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

Murray M, Hine P

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[Intervention Review]

Treating progressive disseminated histoplasmosis in people living with HIV

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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 a 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

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** [a]	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** [b]	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** [c]	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.

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[a]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).
[b]Downgraded two levels for very serious imprecision: the CIs were wide and crossed the line of no effect.
[c]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 effecting 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 posiconazole 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

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

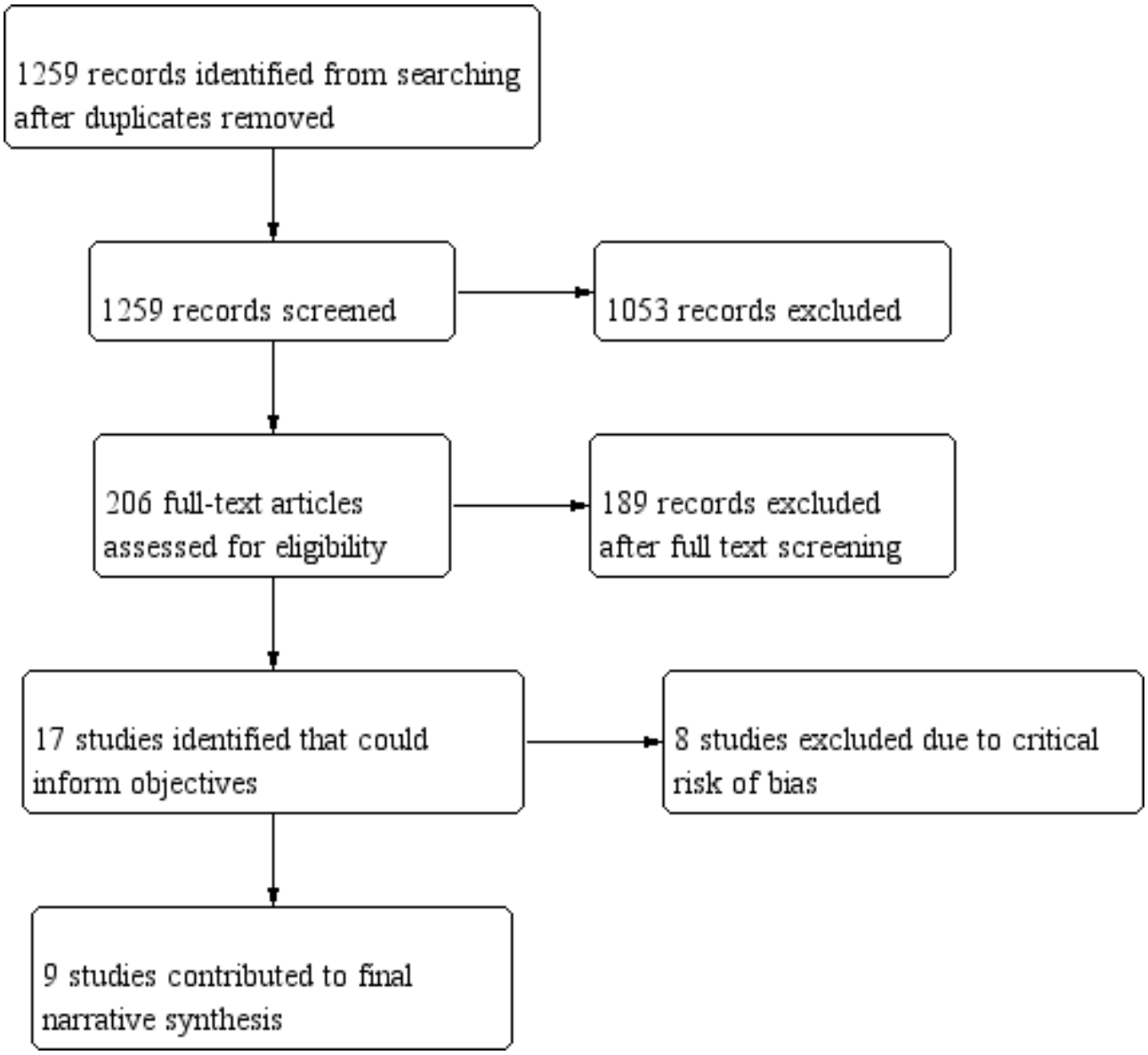
Results of the search

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.

Figure 1. Review flow diagram.



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.

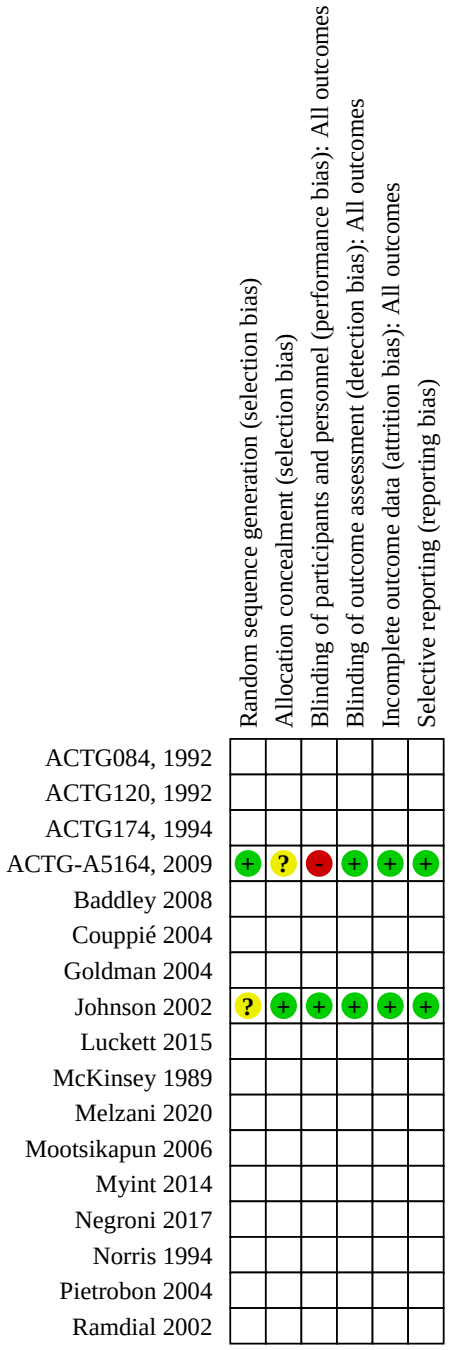
Excluded studies

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.



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').

Itraconazole

One single arm trial of itraconazole in mild-to-moderate PDH reported a treatment success rate of 85% (95% CI 73% to 93%; 1 study, 50/59 participants) at a dose of 300 mg twice daily for three days then 200 mg twice daily for 12 weeks (ACTG120, 1992).

Fluconazole

One single arm trial of fluconazole reported a treatment success rate of 74% (95% CI 59% to 85%; 1 study, 36 successes of 49 participants), at a dose of 1600 mg on day one, then 800 mg once daily for 12 weeks (ACTG174, 1994). This study initially reported a treatment success rate of 80% (95% CI 56% to 94%; 16 successes of 20 participants) for fluconazole 1600 mg on day one followed by 600 mg once daily for eight weeks. However, the protocol was intensified when relapse was subsequently observed in 6/16 participants (37.5%, 95% CI 15% to 64%).

