# WHO GUIDELINE

for the treatment of visceral leishmaniasis in HIV co-infected patients in East Africa and South-East Asia

## WEB ANNEX A.

## A systematic review on the treatment of visceral leishmaniasis in HIV-Leishmania co-infected persons in East Africa and South-East Asia

Cochrane Response

World Health Organization

# A systematic review on the treatment of visceral leishmaniasis in HIV-Leishmania co-infected persons in East Africa and South-East Asia

Cochrane Response

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# Contents

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# Abbreviations

| | |
|---|---|
| AE | Adverse event |
| AmB | Amphotericin B |
| ART | Antiretroviral therapy |
| ATT | Anti-tuberculosis therapy |
| BMBF | The Federal Ministry of Education and Research, Germany |
| CI | Confidence interval |
| DGIS | Dutch Ministry of Foreign Affairs |
| DNDi | The Drugs for Neglected Diseases initiative |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HIV | Human immunodeficiency virus |
| HR | Hazard ratio |
| ITT | Intention to treat |
| MSF | Médecins Sans Frontières |
| RCT | Randomised controlled trial |
| RMRI | Rajendra Memorial Research Institute of Medical Sciences |
| ROBINS-I | Cochrane Risk Of Bias In Non-randomized Studies - of Interventions |
| RD | Risk difference |
| RR | Risk ratio |
| SAE | Serious adverse event |
| SDC | Swiss Agency for Development and Cooperation |
| TB | Tuberculosis |
| VL | Visceral leishmaniasis |
| WHO | World Health Organisation |

# Executive summary

## Objective

The primary objective of this systematic review was to evaluate the efficacy and safety of a combination therapy of intravenous liposomal amphotericin B and oral miltefosine compared with monotherapy of intravenous liposomal amphotericin B for treating people with visceral leishmaniasis (caused by *L. donovani*) and HIV coinfection in East Africa and South-East Asia. The secondary objective was to evaluate the efficacy and safety of secondary prophylaxis compared with no secondary prophylaxis for preventing relapse in people with visceral leishmaniasis and HIV coinfection following the first episode of visceral leishmaniasis in the same settings. In addition, we also searched for evidence on contextual factors (preferences and values, resource use, equity, acceptability, and feasibility) for the combination therapy of intravenous liposomal amphotericin B and oral miltefosine that may help to inform decision making.

## Methods

For the systematic review of efficacy and safety, we included studies conducted in people with visceral leishmaniasis (VL) and HIV coinfection that compared combination therapy of intravenous liposomal amphotericin B and oral miltefosine with monotherapy of intravenous liposomal amphotericin B; for the evaluation of secondary prophylaxis we included studies conducted in people with HIV after initial cure of a VL episode that compared secondary prophylaxis to no secondary prophylaxis. We included only studies based in East Africa and South-East Asia, where *L. donovani* infection is endemic.

For the information on contextual factors (preferences and values, resource use, equity, acceptability, and feasibility) we included studies of any design, except for case reports, that reported qualitative or quantitative information on any of these factors.

We searched electronic databases (The Cochrane Infectious Diseases Group Specialized Register, the Cochrane Central Register of Controlled Trials, Medline, and Embase) and clinical trial registries (Clinicaltrials.gov, ISRCTN, and the WHO Trials Registry) on 1st February 2020 and also received unpublished data from trial authors through the WHO. For the evaluation of secondary prophylaxis versus no secondary prophylaxis (added in August 2020), in addition to the above search we screened a list of selected studies provided by the WHO, and reference lists of included studies.

Two reviewers independently assessed trial eligibility, risk of bias and extracted data. In case of disagreement a third reviewer was consulted.

Results were summarised in GRADE summary of findings tables where the certainty of evidence for each outcome was assessed according to established methodology. Data from RCTs started at high quality, but we downgraded this to moderate, low or very low if there were serious or very serious limitations in the following domains: limitations in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision, or publication bias.

## Results

After removal of duplicates 887 references were screened. Title and abstract screening eliminated 729 references and full-text screening eliminated another 149 references. Five studies (from 9

references) were included in the qualitative synthesis, and three studies were included in the quantitative synthesis.

## Main findings

The certainty of the evidence for all outcomes ranged from low to very low. This means that our confidence in the effect estimates ranges from limited to very little confidence and that the true effect may be or is likely to be substantially different from the estimate of the effect. The main reasons for downgrading were methodological limitations and imprecision.

### Treatment

We identified two randomised studies that provided relevant data on the efficacy and safety of the combination therapy compared with monotherapy for the treatment of visceral leishmaniasis in people with VL-HIV coinfection. One study was based in two centres in Ethiopia and the other was based in a single centre in India.

The evidence is very uncertain about the effect of a combination of liposomal amphotericin B plus miltefosine compared with liposomal amphotericin B monotherapy on mortality, clinical cure, relapse, and relapse-free survival. There was little to no difference between combination therapy and monotherapy on adverse events, but the evidence is very uncertain.

### Secondary prophylaxis

We identified one comparative retrospective cohort from India that reported on the efficacy of secondary prophylaxis with liposomal amphotericin B or amphotericin B deoxycholate compared with no secondary prophylaxis in 53 VL-HIV coinfected patients following initial cure of VL. The results suggest there may be a benefit of secondary prophylaxis compared to no secondary prophylaxis, but the evidence is very uncertain. Additionally, two non-comparative prospective cohort studies from Ethiopia provided evidence on pentamidine as secondary prophylaxis following initial cure of VL, but the evidence is also very uncertain.

### Contextual factors

We did not identify any qualitative studies on contextual factors for the combination therapy of liposomal amphotericin B and oral miltefosine, or secondary prophylaxis to prevent relapse. Where possible, we extracted relevant contextual information from study characteristics of the five included studies, however data was limited. No study reported on intervention effects stratified by gender or age. No data is available on efficacy or safety of these interventions for women of child-bearing potential, pregnant, or breastfeeding women.

## Conclusions

It is difficult to draw overall conclusions on the efficacy and safety of primary treatment and secondary prophylaxis of visceral leishmaniasis (caused by *L. donovani)* in people with VL-HIV coinfection in East Africa and South-East Asia due to the limited data available. The evidence was very uncertain for all critical outcomes due to risk of bias in the included studies and imprecision.

Better quality, larger trials conducted in people with VL-HIV coinfection are required. Research into the values and preferences of patients with regard to these interventions is also needed.

# 1 Scope and purpose of the systematic review

The Leishmaniases are a group of parasitic diseases caused by Leishmania protozoan parasites and are transmitted by the bites of female sand flies. It is one of the neglected tropical diseases affecting the most vulnerable communities and is associated with malnutrition and factors affecting population displacement and social determinants of health. Over 1 billion people residing in these endemic areas are at risk of infection. Three major forms of the disease are prevalent- visceral, the most severe form; cutaneous, the most common form; and mucocutaneous, the most destructive form. Leishmaniasis is endemic in over 94 countries and territories across Africa, Asia, the Americas, and Europe.

The World Health Organization (WHO) estimates 700,000 to 1 million new cases of leishmaniasis annually worldwide and 26,000–65,000 deaths (1). The visceral form (kala-azar or visceral leishmaniasis) is the second most common parasitic killer disease after malaria and is fatal if it remains untreated. Each year, an estimated 50,000–90,000 new cases occur worldwide out of which only 25-45% are reported to the WHO (2). In 2017 more than 95% of the visceral leishmaniasis cases occurred in 9 countries - Bangladesh, Brazil, China, Ethiopia, India, Nepal, Somalia, South Sudan, and Sudan.

Visceral leishmaniasis (VL) is caused by parasites of the *L. donovani* and *L. infantum* complex. Malnutrition and immune suppression, notably HIV infection, predispose to clinical disease. VL may be endemic, sporadic or epidemic, with different clinical presentations in each situation. *L. donovani* infection is endemic in South-East Asia and East Africa where transmission is anthroponotic (transmissible from humans to vectors to humans) with humans as reservoir, whereas *L. infantum* is prevalent in southern Europe, North Africa and West-Central Asia and Americas where transmission is mostly zoonotic. VL is an outbreak prone disease and has caused explosive epidemics leading to huge number of fatalities in the past.

In VL infection, reticuloendothelial hyperplasia results which affects the spleen, the liver, the mucosa of small intestine, the bone marrow, the lymph nodes, resulting into heavy infiltration with parasites. The lifespan of leukocytes and erythrocytes is reduced, causing granulocytopenia and anaemia. Liver functions are altered in later stages leading to hypoalbuminemia and decrease in prothrombin production. Depletion of prothrombin along with thrombocytopenia results into severe mucosal haemorrhage. In many cases diarrhoea occurs because of intestinal parasitisation and ulceration or secondary enteritis, which results in loss of fluid and malabsorption. Hypoalbuminemia is associated with oedema and other features of malnutrition. In advanced states, intercurrent infections are very common, especially pneumonia, dysentery, and tuberculosis, and are common causes of death. There is a state of immunosuppression which is characteristic of VL and is compounded by other conditions causing immune suppression such as human immunodeficiency virus (HIV) infection.

HIV infection is a global challenge with 36.9 million (31.1 million-43.9 million) people living with HIV with occurrence of 1.8 million (1.4 million-2.4 million) new infections in 2017 (3). More than 90% of the HIV infected population live in the areas endemic for leishmaniasis infection.

The HIV/AIDS pandemic has modified the natural history of leishmaniasis. The first case of leishmaniasis infected with HIV was reported in 1985 in European Mediterranean countries. Since then 35 countries (more than one third of endemic countries) have reported coinfections due to expansion and considerable overlap of two diseases. Five to six percent of the total cases of VL–HIV coinfection globally occur in the Mediterranean area. In some areas of Ethiopia, 35% of all leishmaniasis patients are coinfected with HIV, and the trend is spreading to neighbouring countries such as Sudan. In India, the prevalence of VL–HIV coinfection has increased from 0.88% in 2000 to 3.75% in total reported cases to the Ministry of Health in 2018. In Brazil in Latin America, the incidence of coinfection has increased from 0.7% in 2001 to 8.5% in 2012 (1).

HIV and leishmaniasis are mutually reinforcing conditions with a detrimental effect on each other. HIV infection has multitude effects on leishmaniasis by increasing the risk of developing VL by 100 to 2,320 times in endemic areas. VL in coinfected patients cannot be cured, and those with CD4+ counts <200 cells/µl typically relapse more and more frequently until they become non-responsive to all medicines used. These patients harbour very heavy parasite loads and are proven to be highly infective to sand flies, thus contributing in spreading the infection.

In general, treatment of VL faces limited options of antileishmanial drugs. These drugs are not readily available due to price, lack of registration, or toxicity. Moreover, there are single manufacturers for many of these antileishmanial drugs. Since there is no vaccine available against prevention of leishmania infection, it is more challenging to control the disease by ensuring access to diagnostic and treatment services. These VL treatment regimens depend on the species of leishmania parasite and eco-epidemiological regions, therefore WHO recommendations also vary accordingly(4).

The treatment of leishmaniasis in HIV infected patients is a special condition affected by reduced therapeutic options. Several factors affect accessibility of drugs such as prices, lack of registration, toxicity, or ineffectiveness, or because drugs have not yet been tested in these patients. Most of the evidence comes from European Mediterranean countries where *L. infantum* is causing the disease. *L. infantum* has a different virulence and drug susceptibilities in comparison to *L. donovani* in Africa or Asia where the treatment efficacy has not been as strong. Only few studies have been conducted on the efficacy of treatment outside the Mediterranean area, therefore optimal treatment regimens have yet to be established.

Currently, the standard therapy for treatment of VL in coinfected patients, as stated in a WHO expert committee report on the control of leishmaniasis (4) includes using lipid formulations of amphotericin B intravenously at a dose of 3-5 mg/kg daily or intermittently for 10 doses (days 1-5, 10, 17, 24, 31 and 38) up to a total dose of 40 mg/kg (4). However, recent trials have suggested that a combination of intravenous amphotericin B and oral miltefosine may be more effective. Hence, there is a need to revise the WHO recommended treatment regimen for East African and South-East Asian settings, which presently harbour the highest prevalence of VL-HIV coinfection burden.

The aim of this systematic review is to provide evidence to the guideline development group (GDG) of the WHO Department of Control of Neglected Tropical Diseases to update recommendations on the use of combination therapy for VL in VL-HIV coinfected patients.

To address this, we aimed to answer the following questions:

1. What is the efficacy and safety of combination therapy of intravenous (IV) liposomal amphotericin B and oral miltefosine in treating VL (caused by *L. donovani*) in VL-HIV coinfected

patients compared with intravenous liposomal amphotericin B monotherapy in East Africa and South-East Asia?

2. What is the efficacy and safety of secondary prophylaxis compared with no secondary prophylaxis, after the first episode of VL (caused by *L. donovani*) to prevent relapses in VL-HIV coinfected patients in East Africa and South-East Asia? (Added to the systematic review in August 2020)

# 2 Methods

## 2.1. Objectives

- To evaluate the efficacy and safety of combination therapy of intravenous liposomal amphotericin B and oral miltefosine for treating people with visceral leishmaniasis and HIV coinfection compared with intravenous liposomal amphotericin B monotherapy in East Africa and South-East Asia (PICO 1).
- To evaluate the efficacy and safety of secondary prophylaxis for preventing relapse compared with no secondary prophylaxis in people with visceral leishmaniasis and HIV coinfection following the first episode of visceral leishmaniasis in East Africa and South-East Asia. (PICO 2)
- To identify the evidence on contextual factors (preferences and values, resource use, equity, acceptability, and feasibility) on the combination therapy of intravenous liposomal amphotericin B and oral miltefosine compared with intravenous liposomal amphotericin B monotherapy and for secondary prophylaxis to prevent relapse compared with no secondary prophylaxis.

## 2.2. Inclusion criteria

### 2.2.1. Types of studies

All comparative study designs were considered for inclusion in the systematic review of efficacy and safety, including randomised controlled trials (RCTs), non-RCTs, controlled before-and-after studies, interrupted time-series studies, and case-control studies. Observational studies with no control group, such as single arm cohorts and case-series were not included in the main analysis, but the results have been tabulated for completeness. Case reports of five participants or fewer were excluded.

For the information on contextual factors (preferences and values, resource use, equity, acceptability, and feasibility), we included studies of any design, except for case reports, which reported qualitative or quantitative information on any of the domains in the framework.

We included published articles, conference abstracts, and unpublished data where available. Relevant unpublished data was provided by triallists through the WHO. We included studies irrespective of their publication status and language of publication.

### 2.2.2. Population

#### PICO 1. Treatment

People with a diagnosis of HIV and coinfection with visceral leishmaniasis of all age groups.

#### PICO 2. Secondary Prophylaxis

People with a diagnosis of HIV of all age groups, following an episode of visceral leishmaniasis.

Studies with indirect populations, such as HIV-negative people with VL, healthy populations, or populations in other settings (settings other than East Africa and South East Asia) were excluded.

### 2.2.3. Intervention

#### PICO 1. Treatment

- **East Africa:** combination therapy of IV liposomal amphotericin B (up to 30 mg/kg @5 mg/kg on days 1, 3, 5, 7, 9 and 11) and oral miltefosine (100 mg/day for 28 days) to treat visceral leishmaniasis in HIV positive patients.
- **South-East Asia:** combination therapy of IV liposomal amphotericin B (up to 30 mg/kg @5 mg/kg on days 1, 3, 5, 7, 9 and 11) and oral miltefosine (100 mg/day for 14 days) to treat visceral leishmaniasis in HIV positive patients.

#### PICO 2. Secondary prophylaxis

**East Africa and South-East Asia**: Any secondary prophylaxis to prevent relapse of visceral leishmaniasis in VL-HIV coinfected people.

Details of any co-interventions (e.g. antiretroviral therapy) reported in participants receiving the intervention were also extracted and reported.

### 2.2.4. Comparison

#### PICO 1. Treatment

**East Africa and South-East Asia**: monotherapy of IV liposomal amphotericin B at a dose of 3-5 mg/kg daily or intermittently for 10 doses (days 1-5, 10, 17, 24, 31 and 38) up to a total dose of 40 mg/kg.

#### PICO 2. Secondary prophylaxis

**East Africa and South-East Asia**: no secondary prophylaxis intervention.

### 2.2.5. Outcomes

For the systematic review of efficacy and safety, the following outcomes were assessed:

- All-cause mortality – at the longest timepoint reported by the included studies

- Clinical cure – at the time of completion of the treatment and at 6 months after completion of treatment
- Relapse – defined as recurrence of the disease any time after successful treatment (clinical cure). All patients reporting recurrence of the disease signs and symptoms should be confirmed by parasitological diagnosis at appropriate health facilities.
- Relapse-free survival, i.e., alive and disease-free (defined as absence of signs and symptoms of VL or if symptomatic, a negative parasitological assessment by tissue aspirate). This outcome was added post hoc because some studies that reported on relapse-free survival did not report on relapse, and because some studies had relapse-free survival as the primary outcome.
- Treatment adherence – since co-infected patients receive inpatient treatment, adherence will be recorded as those who fail to complete the treatment for various reasons (e.g. death, adverse effects, left against medical advice or unknown reasons).
- Adverse events and serious adverse events – and any serious adverse events related to treatment
- Follow-up of patients – withdrawals for any reason from the studies
- Patient satisfaction

Visceral leishmaniasis is treated by antileishmanial medicines whereas HIV infection is treated by antiretroviral therapy. Increased CD4 counts after antiretroviral therapy (i.e. regain in immunity) may therefore improve patient outcomes (i.e. delay in relapse). Therefore, relapse is considered the most important indicator of both efficacy of treatment and improved immunity.

## 2.3. Search strategy

### 2.3.1. Electronic Search

#### PICO 1. Treatment

An electronic search was conducted in the following databases: The Cochrane Infectious Diseases Group Specialized Register, the Cochrane Central Register of Controlled Trials, Medline, and Embase on 1st February 2020. No date, publication status (published, unpublished, in press, and in progress) or language restrictions were used. In addition, we searched ClinicalTrials.gov, ISRCTN, and the WHO Trials Registry for ongoing studies.

See search strategy in Appendix 1.

#### PICO 2. Secondary prophylaxis

PICO 2 was added to this systematic review in August 2020, after completion of the systematic review for PICO 1 in March 2020. A systematic search was not carried out for PICO 2. Instead, we re-screened the search from PICO 1, screened a list of selected studies provided by the WHO, and screened reference lists of included studies.

### 2.3.2. Searching other resources

#### PICO 1. Treatment

Unpublished data from a recently completed but unpublished study in South Asia (India 2019, CTRI/2015/05/005807) was requested by the WHO and used in this report.

The reference lists of included studies and any systematic reviews identified were screened for relevant studies. Researchers and organisations working in the field were contacted by the WHO for any relevant studies, which were subsequently screened. We also searched proceedings of relevant scientific conferences over the past five years, such as the World Congress of Leishmaniasis 2017, and reports of pertinent WHO partners and Ministry of Health meetings.

## 2.4. Selection of studies

We used DistillerSR (Evidence Partners, Ottawa, Canada) for reference management and screening. Two review authors independently screened all citations and abstracts identified by the search. We obtained full reports for potentially eligible studies and these were independently screened by two review authors. We resolved any disagreements by consensus or by involving a third reviewer.

## 2.5. Data extraction

One reviewer extracted data using pre-tested data extraction forms. A second reviewer cross-checked the extracted data for accuracy. We resolved any disagreements about data extraction by referring to the study report and through discussion. For each included study, data on study methodology, patient characteristics (e.g. clinical and laboratory measures), interventions, and outcome data were extracted.

We also extracted all available data on management of adverse events, screening for pregnancy before start of treatment, and contraception use during the post-treatment period (at least for three months after the completion of treatment) for coinfected females.

## 2.6. Assessment of risk of bias in included studies

For RCTs or quasi-RCTs, we used the Cochrane Risk of Bias tool for RCTs to assess risk of bias(5).

For observational studies with a control group we used the Cochrane Risk of Bias In Non-randomized Studies - of Interventions (ROBINS-I)(6).

We did not assess risk of bias for observational studies with no control group, such as single arm cohorts and case-series.

One reviewer independently assessed the risk of bias of each included study, and a second reviewer cross-checked the assessment. Disagreements were resolved by referring to the study report and through discussion.

The results of the risk of bias assessments are summarised and provide an evaluation of the overall quality of the included studies. These assessments contribute to the GRADE rating of the evidence at the outcome level.

## 2.7. Data analysis

For comparative studies, we have presented data as proportions separately for each study arm and calculated risk ratios (RR) with their respective 95% confidence intervals (CI). We have pooled data in meta-analysis where possible and have also presented stratified data by setting (East Africa or South East Asia).

From observational studies we have prioritised data adjusted for confounding factors and have also presented proportions from each arm and calculated RRs with CIs for outcomes where adjusted data were not available.

## 2.8. Summarizing and interpreting results

### 2.8.1. GRADE

We used the GRADE approach to interpret findings and create a 'Summary of Findings' table following the GRADE handbook (7). The table provides the effect estimate and the associated certainty of evidence for each outcome of interest.

Certainty of evidence from RCTs and non-randomised studies starts at high certainty, but may be downgraded to moderate, low or very low for the following reasons: limitations in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision, or publication bias. To assess publication bias, we planned to test for asymmetry in a funnel plot if there were at least 10 studies in a meta-analysis, however this was not the case.

### 2.8.2. Evidence to decision framework

In order to facilitate moving from empirical evidence to a recommendation during the panel meeting, we collected information for the GRADE Evidence to Decision (EtD) framework directly in GRADEpro (8). This framework includes a synthesis of the available evidence in the following domains as they relate to the review questions:

- Desirable and undesirable effects and certainty of the evidence presented in the effects of interventions section of the review.
- Preferences and values.
- Resource use, including workload of healthcare stuff, cost effectiveness.
- Equity. We used the PROGRESS-plus framework (9) to assess equity in included studies. PROGRESS refers to: Place of residence; Race/ethnicity/culture/language; Occupation; Gender/sex; Religion; Education; Socioeconomic status; Social capital. Plus refers to:
    - personal characteristics associated with discrimination (e.g. age, disability)

- features of relationships (e.g. with parents and family)
- time-dependent relationships (e.g. leaving the hospital, respite care, other instances where a person may be temporarily at a disadvantage)

- Acceptability.
- Feasibility.

We identified all studies with potentially relevant information (qualitative or quantitative) to populate the above domains. This information was extracted and presented in the framework and will be supplemented by a stakeholder survey. All information presented for the above domains is directly relevant to participants with VL-HIV coinfection in the relevant settings (East Africa and South East Asia). Indirect evidence was not included.

# 3 Results

## 3.1. Results of the search

The search of databases was performed on 25th August 2019 and updated on 1st February 2020. In August 2020 a selected list of 10 references provided by the WHO was also screened for PICO 2. A total of 887 references were identified from the searches after de-duplication and were independently screened by two reviewers. Of these, 158 were considered relevant and the full text was screened for inclusion. After screening the full texts, 149 references were excluded, and nine references (five studies) were included in this review. See PRISMA flow chart in Appendix 2.

Of the excluded studies (Appendix 3), the most common reason for exclusion was that the study did not report on the intervention (i.e. combination therapy) or the comparison of interest (n = 108), twenty-three references were excluded because the study design was irrelevant (mostly narrative reviews or commentaries), six studies were excluded because they did not include participants with VL-HIV coinfection, six studies on secondary prophylaxis were excluded as they were from ineligible settings, and there were six systematic reviews. The included studies of these systematic reviews were screened for relevance but did not result in any further included studies.

