |
DATA AND ANALYSES

Comparison 1. Liposomal amphotericin B (lAmB) versus deoxycholate amphotericin B (dAmB)

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|--------------------------|----------------|---------------------|--------------------|-------------|
| 1.1 Clinical success     | 1              | 80                  | Risk Ratio (M-H, Fixed, 95% CI) | 1.46 [1.01, 2.11] |
| 1.2 Death                | 1              | 77                  | Risk Ratio (M-H, Random, 95% CI) | 0.15 [0.02, 1.38] |
| 1.3 Safety outcomes      | 1              |                      | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.3.1 Infusion-related toxicity | 1 | 77 | Risk Ratio (M-H, Fixed, 95% CI) | 0.39 [0.22, 0.69] |
| 1.3.2 Nephrotoxicity     | 1              | 77                  | Risk Ratio (M-H, Fixed, 95% CI) | 0.25 [0.09, 0.67] |
| 1.3.3 Drug discontinuation | 1          | 77                  | Risk Ratio (M-H, Fixed, 95% CI) | 0.23 [0.02, 2.38] |

Analysis 1.1. Comparison 1: Liposomal amphotericin B (lAmB) versus deoxycholate amphotericin B (dAmB), Outcome 1: Clinical success

| Study or Subgroup | lAmB Events | dAmB Events | Total Weight | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-------------|-------------|--------------|-----------------------------|
| Johnson 2002 (1)  | 45          | 14          | 100.0%       | 1.46 [1.01, 2.11] |
| Total (95% CI)    | 55          | 25          | 100.0%       | 1.46 [1.01, 2.11] |

Footnotes (1) Denominators are 55 patients randomised to lAmB, and 25 randomised to dAmB, excluding one patient who died before treatment in the dAmB arm.
Analysis 1.2. Comparison 1: Liposomal amphotericin B (lAmB) versus deoxycholate amphotericin B (dAmB), Outcome 2: Death

| Study or Subgroup | lAmB | dAmB | Weight | Risk Ratio | Risk Ratio |
|-------------------|------|------|--------|------------|------------|
|                   | Events | Total | Events | Total | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Johnson 2002 (1)  | 1     | 53    | 3      | 24    | 0.15 [0.02, 1.38] |
| Total (95% CI)    | 53    | 24    | 100.0% | 0.15 [0.02, 1.38] |
| Total events:     | 1     | 3     |        |        |             |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable

Footnotes
(1) Denominators are safety population, all those receiving at least one dose.

Analysis 1.3. Comparison 1: Liposomal amphotericin B (lAmB) versus deoxycholate amphotericin B (dAmB), Outcome 3: Safety outcomes

| Study or Subgroup | lAmB | dAmB | Weight | Risk Ratio | Risk Ratio |
|-------------------|------|------|--------|------------|------------|
|                   | Events | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| 1.3.1 Infusion-related toxicity | | | | | |
| Johnson 2002 (1)  | 13    | 53    | 15     | 24    | 0.39 [0.22, 0.69] |
| Subtotal (95% CI) | 53    | 24    | 100.0% | 0.39 [0.22, 0.69] |
| Total events:     | 13    | 15    |        |        |             |

Heterogeneity: Not applicable
Test for overall effect: Z = 3.25 (P = 0.001)

1.3.2 Nephrotoxicity

| Study or Subgroup | lAmB | dAmB | Weight | Risk Ratio | Risk Ratio |
|-------------------|------|------|--------|------------|------------|
|                   | Events | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Johnson 2002 (1)  | 5     | 53    | 9      | 24    | 0.25 [0.09, 0.67] |
| Subtotal (95% CI) | 53    | 24    | 100.0% | 0.25 [0.09, 0.67] |
| Total events:     | 5     | 9     |        |        |             |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.76 (P = 0.006)

1.3.3 Drug discontinuation

| Study or Subgroup | lAmB | dAmB | Weight | Risk Ratio | Risk Ratio |
|-------------------|------|------|--------|------------|------------|
|                   | Events | Total | Events | Total | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Johnson 2002 (1)  | 1     | 53    | 2      | 24    | 0.23 [0.02, 2.38] |
| Subtotal (95% CI) | 53    | 24    | 100.0% | 0.23 [0.02, 2.38] |
| Total events:     | 1     | 2     |        |        |             |

Heterogeneity: Not applicable
Test for overall effect: Z = 1.24 (P = 0.22)

Test for subgroup differences: Chi² = 0.72, df = 2 (P = 0.70), P = 0%

Footnotes
(1) Denominators are safety population, all those receiving at least one dose.
### Comparison 2. Early antiretroviral therapy (ART) versus deferred ART

| Outcome or subgroup title                                      | No. of studies | No. of participants | Statistical method                  | Effect size          |
|---------------------------------------------------------------|----------------|---------------------|------------------------------------|----------------------|
| 2.1 Immune reconstitution inflammatory syndrome               | 1              | 10                  | Risk Ratio (M-H, Fixed, 95% CI)    | 0.43 [0.04, 4.82]    |

#### Analysis 2.1. Comparison 2: Early antiretroviral therapy (ART) versus deferred ART, Outcome 1: Immune reconstitution inflammatory syndrome

| Study or Subgroup | Early ART | Deferred ART | Risk Ratio M-H, Fixed, 95% CI |
|-------------------|-----------|--------------|--------------------------------|
| ACTG-A5164, 2009  | 1         | 7            | 0.43 [0.04, 4.82]              |
| Total (95% CI)    | 7         | 3            | 0.43 [0.04, 4.82]              |

**Table 1. Table of studies at critical risk of bias overall (ROBINS-I): disease-related outcomes**

| Study            | Review objective | Domain       | Comment                                                                                                                                 |
|------------------|------------------|--------------|------------------------------------------------------------------------------------------------------------------------------------------|
| McKinsey 1989    | 1 and 2          | Confounding  | Confounding domains were not controlled for. No report of ART use, CD4 counts, or clinical condition of participants. Rationale for selection of treatment regimen not described. |
| Couppié 2004     | 1                | Participant selection | Selection of intervention was made by the treating physician. As more severely ill participants were more likely to get AmB than ITRA selection was strongly related to the outcome. |
| Ramdial 2002     | 1                | Confounding  | Confounders not addressed with respect to treatment regimens. Descriptive account provided of management of participants without detail on severity of conditions, comediations, or comorbidities. No information provided on time to treatment or duration of treatment. |
| Baddley 2008     | 2                | Confounding  | Logistic regression used to determine association of variables with mortality including potential confounders, age, and race. Antifungal treatment data were not included in regression or reported in detail per participant. Authors reported 32/41 participants received ITRA, 22/41 dAmB, and 7/41 lAmB. Switches between medications were not reported. Authors reported 29 participants received ITRA after AmB. Denominator not reported. 8/13 participants who died were receiving an AmB preparation and 5/13 receiving ITRA. Time of transition from AmB to azole not reported. |
Myint 2014  2  Confounding  Physician determined discontinuation of maintenance therapy may have been influenced by prognostic factors that were not controlled for. Multiple logistic regression used to determine variables associated with relapse; however, assignment to treatment arms were based on clinical assessment and viral load. ‘Adherence to therapy’ not defined. Unclear if this referred to ART, ITRA, or both. No evidence of adjustment for time-varying confounding.

Negroni 2017  2  Confounding  Comorbidity and comedications were not reported or controlled for. Outcome data were not linked to disease severity. Outcomes not reported by drug regimen. Treatment regimens varied by drug and duration. There were drug switches.

Norris 1994  2  Confounding  Authors reported no specific criteria to select participants for intervention. Criteria included unavailability of ITRA and preference for oral therapy. Intervention group determined by treating physicians who also evaluated clinical evidence of relapse and side effects. Severity of HIV, comorbidities and comedication were not reported.

Pietrobon 2004  2  Confounding  For outcome 'relapse of histoplasmosis': follow-up periods not reported. Duration of ITRA or FCN not reported. Switches between regimens not reported. Concurrent medication not reported. No statistical methods to control for confounding reported.

For outcome 'death': this study can be considered to be at 'serious risk of bias'. No use of ART during treatment period. Comorbidities mentioned but unclear whether all relevant comorbidities studied. Severity of PDH not reported. No report of statistical methods to control for confounders. ≥ 1 known important domain was not appropriately measured or controlled for. Given the very small numbers, we have not reported further details in synthesis.

For details of risk of bias assessments see Appendix 3.

AmB: amphotericin B; ART: antiretroviral therapy; dAmB: deoxycholate amphotericin B; FCN: fluconazole; ITRA: itraconazole; lAmB: liposomal amphotericin B.

Table 2. Risk of bias Johnson 2002

| Bias                        | Authors’ judgement | Support for judgement                                                                 |
|-----------------------------|--------------------|---------------------------------------------------------------------------------------|
| Random sequence generation  | Unclear risk       | Authors reported randomizations in blocks. Details of method of randomization not provided |
| Allocation concealment      | Low risk           | Closed envelopes                                                                      |
| Blinding of participants and personnel | Low risk | Authors reported that participants received the intervention and comparator by intravenous infusion "in a blinded fashion". It is possible that both participants and personnel were blinded. |
| Blinding of outcome assessment | Low risk           | Clinical and mycological outcomes were predetermined. These included objective components including temperature and laboratory findings. |
Incomplete outcome data | Low risk | Reasons reported for missing data. Proportion of data missing from each group was similar.
---|---|---
Selective reporting | Low risk | No protocol cited; however, reported outcomes are consistent with trial aims.