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" Death	USA	Mild to moderate	Serious	**Clinical success:** 50/59 participants 85% (73% to 93%) **Death:** 1/59	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 ***Revised protocol*** FCN 1200 mg, then 80 mg OD for 8 weeks	"Treatment response"	USA	Mild to moderate	Serious	**Clinical success:** 36/49 participants. 74% (59% to 85%) *Revised protocol*	2 discontinuations due to toxicity, unclear if induction or maintenance.
Johnson 2002	RCT	81 with PDH	lAmB (55 participants) dAmB (26 participants)	Efficacy: "Clinical success" Safety: early discontinuation	USA	Moderate to severe	Low	**Clinical success:** lAmB: 82% (69% to 91%) 45/55 participants. dAmB: 56% (37% to 76%) 14/25 participants. RR 1.46 (1.01 to 2.11) **Death:** lAmB: 1/53 (2%) dAmB: 3/24 (13%) RR 0.15 (0.02 to 1.38)	**Early discontinuation:** 1/53 (2%) with lAmB vs 2/24 (8%) with dAmB RR 0.23 (95% CI 0.02 to 2.38) **Nephrotoxicity:** 5/53 (9%) with lAmB 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 relation to other commonly recognized adverse effects, including anaemia.

Luckett 2015	Retrospective cohort study	56 with HIV and PDH	ITRA/VORI/POSA AmB	Death (90-day histoplasmosis-related) Triazole failure	USA	Mild to severe	Serious	**Death** 5/56 participants. Not reported by treatment regimen. **Clinical success:** triazole induction successful in 20/24 participants 83% (62% to 95%)	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; POSA: posaconazole; RCT: randomized controlled trial; RR: risk ratio; VORI: voriconazole.

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 Death	USA	No ART Median CD4 count 47 cells/µL (35 participants)	Serious	**Relapse:** 2/42 participants (0.5%, 95% CI 0.05% to 16%) Median follow-up 98 weeks **Death:** 1/42 deaths attributed to PDH	Treatment discontinuation in 1/42 participants 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) ITRA 400 mg (18 participants) ITRA 600 mg (2 participants) 4 participants remained on doses > 200 mg. Median duration 64 weeks (range 7–120 weeks)	Relapse	USA	No ART Median CD4 29 cells/μL	Serious	**Relapse:** 2/46 participants (0.4%, 95% CI 0.05% to 14%) Median follow-up 87 weeks **Death:** 1/46 deaths due to relapse	Treatment discontinuation in 8/46 participants. 24/46 participants enrolled known to have died, including discontinuations; pre-ART.
ACTG174, 1994	Single arm trial	49 with PDH, 36 entered maintenance therapy	FCN 400 mg Continuous Median duration 30 weeks *(early termination of study)*	Relapse	USA	No ART Mild to severe	Serious	**Relapse:** 11/36 participants (30%, 95% CI 16% to 48%)	2 discontinuations due to toxicity, unclear if induction or maintenance.

AmB: amphotericin B; ART: antiretroviral therapy; BD: twice daily; dAmB: deoxycholate amphotericin B; FCN: fluconazole; ITRA: itraconazole; n: number of participants; PDH: progressive disseminated histoplasmosis.

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 opportunist infections 10 people with histoplasmosis	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 dies 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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REFERENCES

References to studies included in this review

ACTG084, 1992 *{published data only}*

. A study of itraconazole in preventing the return of histoplasmosis, a fungal infection, in patients with AIDS [Pilot study to determine the feasibility of itraconazole for suppression of relapse of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome]. clinicaltrials.gov/show/NCT00000992 (first received 1 August 2001).

Wheat J, Hafner R, Wulfsohn M, Spencer P, Squires K, Powderly W, et al. Prevention of relapse of histoplasmosis with itraconazole in patients with the acquired immunodeficiency syndrome. *Annals of Internal Medicine* 1993; **118**(8):610-6.

ACTG120, 1992 *{published data only}*

Hecht F, Korzun A, Wheat J, Hafner R. Itraconazole maintenance treatment for histoplasmosis in AIDS: prospective multi-center trial. *Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy* 1995; **35**:241.

Hecht FM, Wheat J, Korzun AH, Hafner R, Skahan KJ, Larsen R, et al. Itraconazole maintenance treatment for histoplasmosis in AIDS: a prospective, multicenter trial. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* 1997; **16**(2):100-7.

. A study of itraconazole in the treatment and prevention of histoplasmosis, a fungal infection, in patients with AIDS [Pilot study to determine the feasibility of itraconazole for primary treatment and suppression of relapse of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome]. clinicaltrials.gov/show/NCT00000975 (first received 31 August 2001).

Wheat J, Hafner R, Korzun AH, Limjoco MT, Spencer P, Larsen RA, et al. Itraconazole treatment of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trial Group. *American Journal of Medicine* 1995; **98**(4):336-42.

Wheat LJ, Connolly P, Haddad N, Le Monte A, Brizendine E, Hafner R. Antigen clearance during treatment of disseminated histoplasmosis with itraconazole versus fluconazole in patients with AIDS. *Antimicrobial Agents and Chemotherapy* 2002; **46**(1):248-50.

ACTG174, 1994 *{published data only}*

. Pilot study to determine the feasibility of fluconazole for induction treatment and suppression of relapse of histoplasmosis in patients with the acquired immunodeficiency syndrome. clinicaltrials.gov/show/NCT00000627 (first received 31 August 2001).

Wheat J, MaWhinney S, Hafner R, McKinsey D, Chen D, Korzun A, et al. Treatment of histoplasmosis with fluconazole in patients with acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Acquired Immunodeficiency Syndrome Clinical Trials Group and Mycoses Study Group. *American Journal of Medicine* 1997; **103**(3):223-32.

Wheat LJ, Connolly P, Haddad N, Le Monte A, Brizendine E, Hafner R. Antigen clearance during treatment of disseminated histoplasmosis with itraconazole versus fluconazole in patients with AIDS. *Antimicrobial Agents and Chemotherapy* 2002; **46**(1):248-50.

Wheat LJ, Connolly P, Smedema M, Brizendine E, Hafner R. Emergence of resistance to fluconazole as a cause of failure during treatment of histoplasmosis in patients with acquired immunodeficiency disease syndrome. *Clinical Infectious Diseases* 2001; **33**(11):1910-3.

ACTG-A5164, 2009 *{published data only}*

Grant PM, Komarow L, Andersen J, Sereti I, Pahwa S, Lederman MM, et al. Risk factor analyses for immune reconstitution inflammatory syndrome in a randomized study of early vs. deferred ART during an opportunistic infection. *PloS One* 2010; **5**(7):e11416.

Zolopa A, Andersen J, Powderly W, Sanchez A, Sanne I, Suckow C, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PloS One* 2009; **4**(5):e5575.

Baddley 2008 *{published data only}*

Baddley JW, Sankara IR, Rodriquez JM, Pappas PG, . Histoplasmosis in HIV-infected patients in a southern regional medical center: poor prognosis in the era of highly active antiretroviral therapy. *Diagnostic Microbiology and Infectious Disease* 2008; **62**(2):151-6.

Couppié 2004 *{published data only}*

Couppié P, Sobesky M, Aznar C, Bichat S, Clyti E, Bissuel F, et al. Histoplasmosis and acquired immunodeficiency syndrome: a study of prognostic factors. *Clinical Infectious Diseases* 2004; **38**(1):134-8.

Goldman 2004 *{published data only}*

Goldman M, Zackin R, Fichtenbaum CJ, Skiest DJ, Koletar SL, Hafner R, et al. Safety of discontinuation of maintenance therapy for disseminated histoplasmosis after immunologic response to antiretroviral therapy. *Clinical Infectious Diseases* 2004; **38**(10):1485-9.

. Withdrawal of antifungal treatment for histoplasmosis in patients after improved immune response to anti-HIV drugs [Discontinuation of antifungal therapy for histoplasmosis following immunologic response to antiretroviral therapy]. clinicaltrials.gov/show/NCT00006316 (first received 31 August 2001).

Johnson 2002 *{published data only}*

Johnson PC, Wheat LJ, Cloud GA, Goldman M, Lancaster D, Bamberger DM, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. *Annals of Internal Medicine* 2002; **137**(2):105-9.