We did not identify any relevant ongoing trials.

## 3.2. Included studies

### 3.2.1. Efficacy and safety

#### PICO 1. Treatment

Two randomised studies provided relevant data on the efficacy and safety of combination therapy compared with monotherapy. The characteristics of the two included studies are presented in Table 1.

One study was based in two centres in Ethiopia (Ethiopia 2019) and the other was based in a single centre in India (India 2019).

Both were randomised studies, which were designed to show the efficacy and safety of both the combination therapy and monotherapy.

The study from Ethiopia had a sequential design with stopping rules and interim analyses after every 10 participants. In the monotherapy arm of this trial, recruitment was stopped after the first 10 participants reached day 29 (total n = 19), while recruitment continued in the combination therapy arm. The combination therapy arm stopped recruitment after the first 20 participants reached day 29 (total n = 39).

The study from India recruited a total of 150 participants, 75 in each arm.

In addition, four single arm cohort studies evaluating combination therapy were identified. These were not included in the review, however, a summary of the results from these studies is reported in Appendix 7.

**Table 1. Characteristics of included studies for PICO 1 efficacy and safety outcomes**

| **Study name, location** | **Ethiopia 2019**<br>Two facilities in Ethiopia, the teaching hospital of the University of Gondar, and the Abdurafi Health Centre | **India 2019**<br>Hospital based study, Rajendra Memorial Research Institute (RMRIMS), Patna, Bihar state, India |
|---|---|---|
| **Methods, study dates** | Randomized, open-label trial. Sequential design with stopping rules and interim analyses by an independent data safety monitoring board after every 10 patients<br>Recruitment: 14 August 2014 and 18 August 2015 | Randomized, parallel arm, open-label, clinical trial<br>Recruitment: January 2017 to April 2018 |
| **N randomized, age, gender** | N = 59; 20 in monotherapy; 39 in combination therapy arm<br>Age: 21 to 51 years<br>Gender: 57 males, 1 female | N = 150; 75 in monotherapy arm; 75 in combination therapy arm<br>Age: 18 to 64 years<br>Gender: 118 males, 32 females |
| **Diagnosis of leishmaniasis** | Visual parasite confirmation by microscopy in tissue aspirate (spleen aspirate was the preferred methodology, or bone marrow aspirate in case of contra-indication). Patients were eligible regardless of whether this was the first episode of VL (primary case) or whether it was a relapse case with single or multiple relapses. | Visual parasite confirmation through bone marrow or spleen aspiration. |
| **Diagnosis of HIV** | HIV status determined by two rapid tests followed by a third confirmatory test in case of discrepancy. Within the trial, it was reconfirmed using an enzyme immunoassay (ImmunoComb II HIV 1&2 BiSpot, Orgenics Ltd.) | Confirmed HIV positive test (two rapid diagnostics tests as per National Programme guidelines, Western Blot for any discrepancy) |
| **Pregnancy** | Pregnant women were excluded from the trial. Pregnancies that occurred during the | Pregnancy test was conducted in all female patents under the age of 50 at baseline. |

| | | |
|---|---|---|
| | trial were reported as serious adverse events and birth outcomes were assessed. | Pregnant women were excluded from the study and treated with 40mg/kg amphotericin B arm outside the study. |
| **Contraception use** | Women of child-bearing potential (defined as women who have achieved menarche) who are not using an assured method of contraception or are unwilling to use an assured method of contraception for the duration of treatment and four months after were excluded. | Women of child-bearing potential who are not using an assured method of contraception or are unwilling to use an assured method of contraception for the duration of treatment and three months after were excluded. |
| **Intervention** | Liposomal amphotericin B: 30 mg/kg total dose; IV slow infusion of 5 mg/kg on days 1, 3, 5, 7, 9, and 11<br><br>Miltefosine: 50 mg capsule orally twice a day for 28 days | Amphotericin B: 30 mg/kg total dose; IV infusion 5 mg/kg on day 1, 3, 5, 7, 9, 11<br><br>Miltefosine: Oral 100mg in two divided doses (i.e. 2 x 50mg capsules) every day for 14 days. |
| **Comparison** | Liposomal amphotericin B: 40 mg/kg total dose administered by IV infusion of 5 mg/kg on days 1 to 5, 10, 17, and 24 | Liposomal amphotericin B:<br>40 mg/kg total dose administered by IV infusion of 5 mg/kg on day 1-4, 8, 10, 17, 24 |
| **Co-interventions / medications** | At admission, approximately 70% of patients were on antiretroviral treatment (ART). All newly diagnosed HIV patients started ART after completion of the VL treatment, except for one refusal. Three patients changed their ART regimen during the VL treatment. | In this study, unless clinically contra-indicated, all patients started on ART on day 15 during the inpatient stay, and observed on ART until day 29, after which (if Leishmania negative) they were discharged and ART care was continued through their local ART centre. Those who were already on ART continued the same regimen throughout the study unless there was a clinical indication to change.<br><br>Patients who were newly diagnosed with TB infection would commence Anti-tuberculosis therapy (ATT) on day 15 and commence ART on day 30 unless there was a clinical indication to start before or later. |

### PICO 2. Secondary prophylaxis

*Amphotericin B secondary prophylaxis compared with no secondary prophylaxis*

One comparative observational retrospective cohort study provided relevant data on the efficacy and safety of secondary prophylaxis (monthly 1 mg/kg liposomal amphotericin B (n=15), deoxycholate amphotericin B (n=12)) compared with no secondary prophylaxis (n=24) (India 2017).

*Pentamidine secondary prophylaxis (single arm studies only)*

In addition, one single arm study (Ethiopia 2015) and a follow-up study to the Ethiopia 2019 trial (Ethiopia 2019b) assessing pentamidine as secondary prophylaxis were included. Ethiopia 2019b evaluated non-comparative groups, therefore only the arm of study receiving pentamidine was considered relevant and had data included in this review. Patients in this study (n=54) received

pentamidine as secondary prophylaxis based on a CD4 cell count <=200 (n=29), while patients with a CD4 cell count of >200 did not receive any secondary prophylaxis, (n=22).

The characteristics of the three studies included for efficacy and safety outcomes on secondary prophylaxis are presented in Table 2.

**Table 2. Characteristics of included studies for PICO 2 efficacy and safety outcomes**

| Study name, location | Methods, study dates | N included, age, gender | Treatment/ comparison for secondary prophylaxis | Initial treatment regimen and cure |
|---|---|---|---|---|
| **India 2017**<br>Eastern India, Kolkata, India | Comparative retrospective observational cohort study<br>January 2005 to February 2015 | N=51; 27 secondary prophylaxis, 24 no secondary prophylaxis<br>Mean age (SD): 34 (8)<br>41 male, 10 female | Secondary prophylaxis (n = 27) with monthly 1 mg/kg amphotericin B (15 liposomal, 12 deoxycholate)<br>No secondary prophylaxis (n=24) | Liposomal amphotericin B; 26 received amphotericin B deoxycholate |
| **Ethiopia 2015**<br>Northwest Ethiopia | Non-comparative prospective cohort study<br>November 2011 to September 2013 | N=74. Sixty were current VL cases (25 primary and 35 relapsed), while the rest (N=14) were past VL cases<br>Mean age: 32 (range 28-37)<br>71 male, 3 female | Secondary prophylaxis (N=74) with monthly infusions of 4 mg/kg pentamidine-isethionate diluted in normal-saline for 12 months. | Sodium stibogluconate alone or in combination with paromomycin and liposomal amphotericin B alone or in combination with miltefosine. |
| **Ethiopia 2019b**<br>Northwest Ethiopia, two large leishmaniasis treatment centres | Non-comparative prospective cohort study<br>14th August 2014 - 12th August 2016 | N=29 with CD4 cell counts below 200/µL at the end of VL treatment<br>Age (median): 33<br>28 male, 1 female | Secondary prophylaxis with pentamidine starting one month after parasitological cure | Amphotericin B total dose of 40 mg/kg or amphotericin B total dose of 30 mg/kg +miltefosine 100mg/day/28 days. |

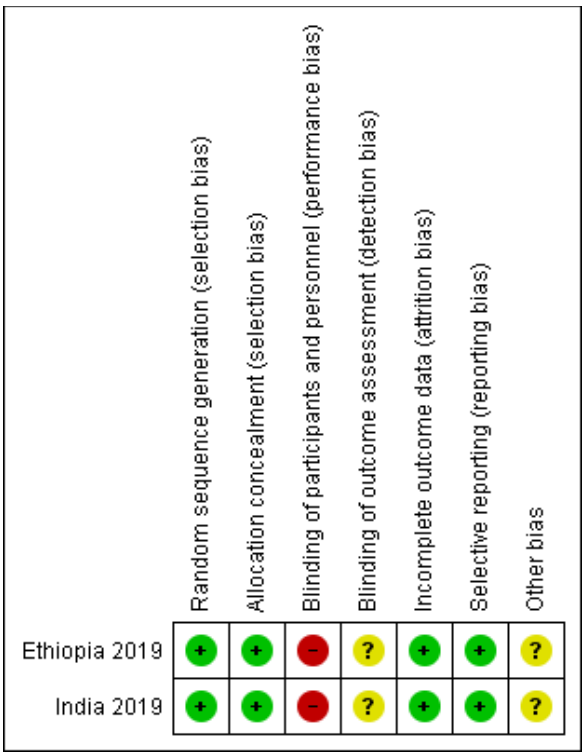
### 3.2.2. Contextual factors

We did not identify any eligible studies that provided relevant information for the third review question on preferences and values, resource use, equity, feasibility, and acceptability. We have extracted relevant information from the participant characteristics of the included studies (for PICOs 1 and 2) in this review and this is presented in section 3.5.

## 3.3. Risk of bias in included studies

See Figure 1 for an overall summary of the risk of bias of the included randomised studies and Appendix 4 for full assessments of the risk of bias in each included study.

**Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item**




One observational study with a control group was identified for PICO 2 (India 2017). See Table 3 below for the summary and Appendix 4 for full assessments of the risk of bias.

**Table 3. Risk of bias summary: review authors' judgements about each ROBINS-I risk of bias item for included comparative observational study**

| **Domain** | | **Assessment** |
|---|---|---|
| **India 2017** | | |
| Bias due to confounding | Mortality, adjusted estimate | Moderate |
| | All other outcomes | Serious |
| Selection bias | | Serious |
| Bias in classification of intervention | | Low |
| Bias due to departure from intervention | | No information |
| Bias due to missing data | | Low |
| Bias in measurement of outcomes | | Low |
| Bias in selection of the reported result | | Moderate |

## 3.4. Certainty of the evidence

We assessed the certainty of the evidence for each relevant outcome using the GRADE approach and presented our findings in a 'Summary of findings' table.

#### PICO 1. Treatment

Two randomised studies Ethiopia (Ethiopia 2019) and India (India 2019) were included in this comparison.

The certainty of the evidence for all outcomes ranged from low to very low. This means that our confidence in the effect estimate ranges from limited to very little confidence and that the true effect may be or is likely to be substantially different from the estimate of the effect.

The main reasons for downgrading the certainty of the evidence were limitations in study design and imprecision. Both trials were open label (i.e. unblinded), and they were not sufficiently powered to detect differences between group. The studies reported few events, and for several outcomes the confidence interval incorporated no effect, a potential benefit, and a potential harm. The trials included people presenting with an initial case of VL as well as people who had relapsed, and data is not reported separately for these populations.

#### PICO 2. Secondary prophylaxis

One comparative retrospective cohort from India (India 2017) and two non-comparative prospective cohort studies (Ethiopia 2019b, Ethiopia 2015) were included in this comparison.

The overall certainty of the evidence for all outcomes was assessed as very low. This means that our confidence in the effect estimate is very low and that the true effect is likely to be substantially different from the estimate of the effect.

The main reasons for downgrading the certainty of the evidence were limitations with study design, as these were non-randomized studies (or non-comparative so did not have a control group) and they did not adjust for confounding between groups. In addition, the studies included a small sample size, and selection bias was detected.

## 3.5. Effect of interventions: efficacy and safety

### 3.5.1. PICO 1. Treatment

See Summary of Findings table 1 in which we present the overall certainty of the evidence for each outcome and Appendix 5 for main analyses of PICO 1. See also Summary of Findings tables 3 and 4 in Appendix 6 for additional subgroup analyses by setting.

Data from two randomised studies reported on the efficacy of combination therapy compared with monotherapy (Ethiopia 2019, India 2019).

### All-cause mortality

Both studies reported on all-cause mortality (Ethiopia 2019, India 2019). There may be little or no difference between combination therapy and monotherapy on all-cause mortality at up to 86 days; however, the evidence is very uncertain (RR 0.66; 95% CI 0.17 to 2.66; 2 RCTs; 209 participants; $I^2$ = 0%; Analysis 1.1).

### Clinical cure

Both trials reported on clinical cure (Ethiopia 2019, India 2019). There may be little or no difference between combination therapy and monotherapy on relapse at day 29; however, the evidence is very uncertain (RR 1.21; 95% CI 0.64 to 2.28; 2 RCTs; 208 participants; $I^2$ = 75%; Analysis 1.2).

At 58-day follow-up, one study (Ethiopia 2019) reported that combination therapy may result in more participants being cured compared with monotherapy (RR 1.77, 95% CI 1.08 to 2.90; 1 RCT; 56 participants; Analysis 1.3; low certainty evidence).

### Relapse

Both trials reported on relapse (Ethiopia 2019, India 2019). There may be little or no difference between combination therapy and monotherapy on relapse at up to 390 days; however, the evidence is very uncertain (RR 1.26; 95% CI 0.49, 3.20); 2 RCTs; 201 participants; $I^2$ = 57%; Analysis 1.4).

Although important heterogeneity was observed between both studies, no differences were observed between the treatment and control groups in either setting (Ethiopia: RR 0.89; 95% CI 0.50 to 1.58; and India: RR 2.25; 95% CI 0.72 to 6.99).

### Relapse-free survival

Both trials reported on relapse-free survival (Ethiopia 2019, India 2019). There may be little or no difference between combination therapy and monotherapy on relapse-free survival at up to 390 days; however, the evidence is very uncertain (RR 1.05; 95% CI 0.92 to 1.21; 2 RCTs; 209 participants; $I^2$ = 0%; Analysis 1.5).

### Treatment adherence

One trial reported on treatment adherence (Ethiopia 2019). The evidence suggests that there may be little or no difference between combination therapy and monotherapy on treatment adherence at 58 days (RR 1.26; 95% CI 0.89 to 1.80; 1 RCT; 58 participants; Analysis 1.6; low certainty evidence).

### Serious adverse events

Both trials reported on serious adverse events (Ethiopia 2019, India 2019). The evidence suggests that there may be little or no difference between combination therapy and monotherapy on the occurrence of serious adverse events at up to 86 days (RR 1.04; 95% CI 0.43 to 2.55; 2 RCTs; 208 participants; $I^2$ = 11%; Analysis 1.7; low certainty evidence).

One study (Ethiopia 2019) reported in detail the serious adverse events. Data from this study shows that 8/39 and 2/19 patients in the combination therapy and monotherapy groups, respectively, experienced serious adverse events.

In the combination therapy group there was one participant with anaemia (grade 4 onset on day 48), which was resolved; one participant with Strongyloidiasis (grade 5 onset on day 61) who died; one participant with anaemia (grade 4 onset on day 10), which was resolved; one participant with anaemia (grade 3 onset on day 3) which was resolved; one participant with post herpetic neuralgia (grade 2 onset on day 10), which was resolved; one participant with toxicity to various agents (grade 5 onset on day 33) died - toxicity was related to sodium stibogluconate and paromomycin administered as rescue treatment and to ART drugs (patient received sequentially zidovudine/lamivudine/nevirapine and tenofovir/lamivudine/nevirapine); one participant with encephalitis (grade 5 onset on day 15) and meningitis (grade 5 onset on day 15) died; and one participant with pulmonary tuberculosis (grade 3 onset on day 20) with unknown outcome.

In the Amphotericin B monotherapy group one participant experienced sepsis (grade 3 onset on day 3), which was resolved; one participant with malnutrition (grade 3 onset on day 30), decubitus ulcer (grade 3 onset on day 38), pneumonia (grade 4 onset on day 39) and sepsis (grade 5 onset on day 39) died.

### Adverse events

One trial reported on adverse events (Ethiopia 2019). The evidence suggests that there may be little or no difference between combination therapy and monotherapy on adverse events at 86 days (RR 1.00; 95% CI 0.92 to 1.08; 1 RCT; 58 participants; Analysis 1.8; low certainty evidence).

See also Appendix 8 for detailed information on the adverse events reported in this trial.

### Follow-up of patients

One trial reported on follow-up of patients (Ethiopia 2019). There may be little or no difference between combination therapy and monotherapy on patients lost to follow-up (RR 1.12; 95% CI 0.88 to 1.43; 1 RCT; 59 participants; Analysis 1.9; low certainty evidence).

### Patient satisfaction

No studies were identified that reported on patient satisfaction with the intervention.

## Summary of Findings (SOF) table 1. Combination therapy of liposomal amphotericin B and oral miltefosine compared with liposomal amphotericin B is East Africa and South East Asia

**Patient or population:** HIV-visceral leishmaniasis coinfection

**Setting**: East Africa and South East Asia

**Intervention**: liposomal amphotericin B (30 mg/kg total dose: IV infusion of 5 mg/kg on days 1, 3, 5, 7, 9, and 11) and Miltefosine (50 mg capsule orally twice a day for 14 days (East Africa) or 28 days (South East Asia)) combination therapy

**Comparison**: liposomal amphotericin B monotherapy (40 mg/kg total dose: IV infusion of 5 mg/kg on day 1-4, 8, 10, 17, 24 (South East Asia) or day 1-5, 10, 17, and 24 (East Africa))

| Outcomes | Setting | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|---|
| | | Risk with monotherapy | Risk with combination therapy | | | | |
| **All-cause mortality follow up: up to 86 days** | Ethiopia and India | 42 per 1,000 | 28 per 1,000 (7 to 112) | **RR 0.66** (0.17 to 2.66) | 209 (2 RCTs) | ⊕◯◯◯ VERY LOW [a,b] | See Analysis 1.1 |
| | | **RD: 14 fewer per 1,000** (35 fewer to 70 more) | | | | | |
| **Clinical cure follow up: up to 29 days** | Ethiopia and India | Study population | | **RR 1.21** (0.64 to 2.28) | 208 (2 RCTs) | ⊕◯◯◯ VERY LOW [a,b,c] | See Analysis 1.2 |
| | | 830 per 1,000 | 1,000 per 1,000 (531 to 1,000) | | | | |
| | | **RD: 174 more per 1,000** (299 fewer to 174 more) | | | | | |
| | | India[1] | | | | | |
| | | 650 per 1,000 | 787 per 1,000 (416 to 1,000) | | | | |
| | | **RD: 137 more per 1,000** (234 fewer to 350 more) | | | | | |
| | | Ethiopia[2] | | | | | |
| | | 950 per 1,000 | 1,000 per 1,000 **(608 to 1,000)** | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | **RD: 50 more per 1,000** (342 fewer to 50 more) | | | | | |
| **Clinical cure follow up: up to 58 days** | Ethiopia | 474 per 1,000 | 832 per 1,000 (512 to 1,000) | **RR 1.77** (1.08 to 2.90) | 56 (1 RCT) | ⊕⊕◯◯ LOW [e,f] | See Analysis 1.3 |
| | | **RD: 358 more per 1,000** (38 more to 526 more) | | | | | |
| **Relapse follow up: up to 390 days** | Ethiopia and India | 141 per 1,000 | 178 per 1,000 (69 to 452) | **RR 1.26** (0.49, 3.20) | 201 (2 RCTs) | ⊕◯◯◯ VERY LOW [a,b,d] | See Analysis 1.4 |
| | | **RD: 37 more per 1,000** (72 fewer to 311 more) | | | | | |
| **Relapse-free survival follow up: up to 390 days** | Ethiopia and India | 726 per 1,000 | 763 per 1,000 (668 to 879) | **RR 1.05** (0.92 to 1.21) | 209 (2 RCTs) | ⊕⊕◯◯ LOW [a,e] | See Analysis 1.5 |
| | | **RD 37 more per 1,000** (58 fewer to 153 more) | | | | | |
| **Treatment adherence** | Ethiopia | 650 per 1,000 | 819 per 1,000 (579 to 1,000) | **RR 1.26** (0.89 to 1.80) | 59 (1 RCT) | ⊕⊕◯◯ LOW [e,f] | See Analysis 1.6 |
| | | **RD 169 more per 1,000** (71 fewer to 350 more) | | | | | |
| **Serious adverse events (any cause) follow up: up to 86 days** | Ethiopia and India | 106 per 1,000 | 111 per 1,000 (46 to 271) | **RR 1.04** (0.43 to 2.55) | 208 (2 RCTs) | ⊕◯◯◯ VERY LOW [a,b] | See Analysis 1.7 |
| | | **RD 5 more per 1,000** (60 fewer to 165 more) | | | | | |
| **Adverse events (any cause) follow up: up to 86 days** | Ethiopia | 1,000 per 1,000 | 1000 per 1,000 (920 to 1000) | **RR 1.00** (0.92 to 1.08) | 58 (1 RCT) | ⊕⊕◯◯ LOW [e,f] | See analysis 1.8 |
| | | **RD: 0 per 1,000** (80 fewer to 0 more) | | | | | |
| **Follow-up of patients** | Ethiopia | 800 per 1,000 | 896 per 1,000 (704 to 1,000) | **RR 1.12** (0.88 to 1.43) | 59 (1 RCT) | ⊕⊕◯◯ LOW [e,f] | See analysis 1.9 |
| | | **RD: 96 more per 1,000** (96 fewer to 200 more) | | | | | |

| | |
|---|---|
| **Patient satisfaction** | No studies were identified that reported on this outcome |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[1] Cure rate for VL-HIV patients is 65% in this setting

[2] Cure rate for VL-HIV patients is 95% in this setting

CI: Confidence interval; RR: Risk ratio; RD: risk difference; RCT: randomised controlled trial

**GRADE Working Group grades of evidence**

**High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low certainty**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Explanations**

a. Downgraded one level for serious risk of bias: due to limitations in the study design and execution.

b. Downgraded two levels for very serious imprecision: few events and wide confidence intervals that encompass no effect, a potential benefit, and a potential harm associated with the intervention.

c. Downgraded one level for serious inconsistency: high heterogeneity ($I^2$ = 75%), although CI are partially overlapping.

d. Downgraded one level for serious inconsistency: high heterogeneity ($I^2$ = 66%).

e. Downgraded one level for serious imprecision: few events; the study was not powered to detect a difference between groups.

f. Downgraded one level for risk of bias due to limitations in the study design.

### 3.4.2 PICO 2. Secondary prophylaxis

See Summary of Findings table 2 in which we present the overall certainty of the evidence for each outcome for PICO 2.

Data from one comparative retrospective cohort from India (India 2017) reported on the efficacy of secondary prophylaxis with liposomal amphotericin B or amphotericin B deoxycholate compared with no secondary prophylaxis in 53 VL-HIV coinfected patients following initial cure of VL (initially treated with liposomal amphotericin B or amphotericin B deoxycholate). The evidence for all reported outcomes is very uncertain due to serious limitations in study design and imprecision.

