Evidence summary: systematic review of oral fexinidazole as first line treatment for gambiense Human African Trypanosomiasis

Commissioned by WHO

Cochrane Response

Hanna Bergman, Katrin Probyn, Gemma Villanueva, Nicholas Henschke, Chantelle Garritty

Paul Garner, Cochrane Infectious Diseases Group
Cochrane Review Principle Investigator

Vittoria Lutje, Cochrane Infectious Diseases Group
Lead Cochrane review author

Correspondence to: gvillanueva@cochrane.org

Table of contents

Abbreviations

CI	Confidence interval
CNS	Central nervous system
CSF	Cerebrospinal fluid
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAT	Human African Trypanosomiasis
LR	Likelihood ratio
NECT	Nifurtimox–eflornithine combination therapy
NPV	Negative predictive value
PPV	Positive Predictive Value
RCT	Randomised controlled trial
ROBINS-I	Cochrane Risk Of Bias In Non-randomized Studies - of Interventions
RR	Risk ratio
WBC	White blood cell
WHO	World Health Organisation

Executive summary

Background

Human African trypanosomiasis (HAT), or sleeping sickness, is a neglected tropical disease that occurs in sub-Saharan Africa, within the distributional limits of its vector, the tsetse fly. Two forms of the disease exist: the slow-progressing form, caused by *Trypanosoma brucei gambiense*, which is endemic in western and central Africa; and, the faster progressing form, caused by *Trypanosoma brucei rhodesiense*, found in eastern and southern Africa. This systematic review concerns only *gambiense* HAT.

Currently, the first-line treatment for first-stage gambiense HAT is pentamidine given intramuscularly. For second-stage gambiense HAT, the first-line treatment is nifurtimox–eflornithine combination therapy (NECT) delivered orally (nifurtimox) and intravenously (eflornithine). However, these guidelines are in need of revision because a new therapeutic drug, fexinidazole (delivered orally), has emerged from clinical research and is expected to receive regulatory approval in the coming months.

Objectives

The aim of this systematic review is to provide evidence for the WHO guideline development group to formulate recommendations on the use of oral fexinidazole as first line treatment for gambiense HAT.

Methods

PICOs

To inform the question '*Should fexinidazole be recommended as first line treatment for HAT? only for first-stage HAT? only for second stage? for both?,*' we carried out a systematic review using Cochrane Collaboration methods with the following study inclusion criteria:

For first stage HAT the following inclusion criteria applied:

- studies with at least 30 participants;
- people with first stage HAT defined as evidence of gambiense trypanosomal infection but no cerebrospinal fluid trypanosome, showing a white blood cell (WBC) count of 5 or fewer cells/μL;
- Fexinidazole compared to Pentamidine

For second stage HAT the following inclusion criteria applied:

- studies with at least 30 participants;
- people with second stage HAT defined as evidence of gambiense trypanosomal infection and a cerebrospinal fluid (CSF) analysis showing a white blood cell (WBC) count of more than 5 cells/μL, with no upper limit, and/or the presence of trypanosomes;
- Fexinidazole compared to Nifurtimox–eflornithine combination therapy (NECT)

Due to there being so few comparative studies, we also included studies on fexinidazole in healthy volunteers, single arm studies evaluating fexinidazole, and, for first stage HAT, studies evaluating pentamidine. We evaluated mortality, efficacy and safety outcomes. No studies reported on adherence to treatment.

Search

We searched electronic databases (Medline OVID, Embase OVID, the Cochrane Library and Web of Science) on 14 May 2018, www.Clinicaltrials.gov and the WHO Trials Registry on 1 June 2018, and retrieved unpublished data from the originator company (Sanofi) via the WHO.

Study selection, data extraction, analysis, and interpretation

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 evidence was graded according to established methodology. Data from RCTs start 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. Data from observational studies start at low quality but may be upgraded to moderate or high quality if the pooled estimates reveal a large magnitude of effect, negligible concerns about confounders or a strong dose-response gradient.

Results

The search retrieved 467 records and after removal of duplicates 460 references were screened. Title and abstract screening eliminated 367 references and full-text screening eliminated another 68 references. 19 studies (from 25 references) with 7624 participants were included.

Summary of findings

Fexinidazole as first line treatment for first stage HAT generated four comparisons. No studies were identified that reported on fexinidazole compared to pentamidine.

1. There was very low certainty evidence from two single arm extension trials of 258 child and adult inpatients (Mesu 2018b; Mesu 2018c) on rates of mortality (14-16 per 1000), treatment failure (14-21 per 1000), treatment success (979-986 per 1000), serious adverse events (72-90 per 1000), and adverse events (884-931 per 1000) with oral fexinidazole. No participants withdrew from the treatment phase of the studies. Studies were carried out in the Democratic Republic of the Congo and the Central African Republic.

2. There was very low certainty evidence from two early phase RCTs of 98 healthy adult volunteer inpatients (Tarrall 2014a; Tarrall 2014c) that there is little to no difference between oral fexinidazole compared to placebo on serious adverse events (RR 2.78, 95% CI 0.15 to 52.35, 98 participants, 2 RCTs) and adverse events (RR 5.87, 95% CI 0.36 to 96.97, 72 participants, 1 RCT). No participants withdrew from the treatment phase of the study (reported by one of the two RCTs). The studies did not report on mortality or efficacy outcomes. Studies were carried out in France from 2009 to 2010.

3. There was very low certainty evidence from three early phase single arm trials of 55 healthy adult volunteer inpatients (Tarrall 2014b; Tarrall 2014d; Tarrall 2014e) on rates of serious adverse events (0 of 1000) and adverse events (750-846 per 1000) with oral fexinidazole. Between 77-233 per 1000 participants withdrew from the treatment phase of the studies. The studies did not report on mortality or efficacy outcomes. Studies were carried out in France from 2009 to 2011.

4. There was very low certainty evidence from two RCTs (Burri 2016; Pohlig 2016) and nine observational studies (Balasegaram 2006; Bastide 2011; Doua 1993; Eperon 2006; Jammoneau 2003; Ngoyi 2010; Pohlig 2016; Ruiz 2002; Tongue 2008) of 6722 child and adult patients in ambulatory or hospital care on rates of mortality (0-54 per 1000), death likely due to HAT (0-37 per 1000), relapse (19-241 per 1000), treatment failure (39-46 per 1000), treatment success (593-969 per 1000), serious adverse events (24-175 per 1000), and adverse events (176-985 per 1000) with intramuscular or intravenous pentamidine. Comparison groups of the two RCTs were not included because they evaluated an unlicensed experimental drug. Only two studies measured withdrawals from treatment and found that no participants withdrew (of 178 participants). Studies were carried out in the Democratic Republic of the Congo, Sudan, Angola, Ivory Coast, and Chad from 1981 to 2009.

Fexinidazole as first line treatment for second stage HAT generated two comparisons. Only one study reported on fexinidazole compared to NECT.

1. There was moderate to very low certainty evidence from one RCT (Mesu 2018a) of adult and adolescent inpatients on mortality (low-certainty evidence of little to no difference, RR 2.22, 95% CI 0.49 to 10.11), death likely due to HAT (low-certainty evidence, RR not estimable, no events were reported), relapse (very low-certainty evidence of an increase in relapse with fexinidazole, RR 15.32, 95% CI 0.92 to 254.12), treatment failure (low-certainty evidence of an increase in treatment failure with fexinidazole, RR 4.36, 95% CI 1.35 to 14.11), treatment success (moderate-certainty evidence of a slight decrease in successful treatment with fexinidazole, RR 0.92, 95% CI 0.87 to 0.96), serious adverse events (very low-certainty evidence of little to no difference, RR 1.17, 95% CI 0.64 to 2.17), adverse events (moderate-certainty evidence of little to no difference, RR 1.01, 95% CI 0.95 to 1.06), and withdrawals from treatment (very low-certainty evidence of little to no difference, RR 2.47, 95% CI 0.12 to 51.11) with oral fexinidazole compared to oral Nifurtimox + intravenous eflornithine combination therapy. The study was carried out in the Democratic Republic of the Congo and the Central African Republic from 2012 to 2016.

2. There was very low certainty evidence from two single arm extension trials of 97 child and adult inpatients (Mesu 2018b; Mesu 2018c) on rates of mortality (0 per 1000), treatment failure (0-27 per 1000), treatment success (973-1000 per 1000), serious adverse events (105-146 per 1000), and adverse events (927-1000 per 1000) with oral fexinidazole. No participants withdrew from the treatment phase of the studies. Studies were carried out in the Democratic Republic of the Congo and the Central African Republic.

Conclusions

There is no direct evidence on fexinidazole compared to pentamidine for first stage HAT. Indirect evidence on fexinidazole in healthy volunteers and on pentamidine in people with first stage HAT is of limited use due to very low certainty.

There is moderate-certainty evidence from one RCT comparing fexinidazole with NECT for second stage HAT showing a higher success rate in people receiving NECT. Moderate to very low certainty evidence from the same trial showed little or no difference in adverse events between both treatments.

1 Background

Human African trypanosomiasis (HAT), or sleeping sickness, is a neglected tropical disease that occurs in sub-Saharan Africa, within the distributional limits of its vector, the tsetse fly. Two forms of the disease exist: the slow-progressing form, caused by Trypanosoma brucei gambiense, which is endemic in western and central Africa; and, the faster progressing form, caused by Trypanosoma brucei rhodesiense, found in eastern and southern Africa.

This systematic review concerns only gambiense HAT.

Currently, as stated in the World Health Organization (WHO) guidelines (Tech Rep Ser 984, 2013), the first-line treatment for first-stage gambiense HAT is pentamidine given intramuscularly once daily for s days. For second-stage gambiense HAT, the first-line treatment is nifurtimox–eflornithine combination therapy (NECT). Nifurtimox is delivered orally in 3 daily doses for 10 days, and eflornithine is delivered intravenously in 2 daily infusions for 7 days. Eflornithine (in four intravenous infusions per day × 14 days); and melarsoprol (one intravenous injection per day × 10 days) monotherapies are second or third line alternatives that are rarely used. However, these guidelines are in need of revision because a new therapeutic drug, fexinidazole, has emerged from clinical research and is expected to receive regulatory approval in the coming months[1]. Fexinidazole is administered orally once daily for 10 days and must be accompanied with a meal to achieve sufficient drug absorption. The characteristics of this new therapeutic alternative opens the way for significant modifications in the management of HAT cases. Although the initial clinical trial included only second-stage patients, given the characteristics of the disease it is generally assumed that the efficacy in first-stage patients is equivalent or higher to the efficacy in second-stage patients. To generate direct evidence on this point, the group carrying out the clinical development has also launched two clinical trials to study the same fexinidazole regimen in first-stage disease and in children above 6 years of age.

2 Objectives

- To evaluate the effectiveness and safety of fexinidazole as first-line treatment for treating people with first-stage gambiense HAT.
- To evaluate the effectiveness and safety of fexinidazole as first-line treatment for treating people with second-stage gambiense HAT.

3 Methods

3.1. Review question

This systematic review was carried out to inform the question: Should fexinidazole be recommended as first line treatment for HAT? only for first-stage HAT? only for second stage? for both?

3.2. Inclusion criteria

3.2.1. Types of studies

RCTs, quasi RCTs and cohort studies with at least 30 patients were considered for inclusion. We included full-text studies, conference abstracts, and unpublished data. We included studies

[1] A dossier for the evaluation of fexinidazole was submitted to the European Medicines Agency (EMA) in December 2017, under the art.58 procedure which issues a scientific opinion (not equivalent to a marketing authorization) intended exclusively for countries outside the European Union (EU). This first step of the regulatory pathway must be followed by the registration of the product in at least one endemic country. The regulatory process may be completed in Q1 of 2019 (the earliest), by which time it would be possible for HAT-endemic countries to introduce fexinidazole in the national protocols and start its implementation.

irrespective of their publication status and language of publication. We screened the reference lists of included studies and relevant systematic reviews identified in the search to identify additional studies for inclusion in this review.

3.2.2. Population

People of all ages with a diagnosis of first- or second-stage gambiense HAT were included. The results for people with stage 1 and stage 2 disease were presented and analysed separately. The following diagnostic criteria were used:

- First-stage HAT: evidence of trypanosomal infection but no cerebrospinal fluid trypanosome, showing a white blood cell (WBC) count of 5 or fewer cells/µL.
- Second-stage HAT: having evidence of trypanosomal infection and a cerebrospinal fluid (CSF) analysis showing a white blood cell (WBC) count of more than 5 cells/µL, with no upper limit, and/or the presence of trypanosomes (as defined in Lutje 2013).

In addition, early phase clinical trials evaluating fexinidazole in healthy people were included.

3.2.3. Intervention

Fexinidazole, administered orally once daily for 10 days and accompanied with a meal to achieve sufficient absorption.

3.2.4. Comparison

For first-stage disease

- Pentamidine (given intramuscularly once daily for 7-10 days)
- However, as no studies were identified comparing fexinidazole *versus* pentamidine in people with first-stage HAT, we included all studies evaluating the efficacy and safety of pentamidine and used this to generate indirect evidence for this comparison.

For second-stage disease

- Nifurtimox–eflornithine combination therapy (NECT). Nifurtimox is delivered orally in three doses for 10 days, and eflornithine intravenously in 2 daily infusions for 7 days.

3.2.5. Outcomes

We included the following outcomes[2]:

- Overall mortality (for any reason, including HAT and treatment toxicity) up to 1 month after the start of drug administration.
- Death likely to be due to HAT, up to one month after the start of drug administration.
- Relapse during follow up: trypanosomes detected in any body compartment (blood, lymph, or CSF) at any follow-up examination (between end of treatment and 24 months after the last drug administration); or CSF leukocyte count > 50 WBC/µL CSF, or doubled from previous count, at any follow-up examination; or CSF leukocyte count between 20 and 49 WBC/µL CSF together with symptoms strongly suggestive of relapse (worsened clinical condition since previous examination, with long lasting headache, mental and/or neurological disturbances, increased somnolence, recurrent fever, etc).
- Treatment failure: death, withdrawal, as well as relapse.
- Treatment success: alive, no trypanosomes, no rescue medication, CSF WBC count below threshold.
- Adverse events, including: Central nervous system adverse events: encephalopathy, seizures, confusion; Bone marrow toxicity: anaemia, neutropenia, thrombocytopenia;

[2] This list is partly based on the existing Cochrane systematic review (Lutje 2013)

Gastrointestinal symptoms: diarrhoea, nausea and vomiting; Skin reactions; Infections; Cardiotoxicity

- Adherence to treatment
- Withdrawals

As expected, no studies were identified that reported on adherence to treatment. Therefore, a separate report has been added to this review (please see Appendix 8) to summarise evidence on adherence to oral treatments.

3.3. Search strategy

An electronic search was conducted on May 14th, 2018 across the following databases: Medline OVID, Embase OVID, the Cochrane Library and Web of Science (see Appendix 1). No date, publication status (published, unpublished, in press, and in progress) or language restrictions were used.

The searches were kept sensitive in order to include non-RCTs and not to miss older studies, which are poorly indexed. In total, 110 results were retrieved for fexinidazole and 346 for first-stage HAT (pentamidine). We have reported the flow of studies through the screening process in Appendix 2.

In addition, we searched the ClinicalTrials.gov and the WHO Trials Registry (1 June 2018) where three relevant ongoing studies were identified (see Appendix 3).

Unpublished data (three clinical trial reports on fexinidazole) submitted to the European Medicines Agency by the originator company (Sanofi) were retrieved via the WHO. An additional eight references on pentamidine were forwarded by the WHO as potentially relevant studies.

3.4. Selection of studies

We used DistillerSR software (www.evidencepartners.com) for 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 the WHO. Justifications for excluding full text reports from the review were documented and reported (see Appendix 4). We checked to ensure that all included studies were independent.

3.5. Data extraction and management

We used DistillerSR online software for data extraction. One reviewer extracted data using pre-tested data extraction forms. A second reviewer cross-checked the extracted data. Disagreements about data extraction were resolved by referring to the study report and through discussion.

3.6. Assessment of risk of bias in included studies

We used validated and widely recognized checklists for assessing risk of bias. For RCTs or quasi-RCTs, we used the Cochrane Risk of Bias tool for RCTs. For observational studies with a control group we used the Cochrane Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I). For observational studies with no comparison group, we evaluated the following sources of bias: bias due to confounding, selection bias, bias due to missing data, bias in measurement of outcomes, bias in selection of the reported result, and overall bias.

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. Risk of bias assessments are presented in Appendix 5.

3.7. Data analysis

There were not enough studies evaluating the same intervention for the same population to enable pair-wise meta-analysis. We have presented data from studies with a relevant comparison group in forest plots (risk ratios (RR) with their respective 95% confidence intervals (CIs)), and data from single-arm studies or studies with irrelevant comparison groups in tables.

We stratified data into children and adults. Data and analyses are presented in Appendix 7.

3.8. Summarizing and interpreting results

3.8.1. GRADE

We used the GRADE approach to interpret findings and create 'Summary of findings' tables following the GRADE handbook. These tables provide outcome-specific information concerning the overall certainty of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes of interest.

Data from RCTs start at high certainty, 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. For instance, we downgraded evidence from an open label RCT due to performance bias (risk of exposure to other factors apart from the intervention of interest, such as a different amount of attention, ancillary treatment, and diagnostic investigations, when personnel and participants were not blinded). We did not assess publication bias by testing for asymmetry in a funnel plot because there were less than 10 studies for each outcome.

Data from observational studies start at low quality but may be upgraded to moderate or high quality if the pooled estimates reveal a large magnitude of effect, negligible concerns about confounders or a strong dose-response gradient.

4 Results

We retrieved 467 records and after removal of duplicates we screened 460 references. Title and abstract screening eliminated 367 references and full-text screening eliminated another 68 references. 19 studies (25 references) with 7624 participants were included (see Appendix 2 for PRISMA flow diagram). Studies excluded from full-text screening are listed in Appendix 3 with reasons for exclusion, and ongoing studies in Appendix 4.

Included studies were carried out in the Democratic Republic of the Congo, the Central African Republic, Sudan, Angola, Ivory Coast, and Chad between 1981 and two studies are still ongoing (Mesu 2018b, Mesu 2018c) (see Appendix 6 for detailed study characteristics).

4.1. Summary of findings: Fexinidazole as first line treatment for first stage HAT

4.1.1. Fexinidazole (oral) for first stage Human African Trypanosomiasis

Patient or population: Children and adults with first stage Human African *gambiense* Trypanosomiasis (trypanosomes in blood or nymph node fluid and WBC ≤5 per µL and no trypanosomes in CSF)

Setting: inpatients in the Democratic Republic of the Congo and the Central African Republic

Intervention: Fexinidazole (oral), adults: once daily (days 1-4: 1800 mg, days 5-10: 1200 mg), children ≥35kg: same as in adults, children ≥20kg and <35kg: once daily days 1-4: 1200 mg, days 5-10: 600 mg

Comparison: No comparison group

Outcomes	Summary of results	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Overall mortality at 18 months	Two single arm trials found that 3 deaths occurred in 189 participants (16 per 1000) ≥15-year olds and 1 death occurred in 69 participants) (14 deaths per 1000 participants) 6-15-year olds with **first stage** HAT treated with Fexinidazole.	258 (2 single arm trials)	⨁◯◯◯ VERY LOW[a]	See analysis 3.1 in Appendix 7 [Mesu 2018b; Mesu 2018c]
Death likely due to HAT	No studies reported on this outcome			
Relapse	No studies reported on this outcome			
Treatment failure* at 18 months	Two single arm trials found that treatment failed in 4 of 189 participants (21 failures per 1000 participants) ≥15-year olds and in 1 of 69 participants (14 failures per 1000 participants) 6-15-year olds with **first stage** HAT treated with Fexinidazole.	258 (2 single arm trials)	⨁◯◯◯ VERY LOW[a]	See analysis 3.2 in Appendix 7 [Mesu 2018b; Mesu 2018c]
Treatment success** at 18 months	Two single arm trials found that treatment succeeded in 185 of 189 participants (979 per 1000) ≥15-year olds and in 68 of 69 participants (986 per 1000) 6-15-year olds with **first stage** HAT treated with Fexinidazole.	258 (2 single arm trials)	⨁◯◯◯ VERY LOW[a]	See analysis 3.3 in Appendix 7 [Mesu 2018b; Mesu 2018c]
Serious adverse events at 18 months	Two single arm trials found that 17 of 189 participants (90 per 1000) ≥15-year olds and 5 of 69 participants (72 per 1000) 6-15-year olds with **first stage** HAT treated with Fexinidazole experienced serious adverse events.	258 (2 single arm trials)	⨁◯◯◯ VERY LOW[a]	See analysis 3.4 in Appendix 7 [Mesu 2018b; Mesu 2018c]
Adverse events at 18 months	Two single arm trials found that 176 of 189 participants (931 per 1000) (≥15-year olds and 61 of 69 participants (884 per 1000) 6-15-year olds with **first stage** HAT treated with Fexinidazole experienced adverse events.	258 (2 single arm trials)	⨁◯◯◯ VERY LOW[a]	See analysis 3.5 in Appendix 7 [Mesu 2018b; Mesu 2018c]

Adverse events: central nervous system at 18 months	Two single arm trials found that 112 of 189 participants (593 per 1000) ≥15-year olds and 31 of 69 participants (449 per 1000) 6-15-year olds with **first stage** HAT treated with Fexinidazole experienced adverse events: nervous system.	258 (2 single arm trials)	⊕◯◯◯ VERY LOW[a]	See analysis 3.6 in Appendix 7 [Mesu 2018b; Mesu 2018c]
Adverse events: bone marrow toxicity at 18 months	Two single arm trials found that 12 of 189 participants (63 per 1000) ≥15-year olds and10 of 69 participants (145 per 1000) 6-15-year olds with **first stage** HAT treated with Fexinidazole experienced adverse events: bone marrow toxicity.	258 (2 single arm trials)	⊕◯◯◯ VERY LOW[a]	See analysis 3.7 in Appendix 7 [Mesu 2018b; Mesu 2018c]
Adverse events: gastrointestinal symptoms at 18 months	Two single arm trials found that 143 of 189 participants (757 per 1000) ≥15-year olds and 55 of 69 participants (797 per 1000) 6-15-year olds with **first stage** HAT treated with Fexinidazole experienced adverse events: gastrointestinal symptoms.	258 (2 single arm trials)	⊕◯◯◯ VERY LOW[a]	See analysis 3.8 in Appendix 7 [Mesu 2018b; Mesu 2018c]
Adverse events: skin reactions at 18 months	Two single arm trials found that 12 in 189 participants (63 per 1000) ≥15-year olds and 2 of 69 participants (29 per 1000) 6-15-year olds with **first stage** HAT treated with Fexinidazole experienced adverse events: skin reactions.	258 (2 single arm trials)	⊕◯◯◯ VERY LOW[a]	See analysis 3.9 in Appendix 7 [Mesu 2018b; Mesu 2018c]
Adverse events: infections at 18 months	Two single arm trials found that 11 of 189 participants (58 per 1000) ≥15-year olds and 3 of 69 participants (43 per 1000) 6-15-year olds with **first stage** HAT treated with Fexinidazole experienced adverse events: infections.	258 (2 single arm trials)	⊕◯◯◯ VERY LOW[a]	See analysis 3.10 in Appendix 7 [Mesu 2018b; Mesu 2018c]
Adverse events: cardiotoxicity at 18 months	Two single arm trials found that 16 of 189 (85 per 1000) ≥15-year olds and 2 of 69 participants (29 per 1000) 6-15-year olds with **first stage** HAT treated with Fexinidazole experienced adverse events: cardiotoxicity.	258 (2 single arm trials)	⊕◯◯◯ VERY LOW[a]	See analysis 3.11 in Appendix 7 [Mesu 2018b; Mesu 2018c]
Adherence to treatment	This outcome was not reported among the included inpatients			
Withdrawals from treatment follow-up: end of treatment	Two single arm trials found that 0 of 189 (0 per 1000) ≥15-year olds and 0 of 69 participants (0 per 1000) 6-15-year olds with **first stage** HAT treated with Fexinidazole withdrew from treatment.	258 (2 single arm trials)	⊕◯◯◯ VERY LOW[a]	See analysis 3.12 in Appendix 7 [Mesu 2018b; Mesu 2018c]

*Treatment failure: rescue treatment, death, CSF WBC >20 cells/µL, trypanosomes in the blood, lost to follow-up, consent withdrawal
**Treatment success: Alive, no trypanosomes in body fluid, no rescue medication, CSF WBC ≤20 cells per µL
CI: Confidence interval; **CSF**: cerebrospinal fluid; **HAT:** Human African Trypanosomiasis; **RR:** Risk ratio; **WBC:** white blood cell count

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 for downgrading evidence

a. Non-randomised studies start at low certainty evidence, downgraded one more level for study design: single arm non-comparative study.

4.1.2. Fexinidazole (oral) versus placebo in healthy volunteers

Patient or population: Heathy male volunteers, 18-45 years

Setting: inpatients in France

Intervention: Fexinidazole (oral), ascending doses from 100 to 3,600 mg [Tarrall 2014a] or 1,200, 2,400 and 3,600 mg doses as a single daily dose for 14 days under fasting conditions [Tarrall 2014c]

Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with Fexinidazole				
Overall mortality	This outcome was not reported among the included inpatients					
Death likely due to HAT	This outcome was not reported among the included inpatients					
Relapse	This outcome was not reported among the included inpatients					
Treatment failure	This outcome was not reported among the included inpatients					
Treatment success	This outcome was not reported among the included inpatients					
Serious adverse events (follow-up time not reported)	0 per 1,000	**28 per 1,000**	**RR 2.78** (0.15 to 52.35)	98 (2 RCTs)	⊕◯◯◯ VERY LOW[a,b,c]	See analysis 2.1 in Appendix 7 [Tarrall 2014a; Tarrall 2014c]
Adverse events (follow-up time not reported)	0 per 1,000	**148 per 1,000**	**RR 5.87** (0.36 to 96.97)	72 (1 RCT)	⊕◯◯◯ VERY LOW[a,b,c]	See analysis 2.2 in Appendix 7 [Tarrall 2014a]
Adverse events: central nervous system (follow-up time not reported)	0 per 1,000	**37 per 1,000**	**RR 1.73** (0.09 to 34.39)	72 (1 RCT)	⊕◯◯◯ VERY LOW[a,b,c]	See analysis 2.3 in Appendix 7 [Tarrall 2014a]
Adverse events: skin reactions (follow-up time not reported)	0 per 1,000	**19 per 1,000**	**RR 1.04** (0.04 to 24.37)	72 (1 RCT)	⊕◯◯◯ VERY LOW[a,b,c]	See analysis 2.4 in Appendix 7 [Tarrall 2014a]
Adherence to treatment	Adherence to treatment was not reported among the included participants				-	
Withdrawals from treatment follow-up: end of treatment	0 per 1,000	**0 per 1,000**	Not estimable, see comment	72 (1 RCT)	⊕◯◯◯ VERY LOW[b,c,d]	Relative effect could not be estimated due to no reported events. See analysis 2.5 in Appendix 7 [Tarrall 2014a]

*__The risk in the intervention group__ is based on the number of events and participants in the intervention group, 95% CIs could not be calculated as the risk in the control group was 0.
**Treatment failure: rescue treatment, death, CSF WBC >20 cells/µL, trypanosomes in the blood, lost to follow-up, consent withdrawal
***Treatment success: Alive, no trypanosomes in body fluid, no rescue medication, CSF WBC ≤20 cells per µL
CI: Confidence interval; **CSF**: cerebrospinal fluid; **HAT:** Human African Trypanosomiasis; **RR:** Risk ratio; **WBC:** white blood cell count

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 for downgrading evidence

a. Downgraded two steps for very serious imprecision: Few reported events with wide 95% Cis including both appreciable harm and appreciable benefit with fexinidazole as well as no effect
b. Downgraded one step for serious risk of bias: the trials did not report details on selection, performance, or detection bias.
c. Downgraded one step for serious indirectness: population were healthy volunteers and not people with HAT.
d. Downgraded two steps for very serious imprecision: sample size was too small to assess this rare outcome; no events were reported.

4.1.3. Fexinidazole (oral) in healthy volunteers

Patient or population: Heathy male volunteers, 18-45 years
Setting: inpatients in France
Intervention: Fexinidazole (oral), different schedules **Comparison**: No comparison group

Outcomes	Summary of results	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Overall mortality	No studies reported on this outcome			
Death likely due to HAT	No studies reported on this outcome			
Relapse	No studies reported on this outcome			
Treatment failure	No studies reported on this outcome			
Treatment success	No studies reported on this outcome			
Serious adverse events (follow-up time not reported)	Two single arm trials found that 0 of 25 participants (0 per 1000) healthy male 18-45-year olds administered Fexinidazole (1200mg single dose) experienced serious adverse events.	25 (2 single arm trials)	⨁◯◯◯ VERY LOW[a,b]	See analysis 3.4 in Appendix 7 [Tarrall 2014b; Tarrall 2014d]

Adverse events (follow-up time not reported)	Two single arm trials found that 20 of 25 participants (750-846 per 1000) healthy male 18-45-year olds administered Fexinidazole (1200mg single dose) experienced adverse events. In another single arm trial 98 adverse events were experienced among 30 healthy males (1200 mg to 2400 mg oral fexinidazole for 10 days).	55 (3 single arm trials)	⨁◯◯◯ VERY LOW[a,b]	See analysis 3.5 in Appendix 7 [Tarrall 2014b; Tarrall 2014d; Tarrall 2014e]
Adverse events: central nervous system (follow-up time not reported)	One single arm trial found that 3 of 12 participants (250 per 1000) healthy male 18-45-year olds administered Fexinidazole (1200mg single dose) experienced CNS related adverse events. In another single arm trial 32 CNS related adverse events were experienced among 30 healthy males (1200 mg to 2400 mg oral fexinidazole for 10 days).	42 (2 single arm trials)	⨁◯◯◯ VERY LOW[a,b]	See analysis 3.6 in Appendix 7 [Tarrall 2014d; Tarrall 2014e]
Adverse events: gastrointestinal symptoms (follow-up time not reported)	One single arm trial found that 50 gastrointestinal related adverse events were experienced among 30 healthy males (1200 mg to 2400 mg oral fexinidazole for 10 days).	30 (1 single arm trial)	⨁◯◯◯ VERY LOW[a,b]	See analysis 3.8 in Appendix 7 [Tarrall 2014e]
Adherence to treatment	This outcome was not reported among the included inpatients		-	
Withdrawals from treatment follow-up: end of treatment	Two single arm trials found that 2 of 25 participants (77-83 per 1000) healthy male 18-45-year olds administered Fexinidazole (1200mg single dose) withdrew from treatment. In another single arm trial that 7 of 30 participants (233 per 1000) healthy male 18-45-year olds administered Fexinidazole (1200 mg to 2400 mg oral fexinidazole for 10 days) withdrew from treatment.	55 (3 single arm trials)	⨁◯◯◯ VERY LOW[a,b]	See analysis 3.12 in Appendix 7 [Tarrall 2014e]

***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).
CI: Confidence interval; **CNS:** central nervous system; **CSF**: cerebrospinal fluid; **HAT:** Human African Trypanosomiasis; **RR:** Risk ratio; **WBC:** white blood cell count

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 for downgrading evidence

a. Non-randomised studies start at low certainty evidence, downgraded one more level for study design: single arm non-comparative study.

b. Downgraded one step for serious indirectness: population were healthy volunteers and not people with HAT.