Wheat LJ, Cloud G, Johnson PC, Connolly P, Goldman M, Le Monte A, et al. Clearance of fungal burden during treatment of disseminated histoplasmosis with liposomal amphotericin B versus itraconazole. *Antimicrobials Agents and Chemotherapy* 2001; **45**(8):2354-7.

Luckett 2015 *{published data only}*

Luckett K, Dummer JS, Miller G, Hester S, Thomas L. Histoplasmosis in patients with cell-mediated immunodeficiency: human immunodeficiency virus infection, organ transplantation, and tumor necrosis factor-alpha inhibition. *Open Forum Infectious Diseases* 2015; **2**(1):ofu116.

McKinsey 1989 *{published data only}*

McKinsey DS, Gupta MR, Riddler SA, Driks MR, Smith DL, Kurtin PJ. Long-term amphotericin B therapy for disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome (AIDS). *Annals of Internal Medicine* 1989; **111**(8):655-9.

Melzani 2020 *{unpublished data only}*

Melzani A, de Reynal de Saint Michel R, Ntab B, Djossou F, Epelboin L, Nacher M, et al. Incidence and trends in immune reconstitution inflammatory syndrome associated with Histoplasma capsulatum among people living with HIV: a 20-year case series and literature review. *Clinical Infectious Diseases* 2020; **70**(4):643-52.

Mootsikapun 2006 *{published data only}*

Mootsikapun P, Srikulbutr S. Histoplasmosis and penicilliosis: comparison of clinical features, laboratory findings and outcome. *International Journal of Infectious Diseases* 2006; **10**(1):66-71.

Myint 2014 *{published data only}*

Myint T, Anderson AM, Sanchez A, Farabi A, Hage C, Baddley JW, et al. Histoplasmosis in patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS): multicenter study of outcomes and factors associated with relapse. *Medicine (Baltimore)* 2014; **93**(1):11-8.

Negroni 2017 *{published data only}*

Negroni R, Messina F, Arechavala A, Santiso G, Bianchi M. Efficacy of the treatment and secondary antifungal prophylaxis in AIDS-related histoplasmosis. Experience at the Francisco J. Muñiz Infectious Diseases Hospital in Buenos Aires. *Revista Iberoamericana de Micologia* 2017; **34**(2):94-8.

Norris 1994 *{published data only}*

Norris S, Wheat J, McKinsey D, Lancaster D, Katz B, Black J, et al. Prevention of relapse of histoplasmosis with fluconazole in patients with the acquired immunodeficiency syndrome. *American Journal of Medicine* 1994; **96**(6):504-8.

Pietrobon 2004 *{published data only}*

Pietrobon D, Negro-Marquínez L, Kilstein J, Galíndez J, Greca A, Battagliotti C. Disseminated histoplasmosis and AIDS in an Argentine hospital: clinical manifestations, diagnosis and treatment. *Enfermedades Infecciosas y Microbiologia Clinica* 2004; **22**(3):156-9.

Ramdial 2002 *{published data only}*

Ramdial PK, Mosam A, Dlova NC, Satar NB, Aboobaker J, Singh SM. Disseminated cutaneous histoplasmosis in patients infected with human immunodeficiency virus. *Journal of Cutaneous Pathology* 2002; **29**(4):215-25.

References to studies excluded from this review

Assi 2007 *{published data only}*

Assi MA, Sandid MS, Baddour LM, Roberts GD, Walker RC. Systemic histoplasmosis: a 15-year retrospective institutional review of 111 patients. *Medicine (Baltimore)* 2007; **86**(3):162-9.

Borges 1997 *{published data only}*

Borges AS, Ferreira MS, Silvestre MT, Nishioka Sde A, Rocha A. Histoplasmosis in immunodepressed patients: study of 18 cases seen in Uberlandia, MG. *Revista da Sociedade Brasileira Medicina Tropical* 1997; **30**(2):119-24.

Boulougoura 2019 *{published data only}*

Boulougoura A, Laidlaw E, Roby G, Mejia Y, Pau A, Sheikh V, Sereti I, , . Immune reconstitution inflammatory syndrome in patients with HIV/aids and histoplasmosis: A case series. In: Open Forum Infectious Diseases. Vol. 6. 2019:S195.

Brilhante 2012 *{published data only}*

Brilhante RS, Fechine MA, Mesquita JR, Cordeiro RA, Rocha MF, Monteiro AJ, et al. Histoplasmosis in HIV-positive patients in Ceará, Brazil: clinical-laboratory aspects and in vitro antifungal susceptibility of Histoplasma capsulatum isolates. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2012; **106**(8):484-8.

Casariego 1997 *{published data only}*

Casariego Z, Kelly GR, Perez H, Cahn P, Guelfan L, Kaufman S, et al. Disseminated histoplasmosis with orofacial involvement in HIV-I-infected patients with AIDS: manifestations and treatment. *Oral Diseases* 1997; **3**(3):184-7.

Chaiwarith 2013 *{published data only}*

Chaiwarith R, Praparattanapan J, Nuntachit N, Kotarathititum W, Supparatpinyo K. Discontinuation of primary and secondary prophylaxis for opportunistic infections in HIV-infected patients who had CD4+ cell count <200 cells/mm^3 but undetectable plasma HIV-1 RNA: an open-label randomized controlled trial. *AIDS Patient Care and STDs* 2013; **27**(2):71-6.

Crabtree-Ramírez 2016 *{published data only}*

Crabtree-Ramírez B, Caro-Vega Y, Shepherd BE, Grinsztejn B, Wolff M, Cortes CP, et al. Time to HAART initiation after diagnosis and treatment of opportunistic infections in patients with AIDS in Latin America. *PloS One* 2016; **11**(6):e0153921.

Cunha 2007 *{published data only}*

Cunha VS, Zampese MS, Aquino VR, Cestari TF, Goldani LZ. Mucocutaneous manifestations of disseminated histoplasmosis in patients with acquired immunodeficiency syndrome: particular aspects in a Latin-American population. *Clinical and Experimental Dermatology* 2007; **32**(3):250-5.

Damasceno 2013 *{published data only}*

Damasceno LS, , Alencar CH, Goncalves MV, de Mesquita JR, Soares AT, et al. Disseminated histoplasmosis in HIV-infected patients: determinants of relapse and mortality in a north-eastern area of Brazil. *Mycoses* 2014; **57**(7):406-13.

Damasceno LS, Ramos AN, Alencar CH, Lima DT, Sidrim JJ, Goncalves MV, et al. Disseminated histoplasmosis and aids: relapse and late mortality in endemic area in north-eastern Brazil. *Mycoses* 2013; **56**(5):520-6.

Damasceno-Escoura 2020 *{published data only}*

Damasceno-Escoura AH, Mora DJ, Cardeal AC, Berto-Nascimento JC, Etchebehere RM, de Meneses ACO, Adad SJ, Micheletti AMR, . Histoplasmosis in HIV-Infected Patients: Epidemiological,Clinical and Necropsy Data from a Brazilian TeachingHospital. *Mycopathologia* 2020; **Feb 20**:.

Dismukes 1992 *{published data only}*

Dismukes WE, , Cloud GC, Kauffman CA, Chapman SW, George RB, et al. Itraconazole therapy for blastomycosis and histoplasmosis. *American Journal of Medicine* 1992; **93**(5):489-97.

Falci 2015 *{published data only}*

Falci DR, Da Rosa FB, Pasqualotto AC. Hematological toxicities associated with amphotericin B formulations. *Leukemia and Lymphoma* 2015; **56**(10):2889-94.

Gerber 1995 *{published data only}*

Gerber ME, Rosdeutscher JD, Seiden AM, Tami TA. Histoplasmosis: the otolaryngologist's perspective. *Laryngoscope* 1995; **105**(9 Pt 1):919-23.