### Table 3. Risk of bias ACTG-A5164, 2009

| Bias | Authors' judgement | Support for judgement |
|------|-------------------|-----------------------|
| Random sequence generation | Low | Random sequence was generated by central computer using permuted blocks within strata. Neither block size nor treatment assignments to other sites were public. |
| Allocation concealment | Unclear | No details provided in protocol or included study. |
| Blinding of participants and personnel | High | Protocol stated that for arm B (deferred ART), no study-provided drugs were to be provided initially hence blinding of participants and personnel was not possible. |
| Blinding of outcome assessment | Low | Primary outcome was a composite endpoint of survival and viral load. Detection bias was unlikely. |
| Incomplete outcome data | Low | Equal numbers withdrew without primary endpoint data in each study arm. Details provided for these participants. |
| Selective reporting | Low | Reported outcomes were consistent with protocol. |

### Table 4. Table of studies at serious risk of bias overall (ROBINS-I): disease-related outcomes

**Studies at serious risk of bias outcomes: death, relapse of histoplasmosis**

| Study | Review objective | Domain(s) | Comment |
|-------|------------------|-----------|---------|
| ACTG120, 1992 | 1 and 2 | Confounding; participant selection; intervention classification | Severity of HIV; severity of PDH and comorbidities were not controlled for using appropriate statistical methodology. ART use at baseline of an earlier phase of the trial reported: those who responded to the intervention (ITRA) in the induction phase were selected for the intervention in the maintenance phase: participants started intervention at various doses and had reductions in dose made at variable intervals. While this was likely to have been informed by ITRA blood levels that were being monitored, detailed data were not provided per participant. |
| ACTG174, 1994 | 1 and 2 | Confounding; participant selection | At 3 months, protocol was revised and treatment regimen amended. Analyses were performed on participants who received the revised protocol (higher doses of FCN). Severity and management of HIV was not reported or controlled with appropriate statistical methods: selection into the maintenance arm of the study was related to the effect of the intervention in the induction phase. |
Table 4. Table of studies at serious risk of bias overall (ROBINS-I): disease-related outcomes (Continued)

| Study            | Risk | Intervention classification; outcome measurement | Comments |
|------------------|------|---------------------------------------------------|----------|
| Luckett 2015     | 1    | No information about dose, frequency, and timing of interventions. Information was collected retrospectively. Treatment failure outcome was based on clinician judgement only. This was likely to favour switch fromazole to amphotericin. |
| ACTG084, 1992    | 2    | Confounding                                       | Severity of HIV infection and ART use were not controlled for with appropriate statistical methods. |
| Goldman 2004     | 2    | Participant selection                             | Start of intervention varied – participants enrolled after a range of 14–81 months of antifungal therapy. Unclear how many eligible people were not enrolled. |
| Mooitsikapun 2006| 2    | Confounding; participant selection                | ≥ 1 known important domain was not appropriately measured or controlled for: details of disease severity, comedications and comorbidities not provided for 27 participants discharged from hospital: maintenance therapy was commenced in those who responded to initial treatment on amphotericin B. Timing of start of maintenance therapy was not reported. Selection into this part of the study was related to the intervention. |
| Melzani 2020     | 3    | Confounding                                       | ART was discontinued in 2/22 participants at the physician’s decision; 2/22 due to patient choice. In unmasking group (14 participants), 10/14 received IAmB and 4/14 received ITRA. Paradoxical group (8 participants) physicians continued ART and ITRA for 6/8. Rationale for treatment choices not reported. Appropriate statistical measures to control for confounding were not reported. ≥ 1 known important domain was not appropriately measured or controlled for. |

For details of risk of bias assessment see Appendix 3.
ART: antiretroviral therapy; FCN: fluconazole; ITRA: itraconazole; IAmB: liposomal amphotericin B; PDH: progressive disseminated histoplasmosis.

Table 5. Additional summary 1: amphotericin B formulations versus azoles

Early ART compared with deferred ART for PDH in HIV

Patient or population: adults with HIV and progressive disseminated histoplasmosis

Settings: endemic areas

Intervention: induction therapy with triazoles

Comparison: induction therapy with amphotericin B formulations

| Outcomes | Narrative summary | Certainty of the evidence (GRADE) | Comments |
|----------|-------------------|-----------------------------------|----------|
| Treatment success | No RCTs make direct comparisons of amphotericin B and triazoles. Treatment success of triazoles (other than fluconazole) were 83% and 85% in the 2 studies which reported them. | ⊕⊝⊝⊝ | — |

ART: antiretroviral therapy; PDH: progressive disseminated histoplasmosis; RCT: randomized controlled trial.

a Downgraded two levels for serious imprecision. The CIs are wide due to small numbers of participants.
b Downgraded one level for serious indirectness. No studies report direct comparisons.
Table 6. Additional summary 2: early versus deferred ART

Early ART compared with deferred ART for PDH in HIV

**Patient or population:** adults with HIV and progressive disseminated histoplasmosis

**Settings:** endemic areas

**Intervention:** early ART (<14 days)

**Comparison:** late ART (>14 days)

| Outcomes | Illustrative risks | Relative effect (95% CI) | No of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|----------|--------------------|--------------------------|-----------------------------|---------------------------------|----------|
| IRIS     | 1/3 participants\(^a\) | RR 0.43 (0.04 to 4.82)   | 10 (1 study)                | ☢☢☢☢                           | We do not know if early ART increases the risk of IRIS in people with HIV and PDH. |

\(^a\)1/3 people with histoplasmosis in deferred ART arm developed histoplasma IRIS (day 47). 1/7 people with histoplasmosis in early ART arm developed hepatitis C IRIS (day 14).

\(^b\)Downgraded two levels for serious imprecision. The CI was wide.

\(^c\)Downgraded one level for serious indirectness. The trial only included 10 participants with histoplasmosis and the case definitions were not stated.

**APPENDICES**

**Appendix 1. Detailed search strategies**

**Cochrane Central Register of Controlled Trials Issue 3 of 12, March 2020**

#1 MeSH descriptor: [HIV] explode all trees

#2 MeSH descriptor: [HIV Infections] explode all trees

#3 HIV OR hiv-1 OR hiv-2* OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immunedeficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus )) OR acquired immunodeficiency syndrome OR acquired immunedeficiency syndrome OR acquired immunodeficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immunodeficiency syndrome OR ((acquired immun*) AND (deficiency syndrome))

#4 #1 or #2 or #3

#5 MeSH descriptor: [Histoplasma] explode all trees

#6 MeSH descriptor: [Histoplasmosis] explode all trees

#7 histoplasm*

#8 #5 or #6 or #7

#9 #4 and #8

PubMed (MEDLINE)
| Search set | Search terms |
|------------|--------------|
| 1         | HIV Infections[MeSH] OR HIV[MeSH] OR (Hiv OR hiv-1 OR hiv-2* OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immunodeficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus )) OR acquired immunodeficiency syndrome OR acquired immunodeficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) Field: Title/Abstract |
| 2         | "Histoplasma"[Mesh] OR "Histoplasmosis"[Mesh] or Histoplasm* Field: Title/Abstract |
| 3         | 1 and 2 |
| 4         | "Antifungal Agents"[Mesh] |
| 5         | "Amphotericin B"[Mesh] OR amphotericin Field: Title/Abstract |
| 6         | "Itraconazole"[Mesh] OR itraconazole Field: Title/Abstract |
| 7         | 4 or 5 or 6 |
| 8         | 3 and 7 |
| 9         | "Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type] |
| 10        | randomized or placebo or randomly or trial or groups Field: Title/Abstract |
| 11        | drug therapy [Subheading] |
| 12        | "Interrupted Time Series Analysis"[Mesh] |
| 13        | "Controlled Before-After Studies"[Mesh] |
| 14        | “time series” Field: Title/Abstract |
| 15        | "cross-over studies"[MeSH] or crossover or cross-over Field: Title/Abstract |
| 16        | "longitudinal studies"[MeSH] |
| 17        | Longitudinal or cohort* Field: Title/Abstract |
| 18        | "Systematic Review" [Publication Type] |
| 19        | metaanalysis or meta-analysis or “systematic review” Field: Title/Abstract |
| 20        | 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 |
| 21        | 8 and 20 |

Embbase 1947-Present, updated daily

Search Strategy:

1 HIV infection.mp. or HIV Infections/
2 exp HIV/ or Acquired Immunodeficiency Syndrome/

3 (Hiv or hiv-1 or hiv-2* or hiv1 or hiv2 or hiv infect* or human immunodeficiency virus or human immunodeficiency virus or human immunodeficiency virus or human immunodeficiency virus or human immunodeficiency virus or human immunodeficiency virus or human immunodeficiency virus or human immunodeficiency virus or (human immun* and deficiency virus) or acquired immunodeficiency syndrome or acquired immunodeficiency syndrome or acquired immuno-deficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome or (acquired immun* and deficiency syndrome)).mp.

4 aids.mp. or acquired immune deficiency syndrome/

5 1 or 2 or 3 or 4

6 histoplasma.mp. or Histoplasma/

7 histoplasmosis.mp. or histoplasmosis/

8 6 or 7

9 5 and 8

10 antifungal agents.mp. or antifungal agent/

11 itraconazole.mp. or itraconazole/

12 amphotericin B/ or Amphotericin B.mp.

13 10 or 11 or 12

14 9 and 13

15 randomized controlled trial/ or controlled clinical trial/

16 (randomized or placebo or randomly or trial or groups).mp

17 "time series".mp. or time series analysis/

18 (controlled before and after).mp.

19 crossover procedure/

20 cohort analysis/ or prospective study/ or cohort.mp.

21 longitudinal study.mp. or longitudinal study/

22 systematic review.mp. or "systematic review"/

23 (metaanalysis or meta-analysis).mp.