4.1.4. Pentamidine (IM) for first stage Human African Trypanosomiasis

Patient or population: Children and adults with first stage Human African *gambiense* Trypanosomiasis (trypanosomes in blood or nymph node fluid and WBC ≤5 per µL and no trypanosomes in CSF)*

Setting: inpatients or ambulatory care at trypanosomiasis reference centres or hospitals in the Democratic Republic of the Congo, Sudan, Angola, Ivory Coast, Chad

Intervention: Pentamidine (intramuscular or intravenous) for 7-10 days, with injections every 1-2 days

Comparison: No comparison group

Outcomes	Summary of results	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Overall mortality at 24 months (or follow-up time not reported)	Four studies found that 15 of 952 adults and adolescents ≥ 12 years (0-54 per 1000) and 1 of 309 children 0-15 years (0-19 per 1000) with **first stage** HAT treated with Pentamidine died.	1261 (5 studies)	⨁◯◯◯ VERY LOW[a]	See analysis 4.1 in Appendix 7 [Burri 2016; Doua 1993; Eperon 2006; Pohlig 2016, Ginoux 1984]
Death likely due to HAT at 24 months	Two studies found that 2 of 178 adults and adolescents ≥12 years (0-37 per 1000) with **first stage** HAT treated with Pentamidine died as a likely result of HAT.	178 (2 studies)	⨁◯◯◯ VERY LOW[a]	See analysis 4.2 in Appendix 7 [Ngoyi 2010; Pohlig 2016]
Relapse at 6 to 24 months	Seven studies found that 409 of 5619 adults and adolescents ≥12 years (0-241 per 1000) and 11 of 309 children 0-15 years (19-43 per 1000) with **first stage** HAT treated with Pentamidine relapsed.	5928 (8 studies)	⨁◯◯◯ VERY LOW[a,b]	See analysis 4.3 in Appendix 7 [Bastide 2011; Doua 1993; Eperon 2006; Jammoneau 2003; Ngoyi 2010; Pohlig 2016; Ruiz 2002; Tongue 2008]
Treatment failure** at 12 to 24 months	Four studies found that treatment failed in 48 of 1127 adults and adolescents ≥15 years (39-46 per 1000) and 12 of 309 children 0-15 years (0-43 per 1000) with **first stage** HAT treated with Pentamidine.	1436 (3 studies)	⨁◯◯◯ VERY LOW[a,b]	See analysis 4.4 in Appendix 7 [Balasegaram 2006; Eperon 2006
Treatment success*** at 12 to 24 months	Six studies found that treatment succeeded in 5396 of 5993 adults and adolescents ≥12 years (638-969 per 1000) and 216 of 309 children 0-15 years (593-722 per 1000) with **first stage** HAT treated with Pentamidine.	6302 (6 studies)	⨁◯◯◯ VERY LOW[a,b]	See analysis 4.5 in Appendix 7 [Balasegaram 2006; Bastide 2011; Burri 2016; Eperon 2006; Ngoyi 2010; Pohlig 2016]
Serious adverse events at 24 months	Two studies found that 25 of 178 adults and adolescents ≥12 years (24-175 per 1000) with **first stage** HAT treated with Pentamidine experienced serious adverse events.	178 (2 studies)	⨁◯◯◯ VERY LOW[a]	See analysis 4.6 in Appendix 7 [Burri 2016; Pohlig 2016]
Adverse events at end of treatment	Four studies found that 363 of 896 adults and adolescents ≥12 years (240-985 per 1000) and 56 of 309 children 0-15 years (176-204 per 1000) with **first stage** HAT treated with Pentamidine experienced adverse events.	1178 (4 studies)	⨁◯◯◯ VERY LOW[a]	See analysis 4.7 in Appendix 7 [Burri 2016; Doua 1993; Eperon 2006; Pohlig 2016]

Adverse events: central nervous system at end of treatment	Two studies found that 32 of 287 adults and adolescents ≥12 years (40 to 190 per 1000) with **first stage** HAT treated with Pentamidine experienced CNS-related adverse events.	287 (2 studies)	⊕◯◯◯ VERY LOW[a]	See analysis 4.8 in Appendix 7 [Doua 1993; Pohlig 2016]
Adverse events: gastrointestinal symptoms at end of treatment	One study found that 23 of 137 adults and adolescents ≥12 years (168 per 1000) with **first stage** HAT treated with Pentamidine experienced gastrointestinal -related adverse events.	137 (1 study)	⊕◯◯◯ VERY LOW[a]	See analysis 4.9 in Appendix 7 [Pohlig 2016]
Adverse events: skin reactions at end of treatment	Two studies found that 2 of 287 adults and adolescents ≥12 years (7 per 1000) with **first stage** HAT treated with Pentamidine experienced skin-related adverse events.	287 (2 studies)	⊕◯◯◯ VERY LOW[a]	See analysis 4.10 in Appendix 7 [Doua 1993; Pohlig 2016]
Adverse events: cardiotoxicity at end of treatment	One study found that 86 of 137 adults and adolescents ≥12 years (628 per 1000) with **first stage** HAT treated with Pentamidine experienced cardiovascular-related adverse events.	137 (1 study)	⊕◯◯◯ VERY LOW[a]	See analysis 4.11 in Appendix 7 [Pohlig 2016]
Adherence to treatment	Adherence to treatment was not reported among the included participants			
Withdrawals from treatment follow-up: end of treatment	Two studies found that no adults and adolescents ≥12 years (0 per 1000) with **first stage** HAT treated with Pentamidine withdrew from treatment.	178 (2 studies)	⊕◯◯◯ VERY LOW[a]	See analysis 4.12 in Appendix 7 [Burri 2016; Pohlig 2016]

*Two studies defined first stage as the above definition but with ≤10 WBC per µL [Balasegaram 2006, Ruiz 2002], and three studies provided no definition [Bastide 2011, Ginoux 1984, Tongue 2008]
**Treatment failure: death or relapse, see analysis 4.4 for full definitions
***Treatment success: usually lack of relapse, see analysis 4.5 for full definitions
CI: Confidence interval; **CSF**: cerebrospinal fluid; **HAT:** Human African Trypanosomiasis; **RR:** Risk ratio; **WBC:** white blood cell count

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 for downgrading evidence

a. Non-randomised studies start at low certainty evidence, downgraded one more level for study design: single arm non-comparative study.

b. Downgraded one step for serious indirectness: population included both first stage and early second stage HAT (0-10 WBC per µL).

4.2. Fexinidazole as first line treatment for second stage HAT

4.2.1. Fexinidazole (oral) compared to nifurtimox-eflornithine (oral/IV) for second stage HAT

Patient or population: ≥15-year-old people with late second stage Human African *gambiense* Trypanosomiasis (trypanosomes in blood or nymph node fluid and WBC >20 per µL or trypanosomes in CSF)

Setting: inpatients in the Democratic Republic of the Congo and the Central African Republic

Intervention: Fexinidazole (oral) once daily (days 1-4: 1800 mg, days 5-10: 1200 mg)

Comparison: Nifurtimox-eflornithine (oral/IV): oral nifurtimox given three times a day (days 1–10: 15 mg/kg per day) with eflornithine twice a day as 2 h infusions (days 1–7: 400 mg/kg per day)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with NECT	Risk with Fexinidazole				
Overall mortality at 24 months	15 per 1,000	**34 per 1,000** (8 to 156)	**RR 2.22** (0.49 to 10.11)	394 (1 RCT)	⊕⊕◯◯ LOW [a,b]	See analysis 1.1 in Appendix 7 [Mesu 2018a]
Death likely due to HAT at one month	0 per 1,000	**0 per 1,000**	not estimable, see comment	394 (1 RCT)	⊕⊕◯◯ LOW [a,c]	No events were reported, unable to estimate relative effect See analysis 1.2 in Appendix 7 [Mesu 2018a]
Relapse at 12 months	0 per 1,000	**57 per 1,000****	**RR 15.32** (0.92 to 254.12)	394 (1 RCT)	⊕◯◯◯ VERY LOW [d,e]	See analysis 1.3 in Appendix 7 [Mesu 2018a]
Treatment failure*** at 24 months	24 per 1,000	**103 per 1,000** (32 to 333)	**RR 4.36** (1.35 to 14.11)	389 (1 RCT)	⊕⊕◯◯ LOW [d,f]	See analysis 1.4 in Appendix 7 [Mesu 2018a]
Treatment success**** at 24 months	976 per 1,000	**898 per 1,000** (849 to 937)	**RR 0.92** (0.87 to 0.96)	389 (1 RCT)	⊕⊕⊕◯ MODERATE [d]	See analysis 1.5 in Appendix 7 [Mesu 2018a]
Serious adverse events at 18 months	100 per 1,000	**117 per 1,000** (64 to 217)	**RR 1.17** (0.64 to 2.17)	394 (1 RCT)	⊕◯◯◯ VERY LOW [b,d]	See analysis 1.6 in Appendix 7 [Mesu 2018a]
Adverse events at 18 months	931 per 1,000	**940 per 1,000** (884 to 987)	**RR 1.01** (0.95 to 1.06)	394 (1 RCT)	⊕⊕⊕◯ MODERATE [d]	See analysis 1.7 in Appendix 7 [Mesu 2018a]
Adverse events: central nervous system at 24 months	492 per 1,000	**601 per 1,000** (487 to 734)	**RR 1.22** (0.99 to 1.49)	394 (1 RCT)	⊕⊕◯◯ LOW [d,e]	See analysis 1.8 in Appendix 7 [Mesu 2018a]

Adverse events: bone marrow toxicity at 24 months	138 per 1,000	**109 per 1,000** (64 to 190)	**RR 0.79** (0.46 to 1.37)	394 (1 RCT)	⊕◯◯◯ VERY LOW [b,d]	See analysis 1.9 in Appendix 7 [Mesu 2018a]
Adverse events: gastrointestinal symptoms at 24 months	492 per 1,000	**596 per 1,000** (487 to 729)	**RR 1.21** (0.99 to 1.48)	394 (1 RCT)	⊕⊕◯◯ LOW [d,e]	See analysis 1.10 in Appendix 7 [Mesu 2018a]
Adverse events: skin reactions at 24 months	62 per 1,000	**83 per 1,000** (38 to 182)	**RR 1.35** (0.62 to 2.96)	394 (1 RCT)	⊕◯◯◯ VERY LOW [b,d]	See analysis 1.11 in Appendix 7 [Mesu 2018a]
Adverse events: infections at 24 months	62 per 1,000	**83 per 1,000** (38 to 182)	**RR 1.35** (0.62 to 2.96)	394 (1 RCT)	⊕◯◯◯ VERY LOW [b,d]	See analysis 1.12 in Appendix 7 [Mesu 2018a]
Adverse events: cardiotoxicity at 24 months	54 per 1,000	**68 per 1,000** (29 to 159)	**RR 1.27** (0.54 to 2.95)	394 (1 RCT)	⊕◯◯◯ VERY LOW [b,d]	See analysis 1.13 in Appendix 7 [Mesu 2018a]
Adherence to treatment	Adherence to treatment was not reported among the included inpatients				-	
Withdrawals from treatment follow-up: end of treatment	0 per 1,000	**8 per 1,000****	**RR 2.47** (0.12 to 51.11)	394 (1 RCT)	⊕◯◯◯ VERY LOW [b,d]	See analysis 1.15 in Appendix 7 [Mesu 2018a]

*__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).
** __The risk in the intervention group__ is based on the number of events and participants in the intervention group, 95% CIs could not be calculated as the risk in the control group was 0.
***Treatment failure: rescue treatment, death, CSF WBC >20 cells/µL, trypanosomes in the blood, lost to follow-up, consent withdrawal
****Treatment success: Alive, no trypanosomes in body fluid, no rescue medication, CSF WBC ≤20 cells per µL
CI: Confidence interval; **CSF**: cerebrospinal fluid; **HAT:** Human African Trypanosomiasis; **NECT:** Nifurtimox-eflornithine combination therapy; **RR:** Risk ratio; **WBC:** white blood cell count

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 for downgrading evidence

a. Evidence came from an open label trial but was not downgraded because participants' or trial personnel's' knowledge of treatment allocation was very unlikely to influence this objective outcome.
b. Downgraded two steps for very serious imprecision: Few events and wide CIs that include both appreciable benefit and appreciable harm as well as no effect
c. Downgraded two steps for very serious imprecision: Sample size was too small to assess this rare outcome; no events were reported
d. Downgraded one step for serious risk of bias: Open label trial and consequently risk of performance bias for outcomes that could be influenced by exposure to other factors apart from the intervention of interest.
e. Downgraded one step for serious imprecision: Wide CIs that include both no effect and appreciable benefit with NECT
f. Downgraded one step for serious imprecision: Few reported events

4.2.2. Fexinidazole (oral) for second stage Human African Trypanosomiasis

Patient or population: Children and adults with second stage Human African *gambiense* Trypanosomiasis (early second stage: trypanosomes in blood or nymph node fluid and WBC 6-<= 20 per µL and no trypanosomes in CSF; late second stage: trypanosomes in blood or nymph node fluid and WBC >20 per µL or trypanosomes in CSF)

Setting: inpatients in the Democratic Republic of the Congo and the Central African Republic

Intervention: Fexinidazole (oral), adults: once daily (days 1-4: 1800 mg, days 5-10: 1200 mg), children ≥35kg: same as in adults, children ≥20kg and <35kg: once daily days 1-4: 1200 mg, days 5-10: 600 mg

Comparison: No comparison group

Outcomes	Summary of results	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Overall mortality at 18 months	Two single arm trials found that 1of 41 (24 per 1000) ≥15-year olds and 0 of 19 (0 per 1000) 6-15-year olds with **early second stage** HAT treated with Fexinidazole died.	60 (2 single arm trials)	⨁◯◯◯ VERY LOW [a]	See analysis 3.1 in Appendix 7 [Mesu 2018b; Mesu 2018c]
	One single arm trial found that 0 of 37 (0 per 1000) 6-15-year olds **with late second stage** HAT treated with Fexinidazole died.	37 (1 single arm trial)	⨁◯◯◯ VERY LOW [a]	See analysis 3.1 in Appendix 7 [Mesu 2018c]
Treatment failure** at 18 months	Two single arm trials found that treatment failed in 1 of 41 (24 per 1000) ≥15-year olds and 0 of 19 (0 per 1000) 6-15-year olds with **early second stage** HAT treated with Fexinidazole.	60 (2 single arm trials)	⨁◯◯◯ VERY LOW [a]	See analysis 3.2 in Appendix 7 [Mesu 2018b; Mesu 2018c]
	One single arm trial found that treatment failed in 1 of 37 (27 per 1000) 6-15-year olds **with late second stage** HAT treated with Fexinidazole.	37 (1 single arm trial)	⨁◯◯◯ VERY LOW [a]	See analysis 3.2 in Appendix 7 [Mesu 2018c]
Treatment success*** at 18 months	Two single arm trials found that treatment succeeded in 40 of 41 (977 per 1000) ≥15-year olds and 19 of 19 (1000 per 1000) 6-15-year olds with **early second stage** HAT treated with Fexinidazole.	60 (2 single arm trials)	⨁◯◯◯ VERY LOW [a]	See analysis 3.3 in Appendix 7 [Mesu 2018b; Mesu 2018c]
	One single arm trial found that treatment succeeded in 36 of 37 (973 per 1000) 6-15-year olds **with late second stage** HAT treated with Fexinidazole.	37 (1 single arm trial)	⨁◯◯◯ VERY LOW [a]	See analysis 3.3 in Appendix 7 [Mesu 2018c]
Serious adverse events at 18 months	Two single arm trials found that 6 of 41 (146 per 1000) ≥15-year olds and 2 of 19 (105 per 1000) 6-15-year olds with **early second stage** HAT treated with Fexinidazole experienced serious adverse events.	60 (2 single arm trials)	⨁◯◯◯ VERY LOW [a]	See analysis 3.4 in Appendix 7 [Mesu 2018b; Mesu 2018c]
	One single arm trial found that 4 of 37 (108 per 1000) 6-15-year olds **with late second stage** HAT treated with Fexinidazole experienced serious adverse events.	37 (1 single arm trial)	⨁◯◯◯ VERY LOW [a]	See analysis 3.4 in Appendix 7 [Mesu 2018c]

Adverse events at 18 months	Two single arm trials found that 38 of 41 (927 per 1000) ≥15-year olds and 18 of 19 (947 per 1000) 6-15-year olds with **early second stage** HAT treated with Fexinidazole experienced any adverse events.	60 (2 single arm trials)	⊕◯◯◯ VERY LOW [a]	See analysis 3.5 in Appendix 7 [Mesu 2018b; Mesu 2018c]
	One single arm trial found that 37 of 37 (1000 per 1000) 6-15-year olds with **late second stage** HAT treated with Fexinidazole experienced any adverse events.	37 (1 single arm trial)	⊕◯◯◯ VERY LOW [a]	See analysis 3.5 in Appendix 7 [Mesu 2018c]
Adverse events: central nervous system at 18 months	Two single arm trials found that 30 of 41 (732 per 1000) ≥15-year olds and 10 of 19 (526 per 1000) 6-15-year olds with **early second stage** HAT treated with Fexinidazole experienced CNS-related adverse events.	60 (2 single arm trials)	⊕◯◯◯ VERY LOW [a]	See analysis 3.6 in Appendix 7 [Mesu 2018b; Mesu 2018c]
	One single arm trial found that 20 of 37 (541 per 1000) 6-15-year olds with **late second stage** HAT treated with Fexinidazole experienced CNS-related adverse events.	37 (1 single arm trial)	⊕◯◯◯ VERY LOW [a]	See analysis 3.6 in Appendix 7 [Mesu 2018c]
Adverse events: bone marrow toxicity at 18 months	Two single arm trials found that 2 of 41 (49 per 1000) ≥15-year olds and 4 of 19 (211 per 1000) 6-15-year olds with **early second stage** HAT treated with Fexinidazole experienced bone marrow toxicity-related adverse events.	60 (2 single arm trials)	⊕◯◯◯ VERY LOW [a]	See analysis 3.7 in Appendix 7 [Mesu 2018b; Mesu 2018c]
	One single arm trial found that 6 of 37 (162 per 1000) 6-15-year olds with **late second stage** HAT treated with Fexinidazole experienced bone marrow toxicity-related adverse events.	37 (1 single arm trial)	⊕◯◯◯ VERY LOW [a]	See analysis 3.7 in Appendix 7 [Mesu 2018c]
Adverse events: gastrointestinal symptoms at 18 months	Two single arm trials found that 36 of 41 (878 per 1000) ≥15-year olds and 15 of 19 (789 per 1000) 6-15-year olds with **early second stage** HAT treated with Fexinidazole experienced gastrointestinal -related adverse events.	60 (2 single arm trials)	⊕◯◯◯ VERY LOW [a]	See analysis 3.8 in Appendix 7 [Mesu 2018b; Mesu 2018c]
	One single arm trial found that 28 of 37 (757 per 1000) 6-15-year olds with **late second stage** HAT treated with Fexinidazole experienced gastrointestinal -related adverse events.	37 (1 single arm trial)	⊕◯◯◯ VERY LOW [a]	See analysis 3.8 in Appendix 7 [Mesu 2018c]
Adverse events: skin reactions at 18 months	Two single arm trials found that 1 of 41 (24 per 1000) ≥15-year olds and 0 of 19 (0 per 1000) 6-15-year olds with **early second stage** HAT treated with Fexinidazole experienced skin-related adverse events.	60 (2 single arm trials)	⊕◯◯◯ VERY LOW [a]	See analysis 3.9 in Appendix 7 [Mesu 2018b; Mesu 2018c]
	One single arm trial found that 5 of 37 (135 per 1000) 6-15-year olds with **late second stage** HAT treated with Fexinidazole experienced skin-related adverse events.	37 (1 single arm trial)	⊕◯◯◯ VERY LOW [a]	See analysis 3.9 in Appendix 7 [Mesu 2018c]

Adverse events: infections at 18 months	Two single arm trials found that 3 of 41 (73 per 1000) ≥15-year olds and 2 of 19 (105 per 1000) 6-15-year olds with **early second stage** HAT treated with Fexinidazole experienced infection-related adverse events.	60 (2 single arm trials)	⨁◯◯◯ VERY LOW [a]	See analysis 3.10 in Appendix 7 [Mesu 2018b; Mesu 2018c]
	One single arm trial found that 8 of 37 (216 per 1000) 6-15-year olds with **late second stage** HAT treated with Fexinidazole experienced infection-related adverse events.	37 (1 single arm trial)	⨁◯◯◯ VERY LOW [a]	See analysis 3.10 in Appendix 7 [Mesu 2018c]
Adverse events: cardiotoxicity at 18 months	Two single arm trials found that 1 of 41 (24 per 1000) ≥15-year olds and 1 of 19 (53 per 1000) 6-15-year olds with **early second stage** HAT treated with Fexinidazole experienced cardiotoxicity-related adverse events.	60 (2 single arm trials)	⨁◯◯◯ VERY LOW [a]	See analysis 3.11 in Appendix 7 [Mesu 2018b; Mesu 2018c]
	One single arm trial found that 1 of 37 (27 per 1000) 6-15-year olds with **late second stage** HAT treated with Fexinidazole experienced cardiotoxicity-related adverse events.	37 (1 single arm trial)	⨁◯◯◯ VERY LOW [a]	See analysis 3.11 in Appendix 7 [Mesu 2018c]
Adherence to treatment	Adherence to treatment was not reported among the included inpatients			
Withdrawals from treatment follow-up: end of treatment	Two single arm trials found that 0 of 41 (0 per 1000) ≥15-year olds and 0 of 19 (0 per 1000) 6-15-year olds with **early second stage** HAT treated with Fexinidazole withdrew from treatment.	60 (2 single arm trials)	⨁◯◯◯ VERY LOW [a]	See analysis 3.12 in Appendix 7 [Mesu 2018b; Mesu 2018c]
	One single arm trial found that 0 of 37 (0 per 1000) 6-15-year olds with **late second stage** HAT treated with Fexinidazole withdrew from treatment.	37 (1 single arm trial)	⨁◯◯◯ VERY LOW [a]	See analysis 3.12 in Appendix 7 [Mesu 2018c]

***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).
**Treatment failure: rescue treatment, death, CSF WBC >20 cells/µL, trypanosomes in the blood, lost to follow-up, consent withdrawal
***Treatment success: Alive, no trypanosomes in body fluid, no rescue medication, CSF WBC ≤20 cells per µL
CI: Confidence interval; **CNS**: central nervous system; **CSF**: cerebrospinal fluid; **HAT:** Human African Trypanosomiasis; **RR:** Risk ratio; **WBC:** white blood cell count

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 for downgrading evidence

a. Non-randomised studies start at low certainty evidence, downgraded one more level for study design: single arm non-comparative study.

5 Conclusions

There was no direct evidence on fexinidazole compared to pentamidine for first stage HAT. Indirect evidence on rates of mortality, treatment success, relapse, and adverse events with fexinidazole in single arm trials, fexinidazole versus placebo in healthy volunteers, or pentamidine in single arm or observational studies are all of very low certainty (due to non-randomised study design, indirectness of the population, and/or imprecision in the effects) indicating that the true effect is likely to be substantially different from the results presented.

One RCT with 394 participants evaluated fexinidazole compared to NECT for second stage HAT. There was moderate-certainty evidence that treatment was successful in 8% fewer people receiving fexinidazole compared to NECT, though the absolute numbers for both groups show a high success rate (849-937 per 1000 with fexinidazole and 976 per 1000 with NECT). There was moderate to very low certainty evidence of little or no difference in adverse events, including serious adverse events. Evidence was downgraded due to risk of bias, and/or imprecision in the effects.

All participants that were administered fexinidazole were inpatients. Pentamidine patients were either hospitalised or in ambulatory care. No studies reported on adherence to treatment.

References

Included studies

Balasegaram 2006

Balasegaram M, Harris S, Checchi F, Hamel C, Karunakara U. Treatment outcomes and risk factors for relapse in patients with early-stage human African trypanosomiasis (HAT) in the Republic of the Congo. Bulletin of the World Health Organization. 2006. 84:777-782

Bastide 2011

Bastide S, Priotto G, Ecochard R, Etard JF. Effectiveness of short vs. long treatment schedules with pentamidine in first-stage HAT: A large field cohort study. Tropical Medicine and International Health. 2011. 16:68-69

Burri 2016

Burri C, Yeramian PD, Allen JL, Merolle A, Serge KK, Mpanya A, et al. Efficacy, Safety, and Dose of Pafuramidine, a New Oral Drug for Treatment of First Stage Sleeping Sickness, in a Phase 2a Clinical Study and Phase 2b Randomized Clinical Studies. PLoS Negl Trop Dis. 2016. 10:e0004362

Doua 1993

Doua F, Yapo FB. Human trypanosomiasis in the Ivory Coast: Therapy and problems. Acta Tropica. 1993. 54:163-168

Eperon 2006

Eperon G, Schmid C, Loutan L, Chappuis F. Clinical presentation and treatment outcome of sleeping sickness in Sudanese pre-school children. Acta Tropica. 2007. 101:31-39

Ginoux 1984

Ginoux PY, Bissadidi N, Frezil JL. Complicating occurrences in the course of the treatment of sleeping sickness in Congo. Medecine Tropicale. 1984. 44(4):351-355.

Jammoneau 2003

Jamonneau V, Solano P, Garcia A, Lejon V, Dje N, Miezan TW, et al. Stage determination and therapeutic decision in human African trypanosomiasis: value of polymerase chain reaction and immunoglobulin M quantification on the cerebrospinal fluid of sleeping sickness patients in Cote d'Ivoire. Tropical medicine & international health: Tropical Medicine and International Health. 2003. 8:589-94

Mesu 2018a

Mesu VKBK, Kalonji WM, Bardonneau C, Mordt OV, Blesson S, Simon F, et al. Oral fexinidazole for late-stage African Trypanosoma brucei gambiense trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial. Lancet. 2018 Jan 13;391(10116):144-154.

Mesu 2018b

unpublished trial report

Mesu 2018c

unpublished trial report

Ngoyi 2010

Ngoyi DM, Lejon V, Pyana P, Boelaert M, Llunga M, Menten J, et al. How to shorten patient follow-up after treatment for trypanosoma brucei gambiense sleeping sickness. Journal of Infectious Diseases. 2010. 201:453-463

Pohlig 2016

Pohlig G, Bernhard SC, Blum J, Burri C, Mpanya A, Lubaki JP, et al. Efficacy and Safety of Pafuramidine versus Pentamidine Maleate for Treatment of First Stage Sleeping Sickness in a Randomized, Comparator-Controlled, International Phase 3 Clinical Trial. PLoS Negl Trop Dis. 2016. 10:e0004363

Ruiz 2002

Ruiz JA, Simarro PP, Josenando T. Control of human African trypanosomiasis in the Quicama focus, Angola. Bulletin of the World Health Organization. 2002. 80:738-45

Tarral 2014a

Tarral A, Blesson S, Mordt OV, Torreele E, Sassella D, Bray MA, et al. Determination of an optimal dosing regimen for fexinidazole, a novel oral drug for the treatment of human African trypanosomiasis: first-in-human studies. Clin Pharmacokinet. 2014. 53:565-80

Tarral 2014b

See Tarrall 2014a

Tarral 2014c

See Tarrall 2014a

Tarral 2014d

See Tarrall 2014a

Tarral 2014e

See Tarrall 2014a

Tongue 2008

Tongue LK, Louis F, Dologuele NF. Relapse After Treatment with First Stage Drug in Human African Trypanosomiasis: Contribution of Molecular Biology. International Journal of Infectious Diseases. 2008. 12:E383-E383

Other references

Lutje V, Seixas J, Kennedy A. Chemotherapy for second-stage Human African trypanosomiasis. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD006201. DOI: 10.1002/14651858.CD006201.pub3.

WHO. Control and surveillance of human African trypanosomiasis. World Health Organ Tech Rep Ser 984. 2013; 1–237. http://apps.who.int/iris/bitstream/10665/95732/1/9789241209847_eng.pdf?ua=1

Declarations of interest

Cochrane Response, which is an evidence consultancy operated by The Cochrane Collaboration, was commissioned to perform this review for the WHO. All Cochrane Response authors declare no conflicts of interest.

Vittoria Lutje is a self-employed consultant and works for the Cochrane Infectious Diseases group as Information Specialist. She is the first author of the Cochrane review "Chemotherapy of second-stage Human African trypanosomiasis", last updated in 2013.

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials: Issue 4 of 12, April 2018

Date Run: 14/05/18
Description:

ID	Search	Hits
#1	"african trypanosom*":ti,ab,kw (Word variations have been searched)	
#2	"african trypanosomiasis"	
#3	HAT	
#4	trypanosoma gambiense	
#5	"sleeping sickness"	
#6	MeSH descriptor: [Trypanosomiasis, African] explode all trees	
#7	#1 or #2 or #3 or #4 or #5 or #6	842
#8	pentamidine	192
#9	MeSH descriptor: [Pentamidine] explode all trees	
#10	#8 or #9	
#11	#10 and #7	
#12	fexinidazole	
#13	#12 and #7	

Database: Embase OVID 1947-Present, updated daily

Search Strategy:

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1 Trypanosoma rhodesiense/ or Trypanosoma brucei/ or african trypanosomes.mp. or African trypanosomiasis/
2 Trypanosoma brucei gambiense/
3 "sleeping sickness".mp. or African trypanosomiasis/
4 1 or 2 or 3
5 pentamidine.mp. or pentamidine derivative/ or pentamidine/ or pentamidine mesylate/ or pentamidine isethionate/
6 4 and 5
7 limit 6 to human
8 (randomized or placebo or double-blind* or single-blind*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
9 controlled clinical trial.mp. or Controlled Clinical Trial/
10 follow up/ or cohort analysis/ or cohort.mp.
11 retrospective study.mp. or retrospective study/
12 prospective study.mp. or prospective study/
13 8 or 9 or 10 or 11 or 12
14 7 and 13
15 fexinidazole.mp. or fexinidazole/
16 7 and 15

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) <1946 to May 09, 2018>

Search Strategy:

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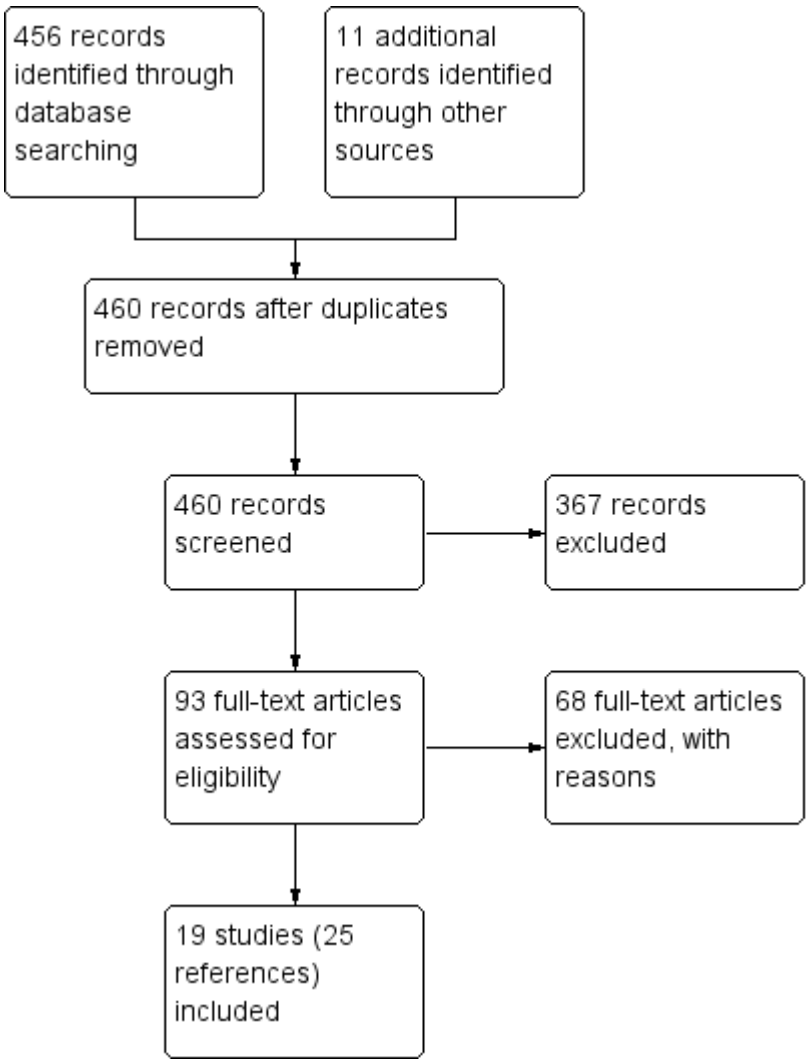
1 Trypanosoma rhodesiense/ or Trypanosoma brucei/ or african trypanosomes.mp. or African trypanosomiasis/
2 Trypanosoma brucei gambiense/
3 "sleeping sickness".mp. or African trypanosomiasis/
4 1 or 2 or 3
5 pentamidine.mp. or pentamidine derivative/ or pentamidine/ or pentamidine mesylate/ or pentamidine isethionate/
6 4 and 5
7 limit 6 to human
8 fexinidazole.mp. or fexinidazole/
9 4 and 8

Web of Science (all databases)

Set	Results	
# 7	89	#6 AND #1 *Timespan=All years* *Search language=Auto*
# 6	122	**TOPIC:** (fexinidazole) *Timespan=All years* *Search language=Auto*
# 5	56	#4 AND #3 *Timespan=All years* *Search language=Auto*
# 4	275,640	**TOPIC:** ("first stage") *OR* **TOPIC:** ("early stage") *Timespan=All years* *Search language=Auto*
# 3	727	#2 AND #1 *Timespan=All years* *Search language=Auto*
# 2	6,161	**TOPIC:** (pentamidine) *Timespan=All years* *Search language=Auto*
# 1	35,530	**TOPIC:** ("african trypanosomes") *OR* **TOPIC:** ("sleeping sickness") *OR* **TOPIC:** ("trypanosomiasis") *Timespan=All years* *Search language=Auto*