Gopalakrishnan 2012 *{published data only}*

Gopalakrishnan R, Nambi PS, Ramasubramanian V, Abdul Ghafur K, Parameswaran A. Histoplasmosis in India: truly uncommon or uncommonly recognised? *Journal of the Association of Physicians of India* 2012; **60**:25-8.

Gutierrez 2005 *{published data only}*

Gutierrez ME, Canton A, Sosa N, Puga E, Talavera L. Disseminated histoplasmosis in patients with AIDS in Panama: a review of 104 cases. *Clinical Infectious Diseases* 2005; **40**(8):1199-202.

Huber 2008 *{published data only}*

Huber F, Nacher M, Aznar C, Pierre-Demar M, El Guedj M, Vaz T, et al. AIDS-related Histoplasma capsulatum var. capsulatum infection: 25 years experience of French Guiana. *AIDS* 2008; **22**(9):1047-53.

Karimi 2002 *{published data only}*

Karimi K, Wheat LJ, Connolly P, Cloud G, Hajjeh R, Wheat E, et al. Differences in histoplasmosis in patients with acquired immunodeficiency syndrome in the United States and Brazil. *Journal of Infectious Diseases* 2002; **186**(11):1655-60.

Lopez Daneri 2016 *{published data only}*

Lopez Daneri AG, Arechavala A, Iovannitti CA, Mujica MT. Disseminated histoplasmosis in patients with AIDS. Buenos Aires, 2009-2014. *Medicina* 2016; **76**(6):332-7.

Mata-Essayag 2008 *{published data only}*

Mata-Essayag S, Colella MT, Rosello A, de Capriles CH, Landaeta ME, de Salazar CP, et al. Histoplasmosis: a study of 158 cases in Venezuela, 2000-2005. *Medicine (Baltimore)* 2008; **87**(4):193-202.

McKinsey 1996 *{published data only}*

McKinsey DS, Kauffman CA, Pappas PG, Cloud GA, Girard WM, Sharkey PK, et al. Fluconazole therapy for histoplasmosis. *Clinical Infectious Diseases* 1996; **23**(5):996-1001.

Meng 2016 *{published data only}*

Meng J, Lv X. A clinical review of 34 cases with progressive disseminated histoplasmosis. *Respirology* 2016; **Volume 21**(Suppl 3):63.

Messina 2018 *{published data only}*

Messina FA, Corti M, Negroni R, Arechavala A, Bianchi M, Santiso G. Histoplasmosis in AIDS patients without tegumentary manifestations. *Revista Chilena de Infectologia* 2018; **35**(5):560-5.

Mora 2008 *{published data only}*

Mora DJ, dos Santos CT, Silva-Vergara ML. Disseminated histoplasmosis in acquired immunodeficiency syndrome patients in Uberaba, MG, Brazil. *Mycoses* 2008; **51**(2):136-40.

Nacher 2014 *{published data only}*

Nacher M, Adenis A, Blanchet D, Vantilcke V, Demar M, Basurko C, et al. Risk factors for disseminated histoplasmosis in a cohort of HIV-infected patients in French Guiana. *PLoS Neglected Tropical Diseases* 2014; **8**(1):7.

Negroni 1997 *{published data only}*

Negroni R, Robles AM, Arechavala AI, Bianchi M, Helou S. Histoplasmosis related to AIDS: present status in Argentina. *Prensa Medica Argentina* 1997; **84**(7):696-700.

Negroni 2004 *{published data only}*

Negroni R, Helou SH, Lopez-Daneri G, Robles AM, Arechavala AI, Bianchi MH. Interruption of antifungal secondary prophylaxis in AIDS-related histoplasmosis. *Revista Iberoamericana de Micologia* 2004; **21**(2):75-8.

Nightingale 1990 *{published data only}*

Nightingale SD, Parks JM, Pounders SM, Burns DK, Reynolds J, Hernandez JA. Disseminated histoplasmosis in patients with AIDS. *Southern Medical Journal* 1990; **83**(6):624-30.

Salzman 1988 *{published data only}*

Salzman SH, Smith RL, Aranda CP. Histoplasmosis in patients at risk for the acquired immunodeficiency syndrome in a nonendemic setting. *Chest* 1988; **93**(5):916-21.

Samayoa 2017 *{published data only}*

Samayoa B, Roy M, Cleveland AA, Medina N, Lau-Bonilla D, Scheel CM, et al. High mortality and coinfection in a prospective cohort of human immunodeficiency virus/acquired immune deficiency syndrome patients with histoplasmosis in Guatemala. *American Journal of Tropical Medicine and Hygiene* 2017; **97**(1):42-8.

Santos 1998 *{published data only}*

Santos J, Palacios R, Esteve A, Garcia V, Rivero A, Marquez M. Fungemia in patients with HIV infection. *Annales de Medecine Interne* 1998; **15**(10):523-7.

Silva 2017 *{published data only}*

Silva TC, Tremea CM, Zara AL, Mendonca AF, Godoy CS, Costa CR, et al. Prevalence and lethality among patients with histoplasmosis and AIDS in the Midwest Region of Brazil. *Mycoses* 2017; **60**(1):59-65.

Subramanian 2005 *{published data only}*

Subramanian S, Abraham OC, Rupali P, Zachariah A, Mathews MS, Mathai D. Disseminated histoplasmosis. *Journal of the Association of Physicians of India* 2005; **53**:185-9.

Thompson 2016 *{published data only}*

. Open-label study of isavuconazole in the treatment of patients with aspergillosis and renal impairment or of patients with invasive fungal disease caused by rare moulds, yeasts or dimorphic fungi. Available from astellasclinicalstudyresults.com/study.aspx?ID=51 (accessed prior to 3 March 2020).

Thompson GR, Rendon A, Ribeiro dos Santos R, Queiroz-Telles F, Ostrosky-Zeichner L, Azie N, et al. Isavuconazole treatment of cryptococcosis and dimorphic mycoses. *Reviews of Infectious Diseases* 2016; **63**(3):356-62.

Tobon 2005 *{published data only}*

Tobon AM, Agudelo CA, Rosero DS, Ochoa JE, De Bedout C, Zuluaga A, et al. Disseminated histoplasmosis: a comparative study between patients with acquired immunodeficiency syndrome and non-human immunodeficiency virus-infected individuals. *American Journal of Tropical Medicine and Hygiene* 2005; **73**(3):576-82.

Wheat 1992 *{published data only}*

Wheat LJ, Connollystringfield P, Blair R, Connolly K, Garringer T, Katz BP, et al. Effect of successful treatment with amphotericin-B on histoplasma-capsulatum variety capsulatum polysaccharide antigen levels in patients with aids and histoplasmosis. *American Journal of Medicine* 1992; **92**(2):153-60.

Wheat 2018 *{published data only}*

Wheat J, Myint T, Guo Y, Kemmer P, Hage C, Terry C, et al. Central nervous system histoplasmosis: multicenter retrospective study on clinical features, diagnostic approach and outcome of treatment. *Medicine (Baltimore)* 2018; **97**(13):e0245.

References to studies awaiting assessment

NCT00002159 *{published data only}*

. A randomized, open, comparative multicenter study of initial treatment with intravenous itraconazole versus amphotericin B followed by consolidation treatment with itraconazole capsules in patients with blastomycosis or histoplasmosis. clinicaltrials.gov/ct2/show/NCT00002159 (first received 31 August 2001).

References to ongoing studies

Pasqualotto 2019 *{unpublished data only}*

Pasqualotto A. Randomized Trial of Liposomal Amphotericin B for Histoplasmosis in AIDS Patients. ClinicalTrials.gov Identifier: NCT04059770 .

Additional references

Adenis 2014

Adenis A, Nacher M, Hanf M, Vantilcke V, Boukhari R, Blachet D, et al. HIV-associated histoplasmosis early mortality and incidence trends: from neglect to priority. *PLoS Neglected Tropical Diseases* 2014; **8**(8):e3100.