Additionally, two non-comparative prospective cohort studies (Ethiopia 2019b, Ethiopia 2015) that reported on pentamidine as secondary prophylaxis following initial cure of VL were also included. The evidence is very uncertain on the effect of pentamidine as secondary prophylaxis compared with no secondary prophylaxis.

#### All-cause mortality

All three included studies reported on this outcome (India 2017, Ethiopia 2019b, Ethiopia 2015).

Following secondary prophylaxis with amphotericin B (India 2017), no participants (0/27) died while 11/24 died in the group receiving no secondary prophylaxis at one-year follow-up. The evidence was very uncertain (Analysis 4.1).

In one study on secondary prophylaxis with pentamidine 5/29 patients died within one-year follow-up (Ethiopia 2019b). The other study reported that 5/71 patients died within two-years follow-up (Ethiopia 2015).

#### Relapse

All three included studies reported on this outcome (India 2017, Ethiopia 2019b, Ethiopia 2015).

Secondary prophylaxis with amphotericin B (India 2017)may reduce relapse (18/24 (75%) relapsed in the group receiving no prophylaxis, versus 0/27 (0%) in AmB secondary prophylaxis group) at up to one-year follow-up , however the evidence was very uncertain (Analysis 4.2 and 4.3).

In one study on secondary prophylaxis with pentamidine, 12 (41%) participants relapsed by one-year follow-up (Ethiopia 2019b). In the other study, 20 (27%) participants relapsed by two-year follow-up (Ethiopia 2015).

#### Relapse-free survival

All three included studies reported on this outcome (India 2017, Ethiopia 2019b, Ethiopia 2015).

Secondary prophylaxis with amphotericin B may increase relapse-free survival (27/27 (100%) in the amphotericin B group compared with 6/24 (25%) in the no prophylaxis group) at 12 months follow up, but the evidence was very uncertain (Analysis 4.4).

One study on secondary prophylaxis with pentamidine (Ethiopia 2015) reported an estimated probability of relapse-free survival at six months follow-up of 79% (95% CI 67% to 87%). At one-year

follow-up the reported probability was 71% (95% CI: 59% to 80%). At 24-36 months follow up the probability of relapse-free survival was 53%.

The other study (Ethiopia 2019b) reported that 46% (95% CI: 26–63%) of patients that received pentamidine as secondary prophylaxis reached relapse-free survival at one-year follow-up.

### Treatment adherence

Two single arm studies assessing pentamidine as secondary prophylaxis reported on treatment adherence (Ethiopia 2015, Ethiopia 2019b).

In one study (Ethiopia 2015), 41/74 (55%) of the participants completed the follow-up taking at least 11 of the planned 12 doses without experiencing relapse, death, or drug-related serious adverse events. 29 patients discontinued pentamidine permanently; 15 (20.3%) of them because of relapse, 7 (9.5%) were lost to follow-up, 5 (6.8%) died, one patient had to stop due to hyperglycaemia, and one patient refused to take the study drug.

The other study (Ethiopia 2019b) reported that 76% (22/29) of patients that received pentamidine as secondary prophylaxis had full compliance for the monthly pentamidine infusions.

### Serious adverse events

Two single arm studies assessing pentamidine as secondary prophylaxis reported on serious adverse events (Ethiopia 2015, Ethiopia 2019b).

One study (Ethiopia 2015) reported 21 serious adverse events in 17/74 (23%) patients at one-year follow-up, and that two events may have been related to pentamidine (renal failure in two patients hospitalised with pneumonia).

The other study (Ethiopia 2019b) reported 8/29 (28%) patients experienced serious adverse events at one-year follow-up. One death due to acute renal failure in a patient with multiple coexisting diseases that could affect renal status was considered possibly related to pentamidine.

### Adverse events

One study reported on this outcome (Ethiopia 2015).

At one-year follow-up there were 42 study-drug related adverse events in 30 (41%) of the 74 study participants. The most common being symptoms of the respiratory system (nasal congestion) during pentamidine infusion – 14 (19%), hypotension – 11 (15%), and renal impairment — 5 (6.8%). Clinical and therapeutic interventions were needed for 11 (14.9%) of the study participants, including additional intravenous fluid during pentamidine administration (n=10), reducing the rate of pentamidine infusion, oral hydrations (n=2), prolonged hospital observation (n=2), additional medication during pentamidine infusion (n=2), and glucose supplementation (n=1).

### Follow-up of patients

Two studies reported on this outcome (Ethiopia 2015).

In one prospective cohort study, 7/74 (9.5%) participants were lost to follow-up after one year, and 10/74 (14%) after two years.

In the other study (Ethiopia 2019b) all patients that started on secondary prophylaxis were followed-up to the end of the study.

### Patient satisfaction

No studies were identified that reported on patient satisfaction with secondary prophylaxis.

## Summary of Findings table 2. Secondary prophylaxis compared with no secondary prophylaxis after the first episode of VL in VL-HIV coinfected patients in East Africa and South East Asia

**Patient or population**: people with VL-HIV coinfection, following the first episode of VL
**Setting**: East Africa and South-East Asia
**Intervention**: Secondary prophylaxis
**Comparison**: No secondary prophylaxis

| Outcomes | Secondary prophylaxis (Studies) | Absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|---|
| | | Risk with No intervention | Risk with Secondary prophylaxis | | | | |
| **All-cause mortality** follow-up: 12-24 months | liposomal AmB or AmB deoxycholate (India 2017) | 11/24 (46%) | 0/27 (0%) | aHR 0.09 (0.03 to 0.31) | 51 (1 retrospective cohort) | ⨁◯◯◯ VERY LOW [a,b] | 12-month follow-up. Absolute effects are from unadjusted data and relative effect from adjusted data** in the study report. |
| | Pentamidine (Ethiopia 2015, Ethiopia 2019b) | At one year follow up one study reported 5/29 (17%) participants (with <200/µl CD4 cells at baseline) died. At two years follow-up one study reported 5/74 (7%) participants died. | | | 103 (2 prospective cohorts) | ⨁◯◯◯ VERY LOW [d] | Non-comparative studies |
| **Relapse** follow-up: 6 months | liposomal AmB or AmB deoxycholate (India 2017) | 18/24 (75%) | 0/27 (0%) | RR 0.02 (0.00 to 0.38) | 51 (1 retrospective cohort) | ⨁◯◯◯ VERY LOW [b,c] | unadjusted data |
| **Relapse** follow-up: 12 months | liposomal AmB or AmB deoxycholate (India 2017) | 18/24 (75%) | 0/27 (0%) | RR 0.02 (0.00 to 0.38) | 51 (1 retrospective cohort) | ⨁◯◯◯ VERY LOW [b,c] | unadjusted data |
| | Pentamidine (Ethiopia 2019b) | 12/29 (41%) participants (with <200/µl CD4 cells at baseline) relapsed (two patients that relapsed later died). | | | 29 (1 prospective cohort) | ⨁◯◯◯ VERY LOW [e] | Non-comparative study |

| Outcomes | Secondary prophylaxis (Studies) | Absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|---|
| | | Risk with No intervention | Risk with Secondary prophylaxis | | | | |
| **Relapse**<br>follow-up: 24 months | Pentamidine<br>(Ethiopia 2015) | 20/74 (27%) | | | 74<br>(1 prospective cohort) | ⊕◯◯◯<br>VERY LOW [e] | Non-comparative study |
| **Relapse-free survival**<br>follow-up: 6 months | Pentamidine<br>(Ethiopia 2015) | The estimated probability of relapse free survival at the end of 6 months was 79% (95% CI: 67%–87%) | | | 74<br>(1 prospective cohort) | ⊕◯◯◯<br>VERY LOW [e] | Non-comparative study |
| **Relapse-free survival**<br>follow-up: 12 months | liposomal AmB or AmB deoxycholate<br>(India 2017) | 6/24 (25%) | 27/27 (100%) | RR 3.78<br>(1.95 to 7.33) | 51<br>(1 retrospective cohort) | ⊕◯◯◯<br>VERY LOW [b,c] | unadjusted data |
| | Pentamidine<br>(Ethiopia 2015, Ethiopia 2019b) | The estimated probability of relapse free survival at the end of 12 months was 71% (95% CI: 59% to 80%) (Ethiopia 2015).At 12-month follow-up 46% (95%CI: 26–63%) of 29 patients (with <200/µl CD4 cells at baseline) reached relapse-free survival (Ethiopia 2019b). | | | 103<br>(2 prospective cohorts) | ⊕◯◯◯<br>VERY LOW [d] | Non-comparative studies |
| **Relapse-free survival**<br>follow-up: 24-36 months | Pentamidine<br>(Ethiopia 2015) | 53% (n=74) | | | 74<br>(1 prospective cohort) | ⊕◯◯◯<br>VERY LOW [e] | Non-comparative study |
| **Treatment adherence** | Pentamidine<br>(Ethiopia 2015, Ethiopia 2019b) | In one study, 41/74 (55%) completed the follow-up taking at least 11/12 doses without experiencing relapse, death or drug-related SAEs. 29 patients discontinued pentamidine permanently; 15 (20.3%) because of relapse, 7 (9.5%) were lost to follow-up, 5 (6.8%) died, one patient had to stop due to hyperglycaemia, and another patient refused to take the study drug.<br>The other study found that 76% (22/29) of patients had 100% compliance for the monthly pentamidine infusions. | | | 103<br>(2 prospective cohorts) | ⊕◯◯◯<br>VERY LOW [d] | Non-comparative studies |

| Outcomes | Secondary prophylaxis (Studies) | Absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|---|
| | | Risk with No intervention | Risk with Secondary prophylaxis | | | | |
| **Serious adverse events (any cause)** | Pentamidine (Ethiopia 2015, Ethiopia 2019b | One study reported 21 serious adverse events in 17 (23%) of the 74 patients; and that two events may have been related to pentamidine (renal failure in two patients hospitalised with pneumonia).<br>The other study reported 8/29 (28%) patients experienced serious adverse events. One death due to acute renal failure in a patient with multiple coexisting diseases that can affect renal status was considered possibly related to pentamidine. | | | 103 (2 prospective cohorts) | ⊕◯◯◯ VERY LOW [d] | Non-comparative studies |
| **Adverse events (any cause)** | Pentamidine (Ethiopia 2015) | 42 study-drug related adverse events in 30 (41%) of the 74 study participants. | | | 74 (1 prospective cohort) | ⊕◯◯◯ VERY LOW [e] | Non-comparative study |
| **Follow-up of patients** | Pentamidine (Ethiopia 2015, Ethiopia 2019b | One study reported 7/74 (9.5%) lost to follow-up after one year, and 10/74 (14%) after two years.<br>The other study reported all patients were followed-up to the end of the study (n=29). | | | 103 (2 prospective cohorts) | ⊕◯◯◯ VERY LOW [d] | Non-comparative studies |
| **Patient satisfaction** | | No studies were identified that reported on this outcome | | | | | |

*The absolute risks are taken from the intervention and comparison arms in the included studies.
**Adjusted for haemoglobin level at baseline, total leukocyte count at baseline, CD4 cell count at 6-month follow-up, and relapse within the first 6 months of follow-up.

AmB: Amphotericin B; CI: Confidence interval; HR: Hazard ratio; RR: Risk ratio; RCT: randomised controlled trial

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Explanations**

[a] Downgraded two levels for risk of bias: retrospective cohort study with serious risk of selection bias.

[b] Downgraded one level for imprecision: 51 participants from one study.

[c] Downgraded two levels for risk of bias: retrospective cohort study with serious risk of selection bias and serious risk of bias due to confounding.

[d] Evidence is considered very low certainty, as data is from two non-comparative studies.

[e] Evidence is considered very low certainty, as data is from one non-comparative study.

## 3.6. Contextual factors

### 3.6.1. Preferences and values

No study reported on patient or healthcare worker preferences and values related to IV liposomal amphotericin B and oral miltefosine combination therapy.

### 3.6.2. Resource use

No study reported on resource use, cost-effectiveness, or workload of healthcare staff related to combination therapy.

### 3.6.3. Equity

#### Gender/sex

The study populations of included studies were predominately male: Ethiopia 2019/Ethiopia 2019b: 98% male, India 2017: 77.4% male, Ethiopia 2015: 96% male. No study reported on intervention effects stratified by gender.

Women of child-bearing potential who were not using an assured method of contraception, or were unwilling to use an assured method of contraception for the duration of treatment and four months after, and pregnant women or breast-feeding mothers were excluded from participation in the randomised trials (Ethiopia 2019, India 2019).

#### Age

The study populations of included studies were adults ≥ 18 years with an age range of 21 to 64 years. Mean age was 37 (monotherapy) and 33 (combination therapy)) in Ethiopia 2019/Ethiopia 2019b; mean age of 34 in India 2017; and mean age of 32 (range 28-37) in Ethiopia 2015. No study reported on intervention effects stratified by age.

#### Health status

Ethiopia 2015 reported that participants were mostly malnourished (76%).

No study reported on place of residence, race/ethnicity/culture/language, religion, education, socioeconomic status, social capital, personal characteristics associated with discrimination, features of relationships, or time-dependent relationships.

### 3.6.4. Acceptability

Because of the teratogenic potential of miltefosine in women of child-bearing potential there is a need to use an assured method of contraception for the duration of treatment and four months after (Ethiopia 2019, India 2019). Oral contraceptives were not considered adequate because of the high prevalence of vomiting and diarrhoea associated with miltefosine treatment (Ethiopia 2019).

*Trial registration:* Efficacy Trial of Ambisome Given Alone and Ambisome Given in Combination With Miltefosine for the Treatment of VL HIV Positive Ethiopian Patients. 2013. Https://clinicaltrials.gov/show/nct02011958.

**India 2019**

Burza S, Pandey K, Mahajan R, Kazmi S, Alexander N, Lasry E, Moreto-Planas L, Goyal V, Das VNR, Das P. A randomized trial of AmBisome® single therapy and combination of AmBisome® and miltefosine for the treatment of Kala Azar in HIV positive patients in India. 2020. *Unpublished data received from the trial authors*.

*Trial registration*: A randomized trial of AmBisome single therapy and combination of AmBisome and miltefosine for the treatment of Kala Azar in HIV positive patients in India. 2015. Http://www.who.int/trialsearch/trial2.aspx?Trialid=ctri/2015/05/005807.

Burza S, Pandey K, Mahajan R, Kazmi S, Alexander N, Lasry E, et al. A randomized trial of AmBisome monotherapy and combination of AmBisome and miltefosine for the treatment of VL in HIV positive patients in India. Trans R Soc Trop Med Hyg. 2019. 113(Supplement 1):S203

### References to included studies (PICO 2)

**India 2017**

Goswami RP, Goswami RP, Basu A, Ray Y, Rahman M, Tripathi SK. Protective efficacy of secondary prophylaxis against visceral leishmaniasis in human immunodeficiency virus coinfected patients over the past 10 years in eastern India. The American Journal of Tropical Medicine and Hygiene. 2017 Feb 8;96(2):285-91.

**Ethiopia 2015**

Diro E, Ritmeijer K, Boelaert M, Alves F, Mohammed R, Abongomera C, Ravinetto R, De Crop M, Fikre H, Adera C, Colebunders R. Use of pentamidine as secondary prophylaxis to prevent visceral leishmaniasis relapse in HIV infected patients, the first twelve months of a prospective cohort study. PLoS Negl Trop Dis. 2015 Oct 2;9(10):e0004087.

Diro E, Ritmeijer K, Boelaert M, Alves F, Mohammed R, Abongomera C, et al. Long-term Clinical Outcomes in Visceral Leishmaniasis/Human Immunodeficiency Virus-Coinfected Patients during and after Pentamidine Secondary Prophylaxis in Ethiopia: A Single-Arm Clinical Trial. Clinical Infectious Diseases. 2018. 66(3):444-451.

**Ethiopia 2019b**

Diro E, Edwards T, Ritmeijer K, Fikre H, Abongomera C, Kibret A, Bardonneau C, Soipei P, Mutinda B, Omollo R, van Griensven J. Long term outcomes and prognostics of visceral leishmaniasis in HIV infected patients with use of pentamidine as secondary prophylaxis based on CD4 level: a prospective cohort study in Ethiopia. PLoS Negl Trop Dis. 2019 Feb 21;13(2):e0007132.

*Trial registration:* Efficacy Trial of Ambisome Given Alone and Ambisome Given in Combination With Miltefosine for the Treatment of VL HIV Positive Ethiopian Patients. 2013. Https://clinicaltrials.gov/show/nct02011958.

**India 2019**

Burza S, Pandey K, Mahajan R, Kazmi S, Alexander N, Lasry E, Moreto-Planas L, Goyal V, Das VNR, Das P. A randomized trial of AmBisome® single therapy and combination of AmBisome® and miltefosine for the treatment of Kala Azar in HIV positive patients in India. 2020. *Unpublished data received from the trial authors*.

*Trial registration*: A randomized trial of AmBisome single therapy and combination of AmBisome and miltefosine for the treatment of Kala Azar in HIV positive patients in India. 2015. Http://www.who.int/trialsearch/trial2.aspx?Trialid=ctri/2015/05/005807.

Burza S, Pandey K, Mahajan R, Kazmi S, Alexander N, Lasry E, et al. A randomized trial of AmBisome monotherapy and combination of AmBisome and miltefosine for the treatment of VL in HIV positive patients in India. Trans R Soc Trop Med Hyg. 2019. 113(Supplement 1):S203

### References to included studies (PICO 2)

**India 2017**

Goswami RP, Goswami RP, Basu A, Ray Y, Rahman M, Tripathi SK. Protective efficacy of secondary prophylaxis against visceral leishmaniasis in human immunodeficiency virus coinfected patients over the past 10 years in eastern India. The American Journal of Tropical Medicine and Hygiene. 2017 Feb 8;96(2):285-91.

**Ethiopia 2015**

Diro E, Ritmeijer K, Boelaert M, Alves F, Mohammed R, Abongomera C, Ravinetto R, De Crop M, Fikre H, Adera C, Colebunders R. Use of pentamidine as secondary prophylaxis to prevent visceral leishmaniasis relapse in HIV infected patients, the first twelve months of a prospective cohort study. PLoS Negl Trop Dis. 2015 Oct 2;9(10):e0004087.

Diro E, Ritmeijer K, Boelaert M, Alves F, Mohammed R, Abongomera C, et al. Long-term Clinical Outcomes in Visceral Leishmaniasis/Human Immunodeficiency Virus-Coinfected Patients during and after Pentamidine Secondary Prophylaxis in Ethiopia: A Single-Arm Clinical Trial. Clinical Infectious Diseases. 2018. 66(3):444-451.

**Ethiopia 2019b**

Diro E, Edwards T, Ritmeijer K, Fikre H, Abongomera C, Kibret A, Bardonneau C, Soipei P, Mutinda B, Omollo R, van Griensven J. Long term outcomes and prognostics of visceral leishmaniasis in HIV infected patients with use of pentamidine as secondary prophylaxis based on CD4 level: a prospective cohort study in Ethiopia. PLoS Negl Trop Dis. 2019 Feb 21;13(2):e0007132.

### Other references


1. Alvar J, Aparicio P, Aseffa A, Den Boer M, Canavate C, Dedet J-P, et al. The relationship between leishmaniasis and AIDS: the second 10 years. Clinical microbiology reviews. 2008;21(2):334-59.
2. WHO. Leishmaniasis Fact Sheet 2019 [Available from: http://www.who.int/mediacentre/factsheets/fs375/en/ (accessed 18 September 2020).
3. UN AIDS Fact Sheet 2019 [Available from: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf (accessed 18 September 2020).
4. WHO. Control of the leishmaniasis: report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22-26 March 2010. (WHO technical report series ; no. 949) 2010.
5. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
6. 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.
7. Schünemann H BJ, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from www.guidelinedevelopment.org/handbook (accessed 18 September 2020).
8. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.
9. O'Neill J, Tabish H, Welch V, Petticrew M, Pottie K, Clarke M, et al. Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health. Journal of clinical epidemiology. 2014;67(1):56-64.