Appendix 2: PRISMA flow chart



Appendix 3. Ongoing studies

Reference	PICO	Status
NCT02169557. Efficacy and Safety of Fexinidazole in Patients With Stage 1 or Early Stage 2 Human African Trypanosomiasis (HAT) Due to T.b. Gambiense: a Prospective, Multicentre, Open-label Cohort Study, plug-in to the Pivotal Study. (accessed from: www.Clinicaltrials.gov on 27 June 2018)	Population: Stage 1 or Early Stage 2 HAT, ≥15 years Intervention: Fexinidazole Comparison: none Outcomes: Treatment success or failure, adverse events	Ongoing: Active, not recruiting Comment: trial record of included Mesu 2018b
NCT02184689. Efficacy and Safety of Fexinidazole in Children at Least 6 Years Old and Weighing Over 20 kg With Human African Trypanosomiasis (HAT) Due to T.b. Gambiense: a Prospective, Multicentre, Open Study, plug-in to the Pivotal Study. (accessed from: www.Clinicaltrials.gov on 27 June 2018)	Population: stage 1, early stage 2, or late stage 2 HAT, 6-15 years Intervention: Fexinidazole Comparison: none Outcomes: Treatment success or failure, adverse events	Ongoing: Active, not recruiting Comment: trial record of included Mesu 2018c
NCT03025789. Fexinidazole in Human African Trypanosomiasis Due to T.b. Gambiense at Any Stage. (accessed from: www.Clinicaltrials.gov on 27 June 2018)	Population: stage 1, early stage 2, or late stage 2 HAT, ≥6 years Intervention: Fexinidazole Comparison: none Outcomes: Treatment success or failure, adverse events, compliance, acceptability	Ongoing: recruiting

Appendix 4. Excluded studies

Excluded studies for first stage HAT (n = 61)

Reference	Reason for exclusion
Moideen SV, Houghton PJ, Rock P, Croft SL, Aboagye-Nyame F. Activity of extracts and naphthoquinones from Kigelia pinnata against Trypanosoma brucei brucei and Trypanosoma brucei rhodesiense. Planta medica. 1999. 65:536-40	Study does not include people with first stage gambiense HAT: in vitro study
Arroe M, Willumsen L, Tvede M, Bennike T. [Acute African trypanosomiasis imported into Denmark]. Akut afrikansk trypanosomiasis importeret til Danmark. 1985. 147:2915-6	Irrelevant study design, case report
Van Nieuwenhove S. Advances in sleeping sickness therapy. Annales de la Societe Belge de Medecine Tropicale. 1992. 72:39-51	Study does not include pentamidine
Eyckmans L. The African Sleeping Sickness. Louvain Medical. 1988. 107:281-286	Irrelevant study design, narrative review (book chapter)
Coulaud JP, Vachon F, Lebigot P, Lagarde P, Pasticier A, Saimot G. [African trypanosomiasis at the Claude-Bernard Hospital (diagnostic circumstances and therapeutic problems)]. La trypanosomiase africaine a l'hopital Claude-Bernard (circonstances de diagnostic et problemes therapeutiques). 1975. 126:671-6	Irrelevant study design, 10 cases in included
Raz B, Iten M, Grether-Buhler Y, Kaminsky R, Brun R. The Alamar Blue assay to determine drug sensitivity of African trypanosomes (T.b. rhodesiense and T.b. gambiense) in vitro. Acta tropica. 1997. 68:139-47	Study does not include people with first stage gambiense HAT; manipulated sample from HAT patient for in vitro study
Chappuis F, Stivanello E, Adams K, Kidane S, Pittet A, Bovier PA. Card agglutination test for trypanosomiasis (CATT) end-dilution titer and cerebrospinal fluid cell count as predictors of human African trypanosomiasis (Trypanosoma brucei gambiense) among serologically suspected individuals in Southern Sudan. American Journal of Tropical Medicine and Hygiene. 2004. 71:313-317	Diagnostic test study, not reported what treatment was provided
Lejon V, Ngoyi DM, Boelaert M, Buscher P. A CATT negative result after treatment for human african trypanosomiasis is no indication for cure. PLoS Neglected Tropical Diseases. 2010. 4:e590	Includes first and second stage HAT patients (with different treatments, results reported overall (CATT). All (n=41) first stage were treated with pentamidine but results were reported for 1st and 2nd stage primary cases together, and for retreated cases
Saliou P, Duvallet G, Binz G, Kangha K. [The center for sleeping sickness in Bouafle (Ivory Coast). Tranactions of the mission from November 22 to December 2 1976]. Le foyer de maladie du sommeil de Bouafle (Coute-d'Ivoire). Compte rendu de la mission effectuee du 22 novembre au 2 decembre 1976. 1978. 71:181-8	This paper describes a community programme to fight HAT. No results on pentamidine provided.
Anonymous. Chemotherapy of sleeping sickness. The Central African journal of medicine. 1979. 25:251	Narrative review. Does not report results on pentamidine.
Simarro PP, Sima FO, Mir M, Mateo MJ, Roche J. Combating human African trypanosomiasis in Luba, Equatorial Guinea: Results of three approaches. Bulletin of the World Health Organization. 1991. 69:451-457	Serological survey, does not report on patient outcomes
Simarro PP, Sima FO, Mir M, Mateo MJ, Roche J. [Control of human African trypanosomiasis in Luba in equatorial Guinea: evaluation of three methods]. La lutte contre la trypanosomiase humaine africaine dans le foyer de Luba en Guinee equatoriale: bilan de trois methodes. 1991. 69:451-7	This study describes the strategy to tackle HAT in Luba, but no outcomes reported
Cattand P, Jannin J. [Correspondence of the World Health Organization relative to the editorial by T. Ancelle (Med. Trop. 1996; 56: 347-348)]. Correspondance de l'Organisation Mondiale	Irrelevant study design; letter

de la Sante relative a l'editorial de T. Ancelle (Med. Trop. 1996; 56: 347-348). 1997. 57:102-4	
Godfrey DG, Lanham SM. Diagnosis of Gambian trypanosomiasis in man by isolating trypanosomes from blood passed through DEAE-cellulose. Bulletin of the World Health Organization. 1971. 45:13-9	Mentions 4 suspected cases previously treated with pentamidine but no useful data
Burri C, Yeramian PD, Allen JL, Tidwell RR, Merolle A, Kyanza SK,et al. Efficacy and safety of DB289, a new oral drug for treatment of first stage sleeping sickness: An open-label, non-controlled Phase IIa Trial. American Journal of Tropical Medicine and Hygiene. 2003. 69:400-401	Study does not include pentamidine, testing DB289
Duggan AJ, Hutchinson MP. The efficacy of certain trypanocidal compounds against Trypanosoma gambiense infection in man. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1951. 44:535-544	Pentamidine dose and schedule is different from current therapy
Doua F, Miezan TW, Sanon Singaro JR, Boa Yapo F, Baltz T. The efficacy of pentamidine in the treatment of early-late stage Trypanosoma brucei gambiense trypanosomiasis. Am J Trop Med Hyg. 1996. 55:586-8	Study does not include people with first stage gambiense HAT, early late stage; 58 patients in early-late stage (early central nervous system involvement) all treated with pentamidine
Muraz. [Extensive measures of chemoprophylaxis by intramuscular injection of aromatic diamidines (lomidine) applied for many years with the aim of eradication of sleeping sickness in the territories of French Africa contaminated by that endemia]. Des tres larges mesures de chimioprophylaxie par injections intramusculaires de diamidines aromatiques (lomidine) mises en oeuvre depuis plusieurs annees deja et tendant a l'eradication de la maladie du sommeil dans les territoires de l'Afrique Noire Francaise (A.O.F., A.E.F., Cameroun et Togo sous mandat), contamines de cette endemie. 1954. 138:614-7	Chemoprophylaxis
Ginoux PY, Lancien P, Frezil JL, Bissadidi N. [Failures in the treatment of T. gambiense trypanosomiasis in the Congo]. Les echecs du traitement de la trypanosomiase a T. gambiense au Congo. 1984. 44:149-54	Study provides insufficient data
Van Hoof L, Lewillon R. A field experiment on the prophylactic value of pentamidine in sleeping sickness. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1945. 39:327-9	Prophylactic pentamidine in high endemic population, people with HAT were excluded
Mpanya A, Hendrickx D, Baloji S, Lumbala C, da Luz RI, Boelaert M,et al. From Health Advice to Taboo: Community Perspectives on the Treatment of Sleeping Sickness in the Democratic Republic of Congo, a Qualitative Study. PLoS Neglected Tropical Diseases. 2015. 9:e0003686	Irrelevant study design, qualitative study about treatment perceptions
Pepin J, Milord F, Guern C. [Human African trypanosomiasis and normality of the cerebrospinal fluid]. Trypanosomiase humaine africaine et normalite du liquide cephalorachidien.. 1989. 49:29-31	Pentamidine-suramin combination therapy
Truc P, Lando A, Penchenier L, Vatunga G, Josenando T. Human African trypanosomiasis in Angola: Clinical observations, treatment, and use of PCR for stage determination of early stage of the disease. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2012. 106:10-14	Study does not include people with first stage gambiense HAT (7/224 were stage 1, the rest were intermediate stage (17) or second stage, all results reported together
Vanhecke C, Guevart E, Ezzedine K, Receveur MC, Jamonneau V, Bucheton B, Camara M, Vincendeau P, Malvy D. Human African Trypanosomiasis in mangrove epidemiologic area. Presentation, diagnosis and treatment in Guinea, 2005-2007. Pathologie Biologie. 2010. 58:110-116	Study includes < 30 participants
Simarro PP, Franco JR,Cecchi G, Paone M, Diarra A, Ruiz Postigo JA, et al. Human African trypanosomiasis in non-endemic countries (2000-2010). Journal of travel medicine. 2012. 19:44-53	Reports baseline data only for 1st and 2nd stage cases separately, deaths are reported but overall with the majority of the sample being 2nd stage

Basson W, Page ML, Myburgh DP. Human trypanosomiasis in Southern Africa. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde. 1977. 51:453-7	Study does not include people with first stage gambiense HAT; 5 case reports, 3 of likely 1st stage but one of these rhodesian HAT and the other 2 unknown but likely to be rhodesian since the cases were from a rhodesian endemic area
Pépin J, Labbé AC, Mamadou-Yaya F, Mbélesso P, Mbadingaï S, Deslandes S, et al. Iatrogenic transmission of human T cell lymphotropic virus type 1 and hepatitis C virus through parenteral treatment and chemoprophylaxis of sleeping sickness in colonial Equatorial Africa. Clin Infect Dis. 2010 Oct 1;51(7):777-84	Risk factors (incl. historical pentamidine use) for HepC and HTLV-1 infection through potential needle contamination when administering HAT treatment was evaluated
Bacchi CJ, Brun R, Croft SL, Alicea K, Buhler Y. In vivo trypanocidal activities of new S-adenosylmethionine decarboxylase inhibitors. Antimicrobial agents and chemotherapy. 1996. 40:1448-53	Animal study
Aroke AH, Asonganyi T, Mbonda E. Influence of a past history of Gambian sleeping sickness on physical growth, sexual maturity and academic performance of children in Fontem, Cameroon. Annals of tropical medicine and parasitology. 1998. 92:829-35	Does include both, 1 and 2 stage of HAT, results not presented individually
Lotte AJ. [Interpretation of experimental results in the chemo-prophylaxis of trypanosomiasis gambiense]. Interpretation des resultats experimentaux de la chimio-prophylaxie dans la maladie du sommeil a T. gambiense.. 1953. 46:397-406	Chemoprophylaxis
Harding RD. Late results of treatment of sleeping sickness in Sierra Leone by antrypol tryparsamide pentamidine and propamidine singly and in various combinations. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1945. 39:99-124	Data not usable, unclear reporting
Buguet A, Chapotot F, Ngampo S, Bouteille B, Cespuglio R. Management of African trypanosomiasis of the CNS: Polysomnography as a noninvasive staging tool. Future Neurology. 2012. 7:453-472	Study of sleep patterns for staging and treatment progress of HAT
Pyana Pati P, Van Reet N, Mumba Ngoyi D, Ngay Lukusa I, Karhemere Bin Shamamba S, Büscher P. Melarsoprol sensitivity profile of Trypanosoma brucei gambiense isolates from cured and relapsed sleeping sickness patients from the Democratic Republic of the Congo. PLoS Negl Trop Dis. 2014. 8:e3212	Animal study
Opigo J, Woodrow C. NECT trial: more than a small victory over sleeping sickness. The Lancet. 2009. 374:7-9	Irrelevant study design, narrative review
Kappagoda S, Ioannidis JPA. Neglected tropical diseases: Survey and geometry of randomised evidence. BMJ (Online). 2012. 345:e6512	Irrelevant study design, systematic review with no relevant studies
Lejon V, Legros D, Savignoni A, Etchegorry MG, Mbulamberi D, Büscher P. Neuro-inflammatory risk factors for treatment failure in "early second stage" sleeping sickness patients treated with pentamidine. Journal of neuroimmunology. 2003. 144:132-138	Study does not include people with first stage gambiense HAT, early second stage
Bronner U, Doua F, Ericsson O, Gustafsson LL., Miezan TW, Rais M, Rombo L. Pentamidine concentrations in plasma, whole blood and cerebrospinal fluid during treatment of Trypanosoma gambiense infection in Cote d'Ivoire. Trans R Soc Trop Med Hyg. 1991. 85:608-11	Irrelevant study design, 11 cases
Arnott MA, Cairns D, Hay J. Pentamidine in blood. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1992. 86:460	Irrelevant study design, letter
Bronner U, Gustafsson LL, Doua F, Ericsson O, Miezan T, Rais M, Rombo L. Pharmacokinetics and adverse reactions after a single dose of pentamidine in patients with Trypanosoma gambiense sleeping sickness. British Journal of Clinical Pharmacology. 1995. 39:289-295	Study does not include people with first stage gambiense HAT; late stage HAT

Pyana PP, Sere M, Kaboré J, De Meeûs T, MacLeod A, Bucheton B, et al. Population genetics of Trypanosoma brucei gambiense in sleeping sickness patients with treatment failures in the focus of Mbuji-Mayi, Democratic Republic of the Congo. Infect Genet Evol. 2015. 30:128-133	Stage and treatment not specified
Degroof D, Bruneel H, Mungoma K, Ruppol JF. The Preliminary-Results Of A Strategy To Address Trypanosomiasis Due To Trypanosoma-Brucei-Gambiense In An Endemic Region In Zaire - The Relationship Between A Serological Exam And The Early Treatment Of Suspected Cases. Bulletin De La Societe De Pathologie Exotique. 1993. 86:260-263	Not a relevant treatment
Van Hoof LNJJ, Henrard C, Peel E. The prophylactic value of pentamidine in sleeping sickness. Annales de la Societe Belge de Medecine Tropicale. 1946. 26:371-384	Study does not include people with first stage gambiense HAT, pentamidine prophylaxis
Pépin J, Khonde N. Relapses following treatment of early-stage Trypanosoma brucei gambiense sleeping sickness with a combination of pentamidine and suramin. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1996. 90:183-186	Irrelevant study design, 4 cases only
Abel PM, Kiala G, Lôa V, Behrend M, Musolf J, Fleischmann H, et al. Retaking sleeping sickness control in Angola. Tropical medicine & international health. 2004. 9:141-8	Unable to use data, not clearly stated that all stage I participants received pentamidine, denominator is unclear
Coulaud J, Caquet R, Froli G, Saimot G, Pasticier A, Payet M. [Severe renal and pancreatic complications during treatment with pentamidine in African trypanosomiasis]. Atteintes renale et pancreatique severes au cours d'un traitement par la pentamidine d'une trypanosomiase africaine. 1975. 126:665-9	Irrelevant study design, case report
Ezzedine K, Darie H, Le Bras M, Malvy D. Skin features accompanying imported human African trypanosomiasis: hemolymphatic Trypanosoma gambiense infection among two French expatriates with dermatologic manifestations. Journal of travel medicine. 2007. 14:192-6	Irrelevant study design, case report
Buguet A, Bisser S, Josenando T, Chapotot F, Cespuglio R. Sleep structure: a new diagnostic tool for stage determination in sleeping sickness. Acta tropica. 2005. 93:107-17	Sleep patterns for staging HAt patients, 3 were 1st stage treated with pentamidine
Kennedy PGE. Sleeping sickness - Human African trypanosomiasis. Practical Neurology. 2005. 5:260-267	Irrelevant study design, narrative review
Pepin J, Milord F. The treatment of human African trypanosomiasis. Advances in Parasitology. 1994. 33:1-47	Irrelevant study design, narrative review
Werbovetz KA, Jeronimo SMB, MacDonald TL, Pearson RD. Treatment of leishmaniasis and trypanosomiasis. Current Opinion in Infectious Diseases. 1992. 5:840-848	Irrelevant study design, narrative review
Pepin J, Mpia B, Iloasebe M. Trypanosoma brucei gambiense African trypanosomiasis: Differences between men and women in severity of disease and response to treatment. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2002. 96:421-426	Results of people treated with pentamidine were not separated from those treated with combination- or other monotherapies
Ilboudo H, Camara O, Ravel S, Bucheton B, Lejon V, Camara M, et al. Trypanosoma brucei gambiense spliced leader RNA Is a more specific marker for cure of human African trypanosomiasis than T. b. gambiense DNA. Journal of Infectious Diseases. 2015. 212:1996-1998	Diagnostic test accuracy study of new tools to diagnose HAT, test sensitivity and specificity were reported
Truc P, Jamonneau V, N'Guessan P, N'Dri L, Diallo PB, Cuny G. Trypanosoma brucei ssp. and T congolense: mixed human infection in Cote d'Ivoire. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1998. 92:537-8	Irrelevant study design, case report
Simon F, Mura M, Pagès F, Morand G, Truc P, Louis F, Gautret P. Urban transmission of human African trypanosomiasis, Gabon. Emerging Infectious Diseases. 2012. 18(1):165-7	Irrelevant study design, case report

Legros D, Erphas O, Protto G, Hutin Y, Mbulamberi DB, Gastellu M, et al. Essai Clinique randomise ouvert comparant le melarsoprol a la pentamidine pour le traitment souffrant de trypanosomaiase a trypanosoma brucei gambiense en stade 2 precoce en Ouganda. Médecine Tropicale. 2001. 278	Study does not include people with first stage gambiense HAT, early second stage
Ollivier G, Legros D. Trypanosomiase humaine africaine: historique de la therapeutique et de ses echecs. Tropical Medicine and International Health. 2001. 6:855-863	Irrelevant study design, narrative review
Conte JE. Pharmacokinetics of intravenous pentamidine in patients with normal renal function or receiving haemodialysis. Journal of Infectious Diseases. 1991. 169-175	Pharmacokinetic outcomes only, includes 24 participants
Dutertre J, Labusquiere R. La therapeutique de la trypanosomiase. Medecine Tropicale. 1966. 342-356	Irrelevant treatment regimen
Jonchère H. Traitement par les diamiadines de la phase lymphatico-sanguine de la trypanosomiase humaine en Afrique Occidentale Française. Bulletin de la Société de Pathologie Exotique et ses Filiales. 1951. 44:603-625	Irrelevant treatment regimen
Neujean G, Evens F. Diagnostic et traitement de la maladie de sommeil à T. gambiense. Bilan de dix ans d'activité au centre de traitement de Léopoldville. Académie Royale des Sciences Colonials: Classes des Sciences Naturelles et Médicales. 1958. Mémoires in 8° 1958; Tome VII	Unclear diagnostic criteria
Stauffert I, Paulini H, Steinmann U, Sippel H, Estler CJ. Investigations on mutagenicity and genotoxicity of pentamidine and some related trypanocidal diamidines. Mutation Research. 245:93-98	Study does not include people with first stage gambiese HAT, test of pentamidine for mutagenic and cytotoxic effects

Excluded studies for second stage HAT (n = 7)

Reference	Reason for exclusion
Burri C. An alternative form of melarsoprol in sleeping sickness: is an old drug always the best basis for a new one? Trends in Parasitology. 2012. 28:354-355	Irrelevant study design, narrative review
Burri C. Antiprotozoals for human African trypanosomiasis: The heart of darkness at dawn. Clinical Investigation. 2014. 4:13-18	Irrelevant study design, narrative review
Jennings FW. Chemotherapy Of CNS-Trypanosomiasis - The Combined Use Of The Arsenicals And Nitrocompounds. Tropical Medicine and Parasitology. 1991. 42:139-142	Mentions 5-nitroimidazoles but published in 1991
Steinmann P, Stone CM, Sutherland CS, Tanner M, Tediosi F. Contemporary and emerging strategies for eliminating human African trypanosomiasis due to Trypanosoma brucei gambiense: review. Trop Med Int Health. 2015. 20:707-18	Systematic review, but no relevant study of fexinidazole was included
Chappuis F. Oral fexinidazole for human African trypanosomiasis. Lancet 2018. 391:100-102	Narrative review/commentary on another RCT
Ormerod WE, Raseroka BH. SCREENING COMPOUNDS FOR SLEEPING SICKNESS THERAPY WITHOUT RELAPSE. Bulletin De La Societe De Pathologie Exotique. 1988. 81:543-547	Animal study
Vetter N. Untitled. British Medical Bulletin. 2012. 104:1-5	Irrelevant study design, narrative review

Appendix 5: Risk of bias assessments

RCTs

Study name	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Pohlig 2016	LOW	LOW	HIGH	UNCLEAR	LOW	LOW	LOW
Burri 2016	LOW	LOW	HIGH	UNCLEAR	LOW	LOW	LOW
Tarral 2014a	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW
Tarral 2014c	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW
Tarral 2014e	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW
Mesu 2018	LOW	LOW	HIGH	LOW	LOW	LOW	LOW

Observational studies

Study name	Bias due to confounding	Bias in selection of participants into the study	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall bias / Study design
Eperon 2006	HIGH	LOW	LOW	LOW	LOW	Retrospective, single arm study, no comparison group
Ginoux 1984	HIGH	UNCLEAR	LOW	UNCLEAR	UNCLEAR	Retrospective observational study describing (all?) cases identified and treated.
Ruiz 2002	HIGH	LOW	UNCLEAR	LOW	UNCLEAR	Retrospective observational study describing cases identified (and subsequently treated) in a seroparasitological survey
Bastide 2011	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	large field cohort study, unclear if prospective or retrospective
Ngoyi 2010	HIGH	LOW	LOW	LOW	LOW	prospective longitudinal study observational study, treatment was given according to guidelines
Doua1993	HIGH	HIGH	UNCLEAR	UNCLEAR	LOW	Retrospective observational study describing all cases treated)
Tongue 2008	HIGH	LOW	UNCLEAR	UNCLEAR	UNCLEAR	Retrospective observational study describing all cases identified (and subsequently treated) in seroparasitological survey
Jamonneau 2003	HIGH	LOW	UNCLEAR	LOW	UNCLEAR	Retrospective observational study of cases identified in a survey (and subsequently treated)

Study name	Bias due to confounding	Bias in selection of participants into the study	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall bias / Study design
Balasegaram 2006	LOW	LOW	LOW	LOW	LOW	Retrospective observational study of cases identified (and subsequently treated)
Mesu 2018b	LOW	LOW	LOW	UNCLEAR	LOW	Prospective, multicentre, open-label, single-arm cohort study
Mesu 2018c	LOW	LOW	LOW	UNCLEAR	LOW	Prospective, multicentre, open-label, single-arm Phase II/III study
Tarral 2014b	LOW	LOW	LOW	LOW	LOW	Prospective, open-label, single-arm pharmacokinetic trial
Tarral 2014d	LOW	LOW	LOW	LOW	LOW	Prospective, open-label, single-arm trial

Appendix 6: Study characteristics

Study Design Dates	Participants N Age Diagnosis	Intervention	Outcomes	Additional details Location Source of funding Study ID
Balasegaram 2006 Design: Retrospective observational study Dates: April 2001 to March 2005	n = 1986 Age: Not reported Diagnosis: First stage HAT: parasite in blood or lymph, WBC 0-10 cells/mm^3	Pentamidine Schedule: 4 mg/kg once daily for 7 days either intramuscularly or by slow intravenous injection	1. Treatment failure: death or recurrence of parasites in any body fluid, CSF WBC >50 cells/mm^3 and at least doubled from the previous measurement, or WBC 11–49 cells/mm^3 with either a significant increase from the previous measurement or with symptoms suggestive of sleeping sickness 2. Treatment success: remained disease free	Location: Republic of the Congo Source of funding: not reported Study ID: not reported
Bastide 2011 Design: large field cohort study, unclear if prospective or retrospective Dates: not reported	n = 8516 Age: not reported Diagnosis: 'parasiologically confirmed first-stage HAT', no further details	1. Pentamidine, Short treament schedule (7/8 days), n = 4597 2. Comparison, Pentamidine long treatment schedule (10 days), n = 3919 Schedule: Pentamidine isothionate 4 mg/kg/day for7/8 days (short treatment schedule) or 10 days (long treatment schedule)	1. Relapse: as diagnosed by the physician-in-charge on the basis of clinical symptoms and laboratory results 2. Treatment success: 'cure'	Location: 18 HAT control programs in six endemic countries Source of funding: not reported Study ID: not reported
Burri 2016 Design: RCT Dates: April 2003 to February 2007	n = 81 Age: 15 to 50 years Diagnosis: first stage HAT: presence of parasites in the blood or lymph and their absence in the CSF, confirmed by <5mm^3 WBC	1. Pentamidine, n = 41 2. Pafuramidine orally, n = 40 Schedule: Pentamidine intramuscular injections 4 mg/kg, once a day for 7 days Comparison group (pafuramidine, experimental unlicensed drug) was not included in this report	1. Overall death 2. Treatment success: absence of parasites in blood, lymph nodes, and CSF, as well as <5mm^3 WBCs in the CSF 3. Serious adverse events 4. Adverse events	Location: Democratic Republic of Congo, two sites Source of funding: Bill and Melinda Gates Foundation, Immtech Pharmaceuticals, Inc Study ID: NCT00803933
Doua 1993 Design: Retrospective observational study Dates: September 1985 to March 1992	n = 150 Age: not reported Diagnosis: first stage HAT: in the blood-lymphatic phase (WBC < 5mm^3, protein <40 mg% and no evidence of trypanosomes in CSF)	Pentamidine Schedule: ten intramuscular or intravenous injections at a dose of 4 mg/kg every 2 days	1. Overall death 2. Relpse 3. Adverse events	Location: Ivory Coast Source of funding: not reported Study ID: not reported

Study Design Dates	Participants N Age Diagnosis	Intervention	Outcomes	Additional details Location Source of funding Study ID
Eperon 2006 Design: retrospective observational study Dates: June 2000 to December 2002	n = 850 Age: 54 pre-school children and 766 older patients Diagnosis: first-stage HAT: trypanosomes in lymph nodes or blood with CSF examination showing no trypanosomes and <5 WBC/mm^3	Pentamidine Schedule: Intramuscular pentamidine isethionate, 4 mg/kg daily for 7 days	1. Overall death 2. Relapse: trypanosomes in blood or CSF, WBC count in the CSF significantly increased, or WBC count showed little variation and the patient had symptoms and signs consistent with HAT 3. Treatment failure: Death or relapse 4. Treatment success: absence of relpse 5. Severe adverse events 6. Adverse events	Location: South Sudan, sleeping sickness treatment centre Source of funding: not reported Study ID: not reported Notes: Data for HAT stage 2 patients were not extracted for this report
Ginoux 1984 Design: Retrospective observational study Dates: 1981 to 1982	n = 90 Age: not reported Diagnosis: first stage HAT: < 4 cells/mm^3 in CSF and albumin <0.22 g/l)	Pentamidine, administered as ambulatory treatment Schedule: 5 daily injections + 5 no-treatment days + 3 daily injections. Each injection 1 ml/10 kg; maximum 5 ml.	Overall mortality	Location: Democratic Republic of the Congo Source of funding: The United Nations Develoment Programme, the World Bank, WHO Special Program for Research and Training on Tropical Diseases Study ID: not reported Notes: Data for HAT stage 2 patients were not extracted for this report
Jamonneau 2003 Design: Retrospective observational study Dates: April and May 2000	n = 31 (first stage), 11 (intermediate stage) Age: not reported Diagnosis: first stage HAT: WBC 0-5 cells/mm^3 and negative in DC, intermediate stage: patients with 20 cells/mm^3	Pentamidine Schedule: not reported	Relapse	Location: Ivory Coast Source of funding: not reported Study ID: not reported

Study Design Dates	Participants N Age Diagnosis	Intervention	Outcomes	Additional details Location Source of funding Study ID
Mesu 2018a Design: RCT Dates: October 2012 to November 2016	n = 394 Age: ≥15 years Diagnosis: late second stage HAT: parasites in blood or lymph node fluid, CSF WBC count >20 cells per µL or trypanosomes in the CSF	1. Fexinidazole, oral once a day (days 1–4: 1800 mg, days 5–10: 1200 mg), n=264 2. NECT, oral nifurtimox three times a day (days 1–10: 15 mg/kg per day) with eflornithine twice a day as 2 h infusions (days 1–7: 400 mg/kg per day), n=130	1. Overall deaths 2. Death due to HAT 3. Relapse: trypanosomes in any body fluid 4. Treatment failure: rescue treatment, death, CSF WBC >20 cells/microL, trypanosomes in the blood, lost to follow-up, consent withdrawal 5. Treatment success 6. Serious adverse events 7. Adverse events	Location: Democratic Republic of the Congo and Central African Republic Source of funding: Drugs for Neglected Diseases initiative Study ID: NCT01685827 Notes: published and unpublished data from this study were used in this report
Mesu 2018b Design: single arm extension trial Dates: ongoing	n = 230 Age: ≥15 years Diagnosis: stage 1 and early stage 2 HAT parasite in the blood or lymph and absence of parasite in the CSF, stratified by stage 1 (CSF WBC ≤5 cells/µL) and early stage 2 HAT (CSF WBC 6 to 20 cells/µL)	Fexinidazole Schedule: 1800mg (3x600-mg tablets) administered orally once daily for 4 days, followed by 1200mg (2x600-mg tablets) administered orally once daily for 6 days, with food	1. Overall deaths 2. Treatment failure 3. Treatment success 4. Serious adverse events 5. Adverse events	Location: Democratic Republic of the Congo Source of funding: Drugs for Neglected Diseases initiative Study ID: NCT02169557 Notes: unpublished data from this study were used in this report
Mesu 2018c Design: single arm extension trial Dates: ongoing	n = 125 Age: 6-15 years Diagnosis: stage 1 (trypanosomes in the blood or lymph, no trypanosomes in the CSF, and CSF WBC ≤5cells/µL), early stage 2 (trypanosomes in the blood or lymph, no trypanosomes in the CSF, and CSF WBC 6 to 20cells/µL), and late stage 2 HAT (trypanosomes in the blood or lymph, and either CSF WBC >20cells/µL or trypanosomes in the CSF)	Fexinidazole Schedule: Fexinidazole orally, with the dosage regimen depending on the child's body weight: • ≥20kg and <35kg: 1200mg (2x600-mg tablets) once daily for 4 days, then 600mg (1 x 600-mg tablet) once daily for 6 days • ≥35kg (same as in adults): 1800mg (3x600-mg tablets) once daily for 4 days, then 1200mg (2x600-mg tablets) once daily for 6 days	1. Overall deaths 2. Treatment failure 3. Treatment success 4. Serious adverse events 5. Adverse events	Location: Democratic Republic of the Congo Source of funding: Drugs for Neglected Diseases initiative Study ID: NCT02184689 Notes: unpublished data from this study were used in this report