24 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

25 14 and 24

26 9 and 24

27 25 or 26

Science Citation Index Expanded (SCI-EXPANDED) Conference Proceedings Citation Index-Science (CPCI-S) and BIOSIS Previews (all from Web of Science)

| # | 9 | #8 AND #5 |
|---|---|-----------|
| # | 8 | #7 OR #6 |
| # | 7 | TOPIC: (antifungal*) |
(Continued)

| #   | TOPIC: (itraconazole or amphotericin) |
|-----|-------------------------------------|
| 6   |                                     |

| #   | TOPIC: (histoplasma or histoplasmosis) |
|-----|---------------------------------------|
| 4   |                                       |

| #   | TOPIC: (HIV OR HIV-1 OR HIV-2* OR HIV1 OR HIV2 OR HIV infect* OR human immunodeficiency virus OR human immunodeficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus )) OR acquired immunodeficiency syndrome OR acquired immunodeficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome))) |
|-----|---------------------------------------------------------------------------------|
| 2   |                                                                                 |

| #   | TOPIC: (HIV or AIDS or "human immunodeficiency virus" or "acquired immunodeficiency syndrome" or AIDS) |
|-----|------------------------------------------------------------------------------------------------------|
| 1   |                                                                                                     |

WHO International Clinical Trials Registry Platform (WHO ICTRP), Clinicaltrials.gov, and ISRCTN registry

histoplasm* and HIV*

Appendix 2. ROBINS-I methodology

Risk of bias: ROBINS-I

Target trial(s)

To determine bias, as defined by systematic differences between a non-randomized study and a hypothetical pragmatic randomized trial, we formulated the following target trial (Sterne 2016).

Design: individually randomized

Participants: HIV-positive children, adolescents, and adults with a clinical diagnosis of progressive disseminated histoplasmosis.

| Objective | Intervention | Comparisons |
|-----------|--------------|-------------|
| 1. Induction | Liposomal amphotericin B (3.0 mg/kg daily) for 1–2 weeks | Lipid complex amphotericin B |
|           |              | Deoxycholate amphotericin B |
|           |              | Other antifungal agents |
| 2. Maintenance | Oral antifungal treatment for < 12 months | Oral antifungal treatment for ≥ 12 months |
| 3. ART | Early initiation (within 4 weeks of commencing antifungal therapy) | Delayed initiation (> 4 weeks after starting antifungal treatment) |

The aim was to assess the effect of assignment to the intervention, that is, we assessed studies on the basis of intention to treat. Judgements were guided by the use of signalling questions at domain level using ROBINS-I methodology (Sterne 2016).

Confounding domains relevant to all or most studies that were determined a priori informed by current literature and clinical expertise.

Table A a priori confounding domains
Confounding domains relevant to all or most studies | Cointerventions that could be different between intervention groups and that could impact on outcomes
---|---
Severity of PDH | ART at time of PDH diagnosis
Severity of HIV (CD4 count) | Supportive therapy
Comorbidities and comedications | —

ART: antiretroviral therapy; PDH: progressive disseminated histoplasmosis

Severity of progressive disseminated histoplasmosis (PDH) and HIV were considered likely to influence clinicians to favour intravenous therapy including liposomal amphotericin B. Comorbidities and comedications were also determined to influence medical management. In particular, use of medications which may interact with azoles may cause a clinician to favour use of amphotericin during induction therapy.

Overall risk of bias judgements were determined using the following table from detailed guidance on the use of ROBINS-I. Sterne JAC, Higgins JPT, Elbers RG, Reeves BC and the development group for ROBINS-I. Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I): detailed guidance, updated 12 October 2016. Available from www.riskofbias.info (accessed 4 June 2019).

### Table B guidance on ROBINS-I judgements

| Response option | Criteria |
|-----------------|----------|
| **Low** risk of bias (the study is comparable to a well-performed randomized trial). | The study is at low risk of bias for all domains. |
| **Moderate** risk of bias (the study appears to provide sound evidence for a non-randomized study but cannot be considered comparable to a well-performed randomized trial). | The study is at low or moderate risk of bias for all domains. |
| **Serious** risk of bias (the study has some important problems). | The study is at serious risk of bias in ≥ 1 domain, but not at critical risk of bias in any domain. |
| **Critical** risk of bias (the study is too problematic to provide any useful evidence and should not be included in any synthesis). | The study is at critical risk of bias in ≥ 1 domain. |
| **No information** on which to base a judgement about risk of bias. | There is no clear indication that the study is at serious or critical risk of bias and there is a lack of information in ≥ 1 key domains of bias. |

Sterne 2016.

### Table C ROBINS-I. Assessments of non-randomized studies

| Study: Luckett 2015. Outcome: treatment success | Confounding domains | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected |
|-----------------------------------------------|---------------------|---------------------|---------------------------------|---------------------------------|---------------------------------|

Treatting progressive disseminated histoplasmosis in people living with HIV (Review)
Severity of PDH | Severe, moderate, and mild illness were defined | No | Yes | —
Severity of HIV | CD4 count and viral load reported | No | Yes | —
Comorbidities and medications | Not reported | No | Not measured | Comorbidities likely to influence clinicians to favour liposomal amphotericin.

Cointerventions

| ART at time of PDH diagnosis | Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? |
|-----------------------------|-------------------------------------------------|-------------------------------------------------|
| No, remains important cointervention. 27% on ART prior to study. 1/3 adherent. | Favour intervention | |

Supportive therapy

| Supportive therapy | Reported level of clinical care (e.g. ICU care) | Favour intervention |

Bias domain

| Bias domain | Signalling questions | Comments | Risk of bias judgement |
|-------------|---------------------|----------|------------------------|
| Bias due to confounding | 1.1–1.8 | Authors described severity of PDH, and reported median and range of CD4 count. Authors did not report any comorbidities or medications. Baseline characteristics of participants in azole and amphotericin groups not reported. Authors did not report use of appropriate statistical methods to control for important baseline confounding. Rationale for treatment choice in azole and amphotericin groups not reported. There was insufficient information to judge bias due to confounding. | No information |
| Bias in participant selection | 2.1–2.5 | No evidence that selection into the study based on participant characteristics observed after intervention. Authors did not report the time between start of follow-up and start of intervention. | Moderate |
| Bias in classification of intervention | 3.1–3.3 | No information about dose, frequency, and timing of interventions. Information was collected retrospectively. | Serious |
| Bias due to deviations from intended intervention | 4.1–4.6 | No evidence of deviations from interventions. No comment on whether patients not on ART were commenced on ART. No measure of adherence to antifungal therapy. | No information |
| Bias due to missing data | 5.1–5.5 | No information regarding loss to follow-up. | No information |
| Bias in measurement of outcomes | 6.1–6.4 | For mortality outcome, unlikely to display measurement bias. For treatment failure outcome, based on clinician judgement only, likely to favour switch from azole to amphotericin. | Serious |
Bias in selection of reported result 7.1–7.3 Limited analysis. No information

Overall bias SERIOUS

**Study: Mootsikapun 2006. Outcome 1: inhospital mortality**

| Confounding domains | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | Risk of bias judgement |
|---------------------|----------------------|------------------------------------------------------------------|------------------------------------------------------|------------------------|
| Severity of PDH      | Not reported         | No                                                               | No information provided                              |                       |
| Severity of HIV      | Not reported         | No                                                               | No information provided                              |                       |
| Comorbidities and comedications | None reported | No                                                               | No information provided                              |                       |

**Cointerventions**

| Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? |
|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| ART at time of PDH diagnosis                                              | No                                                                                         |
| Supportive therapy                                                       | No                                                                                         |

**Bias domain**

| Bias due to confounding | Signalling questions | Comments                                                                 | Risk of bias judgement |
|-------------------------|----------------------|---------------------------------------------------------------------------|------------------------|
|                         | 1.1–1.8              | ≥ 1 known important domain was not appropriately measured or controlled for. Details of disease severity, comedications, and comorbidities not provided for the 3 inhospital deaths. | Serious                |

| Bias in participant selection | Signalling questions | Authors reported data on 29 participants who received AmB 0.7 mg/kg/day. Data not provided on alternate treatment regimens or time to treatment; however, since all participants received the same treatment, it is probable that selection into the study was not related to the outcome. | Moderate               |
| Bias in classification of intervention | Signalling questions | Comparison was between disease populations not intervention groups. Intervention status was well defined. | Moderate               |
| Bias due to deviations from intended intervention | Signalling questions | Deviations were not reported. Important cointerventions were not reported. | No information         |
| Bias due to missing data | Signalling questions | Data reported on inhospital deaths likely to be reasonably complete. | Low                   |

T Treating progressive disseminated histoplasmosis in people living with HIV (Review) Copyright © 2020 The Authors. Cochrane Database of Systematic Reviews published by John Wiley & Sons, Ltd. on behalf of The Cochrane Collaboration.
### Bias in measurement of outcomes

| Domain                  | Bias | Description                                                                 | Risk |
|-------------------------|------|------------------------------------------------------------------------------|------|
| Bias in measurement of outcomes | 6.1–6.4 | The outcome measure was unlikely to be influenced by knowledge of the intervention. | Low  |

### Bias in selection of reported result

| Domain                  | Bias | Description                                                                 | Risk |
|-------------------------|------|------------------------------------------------------------------------------|------|
| Bias in selection of reported result | 7.1–7.3 | There is too little information to make a judgement on bias in reporting in this retrospective review of medical records. | No information |

### Overall bias

| Risk |
|------|
| SERIOUS |

### Study: Mootsikapun 2006. Outcome 2: relapse on maintenance itraconazole. Median follow-up 22 months (1–75 months)

#### Confounding domains

| Domain                  | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator? |
|-------------------------|----------------------|---------------------------------------------------------------------|--------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Severity of PDH         | Not reported         | No                                                                  | —                                                      | —                                                                                             |
| Severity of HIV         | Not reported         | No                                                                  | —                                                      | —                                                                                             |
| Comorbidities and comedications | None reported | No                                                                  | —                                                      | —                                                                                             |

#### Cointerventions

| Domain                  | Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? |
|-------------------------|---------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| ART at time of PDH diagnosis | No                                                                  | —                                                                                         |
| Supportive therapy      | No                                                                  | —                                                                                         |