Armstrong 1988

Armstrong D. Life-threatening opportunistic fungal infection in patients with the acquired immunodeficiency syndrome. *Annals of the New York Academy of Sciences* 1988; **544**:443-50.

Assi 2006

Assi M, McKinsey DS, Driks MR, O'Connor MC, Bonacini M, Graham B, et al. Gastrointestinal histoplasmosis in the acquired immunodeficiency syndrome: report of 18 cases and literature review. *Diagnostic Microbiology and Infectious Disease* 2006; **55**(3):195-201.

Baker 2019

Baker J, Setianingrum F, Wahyuningsih R, Denning D. Mapping histoplasmosis in South East Asia – implications for diagnosis in AIDS. *Emerging Microbes and Infections* 2019; **8**(1):1139-1145.

Barlows 1996

, Luber AD, Jacobs RA, Guglielmo BJ. Hypothermia following the intravenous administration of amphotericin B. *Clinical Infectious Diseases* 1996; **23**(5):1187-8.

Benson 2005

Benson CA, Kaplan JE, Masur H, Pau A, Holmes KK. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/ Infectious Diseases Society of America. *Clinical Infectious Diseases* 2005; **40**(Suppl 3):S131-235.

Bernard 1989

Bernard E, Carles M, Toussaint-Gari M, Fournier J P, Dellamonica P. Value of fluconazole in the treatment of systemic yeast infection. *Pathologie et Biologie* 1989; **37**(5 Pt 2):690-3.

Bonifaz 2009

Bonifaz A, Chang P, Moreno K, Fernandez-Fernandez V, Montes de Oca G, Araiza J, et al. Disseminated cutaneous histoplasmosis in acquired immunodeficiency syndrome: report of 23 cases. *Clinical and Experimental Dermatology* 2009; **34**(4):481-6.

Botero Aguirre 2015

Botero Aguirre JP, Restrepo Hamid AM. Amphotericin B deoxycholate versus liposomal amphotericin B: effects on kidney function. *Cochrane Database of Systematic Reviews* 2015, Issue 11. [DOI: 10.1002/14651858.CD010481]

BSAC 1992

British Society for Antimicrobial Chemotherapy. Antifungal chemotherapy in patients with acquired immunodeficiency syndrome. British Society for Antimicrobial Chemotherapy Working Party. *Lancet* 1992; **340**(8820):648-51.

Cano-Torres 2019

Cano-Torres JO, Olmedo-Reneaum A, Esquivel-Sanchez JM, Camiro-Zuniga A, Perez-Carrisoza A, Madrigal-Iberri C, et al. Progressive disseminated histoplasmosis in Latin America and the Caribbean in people receiving highly active antiretroviral therapy for HIV infection: a systematic review. *Medical Mycology* 2019; **18**:18.

Caplivski 2005

Caplivski D, Salama C, Huprikar S, Bottone EJ. Disseminated histoplasmosis in five immunosuppressed patients: clinical, diagnostic, and therapeutic perspectives. *Reviews in Medical Microbiology* 2005; **16**(1):1-7.

Carme 1993

Carme B, Hayette MP, Ngaporo AI, Ngolet A, Darozzin F, Moyikoua A, et al. African histoplasmosis due to Histoplasma duboisii (Histoplasma capsulatum var. duboisii): fourteen cases observed in Congo during 10 years (1981-1990). *Journal de Mycologie Medicale* 1993; **3**(2):67-73.

Chastain 2017

Chastain DB, Henao-Martinez AF, Franco-Paredes C. Opportunistic invasive mycoses in AIDS: cryptococcosis, histoplasmosis, coccidiodomycosis, and talaromycosis. *Current Infectious Disease Reports* 2017; **19**(10):36.

Del 1990

Del Bianco R, Neves MA, Neves FD, Mendonca M, Prado SP, Stocco MJ, et al. Study of clinic-therapeutic pathology of 10 cases of disseminated histoplasmosis and AIDS in Sao Paulo Brazil. Sixth International Conference on AIDS; June 20-24 1990; San Francisco (CA) 1990.

Eshun-Wilson 2018

Eshun-Wilson I, Okwen MP, Richardson M, Bicanic T. Early versus delayed antiretroviral treatment in HIV-positive people with cryptococcal meningitis. *Cochrane Database of Systematic Reviews* 2018, Issue 7. [DOI: 10.1002/14651858.CD009012.pub3]

Ferguson-Paul 2018

Ferguson-Paul K, Park C, Childress S, Arnold S, Ault B, Bagga B. Disseminated histoplasmosis in pediatric kidney transplant recipients – a report of six cases and review of the literature. *Pediatric Transplantation* 2018; **22**(7):e13274.

Ferreira 2002

Ferreira OG, Cardoso SV, Borges AS, Ferreira MS, Loyola AM. Oral histoplasmosis in Brazil. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 2002; **93**(6):654-9.

Gustafson 1985

Gustafson PR, Henson A. Ketoconazole therapy for AIDS patients with disseminated histoplasmosis. *Archives of Internal Medicine* 1985; **145**(12):2272.

Hage 2011

Hage CA, Kirsch EJ, Stump TE, Kauffman CA, Goldman M, Connolly P, et al. Histoplasma antigen clearance during treatment of histoplasmosis in patients with AIDS determined by a quantitative antigen enzyme immunoassay. *Clinical and Vaccine Immunology* 2011; **18**(4):661-6.

Hajjeh 2001

Hajjeh RA, Pappas PG, Henderson H, Lancaster D, Bamberger DM, Skahan KJ, et al. Multicenter case-control study of risk factors for histoplasmosis in human immunodeficiency virus-infected persons. *Clinical Infectious Diseases* 2001; **32**(8):1215-20.

Hamill 2013

Hamill RJ. Amphotericin B formulations: a comparative review of efficacy and toxicity. *Drugs* 2013; **73**(9):919-34.

Harrison 1990

Harrison LF, Hanson CG, Rosenblatt HM, Blomquist MD, Taber LH, Shearer WT. Lymphocyte function and follow-up of pediatric aids patients presenting with disseminated histoplasmosis. *Journal of Allergy and Clinical Immunology* 1990; **85**(1 Part 2):240.

Hostetler 1991

Hostetler JS, Stevens DA. The treatment of aspergillosis, cryptococcosis and histoplasmosis in immunocompromised patients. Report of experience in the United States. *Medizinische Klinik (Munich, Germany : 1983)* 1991; **86 Suppl 1**:8-10.

Hughes 2010

Hughes CA, Foisy M, Tseng A. Interactions between antifungal and antiretroviral agents. *Expert Opinion on Drug Safety* 2010; **9**(5):723-42.

Hung 2004

Hung CC, Chang SC. Impact of highly active antiretroviral therapy on incidence and management of human immunodeficiency virus-related opportunistic infections. *Journal of Antimicrobial Chemotherapy* 2004; **54**(5):849-53.

Johnson 1986

Johnson PC, Sarosi GA, Septimus EJ, Satterwhite TK. Progressive disseminated histoplasmosis in patients with the

acquired immune deficiency syndrome: a report of 12 cases and a literature review. *Seminars in Respiratory Infections* 1986; **1**(1):1-8.

Johnson 1988

Johnson PC, Khardori N, Najjar AF, Butt F, Mansell PW, Sarosi GA. Progressive disseminated histoplasmosis in patients with acquired immunodeficiency syndrome. *American Journal of Medicine* 1988; **85**(2):152-8.

Johnson 1989

Johnson PC, Hamill RJ, Sarosi GA. Clinical review: progressive disseminated histoplasmosis in the AIDS patient. *Seminars in Respiratory Infections* 1989; **4**(2):139-46.