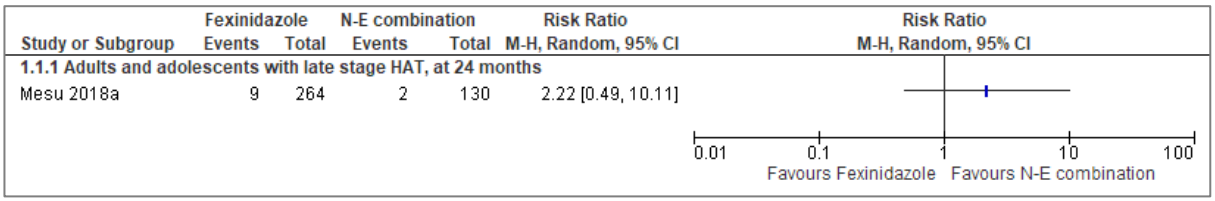
Study Design Dates	Participants N Age Diagnosis	Intervention	Outcomes	Additional details Location Source of funding Study ID
Ngoyi 2010 Design: prospective longitudinal observational study Dates: May 2005 to May 2008	n = 41 Age: ≥12 years Diagnosis: first stage HAT:WBC count 0–5 cells/mL and no trypanosomes in CSF	Pentamidine Schedule: 4 mg/kg/day IM for 8 days	1. HAT related deaths 2. Relapse 3. Treatment success: Clinical and parasitological cure, probable cure	Location: one hospital in the Democratic Republic of the Congo Source of funding: not reported Study ID: not reported
Pohlig 2016 Design: RCT Dates: August 2005 to September 2009	n = 273 Age: >=12 years of age Diagnosis: first stage HAT: trypanosomes in blood and/or lymph, no trypanosomes in CSF, and <=5 WBCs/mm^3 in CSF	1. Pentamidine, n = 137 2. Comparison, pafuramidine orally, n = 136 Schedule: 4 mg/kg pentamidine intramuscular injection once daily for 7 days Comparison group (pafuramidine, experimental unlicensed drug) was not included in this report	1. Overall deaths 2. HAT related deaths 3. Relapse: trypanosomes in any body fluid 4. Treatment success: no evidence for parasitological relapse and <5 WBCs/mm^3 in CSF 5. Serious adverse events 6. Adverse events	Location: one trypanosomiasis reference center in Angola, one hospital in South Sudan, and four hospitals in the Democratic Republic of the Congo Source of funding: the Bill and Melinda Gates Foundation Study ID: ISRCTN85534673
Ruiz 2002 Design: Retrospective observational study Dates: July 1997	n = 79 Age: not reported Diagnosis: first stage HAT: WBC <=5 cells/mL and no trypanosomes in CSF	Pentamidine Schedule: 10 injections of 4 mg/kg body weight/day on alternate days	1. Relapse	Location: Angola Source of funding: not reported Study ID: not reported Notes: 21 participants with WBC 6-10 cells/mL were not included in this report
Tarrall 2014a Design: RCT Dates: September 2009 to October 2010	n = 72 Age: 18-45 years Diagnosis: healthy male volunteers	1. Fexinidazole: ascending doses from 100 to 3,600 mg in the form of an oral suspension 2. Placebo	Adverse events	Location: France Source of funding: Drugs for Neglected Diseases Study ID: NCT00982904 Notes: protocol 1A
Tarrall 2014b Design: RCT Dates: September 2009 to October 2010	n = 13 Age: 18-45 years Diagnosis: healthy male volunteers	Fexinidazole, single-dose fexinidazole, either as a suspension (PIB formulation)	Adverse events	Location: France Source of funding: Drugs for Neglected Diseases Study ID: NCT00982904 Notes: protocol 1B

Study Design Dates	Participants N Age Diagnosis	Intervention	Outcomes	Additional details Location Source of funding Study ID
Tarrall 2014c Design: RCT Dates: September 2009 to October 2010	n = 27 Age: 18-45 years Diagnosis: healthy male volunteers	1. Fexinidazole: 1,200, 2,400 and 3,600 mg doses (tablet formulation) as a single daily dose for 14 days under fasting conditions 2. Placebo	Adverse events	Location: France Source of funding: Drugs for Neglected Diseases Study ID: NCT00982904 Notes: protocol 1C
Tarrall 2014d Design: RCT Dates: February 2011 to April 2011	n = 12 Age: 18-45 years Diagnosis: healthy male volunteers	Fexinidazole: 1,200 mg as oral tablets under fasted conditions or with a meal	Adverse events	Location: France Source of funding: Drugs for Neglected Diseases Study ID: NCT01340157 Notes: protocol 2
Tarrall 2014e Design: RCT Dates: not reported	n = 30 Age: 18-45 years Diagnosis: healthy male volunteers	1. Fexinidazole 2. Placebo Schedule: Cohort 1: fexinidazole 1,800 mg or placebo from day 1 to day 4, then fexinidazole 1,200 mg or placebo from day 5 to day 10. Cohort 2: fexinidazole 2,400 mg or placebo from day 1 to day 4, then fexinidazole 1,200 mg or placebo from day 5 to day 10.	Adverse events	Location: France Source of funding: Drugs for Neglected Diseases Study ID: NCT0148370 Notes: protocol 3
Tongue 2006 Design: Retrospective observational study Dates: March 2006	n = 54 Age: not reported Diagnosis:First stage HAT, no further details reported	Pentamidine Schedule: not reported	Relapse	Location: Chad Source of funding: not reported Study ID: not reported

Appendix 7: Data and analyses

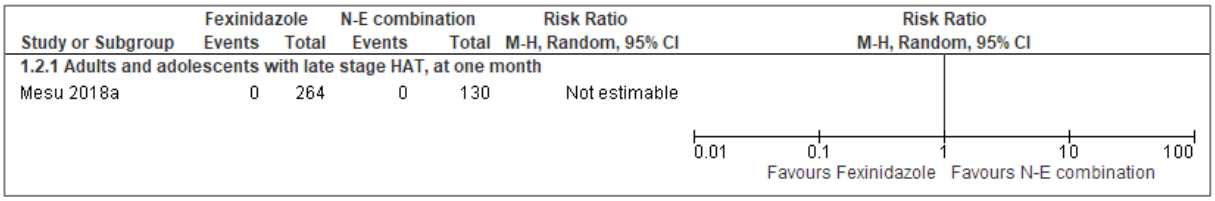
1. Fexinidazole (oral) versus nifurtimox-eflornithine (oral/IV) in second stage HAT

1.1 Overall mortality, follow-up: 24 months



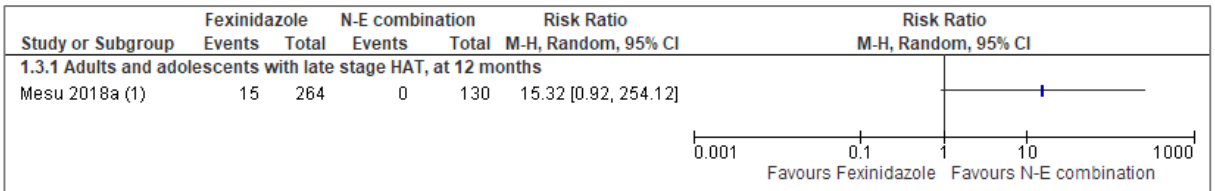
Causes of death: not reported

1.2 Death likely due to HAT, follow-up: 1 month



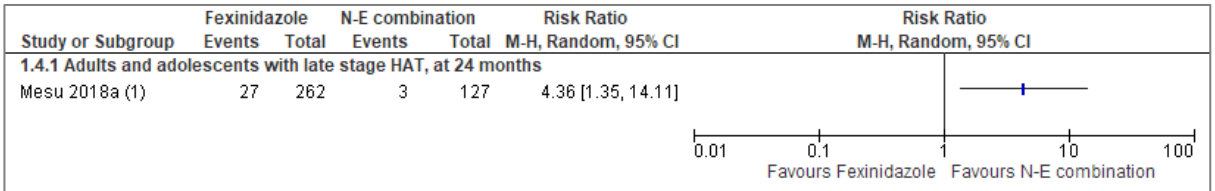
Causes of death: not reported

1.3 Relapse, follow-up: 12 months



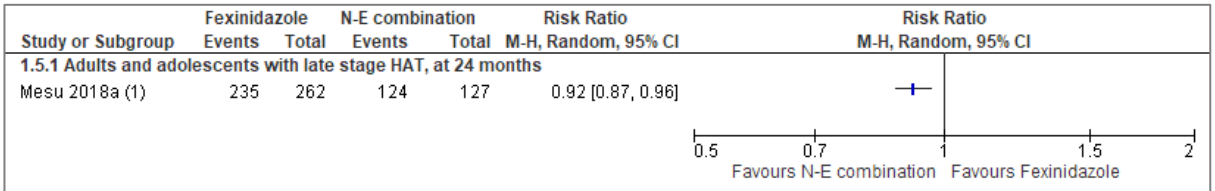
Footnotes
(1) death, loss to follow-up, absence of lumbar puncture; consent withdrawal was not counted as relapse

1.4 Treatment failure, follow-up: 24 months



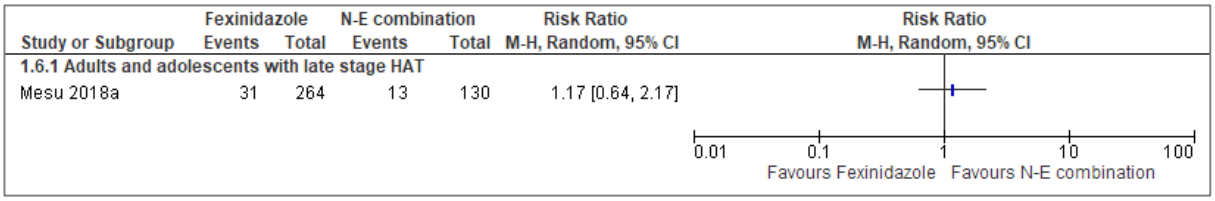
Footnotes
(1) rescue treatment, death, CSF WBC >20 cells/µL, trypanosomes in the blood, lost to follow-up, consent withdrawal

1.5 Treatment success, follow-up: 24 months



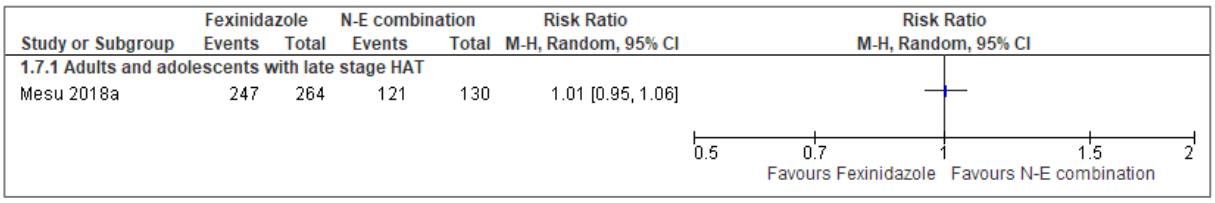
Footnotes
(1) Alive, no trypanosomes in body fluid, no rescue medication, CSF WBC ≤20 cells per µL

1.6 Serious adverse events, follow-up: 18 months

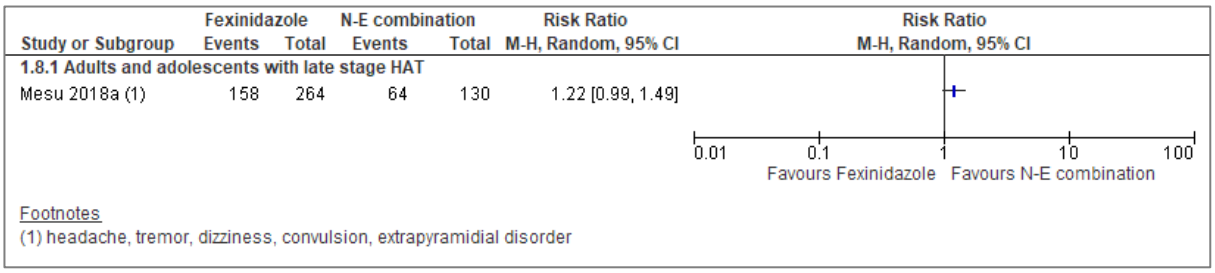


Four serious adverse events reported in three participants who received fexinidazole were considered possibly related to treatment: personality change, acute psychosis, and hyponatraemia. One patient with personality change died later from an unrelated serious adverse event following the use of traditional medicine, and the three other cases recovered

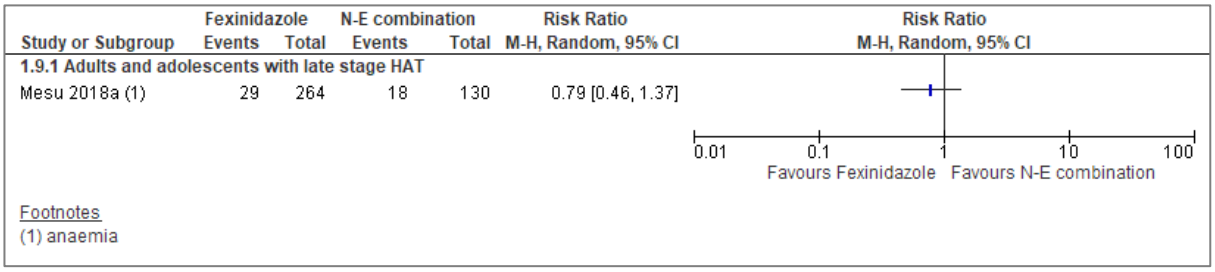
1.7 Adverse events, follow-up: 18 months



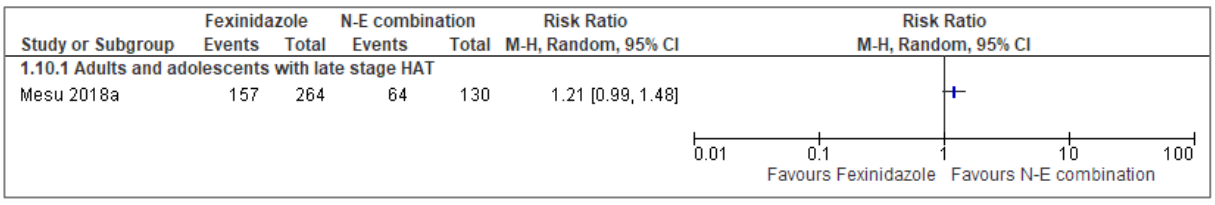
1.8 Adverse events: central nervous system, follow-up: 24 months



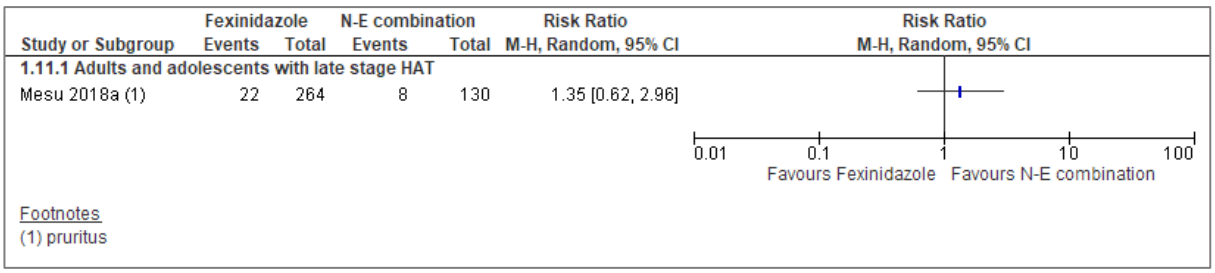
1.9 Adverse events: bone marrow toxicity, follow-up: 24 months



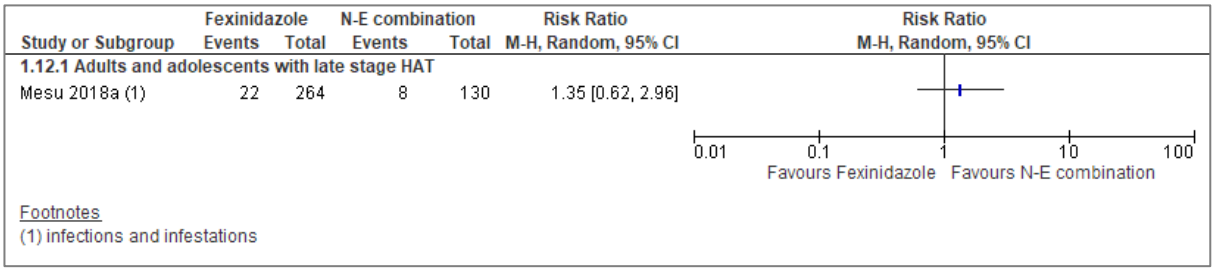
1.10 Adverse events: gastrointestinal symptoms, follow-up: 24 months



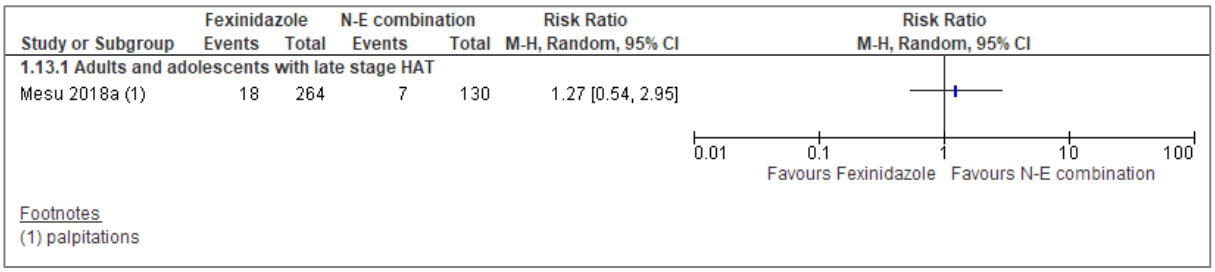
1.11 Adverse events: skin reactions, follow-up: 24 months



1.12 Adverse events: infections, follow-up: 24 months



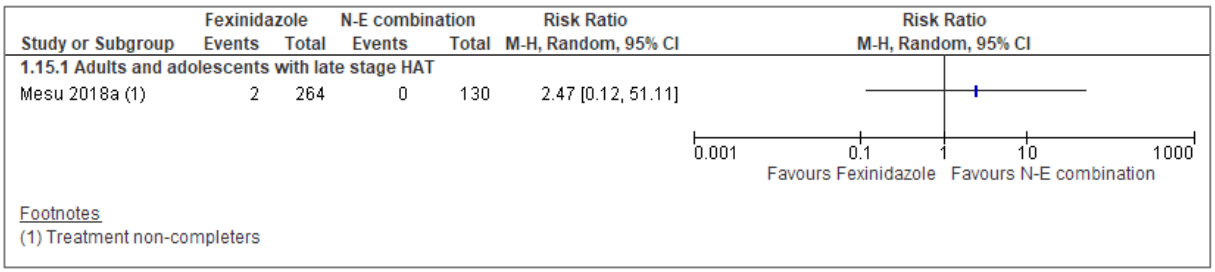
1.13 Adverse events: cardiotoxicity, follow-up: 24 months



1.14 Adherence to treatment

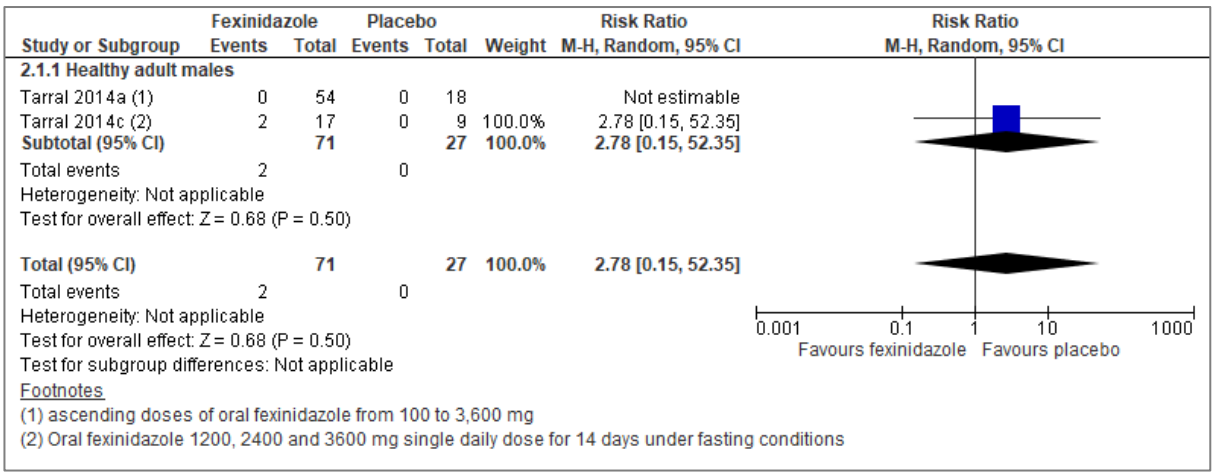
All participants were inpatients and the study did not report on this outcome.

1.15 Withdrawals from treatment, follow-up: end of treatment



2. Fexinidazole (oral) versus placebo in healthy adult male volunteers

2.1 Serious adverse events, follow-up: not reported

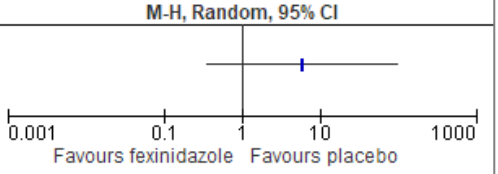


Two SAEs were reported by subjects who received fexinidazole: one subject (2,400 mg) asked to stop the study after 9 days of treatment due to intermittent headache, anxiety, vomiting, liquid stool episodes and myalgia of inferior limbs. Moderate anxiety had started the day preceding the first study drug administration and appeared to be the only cause of hospitalisation. The other SAE, on day 15, was observed in a second subject (3,600 mg) who exhibited a marked elevation in AST (10 times the normal upper limit) and ALT (7.4 times the normal upper limit). The volunteer was kept in the unit for surveillance for 48 h as the decrease was as strong as the increase. The

subject was followed up for an additional 15 days until transaminase values were back to normal. Bilirubinaemia remained normal throughout the follow-up period.

2.2 Adverse events, follow-up: not reported

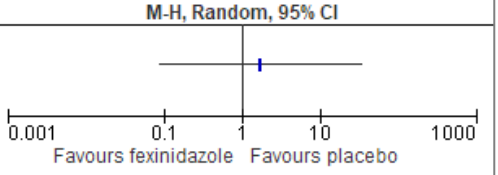
Study or Subgroup	Fexinidazole Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
2.2.1 Healthy adult males					
Tarral 2014a (1)	8	54	0	18	5.87 [0.36, 96.97]



Footnotes
(1) ascending doses of oral fexinidazole from 100 to 3,600 mg

2.3 Adverse events: central nervous system, follow-up: not reported

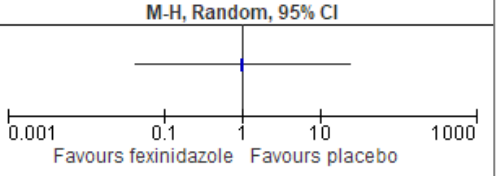
Study or Subgroup	Fexinidazole Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
2.3.1 Healthy adult males					
Tarral 2014a (1)	2	54	0	18	1.73 [0.09, 34.39]



Footnotes
(1) Adverse events possibly related to Fexinidazole administration; ascending doses of oral fexinidazole from 100 to 3,600 mg

2.4 Adverse events: skin reactions, follow-up: not reported

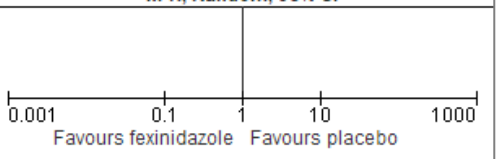
Study or Subgroup	Fexinidazole Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
2.4.1 Healthy adult males					
Tarral 2014a (1)	1	54	0	18	1.04 [0.04, 24.37]



Footnotes
(1) Adverse events possibly related to Fexinidazole administration; ascending doses of oral fexinidazole from 100 to 3,600 mg

2.5 Withdrawals from treatment, follow-up: end of treatment

Study or Subgroup	Fexinidazole Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
2.5.1 Healthy adult males					
Tarral 2014a (1)	0	54	0	18	Not estimable



Footnotes
(1) Adverse events possibly related to Fexinidazole administration; ascending doses of oral fexinidazole from 100 to 3,600 mg

3. Fexinidazole (oral) in adults and children stratified by age and HAT stage (single arm prospective studies)

3.1 Overall mortality at 18 months follow-up

Population		Study*	Events / participants	Rate per 1000	Causes of death
stage	age				
Stage 1	≥15 years	Mesu 2018b	3 / 189	16 per 1000	1 due to meningeal disorder and encephalitis, 1 due to shock, and 1 due to Peritonitis, all were considered as not related to the treatment or to the disease
	6-15 years	Mesu 2018c	1 / 69	14 per 1000	unrelated to treatment: death followed a traumatic aggression that caused 2 SAEs (dyspnoea and injury)
Early stage 2	≥15 years	Mesu 2018b	1 / 41	24 per 1000	from anaemia, pulmonary sepsis and nephropathy
	6-15 years	Mesu 2018c	0 / 19	0 per 1000	None
Late stage 2	6-15 years	Mesu 2018c	0 / 37	0 per 1000	none

* All single arm extension studies to RCT Mesu 2018a

3.2 Treatment failure* at 18 months follow-up

Population		Study	Events / participants	Rate per 1000	Comments
stage	age				
Stage 1	≥15 years	Mesu 2018b	4 / 189	21 per 1000	Single arm extension studies to RCT Mesu 2018a
	6-15 years	Mesu 2018c	1 / 69	14 per 1000	
Early stage 2	≥15 years	Mesu 2018b	1 / 41	24 per 1000	
	6-15 years	Mesu 2018c	0 / 19	0 per 1000	
Late stage 2	6-15 years	Mesu 2018c	1 / 37	27 per 1000	

*death, relapse, loss to follow-up, absence of lumbar puncture, consent withdrawal

3.3 Treatment success* at 18 months follow-up

Population		Study	Events / participants	Rate per 1000	Comments
stage	age				
Stage 1	≥15 years	Mesu 2018b	185 / 189	979 per 1000	Single arm extension studies to RCT Mesu 2018a
	6-15 years	Mesu 2018c	68 / 69	986 per 1000	
Early stage 2	≥15 years	Mesu 2018b	40 / 41	977 per 1000	
	6-15 years	Mesu 2018c	19 / 19	1000 per 1000	
Late stage 2	6-15 years	Mesu 2018c	36 / 37	973 per 1000	

* alive, no trypanosomes in body fluid, no rescue medication, CSF WBC ≤20 cells per μL; after 18 months follow-up

3.4 Serious adverse events at 18 months follow-up

Population		Study	Events / participants	Rate per 1000	Details
stage	age				
Stage 1	≥15 years	Mesu 2018b*	17 / 189	90 per 1000	Infections and infestations 8x, 3 x Gastrointestinal disorders, 1x Injury, poisoning and procedural complications(wound), 1x Uterine leiomyoma, 1x Psychiatric disorders
	6-15 years	Mesu 2018c*	5 / 69	72 per 1000	not reported for the subgroup of HAT stage 1 separately
Early stage 2	≥15 years	Mesu 2018b*	6 / 41	146 per 1000	Cerebral malaria, Pulmonary sepsis, Inguinal hernia 2x, Anaemia, Nephropathy
	6-15 years	Mesu 2018c*	2 / 19	105 per 1000	not reported for the subgroup of HAT stage 2 separately
Late stage 2	6-15 years	Mesu 2018c*	4 / 37	108 per 1000	not reported for the subgroup of HAT stage 2 separately
Healthy	18-45 years	Tarrall 2014b**	0 / 13	0 per 1000	None
		Tarrall 2014d**	0 / 12		

* Single arm extension studies to RCT Mesu 2018a
** single dose of 1200 mg

3.5 Adverse events at 18 months follow-up

Population		Study	Events / participants	Rate per 1000	Comments
stage	age				
Stage 1	≥15 years	Mesu 2018b	176 / 189	931 per 1000	Single arm extension studies to RCT Mesu 2018a
	6-15 years	Mesu 2018c	61 / 69	884 per 1000	
Early stage 2	≥15 years	Mesu 2018b	38 / 41	927 per 1000	
	6-15 years	Mesu 2018c	18 / 19	947 per 1000	
Late stage 2	6-15 years	Mesu 2018c	37 / 37	1000 per 1000	
Healthy	18-45 years	Tarrall 2014b	11 / 13	846 / 1000	single dose of 1200 mg
		Tarrall 2014d	9 / 12	750 per 1000	
		Tarrall 2014e	98 AEs were experienced among 30 participants	Not estimable	1200 mg to 2400 mg oral fexinidazole for 10 days

3.6 Adverse events: central nervous system at 18 months follow-up

Population		Study	Events / participants	Rate per 1000	Comments
stage	age				
Stage 1	≥15 years	Mesu 2018b	112 / 189 *	593 per 1000	Single arm extension studies to RCT Mesu 2018a
	6-15 years	Mesu 2018c	31 / 69 *	449 per 1000	
Early stage 2	≥15 years	Mesu 2018b	30 / 41 *	732 per 1000	
	6-15 years	Mesu 2018c	10 / 19 *	526 per 1000	
Late stage 2	6-15 years	Mesu 2018c	20 / 37 *	541 per 1000	
Healthy	18-45 years	Tarrall 2014d	3 / 12 **	250 per 1000	single dose of 1200 mg
		Tarrall 2014e	32 events were experienced among 30 participants	Not estimable	1200 mg to 2400 mg oral fexinidazole for 10 days

*headache, dizziness, tremor
**headache

3.7 Adverse events: bone marrow toxicity* at 18 months follow-up

Population		Study	Events / participants	Rate per 1000	Comments
stage	age				
Stage 1	≥15 years	Mesu 2018b	12 / 189	63 per 1000	Single arm extension studies to RCT Mesu 2018a
	6-15 years	Mesu 2018c	10 / 69	145 per 1000	
Early stage 2	≥15 years	Mesu 2018b	2 / 41	49 per 1000	
	6-15 years	Mesu 2018c	4 / 19	211 per 1000	
Late stage 2	6-15 years	Mesu 2018c	6 / 37	162 per 1000	

*anaemia, neutropenia

3.8 Adverse events: gastrointestinal symptoms* at 18 months follow-up

Population		Study	Events / participants	Rate per 1000	Comments
stage	age				
Stage 1	≥15 years	Mesu 2018b	143 / 189	757 per 1000	Single arm extension studies to RCT Mesu 2018a
	6-15 years	Mesu 2018c	55 / 69	797 per 1000	
Early stage 2	≥15 years	Mesu 2018b	36 / 41	878 per 1000	
	6-15 years	Mesu 2018c	15 / 19	789 per 1000	
Late stage 2	6-15 years	Mesu 2018c	28 / 37	757 per 1000	
Healthy	18-45 years	Tarrall 2014e	50 events were experienced among 30 participants	Not estimable	1200 mg to 2400 mg oral fexinidazole for 10 days

* vomiting, nausea, dyspepsia, abdominal pain, salivary hypersecretion, constipation, gastritis, hernia, dry mouth

3.9 Adverse events: skin reactions* at 18 months follow-up

Population		Study	Events / participants	Rate per 1000	Comments
stage	age				
Stage 1	≥15 years	Mesu 2018b	12 / 189	63 per 1000	Single arm extension studies to RCT Mesu 2018a
	6-15 years	Mesu 2018c	2 / 69	29 per 1000	
Early stage 2	≥15 years	Mesu 2018b	1 / 41	24 per 1000	
	6-15 years	Mesu 2018c	0 / 19	0 per 1000	
Late stage 2	6-15 years	Mesu 2018c	5 / 37	135 per 1000	

*pruritus

3.10 Adverse events: infections and infestations at 18 months follow-up

Population		Study	Events / participants	Rate per 1000	Comments
stage	age				
Stage 1	≥15 years	Mesu 2018b	11 / 189	58 per 1000	Single arm extension studies to RCT Mesu 2018a
	6-15 years	Mesu 2018c	3 / 69 *	43 per 1000	
Early stage 2	≥15 years	Mesu 2018b	3 / 41	73 per 1000	
	6-15 years	Mesu 2018c	2 / 19 *	105 per 1000	
Late stage 2	6-15 years	Mesu 2018c	8 / 37 *	216 per 1000	

*malaria

3.11 Adverse events: cardiotoxicity* at 18 months follow-up

Population		Study	Events / participants	Rate per 1000	Comments
stage	age				
Stage 1	≥15 years	Mesu 2018b	16 / 189	85 per 1000	Single arm extension studies to RCT Mesu 2018a
	6-15 years	Mesu 2018c	2 / 69	29 per 1000	
Early stage 2	≥15 years	Mesu 2018b	1 / 41	24 per 1000	
	6-15 years	Mesu 2018c	1 / 19	53 per 1000	
Late stage 2	6-15 years	Mesu 2018c	1 / 37	27 per 1000	

*palpitations

3.12 Withdrawals from treatment*, follow-up: end of treatment

Population		Study	Events / participants	Rate per 1000	Comments
stage	age				
Stage 1	≥15 years	Mesu 2018b	0 / 189	0 per 1000	Single arm extension studies to RCT Mesu 2018a
	6-15 years	Mesu 2018c	0 / 69	0 per 1000	
Early stage 2	≥15 years	Mesu 2018b	0 / 41	0 per 1000	
	6-15 years	Mesu 2018c	0 / 19	0 per 1000	
Late stage 2	6-15 years	Mesu 2018c	0 / 37	0 per 1000	
Healthy	18-45 years	Tarrall 2014b	1 / 13	77 per 1000	Single dose of 1200 mg
		Tarrall 2014d	1 / 12	83 per 1000	
		Tarrall 2014e	7 / 30	233 per 1000	1200 mg to 2400 mg oral fexinidazole for 10d

*all patients were hospitalized during the treatment period

4. Pentamidine (IM) in adults and children with first stage HAT stratified by age (evidence from single arm trials or observational studies)

4.1 Overall mortality, follow-up: up to 24 months

Population	Study	Events / participants	Rate per 1000	Causes of death
age				
≥15 years	Burri 2016	1 / 41	24 per 1000	Death not likely to be related to trypanosomiasis, no further details reported
	Doua 1993	4 / 150	27 per 1000	1 death during treatment, due to hyperthermia, 3 deaths in follow up period: 1 of diabetes developed during treatment, 1 of viral hepatitis, 1 from unknown cause
	Eperon 2006	3 / 541	6 per 1000	Not reported
≥ 12 years	Pohlig 2016	7 / 130	54 per 1000	All deaths were considered not related or probably not related to the study drug, no further details reported on pentamidine deaths
6-15 years	Eperon 2006	0 / 255	0 per 1000	none
0-5 years	Eperon 2006	1 / 54	19 per 1000	unknown cause
NR	Ginoux 1984	0 / 90	0 per 1000	none

4.2 Death likely due to HAT, follow-up: 24 months

Population Age	Study	Events / participants	Rate per 1000	Causes of death
≥15 years	Ngoyi 2010	2 / 41	37 per 1000	Not reported other than that it was HAT related
≥12 years	Pohlig 2016	0 / 137	0 per 1000	none

4.3 Relapse

Population age	Study	Follow-up	Events / participants	Rate per 1000	Definition
≥15 years	Bastide 2011	24 months	368 / 4597	80 per 1000	Relapse within 24 months as diagnosed by the physician-in-charge on the basis of clinical symptoms and laboratory results
	Doua 1993	7 months	1 / 146	7 per 1000	Not reported
	Eperon 2006	24 months	21 / 541	39 per 1000	trypanosomes in blood or CSF, or WBC count in the CSF significantly increased, or WBC count in the CSF showed little variation compared to previous control and the patient had symptoms and signs consistent with HAT
	Jammoneau 2003	6 months	0 / 31	0 per 1000	trypanosomes in blood and/or in the CSF
	Ngoyi 2010	24 months	1 / 41	24 per 1000	Not reported
	Ruiz 2002	22 months	2 / 79	25 per 1000	Not reported
	Tongue 2008	6 months	13 / 54	241 per 1000	Increased WBC in CSF, excluding low/wrong dose or poor quality drugs
≥12 years	Pohlig 2016	24 months	3 / 130	23 per 1000	Trypanosomes have been detected in any body fluid
6-15 years	Eperon 2006	24 months	11 / 255	43 per 1000	trypanosomes in blood or CSF, or WBC count in the CSF significantly increased, or WBC count in the CSF showed little variation compared to previous control and the patient had symptoms and signs consistent with HAT
0-5 years	Eperon 2006	24 months	0 / 54	0 per 1000	

4.4 Treatment failure

Population age	Study	Follow-up	Events / participants	Rate per 1000	Definition
≥15 years	Balasegaram 2006	12 months	23 / 586	39 per 1000	Death or recurrence of parasites in any body fluid, CSF WBC count either significantly increased or with symptoms suggestive of sleeping sickness
	Eperon 2006	24 months	25 / 541	46 per 1000	relapse or death occurring during treatment or follow-up (unless an obvious external cause of death was reported)
6-15 years	Eperon 2006	24 months	11 / 255	43 per 1000	
0-5 years	Eperon 2006	24 months	1 / 54	19 per 1000	

4.5 Treatment success

Population age	Study	Follow-up	Events / participants	Rate per 1000	Definition
≥15 years	Balasegaram 2006	12 months	619 / 652	949 per 1000	"remained disease free"; includes participants with first stage and intermediate HAT (0–10 cells WBC /mm³ CSF)
	Bastide 2011	24 months	4229 / 4597	920 per 1000	"cured"
	Burri 2016	24 months	31 / 32	969 per 1000	absence of parasites in blood, lymph nodes, and CSF, as well as <5mL WBCs in the CSF
	Eperon 2006	24 months	404 / 541	747 per 1000	definite or probable cure (absence of relapse 3 to 30 months after discharge)
	Ngoyi 2010	24 months	30 / 41	732 per 1000	"cured"
≥12 years	Pohlig 2016	24 months	83 / 130	638 per 1000	Parasitological cure: no evidence for parasitological relapse and 5 WBCs/mm3 in CSF
6-15 years	Eperon 2006	24 months	184 / 255	722 per 1000	definite or probable cure (absence of relapse 3 to 30 months after discharge)
0-5 years	Eperon 2006	24 months	32 / 54	593 per 1000	

4.6 Serious adverse events

Population age	Study	Follow-up	Events / participants	Rate per 1000	Causes
≥15 years	Burri 2016	24 months	1 / 41	24 per 1000	1 death
≥12 years	Pohlig 2016	24 months	24 / 137	175 per 1000	1 subcutaneous abscess (considered probably related to pentamidine), no details of other SAEs

In addition, Eperon 2006 reported that there were no severe adverse events among 541 adults and adolescents > 15 years, 255 children 6-15 years and 54 children 0-5 years.