# Appendix 1. Search strategy (PICO 1)

**Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R), Ovid EMBASE <1946 to February 1st, 2020>**

Search Strategy:

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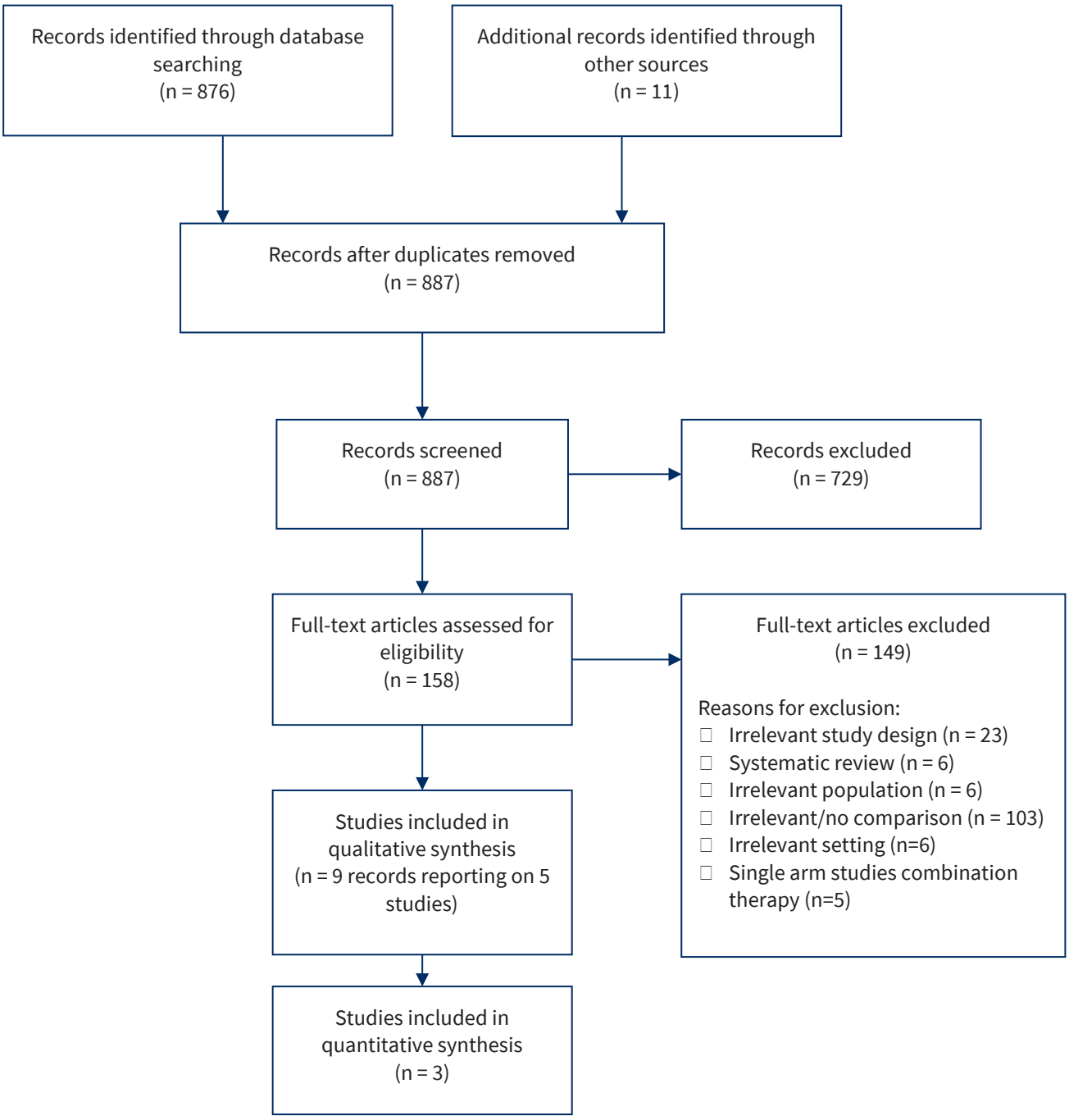
1. exp Leishmaniasis/
2. leishmania*.mp,kf.
3. 1 or 2
4. Amphotericin B/
5. amphotericin.mp,kf.
6. 4 or 5
7. exp HIV/
8. exp hiv infections/ or acquired immunodeficiency syndrome/
9. (hiv or aids).mp,kf.
10. ((human adj (immuno or immune) adj deficiency virus*) or "human immunodeficiency virus*" or "human immunedeficiency virus*").tw.
11. ((acquired adj (immuno or immune) adj deficiency syndrome*) or "acquired immunodeficiency syndrome*" or "acquired immunedeficiency syndrome*").tw.
12. or/7-11
13. 3 and 12
14. 6 and 13
15. exp leishmaniasis/
16. leishmania*.mp.
17. 15 or 16
18. amphotericin/ or amphotericin b/ or amphotericin b cholesterol sulfate/ or amphotericin b deoxycholate/
19. amphotericin b lipid complex/ or amphotericin b methyl ester/
20. amphotericin.mp.
21. 18 or 19 or 20
22. 17 and 21
23. exp Human immunodeficiency virus/
24. exp Human immunodeficiency virus infection/
25. human immunodeficiency virus antibody/ or human immunodeficiency virus antigen/
26. exp Human immunodeficiency virus infected patient/
27. (hiv or aids).tw.
28. ((human adj (immuno or immune) adj deficiency virus*) or "human immunodeficiency virus*" or "human immunedeficiency virus*").tw.
29. ((acquired adj (immuno or immune) adj deficiency syndrome*) or "acquired immunodeficiency syndrome*" or "acquired immunedeficiency syndrome*").tw.
30. or/23-29
31. 22 and 30
32. 14 use ppez
33. 31 use emczd
34. 32 or 33

# Appendix 2. PRISMA flow chart



# Appendix 3. Excluded studies

| | |
|---|---|
| **Reason for exclusion: Systematic review** | |
| 1. | Alemayehu M, Wubshet M, Mesfin N. Magnitude of visceral leishmaniasis and poor treatment outcome among HIV patients: Meta-analysis and systematic review. HIV/AIDS - Research and Palliative Care. 2016;8(pp 75-81):23. |
| 2. | Bush JT, Guerin PJ, Strub WN. Systematic review of clinical trials assessing the therapeutic efficacy of visceral leishmaniasis treatments: A first step to assess the feasibility of establishing an individual patient data sharing platform. PLoS Neglected Tropical Diseases. 2017;11(9): e0005781. |
| 3. | Cota GF, de Sousa MR, Rabello A. Predictors of visceral leishmaniasis relapse in hiv-infected patients: A systematic review. PLoS Neglected Tropical Diseases. 2011;5(6): e1153 . |
| 4. | Cota GF, de Sousa MR, Fereguetti TO, Rabello A. Efficacy of anti-leishmania therapy in visceral leishmaniasis among HIV infected patients: a systematic review with indirect comparison. PLoS Neglected Tropical Diseases. 2013;7(5):e2195. |
| 5. | Gebreyohannes EA, Bhagvathula AS, Abegaz TM, Seid MA. Treatment outcomes of visceral leishmaniasis in Ethiopia from 2001 to 2017: a systematic review and meta-analysis. Infectious Diseases of Poverty. 2018;7(1):108. |
| 6. | Graepp-Fontoura I, Soeiro Barbosa D, Paes AMA, Santos FS, Santos Neto M, Fontoura VM, et al. Epidemiological, clinical and laboratory aspects of human visceral leishmaniasis (HVL) associated with human immunodeficiency virus (HIV) coinfection: a systematic review. Parasitology. 2018;145(14):1801-18. |
| **Reason for exclusion: other irrelevant study design** | |
| 1. | Al-Salem W, Herricks JR, Hotez PJ. A review of visceral leishmaniasis during the conflict in South Sudan and the consequences for East African countries. Parasites and Vectors. 2016;9(1):460. |
| 2. | Alvar J. Leishmaniasis and AIDS co-infection: The Spanish example. Parasitology Today. 1994;10(4):160-3. |
| 3. | Balasegaram M, Mueller M, Davidson R. Reply to comment on: Unresponsiveness to AmBisome in some Sudanese patients with kala-azar. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2007;101(10):1054-5. |
| 4. | Banuls J. Leishmaniasis as a cause of oral disease in HIV infection. AIDS. 1995;9(1):96-8. |
| 5. | Barbosa JF, de Figueiredo SM, Lyon S, Caligiorne RB. An 8-Year Retrospective Study of Human Visceral Leishmaniasis. Current Clinical Pharmacology. 2016;11(4):265-9. |
| 6. | Berenguer J, Cosin J, Miralles P, Lopez JC, Padilla B. [Visceral leishmaniasis associated with human immunodeficiency virus infection (reply)]. Enfermedades Infecciosas y Microbiologia Clinica. 2002;20(3):133. |
| 7. | Das Gupta RK. Kala-azar: Roadmap for elimination. Journal of the Indian Medical Association. 2015;113(12):183-8. |
| 8. | del Mar Sanz M, Rubio R, Casillas A, Guijarro C, Costa JR, Martinez R. Visceral leishmaniasis in HIV-infected patients. AIDS. 1991;5(10):1272-4. |
| 9. | Feldmeier H. Tropical epidemic of Leishmaniasis: New therapy from German research laboratory. Deutsche Apotheker Zeitung. 2000;140(19):40-2. |
| 10. | Foti G. Visceral leishmaniasis in HIV-infected patients: Report of three cases and considerations about the treatment with liposomal amphotericin B (AmBisome). Giornale Italiano di Malattie Infettive. 2001;7(4):220-3. |
| 11. | Lazanas MC, Tsekes GA, Papandreou S, Harhalakis N, Scandali A, Nikiforakis E, et al. Liposomal amphotericin B for leishmaniasis treatment of AIDS patients unresponsive to antimonium compounds. AIDS. 1993;7(7):1018-9. |

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| 12. | Lopez-Velez R. The impact of highly active antiretroviral therapy (HAART) on visceral leishmaniasis in Spanish patients who are co-infected with HIV. Annals of Tropical Medicine and Parasitology. 2003;97(SUPPL. 1):S143-S7. |
| 13. | McBride M. Visceral leishmaniasis following treatment with liposomal amphotericin B. Clinical Infectious Diseases. 1994;19(2):362. |
| 14. | Mistro S, Rodrigues M, Rosa L, Camargo M, Badaro R. Liposomal Amphotericin B drug access for the treatment of leishmaniasis in Brazil. Tropical Medicine & International Health. 2016;21(6):692-3. |
| 15. | Perez-Arellano JL. Protozoan hemoflagellate infections I: Leishmaniasis. Medicine. 2010;10(54):3621-31. |
| 16. | Pintado V. [Visceral leishmaniasis associated with human immunodeficiency virus infection]. [Spanish]. Enfermedades Infecciosas y Microbiologia Clinica. 2001;19(7):353-7. |
| 17. | Rodilla F. Amphotericin B for visceral leishmaniasis resistant to pentavalent antimonial drugs in AIDS. Annals of Pharmacotherapy. 1994;28(11):1305. |
| 18. | Russo R. Clinical survey of Leishmania/HIV co-infection in Catania, Italy: The impact of highly active antiretroviral therapy (HAART). Annals of Tropical Medicine and Parasitology. 2003;97(SUPPL. 1):S149-S55. |
| 19. | Schwartz T, Jensenius M, Blomberg B, Fladeby C, Maeland A, Pettersen FO. Imported visceral leishmaniasis and immunosuppression in seven Norwegian patients. Tropical Diseases, Travel Medicine and Vaccines. 2019;5(1):16. |
| 20. | Sundar S. An update on pharmacotherapy for leishmaniasis. Expert Opinion on Pharmacotherapy. 2015;16(2):237-52. |
| 21. | van Griensven J, Balasegaram M, Meheus F, Alvar J, Lynen L, et al. Combination therapy for visceral leishmaniasis. The Lancet Infectious Diseases. 2010;10(3):184-94. |
| 22. | Wagner U. Disfiguring scars from Leishmania parasites. Pharmazeutische Zeitung. 2002;147(16):44-7. |
| 23. | Weitzel T. Imported leishmaniasis in Germany 2001-2004: data of the SIMPID surveillance network. European Journal of Clinical Microbiology & Infectious Diseases. 2005;24(7):471-6. |
| **Reason for exclusion: not population with co-morbid VL and HIV** | |
| 1. | Fernandez-Redondo D. Effectivity and safety of miltefosine used for the treatment of visceral leishmaniasis. International Journal of Clinical Pharmacy. 2016;581-2. |
| 2. | Hirve S, Boelaert M, Matlashewski G, Mondal D, Arana B, Kroeger A, et al. Transmission Dynamics of Visceral Leishmaniasis in the Indian Subcontinent - A Systematic Literature Review. PLoS Neglected Tropical Diseases. 2016;10(8) |
| 3. | Karimzadeh I, Khalili H. Role of diuretics and lipid formulations in the prevention of amphotericin B-induced nephrotoxicity. European Journal of Clinical Pharmacology. 2013;69(7):1351-68. |
| 4. | Khalil EA, el Hassan AM, Zijlstra EE, Hashim FA, Ibrahim ME, Ghalib HW, et al. Treatment of visceral leishmaniasis with sodium stibogluconate in Sudan: management of those who do not respond. Annals of Tropical Medicine & Parasitology. 1998;92(2):151-8. |
| 5. | Mueller M, Ritmeijer K, Balasegaram M, Koummuki Y, Santana MR, et al. Unresponsiveness to AmBisome in some Sudanese patients with kala-azar. Transactions of the Royal Society of Tropical Medicine & Hygiene. 2007;101(1):19-24. |
| 6. | Ranga S. Haematological manifestation of HIV infection. Indian Journal of Pathology and Microbiology. 1997;40(3):417-31. |
| **Reason for exclusion: irrelevant/no comparison** | |
| 1. | A comparative study to monitor the safety of Amphotericin 50mg per vial A and Ambisome (amphotericin b) 50 mg per vial B in 48 patients. Http://www.Who.int/trialsearch/trial2aspx?Trialid=ctri/2017/03/007993. 2017. |

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| 2. | Aderie EM, Diro E, Zachariah R, da Fonseca MS, Abongomera C, Dolamo BL, et al. Does timing of antiretroviral treatment influence treatment outcomes of visceral leishmaniasis in Northwest Ethiopia? Transactions of the Royal Society of Tropical Medicine and Hygiene. 2017;111(3):107-16. |
| 3. | Albuquerque LC, Mendonça IR, Cardoso PN, Baldaçara LR, Borges MR, Borges Jda C, et al. HIV/AIDS-related visceral leishmaniasis: a clinical and epidemiological description of visceral leishmaniasis in northern Brazil. Revista da Sociedade Brasileira de Medicina Tropical. 2014;47(1):38-46. |
| 4. | Alcoba G. Impact of pediatric and adult acute malnutrition on visceral leishmaniasis RK39 diagnostic test results and clinical outcome in the sudan. American Journal of Tropical Medicine and Hygiene. 2014;Conference(var.pagings):335. |
| 5. | Alexandrino-de-Oliveira P, Santos-Oliveira JR, Dorval ME, Da-Costa Fd, Pereira GR, da Cunha RV, et al. HIV/AIDS-associated visceral leishmaniasis in patients from an endemic area in Central-west Brazil. Memorias do Instituto Oswaldo Cruz. 2010;105(5):692-7. |
| 6. | Arya SC. Treatment of Indian kala-azar with pentavalent antimony. Lancet. 1995;345(8949):584. |
| 7. | Berenguer J, Cosín J, Miralles P, López JC, Padilla B. Discontinuation of secondary anti-leishmania prophylaxis in HIV-infected patients who have responded to highly active antiretroviral therapy. AIDS. 2000;14(18):2946-8. |
| 8. | Bosch RJ, Rodrigo AB, Sánchez P, de Gálvez MV, Herrera E. Presence of Leishmania organisms in specific and non-specific skin lesions in HIV-infected individuals with visceral leishmaniasis. International Journal of Dermatology. 2002;41(10):670-5. |
| 9. | Bouree P, Belec L. Leishmaniasis: Report of 33 cases and a review of the literature. Comparative Immunology, Microbiology and Infectious Diseases. 1993;16(4):251-65. |
| 10. | Lachaud L, Reynes J, Rouanet I, Mahamat A, Bastien P. Long-term monitoring of visceral leishmaniasis in patients with AIDS: Relapse risk factors, value of polymerase chain reaction, and potential impact on secondary prophylaxis. Journal of Acquired Immune Deficiency Syndromes. 2008;48(1):13-9. |
| 11. | Bourgeois N, Bastien P, Reynes J, Makinson A, Rouanet I, Lachaud L. 'Active chronic visceral leishmaniasis' in HIV-1-infected patients demonstrated by biological and clinical long-term follow-up of 10 patients. HIV Medicine. 2010;11(10):670-3. |
| 12. | Burza S, Sinha P, Das P, Gonzalez M, Mitra G, de Weerdt S, Lim N. A 4-year outcome summary of 20 mg/kg liposomal amphotericin B regime for the treatment of primary KA in Bihar India. Clinical Microbiology and Infection. 2012; Conference(var.pagings):709. |
| 13. | Burza S. Combination treatment for visceral leishmaniasis patients co-infected with human immunodeficiency virus in India. International Journal of Infectious Diseases. 2016; Conference(var.pagings):55. |
| 14. | Burza S, Mahajan R, Sinha P, van Griensven J, Pandey K, Lima MA, et al. Visceral leishmaniasis and HIV co-infection in Bihar, India: long-term effectiveness and treatment outcomes with liposomal amphotericin B (AmBisome). PLoS Neglected Tropical Diseases [electronic resource]. 2014;8(8):e3053. |
| 15. | Burza S, Sinha PK, Mahajan R, Lima MA, Mitra G, Verma N, et al. Five-year field results and long-term effectiveness of 20 mg/kg liposomal amphotericin B (Ambisome) for visceral leishmaniasis in Bihar, India. PLoS Neglected Tropical Diseases. 2014;8(1):e2603. |
| 16. | Burza S, Sinha PK, Mahajan B, Lima MA, Mitra G, Verma N, et al. Risk factors for visceral leishmaniasis relapse in immunocompetent patients following treatment with 20 mg/kg liposomal amphotericin B (Ambisome) in Bihar, India. PLoS Neglected Tropical Diseases. 2014;8(1):e2536. |

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| 17. | Casado JL, Lopez-Velez R, Pintado V, Quereda C, Antela A, Moreno S. Relapsing visceral leishmaniasis in HIV-infected patients undergoing successful protease inhibitor therapy. European Journal of Clinical Microbiology and Infectious Diseases. 2001;20(3):202-5. |
| 18. | Casado JL, Abad-Fernández M, Moreno S, Pérez-Elías MJ, Moreno A, Bernardino JI, et al. Visceral leishmaniasis as an independent cause of high immune activation, T-cell senescence, and lack of immune recovery in virologically suppressed HIV-1-coinfected patients. HIV Medicine. 2015;16(4):240-8. |
| 19. | Cascio A, Gradoni L, Scarlata F, Gramiccia M, Giordano S, Russo R, et al. Epidemiologic surveillance of visceral leishmaniasis in Sicily, Italy. American Journal of Tropical Medicine & Hygiene. 1997;57(1):75-8. |
| 20. | Castro A, Ruiz-Giardin JM, Moreno J, San Martin JV, Carrillo E, Castro A. Lymphoproliferative response after stimulation with soluble leishmania antigen (SLA) as a predictor of visceral leishmaniasis (VL) relapse in HIV+ patients. Acta Tropica. 2016;164(pp 345-351):01. |
| 21. | Cenderello G, Pasa A, Dusi A, Dentone C, Izzo M, Toscanini F, et al. Changing spectrum of clinical presentation in visceral leishmania in HIV+ patients: Preliminary results from a clinical registry in Northern Italy. Journal of the International AIDS Society. 2012; Conference(var.pagings):81. |
| 22. | Cenderello G, Pasa A, Dusi A, Dentone C, Toscanini F, Bobbio N, et al. Varied spectrum of clinical presentation and mortality in a prospective registry of visceral leishmaniasis in a low endemicity area of Northern Italy. BMC Infectious Diseases. 2013;13:248. |
| 23. | Cipriano P, Miranda AC, Antunes I, Mansinho K. [Visceral Leishmaniasis in HIV-Infected Patients: The Challenge of Relapse and Treatment Failure]. [Portuguese]. Acta Medica Portuguesa. 2017;30(6):443-8. |
| 24. | Colomba C, Saporito L, Vitale F, Reale S, Vitale G, Casuccio A, et al. Cryptic Leishmania infantum infection in Italian HIV infected patients. BMC Infectious Diseases.9(no pagination):199. |
| 25. | Cota GF, de Sousa MR, de Assis TSM, Pinto BF, Rabello A. Exploring prognosis in chronic relapsing visceral leishmaniasis among HIV-infected patients: Circulating Leishmania DNA. Acta Tropica. 2017;172(pp 186-191):01. |
| 26. | Cota GF, de Sousa MR, de Mendonça AL, Patrocinio A, Assunção LS, de Faria SR, et al. Leishmania-HIV co-infection: clinical presentation and outcomes in an urban area in Brazil. PLoS Neglected Tropical Diseases. 2014;8(4):e2816. |
| 27. | Coutinho JVSC, Santos FSD, Ribeiro RDSP, Oliveira IBB, Dantas VB, Santos ABFS, et al. Visceral leishmaniasis and Leishmaniasis-HIV coinfection: Comparative study. Revista da Sociedade Brasileira de Medicina Tropical. 2017;50(5):670-4. |
| 28. | Daher EF, Fonseca PP, Gerhard ES, Leitão TM, Silva Júnior GB. Clinical and epidemiological features of visceral leishmaniasis and HIV co-infection in fifteen patients from Brazil. Journal of Parasitology. 2009;95(3):652-5. |
| 29. | Davidson RN. Relapse of visceral leishmaniasis in patients who were coinfected with human immunodeficiency virus and who received treatment with liposomal amphotericin B. Clinical Infectious Diseases. 1994;19(3):560. |
| 30. | Davidson RN, Di Martino L, Gradoni L, Giacchino R, Russo R, Gaeta GB, et al. Liposomal amphotericin B (AmBisome) in Mediterranean visceral leishmaniasis: a multi-centre trial. Quarterly Journal of Medicine. 1994;87(2):75-81. |
| 31. | del Giudice P, Mary-Krause M, Pradier C, Grabar S, Dellamonica P, Marty P, et al. Impact of highly active antiretroviral therapy on the incidence of visceral leishmaniasis in a French cohort of patients infected with human immunodeficiency virus. Journal of Infectious Diseases. 2002;186(9):1366-70. |

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| 32. | Di Giorgio C, Faraut-Gambarelli F, Imbert A, Minodier P, Gasquet M, Dumon H. Flow cytometric assessment of amphotericin B susceptibility in Leishmania infantum isolates from patients with visceral leishmaniasis. Journal of Antimicrobial Chemotherapy. 1999;44(1):71-6. |
| 33. | Di Masi F, Ursini T, Iannece MD, Chianura L, Baldasso F, Foti G, et al. Five-year retrospective Italian multicenter study of visceral leishmaniasis treatment. Antimicrobial Agents & Chemotherapy. 2014;58(1):414-8. |
| 34. | Dias TB, Dias Tourinho B, Figueiredo Amancio F, Lencine Ferraz M, Carneiro M. Prognostic factors for death from visceral leishmaniasis in patients treated with liposomal amphotericin B in an endemic state in Brazil. Transactions of the Royal Society of Tropical Medicine & Hygiene. 2017;111(4):163-71. |
| 35. | Diro E, Lynen L, Gebregziabiher B, Assefa A, Lakew W, et al. Clinical aspects of paediatric visceral leishmaniasis in North-west Ethiopia. Tropical Medicine & International Health. 2015;20(1):8-16. |
| 36. | Diro E, Lynen L, Mohammed R, Boelaert M, Hailu A, et al. High parasitological failure rate of visceral leishmaniasis to sodium stibogluconate among HIV co-infected adults in Ethiopia. PLoS Neglected Tropical Diseases. 2014;8(5):e2875. |
| 37. | Domingo P. Treatment of Indian Kala-azar with pentavalent antimony. Lancet. 1995;345(8949):584-5. |
| 38. | Druzian AF, Paniago AMM. Risk factors for death from visceral leishmaniasis in an urban area of Brazil. PLoS Neglected Tropical Diseases. 2015;9(8): e0003982. |
| 39. | de Carvalho IPSF, Peixoto HM, Romero GAS, de Oliveira MRF. Treatment for human visceral leishmaniasis: a cost-effectiveness analysis for Brazil. Tropical medicine & international health. 2019(9):1064-77. |
| 40. | de Carvalho IPSF, Peixoto HM, Romero GAS, de Oliveira MRF. Cost of visceral leishmaniasis care in Brazil. Tropical Medicine and International Health. 2017;22(12):1579-89. |
| 41. | Souza GF, Biscione F, Greco DB, Rabello A. Slow clinical improvement after treatment initiation in Leishmania/HIV coinfected patients. Revista da Sociedade Brasileira de Medicina Tropical. 2012;45(2):147-50. |
| 42. | Ehehalt U, Cramer JP. Leishmaniasis acquired by travellers to endemic regions in Europe: A EuroTravNet multi-centre study. Travel Medicine and Infectious Disease. 2014;12(2):167-72. |
| 43. | El-Hajj L. Azoles and allopurinol: A maintenance therapy for visceral leishmaniasis in HIV patients. Medecine et Maladies Infectieuses. 2001;31(6):446-7. |
| 44. | Ena J. Screening for subclinical leishmania infection in HIV-infected patients living in eastern Spain. Pathogens and Global Health. 2014;108(8):356-61. |
| 45. | Ettorre G, Ceccarelli G, Carnevalini M, Forcina G, Zaffiri L, et al. Central role of interleukin-15 in human immunodeficiency virus (HIV)-infected patients with visceral leishmaniasis. Acta Tropica. 2006;99(1):83-7. |
| 46. | Fernandez-Guerrero ML. Visceral leishmaniasis in immunocompromised patients with and without AIDS: A comparison of clinical features and prognosis. Acta Tropica. 2004;90(1):11-6. |
| 47. | Gjataj A. Overview of epidemiological, clinical and therapeutic features of visceral leishmaniasis/HIV co-infection in Albania. Journal of the International AIDS Society. 2018;Conference(Supplement 8):102. |
| 48. | Hailu W, Weldegebreal T, Hurissa Z, Tafes H, Omollo R, Yifru S, et al. Safety and effectiveness of meglumine antimoniate in the treatment of Ethiopian visceral leishmaniasis patients with and without HIV co-infection. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2010;104(11):706-12. |