#### Bias domain

| Domain                  | Signalling questions | Comments                                                                 | Risk of bias judgement |
|-------------------------|----------------------|-------------------------------------------------------------------------|------------------------|
| Bias due to confounding | 1.1–1.8              | ≥ 1 known important domain was not appropriately measured or controlled for: details of disease severity, comedications, and comorbidities not provided for 27 participants discharged from hospital. | Serious                |
| Bias in participant selection | 2.1–2.5              | Maintenance therapy was commenced in those who responded to initial treatment on AmB. Timing of start of maintenance therapy was not reported. Selection into this part of the study was related to the intervention. | Serious                |
| Bias in classification of intervention | 3.1–3.3              | Authors reported that participants who responded to treatment with AmB received oral itraconazole 400 mg/day for 3 months then 200 mg/day afterwards. Median follow-up for participants was 22 (range 1–75) months. Although response to treatment was likely to have been a clinical decision bias intervention, status appeared to be adequately defined. Range of duration of follow-up was wide. | Moderate               |
Bias due to deviations from intended intervention 4.1–4.6 Cointerventions were not reported. Deviations from practice not reported. Moderate

Bias due to missing data 5.1–5.5 Data obtained from medical records from a 7-year period. Range of follow-up was 1–75 months. Outcome data not provided on individual participants. There was insufficient information to base a judgement about risk of bias for this domain. No information

Bias in measurement of outcomes 6.1–6.4 Retrospective data collection. Unlikely to be assessor bias in participant eligibility for maintenance therapy. Low

Bias in selection of reported result 7.1–7.3 Authors reported no relapse in participants who had itraconazole as long-term therapy; however, range of duration of follow-up was wide. Moderate

Overall bias SERIOUS

Study: Myint 2014. Outcome: relapse of histoplasmosis

| Confounding domains                  | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator |
|--------------------------------------|----------------------|---------------------------------------------------------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Severity of PDH                      | Defined and reported | No                                                                  | —                                                        | —                                                                                             |
| Severity of HIV                      | Defined and reported | No                                                                  | —                                                        | —                                                                                             |
| Comorbidities and comedications      | ART adherence monitored with CD4 count and HIV RNA load            | No                                                                  | —                                                        | —                                                                                             |

Cointerventions

| Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? |
|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| ART at time of PDH diagnosis                                              | 34% in each group (12/35, 19/56)                                                                 |
| Supportive therapy                                                       | Reported                                                                                       |

Bias domain

| Signalling questions | Comments                                      | Risk of bias judgement |
|----------------------|-----------------------------------------------|------------------------|
| Bias due to confounding | 1.1–1.8                                       | Physician determined discontinuation of maintenance therapy may have been influenced by prognostic factors | Critical |
that were not controlled for. Multiple logistic regression used to determine variables associated with relapse; however, assignment to treatment arms was based on clinical assessment and viral load. ‘Adherence to therapy’ not defined. Unclear if this referred to ART, ITRA, or both. No evidence of adjustment for time-varying confounding.

| Bias in participant selection | 2.1–2.5 | — | — |
| Bias in classification of intervention | 3.1–3.3 | — | — |
| Bias due to deviations from intended intervention | 4.1–4.6 | — | — |
| Bias due to missing data | 5.1–5.5 | — | — |
| Bias in measurement of outcomes | 6.1–6.4 | — | — |
| Bias in selection of reported result | 7.1–7.3 | — | — |
| Overall bias | CRITICAL |

**Study:** Myint 2014. **Outcome:** death

| Confounding domains | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator |
|---------------------|----------------------|---------------------------------------------------------------|-----------------------------------------------------|---------------------------------------------------------------------|
| Severity of PDH     | Defined and reported | No                                                            | Yes                                                 | —                                                                   |
| Severity of HIV     | Defined and reported | No                                                            | Yes                                                 | —                                                                   |
| Comorbidities and comedications | ART adherence monitored with CD4 count and HIV RNA load | No | Yes | — |

| Cointerventions | Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? |
|------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| ART at time of PDH diagnosis | No | — |
| Supportive therapy | No | — |

| Bias domain | Signalling questions | Comments | Risk of bias judgement |
|-------------|----------------------|----------|------------------------|------------------------|
|             |                      |          |                        |                        |
### Bias due to confounding

| Study: Negroni 2017. Outcome: response to maintenance therapy |
|---------------------------------------------------------------|
| **Confounding domains** | **Measured variable(s)** | **Is there evidence that controlling for this variable was unnecessary?** | **Is the confounding domain measured validly and reliably?** | **OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator?** |
|------------------------|--------------------------|---------------------------------|-------------------------------------------------|-----------------------------------------------------------------|
| Severity of PDH        | Not defined              | No                              | —                                               | —                                                               |
| Severity of HIV        | CD4 count                | No                              | —                                               | —                                                               |
| Comorbidities and comedications | 17.5% on ART at baseline | 41% of participants discharged from hospital continued with follow-up of ART and maintenance therapy. Authors reported use of AmB in participants who were more ill and in those on medication likely to interact with itraconazole such as rifampicin suggesting there could have been comorbid TB. | No | — |
| **Cointerventions**    | **Is there evidence that controlling for this cointervention was unnecessary?** | **Is presence of this cointervention likely to favour outcomes in the intervention or comparator?** |
| ART at time of PDH diagnosis | No                      | —                               |
| Supportive therapy     | No                       | —                               |
### Bias domain

| Bias due to confounding | 1.1–1.8 | Comorbidity and comedications were not reported or controlled for. Outcome data were not linked to disease severity. Outcomes not reported by drug regimen. Treatment regimens varied by drug and duration. There were drug switches. | Critical |
|-------------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| Bias in participant selection | 2.1–2.5 | —                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | —       |
| Bias in classification of intervention | 3.1–3.3 | —                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | —       |
| Bias due to deviations from intended intervention | 4.1–4.6 | —                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | —       |
| Bias due to missing data | 5.1–5.5 | —                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | —       |
| Bias in measurement of outcomes | 6.1–6.4 | —                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | —       |
| Bias in selection of reported result | 7.1–7.3 | —                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | —       |

#### Overall bias

**CRITICAL**

### Study: Norris 1994. Outcome: relapse of histoplasmosis

#### Confounding domains

| Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator |
|----------------------|-----------------------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Severity of PDH      | —                                                                    | —                                                      | —                                                                                         |
| Severity of HIV      | —                                                                    | —                                                      | —                                                                                         |
| Comorbidities and comedications | —                                                              | —                                                      | —                                                                                         |

**Treating progressive disseminated histoplasmosis in people living with HIV (Review)**

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Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator?
---|---
ART at time of PDH diagnosis | No | —
Supportive therapy | No | —

| Bias domain | Signalling questions | Comments | Risk of bias judgement |
|---|---|---|---|
| Bias due to confounding | 1.1–1.8 | Authors reported no specific criteria to select participants for intervention. Criteria included unavailability of ITRA and preference for oral therapy. Intervention group determined by treating physicians who also evaluated clinical evidence of relapse and adverse effects. Severity of HIV, comorbidities, and comedication were not reported. | Critical |
| Bias in participant selection | 2.1–2.5 | — | — |
| Bias in classification of intervention | 3.1–3.3 | — | — |
| Bias due to deviations from intended intervention | 4.1–4.6 | — | — |
| Bias due to missing data | 5.1–5.5 | — | — |
| Bias in measurement of outcomes | 6.1–6.4 | — | — |
| Bias in selection of reported result | 7.1–7.3 | — | — |

Overall bias: CRITICAL

Study: Pietrobon 2004. Outcome: mortality

| Confounding domains | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator |
|---|---|---|---|---|
| Severity of PDH | Not defined or reported. | No | No | — |
### Severity of HIV

Authors reported 11/16 participants with histoplasmosis had CD4 count < 50 cells/μL.

- **No**
- **Yes**

### Comorbidities and comedications

Authors reported none of participants were receiving ART. Study population was 16. Comorbidities mentioned but not systemically.

- **No**
- **No**

### Cointerventions

| Cointervention                          | Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? |
|----------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| ART at time of PDH diagnosis           | No                                                                       | —                                                                                           |
| Supportive therapy                     | No                                                                       | —                                                                                           |

### Bias domain

| Bias domain                                   | Signalling questions | Comments                                                                 | Risk of bias judgement |
|-----------------------------------------------|----------------------|--------------------------------------------------------------------------|------------------------|
| Bias due to confounding                       | 1.1–1.8              | No use of ART during treatment period. Comorbidities mentioned but unclear whether all relevant comorbidities studied. Severity of PDH not reported. No report of statistical methods to control for confounders. ≥ 1 known important domain was not appropriately measured or controlled for. | **Serious**            |
| Bias in participant selection                | 2.1–2.5              | Drug treatment for the initial phase provided for all participants – all received AmB. Time to commencement of treatment not reported. Data reported were retrospective analyses of medical records of patients with HIV and opportunistic infections. | **No information**     |
| Bias in classification of intervention       | 3.1–3.3              | Intervention for management of acute phase was well defined.             | **Low**                |
| Bias due to deviations from intended intervention | 4.1–4.6             | Deviations not reported.                                                 | **No information**     |
| Bias due to missing data                     | 5.1–5.5              | Data were reasonably complete.                                           | **Low**                |
| Bias in measurement of outcomes              | 6.1–6.4              | Measurement of mortality outcome unlikely to be influenced by knowledge of intervention received. | **Low**                |
| Bias in selection of reported result         | 7.1–7.3              | Descriptive retrospective study. No protocol; however, there was no indication of selection of the cohort for analysis and reporting on the basis of the result. | **Moderate**           |

### Overall bias

**Serious**
### Study: Pietrobon 2004. Outcome: relapse of histoplasmosis

| Confounding domains | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator? |
|---------------------|----------------------|---------------------------------------------------------------------|----------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Severity of PDH     | Not defined or reported. | No                                                                  | No                                                      | —                                                                                              |
| Severity of HIV     | Authors reported 8/12 participants with histoplasmosis had CD4 count < 50 cells/μL | No                                                                  | Yes                                                     | —                                                                                              |
| Comorbidities and comedications | Authors reported none of participants were receiving ART. Study population was 16. This included participants with various opportunistic infections. Coinfection with Cryptococcus neoformans reported in 1 participant; however, authors did not specify if this participant also had histoplasmosis. | No                                                                  | No                                                      | —                                                                                              |