4.7 Any adverse events

Population age	Study	Follow-up	Events / participants	Rate per 1000
≥15 years	Burri 2016	Not reported	38 / 41	927 per 1000
	Eperon 2006	Not reported	154 / 541	285 per 1000
	Doua 1993	End of treatment	36 / 150	240 per 1000
≥12 years	Pohlig 2016	End of treatment	135 / 137	985 per 1000
6-15 years	Eperon 2006	Not reported	45 / 255	176 per 1000
0-5 years	Eperon 2006	Not reported	11 / 54	204 per 1000

4.8 Adverse events: Nervous system disorders, follow-up: end of treatment

Population age	Study	Events / participants	Rate per 1000	Comments
≥15 years	Doua 1993	6 / 150	40 per 1000	headache, dizziness, dysgeusia
≥12 years	Pohlig 2016	26 / 137	190 per 1000	

4.9 Adverse events: Gastrointestinal disorders, follow-up: end of treatment

Population age	Study	Events / participants	Rate per 1000
≥15 years	Pohlig 2016	23 / 137	168 per 1000

4.10 Adverse events: Skin disorders, follow-up: end of treatment

Population age	Study	Events / participants	Rate per 1000	Comments
≥15 years	Doua 1993	1 / 150	7 per 1000	pruritus
≥12 years	Pohlig 2016	1 / 137	7 per 1000	

4.11 Adverse events: Cardiovascular, follow-up: end of treatment

Population age	Study	Events / participants	Rate per 1000	Comments
≥12 years	Pohlig 2016	86 / 137	628 per 1000	blood pressure disorders, shock

4.12 Withdrawals from treatment, follow-up: end of treatment

Population age	Study	Events / participants	Rate per 1000
≥15 years	Burri 2016	0 / 41	0 per 1000
≥12 years	Pohlig 2016	0 / 137	0 per 1000

Appendix 8. Summary of studies evaluating adherence

Introduction

In order to inform recommendations about the use of fexinidazole for the management of HAT, the guideline expert group needs an estimate of the expected adherence to a 10-day fexinidazole oral regimen in rural African populations. Additional information regarding observed differences in adherence between particular subgroups, and which interventions have an impact on adherence in these settings, are also needed.

An unsuccessful treatment for HAT has potentially fatal consequences. With an oral administration, treatment effectiveness will depend in part on adherence to the 10-day regimen, and poor adherence to oral treatments have been flagged as a potential problem if fexinidazole is to be administered in the community. In addition, if there are observed differences in adherence within particular population subgroups (e.g. due to educational level or age) specific interventions may be needed to ensure sufficient adherence. These aspects can help inform the interpretation of the available evidence and formulation of recommendations.

Objectives

The main focus of this report is to summarise the evidence on adherence to oral malaria treatment, as a proxy of what would be the expected adherence to the 10-day fexinidazole oral regimen in rural African populations. Where available, we have also reported on predictors of adherence in this setting and if particular interventions have been shown to impact on adherence.

Other aspects of adherence to treatment, such as attitudes of patients, barriers and facilitators are outside of the scope of this report.

Search and study selection

A non-systematic search was conducted in Pubmed, Epistemonikos, Trip Database and Google Scholar to identify relevant studies that assessed adherence to malaria treatment. The keywords used were “adherence”, “compliance”, “malaria” and “Africa”. Systematic reviews were prioritised for inclusion in the first instance, and the words “review” and “systematic review” were used to limit the search.

The list of titles retrieved from each database was scanned for potentially relevant references, however systematic title, abstract and full-text screening was not conducted.

Four recent systematic reviews were identified (Banek 2014, Bruxvoort 2014, Fuangchan 2014, Yakasai 2015). Additional primary studies were identified but were not included in this report as the evidence from the systematic reviews was considered sufficient.

Summary of included systematic reviews

A full grading of the evidence has not been conducted, as it was not considered appropriate, however evidence from these systematic reviews is summarised in the tables below (

Summary of results

Four systematic reviews reported on adherence to antimalarial drugs and included 16 to 55 studies per review. The studies reported a wide range of adherence to antimalarial drugs, from 1.5% to 100% (Table 2).

Three systematic reviews reported on factors associated with adherence to antimalarial drugs (Table 3). Factors associated with adherence to antimalarial drugs included having an older compared to a younger caregiver; being an older compared to a younger patient; higher literacy-

, education-, or income level; having received instructions or explanations about the treatment, including instructive packaging; having greater knowledge of the disease; first dose administered at health centre; and given the exact number of tablets. Factors associated with non-adherence to antimalarial drugs included being male; experiencing vomiting; experiencing adverse events; caregivers' perception that the condition is not severe; and belief in traditional medicine.

Types of interventions that have been used to promote adherence to antimalarial drugs were reported in three systematic reviews (Table 4). Interventions included subsidizing medication; supervised dosing or directly-observed therapy (DOT); more convenient dosing regimen, including shorter duration of treatment; training of shopkeepers or community health workers; supply through community health workers; caregiver education; pre-packaged drugs, including age targeted packaging and packaging with pictorial aids; verbal, poster, video, or visual media instructions; and different combinations of these types of interventions. See Tables 1-4.

Table 1. Characteristics of included systematic reviews

Study details	Population[1]	Country	Treatment	Interventions	Measurement method
Banek 2014 Banek K, Lalani M, Staedke SG, Chandramohan D. Adherence to artemisinin-based combination therapy for the treatment of malaria: a systematic review of the evidence. Malaria journal. 2014. 13(1):7. **Study design** Systematic review **Objective** To summarize the current evidence base on artemisin-based combination (ACT) adherence for the treatment of malaria. **Search dates** 1990 - April 2013 **Databases** Medline, Embase and Global Health **Other criteria** Peer-reviewed, English-language	All ages (Alba 2010, Barnes 2005, Cohen 2012, Congpuong 2010, Fogg 2004, Kabanywanyi 2010, Lawford 2011, Meankaew 2010, Mubi 2011, Na-Bangchang 1997, Shwe 1998, Yeung 2008, Zaw Win 2012) Infants and young children (Achan 2009, Ajayi 2008a, Ajayi 2008b, Beer 2009, Chinbuah 2006, Depoortere 2004a, Depoortere 2004b, Kachur 2004, Kalyango 2013, Kangwana 2011, Ngasala 2011, Ogolla 2013, Ratsimbasoa 2012, Simba 2012) Infants and young children (Dunyo 2011) Infants, children and adolescents (Onyango 2012, Watsierah 2011) Infants, children, adolescents and adults (Gerstl 2010, Lemma 2011, Mace 2011, Rahman 2008) Children, adolescents and adults (Bell 2009, Faucher 2009) Adolescents and adults (Asante 2009)	**Africa** Benim (Faucher 2009); Ethiopia (Lemma 2011); Gambia (Dunyo 2011); Ghana (Asante 2009, Ajayi 2008a, Ajayi 2008b, Cinbuah 2006); Kenya (Lawford 2011, Kangwana 2011, Ogolla 2013, Onyango 2012, Watsierah 2011); Madagascar (Ratsimbasoa 2012); Malawi (Bell 2009, Mace 2011); Nigeria (Ajayi 2008a, Ajayi 2008b); Sierra Leone (Gerstl 2010); South Africa (Barnes 2005); South Sudan (Depoortere 2004b); Tanzania (Alba 2010, Kabanwanyi 2010, Kachur 2004, Ngasala 2011, Mubi 2011, Simba 2012); Uganda (Acham 2009, Ajayi 2008a, Ajayi 2008b Cohen 2012, Fogg 2004, Kalyango 2013); Zanzibar (Beer 2009); Zambia (Depoortere 2004) **Asia** Bangladesh (Rahman 2008); Cambodia (Yeung 2008); Myanmar (Shwe 1998, Zaw Win 2012); Thailand (Conpuong 2010, Meankawe 2010, Na-Bangchang 1997)	Antimalarial drugs AL (Ajayi 2008a, Ajayi 2008b, Barnes 2005, Bell 2009, Chinbuah 2006, Cohen 2012, Depoortere 2004b, Dunyo 2011, Faucher 2009, Fogg 2004, Kalyango 2013, Kabanwanyi 2010, Kangwana 2011, Lawford 2011, Lemma 2011, Mace 2011, Mubi 2011, Ngasala 2011, Ogolla 2013, Simba 2012, Zaw Win 2012) AL+Q (Achan 2009) AQ+AS (Ajayi 2008a, Ajayi 2008b, Asante 2009, Beer 2009, Faucher 2009, Gerstl 2010, Ratsimbasoa 2012) AS+MQ (Congpuong 2010, Meankaew 2010, Na-Bangchang 1997, Shwe 1998, Yeung 2008) AS+SP (Depoortere 2004a, Kachur 2004) CPD (Bell 2009, Dunyo 2011) SP (Bell 2009, Faucher 2009) Not reported (Onyango 2012, Watsierah 2011) Treatment duration was not reported.	Not applicable	Method of assessing adherence Bioassay (Ngasala 2011, Na-Bangchang 1997, Shwe 1998) Bioassay & self-report (Simba 2012, Congpuong 2010) Bioassay or self-report or MEMS (Bell 2009) Pill counts (Asante 2009, Faucher 2009) Pill counts & self-report/ caregiver self-report (Kabaywany 2011, Lemma 2011, Mace 2008, Ogolla 2013, Lawford 2011, Kalyango 2013, Zaw Win 2012, Chinbuah 2006, Mubi 2011, Beer 2009, Dunyo 2011, Gerstl 2010, Depoortere 2004a, Depoortere 2004b, Kachur 2004, Achan 2009) Pill counts or self-report (Cohen 2012) Pill counts, self-report & bioassay (Rahman 2008, Fogg 2004) Self-report (Alba 2010, Barnes 2005, Kangwana 2011, Ratsimbasoa 2012, Ajayi 2008a, Ajayi 2008b, Yeung 2008, Meankaew 2010)
Bruxvoort 2014 Bruxvoort K, Goodman C, Kachur SP, Schellenberg D. How patients take malaria treatment: a systematic review of the literature on adherence	Subjects included all age groups in 25 studies, only children <5 in 19 studies, both children <5 and older children in an additional 7 studies, and only adults in 4 studies. No additional details reported.	**Africa** Benim (Faucher 2009); Burkina Faso (Krause 2000, Sirima 2003); Ethiopia (Lemma 2011); Gambia (Dunyio 2010); Ghana (Abuaku 2004, Ajayi 2008, Agyepong 2002, Ansah 2001, Chinbuah 2006, Yenboah-Antwi	Antimalarial drugs AL - 3 days (Achan 2009, Bell 2009, Chinbuah 2006, Cohen 2012, Depoortere 2004b, Dunyo 2010, Faucher 2009, Fogg 2004, Kabanywanyi 2010, Kalyango 2013, Kangwana 2011, Lawford 2011,	Interventions evaluated Age-based packaging of syrup & tablets (Yeboah-Antwi 2001) Community health worker training (Winch 2003)	Method of assessing adherence: Laboratory assay (Na-Bangchang 1997, Shwe 1998) Pill count (Krause 2000)

to antimalarial drugs. PloS one. 2014. 20;9(1):e84555. **Study design** Systematic review **Objective** To review studies reporting quantitative results on adherence to antimalarials, and to explore factors associated with adherence. **Search dates** Not reported **Databases** Pubmed. List from studies and reviews identified were also searched for references **Other criteria** Not reported		2001); Kenya (Amin 2004, Kangwana 2011, Lawford 2011, Marsh 1999, Marsh 2004, Onyango 2012); Malawi (Bell 2009, Mace 2011); Mali (Thera 2000, Winch, 2003); Nigeria (Ajayi 2008, Okonkwo 2001); Rwanda (Twagirumukiza 2010); Senegal (Soaures 2008); Sierra Leone (Gerstl 2010); South Africa (Barnes 2005); South Sudan (Depoortere 2004b); Tanzania (Kabanywanyi 2010, Kachur 2004, Simba 2012); Togo (Deming 1989); Uganda (Achan 2009, Ajayi 2008, Cohen 2006, Fogg 2004, Kalyango 2013, Kolaczinski 2006, Nshakira 2002, Nsungwa-Sabiiti 2005); Zambia (Depoortere 2004a); Zanzibar (Beer 2009) **Asia** Bangladesh (Rahman 2008); Cambodia (Denis 1998); China (Qingjun 1998); Myanmar (Shwe 1998); Papua New Guinea (Lauwo 2006); Sri Lanka (Reilley 2002); Thailand (Congpuong 2010, Fungladda 1998, Khantibul 2009, Na-Bangchang 1997, Takeuchi 2010) **Latin-America** Brazil (Duarte 2003, Pereira 2011); Ecuador (Yepez 2000); Peru (Peeters-Grietens 2010)	Lemma 2011, Mace 2011, Rahman 2008, Simba 2012); duration not reported (Ajayi 2008, Barnes 2005, Onyango 2012) AQ+AS 3 days (Souares 2008) AS 4 days (Fungladda 1998) AS+AQ 3 days (Ajayi 2008, Beer 2009, Faucher 2009, Gerstl 2010) AS+MQ - 2 days (Na-Bangchang 1997); AS+MQ 3 days (Shwe 1998) AS+SP 3 days (Depoortere 2004a, Kachur 2004) CPD 3 days (Bell 2009, Dunyo 2003) CQ - 3 days (Agyepong 2002, Ansah 2001, Nshakira 2002, Winch 2003, Yeboah-Antwi 2001); duration not reported (Deming 1989, Krause and Sauerborn 2000, Marsh 1999, Nsunga-Sabite 2005, Okonkwo 2001, Sirima 2003, Thera 2000) CQ+PQ - 5 days (Reilley 2002); 7 days (Pereira 2011, Yepez 2000); 8 days (Qingjun 1998); 14 days (Duarte 2003, Khantikul 2009, Takeuchi 2010) CQ+SP - 3 days (Kolaczinski 2006, Lauwo 2006); duration not reported (Marsh 2004, Nsunga-Sabite 2005) PQ - 7 days (Peeters-Grietens 2010 (Congpoung 2010 Q 7 days (Achan 2009, Twagirumukiza 2010); duration not reported (Krause and Sauerborn 2000) Q+DX 7 days (Duarte 2003) Q+TT 7 days (Denis 1998, Fungladda 1998)	Drug label & verbal instructions (Agyepong 2002) Introduction of tablets to replace syrup (Ansah 2001) Packaging & availability through community health workers (Sirima 2003) Packaging & counselling (Lauwo 2006) Packaging (Qinjun 1998) Packaging and training (Shwe 1998) Pictorial insert & verbal instructions (Okokwo 2001) Posters & video (Denis 1998) Shop-keeper training (Marsh 1999, Marsh 2004) Subsidised AL, shopkeeper training & community awareness activities (Kanwana 2011)	Self-report (Agyepong 2002, Chinbuah 2006, Kabanywanyi 2010, Khantibul 2009, Nshakira 2002, Reilley 2002) Self-report & drug assays (Congpoung 2010) Self-report & laboratory assay (Qingjun 1998, Souares 2008) Self-report & lumefrantine assay (Simba 2012) Self-report & measurement of remaining syrup (Okonkwo 2001) Self-report & pill-count (Achan 2009, Beer 2009, Cohen 2012, Denis 1998, Depportere 2004a, Depportere 2004b, Dunyo 2010, Faucher 2009, Fungladda 1998, Gerstl 2010, Kachur 2004, Kalyango 2013, Kolaczinski 2006, Lawford 2011, Lemma 2011, Mace 2011, Pereira 2011) Self-report & triangulation with health centre records (Peeters-Grietens 2010) Self-report, electronic pill boxes & laboratory assay (Bell 2009) Self-report, pill count & electronic pill boxes (Twagirumukiza 2010) Self-report, pill count or measurement of remaining syrup (Ansah 2001, Winch 2003, Yeboah-Antwi 2001) Self-report, pill-count & lumefrantine assay (Fogg 2004, Rahman 2008, Survey (Abuaku 2004, Ajayi 2008, Amin 2004, Barnes 2005, Deming 1989, Duarte 2003, Kangwana 2011, Lauwo 2006, Marsh 2004, Nsungwa-Sabiti 2005, Onyango 2012, Sirima 2003, Takeucho 2010, Thera 2000, Yepez 2000) Survey & laboratory assay (Marsh 1999, Follow-up ranged from 2 to 8 days

			SP+CQ+AQ duration not reported (Abuaku 2004)		
Fuangchan 2014 Fuangchan A, Dhippayom T, Kongkaew C. Intervention to promote patients' adherence to antimalarial medication: a systematic review. The American journal of tropical medicine and hygiene. 2014. 8;90(1):11-9. **Study design** Systematic review **Objective** To explore the effectiveness of existing interventions promoting adherence to antimalarial drugs. **Search dates** Up to March 2013 **Databases** Medline, Embase, Cinahl and Cochrane CENTRAL **Other criteria** Not reported	Outpatients with uncomplicated malaria Infants and young children (Winch 2003) Young children (Kangwana 2011) Children (Achan 2009, Afenyadu 2005, Ansah 2001, Dunyo 201, Faucher 2009, Okonwo 2001) Adolescents and adults (Fungladda 1998) Not specified (Agyepong 2002, Denis 1998, Lauwo 2006, Quingjun 1998, Rahman 2008, Takeuchi 2010, Yeboah 2001,)	**Africa** Benim (Faucher 2009); Gambia (Dunyo 2011); Ghana (Afenyadu 2005, Agyepong 2002, Amshah 2001, Yeboah 2001); Kenya (Kangwana 2011); Mali (Winch 2003); Nigeria (Okonkwo 2001); Uganda (Achan 2009) **Asia** Bangladesh (Rahman 2008); Cambodia (Denis 1998); China (Quingjun 1998); Papua New Guinea (Lauwo 2006); Thailand (Fungladda 1998, Takeuchi 2010)	Antimalarial drugs AL 3 days (Kanwana 2011, Rahman 2008) CD or AL 3 days (Dunyo 2011) CQ+PQ 14 days (Takeuchi 2010) CQ 3 days (Afenyadu 2005, Ansah 2001, Yeboah 2001, Okonkwo 2001, Agyepong 2002, Winch 2003) CQ 3 days + PQ 8 days (Qingjun 1998) CQ 3 days + SP single dose (Lauwo 2006) Q+TT 7 days or AS 5 days (Fungladda 1998) Q 7 days or AL 3 days (Achan 2009) Q+TT 7 days (Denis 1998) SP or ASAQ or AL 3 days (Faucher 2009)	Interventions evaluated Community education (Denis 1998, Kangwana 2011, Winch 2003,) Convenient regimen (Achan 2009, Dunyo 2011, Faucher 2009, Fungladda 1998) Medication supervision (Rahman 2008, Takeuchi 2010) Pre-packaging (Afenyadu 2005, Ansha 2001, Lauwo 2006, Qingjun 1998, Yeboah 2001) Visual media (Okonkwo 2001) Visual media + verbal information (Agyenpong 2002, Okonkwo 2001)	Method of assessing adherence Drug concentration measurement (Quingjun 1998) Interview (Kanwana 2011, Lauwo 2006, Takeuchi 2010) Remaining drug count (Faucher 2009) Remaining drug count & (caregivers) interview (Afenyadu 2005, Ansah 2001, Denis 1998, Dunyo 2011, Fungladda 1998) Remaining drug count & questionnaire (Okonkwo 2001, Rahman 2008, Winch 2003) Remaining drug count & self-report (Agyepong 2002) Remaining drug count, questionnaire & interview (Yeboah 2001) Self-report (Quingjun 1998) Remaining drug count & parents or guardians report (Achan 2009)
Yakasai 2015 Yakasai AM, Hamza M, Dalhat MM, Bello M, Gadanya MA, Yaqub ZM, Ibrahim DA, Hassan-Hanga F. Adherence to artemisinin-based combination therapy for the treatment of uncomplicated malaria: a systematic review and meta-analysis. Journal of tropical medicine. 2015. **Study design**	People with uncomplicated malaria. Participants were mainly children, adolescents and adults. No additional details reported.	**Africa** DR Congo (Siddiqui 2015); Ethiopia (Lemma 2011); Ghana (Ajayi 2008, Amponsah 2015, Asante 2009, Chinbuah 2006); Kenya (Gore-Langon 2015, Ogolla 2013, Lawford 2011, Ontango 2012); Malawi (Bell 2009, Ewing 2015, Mace 2011); Nigeria (Ajayi 2008); Sierra Leone (Gersl 2010); Tanzania (Beer 2009, Bruxvoort 2015, Kabanywanyi 2010, Kachur 2004, Simba 2012); Uganda (Achan 2009, Ajayi 2008, Cohen	Antimalarial drugs AL (Ajayi 2008, Bell 2009, Chinbuah 2009, Fogg 2004Kabanywanyi 2010, Lawford 2011, Mace 2011, Simba 2012, Lemma 2011, Onyango 2012, Cohen 2012, Achan 2009, Amponsah 2015, Aung 2015, Bruxvoort 2015, Ewing 2015, Gore-Langton 2015, Ogolla 2013)	Although this review does not evaluate different interventions, the following sub-group comparison of interest was reported: Studies conducted in the public sector[2] (Achan 2009, Aung 2015, Bruxvoort 2015, Congpoung 2010, Ewing 2015, Gore-Langton 2015, Siddiqui 2015, Ogolla 2013, Ajayi 2008, Asante 2009, Bell 2009, Chinbuah 2006, Fogg 2004, Kabanywanyi 2010, Kachur 2004, Lawford 2011, Mace 2011, Beer	Method of assessing adherence Blister pack (Asante 2009, Chinbuah 2006, Foog 2004, Kabanywanyi 2010, Depoortere 2004, Gerstl 2010, Achan 2009, Gore-Langton 2015, Siddiqui 2015) Blister pack & self-report/ caregivers report (Ajayi 2008, Beer 2009, Cohen 2012, Kachur 2004, Lawford 2011, Lemma 2011)

Systematic review and meta-analysis **Objective** To determine the prevalence and predictors of adherence to artemisin-based combination (ACT) for the treatment of uncomplicated malaria. **Search dates** Up to April 2015 **Databases** Google Scholar, Medline, Embase, AJOL, Web of Science and Cochrane **Other criteria** Peer-reviewed, English-language		2012, Fogg 2004); Zambia (Depoortere 2004) **Asia** Myanmar (Aung 2015); Thailand (Conpuong 2010)	AS+AQ (Ajayi 2008, Asante 2009, Beer 2009, Gerstl 2010, Amponsah 2015, Siddiqqui 2015) AS+SP (Kachur 2004, Depoortere 2004) AS+PP (Amponsah 2015) AS+ MQ (Congpuong 2010) DA/ PQ (Ewing 2015) Treatment duration was not reported.	2009, Simba 2012, Depoortere 2004, Gersl 2010, Lemma 2011) *vs* studies conducted in the retail sector (Amponsah 2015, Bruxvoort 2015, Cohen 2012, Onyango 2012) *vs* studies conducted in the retail sector (Amposah 2015, Bruxvoort 2015, Cohen 2012, Onyango 2012) Copacked (Ajayi 2008, Amponsah 2015, Asante 2009, Beer 2009, Bruxvoort 2015, Congpuong 2010, Depoortere 2004, Ewing 2015, Gerstl 2010, Kachur 2004, Siddiqui 2015) *vs* fixed drug combination (Ajayi 2008, Achan 2009, Amponsah 2015, 39, Bell 2009, Bruxvoort 2015, Chinbuah 2006, Cohen 2012, Ewing 2015, Fogg 2004, Gore-Langton 2015, Kabanywanyi 2010, Lawford 2011, Lemma 2011, Mace 2011, Simba 2012, Onyango 2012, Ogolla 2013, Siddiqui 2015) Twice daily (Achan 2009, Amponsah 2015, Ajayi 2008, Asate 2009, Bell 2009, Bruxvoort 2015, Chinbuah 2006, Cohen 2012, Ewing 2015, Fogg 2004, Gore-Langton 2015, Kabanywanyi 2010, Lawford 2011, Lemma 2011, Mace 2011, Simba 2012, Onyango 2012, Ogolla 2013) *vs* once daily (Ajayi 2008, Amponsah 2015, Beer 2009, Congpuong 2010, Depoortere 2004, Ewing 2015, Gerstl 2010, Kachur 2004, Siddiqui 2015)	Day 3 whole blood MQ/ self-report (Congpuong 2010) Pill-count (Amponsah 2015) Pill-count & dose recall (Mace 2011) Pill-count & self-report (Aung 2015, Bruxvoort 2015, Onyango 2012,) Pill-count, blister pack & self-report (Ewing 2015, Ogolla 2013) Questionnaire & electronic device (Bell 2009) Self-report (Simba 2012)

[1]Where possible, WHO age groups were used: 0 to 30 days: neonate; 1 month to 2 years: infant; 2 to 6 years: young children; 6 to 12 years: children; 12 to 18 years: adolescents; >18 years: adults; [2]In the public sector, medications were given for free, and dispensed by health care professionals with clear instructions; in the retail sector medications are bought from drug stores or supermarkets without proper instructions on how to take them.