| | |
|---|---|
| 49. | Henn GAL, Ramos Júnior AN, Colares JKB, Mendes LP, Silveira JGC, Lima AAF, et al. Is Visceral Leishmaniasis the same in HIV-coinfected adults? Brazilian Journal of Infectious Diseases. 2018;22(2):92-8. |
| 50. | Hernandez-Torres A. Visceral leishmaniasis in Murcia: Multicentric study 1997-2013. Infectio. 2015;19(1):24-30. |
| 51. | Herrero M, Bern C. Natural history of a visceral leishmaniasis outbreak in highland Ethiopia. American Journal of Tropical Medicine and Hygiene. 2009;81(3):373-7. |
| 52. | Horrillo L, Castro A, Matía B, Molina L, García-Martínez J, Jaqueti J, et al. Clinical aspects of visceral leishmaniasis caused by L. infantum in adults. Ten years of experience of the largest outbreak in Europe: what have we learned? Parasites & Vectors. 2019;12(1):359. |
| 53. | Houghton RL, Petrescu M, Benson DR, Skeiky YA, Scalone A, Badaró R, et al. A cloned antigen (recombinant K39) of Leishmania chagasi diagnostic for visceral leishmaniasis in human immunodeficiency virus type 1 patients and a prognostic indicator for monitoring patients undergoing drug therapy. Journal of Infectious Diseases. 1998;177(5):1339-44. |
| 54. | Hurissa Z, Gebre-Silassie S, Hailu W, Tefera T, Lalloo DG, Cuevas LE, et al. Clinical characteristics and treatment outcome of patients with visceral leishmaniasis and HIV co-infection in northwest Ethiopia. Tropical Medicine and International Health. 2010;15(7):848-55. |
| 55. | Khalil EAG. Visceral leishmaniasis HIV, hepatitis B and hepatitis co-infections. Clinical Chemistry and Laboratory Medicine. 2011;Conference(var.pagings):S40. |
| 56. | Kokaia N. A retrospective analysis of 400 cases treated for visceral leishmaniasis in georgia. American Journal of Tropical Medicine and Hygiene. 2013;Conference(var.pagings):92-3. |
| 57. | Lachaud L, Bourgeois N, Plourde M, Leprohon P, Bastien P, et al. Parasite susceptibility to amphotericin B in failures of treatment for visceral leishmaniasis in patients coinfected with HIV type 1 and Leishmania infantum. Clinical Infectious Diseases. 2009;48(2):e16-e22. |
| 58. | Laguna F, Torre-Cisneros J, Moreno V, Villanueva JL, Valencia E. Efficacy of intermittent liposomal amphotericin B in the treatment of visceral leishmaniasis in patients infected with human immunodeficiency virus. Clinical Infectious Diseases. 1995;21(3):711-2. |
| 59. | Laguna F, Adrados M, Alvar J, Soriano V, Valencia ME, Moreno V, et al. Visceral leishmaniasis in patients infected with the human immunodeficiency virus. European Journal of Clinical Microbiology & Infectious Diseases. 1997;16(12):898-903. |
| 60. | Laguna F, López-Vélez R, Pulido F, Salas A, Torre-Cisneros J, Torres E, et al. Treatment of visceral leishmaniasis in HIV-infected patients: a randomized trial comparing meglumine antimoniate with amphotericin B. Spanish HIV-Leishmania Study Group. AIDS. 1999;13(9):1063-9. |
| 61. | Laguna F, Videla S, Jiménez-Mejías ME, Sirera G, Torre-Cisneros J, Ribera E, et al. Amphotericin B lipid complex versus meglumine antimoniate in the treatment of visceral leishmaniasis in patients infected with HIV: a randomized pilot study. Journal of Antimicrobial Chemotherapy. 2003;52(3):464-8. |
| 62. | Lopez-Velez R, Perez-Molina JA, Guerrero A, Baquero F, Villarrubia J, Escribano L, et al. Clinicoepidemiologic characteristics, prognostic factors, and survival analysis of patients coinfected with human immunodeficiency virus and Leishmania in an area of Madrid, Spain. American Journal of Tropical Medicine and Hygiene. 1998;58(4):436-43. |
| 63. | Luis H, Alicia C, Belen M, Laura M, Jesus G-M, Jeronimo J, et al. Clinical aspects of visceral leishmaniasis caused by L. infantum in adults. Ten years of experience of the |

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|---|---|
| | largest outbreak in Europe: what have we learned? Parasites & vectors. 2019;12(1):359. |
| 64. | Lukas D. Leishmaniasis in Croatia. Tropical Medicine and International Health. 2013;Conference(var.pagings):139. |
| 65. | Luz JGG, Naves DB, Carvalho AG, Meira GA, Dias JVL, Fontes CJF. Visceral leishmaniasis in a Brazilian endemic area: an overview of occurrence, HIV coinfection and lethality. Revista do Instituto de Medicina Tropical de Sao Paulo. 2018;60:e12. |
| 66. | Malik AN, John L, Bruceson AD, Lockwood DN. Changing pattern of visceral leishmaniasis, United Kingdom, 1985-2004. Emerging Infectious Diseases. 2006;12(8):1257-9. |
| 67. | Mira JA, Corzo JE, Rivero A, Macias J, De Leon FL, Torre-Cisneros J, et al. Frequency of visceral leishmaniasis relapses in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy. American Journal of Tropical Medicine and Hygiene. 2004;70(3):298-301. |
| 68. | Montalban C., Calleja JL, Erice A, Laguna F, Clotet B, Podzamczer D, et al Visceral leishmaniasis in patients infected with human immunodeficiency virus. Journal of Infection. 1990;21(3):261-70. |
| 69. | Morales MA, Cruz I, Rubio JM, Chicharro C, Cañavate C, Laguna F, et al. Relapses versus reinfections in patients coinfected with Leishmania infantum and human immunodeficiency virus type 1. Journal of Infectious Diseases. 2002;185(10):1533-7. |
| 70. | Mueller M, Balasegaram M. A comparison of liposomal amphotericin B with sodium stibogluconate for the treatment of visceral leishmaniasis in pregnancy in Sudan. Journal of Antimicrobial Chemotherapy. 2006;58(4):811-5. |
| 71. | Nascimento ET, Jeronimo SM. The emergence of concurrent HIV-1/AIDS and visceral leishmaniasis in Northeast Brazil. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2011;105(5):298-300. |
| 72. | Pasquau F, Ena J, Sanchez R, Cuadrado JM, Amador C, Flores J, et al. Leishmaniasis as an opportunistic infection in HIV-infected patients: Determinants of relapse and mortality in a collaborative study of 228 episodes in a Mediterreanean region. European Journal of Clinical Microbiology and Infectious Diseases. 2005;24(6):411-8. |
| 73. | Petit N, Parola P, Dhiver C, Gastaut JA. Efficacy and tolerance of amphotericin B in a lipid emulsion in the treatment of visceral leishmaniasis in AIDS patients. Journal of Antimicrobial Chemotherapy. 1996;38(1):154-7. |
| 74. | Ramos JM, León R, Merino E, Montero M, Aljibe A, Blanes M, et al. Is visceral leishmaniasis different in immunocompromised patients without human immunodeficiency virus? A comparative, multicenter retrospective cohort analysis. American Journal of Tropical Medicine and Hygiene. 2017;97(4):1127-33. |
| 75. | Reus S, Sánchez R, Portilla J, Boix V, Priego M, Merino E, et al. Visceral leishmaniasis: Comparative study in patients with and without HIV infection. Enfermedades Infecciosas y Microbiologia Clinica. 1999;17(10):515-20. |
| 76. | Riera C, Fisa R, Lopez P, Ribera E, Carrió J, Falcó V, et al. Evaluation of a latex agglutination test (KAtex) for detection of Leishmania antigen in urine of patients with HIV-Leishmania coinfection: Value in diagnosis and post-treatment follow-up. European Journal of Clinical Microbiology and Infectious Diseases. 2004;23(12):899-904. |
| 77. | Ritmeijer K, Veeken H, Melaku Y, Leal G, Amsalu R, Seaman J, et al. Ethiopian visceral leishmaniasis: Generic and proprietary sodium stibogluconate are equivalent; HIV co-infected patients have a poor outcome. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2001;95(6):668-72. |
| 78. | Ritmeijer K, ter Horst R, Chane S, Aderie EM, Piening T, Collin SM, et al. Limited effectiveness of high-dose liposomal amphotericin B (AmBisome) for treatment of |

| | |
|---|---|
| | visceral leishmaniasis in an Ethiopian population with high HIV prevalence. Clinical Infectious Diseases. 2011;53(12):e152-e8. |
| 79. | Rosenthal E. Visceral leishmaniosis and HIV infection in southern France. Presse Medicale. 1995;24(35):1666. |
| 80. | Rosenthal E, Marty P, Poizot-Martin I, Reynes J, Pratlong F, Lafeuillade A, et al. Visceral leishmaniasis and HIV-1 co-infection in southern France. Transactions of the Royal Society of Tropical Medicine & Hygiene. 1995;89(2):159-62. |
| 81. | Russo R, Nigro LC, Minniti S, Montineri A, Gradoni L, Caldeira L, et al. Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B (AmBisome). Journal of Infection. 1996;32(2):133-7. |
| 82. | Salih NA, van Griensven J, Chappuis F, Antierens A, Mumina A, Hammam O, et al. Liposomal amphotericin B for complicated visceral leishmaniasis (kala-azar) in eastern Sudan: how effective is treatment for this neglected disease? Tropical Medicine & International Health. 2014;19(2):146-52. |
| 83. | Santos GO, De Jesus NPS, Cerqueira-Braz JV, Santos VS, De Lemos LMD. Prevalence of HIV and associated factors among visceral leishmaniasis cases in an endemic area of Northeast Brazil. Revista da Sociedade Brasileira de Medicina Tropical. 2019;52:e20180257. |
| 84. | Santos GO, De Lemos LMD. Prevalence of HIV and associated factors among visceral leishmaniasis cases in an endemic area of Northeast Brazil. Revista da Sociedade Brasileira de Medicina Tropical. 2018;52(no pagination):e20180257. |
| 85. | Silva de Lima UR, Vanolli L, Moraes EC, Ithamar JS, Pedrozo e Silva de Azevedo CDM. Visceral leishmaniasis in Northeast Brazil: What is the impact of HIV on this protozoan infection? PloS one. 2019;14(12):e0225875. |
| 86. | Silva-Freitas ML, Cota GF, Machado-de-Assis TS, Giacoia-Gripp C, Rabello A, Da-Cruz AM, et al. Immune activation and bacterial translocation: A link between impaired immune recovery and frequent visceral leishmaniasis relapses in HIV-infected patients. PloS one. 2016;11(12): e0167512. |
| 87. | Singh S, Dwivedi SN, Sood R, Wali JP. Hepatitis B, C and human immunodeficiency virus infections in multiply-injected kala-azar patients in Delhi. Scandinavian Journal of Infectious Diseases. 2000;32(1):3-6. |
| 88. | Singh S, Dahal P, Ngu R, Maguire B, Olliaro P, Stepniewska K, et al. Estimation of incidence rate of mortality for antileishmanial therapies: A systematic review of published literature from 1980 to 2018. American Journal of Tropical Medicine and Hygiene. 2019;101(5 Supplement):400. |
| 89. | Singh S, Dahal P, Ngu R, Maguire B, Olliaro PL, Stepniewska K, et al. Estimation of incidence risk of mortality and serious adverse events for antileishmanial therapies: An infectious diseases data observatory systematic review of published literature from 1980 to 2018. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2019;113(Supplement 1):S69. |
| 90. | Singh S, Kumar J, Singh R, Dwivedi SN. Hepatitis B and C viral infections in Indian kala-azar patients receiving injectable anti-leishmanial drugs: a community-based study. International Journal of Infectious Diseases. 2000;4(4):203-8. |
| 91. | Sinha K. Liposomal amphotericin B for visceral leishmaniasis in HIV coinfected patients: 2-year treatment outcomes in Bihar, India. Tropical Medicine and International Health. 2011;Conference(var.pagings):189. |
| 92. | Sinha PK, van Griensven J, Pandey K, Kumar N, Verma N, Mahajan R, et al. Liposomal amphotericin B for visceral leishmaniasis in human immunodeficiency virus-coinfected patients: 2-year treatment outcomes in Bihar, India. Clinical Infectious Diseases. 2011;53(7):e91-e8. |

| | |
|---|---|
| 93. | Takele Y, Abebe T, Weldegebreal T, Hailu A, Hailu W, Hurissa Z, et al. Arginase Activity in the Blood of Patients with Visceral Leishmaniasis and HIV Infection. PLoS Neglected Tropical Diseases. 2013;7(1): e1977. |
| 94. | Tavora LG, Nogueira MB, Gomes ST. Visceral Leishmaniasis/HIV co-infection in northeast Brazil: Evaluation of outcome. Brazilian Journal of Infectious Diseases. 2015;19(6):651-6. |
| 95. | ter Horst R, Collin SM, Ritmeijer K, Bogale A, Davidson RN. Concordant HIV infection and visceral leishmaniasis in Ethiopia: The influence of antiretroviral treatment and other factors on outcome. Clinical Infectious Diseases. 2008;46(11):1702-9. |
| 96. | Torre-Cisneros J. Efficacy of liposomal amphotericin B in the treatment of visceral leishmaniasis in patients coinfected with the human immunodeficiency virus. Clinical Infectious Diseases. 1995;20(1):191. |
| 97. | Tortajada C, Pérez-Cuevas B, Moreno A, Martínez E, Mallolas J, García F, et al. Highly active antiretroviral therapy (HAART) modifies the incidence and outcome of visceral leishmaniasis in HIV-infected patients. Journal of Acquired Immune Deficiency Syndromes. 2002;30(3):364-6. |
| 98. | Toumi A, Kilani B, Ammari L, Tiouiri H, Kanoun F, Belhadj S, et al. [Demographic, clinical and therapeutic features of adult visceral leishmaniasis at the Rabta hospital in Tunis (46unisia) from 1983 to 2002]. [French]. Bulletin de la Societe de Pathologie Exotique. 2007;100(4):282-6. |
| 99. | Troya J, Casquero A, Muñiz G, Fernández-Guerrero ML, Górgolas M. The role of splenectomy in HIV-infected patients with relapsing visceral leishmaniasis. Parasitology. 2007;134(5):621-4. |
| 100. | Vallejo A, Abad FM, Moreno S, Moreno A, Perez-Elias MJ, Dronda F, et al. High levels of CD4+ CTLA-4+ Treg cells and CCR5 density in HIV-1-infected patients with visceral leishmaniasis. European Journal of Clinical Microbiology & Infectious Diseases. 2014;34. |
| 101. | van Griensven J, Mengesha B, Mekonnen T, Fikre H, Takele Y, Adem E, et al. Leishmania antigenuria to predict initial treatment failure and relapse in Visceral Leishmaniasis/HIV coinfected patients: An exploratory study nested within a clinical trial in Ethiopia. Frontiers in Cellular and Infection Microbiology. 2018;8(MAR):94. |
| 102. | van Griensven J, Simegn T, Endris M, Diro E. Visceral leishmaniasis and HIV co-infection in Northwest Ethiopia: Antiretroviral treatment and burden of disease among patients enrolled in HIV care. American Journal of Tropical Medicine and Hygiene. 2018;98(2):486-91. |
| 103. | Villanueva JL, Alarcón A, Bernabeu-Wittel M, Cordero E, Prados D, Regordán C, et al. Prospective evaluation and follow-up of European patients with visceral leishmaniasis and HIV-1 coinfection in the era of highly active antiretroviral therapy. European Journal of Clinical Microbiology & Infectious Diseases. 2000;19(10):798-801. |
| **Reason for exclusion: irrelevant setting (PICO 2)** | |
| 1. | Bossolasco S, Gaiera G, Olchini D, Gulletta M, Martello L, et al. Real-time PCR assay for clinical management of human immunodeficiency virus-infected patients with visceral leishmaniasis. Journal of Clinical Microbiology. 2003;41(11):5080-4. |
| 2. | Delgado Fernández M, García Ordoñez MA, Martos Pérez F, Reguera Iglesias JM, Jiménez Oñate F, Colmenero Castillo JD. [The clinical and evolutional characteristics of visceral leishmaniasis in patients with HIV infection]. [Spanish]. Anales de Medicina Interna. 1997;14(10):506-10. |
| 3. | López-Vélez R, Videla S, Márquez M, Boix V, Jiménez-Mejías ME, Górgolas M, et al. Amphotericin B lipid complex versus no treatment in the secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. Journal of Antimicrobial Chemotherapy. 2004;53(3): 540-3. |

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| 4. | Marques N, Sá R, Coelho F, Oliveira J, Saraiva Da Cunha J, Meliço-Silvestre A. Miltefosine for visceral leishmaniasis relapse treatment and secondary prophylaxis in HIV-infected patients. Scandinavian Journal of Infectious Diseases. 2008;40(6-7):523-6. |
| 5. | Molina I. Efficacy of liposomal amphotericin B for secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. Journal of Antimicrobial Chemotherapy. 2007;60(4):837-42. |
| 6. | Pintado V, Martín-Rabadán P, Rivera ML, Moreno S, Bouza E. Visceral leishmaniasis in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients. A comparative study. Medicine. 2001;80(1):54-73. |
| **Reason for exclusion: Single arm studies combination therapy (PICO 1)** | |
| 1. | Abongomera, C., Abongomera, C. The Risk and Predictors of Visceral Leishmaniasis Relapse in Human Immunodeficiency Virus-Coinfected Patients in Ethiopia: A Retrospective Cohort Study. Clinical Infectious Diseases. 2017. 65:1703-1710 |
| 2. | Abongomera, C, Abongomera, Charles, de Lima Pereira, Alan, et al. The initial effectiveness of liposomal amphotericin Band miltefosine combination for treatment of visceral leishmaniasis in HIV co-infected patients in Ethiopia: A retrospective cohort study. PLoS Neglected Tropical Diseases 2018. |
| 3. | Ritmeijer, K. Visceral leishmaniasis-HIV coinfection: Experience from the field. Tropical Medicine and International Health. 2011. Conference:17 |
| 4. | Mahajan R. Combination treatment for visceral leishmaniasis patients co-infected with human immunodeficiency virus in India. Tropical Medicine and International Health. 2015;Conference(var.pagings):207. |
| 5. | Mahajan R, Das P, Isaakidis P, Sunyoto T, Sagili K. Combination Treatment for Visceral Leishmaniasis Patients Coinfected with Human Immunodeficiency Virus in India. Clinical Infectious Diseases. 2015;61(8):1255-62. |

# Appendix 4. Risk of bias assessment

### Ethiopia 2019 (Cochrane risk of bias tool for RCTs)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | "Subjects were allocated to treatment using random block sizes, stratified by site (Gondar & Abdurafi) and by patient type (whether the VL episode at screening was a primary or relapse case)." "The randomization list was prepared by the data management team. Site investigators were blinded to block sizes." |
| **Allocation concealment (selection bias)** | Low risk | "Randomization codes were prepared in sealed, sequentially numbered, opaque envelopes and were under the control of the site investigator" |
| **Blinding of participants and personnel (performance bias)** | High risk | This is an un-blinded study.<br>"Patients and treating physicians were not masked to study treatment due to the considerable differences in the administration of the treatment arms (different dosing schedule of an infused treatment plus oral administration)". |
| **Blinding of outcome assessment (detection bias)** | Unclear risk | Not reported, but primary outcome (parasitic clearance) would presumably be objective measure which is unlikely to be biased. Other outcomes measures (e.g. patient symptoms, adverse events) were unblinded and may be at risk of bias. Relationship between serious adverse events and treatment determined by study investigator. |
| **Incomplete outcome data (attrition bias)** | Low risk | "There were no missing outcome data. One patient died after randomization before receiving any treatment and was excluded from all analyses." |
| **Selective reporting (reporting bias)** | Low risk | outcomes specified in published protocol and trial record (https://clinicaltrials.gov/ct2/show/NCT02011958) were reported, except long-term follow-up which will be reported in a separate publication |
| **Other bias** | Unclear risk | Non-comparative sequential trial design which was stopped early for lack of efficacy. Groups were unbalanced in size and analysis did not account for confounding.<br>Study was underpowered to detect difference between groups.<br>Financed by the European Union Seventh Framework Programme; the Dutch Ministry of Foreign Affairs (DGIS); the Federal Ministry of Education and Research (BMBF through KfW), Germany; Medecins Sans Frontières/Doctors without Borders; the Medicor Foundation, Liechtenstein; UK aid; the Swiss Agency for Development and Cooperation (SDC)<br>Trial ID: NCT02011958 |

### India 2019 (Cochrane risk of bias tool for RCTs)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| **Random sequence generation (selection bias)** | Low risk | A computer-generated randomization code was used for patient treatment allocation to one of the two treatment arms (monotherapy or combination therapy). Randomization code was generated using block randomization method by an Independent Statistician not directly involved in the trial. |
| **Allocation concealment (selection bias)** | Low risk | The Trial Statistician used this list to produce one set of 150 individual, opaque, sealed and sequentially numbered envelopes containing the first 150 allocations. The password protected randomization list was held by the Trial Statistician and was not accessible to other members of the study team. |
| **Blinding of participants and personnel (performance bias)** | High risk | This is an un-blinded study. |
| **Blinding of outcome assessment (detection bias)** | Unclear | Not reported, but primary outcome (parasitic clearance) would presumably be objective measure which is unlikely to be biased. Other outcomes measures (e.g. patient symptoms, adverse events) were unblinded and may be at risk of bias. Relationship between serious adverse events and treatment determined by study investigator. |
| **Incomplete outcome data (attrition bias)** | Low risk | All 150 patients were included in the ITT analysis. No loss to follow up in the study |
| **Selective reporting (reporting bias)** | Low risk | All specified primary outcomes reported, protocol checked |
| **Other bias** | Unclear risk | Non-comparative trial. Limited details (unpublished) available on participant characteristics and treatment adherence.<br>Study was unpowered to detect difference between groups<br>Financed by: MSF Spain acted as sponsor - investigator for the study (i.e. funding was from MSF Spain). RMRI acted as Investigator and was sole study site. Support for site monitoring and data management was provided by DNDi.<br>Trial ID: CTRI/2015/05/005807 |

### India 2017 (ROBINS-I for observational studies)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| **Bias due to confounding** | Moderate / Serious | Comment: CD4 levels were similar in the two groups at baseline, but there was no information on balance between groups on previous relapses or other confounding factors at baseline. The |