### Cointerventions

| Cointerventions | Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? |
|-----------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| ART at time of PDH diagnosis | No                                                                        | —                                                                                           |
| Supportive therapy | No                                                                        | —                                                                                           |

### Bias domain

| Bias domain                     | Signalling questions | Comments                                                                                                                                                                                                 | Risk of bias judgement |
|---------------------------------|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Bias due to confounding         | 1.1–1.8              | Follow-up periods not reported. Duration of ITRA or FCN not reported. Switches between regimens not reported. Concurrent medication not reported. No statistical methods to control for confounding reported. | Critical               |
| Bias in participant selection   | 2.1–2.5              | Participants treated with maintenance therapy would have responded to initial treatment. Time to commencement of maintenance therapy not reported. Insufficient information to judge if start of follow-up and start of intervention coincided for most participants. | No information         |
### Bias in classification of intervention

| 3.1–3.3 | Commencement of maintenance therapy was dependent on response to initial therapy with AmB. Intervention status was not well defined. | **Serious** |

### Bias due to deviations from intended intervention

| 4.1–4.6 | No reported deviations from intended intervention. | **No information** |

### Bias due to missing data

| 5.1–5.5 | Outcome data available for all participants. | **Low** |

### Bias in measurement of outcomes

| 6.1–6.4 | Relapse was not clearly defined. Time periods were not reported. The outcome measure was subjective and assessed by assessors aware of the intervention. | **Serious** |

### Bias in selection of reported result

| 7.1–7.3 | Descriptive retrospective study. No protocol; however, there was no indication of selection of the cohort for analysis and reporting on the basis of the result. | **Moderate** |

### Overall bias

| **Critical** |

---

**Study:** Baddley 2008. **Outcome:** all-cause mortality at 3 months postdiagnosis

| Confounding domains | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator? |
|--------------------|----------------------|-------------------------------------------------|-------------------------------------------------|-----------------------------------------------------------------|
| Severity of PDH    | Clinical parameters were defined and laboratory confirmation criteria were specified. | No | — | — |
| Severity of HIV    | CD4 count and HIV viral load | No | — | — |
| Comorbidities and comedications | Among those with previously diagnosed HIV 21.7% reported ART use. | No | — | — |

| Cointerventions | Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? |
|----------------|-------------------------------------------------|----------------------------------------------------------------------------------|
| ART at time of PDH diagnosis | No | — |
| Supportive therapy | No | — |
### Bias domain

| Bias domain                                      | Signalling questions | Comments                                                                                                                                                                                                 | Risk of bias judgement |
|-------------------------------------------------|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Bias due to confounding                         | 1.1–1.8              | Logistic regression used to determine association of variables with mortality including potential confounders, age, and race. Antifungal treatment data were not included in regression or reported in detail per participant. Authors reported 32/41 participants received ITRA, 22/41 received dAmB, 7/41 received lAmB formulation. Switches between medications were not reported. Authors reported 29 participants received ITRA after AmB. Denominator not reported. 8/13 participants who died received an AmB preparation and 5/13 received ITRA. Time of transition from AmB to azole not reported.   | Critical               |
| Bias in participant selection                   | 2.1–2.5              | —                                                                                                                                                                                                       | —                      |
| Bias in classification of intervention          | 3.1–3.3              | —                                                                                                                                                                                                       | —                      |
| Bias due to deviations from intended intervention | 4.1–4.6              | —                                                                                                                                                                                                       | —                      |
| Bias due to missing data                        | 5.1–5.5              | —                                                                                                                                                                                                       | —                      |
| Bias in measurement of outcomes                 | 6.1–6.4              | —                                                                                                                                                                                                       | —                      |
| Bias in selection of reported result            | 7.1–7.3              | —                                                                                                                                                                                                       | —                      |
| Overall bias                                    |                      |                                                                                                                                             | Critical               |

### Study: Couppié 2004. Outcome: death within 1 month of starting antifungal treatment

| Confounding domains | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator |
|---------------------|----------------------|-----------------------------------------------------------------------|---------------------------------------------------------|------------------------------------------------------------------------------------------|
| Severity of PDH     | Severe was defined as either shock that required treatment with vasopressors or respiratory failure that required mechanical ventilation. | No                                                                 | ’Non-severe’ included a wide range of severity.                                           | —                                                                                       |
Other cases were defined as ‘non severe’.

| Severity of HIV | CD4 count | Yes | — |
|----------------|-----------|-----|---|
| Comorbidities and comedications | 17.1% of participants were taking antiretroviral medication. | No | Not enough information. | — |

| Cointerventions | Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? | — |
|-----------------|-------------------------------------------------|-------------------------------------------------|---|
| ART at time of PDH diagnosis | No | — |
| Supportive therapy | No | — |

| Bias domain | Signalling questions | Comments | Risk of bias judgement |
|-------------|----------------------|----------|------------------------|
| Bias due to confounding | 1.1–1.8 | Choice of first-line antifungal treatment was made by the treating physician based on severity of histoplasmosis and renal function. Authors reported higher rate of mortality in participants treated with AmB than those treated with ITRA in univariate analysis. However, as participants who were more clinically ill were more likely to have been commenced on AmB by the treating physician, authors recognized that this was a confounding factor. Appropriate methods to control for this were not reported. | Severe |
| Bias in participant selection | 2.1–2.5 | Selection of intervention was made by the treating physician. As more severely ill participants were more likely to get AmB than ITRA, selection was strongly related to the outcome. | Critical |
| Bias in classification of intervention | 3.1–3.3 | Classification of intervention status could have been affected by risk of the outcome. | Moderate |
| Bias due to deviations from intended intervention | 4.1–4.6 | Details of treatment regimens were not provided. | No information |
| Bias due to missing data | 5.1–5.5 | Participants lost at follow-up in the first 30 days were excluded. No information on proportion missing with respect to the outcome. | No information |
| Bias in measurement of outcomes | 6.1–6.4 | The outcome measure was unlikely to have been influenced by knowledge of the intervention. | Low |
| Bias in selection of reported result | 7.1–7.3 | Prospective study that determined a priori to report death as dichotomous variable: death within 30 days of starting antifungal treatment and no death during the first 30 days of treatment. Data presented for both outcomes. | Low |

| Overall bias | Critical |

Treating progressive disseminated histoplasmosis in people living with HIV (Review)
### Confounding domains

| Measured variable(s)                                                                 | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator? |
|-----------------------------------------------------------------------------------|------------------------------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Evidence of histoplasmosis infection AND remission with antigen concentrations < 4.1 units and negative blood culture. | No                                                                      | Yes                                                      | —                                                                                               |
| CD4 – required to have > 150 cells/μL for study entry.                           | No                                                                      | Yes                                                      | —                                                                                               |
| Required to have received both antifungal and ART treatment for ≥ 12 months prior to starting trial. | No                                                                      | Yes                                                      | —                                                                                               |

### Bias domain

| Bias due to confounding | 1.1–1.8 | Protocol stipulated eligibility criteria for all the confounding domains cited above. | Low |
| Bias in participant selection | 2.1–2.5 | Start of intervention varied – participants enrolled after a range of 14–81 months of antifungal therapy. Unclear how many eligible patients not enrolled. | Serious |
| Bias in classification of intervention | 3.1–3.3 | Intervention was well-defined – discontinuation of antifungal treatment | Low |
| Bias due to deviations from intended intervention | 4.1–4.6 | Regular monitoring of participants ensured that intervention was delivered as intended. | Low |
| Bias due to missing data | 5.1–5.5 | Details on missing data were reported. | Low |
| Bias in measurement of outcomes | 6.1–6.4 | Relapse of histoplasmosis was clearly defined in the protocol. | Low |
(Continued)

| Bias in selection of reported result | Outcome of interest was determined in the protocol and reported. | Low |
|--------------------------------------|------------------------------------------------------------------|-----|

| Overall bias | Serious |
|--------------|---------|

**Study: Ramdial 2002. Outcome: death at 32 months**

| Confounding domains | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator? |
|---------------------|----------------------|---------------------------------------------------------------------|----------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Severity of PDH     | Organ involvement    | No                                                                  | Not according to standard classification                | —                                                                                           |
| Severity of HIV     | CD4 count            | No                                                                  | Yes                                                     | —                                                                                           |
| Comorbidities and medications | Not reported | No                                                                  | —                                                      | —                                                                                           |

| Cointerventions | Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? |
|-----------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| ART at time of PDH diagnosis | No. ART use was not reported.                                                | —                                                                                           |
| Supportive therapy | No. Not reported.                                                           | —                                                                                           |

| Bias domain | Signalling questions | Comments | Risk of bias judgement |
|-------------|----------------------|----------|------------------------|
| Bias due to confounding | 1.1–1.8 | Confounders not addressed with respect to treatment regimens. Descriptive account provided of management of participants without detail on severity of conditions, comedications, or comorbidities. No information provided on time to treatment or duration of treatment. | Critical |
| Bias in participant selection | 2.1–2.5 | Some of these cases are likely to have been Emergomyces. | — |
| Bias in classification of intervention | 3.1–3.3 | — | — |
| Bias due to deviations from intended intervention | 4.1–4.6 | — | — |
| Bias due to missing data | 5.1–5.5 | — | — |
Bias in measurement of outcomes | 6.1–6.4 | — | —
--- | --- | --- | ---
Bias in selection of reported result | 7.1–7.3 | — | —
**Overall bias** | **Critical**