Karimzadeh 2013

Karimzadeh I, Khalili H, Farsaei S, Dashti-Khavidaki S, Sagheb MM. Role of diuretics and lipid formulations in the prevention of amphotericin B-induced nephrotoxicity. *European Journal of Clinical Pharmacology* 2013; **69**(7):1351-68.

Kassamali 2012

Kassamali Z, Danziger L, Glowacki R, Schwartz D. How low can you go? Use of low- and standard-dose liposomal amphotericin B for treatment of invasive fungal infections at a USA public hospital. *Clinical Microbiology and Infection* 2012; **3**:178-9.

Keating 2005

Keating GM. Posaconazole. *Drugs* 2005; **65**(11):1553-67; discussion 1568.

LeMonte 2000

LeMonte AM, Washum KE, Smedema ML, Schnizlein-Bick C, Kohler SM, Wheat LJ. Amphotericin B combined with itraconazole or fluconazole for treatment of histoplasmosis. *Journal of Infectious Diseases* 2000; **182**(2):545-50.

Lewin 1995

Lewin SR, Street AC. Disseminated histoplasmosis: successful maintenance therapy with oral fluconazole. *Australian and New Zealand Journal of Medicine* 1995; **25**(1):56.

Machado 1991

Machado AA, Coelho IC, Roselino AM, Trad ES, Figueiredo JF, Martinez R, et al. Histoplasmosis in individuals with acquired immunodeficiency syndrome (AIDS): report of six cases with cutaneous-mucosal involvement. *Mycopathologia* 1991; **115**(1):13-8.

Majluf-Cruz 1993

Majluf-Cruz AS, Hurtado Monroy R, Souto-Meirino C, del Rio Chiriboga C, Simon J. Hemophagocytic syndrome associated with histoplasmosis in the acquired immunodeficiency syndrome: description of 3 cases and review of the literature. *Sangre* 1993; **38**(1):51-5.

Marianelli 2014

Marianelli LG, Frassone N, Marino M, Debes J. Immune reconstitution inflammatory syndrome as histoplasmosis osteomyelitis in South America. *AIDS* 2014; **28**(12):1848-50.

Mashayekhi 2016

Mashayekhi M, Langone A. Analysis of a large single-center cohort of renal transplant recipients with histoplasmosis. *American Journal of Transplantation* 2016; **16 (Suppl 3)**:732.

Mazumder 2007

Mazumder S, Hota B, Pulvirenti J, Muppidi U, Adeyemi O. Clinical predictors of disseminated histoplasmosis (DH) in hospitalized HIV plus patients. *Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy* 2007; **47**:308.

Moazeni 2009

Moazeni M, Haghmorad D, Mirshafiey A. Opportunistic fungal infections in patients with HIV and AIDS. *Journal of Chinese Clinical Medicine* 2009; **4**(2):106-20.

Moen 2009

Moen MD, Lyseng-Williamson KA, Scott LJ. Liposomal amphotericin B: a review of its use as empirical therapy in febrile neutropenia and in the treatment of invasive fungal infections. *Drugs* 2009; **69**(3):361-92.

Murphy 2015

Murphy RA, Gounder L, Manzini TC, Ramdial PK, Castilla C, Moosa MY. Challenges in the management of disseminated progressive histoplasmosis in human immunodeficiency virus-infected patients in resource-limited settings. *Open Forum Infectious Diseases* 2015; **2**(1):ofv025.

Negroni 1990

Negroni R, Taborda A, Benetucci J, Da Bouza J, Macias J. Mucocutaneous manifestations of histoplasmosis in AIDS patients. *Revista Argentina de Dermatologia* 1990; **71**(2):71-8.

Negroni 1992

Negroni R, Taborda A, Robies AM, Archevala A. Itraconazole in the treatment of histoplasmosis associated with AIDS. *Mycoses* 1992; **35**(11-12):281-7.

Neubauer 1992

Neubauer MA, Bodensteiner DC. Disseminated histoplasmosis in patients with AIDS. *Southern Medical Journal* 1992; **85**(12):1166-70.

Oliveira 2007

Oliveira FM, Fernandes SS, Severo CB, Guazzelli LS, Severo LC. Histoplasma capsulatum fungemia in patients with acquired immunodeficiency syndrome: Detection by lysis-centrifugation blood-culturing technique. *Revista do Instituto de Medicina Tropical de Sao Paulo* 2007; **49**(3):135-8.

Pamnani 2009

Pamnani R, Rajab JA, Githang'a J, Kasmani R. Disseminated histoplasmosis diagnosed on bone marrow aspirate cytology: report of four cases. *East African Medical Journal* 2009; **86**(12 Suppl):S102-5.

Pan 2013

Pan B, Chen M, Pan W, Liao W. Histoplasmosis: a new endemic fungal infection in China? Review and analysis of cases. *Mycoses* 2013; **56**(3):212-21.

Popay 2006

Popay J, Roberts H, Sowden A, et al. Guidance on the Conduct of Narrative Synthesis in Systematic Reviews. A Product from the ESRC Methods Programme 2006.

Restrepo 2007

Restrepo A, Tobon A, Clark B, Graham DR, Corcoran G, Bradsher RW, et al. Salvage treatment of histoplasmosis with posaconazole. *Journal of Infection* 2007; **54**(4):319-27.

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Reyes 2003

Reyes M, Arenas LR, Pichardo P, Vick R, Torres A, Zacarias R. Cutaneous histoplasmosis and AIDS. *Gaceta Medica de Mexico* 2003; **139**(3):270-5.

Scharfstein 1997

Scharfstein JA, David Paltiel A, Freedberg KA. The cost-effectiveness of fluconazole prophylaxis against primary systemic fungal infections in AIDS patients. *Medical Decision Making* 1997; **17**(4):373-81.

Siberry 2013

Siberry GK, Abzug MJ, Nachman S, Steinbach WJ, Kleiman MB, Gaur A, et al. Executive summary: guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children: recommendations from the National Institutes of Health, the Centers for Disease Control and Prevention, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *Journal of the Pediatric Infectious Diseases Society* 2013; **2**(4):293-308.

Slain 2001

Slain D, Rogers PD, Cleary JD, Chapman SW. Intravenous itraconazole. *Annals of Pharmacotherapy* 2001; **35**(6):720-9.

Sterne 2016

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355**:i4919. [DOI: dx.doi.org/10.1136/bmj.i4919]

Tenforde 2018

Tenforde MW, Shapiro AE, Rouse B, Jarvis JN, Li T, Eshun-Wilson I, et al. Treatment for HIV-associated cryptococcal meningitis. *Cochrane Database of Systematic Reviews* 2018, Issue 7. [DOI: 10.1002/14651858.CD005647]

Townsend 2015

Townsend JL, Shanbhag S, Hancock J, Bowman K, Nijhawan AE. Histoplasmosis-induced hemophagocytic syndrome: a case series and review of the literature. *Open Forum Infectious Diseases* 2015; **2**(2):ofv055.

Vantilcke 2014

Vantilcke V, Boukhari R, Jolivet A, Vautrin C, Misslin C, Adenis A, et al. Fever in hospitalized HIV-infected patients in Western French Guiana: first think histoplasmosis. *International Journal of STD & AIDS* 2014; **25**(9):656-61.

Wheat 2006

Wheat LJ, Connolly P, Smedema M, Durkin M, Brizendine E, Mann P, et al. Activity of newer triazoles against Histoplasma capsulatum from patients with AIDS who failed fluconazole. *Journal of Antimicrobial Chemotherapy* 2006; **57**(6):1235-9.

Wheat 2007

Wheat LJ, Freifeld AG, Kleiman MB, Baddley JW, McKinsey DS, Loyd JE, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2007; **45**(7):807-25.

References to other published versions of this review

CRD42019126075

Murray M, Hine P, Garner P. Treatment regimens for progressive disseminated histoplasmosis in people living with HIV. www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019126075 (accessed prior to 13 September 2019).