Abbreviations: AL: artemether-lumefantrine; AL+Q: artemether-lumefantrine + quinina; AS: artesunate; AS+AQ: artesunate + amodiaquine; AS+MQ: artesunate + mefloquine AS+SP: artesunate + sulphadoxine-pyrimethamine; AS+PP: artesunate + piperazine; CDP: chlorproguanil-dapsone; CQ: chloriquidine; CQ+PQ: chloriquidine + primaquine; CQ+SP: chloriquidine + sulphadoxine-pyrimethamine; DHA-PQ: Dihydroartemisinin-piperaquine; DOT: Directly observed therapy; CD: chlorproguanil-dapsone; MEMS: medical event monitoring system; PQ: primaquine; Q: quinine; Q+DX: quinine + doxycycline Q+TT: quinine + tetracycline; TT: tetracycline; SP: sulphadoxine-pyrimethamine

Table 2. Summary of systematic reviews reporting on adherence to malaria treatment

Reference	Number of included studies and sample size	Reported adherence
Banek 2014 Banek K, Lalani M, Staedke SG, Chandramohan D. Adherence to artemisinin-based combination therapy for the treatment of malaria: a systematic review of the evidence. Malaria journal. 2014. 13(1):7.	37 studies Sample size ranged from 32 to 3,288	Pooled prevalence of adherence: not reported Adherence ranged from 38.7% to 99.2% Adherence for studies conducted in Africa ranged from 38.7% (Ethiopia) to 99.2% (Uganda)
Bruxvoort 2014 Bruxvoort K, Goodman C, Kachur SP, Schellenberg D. How patients take malaria treatment: a systematic review of the literature on adherence to antimalarial drugs. PloS one. 2014. 20;9(1):e84555.	55 studies Sample size ranged from 31 to 1,806	Pooled prevalence of adherence: not reported Adherence ranged from 1.5% to 100% Adherence for studies conducted in Africa ranged from 1.5% (Mali) to 100% (Ghana, Malawi)
Fuangchan 2014 Fuangchan A, Dhippayom T, Kongkaew C. Intervention to promote patients' adherence to antimalarial medication: a systematic review. The American journal of tropical medicine and hygiene. 2014. 8;90(1):11-9.	16 studies N = 9,248 participants. Sample size ranged from 137 to 2,749	Pooled prevalence of adherence: not reported Adherence ranged from 0.5% to 93.1% (these values were taken from the control group or before the intervention was implemented) Adherence for studies conducted in Africa ranged from 21.6% (Mali) to 88.9% (Ghana) (these values were taken from the control group or before the intervention was implemented)
Yakasai 2015 Yakasai AM, Hamza M, Dalhat MM, Bello M, Gadanya MA, Yaqub ZM, Ibrahim DA, Hassan-Hanga F. Adherence to artemisinin-based combination therapy (ACT) for the treatment of uncomplicated malaria: a systematic review and meta-analysis. Journal of tropical medicine. 2015.	25 studies (and 6 sub-studies included in the analysis) Sample size ranged from 26 to 918	Pooled prevalence of adherence (95% CI) = 69.77% (62.11% to 77.43%); however significant statistical heterogeneity was present (I^2=96.3%, p=0.000) Adherence ranged from 34.21% to 97.39%

Abbreviations: ACT: artemisinin-based combination therapy; CI: confidence interval; km: kilometres; OR: odds ratio

Table 3. Summary of systematic reviews reporting on factors associated with adherence to malaria treatment

Reference	Number of included studies and sample size	Factors associated with adherence
Banek 2014 Banek K, Lalani M, Staedke SG, Chandramohan D. Adherence to artemisinin-based combination therapy for the treatment of	37 studies Sample size ranged from 32 to 3,288	**Socio-demographic factors** Overall, sex, socio-economic status or age were not significantly or consistently associated with adherence (15 studies). However, 1 study reported that older caregivers (25 to 50 years) were more likely to be fully adherent, compared to younger caregivers (OR 1.65; 95% CI 1.10 to 1.85). The study also found that older patients (15+ years) were more likely to be adherent compared to those <15 years (OR 1.37;

malaria: a systematic review of the evidence. Malaria journal. 2014. 13(1):7.		95% CI 1.02 to 1.85). Likewise, another study also reported that patients <5 years of age were less likely to be adherent (OR 0.05; 95% CI 0.3 to 0.8) compared to older patients (18+ years). Education levels and literacy were both found to be significantly associated with ACT adherence in 5 studies, with higher levels of education and/or literacy positively associated with adherence. **Treatment instructions and treatment supervision** In 2 studies patient/ caregiver knowledge or understanding of treatment dose was found to be a significant predictor of adherence. Another study found that caregivers receiving instructions for treatment administration with a visual aide or medication package were slightly more likely to adhere (OR 2.5; *p*-value = 0.02). Also, 1 study found that giving instructions on administration of treatment to caregivers in their mother tongue lowered the risk of non-adherence (OR 0.46; 95% CI 0.28 to 0.77). In addition, in another study patients given the first dose as directly observed treatment (DOT) at the health centre were 2.4 times more likely to be adherent (*p*-value = 0.009). **Pre-packaging** 1 study reported that giving the exact number of tablets for the prescribed dose was associated with adherence. In another study, almost all of the patients reported that the blister packaging depicting the correct treatment doses and the pictogram printed on the packages and were helpful. **Patient acceptability and adverse events** Patient preference or dislike for a specific drug or ACT was found to be associated with adherence in 2 studies. Also 1 study found that some signs and symptoms of patients such as no reported fever (OR 3.3), caregivers' perception that disease was not severe (OR 2.0) and vomiting (OR 2.6) were all found to be associate with non-adherence. Likewise, another study also found that vomiting was predictor of non-adherence (*p*-value = 0.02).
Bruxvoort 2014 Bruxvoort K, Goodman C, Kachur SP, Schellenberg D. How patients take malaria treatment: a systematic review of the literature on adherence to antimalarial drugs. PloS one. 2014. 20;9(1):e84555.	55 studies Sample size ranged from 31 to 1,806	**Factors significantly associated with adherence** Demographic factors, including patient or caregiver higher education (3 studies); ownership of radio (1 study) and high-income (1 study) Treatment-seeking behaviour, such as not having sought treatment at a public health facility (1 study) Factors related to the consultation, including having received exact number of pills to complete treatment (1 study); reporting having been given instructions at the shop and that instructions given were clear (1 study), package used as visual aid by dispenser to explain how to take the drug (1 study); received written instructions (1 study); quality of history taking (i.e. nurses at the consultation asked questions about history, symptoms, and previous care) (1 study) Behaviour, including taking first dose at healthcare facility (1 study) and taking medication with food or oil (1 study) Knowledge and perceptions, including being able to cite at least one correct instruction on how to take treatment and belief that malaria cannot be treated traditionally (1 study); knowledge of the seriousness of the infection (1 study); knowledge of malaria aetiology (2 studies) and access to information about antimalarials (1 study) Satisfaction, including having an improved condition at follow-up and lower expectation of getting malaria in the next 30 days (1 study); not reporting side-effects to medication (1 study) and satisfaction with received information (1 study) **Factors significantly associated with non-adherence** Demographic factors, including being male (2 studies) and lack of education (2 studies) Caregiver's perception that illness is not severe (1 study) Experiencing adverse events, such as vomiting (2 studies) **Conflicting results for the effects on adherence** Patient age: older age was associated with adherence in 1 study, and non-adherence in another, while 2 other studies found younger age associated with adherence and non-adherence Number of days after onset of symptoms that treatment was sought: 1 study found that patients who waited more than one day to seek care after onset of fever were more likely to be adherent. However, waiting ≥2 days was associated with nonadherence in 2 studies. Other study showed that seeking care within 24 hours of symptom onset was associated with adherence
Yakasai 2015	25 studies (and 6 sub-studies included in the analysis)	**Socio-demographic predictors** - reported as OR (95% CI)[1]: Age <5 years: OR 0.68 (0.39 to 1.15)

Yakasai AM, Hamza M, Dalhat MM, Bello M, Gadanya MA, Yaqub ZM, Ibrahim DA, Hassan-Hanga F. Adherence to artemisinin-based combination therapy (ACT) for the treatment of uncomplicated malaria: a systematic review and meta-analysis. Journal of tropical medicine. 2015.	Sample size ranged from 26 to 918	Age >15 years: OR 1.29 (CI cannot be extracted) Age >20 years: OR 1.69 (0.82 to 3.56) At least 7 years of education: OR 1.64 (1.05 to 2.55) Male sex: OR 1.08 (0.86 to 1.35) Higher income: OR 2.02 (1.37 to 2.98) Belief in traditional medication: OR 0.11 (0.02 to 0.80) Ownership of radio: OR 3.83 (1.69 to 8.75) >30 minutes to ACT source: OR 0.82 (0.53 to 1.30) <5 km to health facility: OR 1.47 (0.86 to 2.65) **Clinical and dispensing-related predictors of ACT adherence** - reported as OR (95% CI)[1]: Ability to read: OR 3.55 (2.05 to 6.36) Visual aid available: OR 1.52 (0.58 to 3.97) Taking ACT with food: OR 1.13 (0.87 to 1.52) Taking ACT with fatty food: OR 4.57 (2.52 to 8.46) Vomiting: OR 1.16 (0.58 to 2.44) Knowledge of correct dose: OR 1.79 (1.34 to 2.36) Jaundice: OR 2.78 (0.63 to 12.14) Taking first dose at clinic: OR 2.42 (1.34 to 4.65) Exact number of pills given: OR 4.07 (1.65 to 10.72) Being told child has malaria: OR 1.71 (0.29 to 10.43) No additional diagnosis: OR 1.52 (0.74 to 3.55) Temperature 38.5 to 39.5: OR 1.63 (0.60 to 4.54) >1 day delay in seeking treatment: OR 5.39 (1.81 to 15.89) Buying ACT from chemist: OR 0.47 (0.08 to 5.15)

[1]Data extracted from graphic

Abbreviations: ACT: artemisinin-based combination therapy; CI: confidence interval; km: kilometres; OR: odds ratio,

Table 4. Summary of systematic reviews reporting on interventions to promote adherence to malaria treatment

Reference	Number of included studies and sample size	Summary of results
Bruxvoort 2014 Bruxvoort K, Goodman C, Kachur SP, Schellenberg D. How patients take malaria treatment: a systematic review of the literature on adherence to antimalarial drugs. PloS one. 2014. 20;9(1):e84555.	13 studies evaluated interventions to improve adherence (out of 55 included studies)	[Results reported as level of adherence without intervention vs with intervention] **Age-based packaging of syrup & tablets** 1 RCT – Tablets: 60.5% (n=152) before vs 82.0% (n=167) after the intervention; Syrup: 32.6% (n=95) before vs 54.7% (n=95) after the intervention **Community health worker training** 1 RCT – 1.5% (n=131) before vs 42.1% (n=151) after the intervention **Drug label and verbal instructions** 1 controlled pre- and post- intervention study - 24% (n=205) before vs 27% (n=78) for control group and 39% (n=121) for intervention group after the intervention

		Introduction of tablets to replace syrup 1 RCT - 42% (n=144) before vs 91% (n=155) (follow-up 4 days) after the intervention **Packaging & availability through community health workers** 1 post-intervention only study – 52% (n=1806) after the intervention **Packaging & counselling** 1 RCT – 76.5% (n=119) before vs 92.9% (n=112) for the counselling only group and 95.5% (n=91) for the counselling and packaging group after the intervention **Packaging** 1 RCT – 80.5% (n=134) before vs 97% (n=138) after the intervention **Packaging and training** 1 post-intervention only study – 99.5% (n=380) after the intervention **Pictorial insert & verbal instructions** 1 RCT - 36.5% (n=190) before vs 51.9% (n=225) for the pictorial insert only group and 73.3 % (n=217) for the pictorial insert & verbal instructions group after the intervention **Posters and video** 1 controlled pre- and post- intervention study - Posters only: 10% (n=82) before vs 15% (n=120) after the intervention; Posters and video: 1% (n=95) before vs 39% (n=88) after the intervention **Shopkeeper training** 1 uncontrolled pre- and post-intervention study – 3.7% (n=109) before vs 75% (n=108) after the intervention 1 uncontrolled pre- and post-intervention study – 8% (n=160) before vs 64% (n=441) after the intervention **Subsidised AL, shopkeeper training and community awareness activities** 1 RCT – 40.5% (n=26) before vs 24.8% (n=89) after the intervention for the control group; 53.1% (n=30) before vs 67% (n=221) after the intervention for the intervention group
Fuangchan 2014 Fuangchan A, Dhippayom T, Kongkaew C. Intervention to promote patients' adherence to antimalarial medication: a systematic review. The American journal of tropical medicine and hygiene. 2014. 8;90(1):11-9.	16 studies N = 9,248 participants. Sample size ranged from 137 to 2,749	**Community education *vs* no intervention or control** 2 RCTs and 1 prospective study reported a median RR 2.7 (IQR 1.7 to 22.4) In 1 RCT, the group of parents that were counselled on the administration of treatment reported higher adherence than those in the control group (71.7% *vs* 21.6%; statistically significant difference, exact *p*-value not reported). Similarly, another RCT showed that the provision of subsidized packs of paediatric ACT to retail outlets, training of retail staff and community awareness activities improved antimalarial adherence from 49.4% to 66.5% (statistically significant difference, exact *p*-value not reported). In 1 prospective study, an intervention including a video and posters also increased adherence from 0.5% to 20.4% (*p*-value < 0.001) in a 7-day course treatment. **Medication supervision *vs* no supervision** 2 RCTs using supervised dosing or directly observed treatment (DOT) showed a high adherence rate to antimalarial medication (statistically significant difference, exact *p*-value not reported). The adherence rate in the DOT *vs* the non-DOT group was 100% *vs* 93.1% in 1 trial, and 100% *vs* 80.4% in the other trial. **Pre-packaging aids no pre-packaging aids, other formulation or control**

		4 RCTs and 1 quasi-experimental study reported a median RR 1.4 (IQR 1.1 to 1.9) 2 RCTs showed a higher adherence rate in people receiving pre-packaging medications compared with bulk package. Another 2 studies also showed that blister packaging and pre-packaging had a greater adherence (*p*-value not reported). However, there was 1 study did not find any effect of packaging on adherence to antimalarial drugs in children. **Visual media *vs* control** In 1 study, using a pictorial insert without verbal instruction increased the adherence rate compared with control when guardians administered treatment to children (51.9% *vs* 36.5%; *p*-value < 0.001) **Visual media + verbal information *vs* control** 1 RCT and 1 quasi-experimental study reported a median RR 1.7 (IQR 1.4 to 2.0) In 1 study, more mothers in the intervention group administered the treatment to their children, compared to mother in the control group (73.3% *vs* 36.5%; *p*-value < 0.001). Likewise, in the other study, the adherence rate in outpatients who received the intervention increased from 52.7% to 72.3% (statistically significant difference, exact *p*-value not reported). **Convenient regimen** Once daily *vs* twice daily dosing: 2 RCTs showed a median RR 1.2 (IQR 1.1–1.4) Both RCTs showed a higher rate of adherence for once daily *vs* twice daily regimens in children (90.6% *vs* 65.0%; statistically significant difference, exact *p*-value not reported and 83.3% *vs* 78.5%; *p*-value not reported). **Short vs long duration of treatment** 2 RCTs showed a median RR 1.6 (IQR 1.2 to 2.0) 2 studies evaluated duration of treatment. 1 study showed that adherence was improved when patients underwent a 3-day course treatment, compared with those treated for 7 days (79.8% *vs* 39.5%; statistically significant difference, exact *p*-value not reported). However, 1 RCT showed no difference in adherence rate when comparing a 7-day to 5 days of treatment (63.3% *vs* 77.9%; *p*-value > 0.05).
Yakasai 2015 Yakasai AM, Hamza M, Dalhat MM, Bello M, Gadanya MA, Yaqub ZM, Ibrahim DA, Hassan-Hanga F. Adherence to artemisinin-based combination therapy for the treatment of uncomplicated malaria: a systematic review and meta-analysis. Journal of tropical medicine. 2015.	25 studies (and 6 sub-studies included in the analysis) Sample size ranged from 26 to 918	**Copacked *vs* fixed drug Combination ACTs** The pooled prevalence of adherence to ACT derived from the 11 studies that used co-packaged ACT was 66.53% (95% CI 54.23% to 78.83%) compared to 70.11% (95% CI 60.88% to 79.34%) from the 19 studies that administered fixed drug combination. **Public sector *vs* retail sector** In the public sector, medications were given for free, and dispensed by health care professionals with clear instructions; in the retail sector medications are bought from drug stores or supermarkets without proper instructions on how to take them. Pooled prevalence of adherence (95% CI) in the studies conducted in the public sector was 75.78% (68.08% to 83.94%). Significant heterogeneity was present (I^2=95.3%, p=0.000). Adherence ranged from 38.71% to 97.39%. Pooled prevalence of adherence (95% CI) in the studies conducted in the retail sector was 44.75% (36.90% to 77.43%). Significant heterogeneity was present (I^2=96.3%, p=0.000). Prevalence ranged from 34.21% to 61.60%. **Twice daily *vs* once daily** Pooled prevalence of adherence for the 18 studies that used twice daily ACT was 69.33% (95% CI 59.57% to 79.09%) compared to 66.01% (95% CI 52.72% to 79.29%) from the 10 studies that used once daily ACT.

Abbreviations: DOT: directly observed treatment; IQR: interquartile range; RCT: randomised controlled trial; RR: relative risk

Limitations of this report

The results presented in this report should be considered with caution as there are a number of limitations of the review process.

Firstly, a full systematic search of the literature was not performed. Instead, a broad search was conducted in the major databases and these four systematic reviews were identified. An additional search for primary studies was not done, as systematic reviews are considered to be the strongest level of evidence and therefore were prioritised for inclusion. As such, there may exist other systematic reviews on this topic not included in this report.

In addition, some limitations should be considered in relation to the included systematic reviews, and the primary studies included within the reviews. Only one of the systematic reviews conducted a meta-analysis, but in this analysis, different study designs were pooled together, and heterogeneity was not adequately explored. The other three reviews report the results narratively. It is important to note that most of the studies were included in more than one systematic review.

All the systematic reviews included in this report were limited to studies aimed to assess adherence to antimalarials. Whilst there are similarities between malaria and gambiense HAT treatment, this evidence should be considered as indirect, as there are also differences in terms of severity of the condition, length of treatment (malaria treatment is usually shorter in duration, lasting 3 to 7 days), importance of taking HAT treatment with a full meal (to ensure absorption of fexinidazole), and treatment-related adverse events. Moreover, some of the studies were conducted in Asia or Latin America, which may limit further the applicability of the results to the population of interest.

Measuring adherence to treatment is complex. Although most studies used more than one adherence measure, it is unclear how the overall adherence rate was calculated. Also, some of the included studies only relied on subjective measures of adherence, such as self-report or interview, which are known to be subject to recall bias.

Finally, this report summarises factors associated with adherence and non-adherence to malaria treatment, as well as interventions and strategies that may be useful to improve adherence. However, it does not explore health beliefs and barriers associated with medication-taking behaviour, which may also be important to understand which people would benefit most from different treatment regimens.

References

Banek 2014

Banek K, Lalani M, Staedke SG, Chandramohan D. Adherence to artemisinin-based combination therapy for the treatment of malaria: a systematic review of the evidence. Malaria journal. 2014. 13(1):7.

Studies included in the review:

- Achan J, Tibenderana JK, Kyabayinze D, Wabwire Mangen F, Kamya MR, Dorsey G, D'Alessandro U, Rosenthal PJ, Talisuna AO. Effectiveness of quinine versus artemether-lumefantrine for treating uncomplicated falciparum malaria in Ugandan children: randomised trial. BMJ. 2009. 339:b2763.
- Ajayi IO, Browne EN, Bateganya F, Yar D, Happi C, Falade CO, Gbotosho GO, Yusuf B, Boateng S, Mugittu K, Cousens S, Nanyunja M, Pagnoni F. Effectiveness of artemisinin-based combination therapy used in the context of home management of malaria: A report from three study sites in sub-Saharan Africa. Malar J. 2008a. 7:190.
- Ajayi IO, Browne EN, Garshong B, Bateganya F, Yusuf B, Agyei-Baffour P, Doamekpor L, Balyeku A, Munguti K, Cousens S, Pagnoni F. Feasibility and acceptability of artemisinin-based combination therapy for the home management of malaria in four African sites. Malar J. 2008b. 7:6.
- Alba S, Hetzel MW, Goodman C, Dillip A, Liana J, Mshinda H, Lengeler C. Improvements in access to malaria treatment in Tanzania after switch to artemisinin combination therapy and the introduction of accredited drug dispensing outlets - a provider perspective. Malar J. 2010. 9:164.
- Asante KP, Owusu R, Dosoo D, Awini E, Adjei G, Etego SA, Chandramohan D, Owusu-Agyei S. Adherence to artesunate-amodiaquine therapy for uncomplicated malaria in rural Ghana: a randomised trial of supervised versus unsupervised drug administration. J Trop Med. 2009.
- Barnes KI, Durrheim DN, Little F, Jackson A, Mehta U, Allen E, Dlamini SS, Tsoka J, Bredenkamp B, Mthembu DJ, White NJ, Sharp BL. Effect of artemether-lumefantrine policy and improved vector control on malaria burden in KwaZulu-Natal. South Africa. PLoS Med. 2005. 2:e330.

- Beer N, Ali AS, Rotllant G, Abass AK, Omari RS, Al-mafazy A-wH, Bjorkman A, Kallander K. Adherence to artesunate-amodiaquine combination therapy for uncomplicated malaria in children in Zanzibar, Tanzania. Trop Med Int Health. 2009. 14:766-774.
- Bell DJ, Wootton D, Mukaka M, Montgomery J, Kayange N, Chimpeni P, Hughes DA, Molyneux ME, Ward SA, Winstanley PA, Lalloo DG. Measurement of adherence, drug concentrations and the effectiveness of artemether-lumefantrine, chlorproguanil-dapsone or sulphadoxine-pyrimethamine in the treatment of uncomplicated malaria in Malawi. Malar J. 2009. 8:204.
- Chinbuah AM, Gyapong JO, Pagnoni F, Wellington EK, Gyapong M. Feasibility and acceptability of the use of artemether-lumefantrine in the Home-management of uncomplicated malaria in children 6–59 months old in Ghana. Trop Med Int Health. 2006. 11:1003–1016.
- Cohen JL, Yavuz E, Morris A, Arkedis J, Sabot O. Do patients adhere to over-the-counter artemisinin combination therapy for malaria? evidence from an intervention study in Uganda. Malar J. 2012. 11:83.
- Congpuong K, Bualombai P, Banmairuroi V, Na-Bangchang K. Compliance with a three-day course of artesunate-mefloquine combination and baseline anti-malarial treatment in an area of Thailand with highly multidrug resistant falciparum malaria. Malar J. 2010. 9:43.
- Depoortere E, Guthmann J-P, Sipilanyambe N, Nkandu E, Fermon F, Balkan S, Legros D. Adherence to the combination of sulphadoxine-pyrimethamine and artesunate in the Maheba refugee settlement, Zambia. Trop Med Int Health. 2004a. 9:62-67.
- Depoortere E, Salvador ETC, Stivanello E, Bisoffi Z, Guthmann JP. Adherence to a combination of artemether and lumefantrine (Coartem) in Kajo Keji, southern Sudan. Ann Trop Med Parasitol. 2004b. 98:635–637.
- Dunyo S, Sirugo G, Sesay S, Bisseye C, Njie F, Adiamoh M, Nwakanma D, Diatta M, Janha R, Sisay Joof F, Temple B, Snell P, Conway D, Walton R, Cheung YB, Milligan P. Randomized trial of safety and effectiveness of chlorproguanil-dapsone and lumefantrine-artemether for uncomplicated malaria in children in the Gambia. PLoS One. 2011. 6:e17371.
- Faucher JF, Aubouy A, Adeothy A, Cottrell G, Doritchamou J, Gourmel B, Houzé P, Kossou H, Amedome H, Massougbodji A. Comparison of sulfadoxine-pyrimethamine, unsupervised artemether-lumefantrine, and unsupervised artesunate-amodiaquine fixed-dose formulation for uncomplicated Plasmodium falciparum malaria in Benin: a randomized effectiveness noninferiority trial. J Infect Dis. 2009. 200:57-65
- Fogg C, Bajunirwe F, Piola P, Biraro S, Checchi F, Kiguli J, Namiiro P, Musabe J, Kyomugisha A, Guthmann J-P. Adherence to a six-dose regimen of artemether-lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in Uganda. Am J Trop Med Hyg. 2004. 71:525-530.
- Gerstl S, Dunkley S, Mukhtar A, Baker S, Maikere J. Successful introduction of artesunate combination therapy is not enough to fight malaria: results from an adherence study in Sierra Leone. Trans R Soc Trop Med Hyg 2010, 104:328–335.
- Kabanywanyi AM, Lengeler C, Kasim P, King'eng'ena S, Schlienger R, Mulure N, Genton B. Adherence to and acceptability of artemether-lumefantrine as first-line anti-malarial treatment: evidence from a rural community in Tanzania. Malar J. 2010. 9:48.
- Kachur SP, Khatib RA, Kaizer E, Fox SS, Abdulla SM, Bloland PB. Adherence to antimalarial combination therapy with sulfadoxine-pyrimethamine and artesunate in rural Tanzania. Am J Trop Med Hyg. 2004. 71:715-722.
- Kalyango JN, Rutebemberwa E, Karamagi C, Mworozi E, Ssali S, Alfven T, Peterson S. High adherence to antimalarials and antibiotics under integrated community case management of illness in children less than five years in eastern Uganda. PLoS One. 2013. 8:e60481.
- Kangwana BP, Kedenge SV, Noor AM, Alegana VA, Nyandigisi AJ, Pandit J, Fegan GW, Todd JE, Brooker S, Snow RW, Goodman CA. The impact of retail-sector delivery of artemether-lumefantrine on malaria treatment of children under five in Kenya: a cluster randomized controlled trial. PLoS Med. 2011. 8:e1000437.
- Lawford H, Zurovac D, O'Reilly L, Hoibak S, Cowley A, Munga S, Vulule J, Juma E, Snow RW, Allan R. Adherence to prescribed artemisinin-based combination therapy in Garissa and Bunyala districts. Kenya. Malar J. 2011. 10:281.
- Lemma H, Lofgren C, San Sebastian M. Adherence to a six-dose regimen of artemether-lumefantrine among uncomplicated Plasmodium falciparum patients in the Tigray Region. Ethiopia. Malar J. 2011. 10:349.
- Mace KE, Mwandama D, Jafali J, Luka M, Filler SJ, Sande J, Ali D, Kachur SP, Mathanga DP, Skarbinski J. Adherence to treatment with artemether-lumefantrine for uncomplicated malaria in rural Malawi. Clin Infect Dis. 2011. 53:772-779.
- Meankaew P, Kaewkungwal J, Khamsiriwatchara A, Khunthong P, Singhasivanon P, Satimai W. Application of mobile-technology for disease and treatment monitoring of malaria in the. Malar J. 2010. 9:237.
- Mubi M, Janson A, Warsame M, Mårtensson A, Källander K, Petzold MG, Ngasala B, Maganga G, Gustafsson LL, Massele A. Malaria rapid testing by community health workers is effective and safe for targeting malaria treatment: randomised cross-over trial in Tanzania. PLoS One. 2011. 6:e19753.
- Na-Bangchang K, Congpuong K, Sirichaisinthop J, Suprakorb K, Karbwang J. Compliance with a 2-day course of artemether-mefloquine in an area of highly multi-drug resistant Plasmodium falciparum malaria. Br J Clin Pharmacol. 1997. 43:639–642.

- Ngasala BE, Malmberg M, Carlsson AM, Ferreira PE, Petzold MG, Blessborn D, Bergqvist Y, Gil JP, Premji Z, Martensson A. Effectiveness of artemetherlumefantrine provided by community health workers in under-five children with uncomplicated malaria in rural Tanzania: an open label prospective study. Malar J. 2011. 10:64.
- Ogolla JO, Ayaya SO, Otieno CA. Levels of adherence to Coartem© in the routine treatment of un-complicated malaria in children aged below five years, in Kenya. Iran J Public Health. 2013. 42:129-133.
- Onyango EO, Ayodo G, Watsierah CA, Were T, OkumuW, Anyona SB, Raballah E, Okoth JM, Gumo S, Orinda GO. Factors associated with non-adherence to Artemisinin-based Combination Therapy (ACT) to malaria in a rural population from holoendemic region of western Kenya. BMC Infect Dis. 2012. 12:143.
- Rahman MM, Dondorp AM, Day NPJ, Lindegardh N, Imwong M, Faiz MA, Bangali AM, Kamal ATMM, Karim J, Kaewkungwal J, Singhasivanon P. Adherence and efficacy of supervised versus non-supervised treatment with artemether/lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria in Bangladesh: a randomised controlled trial. Trans R Soc Trop Med Hyg. 2008. 102:861-867.
- Ratsimbasoa A, Ravony H, Vonimpaisomihanta J-A, Raherinjafy R, Jahevitra M, Rapelanoro R, Rakotomanga JDDM, Malvy D, Millet P, Menard D. Compliance, safety, and effectiveness of fixed-dose artesunate-amodiaquine for presumptive treatment of non-severe malaria in the context of home management of malaria in Madagascar. Am J Trop Med Hyg. 2012. 86:203-210.
- Shwe T, Lwin M, Aung S. Influence of blister packaging on the efficacy of artesunate + mefloquine over artesunate alone in community-based treatment of non-severe falciparum malaria in Myanmar. Bull World Health Organ. 1998. 76(Suppl 1):35-41.
- Simba DO, Kakoko D, Tomson G, Premji Z, Petzold M, Mahindi M, Gustafsson LL. Adherence to artemether/lumefantrine treatment in children under real-life situations in rural Tanzania. Trans R Soc Trop Med Hyg. 2012. 106:3-9.
- Watsierah CA, Jura WGZO, Raballah E, Kaseje D, Abong'o B, Ouma C. Knowledge and behaviour as determinants of anti-malarial drug use in a peri-urban population from malaria holoendemic region of western Kenya. Malar J. 2011. 10:99.
- Yeung S, Van Damme W, Socheat D, White NJ, Mills A. Access to artemisinin combination therapy for malaria in remote areas of Cambodia. Malar J. 2008. 7:96.
- Zaw Win T, Zaw L, Khin W, Khin L, Myitzu Tin O, Thar Tun K, Kyaw Zin T. Adherence to the recommended regimen of artemether-lumefantrine for treatment of uncomplicated falciparum malaria in Myanmar. Myanmar Health Sci Res J. 2012. 24:48-53.

Bruxvoort 2014

Bruxvoort K, Goodman C, Kachur SP, Schellenberg D. How patients take malaria treatment: a systematic review of the literature on adherence to antimalarial drugs. PloS one. 2014. 20;9(1):e84555.

Studies included in this review:

- Abuaku BK, Koram KA, Binka FN. Antimalarial drug use among caregivers in Ghana. Afr Health Sci. 2004. 4: 171-177.
- Achan J, Tibenderana JK, Kyabayinze D, Wabwire Mangen F, Kamya MR, Dorsey G, D'Alessandro U, Rosenthal PJ, Talisuna AO. Effectiveness of quinine versus artemether-lumefantrine for treating uncomplicated falciparum malaria in Ugandan children: randomised trial. BMJ. 2009. 339:b2763.
- Agyepong IA, Ansah E, Gyapong M, Adjei S, Barnish G, Evans D. Strategies to improve adherence to recommended chloroquine treatment regimens: a quasi-experiment in the context of integrated primary health care delivery in Ghana. Soc Sci Med. 2002. 55:2215-2226.
- Ajayi IO, Browne EN, Bateganya F, Yar D, Happi C, Falade CO, Gbotosho GO, Yusuf B, Boateng S, Mugittu K, Cousens S, Nanyunja M, Pagnoni F. Effectiveness of artemisinin-based combination therapy used in the context of home management of malaria: A report from three study sites in sub-Saharan Africa. Malar J. 2008. 7:190.
- Amin AA, Hughes DA, Marsh V, Abuya TO, Kokwaro GO, et al. The difference between effectiveness and efficacy of antimalarial drugs in Kenya. Trop Med Int Health. 2004. 9:967-974.
- Ansah EK, Gyapong JO, Agyepong IA, Evans DB. Improving adherence to malaria treatment for children: the use of pre-packed chloroquine tablets vs. chloroquine syrup. Trop Med Int Health. 2001. 6:496-504.
- Barnes KI, Durrheim DN, Little F, Jackson A, Mehta U, Allen E, Dlamini SS, Tsoka J, Bredenkamp B, Mthembu DJ, White NJ, Sharp BL. Effect of artemether-lumefantrine policy and improved vector control on malaria burden in KwaZulu-Natal. South Africa. PLoS Med. 2005. 2:e330.
- Beer N, Ali AS, Rotllant G, Abass AK, Omari RS, Al-mafazy A-wH, Bjorkman A, Kallander K. Adherence to artesunate-amodiaquine combination therapy for uncomplicated malaria in children in Zanzibar, Tanzania. Trop Med Int Health. 2009. 14:766-774.
- Bell DJ, Wootton D, Mukaka M, Montgomery J, Kayange N, Chimpeni P, Hughes DA, Molyneux ME, Ward SA, Winstanley PA, Lalloo DG. Measurement of adherence, drug concentrations and the effectiveness of artemether-lumefantrine, chlorproguanil-dapsone or sulphadoxine-pyrimethamine in the treatment of uncomplicated malaria in Malawi. Malar J. 2009. 8:204.
- Chinbuah AM, Gyapong JO, Pagnoni F, Wellington EK, Gyapong M. Feasibility and acceptability of the use of artemether-lumefantrine in the Home-management of uncomplicated malaria in children 6–59 months old in Ghana. Trop Med Int Health. 2006. 11:1003–1016.