**Study: McKinsey 1989. Outcome: 2-year survival**

| Confounding domains | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator? |
|---------------------|----------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Severity of PDH | Not defined or reported | No | No | — |
| Severity of HIV | Not defined or reported | No | No | — |
| Comorbidities and comediations | Not reported | No | No | — |

| Cointerventions | Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? |
|-----------------|-------------------------------------------------|-------------------------------------------------|
| ART at time of PDH diagnosis | No. No report of ART use. | — |
| Supportive therapy | No. Not described. | — |

| Bias domain | Signalling questions | Comments | Risk of bias judgement |
|-------------|----------------------|----------|------------------------|
| Bias due to confounding | 1.1–1.8 | Confounding domains were not controlled for. Rationale for selection of treatment regimen not described. No report of ART use, CD4 counts, or clinical condition of participants. | Critical |
| Bias in participant selection | 2.1–2.5 | — | — |
| Bias in classification of intervention | 3.1–3.3 | — | — |
| Bias due to deviations from intended intervention | 4.1–4.6 | — | — |
| Bias due to missing data | 5.1–5.5 | — | — |
| Bias in measurement of outcomes | 6.1–6.4 | — | — |
### Bias in selection of reported result

| Risk of bias judgement | 7.1–7.3 | — | — |

### Overall bias

| Critical |

### Study: McKinsey 1989. Outcome: relapse of histoplasmosis

#### Confounding domains

| Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator |
|----------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Severity of PDH       | Not defined or reported                          | No                                              | No                                              | — |
| Severity of HIV       | Not defined or reported                          | No                                              | No                                              | — |
| Comorbidities and comedinations | Not reported | No                                              | No                                              | — |

#### Cointerventions

| Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? |
|--------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| ART at time of PDH diagnosis                                             | No. No report of ART use.                                                          | — |
| Supportive therapy                                                      | No. Not reported.                                                                 | — |

#### Bias domain

| Signalling questions | Comments | Risk of bias judgement |
|----------------------|----------|------------------------|
| Bias due to confounding | 1.1–1.8 | Confounding domains were not controlled for. Rationale for selection of treatment regimen not described. No report of ART use, CD4 counts or clinical condition of participants | Critical |

| Bias in participant selection                  | 2.1–2.5 | — | — |
| Bias in classification of intervention         | 3.1–3.3 | — | — |
| Bias due to deviations from intended intervention | 4.1–4.6 | — | — |
| Bias due to missing data                       | 5.1–5.5 | — | — |
| Bias in measurement of outcomes                | 6.1–6.4 | — | — |

### Overall bias

| Critical |
### Study: ACTG084, 1992

**Outcome:** response to therapy (prevention of relapse)

| Confounding domains | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favor intervention or comparator |
|---------------------|----------------------|---------------------------------------------------------------------|---------------------------------------------------------|-------------------------------------------------------------------------------------|
| Severity of PDH     | Participants required to have been treated successfully for confirmed disseminated histoplasmosis within 6 weeks of enrolment. | No                                                                  | Unsure                                                                   | —                                                                                     |
| Severity of HIV     | CD4                  | No                                                                  | Yes                                                                     | —                                                                                     |
| Comorbidities and comedications | Protocol stipulated parameters on comorbidities and comedications. | No                                                                  | Probably                                                               | —                                                                                     |

#### Cointerventions

| Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? |
|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| ART at time of PDH diagnosis                                              | No. Zidovudine use reported.                                                                | —                                                                          |
| Supportive therapy                                                       | —                                                                                           | —                                                                          |

| Bias domain | Signalling questions | Comments | Risk of bias judgement |
|-------------|----------------------|----------|------------------------|
| Bias due to confounding-ing | 1.1–1.8 | Severity of HIV infection and ART use were not controlled for with appropriate statistical methods. | Serious |
| Bias in participant selection | 2.1–2.5 | Selection into the study may have been related to the intervention and outcome. Start of follow-up and start of intervention coincided for all participants. | Moderate |
| Bias in classification of intervention | 3.1–3.3 | Intervention status was clearly defined. | Low |
| Bias due to deviations from intended intervention | 4.1–4.6 | No reported deviations from usual practice. Management of HIV not reported. | No information |
| Bias due to missing data | 5.1–5.5 | Outcome data available for all participants. | Low |
## Bias in measurement of outcomes

| Bias in measurement of outcomes | 6.1–6.4 | Relapse was determined by clinical assessment, Histoplasma c. antigen levels in urine and serum and blood cultures at predetermined intervals. |
|---------------------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------|

## Bias in selection of reported result

| Bias in selection of reported result | 7.1–7.3 | Reported results are consistent with preregistered protocol. |
|------------------------------------|---------|----------------------------------------------------------------|

## Overall bias

| Overall bias | Serious |
|--------------|---------|

---

### Study: ACTG174, 1994. Outcome: response to therapy

| Confounding domains | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator? |
|---------------------|----------------------|-------------------------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------------------------------|
| Severity of PDH      | Defined with clinical and laboratory parameters including Histoplasma capsulatum antigen in blood or urine. | No                                                               | Yes                                                                      | —                                                                                 |
| Severity of HIV      | CD4                  | No                                                               | Yes                                                                      | —                                                                                 |
| Comorbidities and comedication | Comorbidities and medications not clearly reported. Exclusions included various medications, allergies, adrenal insufficiency, and pregnancy. | No                                                               | —                                                                      | —                                                                                 |

### Cointerventions

| Cointerventions | Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? |
|-----------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| ART at time of PDH diagnosis | No. Number of participants on ART at baseline was reported (33%). | —                                                                                             |
| Supportive therapy | No.                                                                             | —                                                                                             |

### Bias domain

| Bias domain | Signalling questions | Comments | Risk of bias judgement |
|-------------|----------------------|----------|------------------------|
| Bias due to confounding | 1.1–1.8             | At 3 months, protocol was revised and treatment regimen amended. Analyses were performed on participants who received the revised | Serious |
protocol (higher doses of FCN). Severity and management of HIV was not reported or controlled with appropriate statistical methods.

### Bias in participant selection

| Level | Description |
|-------|-------------|
| 2.1–2.5 | Selection into the maintenance arm of the study was related to the effect of the intervention in the induction phase. |

### Bias in classification of intervention

| Level | Description |
|-------|-------------|
| 3.1–3.3 | Intervention was well defined based on information collected at the time of intervention. |

### Bias due to deviations from intended intervention

| Level | Description |
|-------|-------------|
| 4.1–4.6 | The possibility of a requirement to modify the original protocol was raised a priori. Some deviations from intervention were reported such as 3 participants who relapsed when receiving FCN 400 mg being given 800 mg prior to successful treatment with AmB; however, there was insufficient information reported on deviation from the intended intervention to make a judgement in this domain. |

### Bias due to missing data

| Level | Description |
|-------|-------------|
| 5.1–5.5 | Some missing data in outcome measurement. |

### Bias in measurement of outcomes

| Level | Description |
|-------|-------------|
| 6.1–6.4 | Definition and proposed measurement of relapse were clearly defined a priori. Some cultures were missing or not done in the induction phase; however, 6/7 non-responders to induction had cultures taken. |

### Bias in selection of reported result

| Level | Description |
|-------|-------------|
| 7.1–7.3 | Results correspond to intended outcomes. Analysis restriction to those treated per the revised protocol was not predetermined. |

### Overall bias

| Level | Description |
|-------|-------------|
| Serious | |

**Study:** ACTG120, 1992. **Outcome:** relapse of histoplasmosis – maintenance phase

| Confounding domain | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator |
|--------------------|----------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Severity of PDH     | Defined – severe disease excluded. | No | Yes | — |
| Severity of HIV     | CD4                  | No | No. Not reported after baseline of induction phase. | — |
| Comorbidities and comedications | Participants receiving concurrent treatment with drugs that interact with ITRA including ri- | No | No | — |
Cointerventions

Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator?

ART at time of PDH diagnosis

No. ART use not reported. Median CD4 at baseline of induction phase was 29 (range 2–346) cells/μL. CD4 count at baseline of maintenance phase was not reported.

Supportive therapy

No —

| Bias domain                      | Signalling questions | Comments                                                                 | Risk of bias judgement |
|----------------------------------|----------------------|--------------------------------------------------------------------------|------------------------|
| Bias due to confounding          | 1.1–1.8              | Severity of HIV; severity of PDH and comorbidities were not controlled for using appropriate statistical methodology. ART use at baseline of an earlier phase of the trial reported. | Serious                |
| Bias in participant selection    | 2.1–2.5              | Those who responded to the intervention (ITRA) in the induction phase were selected for the intervention in the maintenance phase. | Serious                |
| Bias in classification of intervention | 3.1–3.3            | Participants started intervention at various doses and had reductions in dose made at variable intervals. While this is likely to have been informed by ITRA blood levels that were being monitored detailed data is not provided per participant. | Serious                |
| Bias due to deviations from intended intervention | 4.1–4.6            | Data reported indicates that deviations from the intended intervention were not beyond that expected in usual practice. | Low                   |
| Bias due to missing data         | 5.1–5.5              | 12/46 participants withdrew from the study. Reasons reported for all. | Low                   |
| Bias in measurement of outcomes  | 6.1–6.4              | Definition and proposed measurement of relapse were clearly defined a priori. | Low                   |
| Bias in selection of reported result | 7.1–7.3            | Reported results correspond to intended outcomes. | Low                   |