CHARACTERISTICS OF STUDIES

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

ACTG-A5164, 2009

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

ACTG-A5164, 2009 *(Continued)*

	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.

ACTG-A5164, 2009 *(Continued)*

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) lAmB (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

Couppié 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/m^3
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

Johnson 2002 *(Continued)*

	Clinical success in 45/51 lAmB vs 14/22 dAmB **Safety**: early discontinuation 77 participants evaluated for safety in ITT analysis Early discontinuation: 1/53 (2%) lAmB vs 2/24 (8%) dAmB Nephrotoxicity: 5/53 (9%) lAmB vs 9/24 (37%) dAmB **Death:** 1/53 (2%) lAmB (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) All outcomes	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) All outcomes	Low risk	Clinical and mycological outcomes were predetermined. These included objective components including temperature and laboratory findings.
Incomplete outcome data (attrition bias) All outcomes	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 keto-conazole; 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, lAmB 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	

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	

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

Ramdial 2002 *(Continued)*

	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: opportunist infection; PDH: progressive disseminated histoplasmosis; PO_2: 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-Ramírez 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-Escoura 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

Pasqualotto 2019 *(Continued)*

Notes	-

DATA AND ANALYSES

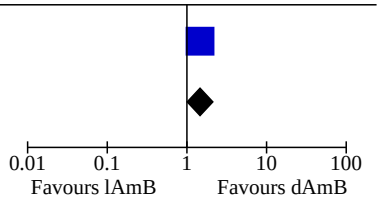
Comparison 1. Liposomal amphotericin B (lAmB) versus deoxycholate amphotericin B (dAmB)

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

Heterogeneity: Not applicable
Test for overall effect: Z = 2.01 (P = 0.04)
Test for subgroup differences: Not applicable



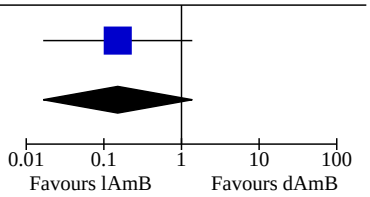
Footnotes

(1) Denominators are 55 patients randomised to lAmB, and 25 randomised to dAmB, excluding one patient who died before treatment in the dAmB a

Analysis 1.2. Comparison 1: Liposomal amphotericin B (lAmB) versus deoxycholate amphotericin B (dAmB), Outcome 2: Death

Study or Subgroup	lAmB Events	lAmB Total	dAmB Events	dAmB Total	Weight	Risk Ratio M-H, Random, 95% CI
Johnson 2002 (1)	1	53	3	24	100.0%	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

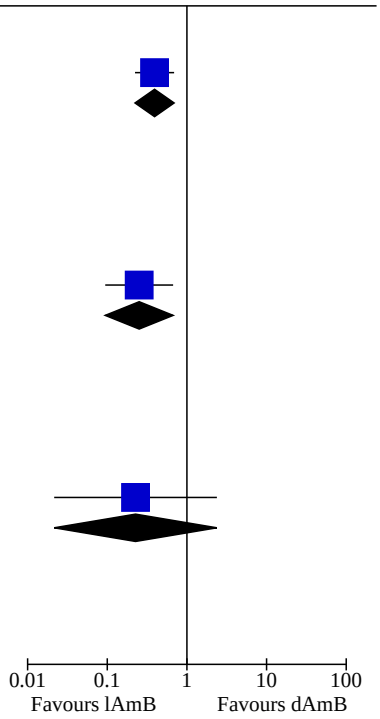


Footnotes
(1) Denominators are safety population, all those receiving at least one dose.

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

Study or Subgroup	lAmB Events	lAmB Total	dAmB Events	dAmB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Infusion-related toxicity						
Johnson 2002 (1)	13	53	15	24	100.0%	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						
Johnson 2002 (1)	5	53	9	24	100.0%	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						
Johnson 2002 (1)	1	53	2	24	100.0%	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: $Chi^2 = 0.72$, df = 2 (P = 0.70), $I^2 = 0\%$

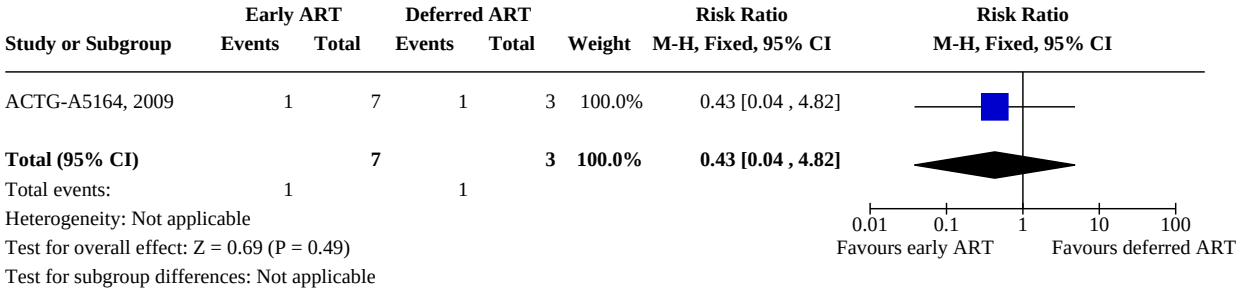


Footnotes
(1) Denominators are safety population, all those receiving at least one dose.

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



ADDITIONAL TABLES

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

Studies at critical risk of bias outcomes: death, relapse of histoplasmosis			
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, comedications, 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

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

			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 co morbidities 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.
Luckett 2015	1	Intervention classification; outcome measurement	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 from azole 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.
Mootsikapun 2006	2	Confounding; partici-	≥ 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

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

		pant selection	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 lAmB 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; lAmB: 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.	⊕⊖⊖⊖ **Very low** [a,b]	—

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

Table 6. Additional summary 2: early versus deferred ART *(Continued)*

IRIS	1/3 participants[a]	1/7 participants[a]	**RR 0.43** (0.04 to 4.82)	10 (1 study)	⊕⊖⊖⊖ **Very low** [b,c]	We do not know if early ART increases the risk of IRIS in people with HIV and PDH.

ART: antiretroviral therapy; IRIS: immune reconstitution inflammatory syndrome; PDH: progressive disseminated histoplasmosis; RCT: randomized controlled trial; RR: risk ratio.

[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 immuno-deficiency syndrome OR acquired immune-deficiency 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 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 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]

(Continued)

5	"Amphotericin B"[Mesh]) OR amphotericin Field: Title/Abstract
6	"Itraconazole"[Mesh]) OR itraconazole Field: Title/Abstract
7	4 or 5or 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

Embase 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 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 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*)
#	6	**TOPIC:** (itraconazole or amphotericin)
#	5	#4 AND #3
#	4	**TOPIC:** (histoplasma or histoplasmosis)
#	3	#2 OR #1
#	2	**TOPIC:** (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 immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)))

(Continued)

# 1	**TOPIC:** (HIV OR AIDS OR "human immunodeficiency virus" or "acquired immunodeficiency syndrome" or AIDS)

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 to favour intervention or comparator
Severity of PDH	Severe, moderate, and mild illness were defined	No	Yes	—
Severity of HIV	CD4 count and viral	No	Yes	—

(Continued)

	load reported			
Comorbidities and comedications	Not reported	No	Not measured	Comorbidities likely to influence clinicians to favour liposomal amphotericin.