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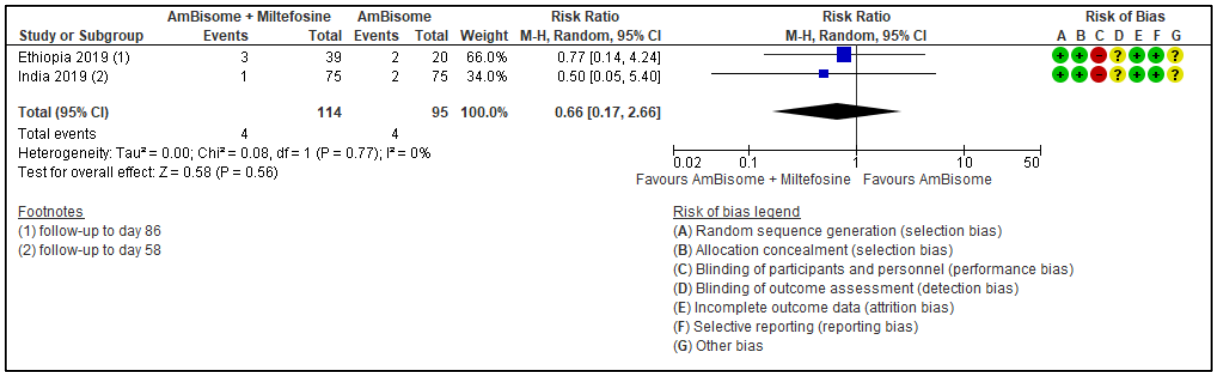
| | | following factors were controlled in the adjusted analysis on time to mortality: hemoglobin level at baseline, total leukocyte count at baseline, CD4 cell count at 6-month follow-up, and relapse within the first 6 months of follow-up. However, some residual confounding is likely to remain, especially for a retrospective study.<br><br>Assessed as moderate for time to mortality and serious for all other outcomes. |
| **Selection bias** | Serious | Quote: All patients admitted at the STM [School of Tropical Medicine] from January 2005 to February 2015 with VL were retrospectively included.<br><br>Quote: Records of HIV–VL patients who were offered secondary prophylaxis were documented in terms of drugs and doses used and the duration of secondary prophylaxis.<br><br>Comment: It is unclear when the follow up of the patients started since exposure to treatment is at any time during hospitalization and analysis is performed after the completion of the study. Therefore, there is risk for immortal time bias, which has not been controlled for. |
| **Bias in classification of intervention** | Low | Quote: Hospital records of routinely collected data generated during inpatient management were analyzed with permission from the appropriate authorities.<br><br>Comment: Treatment groups were classified using clearly defined criteria (receipt vs non receipt of secondary prophylaxis). |
| **Bias due to departure from intervention** | No information | Comment: The information reported is inadequate to assess whether there are deviations from the intended intervention beyond what would be expected in usual practice. Patients were all given anti-retroviral treatment during follow-up, but there is no information on other co-interventions during the 20-year data collection period. |
| **Bias due to missing data** | Low | Comment: data were missing for 5/56 (9%) patients that were initially included, 3 were lost to follow-up before initiation of secondary prophylaxis and 2 died during the initial treatment before initiation of secondary prophylaxis. |
| **Bias in measurement of outcomes** | Low | Comment: Retrospective data collection from hospital records, measurement of outcomes likely to not be biased to the intervention. |
| **Bias in selection of the reported result** | Moderate | Comment: The outcomes and analyses are clearly defined in the Methods section. There is no a-priori registered protocol or statistical analysis plan available. |

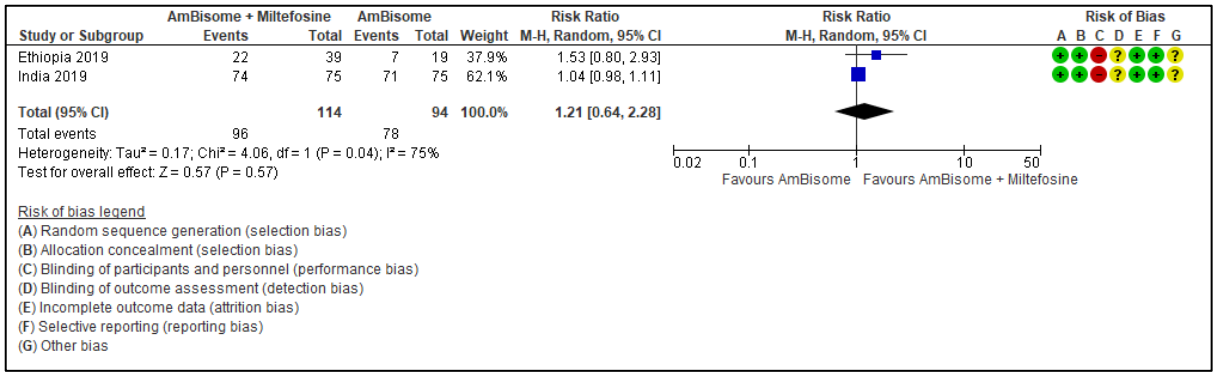
# Appendix 5. Analyses

## Combination therapy of liposomal amphotericin B and oral miltefosine with the monotherapy of liposomal amphotericin B

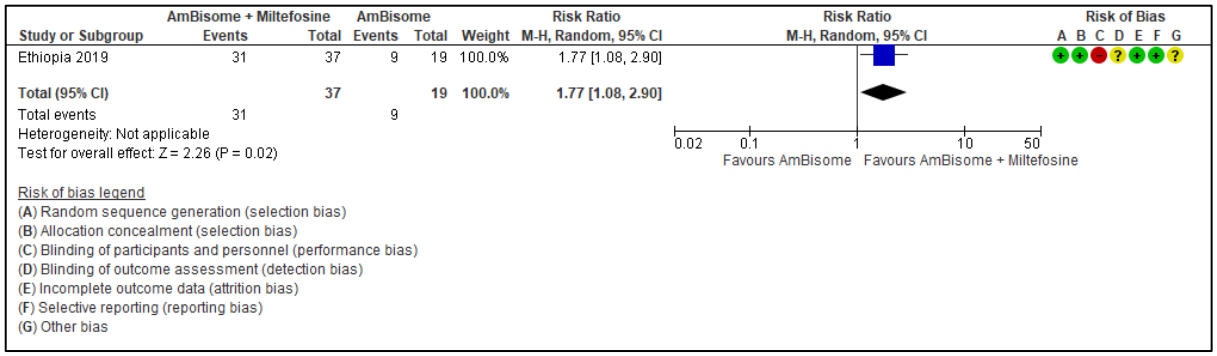
### Analysis 1. 1 All -cause mortality, up to day 86



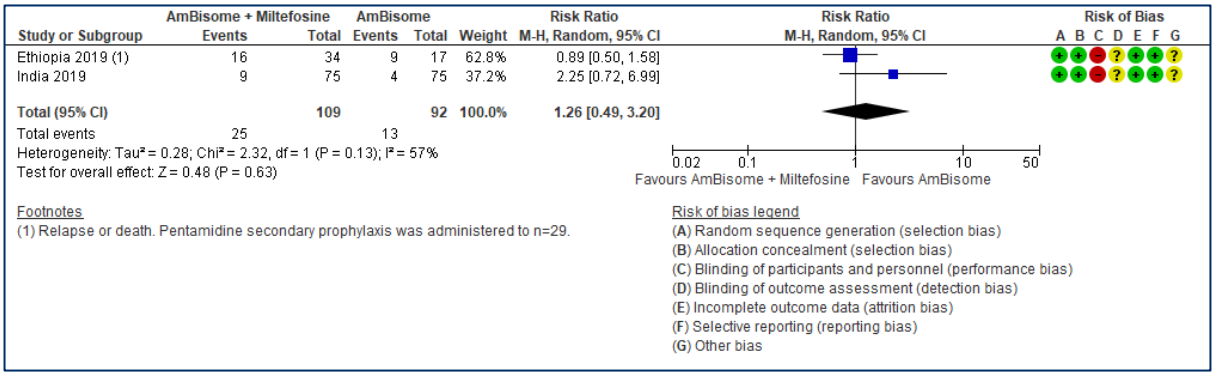

### Analysis 1. 2 Clinical cure, day 29



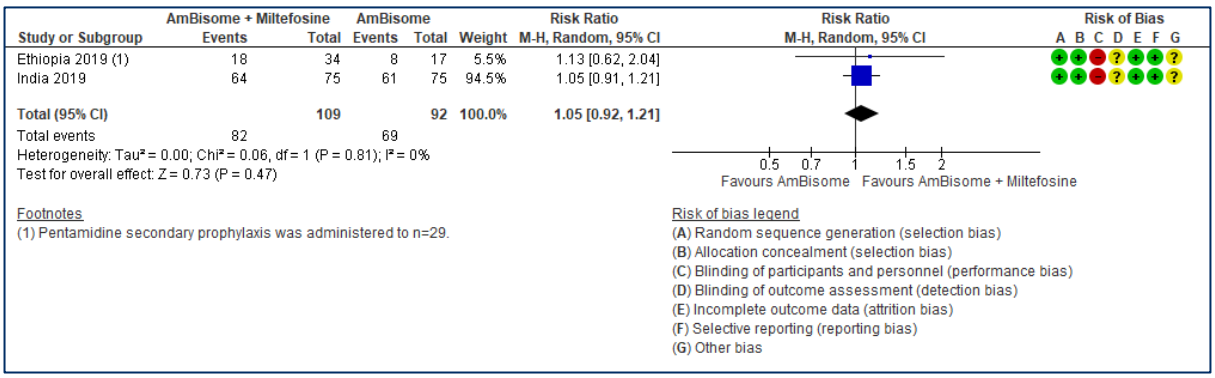

### Analysis 1. 3 Clinical cure, day 58



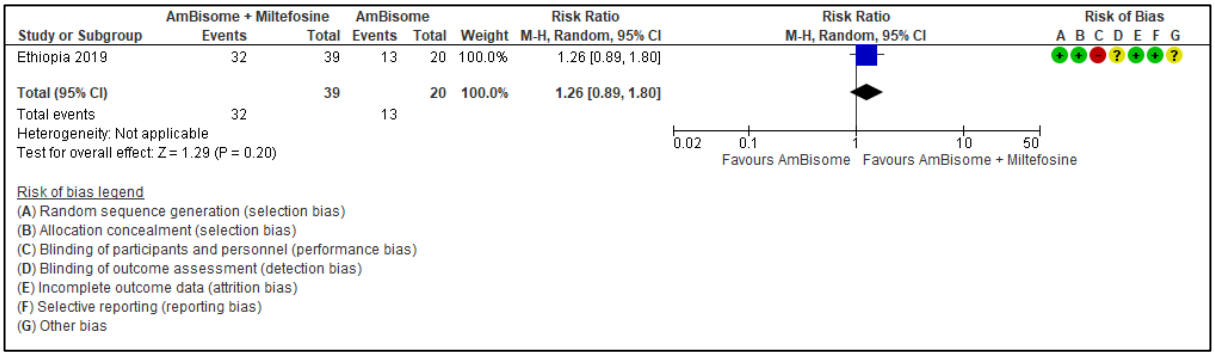
## Analysis 1. 4 Relapse, day 390



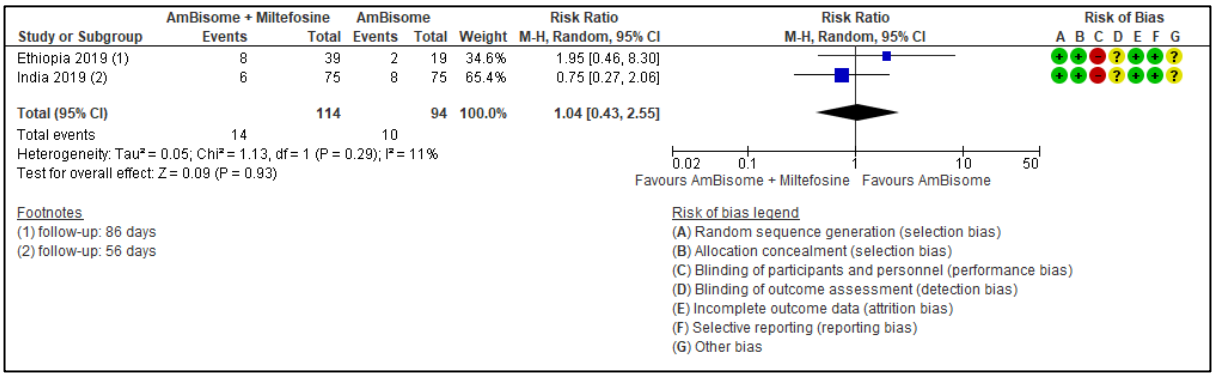

## Analysis 1. 5 Relapse-free survival, at day 390




## Analysis 1. 6 Treatment adherence



## Analysis 1. 7 Serious adverse events (any cause), up to day 86



| Study or Subgroup | AmBisome + Miltefosine Events | Total | AmBisome Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Ethiopia 2019 (1) | 8 | 39 | 2 | 19 | 34.6% | 1.95 [0.46, 8.30] |
| India 2019 (2) | 6 | 75 | 8 | 75 | 65.4% | 0.75 [0.27, 2.06] |
| **Total (95% CI)** | | **114** | | **94** | **100.0%** | **1.04 [0.43, 2.55]** |
| Total events | 14 | | 10 | | | |

Heterogeneity: Tau² = 0.05; Chi² = 1.13, df = 1 (P = 0.29); I² = 11%
Test for overall effect: Z = 0.09 (P = 0.93)

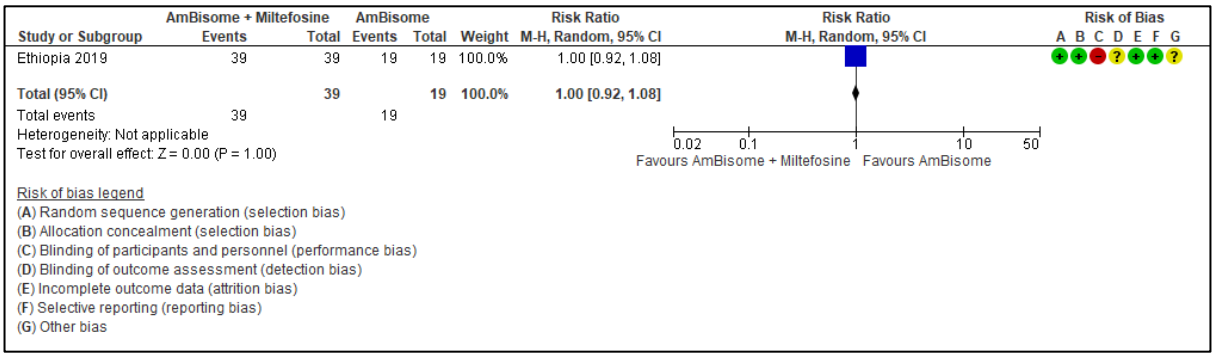
Risk Ratio M-H, Random, 95% CI: 0.02, 0.1, 1, 10, 50
Favours AmBisome + Miltefosine | Favours AmBisome

Risk of Bias: A B C D E F G

Footnotes
(1) follow-up: 86 days
(2) follow-up: 56 days

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 1. 8 Adverse events (any cause), up to day 86



| Study or Subgroup | AmBisome + Miltefosine Events | Total | AmBisome Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Ethiopia 2019 | 39 | 39 | 19 | 19 | 100.0% | 1.00 [0.92, 1.08] |
| **Total (95% CI)** | | **39** | | **19** | **100.0%** | **1.00 [0.92, 1.08]** |
| Total events | 39 | | 19 | | | |

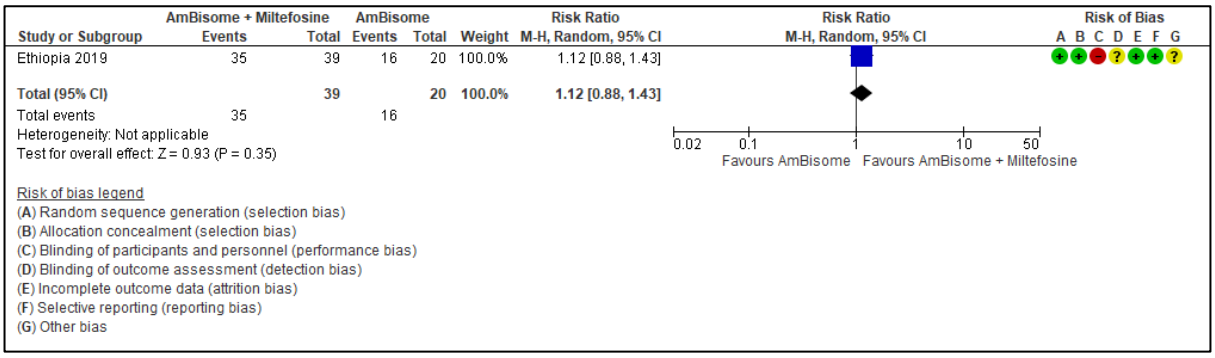
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

Risk Ratio M-H, Random, 95% CI: 0.02, 0.1, 1, 10, 50
Favours AmBisome + Miltefosine | Favours AmBisome

Risk of Bias: A B C D E F G

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 1. 9 Follow-up of patients



| Study or Subgroup | AmBisome + Miltefosine Events | Total | AmBisome Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Ethiopia 2019 | 35 | 39 | 16 | 20 | 100.0% | 1.12 [0.88, 1.43] |
| **Total (95% CI)** | | **39** | | **20** | **100.0%** | **1.12 [0.88, 1.43]** |
| Total events | 35 | | 16 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)

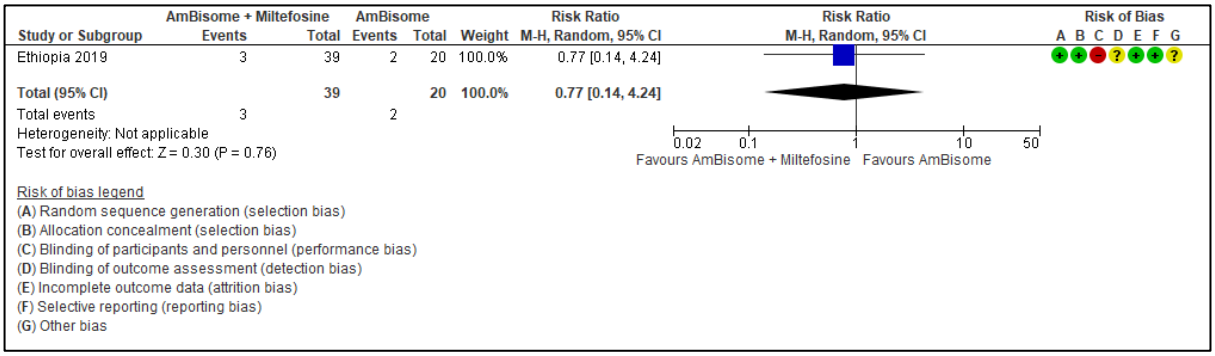
Risk Ratio M-H, Random, 95% CI: 0.02, 0.1, 1, 10, 50
Favours AmBisome | Favours AmBisome + Miltefosine

Risk of Bias: A B C D E F G

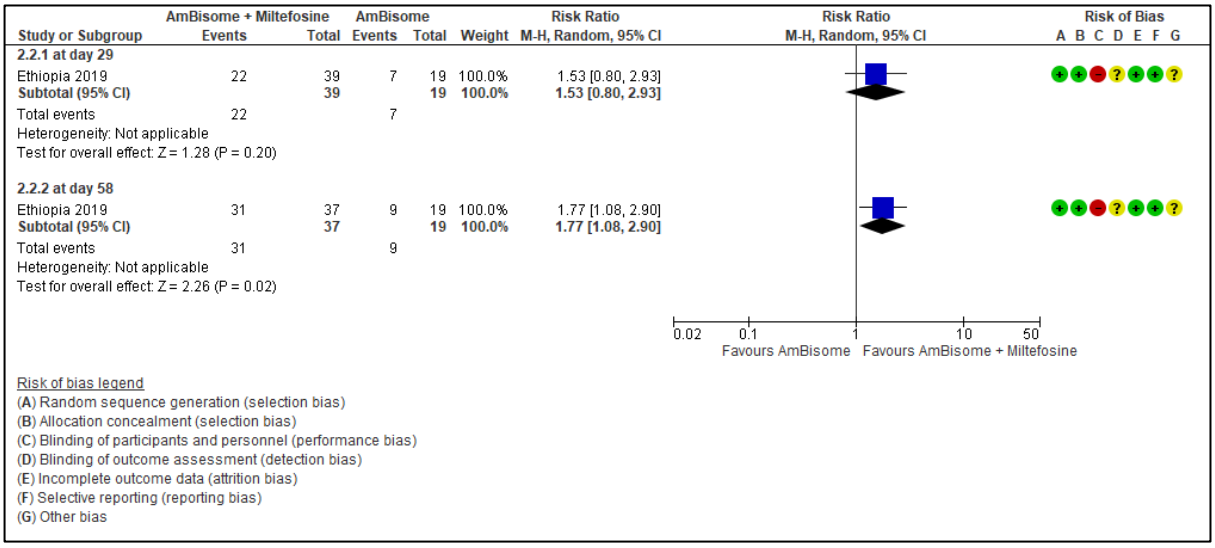
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Combination therapy of liposomal amphotericin B and oral miltefosine with the monotherapy of liposomal amphotericin B in Ethiopia

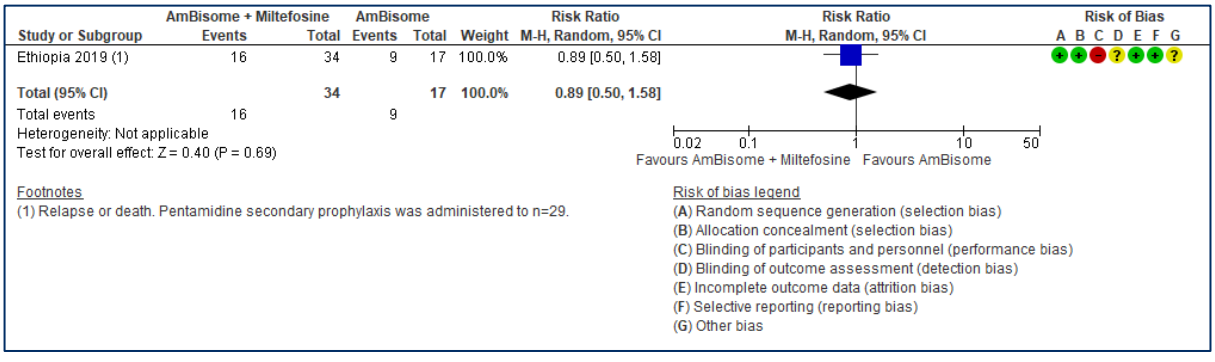
### Analysis 2. 1 All-cause mortality, day 86