- Cohen JL, Yavuz E, Morris A, Arkedis J, Sabot O. Do patients adhere to over-the-counter artemisinin combination therapy for malaria? evidence from an intervention study in Uganda. Malar J. 2012. 11:83.
- Congpuong K, Bualombai P, Banmairuroi V, Na-Bangchang K. Compliance with a three-day course of artesunate-mefloquine combination and baseline anti-malarial treatment in an area of Thailand with highly multidrug resistant falciparum malaria. Malar J. 2010. 9:43.
- Deming MS, Gayibor A, Murphy K, Jones TS, Karsa T. Home treatment of febrile children with antimalarial drugs in Togo. Bull World Health Organ. 1989. 67: 695-700.
- Denis MB. Improving compliance with quinine + tetracycline for treatment of malaria: evaluation of health education interventions in Cambodian villages. Bull World Health Organ. 1998. 76 (Suppl 1):43-49.
- Depoortere E, Guthmann J-P, Sipilanyambe N, Nkandu E, Fermon F, Balkan S, Legros D. Adherence to the combination of sulphadoxine-pyrimethamine and artesunate in the Maheba refugee settlement, Zambia. Trop Med Int Health. 2004a. 9:62-67.
- Depoortere E, Salvador ETC, Stivanello E, Bisoffi Z, Guthmann JP. Adherence to a combination of artemether and lumefantrine (Coartem) in Kajo Keji, southern Sudan. Ann Trop Med Parasitol. 2004b. 98:635–637.
- Duarte EC, Gyorkos TW. Self-reported compliance with last malaria treatment and occurrence of malaria during follow-up in a Brazilian Amazon population. Trop Med Int Health. 2003. 8:518-524.
- Dunyo S, Sirugo G, Sesay S, Bisseye C, Njie F, Adiamoh M, Nwakanma D, Diatta M, Janha R, Sisay Joof F, Temple B, Snell P, Conway D, Walton R, Cheung YB, Milligan P. Randomized trial of safety and effectiveness of chlorproguanildapsone and lumefantrine-artemether for uncomplicated malaria in children in the Gambia. PLoS ONE. 2011. 6:e17371.
- Faucher JF, Aubouy A, Adeothy A, Cottrell G, Doritchamou J, Gourmel B, Houze P, Kossou H, Amedome H, Massougbodji A, Cot M, Deloron P. Comparison of sulfadoxinepyrimethamine, unsupervised artemether-lumefantrine, and unsupervised artesunate-amodiaquine fixed-dose formulation for uncomplicated Plasmodium falciparum malaria in Benin: a randomized effectiveness noninferiority trial. J Infect Dis. 2009. 200:57-65.
- Fogg C, Bajunirwe F, Piola P, Biraro S, Checchi F, Kiguli J, Namiiro P, Musabe J, Kyomugisha A, Guthmann J-P. Adherence to a six-dose regimen of artemether-lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in Uganda. Am J Trop Med Hyg. 2004. 71:525-530.
- Fungladda W, Honrado ER, Thimasarn K, Kitayaporn D, Karbwang J, Kamolratanakul P, Masngammueng R. Compliance with artesunate and quinine + tetracycline treatment of uncomplicated falciparum malaria in Thailand. Bull World Health Organ. 1998. 76(Suppl 1):59-6.
- Gerstl S, Dunkley S, Mukhtar A, Baker S, Maikere J. Successful introduction of artesunate combination therapy is not enough to fight malaria: results from an adherence study in Sierra Leone. Trans R Soc Trop Med Hyg 2010, 104:328–335.
- Kabanywanyi AM, Lengeler C, Kasim P, King'eng'ena S, Schlienger R, Mulure N, Genton B. Adherence to and acceptability of artemether-lumefantrine as first-line anti-malarial treatment: evidence from a rural community in Tanzania. Malar J. 2010. 9:48.
- Kachur SP, Khatib RA, Kaizer E, Fox SS, Abdulla SM, Bloland PB. Adherence to antimalarial combination therapy with sulfadoxine-pyrimethamine and artesunate in rural Tanzania. Am J Trop Med Hyg. 2004. 71:715-722.
- Kalyango JN, Rutebemberwa E, Karamagi C, Mworozi E, Ssali S, Alfven T, Peterson S. High adherence to antimalarials and antibiotics under integrated community case management of illness in children less than five years in eastern Uganda. PLoS One. 2013. 8:e60481.
- Kangwana BP, Kedenge SV, Noor AM, Alegana VA, Nyandigisi AJ, Pandit J, Fegan GW, Todd JE, Brooker S, Snow RW, Goodman CA. The impact of retail-sector delivery of artemether-lumefantrine on malaria treatment of children under five in Kenya: a cluster randomized controlled trial. PLoS Med. 2011. 8:e1000437.
- Khantikul N, Butraporn P, Kim HS, Leemingsawat S, Tempongko MA, et al. Adherence to antimalarial drug therapy among vivax malaria patients in northern Thailand. J Health Popul Nutr. 2009. 27:4-13.
- Kolaczinski JH, Ojok N, Opwonya J, Meek S, Collins A. Adherence of community caretakers of children to pre-packaged antimalarial medicines (HOMAPAK) among internally displaced people in Gulu district, Uganda. Malar J. 2006. 5:40.
- Krause G, Sauerborn R. Comprehensive community effectiveness of health care. A study of malaria treatment in children and adults in rural Burkina Faso. Ann Trop Paediatr. 200.0 20:273-282.
- Lauwo JA, Hombhanje FW, Tulo SP, Maibani G, Bjorge S. Impact of pre-packaging antimalarial drugs and counseling on compliance with malaria treatment at Port Moresby General Hospital Adult Outpatient Department. PNG Med J. 2006. 49:14-21.
- Lawford H, Zurovac D, O'Reilly L, Hoibak S, Cowley A, Munga S, Vulule J, Juma E, Snow RW, Allan R. Adherence to prescribed artemisinin-based combination therapy in Garissa and Bunyala districts. Kenya. Malar J. 2011. 10:281.
- Lemma H, Lofgren C, San Sebastian M. Adherence to a six-dose regimen of artemether-lumefantrine among uncomplicated Plasmodium falciparum patients in the Tigray Region. Ethiopia. Malar J. 2011. 10:349.
- Mace KE, Mwandama D, Jafali J, Luka M, Filler SJ, Sande J, Ali D, Kachur SP, Mathanga DP, Skarbinski J. Adherence to treatment with artemether-lumefantrine for uncomplicated malaria in rural Malawi. Clin Infect Dis. 2011. 53:772-779.
- Marsh VM, Mutemi WM, Muturi J, Haaland A, Watkins WM, et al. Changing home treatment of childhood fevers by training shop keepers in rural Kenya. Trop Med Int Health. 1999. 4:383-389.

- Marsh VM, Mutemi WM, Willetts A, Bayah K, Were S, et al. Improving malaria home treatment by training drug retailers in rural Kenya. Trop Med Int Health. 2004. 9:451-460.
- Na-Bangchang K, Congpuong K, Sirichaisinthop J, Suprakorb K, Karbwang J. Compliance with a 2-day course of artemether-mefloquine in an area of highly multi-drug resistant Plasmodium falciparum malaria. Br J Clin Pharmacol. 1997. 43:639–642.
- Nshakira N, Kristensen M, Ssali F, Whyte SR. Appropriate treatment of malaria? Use of antimalarial drugs for children's fevers in district medical units, drug shops and homes in eastern Uganda. Trop Med Int Health. 2002. 7:309-316.
- Nsungwa-Sabiiti J, Tomson G, Pariyo G, Ogwal-Okeng J, Peterson S. Community effectiveness of malaria treatment in Uganda–a long way to Abuja targets. Ann Trop Paediatr. 2005. 25:91-100.
- Okonkwo PO, Akpala CO, Okafor HU, Mbah AU, Nwaiwu O. Compliance to correct dose of chloroquine in uncomplicated malaria correlates with improvement in the condition of rural Nigerian children. Trans R Soc Trop Med Hyg. 2001. 95:320-324.
- Onyango EO, Ayodo G, Watsierah CA, Were T, OkumuW, Anyona SB, Raballah E, Okoth JM, Gumo S, Orinda GO. Factors associated with non-adherence to Artemisinin-based Combination Therapy (ACT) to malaria in a rural population from holoendemic region of western Kenya. BMC Infect Dis. 2012. 12:143.
- Peeters Grietens K, Soto V, Erhart A, Ribera JM, Toomer E, et al. Adherence to 7-day primaquine treatment for the radical cure of P. vivax in the Peruvian Amazon. Am J Trop Med Hyg. 2010. 82:1017-1023.
- Pereira EA, Ishikawa EA, Fontes CJ. Adherence to Plasmodium vivax malaria treatment in the Brazilian Amazon Region. Malar J. 2011. 10:355.
- Qingjun L, Jihui D, Laiyi T, Xiangjun Z, Jun L, Hay A, Shires S, Navaratnam V. The effect of drug packaging on patients' compliance with treatment for Plasmodium vivax malaria in China. Bull World Health Organ. 1998. 76 (Suppl 1):21-27.
- Rahman MM, Dondorp AM, Day NPJ, Lindegardh N, Imwong M, Faiz MA, Bangali AM, Kamal ATMM, Karim J, Kaewkungwal J, Singhasivanon P. Adherence and efficacy of supervised versus non-supervised treatment with artemether/lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria in Bangladesh: a randomised controlled trial. Trans R Soc Trop Med Hyg. 2008. 102:861-867.
- Reilley B, Abeyasinghe R, Pakianathar MV. Barriers to prompt and effective treatment of malaria in northern Sri Lanka. Trop Med Int Health. 2002. 7:744-749.
- Shwe T, Lwin M, Aung S. Influence of blister packaging on the efficacy of artesunate + mefloquine over artesunate alone in community-based treatment of non-severe falciparum malaria in Myanmar. Bull World Health Organ. 1998. 76(Suppl 1):35-.
- Simba DO, Kakoko D, Tomson G, Premji Z, Petzold M, Mahindi M, Gustafsson LL. Adherence to artemether/lumefantrine treatment in children under real-life situations in rural Tanzania. Trans R Soc Trop Med Hyg. 2012. 106:3-.
- Sirima SB, Konate A, Tiono AB, Convelbo N, Cousens S, et al. Early treatment of childhood fevers with pre-packaged antimalarial drugs in the home reduces severe malaria morbidity in Burkina Faso. Trop Med Int Health. 2003. 8:133-139.
- Souares A, Lalou R, Sene I, Sow D, Le Hesran JY. Adherence and effectiveness of drug combination in curative treatment among children suffering uncomplicated malaria in rural Senegal. Trans R Soc Trop Med H. 2008. 102:751-758.
- Takeuchi R, Lawpoolsri S, Imwong M, Kobayashi J, Kaewkungwal J, Pukrittayakamee S, Puangsa-Art S, Thanyavanich N, Maneeboonyang W, Day NP, Singhasivanon P. Directly-observed therapy (DOT) for the radical 14-day primaquine treatment of Plasmodium vivax malaria on the Thai-Myanmar border. Malar J. 2010. 9:308.
- Thera MA, D'Alessandro U, Thiero M, Ouedraogo A, Packou J, et al. Child malaria treatment practices among mothers in the district of Yanfolila, Sikasso region, Mali. Trop Med Int Health. 2000. 5:876-881.
- Twagirumukiza M, Kayumba PC, Kips JG, Vrijens B, Stichele RV, et al. Evaluation of medication adherence methods in the treatment of malaria in Rwandan infants. Malar J. 2010. 9:206.
- Winch PJ, Bagayoko A, Diawara A, Kane M, Thiero F, Gilroy K, Daou Z, Berthe Z, Swedberg E. Increases in correct administration of chloroquine in the home and referral of sick children to health facilities through a community-based intervention in Bougouni District, Mali. Trans R Soc Trop Med Hyg. 2003 97: 481-490.
- Yeboah-Antwi K, Gyapong JO, Asare IK, Barnish G, Evans DB, Adjei S. Impact of prepackaging antimalarial drugs on cost to patients and compliance with treatment. Bull World Health Organ. 2001. 79:394-399.
- Yepez MC, Zambrano D, Carrasco F, Yepez RF. The factors associated with noncompliance with antimalarial treatment in Ecuadorian patients. Rev Cubana Med Trop 2000. 52:81-89.

Fuangchan 2014

Fuangchan A, Dhippayom T, Kongkaew C. Intervention to promote patients' adherence to antimalarial medication: a systematic review. The American journal of tropical medicine and hygiene. 2014. 8;90(1):11-9.

Studies included in this review:

- Achan J, Tibenderana JK, Kyabayinze D, Wabwire Mangen F, Kamya MR, Dorsey G, D'Alessandro U, Rosenthal PJ, Talisuna AO. Effectiveness of quinine versus artemetherlumefantrine for treating uncomplicated falciparum malaria in Ugandan children: randomized trial. BMJ. 2009. 339:b2763.
- Afenyadu GY, Agyepong IA, Barnish G, Adjei S. Improving access to early treatment of malaria: a trial with primary school teachers as care providers. Trop Med Int Health. 2005. 10:1065-1072.
- Agyepong IA, Ansah E, Gyapong M, Adjei S, Barnish G, Evans D. Strategies to improve adherence to recommended chloroquine treatment regimens: a quasi-experiment in the context of integrated primary health care delivery in Ghana. Soc Sci Med. 2002. 55:2215-2226.
- Ansah EK, Gyapong JO, Agyepong IA, Evans DB. Improving adherence to malaria treatment for children: the use of pre-packed chloroquine tablets vs. chloroquine syrup. Trop Med Int Health. 2001. 6:496-504.
- Denis MB. Improving compliance with quinine + tetracycline for treatment of malaria: evaluation of health education interventions in Cambodian villages. Bull World Health Organ. 1998. 76 (Suppl 1):43-49.
- Dunyo S, Sirugo G, Sesay S, Bisseye C, Njie F, Adiamoh M, Nwakanma D, Diatta M, Janha R, Sisay Joof F, Temple B, Snell P, Conway D, Walton R, Cheung YB, Milligan P. Randomized trial of safety and effectiveness of chlorproguanildapsone and lumefantrine-artemether for uncomplicated malaria in children in the Gambia. PLoS ONE. 2011. 6:e17371.
- Faucher JF, Aubouy A, Adeothy A, Cottrell G, Doritchamou J, Gourmel B, Houze P, Kossou H, Amedome H, Massougbodji A, Cot M, Deloron P. Comparison of sulfadoxinepyrimethamine, unsupervised artemether-lumefantrine, and unsupervised artesunate-amodiaquine fixed-dose formulation for uncomplicated Plasmodium falciparum malaria in Benin: a randomized effectiveness noninferiority trial. J Infect Dis. 2009. 200:57-65.
- Fungladda W, Honrado ER, Thimasarn K, Kitayaporn D, Karbwang J, Kamolratanakul P, Masngammueng R. Compliance with artesunate and quinine + tetracycline treatment of uncomplicated falciparum malaria in Thailand. Bull World Health Organ. 1998. 76(Suppl 1):59-66.
- Kangwana BP, Kedenge SV, Noor AM, Alegana VA, Nyandigisi AJ, Pandit J, Fegan GW, Todd JE, Brooker S, Snow RW, Goodman CA. The impact of retail-sector delivery of artemether-lumefantrine on malaria treatment of children under five in Kenya: a cluster randomized controlled trial. PLoS Med. 2011. 8:e1000437.
- Lauwo JA, Hombhanje FW, Tulo SP, Maibani G, Bjorge S. Impact of pre-packaging antimalarial drugs and counseling on compliance with malaria treatment at Port Moresby General Hospital Adult Outpatient Department. PNG Med J. 2006. 49:14-21.
- Okonkwo PO, Akpala CO, Okafor HU, Mbah AU, Nwaiwu O. Compliance to correct dose of chloroquine in uncomplicated malaria correlates with improvement in the condition of rural Nigerian children. Trans R Soc Trop Med Hyg. 2001. 95:320-324.
- Qingjun L, Jihui D, Laiyi T, Xiangjun Z, Jun L, Hay A, Shires S, Navaratnam V. The effect of drug packaging on patients' compliance with treatment for Plasmodium vivax malaria in China. Bull World Health Organ. 1998. 76 (Suppl 1):21-27.
- Rahman MM, Dondorp AM, Day NPJ, Lindegardh N, Imwong M, Faiz MA, Bangali AM, Kamal AT, Karim J, Kaewkungwal J, Singhasivanon P. Adherence and efficacy of supervised versus non-supervised treatment with artemether/lumefantrine for the treatment of uncomplicated Plasmodium falciparum malaria in Bangladesh: a randomized controlled trial. Trans R Soc Trop Med Hyg. 2008. 102:861-867.
- Takeuchi R, Lawpoolsri S, Imwong M, Kobayashi J, Kaewkungwal J, Pukrittayakamee S, Puangsa-Art S, Thanyavanich N, Maneeboonyang W, Day NP, Singhasivanon P. Directly-observed therapy (DOT) for the radical 14-day primaquine treatment of Plasmodium vivax malaria on the Thai-Myanmar border. Malar J. 2010. 9:308.
- Winch PJ, Bagayoko A, Diawara A, Kane M, Thiero F, Gilroy K, Daou Z, Berthe Z, Swedberg E. Increases in correct administration of chloroquine in the home and referral of sick children to health facilities through a community-based intervention in Bougouni District, Mali. Trans R Soc Trop Med Hyg. 2003 97: 481-490.
- Yeboah-Antwi K, Gyapong JO, Asare IK, Barnish G, Evans DB, Adjei S. Impact of prepackaging antimalarial drugs on cost to patients and compliance with treatment. Bull World Health Organ. 2001. 79:394-399.

Yakasai 2015

Yakasai AM, Hamza M, Dalhat MM, Bello M, Gadanya MA, Yaqub ZM, Ibrahim DA, Hassan-Hanga F. Adherence to artemisinin-based combination therapy for the treatment of uncomplicated malaria: a systematic review and meta-analysis. Journal of tropical medicine. 2015.

Studies included in the review:

- Achan J, Tibenderana JK, Kyabayinze D, Wabwire Mangen F, Kamya MR, Dorsey G, D'Alessandro U, Rosenthal PJ, Talisuna AO. Effectiveness of quinine versus artemether-lumefantrine for treating uncomplicated falciparum malaria in Ugandan children: randomised trial. BMJ. 2009. 339:b2763.
- Ajayi IO, Browne EN, Garshong B, Bateganya F, Yusuf B, Agyei-Baffour P, Doamekpor L, Balyeku A, Munguti K, Cousens S, Pagnoni F. Feasibility and acceptability of artemisinin-based combination therapy for the home management of malaria in four African sites. Malar J. 2008. 7:6.
- Amponsah AO, Vosper H, Marfo AF. Patient related factors affecting adherence to antimalarial medication in an Urban Estate in Ghana. Malaria research and treatment. 2015.

- Asante KP, Owusu R, Dosoo D, Awini E, Adjei G, Etego SA, Chandramohan D, Owusu-Agyei S. Adherence to artesunate-amodiaquine therapy for uncomplicated malaria in rural Ghana: a randomised trial of supervised versus unsupervised drug administration. J Trop Med. 2009.
- Aung W, Dondorp AM, Min M, Kyaw TT, Lawpoolsri S, Krudsood S, Singhasivanon P. Assessment of adherence to three-day course of artemeter-lumefantrine treatment in Rhakine state, Myanmar. JITMM Proceedings. 2015. 6;3:16-23.
- Beer N, Ali AS, Rotllant G, Abass AK, Omari RS, Al-mafazy A-wH, Bjorkman A, Kallander K. Adherence to artesunate-amodiaquine combination therapy for uncomplicated malaria in children in Zanzibar, Tanzania. Trop Med Int Health. 2009. 14:766-774.
- Bell DJ, Wootton D, Mukaka M, Montgomery J, Kayange N, Chimpeni P, Hughes DA, Molyneux ME, Ward SA, Winstanley PA, Lalloo DG. Measurement of adherence, drug concentrations and the effectiveness of artemether-lumefantrine, chlorproguanil-dapsone or sulphadoxine-pyrimethamine in the treatment of uncomplicated malaria in Malawi. Malar J. 2009. 8:204.
- Bruxvoort K, Kalolella A, Cairns M, Festo C, Kenani M, Lyaruu P, Kachur SP, Schellenberg D, Goodman C. Are Tanzanian patients attending public facilities or private retailers more likely to adhere to artemisinin-based combination therapy? Malaria journal. 2015. 14(1):87.
- Chinbuah AM, Gyapong JO, Pagnoni F, Wellington EK, Gyapong M. Feasibility and acceptability of the use of artemether-lumefantrine in the Home-management of uncomplicated malaria in children 6–59 months old in Ghana. Trop Med Int Health. 2006. 11:1003–1016.
- Cohen JL, Yavuz E, Morris A, Arkedis J, Sabot O. Do patients adhere to over-the-counter artemisinin combination therapy for malaria? evidence from an intervention study in Uganda. Malar J. 2012. 11:83.
- Congpuong K, Bualombai P, Banmairuroi V, Na-Bangchang K. Compliance with a three-day course of artesunate-mefloquine combination and baseline anti-malarial treatment in an area of Thailand with highly multidrug resistant falciparum malaria. Malar J. 2010. 9:43.
- Depoortere E, Guthmann J-P, Sipilanyambe N, Nkandu E, Fermon F, Balkan S, Legros D. Adherence to the combination of sulphadoxine-pyrimethamine and artesunate in the Maheba refugee settlement, Zambia. Trop Med Int Health. 2004. 9:62-67.
- Ewing VL, Terlouw DJ, Kapinda A, Pace C, Richards E, Tolhurst R, Lalloo DG. Perceptions and utilization of the anti-malarials artemether-lumefantrine and dihydroartemisinin-piperaquine in young children in the Chikhwawa District of Malawi: a mixed methods study. Malaria journal. 2015. 14(1):13.
- Fogg C, Bajunirwe F, Piola P, Biraro S, Checchi F, Kiguli J, Namiiro P, Musabe J, Kyomugisha A, Guthmann J-P. Adherence to a six-dose regimen of artemether-lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in Uganda. Am J Trop Med Hyg. 2004. 71:525-530
- Gerstl S, Dunkley S, Mukhtar A, Baker S, Maikere J. Successful introduction of artesunate combination therapy is not enough to fight malaria: results from an adherence study in Sierra Leone. Trans R Soc Trop Med Hyg 2010, 104:328–335.
- Gore-Langton GR, Alenwi N, Mungai J, Erupe NI, Eves K, Kimwana FN, Soti D, Akhwale W, Hassan FA, Juma E, Allan R. Patient adherence to prescribed artemisinin-based combination therapy in Garissa County, Kenya, after three years of health care in a conflict setting. Malaria journal. 2015. 14(1):125.
- Kabanywanyi AM, Lengeler C, Kasim P, King'eng'ena S, Schlienger R, Mulure N, Genton B. Adherence to and acceptability of artemether-lumefantrine as first-line anti-malarial treatment: evidence from a rural community in Tanzania. Malar J. 2010. 9:48
- Kachur SP, Khatib RA, Kaizer E, Fox SS, Abdulla SM, Bloland PB. Adherence to antimalarial combination therapy with sulfadoxine-pyrimethamine and artesunate in rural Tanzania. Am J Trop Med Hyg. 2004. 71:715-722.
- Lawford H, Zurovac D, O'Reilly L, Hoibak S, Cowley A, Munga S, Vulule J, Juma E, Snow RW, Allan R. Adherence to prescribed artemisinin-based combination therapy in Garissa and Bunyala districts. Kenya. Malar J. 2011. 10:281.
- Lemma H, Lofgren C, San Sebastian M. Adherence to a six-dose regimen of artemether-lumefantrine among uncomplicated Plasmodium falciparum patients in the Tigray Region. Ethiopia. Malar J. 2011. 10:349.
- Mace KE, Mwandama D, Jafali J, Luka M, Filler SJ, Sande J, Ali D, Kachur SP, Mathanga DP, Skarbinski J. Adherence to treatment with artemetherlumefantrine for uncomplicated malaria in rural Malawi. Clin Infect Dis. 2011. 53:772-779.
- Ogolla JO, Ayaya SO, Otieno CA. Levels of adherence to Coartem© in the routine treatment of un-complicated malaria in children aged below five years, in Kenya. Iran J Public Health. 2013. 42:129-133.
- Onyango EO, Ayodo G, Watsierah CA, Were T, OkumuW, Anyona SB, Raballah E, Okoth JM, Gumo S, Orinda GO. Factors associated with non-adherence to Artemisinin-based Combination Therapy (ACT) to malaria in a rural population from holoendemic region of western Kenya. BMC Infect Dis. 2012. 12:143.
- Siddiqui MR, Willis A, Bil K, Singh J, Mukomena Sompwe E, Ariti C. Adherence to artemisinin-based combination therapy for the treatment of uncomplicated malaria in Democratic Republic of the Congo. F1000 Research. 2015. 4(51):1-16.
- Simba DO, Kakoko D, Tomson G, Premji Z, Petzold M, Mahindi M, Gustafsson LL. Adherence to artemether/lumefantrine treatment in children under real-life situations in rural Tanzania. Trans R Soc Trop Med Hyg. 2012. 106:3-9.

Appendix 9. Post-hoc subgroup analyses of pooled data from the three fexinidazole studies

1 Background

In response to the European Medicines Agency's (EMA) questions relating to the clinical efficacy of fexinidazole, the manufacturer Sanofi and Drugs for Neglected Diseases initiative (DNDi) submitted a report that included post hoc analyses of pooled data from the three fexinidazole studies exploring the efficacy of fexinidazole in different subgroups of people with HAT.

2 Objective

To review the evidence of an exploratory post-hoc analysis of pooled data on treatment failure from the three fexinidazole studies.

3 Methods

3.1. Included evidence

To inform the question '*Should fexinidazole be recommended as first line treatment for HAT? only for first-stage HAT? only for second stage? for both?,*' we reviewed the evidence of an unpublished post hoc analysis of pooled data shared with Cochrane Response researchers under a confidentiality agreement. The pooled data were from the three fexinidazole studies: Mesu 2018a, an RCT comparing fexinidazole with NECT in 394 adults and adolescents (>15 years) with late second stage HAT; Mesu 2018b, a single arm trial that included 230 adults and adolescents (>15 years) with first stage and early second stage HAT; Mesu 2018c, a single arm trial that included 125 children (6-15 years) with all stages of HAT.

3.2. Data extraction

One reviewer extracted and analysed the data and another reviewer cross-checked the extracted data and analyses. There were no disagreements.

Data was extracted for the intention-to-treat (ITT), modified intention-to-treat (mITT) and evaluable (EP) populations, where available, as defined in the manufacturer's report.

- Intention to treat (ITT) - This set can be considered the best one for comparing 2 randomized treatments. With randomization, the 2 groups of treatments should be comparable on known confounding factors. It is appropriate for comparing NECT and fexinidazole.
- Modified ITT (mITT) - This set is appropriate to compare NECT and fexinidazole because some specific lost to follow-up due to an armed conflict in the region were reported and therefore discarded from the set.
- Evaluable population (EP) - Given the fact that the success/ failure rate includes also deaths for any reason or patients lost to follow-up, this set is appropriate to compare failure rates that are most possibly due to treatment or disease evolution. Failure imputed to lost to follow up at 18 months or to death for a cause which is completely independent from the drug or disease cannot be predicted. Comparison of properties of predictors of this set of patients that excludes quasi unpredictable events is appropriate because a good predictor should be able to detect failures and successes related to drug and disease.

3.3. Assessment of risk of bias

We did not conduct a full risk of bias assessment for the reported subgroup analyses, as data was derived from the same studies already assessed in the main report.

3.4. Data analysis

3.4.1. Treatment efficacy and rates of treatment failure

In the Sanofi/DNDi report, data on treatment failure (defined as rescue treatment, death, CSF WBC >20 cells/µL, trypanosomes in the blood, lost to follow-up, consent withdrawal) from the three fexinidazole studies were reported for the following subgroups:

- Symptom score ≥12 or <12 at entry (no lumbar puncture required)
- Symptom score ≥10 or < 10 at entry (no lumbar puncture required)
- Trypanosomes or no trypanosomes in the CSF at entry
- >100 or ≤100 WBC in CSF at entry
- >400 or ≤400 WBC in CSF at entry

For each subgroup, data were reported for the following populations:

- Adults and adolescents with late second stage HAT (intention-to-treat (ITT), modified ITT (mITT), and evaluable population (EP) populations), derived from the RCT Mesu 2018a
- Adults and children with early and late second stage HAT (mITT and EP populations), derived from all three studies
- Adults and children with HAT of any stage (mITT and EP populations), derived from all three studies

We calculated risk ratios (RR) with 95% confidence intervals (CI) for the randomised controlled trial to estimate efficacy of fexinidazole compared with NECT in late second stage adults and adolescents in the different subgroups. For all populations in all subgroups we estimated treatment failure rates per 1,000. Calculations were made for the ITT, mITT and EP populations, although results from the EP population were prioritised (at request from the WHO), for GRADE assessment.

3.4.2. Accuracy of clinical predictors (to predict treatment outcome)

Using each subgroup as a predictor of treatment failure, we calculated sensitivity with 95% CIs, specificity with 95% CIs, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios (LR). We followed guidance from the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Macaskill 2010).

Table 5. Model of table used for the predictive assessment of a criterion (CHMP D120)

Prediction through the rule	**Actual outcome**		**Total number**
	Failure	**Success**	
Prediction of failure	*Number of true failures (TF)*	*Number of false failures (FF)*	Number of predicted failure
Prediction of success	*Number of false successes (FS)*	*Number of true successes (TS)*	Number of predicted successes
Total number	Number of observed failures	Number of observed successes	N (sample size)

Calculations were done using the online programme MEDCALC (Available from: https://www.medcalc.org/calc/diagnostic_test.php)

Statistic	**Definition**	**Formula**
Sensitivity	The proportion of observed failures at 18 months and detected at baseline through the use of the predictor OR Good detection of failures	True failures/ (True failures + False successes) OR 1 – specificity

Specificity	The proportion of observed successes at 18 months that were detected at baseline using the predictor OR Good detection of successes	True successes/ (False failures + True successes) OR 1 – sensitivity
Positive likelihood ratio (LR+)	Ratio between the probability of a predicted treatment failure (with fexinidazole) given an actual treatment failure and the probability of a predicted treatment failure given an actual treatment success	True positive rate / False positive rate OR Sensitivity/ 1 - specificity
Negative likelihood ratio (LR-)	Ratio between the probability of a predicted treatment failure (with fexinidazole) given an actual treatment success and the probability of a predicted treatment success with fexinidazole given an actual treatment success	False negative rate / True negative rate OR 1 – sensitivity/ specificity
Positive predictive value (PPV)	The estimation of the probability that a predicted failure is a real treatment failure OR The proportion of correctly predicted failures	True failures/ (True failures + False failures)
Negative predictive value (NPV)	The estimation of the probability that a predicted success is a real treatment success OR The proportion of correctly predicted successes	True successes/ (False successes + True successes)

3.5. Summarising results

3.5.1. Treatment efficacy and rates of treatment failure

We used the GRADE approach to interpret findings and create 'Summary of findings' tables following the GRADE handbook. These tables provide outcome-specific information concerning the overall certainty of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes of interest.

3.5.2. Accuracy of clinical predictors (to predict treatment outcome)

As noted above, we calculated sensitivity with 95% CIs, specificity with 95% CIs, PPV, NPV, and LRs for each subgroup from the data reported in the unpublished post-hoc analysis.

As a full systematic review was not conducted, we did not assess the quality of evidence and can therefore not judge the overall certainty of the evidence of the assessed subgroups as predictors.

4 Results

Unless otherwise specified, we reported on the EP population from the unpublished post hoc analyses.

4.1. Comparative treatment efficacy

There was very low certainty evidence on treatment failure in adult and adolescent inpatients with late second stage HAT.

For participants above predictor thresholds at entry (symptom score ≥12, symptom score ≥10, trypanosomes in CSF, >100 WBC in CSF, and >400 WBC in CSF) there were increases in treatment failure at 18 months with fexinidazole compared with NECT (very low certainty evidence, RR ranging from 5.8.65 to 20.24, with 95% CIs including either only benefit with NECT (symptom score ≥10, trypanosomes in CSF, >100 WBC in CSF) or both benefit with NECT and no effect (symptom score ≥12, >400 WBC in CSF). See Table 6. SOF table: Fexinidazole as first line treatment for second stage HAT – post hoc subgroup analyses and **Error! Reference source not found.** .

For participants below predictor thresholds at entry (symptom score <12, symptom score <10, no trypanosomes in CSF, ≤100 WBC in CSF, and ≤400 WBC in CSF) there was little or no difference in treatment failure at 18 months with fexinidazole compared with NECT (very low certainty evidence, RR ranging from 0.95 to 5.17 with 95% CIs including benefit with both fexinidazole and NECT. See Table 6. SOF table: Fexinidazole as first line treatment for second stage HAT – post hoc subgroup analyses and **Error! Reference source not found.**.