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, remains important cointervention. 27% on ART prior to study. 1/3 adherent.	Favour intervention
Supportive therapy	Reported level of clinical care (e.g. ICU care)	Favour intervention

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 comedications. 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?**	**OPTIONAL Is failure to adjust for this variable expected to favour intervention or comparator**
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	**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 the 3 inhospital deaths.	**Serious**
Bias in participant selection	2.1–2.5	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	3.1–3.3	Comparison was between disease populations not intervention groups. Intervention status was well defined.	**Moderate**
Bias due to deviations from intended intervention	4.1–4.6	Deviations were not reported. Important cointerventions were not reported.	**No information**
Bias due to missing data	5.1–5.5	Data reported on inhospital deaths likely to be reasonably complete.	**Low**
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	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**

(Continued)

Overall bias	**SERIOUS**

Study: Mootsikapun 2006. **Outcome 2: relapse on maintenance itraconazole. Median follow-up 22 months (1–75 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	Not reported	No	—	—
Severity of HIV	Not reported	No	—	—
Comorbidities and comedications	None 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	—
Supportive therapy	No	—

Bias 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**

(Continued)

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 that were not controlled for. Multiple logistic regression used to determine variables associated with relapse; how-	**Critical**

(Continued)

		ever, 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	1.1–1.8	Participants in the physician continued therapy group are likely to have been	**Critical**

(Continued)

		more ill and therefore at higher risk of death.	
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: 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	—

(Continued)

Supportive therapy	No	—	

Bias domain	Signalling questions	Comments	Risk of bias judgement
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	Not reported. All participants had completed induction treatment for histoplasmosis before study started. Successful induction determined clinically. Fungal cultures not performed in all patients to confirm success of induction.	—	—	—
Severity of HIV	No measured variable reported.	—	—	—

(Continued)

Comorbidities and comedications	Multiple drug regimens used prior to intervention. HIV management not 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	**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**

(Continued)

				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	**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	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**

(Continued)

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	**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**

(Continued)

			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	—	—

(Continued)

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	**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 fail-**

(Continued)

				ure 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. Other cases were defined as 'non severe'.	No	'Non-severe' included a wide range of severity.	—
Severity of HIV	CD4 count	No	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**

(Continued)

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**

Study: Goldman 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	Evidence of histoplasmosis infection AND remission with antigen concentrations < 4.1 units and negative blood culture.	No	Yes	—
Severity of HIV	CD4 – required to have > 150 cells/μL for study entry.	No	Yes	—
Comorbidities and comedications	Required to have received both antifungal and ART treatment for ≥ 12 months prior to starting trial.	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?**	

(Continued)

ART at time of PDH diagnosis	All participants were required to be on ART at time of initiation into trial.	—
Supportive therapy	Not reported	—

Bias domain	Signalling questions	Comments	Risk of bias judgement
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**
Bias in selection of reported result	7.1–7.3	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 comedications	Not reported	No	—	—

(Continued)

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 comedications	Not reported	No	No	—

(Continued)

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	7.1–7.3	—	—
Overall bias			**CRITICAL**

Study: McKinsey 1989. Outcome: r**elapse 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 comedications	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?

(Continued)

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	—	—
Bias in selection of reported result	7.1–7.3	—	—
Overall bias			**Critical**

Study: ACTG084, 1992.**O**utcome: 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 favour 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	—

(Continued)

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	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	6.1–6.4	Relapse was determined by clinical assessment, Histoplasma c. antigen levels in urine and serum and blood cultures at predetermined intervals.	**Low**
Bias in selection of reported result	7.1–7.3	Reported results are consistent with preregistered protocol.	**Low**
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	No	Yes	—

(Continued)

	parameters including Histoplasma capsulatum antigen in blood or urine.			
Severity of HIV	CD4	No	Yes	—
Comorbidities and comedications	Comorbidities and comedications not clearly reported. Exclusions included various medications, allergies, adrenal insufficiency, and pregnancy.	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. Number of participants on ART at baseline was reported (33%).	—
Supportive therapy	No.	—

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 protocol (higher doses of FCN). Severity and management of HIV was not reported or controlled with appropriate statistical methods.	**Serious**
Bias in participant selection	2.1–2.5	Selection into the maintenance arm of the study was related to the effect of the intervention in the induction phase.	**Serious**
Bias in classification of intervention	3.1–3.3	Intervention was well defined based on information collected at the time of intervention.	**Low**
Bias due to deviations from intended intervention	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.	**No Information**
Bias due to missing data	5.1–5.5	Some missing data in outcome measurement.	**No information**
Bias in measurement of outcomes	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.	**Low**

(Continued)

Bias in selection of reported result	7.1–7.3	Results correspond to intended outcomes. Analysis restriction to those treated per the revised protocol was not predetermined.	**Moderate**
Overall bias			**Serious**

Study: ACTG120, 1992 **. O**utcome: relapse of histoplasmosis – 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 comedications	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/μL. CD4 count at baseline of maintenance phase was not reported.	A2—
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

(Continued)

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**
Severity of PDH	Defined – severe disease excluded.	No	Yes	—
Severity of HIV	CD4	No	No. Only baseline reported	—
Comorbidities and comedications	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?**	

(Continued)

ART at time of PDH diagnosis	No. Report 35/59 using ART at baseline. No further data provided on HIV management.	—
Supportive therapy	Those requiring intensive supportive therapy were excluded.	—

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

(Continued)

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 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
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**

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 comedications	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	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	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

(Continued)

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**

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. lAmB 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.	—

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 lAmB 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 intervention	3.1–3.3	Detailed information on type, dose, and timing of interventions not reported.	No information
Bias due to deviations from intended intervention	4.1–4.6	Deviations are likely to be consistent with usual practice.	Low
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 result	7.1–7.3	Reported results correspond to all intended outcomes.	Low
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; lAmB: 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

(Continued)

Botero Aguirre 2015	Cochrane review, robust methods.	lAmB 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.	lAmB 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.

AmB: amphotericin B; ART: antiretroviral therapy; FCN: fluconazole; HAART: highly active antiretroviral therapy; ITRA: itraconazole; lAmB: liposomal amphotericin B; PDH: progressive disseminated 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
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.

(Continued)

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.
Lewin 1995	Case report.
Machado 1991	Case series of 6 people living with HIV with cutaneous-mucosal involvement of histoplasmosis.
Majluf-Cruz 1993	Case series of 3 cases with haemophagocytic syndrome associated with histoplasmosis and AIDS.
Marianelli 2014	Case report of IRIS in people living with HIV with histoplasmosis osteomyelitis.
Mashayekhi 2016	Renal transplant recipients with histoplasmosis.
Mazumder 2007	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.
Moazeni 2009	Clinical overview of OIs in people living with HIV and AIDS.
Murphy 2015	Case series of 3 participants highlighting difficulties managing PDH in resource-limited settings where lAmB and ITRA are not readily available.
Negroni 1990	Case series. Provided information on outcomes by treatment regimen.
Negroni 1992	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.
Neubauer 1992	Case series of 23 patients with AIDS and PDH. 21/23 patients treated with AmB therapy; formulation not specified.
Oliveira 2007	Case series of 21 patients with PDH and AIDS.
Pamnani 2009	Case series of 4 patients with PDH. 2 were people living with HIV.
Restrepo 2007	Case series. 6 patients. 3 were people living with HIV and PDH.
Reyes 2003	Case series. 3 patients with AIDS and cutaneous manifestations of histoplasmosis.
Scharfstein 1997	Cost-effectiveness modelling for FCN used as prophylaxis for AIDS-related systemic fungal infections.
Townsend 2015	Case series of histoplasmosis-induced haemophagocytic syndrome.
Vantilcke 2014	Case series. PDH found to be the most common febrile OI in Western French Guiana.
Wheat 2006	Susceptibility testing on paired isolates from patients with AIDS who failed on treatment with FCN for histoplasmosis.
Wheat 2007	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; HIVMA: HIV Medicine Association; IRIS: immune reconstitution inflammatory syndrome; ITRA: itraconazole; IV: intravenous; lAmB: liposomal amphotericin B; MIC: minimal inhibitory concentration; NIH: National Institutes of Health; OI: opportunist 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.

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Internal sources

- Liverpool School of Tropical Medicine, UK

External sources

- Department for International Development, UK

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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.