Overall bias

Serious

Study: ACTG120, 1992. Outcome: relapse of histoplasmosis – induction phase

Confounding domains

Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator

(Continued)
(Continued)

| Bias domain                          | Signalling questions | Comments                                                                 | Risk of bias judgement |
|--------------------------------------|----------------------|--------------------------------------------------------------------------|------------------------|
| Bias due to confounding              | 1.1–1.8              | Severity of HIV; severity of PDH and comorbidities were not controlled for using appropriate statistical methodology. | Serious                |
| Bias in participant selection       | 2.1–2.5              | Selection into the study may have been related to the intervention and outcome as those with less severe histoplasmosis were more likely to be selected; however, start of follow-up and intervention appear to coincide. | Moderate               |
| Bias in classification of intervention | 3.1–3.3              | Data provided per participant for ITRA levels in non-responders. Detailed data on ITRA levels not reported for remaining participants. ITRA levels determined dose of intervention. | Serious                |
| Bias due to deviations from intended intervention | 4.1–4.6              | Deviations from intended intervention were consistent with usual practice. Data reported for toxicity and clinical reasons for discontinuation of intervention. | Low                   |
| Bias due to missing data             | 5.1–5.5              | Data were reasonably complete.                                           | Low                   |
| Bias in measurement of outcomes     | 6.1–6.4              | Outcome measures were confirmed by laboratory assessments such as blood culture. | Low                   |
| Bias in selection of reported result | 7.1–7.3              | Reported results correspond to intended outcomes.                        | Low                   |

Overall bias: Serious
### Study: ACTG120, 1992

**Outcome:** mortality – maintenance phase

| Confounding domains | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator |
|---------------------|----------------------|---------------------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------|
| Severity of PDH     | Defined – severe disease excluded. | No                                                                  | Yes                                                   | —                                               |
| Severity of HIV     | CD4                  | No                                                                  | No. Not reported after baseline of induction phase.    | —                                               |
| Comorbidities and comedication | Participants receiving concurrent treatment with drugs that interact with ITRA including rifampin were excluded. | No                                                                  | No                                                   | —                                               |
| **Cointerventions** | **Is there evidence that controlling for this cointervention was unnecessary?** | **Is presence of this cointervention likely to favour outcomes in the intervention or comparator?** |
| ART at time of PDH diagnosis | No. ART use not reported. Median CD4 at baseline of induction phase was 29 (range 2–346) cells/dL. CD4 count at baseline of maintenance phase was not reported. | —                                                   |
| Supportive therapy  | No                   | —                                                                  | —                                                     | —                                               |

### Bias domain

| Signalling questions | Comments | Risk of bias judgement |
|----------------------|----------|------------------------|
| Bias due to confounding | 1.1–1.8 | Severity of HIV; severity of PDH and comorbidities were not controlled for using appropriate statistical methodology. ART use at baseline of an earlier phase of the trial reported. | Serious |
| Bias in participant selection | 2.1–2.5 | Participants who responded to the intervention (ITRA) in the induction phase were selected for the intervention in the maintenance phase. | Serious |
| Bias in classification of intervention | 3.1–3.3 | Participants started intervention at various doses and had reductions in dose made at variable intervals. While this is likely to have been informed by ITRA blood levels that were being monitored, detailed data were not provided per participant. | Serious |
| Bias due to deviations from intended intervention | 4.1–4.6 | Deviations from intended intervention were consistent with usual practice. Data reported for toxicity and clinical reasons for discontinuation of intervention. | Low |
| Bias due to missing data | 5.1–5.5 | 12/46 participants withdrew from the study. Reasons reported for all. | Low |
(Continued)

| Bias in measurement of outcomes | 6.1–6.4 | The outcome measure was unlikely to be influenced by knowledge of the intervention received. | Low |
|--------------------------------|---------|-----------------------------------------------------------------------------------|-----|
| Bias in selection of reported result | 7.1–7.3 | Reported results correspond to intended outcomes. | Low |

**Overall bias**

| Study: ACTG120, 1992. Outcome: mortality – induction |
|-----------------------------------------------|

| Confounding domains | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator |
|---------------------|----------------------|----------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Severity of PDH     | Defined – severe disease excluded | No                                                              | Yes                                              |                                                  |
| Severity of HIV     | CD4                  | No                                                              | No. Only baseline data reported.                |                                                  |
| Comorbidities and comedication | Participants receiving concurrent treatment with drugs that interact with ITRA including rifampin were excluded. | No                                                              | No. Limited data reported.                        |                                                  |

**Cointerventions**

| Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? |
|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| ART at time of PDH diagnosis                                             | No                                                                                             |
| Supportive therapy                                                       | No                                                                                             |

**Bias domain**

| Bias due to confounding | Signalling questions | Comments | Risk of bias judgement |
|-------------------------|----------------------|----------|------------------------|
| 1.1–1.8                 | 1.1–1.8              | Severity of HIV; severity of PDH and comorbidities were not controlled for using appropriate statistical methodology. | Serious |

| Bias in participant selection | 2.1–2.5 | Selection into the study may have been related to the intervention and outcome as those with less severe histoplasmosis were more likely to be selected; however, start of follow-up and intervention appear to coincide. | Moderate |

| Bias in classification of intervention | 3.1–3.3 | 1 of the 2 deaths was reported to have died after 1 week of AmB. | Serious |
Bias due to deviations from intended intervention  4.1–4.6
Data reported indicates that deviations from the intended intervention were not beyond that expected in usual practice.  Low

Bias due to missing data  5.1–5.5
Detailed data provided for non-responders. 1/9 lost to follow-up.  Low

Bias in measurement of outcomes  6.1–6.4
The outcome measure was unlikely to be influenced by knowledge of the intervention received.  Low

Bias in selection of reported result  7.1–7.3
Reported results correspond to intended outcomes.  Low

Overall bias  
Serious

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**Study:** Melzani 2020. **Outcome:** incidence paradoxical and unmasking IRIS

| Confounding domains | Measured variable(s) | Is there evidence that controlling for this variable was unnecessary? | Is the confounding domain measured validly and reliably? | OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator? |
|---------------------|----------------------|---------------------------------------------------------------|---------------------------------------------------|---------------------------------------------------------------------|
| Severity of PDH     | Severity of IRIS defined. IAmB considered as proxy for histoplasmosis-related IRIS severity. Severity of PDH not reported. | —                                                      | —                                                    | —                                                                   |
| Severity of HIV     | CD4 and HIV viral load | No                                                             | Yes                                                 | —                                                                   |
| Comorbidities and comedications | TB excluded. No information reported on comorbidities. ART, antifungal, and steroid use described. 2/22 participants received steroids. | No                                                                  | Yes. Taken from medical records.                                  | —                                                                   |

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Cointerventions

| Is there evidence that controlling for this cointervention was unnecessary? | Is presence of this cointervention likely to favour outcomes in the intervention or comparator? |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| ART at time of PDH diagnosis                                              | No                                                                                           | —                                                                 |
| Supportive therapy                                                       | No. Clinical management was reported.                                                         | —                                                                 |
(Continued)

| Bias domain                        | Signalling questions | Comments                                                                                                                                                                                                                                                                                                                                 | Risk of bias judgement |
|-----------------------------------|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| Bias due to confounding           | 1.1–1.8              | ART was discontinued in 2/22 participants at the physician’s decision; 2/22 due to patient choice. In unmasking group, 10/14 participants received IAmB and 4/14 received ITRA. Paradoxical group physicians continued ART and ITRA for 6/8. Rationale for treatment choices not reported. Appropriate statistical measures to control for confounding were not reported. ≥ 1 known important domain was not appropriately measured or controlled for. | Serious                |
| Bias in participant selection     | 2.1–2.5              | Information on timelines not provided.                                                                                                                                                                                                                                                                                                    | No information         |
| Bias in classification of interven-| 3.1–3.3              | Detailed information on type, dose, and timing of interventions not reported.                                                                                                                                                                                                                                                              | No information         |
| tion                              |                      |                                                                                                                                                                                                                                                                                                                                            |                        |
| Bias due to deviations from intend-| 4.1–4.6              | Deviations are likely to be consistent with usual practice.                                                                                                                                                                                                                                                                               | Low                    |
| ed intervention                   |                      |                                                                                                                                                                                                                                                                                                                                            |                        |
| Bias due to missing data          | 5.1–5.5              | Authors reported that data were missing and files were difficult to review due to poor storage conditions. Insufficient information to make an informed judgement in this domain.                                                                                                                                                                    | No Information         |
| Bias in measurement of outcomes   | 6.1–6.4              | Outcome measure was unlikely to be influenced by knowledge of the intervention.                                                                                                                                                                                                                                                             | Low                    |
| Bias in selection of reported re-| 7.1–7.3              | Reported results correspond to all intended outcomes.                                                                                                                                                                                                                                                                                      | Low                    |
| sult                              |                      |                                                                                                                                                                                                                                                                                                                                            |                        |

Overall bias: Serious

AmB: amphotericin B; ART: antiretroviral therapy; dAmB: deoxycholate amphotericin B; FCN: fluconazole; ICU: intensive care unit; IRIS: immune reconstitution inflammatory syndrome; ITRA: itraconazole; IAmB: liposomal amphotericin B; PDH: progressive disseminated histoplasmosis; RNA: ribonucleic acid; TB: tuberculosis.

Notes

Appropriate methods to control for measured confounders: stratification; regression; matching; standardization; g-estimation; and inverse probability weighting.

Time-varying confounding – when intervention received can change over time. The effect of interest is 'starting and adhering' (per-protocol) NOT 'assignment to intervention' (intention to treat).

Appendix 3. Excluded studies: not eligible due to study design, but may inform PICO

Review papers (0)
We excluded reviews from our protocol, but present them in this report for completeness.

| Review             | Commentary on methods | Commentary on outcome |
|--------------------|------------------------|-----------------------|
| Botero Aguirre 2015| Cochrane review, robust methods. | IAmB less nephrotoxic. |
Cano-Torres 2019 No protocol, registration with PROSPERO or quality assessment. Aimed to provide estimate of frequency and mortality of histoplasmosis in people living with HIV on HAART in Latin America but heterogeneity precluded aggregated estimates.

Hamill 2013 Single author, narrative drug review. No protocol, registration with PROSPERO, or quality assessment. Limited search strategy. IAmB safer than conventional AmB with at least equivalent efficacy.

Hughes 2010 Details of methodology not provided. No protocol, registration with PROSPERO, or quality assessment reported. Limited search strategy. Azoles (except FCN) posed greatest risk of interactions with ART. There was limited evidence that risk was lower with echinocandins. Tenofovir should be used with caution with AmB with close monitoring of renal function advised.