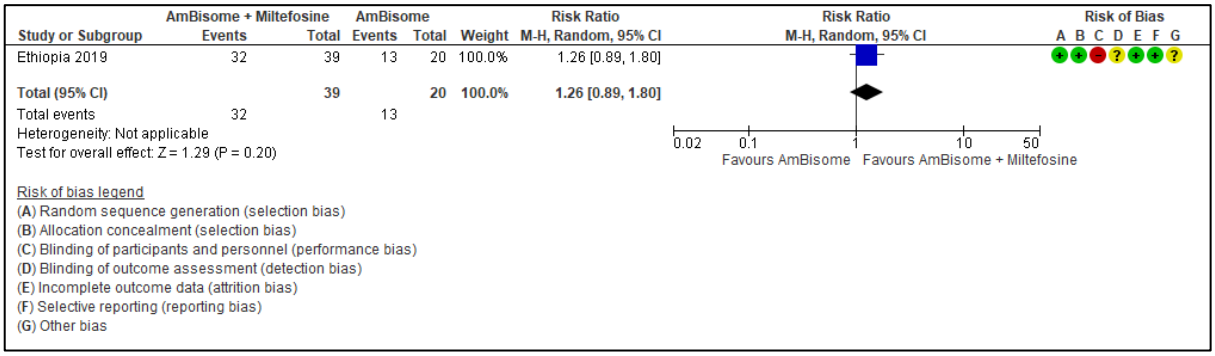

### Analysis 2. 2 Clinical cure, up to day 58



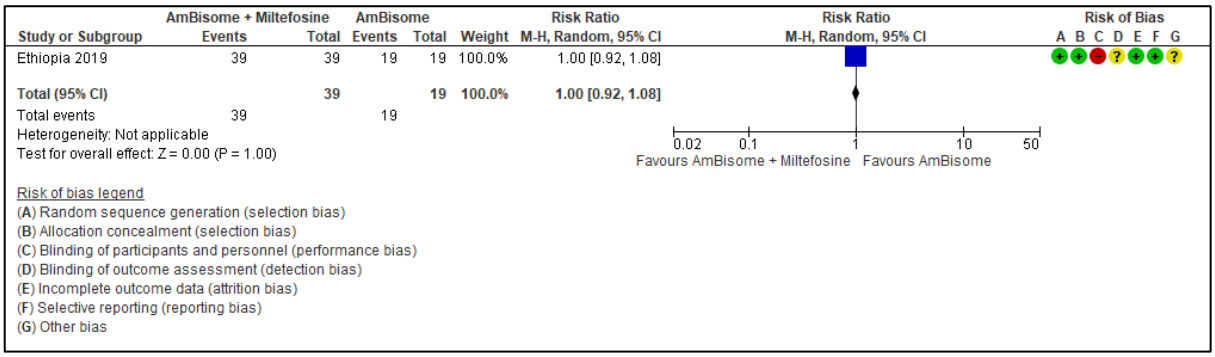

### Analysis 2. 3 Relapse, at day 390



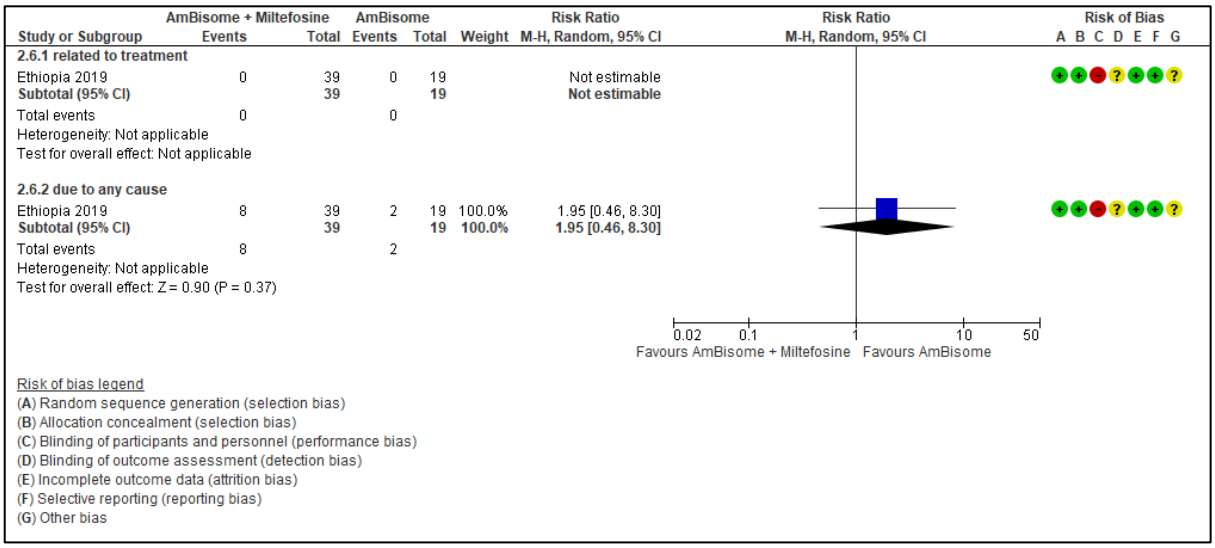
## Analysis 2. 4 Treatment adherence



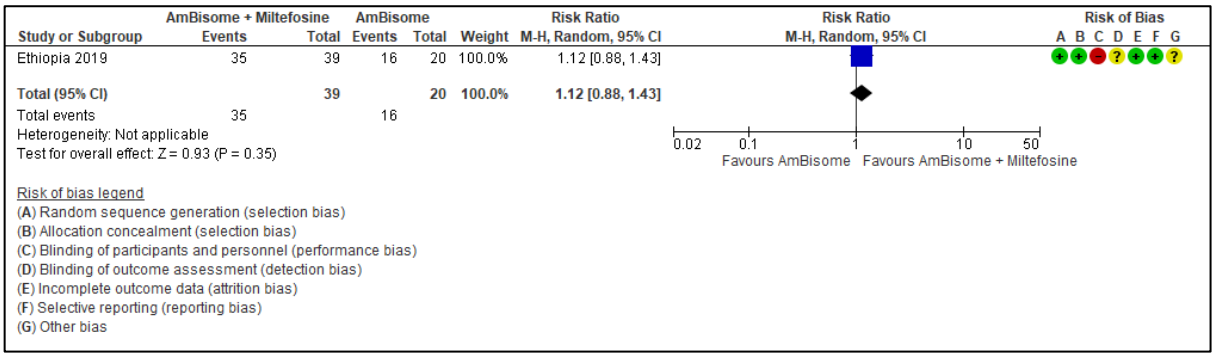

## Analysis 2. 5 Adverse events




## Analysis 2. 6 Serious adverse events, at day 86

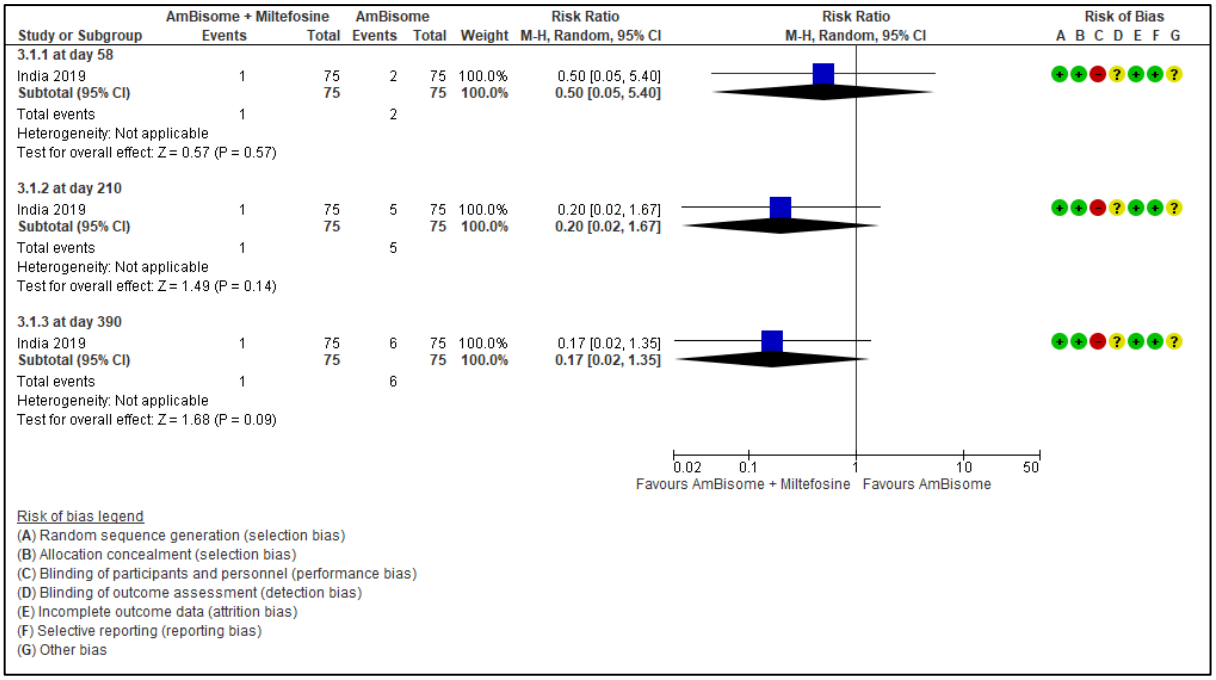


## Analysis 2. 7 Follow-up of patients

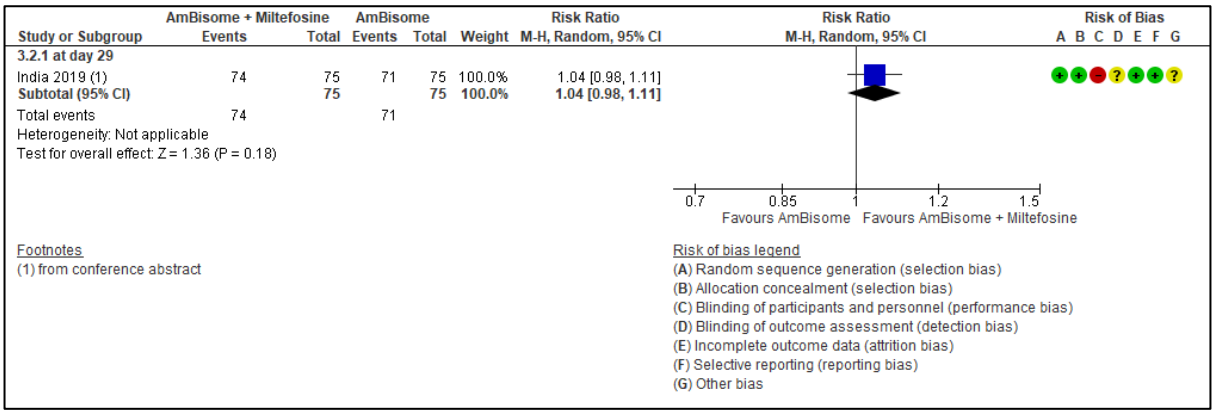



# Combination therapy of liposomal amphotericin B and oral miltefosine with the monotherapy of liposomal amphotericin B in South Asia

## Analysis 3. 1 All-cause mortality, up to day 390



## Analysis 3. 2 Clinical cure (day 29)



| Study or Subgroup | AmBisome + Miltefosine Events | Total | AmBisome Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **3.2.1 at day 29** | | | | | | |
| India 2019 (1) | 74 | 75 | 71 | 75 | 100.0% | 1.04 [0.98, 1.11] |
| **Subtotal (95% CI)** | | **75** | | **75** | **100.0%** | **1.04 [0.98, 1.11]** |
| Total events | 74 | | 71 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.36 (P = 0.18) | | | | | | |

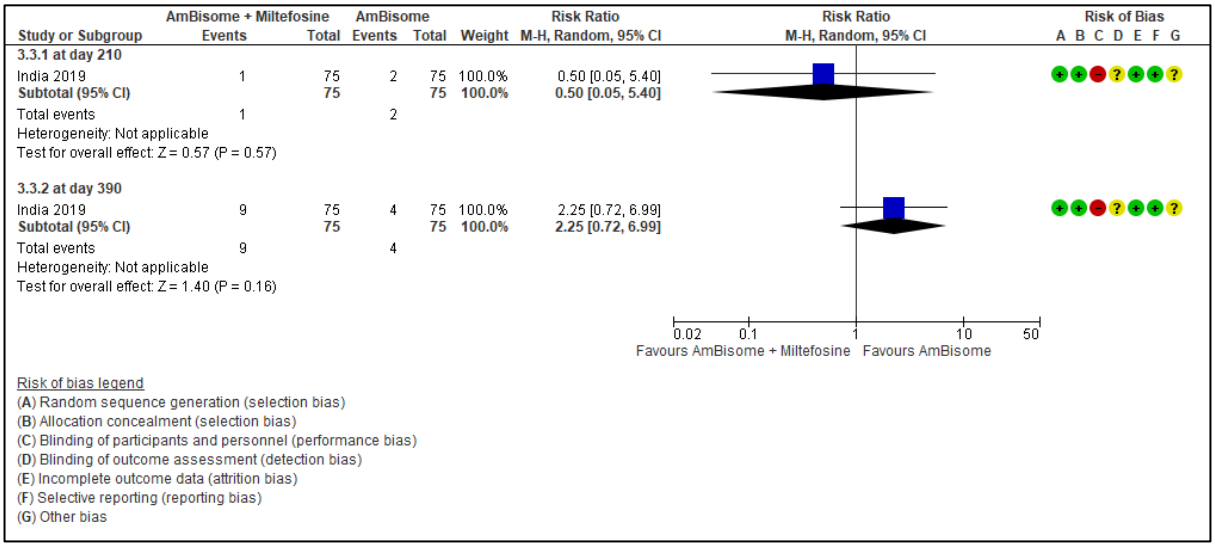
Risk of Bias: A B C D E F G

Risk Ratio M-H, Random, 95% CI: 0.7, 0.85, 1, 1.2, 1.5; Favours AmBisome; Favours AmBisome + Miltefosine

Footnotes
(1) from conference abstract

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3. 3 Relapse, up to day 390



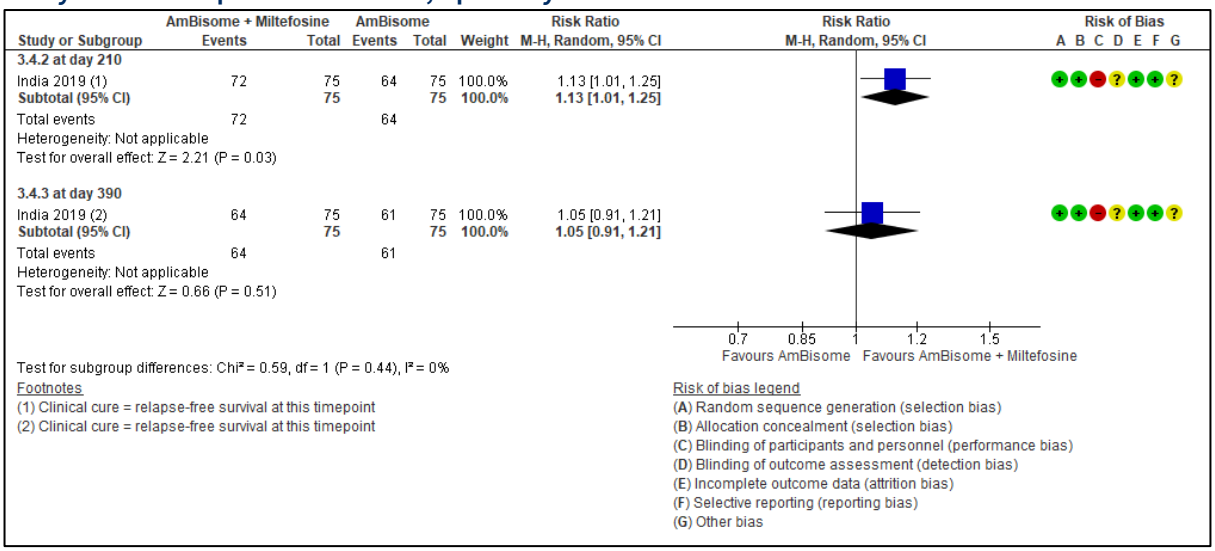
| Study or Subgroup | AmBisome + Miltefosine Events | Total | AmBisome Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **3.3.1 at day 210** | | | | | | |
| India 2019 | 1 | 75 | 2 | 75 | 100.0% | 0.50 [0.05, 5.40] |
| **Subtotal (95% CI)** | | **75** | | **75** | **100.0%** | **0.50 [0.05, 5.40]** |
| Total events | 1 | | 2 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.57 (P = 0.57) | | | | | | |
| **3.3.2 at day 390** | | | | | | |
| India 2019 | 9 | 75 | 4 | 75 | 100.0% | 2.25 [0.72, 6.99] |
| **Subtotal (95% CI)** | | **75** | | **75** | **100.0%** | **2.25 [0.72, 6.99]** |
| Total events | 9 | | 4 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 1.40 (P = 0.16) | | | | | | |

Risk of Bias: A B C D E F G

Risk Ratio M-H, Random, 95% CI: 0.02, 0.1, 1, 10, 50; Favours AmBisome + Miltefosine; Favours AmBisome

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

## Analysis 3. 4 Relapse-free survival, up to day 390



| Study or Subgroup | AmBisome + Miltefosine Events | Total | AmBisome Events | Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| **3.4.2 at day 210** | | | | | | |
| India 2019 (1) | 72 | 75 | 64 | 75 | 100.0% | 1.13 [1.01, 1.25] |
| **Subtotal (95% CI)** | | **75** | | **75** | **100.0%** | **1.13 [1.01, 1.25]** |
| Total events | 72 | | 64 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 2.21 (P = 0.03) | | | | | | |
| **3.4.3 at day 390** | | | | | | |
| India 2019 (2) | 64 | 75 | 61 | 75 | 100.0% | 1.05 [0.91, 1.21] |
| **Subtotal (95% CI)** | | **75** | | **75** | **100.0%** | **1.05 [0.91, 1.21]** |
| Total events | 64 | | 61 | | | |
| Heterogeneity: Not applicable | | | | | | |
| Test for overall effect: Z = 0.66 (P = 0.51) | | | | | | |

Risk of Bias: A B C D E F G

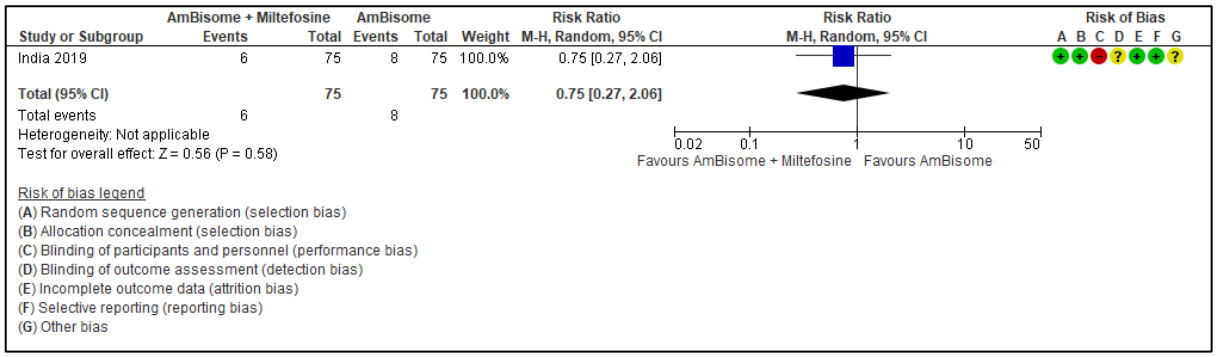
Risk Ratio M-H, Random, 95% CI: 0.7, 0.85, 1, 1.2, 1.5; Favours AmBisome; Favours AmBisome + Miltefosine

Test for subgroup differences: Chi² = 0.59, df = 1 (P = 0.44), I² = 0%

Footnotes
(1) Clinical cure = relapse-free survival at this timepoint
(2) Clinical cure = relapse-free survival at this timepoint

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

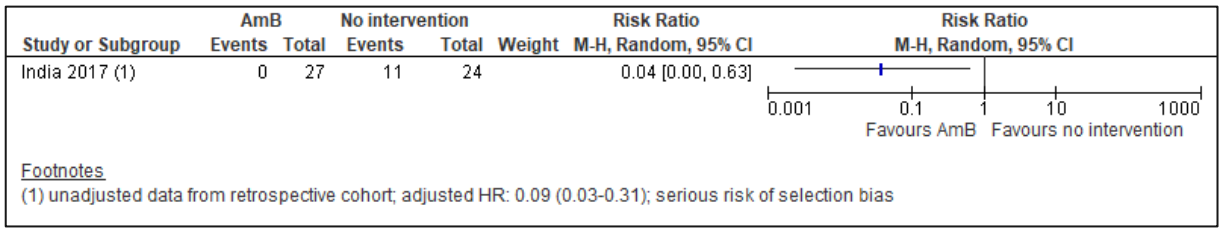
### Analysis 3. 5 Serious adverse events due to any case, at day 58



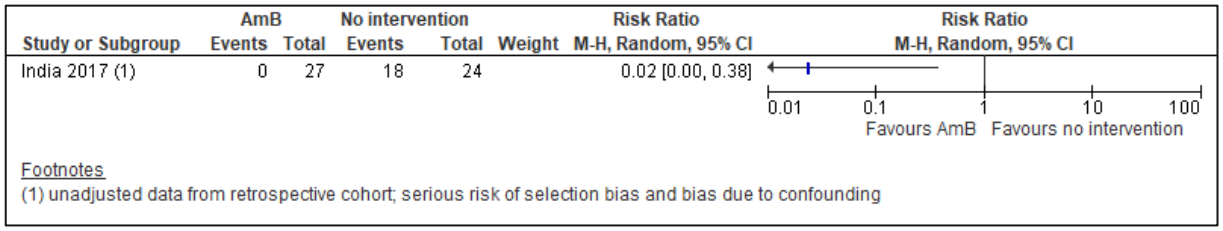

## PICO 2. Secondary prophylaxis

### Main analysis. Secondary prophylaxis compared with no secondary prophylaxis for preventing relapse in people with visceral leishmaniasis and HIV coinfection following the first episode of visceral leishmaniasis in East Africa and South East Asia

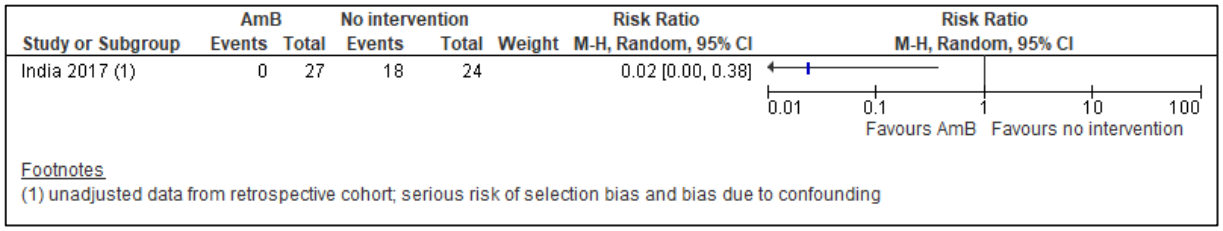
### Analysis 4. 1 All-cause mortality, at 12 months



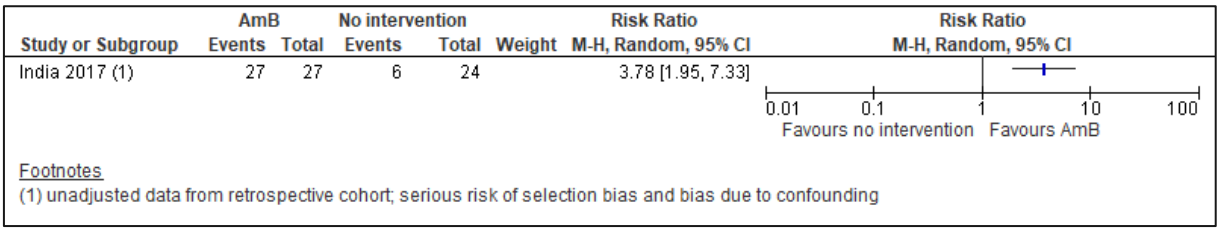

### Analysis 4. 2 Relapse, at 6 months




### Analysis 4. 3 Relapse, at 12 months



### Analysis 4. 4 Relapse-free survival, at 12 months




### Evidence from single-arm and non-comparative studies: Results on secondary prophylaxis for preventing relapse of visceral leishmaniasis in people with HIV

| Outcome | Results from Ethiopia 2015 | Results from Ethiopia 2019b |
|---|---|---|
| | Prospective cohort of 74 participants with HIV that received pentamidine for VL relapse prevention | Follow-up cohort from randomised study of 29 patients with <200/µl CD4 cells at baseline that received pentamidine as secondary prophylaxis and 22 patients with ≥200/µl CD4 cells at baseline that received no secondary prophylaxis |
| All-cause mortality | At 2-year follow-up 5 (7%) had died. | Deaths at one-year follow-up:<br><200 CD4 pentamidine group: 5/29 (17%)<br>≥200 CD4 no pentamidine group: 1/22 (5%) |
| Relapse | At 2-year follow-up 20 (27%) had relapsed. | Relapse at one-year follow-up:<br><200 CD4 pentamidine group:12/29 (41%)<br>≥200 CD4 no pentamidine group: 9/22 (41%) |
| Relapse-free survival | The probability of relapse-free survival at 6 months, 12 months, and 2 years was 79%, 71%, and 53% respectively. | Relapse-free survival at one-year follow-up:<br><200 CD4 pentamidine group: 46% (26–63%)<br>≥200 CD4 no pentamidine group: 53% (30–71%) |
| Adherence | 41/74 (55%) of the participants completed the follow-up taking at least 11 of the planned 12 doses without experiencing relapse, death or drug-related SAEs. 29 patients discontinued pentamidine permanently; 15 (20.3%) of them because of relapse, 7 (9.5%) were lost to follow-up, 5 (6.8%) died, one patient had to stop due to hyperglycemia, and another patient refused to take the study drug. | Adherence at one-year follow-up:<br><200 CD4 pentamidine group: 76% (22/29) with 100% compliance for the monthly pentamidine infusions. |
| Serious adverse events | During 12 months follow-up there were 21 serious adverse events in 17 of the 74 included patients, two may have been related to pentamidine (renal failure in two patients hospitalised with pneumonia). | Serious adverse events at one-year follow-up:<br><200 CD4 pentamidine group: 8*/29 (28%)<br>≥200 CD4 no pentamidine group: 1**/22 (5%) |
| Adverse events | During 12 months follow-up there were 42 study-drug related adverse events in 30 of the 74 study participants. The most common being symptoms of the respiratory system (nasal congestion) during pentamidine infusion– 14 (19%), | No information |

| | | |
|---|---|---|
| | hypotension– 11 (15%) and renal impairment—5 (6.8%). Clinical and therapeutic interventions for pentamidine related adverse events were needed for 11 (14.9%) of the study participants, including additional intravenous fluid during pentamidine administration (n=10), reducing the rate of pentamidine infusion (n=10), oral hydrations (n=2), prolonged hospital observation (n=2), additional medication during pentamidine infusion (n=2), glucose supplementation (n=1). | |
| Follow-up | At one-year follow-up 7 (9.5%) and at two years follow-up 10 (14%) were lost to follow-up. | All patients that started on secondary prophylaxis were followed-up to the end of the study. Before initiation of secondary prophylaxis, three patients withdrew from the study (contraindication, n=1; refused/early withdrawal, n=2). |
| Predictors of relapse | After 12 months, more patients failed among those with a CD4-cell count ≤ 50 cells/µl, 5/7 (71.4%) than those with counts above 200 cells/µl, 2/12 (16.7%), (p = 0.005). 2-year risk of relapse was highest for those with a history of VL relapse and low baseline CD4 count. | In patients with <200 CD4 cells/µL that received pentamidine, no statistically significant risk factors for relapse or death were identified.<br>In patients with ≥200 CD4 cells/µL that received no secondary prophylaxis, higher rates of relapse or death were detected in relapse cases compared to primary cases, in patients with normal BMI compared to low BMI (<18.5kg/m2), and in patients previously treated with monotherapy compared with the combination regimen for the VL episode. |

* Strongyloidiasis leading to death, Cerebral toxoplasmosis (life threatening, resolved), Plasma cell myeloma and renal failure leading to death, retroviral infection leading to death, splenic haemorrhage (life threatening, resolved), choestatic hepatitis (life threatening, resolved), septic shock leading to death, sepsis leading to death

**Septic shock leading to death

# Appendix 6. Additional Summary of Findings (SOF) tables

### Summary of Findings (SOF) table 3. Combination therapy of liposomal amphotericin B and oral miltefosine in treating VL in HIV coinfected patients compared with the monotherapy of liposomal amphotericin B in East Africa

**Patient or population**: People with a diagnosis of HIV and coinfection with visceral leishmaniasis

**Setting**: East Africa (Ethiopia)

**Intervention**: infusion of liposomal amphotericin B (up to 30 mg/kg @5 mg/kg on days 1, 3, 5, 7, 9 and 11) and oral miltefosine (100 mg/day for 28 days)

**Comparison**: monotherapy of liposomal amphotericin B at a dose of 5 mg/kg daily or intermittently for 10 doses (days 1-5, 10, 17, 24) up to a total dose of 40 mg/kg.

| Outcomes | Rate in monotherapy group | Rate in combination therapy group | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| **All-cause mortality**<br>Up to 86 days | 2/20 (10%) | 3/39 (8%) | RR 0.77<br>(0.14 to 4.24) | 59 participants<br>1 non-comparative RCT | ⨁◯◯◯<br>VERY LOW [a, b] | One death in the combination therapy group occurred slightly after the treatment phase recording period but is reported here as first symptoms were reported during the period; one death in the monotherapy group occurred after randomisation but before treatment had started |
| **Clinical cure**[1]<br>Day 29 | 7/19 (37%) | 22/39 (56%) | RR 1.53<br>(0.80 to 2.93) | 59 participants<br>1 non-comparative RCT | ⨁◯◯◯<br>VERY LOW [a, b] | ITT and per-protocol analysis<br>Estimates adjusted for trial design: combination 81% (95% CI 67 to 90); monotherapy 70% (95% CI 45 to 87) |
| **Clinical cure**[1]<br>Day 29 | 7/19 (37%) | 22/39 (56%) | | 58 participants<br>1 non-comparative RCT | ⨁◯◯◯<br>VERY LOW [a, b] | ITT and per-protocol analysis with over run[6]<br>Estimates adjusted for trial design: combination 67% (95% CI 48 to 82); monotherapy 50% (95% CI 27 to 73) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Clinical cure**[2]<br>Day 58 | 9/16 (56%) | 31/35 (89%) | | 51 participants<br>1 non-comparative RCT | ⊕◯◯◯<br>VERY LOW [a, b] | Per-protocol analysis<br>Estimates adjusted for trial design: combination 95% (95% CI 90 to 100); monotherapy 70% (95% CI 46 to 94) |
| **Clinical cure**[2]<br>Day 58 | 9/19 (47%) | 31/37 (84%) | RR 1.77<br>(1.08 to 2.90) | 56 participants<br>1 non-comparative RCT | ⊕⊕◯◯<br>LOW [a, c] | ITT analysis<br>Estimates adjusted for trial design: combination 93% (95% CI 87 to 99); monotherapy 68% (95% CI 44 to 91) |
| **Clinical cure**[2]<br>Day 58 | 9/16 (56%) | 31/35 (89%) | | 51 participants<br>1 non-comparative RCT | ⊕◯◯◯<br>VERY LOW [a, b] | Per-protocol analysis with over run[6]<br>Estimates adjusted for trial design: combination 91% (95% CI 82 to 100); monotherapy 59% (95% CI 35 to 83) |
| **Clinical cure**[2]<br>Day 58 | 9/19 (47%) | 31/37 (84%) | | 58 participants<br>1 non-comparative RCT | ⊕◯◯◯<br>VERY LOW [a, b] | ITT analysis with over run[6]<br>Estimates adjusted for trial design: combination 88% (95% CI 79 to 98); monotherapy 55% (95% CI 32 to 78) |
| **Relapse**[3]<br>Day 390 | 3/10 (30%) | 10/19 (53%) | RR 0.89<br>(0.50, 1.58)) | 51 participants<br>1 non-comparative RCT | ⊕◯◯◯<br>VERY LOW [a, b] | Subgroup of patients that had CD4 <200 cells/μL and received pentamidine after treatment |
| **Relapse**[3]<br>Day 390 | 6/7 (86%) | 6/15 (40%) | | | | Subgroup of patients that CD4 >200 cells/μL and did not receive pentamidine |
| **Treatment adherence**[4]<br>Day 58 | 13/20 (65%) | 32/39 (82%) | RR 1.26<br>(0.89 to 1.80) | 58 participants<br>1 non-comparative RCT | ⊕⊕◯◯<br>LOW [a, c] | Monotherapy arm: died (n=2); rescue treatment (n=5)<br>Combination arm: died (n=2); rescue treatment (n=3); lost to follow-up (n=2) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Adverse events[5] - any cause**<br>Up to 86 days | 19/19 (100%) | 39/39 (100%) | RR 1.00<br>(0.92 to 1.08) | 58 participants<br>1 non-comparative RCT | ⊕⊕◯◯<br>LOW [a, c] | No adverse event led to treatment discontinuation |
| **Serious adverse events[5] - related to treatment**<br>Up to 86 days | 0/19 (0%) | 0/39 (0%) | Not estimable | 58 participants<br>1 non-comparative RCT | ⊕◯◯◯<br>VERY LOW [a, d] | |
| **Serious adverse events[5] – any cause**<br>Up to 86 days | 2/19 (11%) | 8/39 (21%) | RR 1.95<br>(0.46 to 8.30) | 58 participants<br>1 non-comparative RCT | ⊕◯◯◯<br>VERY LOW [a, b] | Number of patients with at least one SAE |
| **Follow-up of patients** | 16/20 (80%) | 35/39 (90%) | RR 1.12<br>(0.88 to 1.43) | 59 participants<br>1 non-comparative RCT | ⊕⊕◯◯<br>LOW [a, c] | |
| **Patient satisfaction** No studies were identified that reported on this outcome | | | | | | |

[1] Treatment success - clinical and parasitological examination, absence of parasites in tissue aspirate (spleen or bone marrow aspiration). Patients with negative parasitology were considered cured of VL (treatment failure = presence of parasites at the D29 assessment, or death prior to the D29 assessment, or no clinical response to treatment requiring rescue medication on or before D29)

[2] Treatment success - D58 treatment success was defined as: (i) being parasite free at D29 and no recurrence of symptoms by D58 or (ii) being parasite free at D58 after extended treatment. Thus, D58 failures were patients who (i) received rescue treatment prior to, or at, the D58 visit, or (ii) were confirmed to be parasite positive at D58 or (iii) died up to D58. A patient with detectable parasites at D29 who then received extended treatment would be a treatment failure at D29 but a success at D58 if no parasites were detected at D58

[3] No definition provided

[4] No definition provided

[5] See Table 3 for details of individual adverse events

[6] This 'over-run' includes participants who had not reached the primary endpoint (day 29) when the interim analysis was performed and the recruitment was stopped.

**CI:** confidence interval; **HIV:** human immunodeficiency virus; **ITT:** intention to treat; **RCT:** randomised controlled trial; **SAE:** serious adverse event; **VL:** visceral leishmaniasis

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Explanations**

[a] Downgraded one level for limitations in study design: due to limitations in the study design and execution.

[b] Downgraded two levels for serious imprecision: few events and confidence intervals that encompass no effect, a potential benefit, and a potential harm associated with the intervention; the study was not powered to detect a difference between groups

[c] Downgraded one level for imprecision: few events; the study was not powered to detect a difference between groups

[d] Downgrade two levels for serious imprecision: no events recorded; the study was not powered to detect a difference between groups

## Summary of Findings (SOF) table 4. Combination therapy of liposomal amphotericin B and oral miltefosine in treating VL in HIV coinfected patients compared with the monotherapy of liposomal amphotericin B in South Asia

**Patient or population**: People with a diagnosis of HIV and coinfection with visceral leishmaniasis

**Setting**: South Asia (India)

**Intervention**: infusion of liposomal amphotericin B (up to 30 mg/kg @5 mg/kg on days 1, 3, 5, 7, 9 and 11) and oral miltefosine (100 mg/day for 14 days)

**Comparison**: monotherapy of liposomal amphotericin B at a dose of 5 mg/kg daily or intermittently for 10 doses (days 1-4, 8, 10, 17, 24) up to a total dose of 40 mg/kg.

| Outcomes | Rate in monotherapy group | Rate in combination therapy group | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| **All-cause mortality**<br>Day 58 | 2/75 (3%) | 1/75 (1%) | RR 0.50<br>(0.05 to 5.40) | 150 participants<br>1 non-comparative RCT | ⨁⨁◯◯<br>LOW [a, b] | ITT analysis |
| **All-cause mortality**<br>Day 210 | 5/75 (7%) | 1/75 (1%) | RR 0.20<br>(0.02 to 1.67) | 150 participants<br>1 non-comparative RCT | ⨁⨁◯◯<br>LOW [a, b] | ITT analysis |
| **All-cause mortality**<br>Day 390 | 6/75 (8%) | 1/75 (1%) | RR 0.17<br>(0.02 to 1.35) | 150 participants<br>1 non-comparative RCT | ⨁⨁◯◯<br>LOW [a, b] | ITT analysis |
| **Clinical cure**<br>Day 29 | 71/75 (95%) | 74/75 (99%) | RR 1.04<br>(0.98 to 1.11) | 150 participants<br>1 non-comparative RCT | ⨁⨁◯◯<br>LOW [c, d] | ITT analysis |
| **Relapse-free survival**[1]<br>Day 210 | 64/75 (85%) | 72/75 (96%) | RR 1.13<br>(1.01 to 1.25) | 150 participants<br>1 non-comparative RCT | ⨁⨁◯◯<br>LOW [c, d] | ITT analysis |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Relapse-free survival**[2]<br>Day 390 | 61/75 (81%) | 64/75 (85%) | RR 1.05<br>(0.91 to 1.21) | 150 participants<br>1 non-comparative RCT | ⊕⊕◯◯<br>LOW [c, d] | ITT analysis |
| **Relapse**[3]<br>Day 210 | 2/75 (3%) | 1/75 (1%) | RR 0.50<br>(0.05 to 5.40) | 150 participants<br>1 non-comparative RCT | ⊕◯◯◯<br>VERY LOW [b, d] | ITT analysis |
| **Relapse**[3]<br>Day 390 | 4/75 (5%) | 9/75 (12%) | RR 2.25<br>(0.72 to 6.99) | 150 participants<br>1 non-comparative RCT | ⊕◯◯◯<br>VERY LOW [b, d] | ITT analysis |
| **Treatment adherence** | No studies were identified that reported on this outcome | | | | | |
| **Adverse events - any cause**<br>**Up to 58 days** | 300 events in 75 participants | 324 events in 75 participants | Not estimable | 150 participants<br>1 non-comparative RCT | ⊕⊕◯◯<br>LOW [c, d] | |
| **Severe adverse events – any cause**<br>**Up to 58 days** | 8/75 (11%) | 6/75 (8%) | RR 0.75<br>(0.27 to 2.06) | 150 participants<br>1 non-comparative RCT | ⊕◯◯◯<br>VERY LOW [b, d] | |
| **Patient satisfaction** | No studies were identified that reported on this outcome | | | | | |

[1] Being alive and disease free (defined as absence of signs and symptoms of VL or if symptomatic, a negative parasitological assessment by tissue aspirate) at day 210

[2] Relapse-free survival defined as: the patient is alive and disease-free (defined as absence of signs and symptoms of VL or if symptomatic, a negative parasitological assessment by tissue aspirate) from day 210 (if initially cured) and remains disease-free until the last follow up assessment (i.e. day 390).

[3] No definition provided

**CI:** confidence interval; **HIV:** human immunodeficiency virus; **ITT:** intention to treat; **RCT:** randomised controlled trial; **SAE:** serious adverse event; **VL:** visceral leishmaniasis

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Explanations**

[a] Note that this is an open-label study; however, we have not downgraded for risk of bias on mortality outcomes

[b] Downgraded two levels for serious imprecision: few events and confidence intervals that encompass no effect, a potential benefit, and a potential harm associated with the intervention

[c] Downgraded one level for imprecision: few events; the study was not powered to detect a difference between groups

[d] Downgraded one level for limitations in study design: due to limitations in the study design and execution.

# Appendix 7. Evidence from single arm studies on combination therapy (PICO 1)

| Bibliography | Dates<br>Study type<br>Country/ setting | Population (n, sex, age, relapse status) | Intervention, (regimen/dose) | Initial cure rate | Relapse rate/ parasitological failure/ death | Predictors of failure/ death | Main conclusion |
|---|---|---|---|---|---|---|---|
| Ritmeijer, K. Visceral leishmaniasis-HIV coinfection: Experience from the field. Tropical Medicine and International Health. 2011. Conference:17 | Combination therapy cohort: 2010 to 2011,<br>Retrospective cohort<br>Medecins Sans Frontières supported health centre in north-west Ethiopia | 13 VL-HIV-positive patients<br>9 primary VL; 4 relapse VL<br>No details on age or sex of participants | Amphotericin B at a total dose of 30 mg/kg IV in 6 doses on alternate days and miltefosine (100 mg PO for 28 days) | 92% | Not reported | Not reported | Combination treatment with Amphotericin B and miltefosine seems to enhance treatment effectiveness and may delay the onset of drug-unresponsiveness. |
| Mahajan R, Das P, Isaakidis P, Sunyoto T, Sagili KD, Lima MA, Mitra G, Kumar D, Pandey K, Van Geertruyden JP, Boelaert M. Combination treatment for visceral leishmaniasis patients coinfected with human | Combination therapy cohort July 2012 and September 2014.<br>Retrospective cohort<br>Médecins Sans Frontières treatment center, Bihar, India | 102 VL-HIV-positive patients<br>77 male, 25 female<br>Median age 36 (30-45)<br>47 primary episode, 42 first relapse, 13 second or more relapses | 30 mg/kg body weight AmBisome and 14 days of oral miltefosine. The dose of miltefosine was calculated according to patient weight (≥25 kg 50 mg twice daily; Weight 12–<25 kg, 50 mg once daily | 98% discharged as initially cured (100/102) | Cumulative incidence of mortality at 6, 12, and 18 months was 11.7%, 14.5%, and 16.6%, respectively<br>The estimated risk of relapse was 2.5%, 6.0% and 13.9% at 6, 12 and 18 months respectively. | Failure to start ART was an independent risk factor for mortality<br>Concurrent tuberculosis was independent risk factor for poor outcome | Combination therapy of AmBisome and miltefosine appears safe and effective among HIV-VL coinfected patients under programme conditions in India. |

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|---|---|---|---|---|---|---|---|
| immunodeficiency virus in India. Clinical Infectious Diseases. 2015 Oct 15;61(8):1255-62. | | | | | | | |
| Abongomera, C., Abongomera, C. The Risk and Predictors of Visceral Leishmaniasis Relapse in Human Immunodeficiency Virus-Coinfected Patients in Ethiopia: A Retrospective Cohort Study. Clinical Infectious Diseases. 2017. 65:1703-1710 | January 2011 to August 2014<br>Retrospective cohort<br>Medecins Sans Frontières supported health centre in north-west Ethiopia | 173 VL-HIV co-infected patients<br>48% primary VL; 52% relapse VL<br>Sex: 170 males (98.3%), 3 females (1.7%)<br>Median age = 32 years (range: 28-39) | Combination of liposomal amphotericin B (Amphotericin B, Gilead Sciences) at a total dose of 30 mg/kg, divided into 6 infusions of 5 mg/kg on alternate days and miltefosine (Impavido, Paladin Labs, Montreal, Canada) administered orally for 28 days (100 mg/day). | 83.8% (95% CI 77.6±88.6)<br>(145/173) | Parasitological failure: 3.5% (95% CI, 1.6±7.4)<br>Death: 12.7%; 95% CI, 8.5 to 18.5) (22/173) | Tuberculosis co-infection at VL diagnosis was predictive of initial parasitological failure<br>There was a statistically nonsignificant association between high tissue parasite load (parasite grade 6+) at VL diagnosis and initial parasitological failure.<br>VL treatment history was not significantly associated with initial parasitological failure | Initial parasitological failure rates were very low with Amphotericin B and miltefosine combination therapy.<br>This regimen seems a suitable treatment option. Knowledge of predictors of poor outcome may facilitate better management. |
| Abongomera, C, Abongomera, Charles, de Lima | Combination therapy cohort 2011-2013 | 146 VL-HIV coinfected patients | Combination therapy of Amphotericin B at | 69.8% (102/146) | VL relapse: 30.1% (44/146) | Being on ART at VL diagnosis or starting ART | The risk of VL relapse in coinfected patients |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pereira, Alan, et al. The initial effectiveness of liposomal amphotericin Band miltefosine combination for treatment of visceral leishmaniasis in HIV co-infected patients in Ethiopia: A retrospective cohort study. PLoS Neglected Tropical Diseases 2018. | Retrospective cohort<br>Medecins Sans Frontières supported<br>health centre in north-west Ethiopia | 75%primary VL<br>Sex= 140 males (95.9%), 6 females (4.1%)<br>Median age = 31 years (range: 27-28) | a total dose of 30 mg/kg divided into 6 infusions of 5 mg/kg on alternate days and miltefosine (Impavido, Paladin Labs, Montreal, Canada) administered orally for 28 days (100 mg/day in patients >25 kg and 50 mg/day in those ≤25 kg) | | | during VL treatment was associated with a lower risk of relapse.<br>Those with a high tissue parasite load (parasite grade 6+) at VL diagnosis were at increased risk. | was high, particularly in those not on ART or presenting with a high tissue parasite load.<br>These patients should be preferentially targeted for secondary prophylaxis and/or regular medical follow-up.<br>Timely ART initiation in all coinfected patients is crucial. |

# Appendix 8. Adverse event data

### Table 4. Details of individual adverse events from Ethiopia 2019

| **Adverse events** | **Monotherapy** (amphotericin B) **N=19** | **Combination therapy** (amphotericin B **+ miltefosine N=39** | **Notes** |
|---|---|---|---|
| **Adverse drug reactions possibly related to study drug** | | | |
| Abdominal pain | 0 | 1 | |
| Diarrhoea | 1 | 0 | |
| Dyspepsia | 2 | 8 | |
| Gastritis | 0 | 9 | |
| Glossitis | 1 | 0 | |
| Nausea | 0 | 1 | |
| Peptic ulcer | 1 | 2 | |
| Stomatitis | 1 | 0 | |
| Vomiting | 3 | 11 | |
| Pain | 1 | 0 | |
| Folliculitis | 0 | 1 | |
| Blood creatinine increased | 5 | 11 | |
| Hypokalaemia | 4 | 6 | |
| Back pain | 1 | 1 | |
| Neck pain | 1 | 0 | |
| Polyarthritis | 0 | 1 | |
| Cluster headache | 0 | 1 | |
| Headache | 0 | 1 | |
| Pruritus | 0 | 1 | |
| Rash papular | 0 | 1 | |
| **Serious adverse events (no SAEs were judged to be related to study drugs)** | | | |
| Sepsis | 1 | 0 | Resolved |
| Sepsis | 1 | 0 | In the same patient, patient died |
| Malnutrition | 1 | 0 | |
| Decubitus ulcer | 1 | 0 | |
| Pneumonia | 1 | 0 | |
| Anaemia | 0 | 3 | All 3 resolved |
| Strongyloidiasis | 0 | 1 | Patient died |
| Post herpetic neuralgia | 0 | 1 | Resolved |
| Toxicity to various agents* | 0 | 1 | Patient died |
| Encephalitis | 0 | 1 | In the same patient, patient died |
| Meningitis | 0 | 1 | |
| Pulmonary tuberculosis | 0 | 1 | Unknown outcome |

*Toxicity was related to sodium stibogluconate and paromomycin administered as rescue treatment and to ART drugs (patient received sequentially zidovudine/lamivudine/nevirapine and tenofovir/lamivudine/nevirapine)

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