Karimzadeh 2013 5 databases searched. Details of screening not provided. Language restriction. No protocol, registration with PROSPERO, or quality assessment reported. Coadministration of mannitol did not show any clinically significant benefit in preventing AmB-induced nephrotoxicity. Lipid formulations are clinically effective and safe at preventing AmB-induced nephrotoxicity.

Keating 2005 Single author drug profile. Posaconazole was associated with 100% success rate in histoplasmosis.

Moen 2009 Methodology not reported in detail. Databases searched from 1980 to 2009. No protocol, registration with PROSPERO, or quality assessment reported. For the treatment of confirmed invasive fungal infections, liposomal AmB was more effective than AmB and remained first-line option for empirical therapy in people with disseminated histoplasmosis.

Pan 2013 3 databases (English and Chinese) searched. Papers independently reviewed by 2 authors. No protocol or quality assessment reported. 300 cases of histoplasmosis were reported in China from 1990 to 2011, of which 257 had PDH. Cases had a prominent geographical distribution, mainly in vicinity of Yangtze river.

Siberry 2013 Guideline for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children. Specialists reviewed the literature for new information since publication of the last guidelines (2009). AmB is preferred for initial treatment of moderately severe-to-severe infections.

Slain 2001 Therapeutic review. Included data from in vitro and preclinical studies as well as Phase 2 and 3 clinical trials. 1 database searched. Intravenous ITRA is less toxic alternative to AmB for people with pulmonary and extrapulmonary histoplasmosis.

**Case series or unclear study design (6–7)**

We present a simple list of excluded case reports and case series which may inform PICO, but are not included in the main review due to their design.

| Study   | Commentary |
|---------|------------|
|         | AmB: amphotericin B; ART: antiretroviral therapy; FCN: fluconazole; HAART: highly active antiretroviral therapy; ITRA: itraconazole; IAmb: liposomal amphotericin B; PDH: progressive disseminated histoplasmosis. |
| Reference   | Description                                                                 |
|-------------|-----------------------------------------------------------------------------|
| Armstrong 1988 | Overview of the treatment of opportunistic infections in people with AIDS. Highlights lack of evidence for maintenance regimens. |
| Assi 2006    | Case series of gastrointestinal histoplasmosis. None of the patients identified had received HAART. |
| Barlows 1996 | Case study of hypothermia following IV AmB.                                   |
| Benson 2005  | Guidelines for treatment of OI in HIV-infected adults and children; CDC, NIH, and HIVMA. |
| Bernard 1989 | Case series of treatment with FCN. 1 person with histoplasmosis. Urine still positive at day 75. 20 participants. 10 people living with HIV. Did not report HIV status of the person with histoplasmosis. |
| Bonifaz 2009 | Case series of PDH. Authors did not report any use of ART.                   |
| BSAC 1992    | Treatment recommendations from British Society for Antimicrobial Chemotherapy. |
| Caplivski 2005 | Case series. 4 participants had histoplasmosis and AIDS.                     |
| Carme 1993   | Case series. 14 participants with *Histoplasma duboisii* seen in Congo.       |
| Chastain 2017 | Review update on epidemiology, diagnosis, and management of OIs in people living with HIV. |
| Del 1990     | Case series; authors do not report outcomes by treatment regimen.            |
| Ferguson-Paul 2018 | Case series of disseminated histoplasmosis in paediatric kidney transplant recipients. |
| Ferreira 2002 | Case series of participants with oral manifestations of histoplasmosis. 8/10 people living with HIV. |
| Gustafson 1985 | Case report in letter to editor of *Archives of Internal Medicine* detailing failure of ketoconazole as maintenance therapy. |
| Hage 2011    | Antigen clearance study.                                                     |
| Hajjeh 2001  | Case-control study to identify risk factors for histoplasmosis among people living with HIV. |
| Harrison 1990 | Case report of 2 children. Participant 1 had AIDS and was treated successfully with AmB for induction and maintenance. Participant 2 was HIV positive and died 6 months after diagnosis. |
| Hostetler 1991 | Review of use of ITRA in treatment of systemic fungal infections. 8 participants had histoplasmosis and AIDS. Authors did not report outcomes by treatment regimen or detail ART. |
| Hung 2004    | Prospective single arm. 1 or 2 participants with histoplasmosis. No data on management. |
| Johnson 1989 | Clinical review. Comparison of case series of 64 participants with PDH and AIDS with summaries of 61 participants in published literature. |
| Johnson 1986 | Case series. Comparison of case series of 12 cases with summaries of 20 previously reported cases. |
| Johnson 1988 | Case series. 48 participants with PDH and AIDS. Concluded that because of the permanence of immunodeficiency, PDH was resistant to treatment in this population. |
| Kassamali 2012 | Case series, some of whom may have had PDH, but insufficient data reported. |
| LeMonte 2000 | MICs determined to 10 clinical isolates to investigate efficacy of combined treatment with FCN and AmB. Caution against use of FCN+AmB for treatment of histoplasmosis. |
| Year    | Author(s)                  | Description                                                                 |
|---------|----------------------------|-----------------------------------------------------------------------------|
| 1991    | Machado                    | Case series of 6 people living with HIV with cutaneous-mucosal involvement of histoplasmosis. |
| 1993    | Majluf-Cruz                | Case series of 3 cases with haemophagocytic syndrome associated with histoplasmosis and AIDS. |
| 2014    | Marianelli                 | Case report of IRIS in people living with HIV with histoplasmosis osteomyelitis. |
| 2016    | Mashayekhi                | Renal transplant recipients with histoplasmosis.                            |
| 2007    | Mazumder                   | Retrospective case-control study of people living with HIV with CD4 count < 50 cells/μL and PDH. 26 cases, 42 controls. On multivariate analysis high alkaline phosphatase and weight loss were independent predictors of PDH. |
| 2009    | Moazeni                    | Clinical overview of OIs in people living with HIV and AIDS.                |
| 2015    | Murphy                     | Case series of 3 participants highlighting difficulties managing PDH in resource-limited settings where iAmB and ITRA are not readily available. |
| 1990    | Negroni                    | Case series. Provided information on outcomes by treatment regimen.          |
| 1992    | Negroni                    | Case series of 27 patients with AIDS and PDH. Treated with ITRA 200 mg or 400 mg for 6 months. 23/27 patients assessed as responders given ITRA 100 mg. Mean survival 7.8 months. |
| 1992    | Neubauer                   | Case series of 23 patients with AIDS and PDH. 21/23 patients treated with AmB therapy; formulation not specified. |
| 2007    | Oliveira                   | Case series of 21 patients with PDH and AIDS.                               |
| 2009    | Pamnani                    | Case series of 4 patients with PDH. 2 were people living with HIV.          |
| 2007    | Restrepo                   | Case series. 6 patients. 3 were people living with HIV and PDH.             |
| 2003    | Reyes                      | Case series. 3 patients with AIDS and cutaneous manifestations of histoplasmosis. |
| 1997    | Scharfstein                | Cost-effectiveness modelling for FCN used as prophylaxis for AIDS-related systemic fungal infections. |
| 2015    | Townsend                   | Case series of histoplasmosis-induced haemophagocytic syndrome.             |
| 2014    | Vantilicke                 | Case series. PDH found to be the most common febrile OI in Western French Guiana. |
| 2006    | Wheat                      | Susceptibility testing on paired isolates from patients with AIDS who failed on treatment with FCN for histoplasmosis. |
| 2007    | Wheat                      | Guidelines for the management of people with histoplasmosis: 2007 update by the Infection Diseases Society of America. |

AmB: amphotericin B; ART: antiretroviral therapy; CDC: Centers for Disease Control and Prevention; FCN: fluconazole; HAART: highly active antiretroviral therapy; HICMA: HIV Medicine Association; IRIS: immune reconstitution inflammatory syndrome; ITRA: itraconazole; IV: intravenous; iAmB: liposomal amphotericin B; MIC: minimal inhibitory concentration; NIH: National Institutes of Health; OI: opportunistic infection; PDH: progressive disseminated histoplasmosis.

HISTORY

Review first published: Issue 4, 2020
CONTRIBUTIONS OF AUTHORS

MM and PH drafted the protocol, extracted data, and assessed risk of bias.

PH analysed results.

MM and PH drafted the final review and approved the final version.

DECLARATIONS OF INTEREST

MM was previously employed by the CIDG.

PH was previously employed full-time by the CIDG, and currently works full-time within the UK National Health Service (NHS). He received a Registration Scholarship to attend the 23rd Annual British HIV Association Conference 2017 from ViiV Healthcare. ViiV had no involvement in the selection of recipients of the scholarship. In 2018, he attended a continuing professional development-certified clinical research training programme organized and funded by Gilead Sciences Europe Ltd. To the best of his knowledge, neither financial nor non-financial conflicts of interests have influenced the current submitted work.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK

External sources

- Department for International Development, UK

- Project number 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We initially prepared this review as a rapid review for a Pan American Health Organization/World Health Organization guidelines development group meeting. We registered the protocol on the PROSPERO International prospective register of systematic reviews (CRD42019126075). We used a modified risk of bias assessment in the rapid review. Following completion of the rapid review, the protocol was approved by CIDG Editors, and we performed a further iteration of the review using the methodology described under Methods.

INDEX TERMS

Medical Subject Headings (MeSH)

- Amphotericin B [adverse effects]; Anti-HIV Agents [therapeutic use]; Antifungal Agents [adverse effects]; [*therapeutic use]; Cohort Studies; Deoxycholic Acid; Drug Administration Schedule; Fluconazole [therapeutic use]; Histoplasmosis [*drug therapy]; [mortality]; HIV Infections [*complications] [drug therapy]; Induction Chemotherapy; Itraconazole [therapeutic use]; Kidney [drug effects]; Liposomes; Maintenance Chemotherapy; Randomized Controlled Trials as Topic

MeSH check words

- Humans