Table 6. SOF table: Fexinidazole as first line treatment for second stage HAT – post hoc subgroup analyses

4.1.1. Fexinidazole (oral) compared to nifurtimox-eflornithine (oral/IV) for late second stage HAT – post hoc subgroup analyses

Patient or population: ≥15-year-old people with late second stage Human African *gambiense* Trypanosomiasis (trypanosomes in blood or nymph node fluid and WBC >20 per µL or trypanosomes in CSF)

Setting: inpatients in the Democratic Republic of the Congo and the Central African Republic

Intervention: Fexinidazole (oral) once daily (days 1-4: 1800 mg, days 5-10: 1200 mg)

Comparison: Nifurtimox-eflornithine (oral/IV): oral nifurtimox given three times a day (days 1–10: 15 mg/kg per day) with eflornithine twice a day as 2 h infusions (days 1–7: 400 mg/kg per day)

Outcome: Treatment failure, rescue treatment, death, CSF WBC >20 cells/µL, trypanosomes in the blood, lost to follow-up, consent withdrawal, measured at 18 months follow-up

All results are for EP population. See results for ITT and mITT (specific loss to follow-up due to an armed conflict were discarded) in comments column

Subgroups	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments	Predictive value EP	
	Risk with NECT	Risk with Fexinidazole					Fexinidazole	NECT

Signs and symptom score ≥12	Not estimable* *	Not estimable* *	**RR 14.34** (0.88 to 235.00)	134 (1 study)	⊕◯◯◯ VERY LOW a,b	See table 2 CHMP D120 unpublished report ITT: RR 7.42 (1.01 to 54.40), n=136 mITT: 14.34 (0.88 to 235.00), n=134	• Sensitivity 63.64% (40.66% to 82.80%) • Specificity 67.80% (61.43% to 73.71%) • LR+ 1.98 (1.37 to 2.85) • LR- 0.54 (0.31 to 0.94) • PPV 15.56% (11.33% to 20.99%) • NPV 95.24 % (91.95% to 97.22%)	• Sensitivity 0.00% (0.00% to 97.50%) • Specificity 64.52 % (55.42% to 72.90%) • LR+ 0.00 • LR- 1.55 (1.36 to 1.77) • PPV 0 • NPV 98.77 % (98.60% to 98.91%)
Signs and symptoms score <12	12 per 1,000	**48 per 1,000** (6 to 374)	**RR 3.86** (0.49 to 30.32)	249 (1 study)	⊕◯◯◯ VERY LOW a,b	See table 2 CHMP D120 unpublished report ITT: RR 0.98 (0.35 to 2.78), n=258 mITT: RR 1.45 (0.40 to 5.21), n=255		
Signs and symptoms score ≥10	18 per 1,000	**154 per 1,000** (21 to 1,000)	**RR 8.65** (1.18 to 63.37)	166 (1 study)	⊕◯◯◯ VERY LOW a,c	See table 5 CHMP D120 unpublished report ITT: RR 3.28 (1.01 to 10.63), n=170 mITT: RR 9.08 (1.24 to 66.29), n=167	• Sensitivity 77.27% (54.63% to 92.18%) • Specificity 60.59 % (54.05% to 66.87%) • LR+ 1.96 (1.49 to 2.59) • LR- 0.38 (0.17 to 0.82) • PPV 15.45% (12.18% to 19.42%) • NPV 96.62 % (92.93% to 98.42%)	• Sensitivity 100.00% (2.50% to 100.00%) • Specificity 55.65 % (46.45% to 64.56%) • LR+ 2.25 (1.85 to 2.75) • LR- 0.00 • PPV 1.79% (1.47% to 2.17%) • NPV 100.00 %
Signs and symptoms score <10	Not estimable* *	Not estimable* *	**RR 5.17** (0.29 to 92.16)	217 (1 study)	⊕◯◯◯ VERY LOW a,b	See table 5 CHMP D120 unpublished report ITT: RR 0.95 (0.24 to 3.68), n=224 mITT: RR 1.18 (0.23 to 5.91), n=222		
Presence of trypanosomes in CSF	11 per 1,000	**110 per 1,000** (15 to 812)	**RR 9.61** (1.31 to 70.61)	259 (1 study)	⊕◯◯◯ VERY LOW a,c	See table 17 CHMP D120 unpublished report ITT: RR 2.83 (1.01 to 7.96), n=265 mITT: RR 5.09 (1.22 to 21.27), n=261	• Sensitivity 86.36% (65.09% to 97.09%) • Specificity 34.89 % (28.81% to 41.36%) • LR+ 1.33 (1.10 to 1.61) • LR- 0.39 (0.13 to 1.13) • PPV 11.05% (9.31% to 13.06%) • NPV 96.47 % (90.40% to 98.76%)	• Sensitivity 100.00% (2.50% to 100.00%) • Specificity 30.65 % (22.68% to 39.56%) • LR+ 1.44 (1.28 to 1.62) • LR- 0.00 • PPV 1.15% (1.02% to 1.29%) • NPV 100.00 %
No trypanosomes in CSF	Not estimable* *	Not estimable* *	**RR 3.17** (0.17 to 59.98)	123 (1 study)	⊕◯◯◯ VERY LOW a,b	See table 17 CHMP D120 unpublished report ITT: RR 0.68 (0.12 to 3.92), n=128 mITT: RR 1.33 (0.14 to 12.38), n=127		

Presence of WBC in CSF at entry >100	Not estimable* *	Not estimable* *	**RR 20.24** (1.24 to 330.28)	234 (1 study)	⨁◯◯◯ VERY LOW a,c	See table 20 CHMP D120 unpublished report ITT: RR 3.64 (1.12 to 11.81), n=241 mITT: RR 10.24 (1.40 to 74.72), n=238	• Sensitivity 90.91% (70.84% to 98.88%) • Specificity 41.95% (35.58% to 48.53%) • LR+ 1.57 (1.32 to 1.86) • LR- 0.22 (0.06 to 0.82) • PPV 12.74% (10.96% to 14.76%) • NPV 98.02% (92.90% to 99.47%)	• Sensitivity 0.00% (0.00% to 97.50%) • Specificity 37.90 % (29.35% to 47.05%) • LR+ 0.00 • LR- 2.64 (2.11 to 3.30) • PPV 0 • NPV 97.92 % (97.40% to 98.33%)
Presence of WBC in CSF at entry ≤100	21 per 1,000	**20 per 1,000** (2 to 213)	**RR 0.95** (0.09 to 10.23)	149 (1 study)	⨁◯◯◯ VERY LOW a,b	See table 20 CHMP D120 unpublished report ITT: RR 0.49 (0.10 to 2.32), n=153 mITT: RR 0.45 (0.07 to 3.10), n=158		
Presence of WBC in CSF at entry >400	Not estimable* *	Not estimable* *	**RR 10.76** (0.66 to 176.58)	111 (1 study)	⨁◯◯◯ VERY LOW a,b	See table 23 CHMP D120 unpublished report ITT: RR 5.59 (0.76 to 41.09), n=113 mITT: RR 5.59 (0.76 to 41.09), n=113	• Sensitivity 54.55% (32.21% to 75.61%) • Specificity 72.03% (65.84% to 77.66%) • LR+ 1.95 (1.27 to 3.01) • LR- 0.63 (0.40 to 1.00) • PPV 15.38% (10.55% to 21.89%) • NPV 94.44 % (91.44% to 96.44%)	• Sensitivity 0.00% (0.00% to 97.50%) • Specificity 73.39 % (64.70% to 80.92%) • LR+ 0.00 • LR- 1.36 (1.23 to 1.52) • PPV 0 • NPV 98.91% (98.79% to 99.02%)
Presence of WBC in CSF at entry ≤400	11 per 1,000	**56 per 1,000** (7 to 427)	**RR 5.11** (0.66 to 39.32),	272 (1 study)	⨁◯◯◯ VERY LOW a,b	See table 23 CHMP D120 unpublished report ITT: RR 1.25 (0.45 to 3.43), n=281 mITT: RR 2.54 (0.57 to 11.36), n=276		

***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).
** **The risk in the intervention group** is derived from the number of events and participants in the comparison group and the risk ratio and its 95% CIs which could not be calculated as the risk in the comparison group was 0 (no events were reported).
***Treatment failure: rescue treatment, death, CSF WBC >20 cells/µL, trypanosomes in the blood, lost to follow-up, consent withdrawal
****Treatment success: Alive, no trypanosomes in body fluid, no rescue medication, CSF WBC ≤20 cells per µL
CI: Confidence interval; **CSF**: cerebrospinal fluid; **EP**: evaluable population; **HAT:** Human African Trypanosomiasis; **ITT**: intention-to-treat; **mITT**: modified intention-to-treat; **NECT:** Nifurtimox-eflornithine combination therapy; **NPV**: negative predictive value; **PPV**: positive predictive value; **RR:** Risk ratio; **WBC:** white blood cell count

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 for downgrading evidence

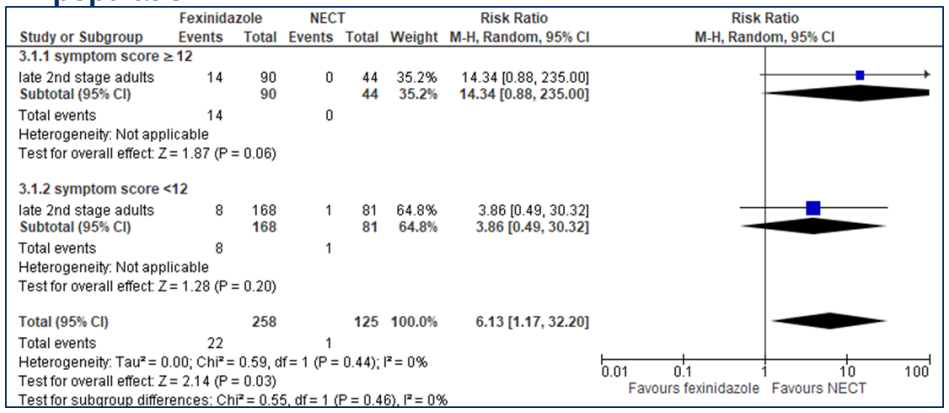
a. Downgraded two steps for serious risk of bias: Post hoc subgroup analysis from open label trial and consequently risk of performance bias for outcomes that could be influenced by exposure to other factors apart from the intervention of interest.

b. Downgraded two steps for serious imprecision: few events and wide CIs that include both appreciable benefit/no difference and appreciable harm with Fexinidazole

c. Downgraded one step for serious imprecision: Few reported events

Figure 1. Treatment failure of fexinidazole compared with NECT for subgroups with signs and symptoms score ≥12 and <12

EP population



mITT population

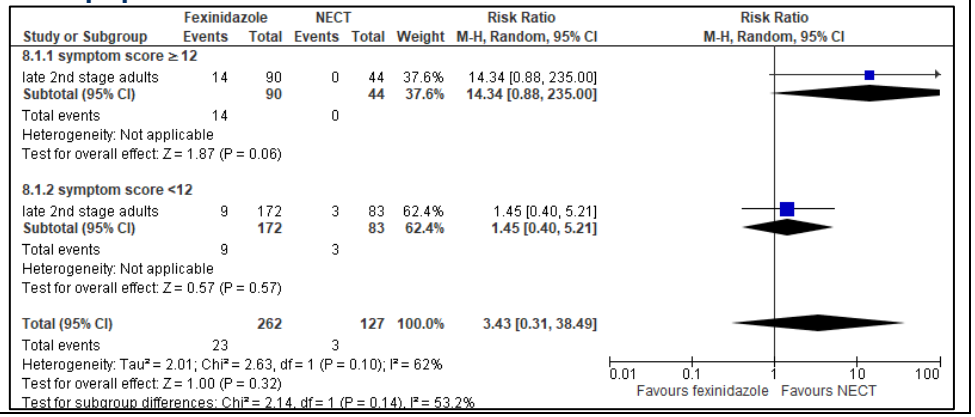
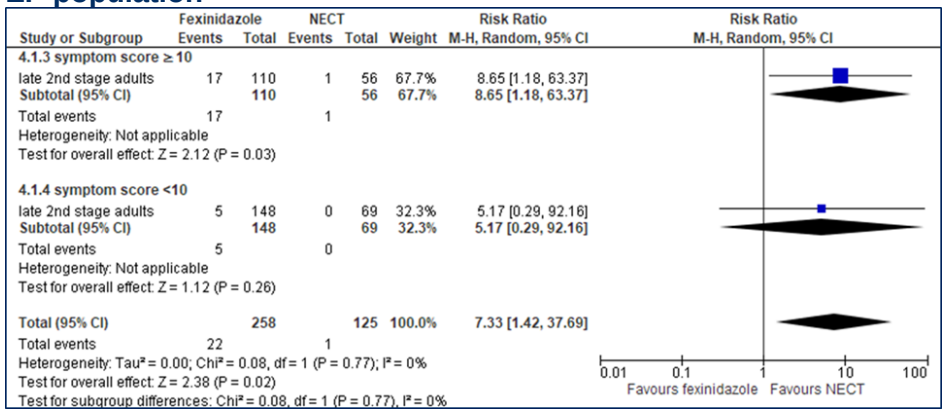


Figure 2. Treatment failure of fexinidazole compared with NECT for subgroups with signs and symptoms score ≥10 and <10

EP population



mITT population

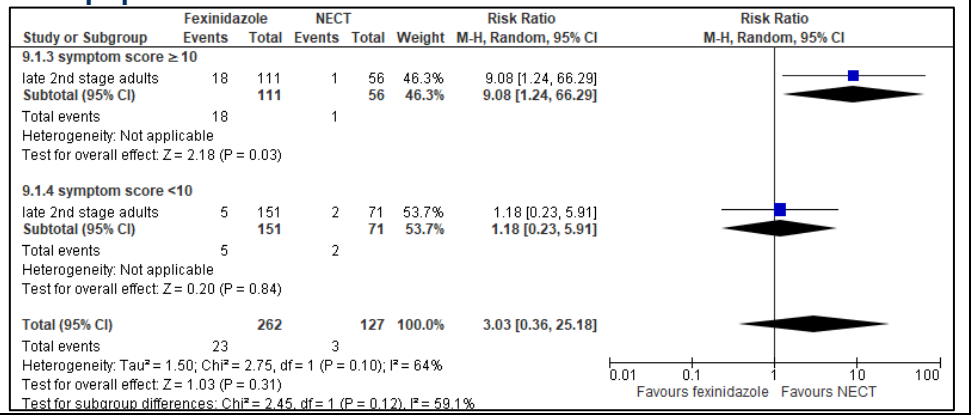
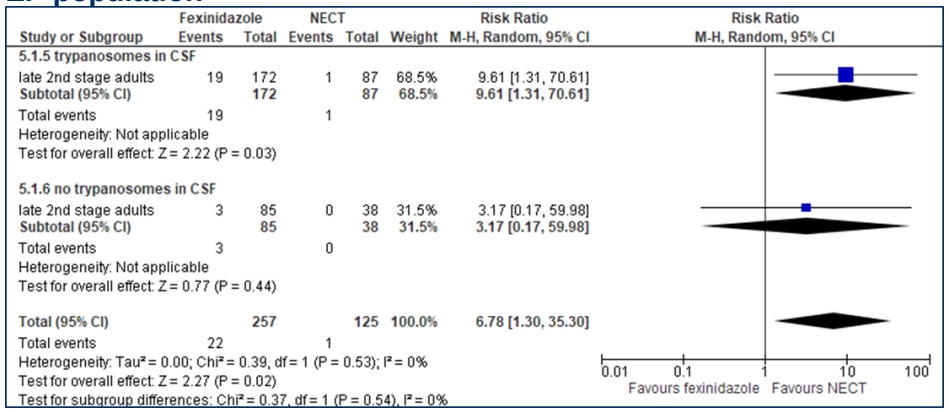


Figure 3. Treatment failure of fexinidazole compared with NECT for subgroups with and without tripanosomes in CSF

EP population



mITT population

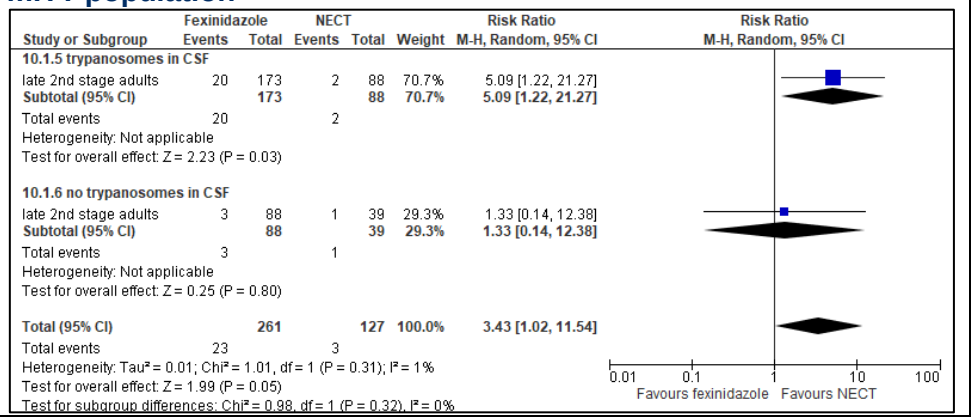
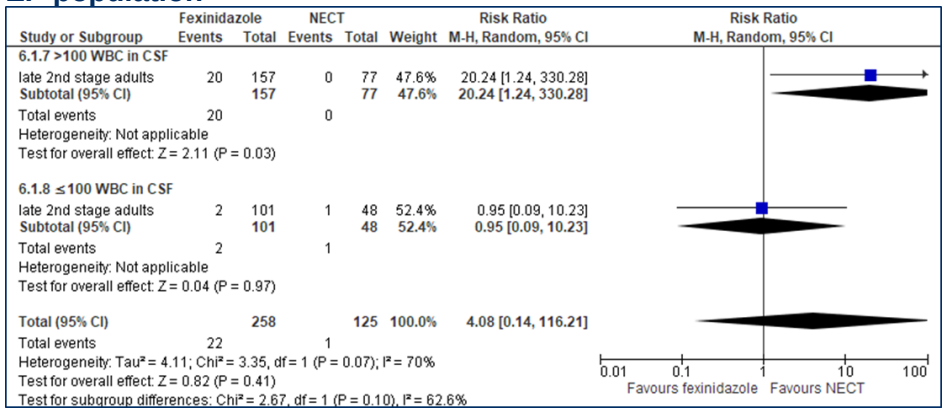


Figure 4. Treatment failure of fexinidazole compared with NECT for subgroups with >100 or ≤100 WBC in CFS

EP population



mITT population

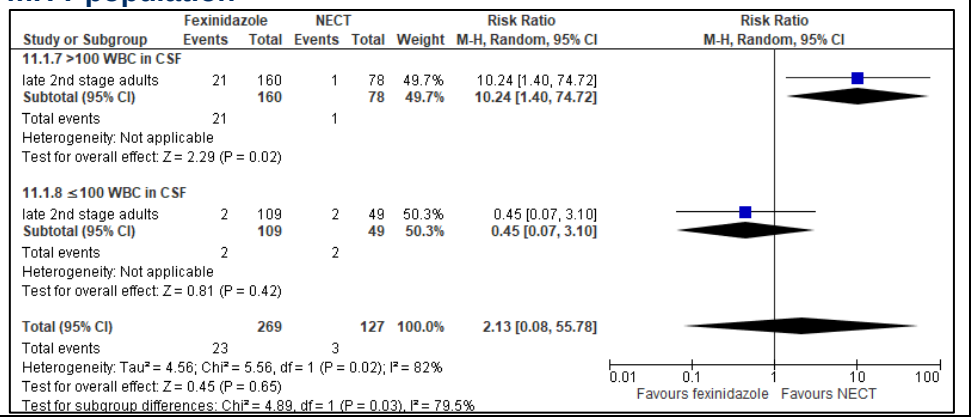
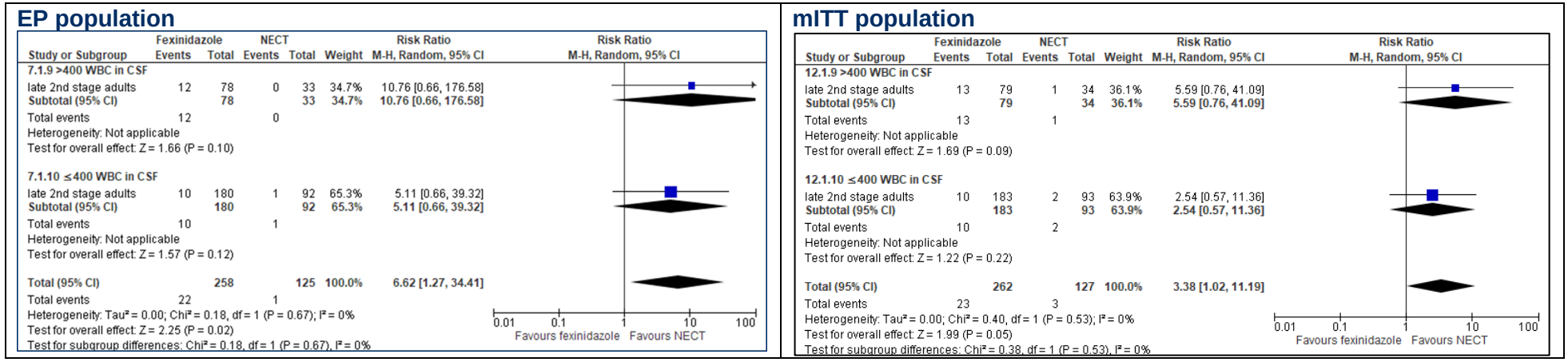


Figure 5. Treatment failure of fexinidazole compared with NECT for subgroups with >400 or ≤400 WBC in CFS



4.2. Rates of treatment failure

Rates of treatment failure were consistently higher in participants above predictor threshold compared to those below predictor thresholds for late second stage adults, early and late second stage children and adults (See Table 7. SOF table: Fexinidazole for all second stage HAT – post hoc subgroup analyses), and all stages children and adults (See Table 8. SOF table: Fexinidazole for all stages HAT – post hoc subgroup analyses).

Table 7. SOF table: Fexinidazole for all second stage HAT – post hoc subgroup analyses

4.2.1. Fexinidazole (oral) for all stage-2 Human African Trypanosomiasis treated with fexinidazole (adults and children) – post hoc subgroup analyses

Patient or population: Children and adults with second stage Human African *gambiense* Trypanosomiasis (early second stage: trypanosomes in blood or nymph node fluid and WBC 6-<= 20 per µL and no trypanosomes in CSF; late second stage: trypanosomes in blood or nymph node fluid and WBC >20 per µL or trypanosomes in CSF)

Setting: inpatients in the Democratic Republic of the Congo and the Central African Republic

Intervention: Fexinidazole (oral), adults: once daily (days 1-4: 1800 mg, days 5-10: 1200 mg), children ≥35kg: same as in adults, children ≥20kg and <35kg: once daily days 1-4: 1200 mg, days 5-10: 600 mg

Comparison: No comparison group

Outcome: Treatment failure, rescue treatment, death, CSF WBC >20 cells/µL, trypanosomes in the blood, lost to follow-up, consent withdrawal, measured at 18 months follow-up

All results are for EP population. See results for mITT population (specific loss to follow-up due to an armed conflict were discarded) in comments column

Subgroups	Summary of results	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments	Predictive value [EP] Fexinidazole
Signs and symptoms score ≥12	Treatment failed in 14 of 99 (141 failures per 1000) children and adults with **early and late second stage** HAT treated with Fexinidazole.	99 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 3 CHMP D120 unpublished report mITT: 14 / 99 (141 per 1,000)	• Sensitivity 60.87% (38.54% to 80.29%) • Specificity 74.32 % (69.26% to 78.94%) • LR+ 2.37 (1.63 to 3.45) • LR- 0.53 (0.32 to 0.88) • PPV 14.14% (10.16% to 19.34%) • NPV 96.47% (94.24% to 97.86%)
Signs and symptoms score <12	Treatment failed in 9 of 255 (35 failures per 1000) children and adults with **early and late second stage** HAT treated with Fexinidazole.	255 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 3 CHMP D120 unpublished report mITT: 11 / 260 (42 per 1,000)	
Signs and symptoms score ≥10	Treatment failed in 17 of 127 (134 failures per 1000) children and adults with **early and late second stage** HAT treated with Fexinidazole.	127 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 6 CHMP D120 unpublished report mITT: 18 / 128 (141 per 1,000)	• Sensitivity 73.91% (51.59% to 89.77%) • Specificity 66.77 % (61.41% to 71.82%) • LR+ 2.22 (1.67 to 2.96) • LR- 0.39 (0.20 to 0.78) • PPV 13.39% (10.39% to 17.07%) • NPV 97.36 % (94.85% to 98.66%)
Signs and symptoms score <10	Treatment failed in 6 of 227 (26 failures per 1000) children and adults with **early and late second stage** HAT treated with Fexinidazole.	227 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 6 CHMP D120 unpublished report mITT: 7 / 231 (30 per 1,000)	
Presence of trypanosomes in CSF	Treatment failed in 20 of 197 (102 failures per 1000) children and adults with **early and late second stage** HAT treated with Fexinidazole.	197 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 18 CHMP D120 unpublished report mITT: 21 / 198 (106 per 1,000)	• Sensitivity 86.96% (66.41% to 97.22%) • Specificity 46.36 % (40.89% to 51.91%) • LR+ 1.62 (1.34 to 1.96) • LR- 0.28 (0.10 to 0.81) • PPV 10.15% (8.57% to 11.99%) • NPV 98.08 % (94.64% to 99.33%)
No trypanosomes in CSF	Treatment failed in 3 of 156 (19 failures per 1000) children and adults with **early and late second stage** HAT treated with Fexinidazole.	156 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 18 CHMP D120 unpublished report mITT: 4 / 160 (25 per 1,000)	

Presence of WBC in CSF at entry >100	Treatment failed in 21 of 184 (114 failures per 1000) children and adults with **early and late second stage** HAT treated with Fexinidazole.	184 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 21 CHMP D120 unpublished report mITT: 22 / 187 (118 per 1,000)	• Sensitivity 91.30% (71.96% to 98.93%) • Specificity 50.76 % (45.23% to 56.26%) • LR+ 1.85 (1.57 to 2.19) • LR- 0.17 (0.05 to 0.65) • PPV 11.41% (9.83% to 13.21%) • NPV 98.82 % (95.70% to 99.69%)
Presence of WBC in CSF at entry ≤100	Treatment failed in 2 of 170 (12 failures per 1000) children and adults with **early and late second stage** HAT treated with Fexinidazole.	170 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 21 CHMP D120 unpublished report mITT: 3 / 172 (17 per 1,000)	
Presence of WBC in CSF at entry >400	Treatment failed in 12 of 84 (143 failures per 1000) children and adults with **early and late second stage** HAT treated with Fexinidazole.	84 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 24 CHMP D120 unpublished report mITT: 13 / 85 (153 per 1,000)	• Sensitivity 52.17% (30.59% to 73.18%) • Specificity 78.25 % (73.41% to 82.57%) • LR+ 2.40 (1.54 to 3.73) • LR- 0.61 (0.40 to 0.94) • PPV 14.29% (9.68% to 20.58%) • NPV 95.93 % (93.87% to 97.31%)
Presence of WBC in CSF at entry ≤400	Treatment failed in 11 of 270 (41 failures per 1000) children and adults with **early and late second stage** HAT treated with Fexinidazole.	270 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 24 CHMP D120 unpublished report mITT: 12 / 274 (44 per 1,000)	

*__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).
**Treatment failure: rescue treatment, death, CSF WBC >20 cells/µL, trypanosomes in the blood, lost to follow-up, consent withdrawal
***Treatment success: Alive, no trypanosomes in body fluid, no rescue medication, CSF WBC ≤20 cells per µL
CI: Confidence interval; **CSF**: cerebrospinal fluid; **EP**: evaluable population; **HAT:** Human African Trypanosomiasis; **ITT**: intention-to-treat; **mITT**: modified intention-to-treat; **NECT:** Nifurtimox-eflornithine combination therapy; **NPV**: negative predictive value; **PPV**: positive predictive value; **RR:** Risk ratio; **WBC:** white blood cell count

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 for downgrading evidence

a. Non-randomised studies start at low certainty evidence, downgraded one more level for study design: post hoc analysis from two single arm non-comparative studies and the intervention arm of an RCT.

Table 8. SOF table: Fexinidazole for all stages HAT – post hoc subgroup analyses

4.2.2. Fexinidazole (oral) for all stages Human African Trypanosomiasis treated with fexinidazole (adults and children) – post hoc subgroup analyses

Patient or population: Children and adults with first or second stage Human African *gambiense* Trypanosomiasis (first stage: WBC ≤5cells/µL and no trypanosomes in CSF; early second stage: trypanosomes in blood or nymph node fluid and WBC 6-<= 20 per µL and no trypanosomes in CSF; late second stage: trypanosomes in blood or nymph node fluid and WBC >20 per µL or trypanosomes in CSF)

Setting: inpatients in the Democratic Republic of the Congo and the Central African Republic

Intervention: Fexinidazole (oral), adults: once daily (days 1-4: 1800 mg, days 5-10: 1200 mg), children ≥35kg: same as in adults, children ≥20kg and <35kg: once daily days 1-4: 1200 mg, days 5-10: 600 mg

Comparison: No comparison group

Outcome: Treatment failure, rescue treatment, death, CSF WBC >20 cells/µL, trypanosomes in the blood, lost to follow-up, consent withdrawal, measured at 18 months follow-up

All results are for EP population. See results for mITT population (specific loss to follow-up due to an armed conflict were discarded) in comments column

Subgroups	Summary of results	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments	Predictive value [EP] Fexinidazole
Signs and symptoms score ≥12	Treatment failed in 14 of 100 (140 failures per 1000) children and adults with **HAT of any stage** treated with Fexinidazole.	100 (2 single arm trials, intervention arm of 1 RCT)	⨁◯◯◯ VERY LOW [a]	See table 4 CHMP D120 unpublished report mITT: 14 / 100 (140 per 1,000)	Sensitivity 58.33% (36.64% to 77.89%) Specificity 85.27 % (82.14% to 88.05%) LR+ 3.96 (2.68 to 5.85) LR- 0.49 (0.30 to 0.79) PPV 14.00% (.92% to 19.39%) NPV 98.03 % (96.87% to 98.77%)
Signs and symptoms score <12	Treatment failed in 10 of 508 (20 failures per 1000) children and adults with **HAT of any stage** treated with Fexinidazole.	508 (2 single arm trials, intervention arm of 1 RCT)	⨁◯◯◯ VERY LOW [a]	See table 4 CHMP D120 unpublished report mITT: 16 / 517 (31 per 1,000)	
Signs and symptoms score ≥10	Treatment failed in 17 of 135 (126 failures per 1000) children and adults with **HAT of any stage** treated with Fexinidazole.	135 (2 single arm trials, intervention arm of 1 RCT)	⨁◯◯◯ VERY LOW [a]	See table 7 CHMP D120 unpublished report mITT: 18 / 136 (132 per 1,000)	Sensitivity 70.83% (48.91% to 87.38%) Specificity 79.79 % (76.31% to 82.98%) LR+ 3.51 (2.59 to 4.75) LR- 0.37 (0.20 to 0.68)

Signs and symptoms score <10	Treatment failed in 7 of 473 (15 failures per 1000) children and adults with **HAT of any stage** treated with Fexinidazole.	473 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 7 CHMP D120 unpublished report mITT: 12 / 148 (25 per 1,000)	PPV 12.59% (9.62% to 16.32%) NPV 98.52 % (97.27% to 99.20%)
Presence of trypanosomes in CSF	Treatment failed in 20 of 197 (102 failures per 1000) children and adults with **HAT of any stage** treated with Fexinidazole.	197 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 19 CHMP D120 unpublished report mITT: 21 / 198 (106 per 1,000)	Sensitivity 83.33% (62.62% to 95.26%) Specificity 69.64 % (65.73% to 73.35%) LR+ 2.74 (2.21 to 3.41) LR- 0.24 (0.10 to 0.59) PPV 10.15% (8.34% to 12.31%) NPV 99.02 % (97.64% to 99.60%)
No trypanosomes in CSF	Treatment failed in 4 of 410 (10 failures per 1000) children and adults with **HAT of any stage** treated with Fexinidazole.	410 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 19 CHMP D120 unpublished report mITT: 9 / 418 (22 per 1,000)	
Presence of WBC in CSF at entry >100	Treatment failed in 21 of 184 (114 failures per 1000) children and adults with **HAT of any stage** treated with Fexinidazole.	184 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 22 CHMP D120 unpublished report mITT: 22 / 187 (118 per 1,000)	Sensitivity 87.50% (67.64% to 97.34%) Specificity 72.09 % (68.26% to 75.69%) LR+ 3.13 (2.57 to 3.83) LR- 0.17 (0.06 to 0.50) PPV 11.41% (9.54% to 13.59%) NPV 99.29 % (97.99% to 99.75%)
Presence of WBC in CSF at entry ≤100	Treatment failed in 3 of 424 (7 failures per 1000) children and adults with **HAT of any stage** treated with Fexinidazole.	424 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 22 CHMP D120 unpublished report mITT: 8 / 430 (19 per 1,000)	
Presence of WBC in CSF at entry >400	Treatment failed in 12 of 84 (143 failures per 1000) children and adults with **HAT of any stage** treated with Fexinidazole.	84 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 25 CHMP D120 unpublished report mITT: 13 / 85 (153 per 1,000)	Sensitivity 50.00% (29.12% to 70.88%) Specificity 87.67 % (84.73% to 90.23%) LR+ 4.06 (2.57 to 6.39) LR- 0.57 (0.38 to 0.85) PPV 14.29% (9.56% to 20.80%) NPV 97.71 % (96.62% to 98.46%)
Presence of WBC in CSF at entry ≤400	Treatment failed in 12 of 524 (23 failures per 1000) children and adults with **HAT of any stage** treated with Fexinidazole.	524 (2 single arm trials, intervention arm of 1 RCT)	⊕◯◯◯ VERY LOW [a]	See table 25 CHMP D120 unpublished report mITT: 12 / 532 (32 per 1,000)	

*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).
**Treatment failure: rescue treatment, death, CSF WBC >20 cells/μL, trypanosomes in the blood, lost to follow-up, consent withdrawal
***Treatment success: Alive, no trypanosomes in body fluid, no rescue medication, CSF WBC ≤20 cells per μL
CI: Confidence interval; **CSF**: cerebrospinal fluid; **EP**: evaluable population; **HAT:** Human African Trypanosomiasis; **ITT**: intention-to-treat; **mITT**: modified intention-to-treat; **NECT:** Nifurtimox-eflornithine combination therapy; **NPV**: negative predictive value; **PPV**: positive predictive value; **RR:** Risk ratio; **WBC:** white blood cell count

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 for downgrading evidence

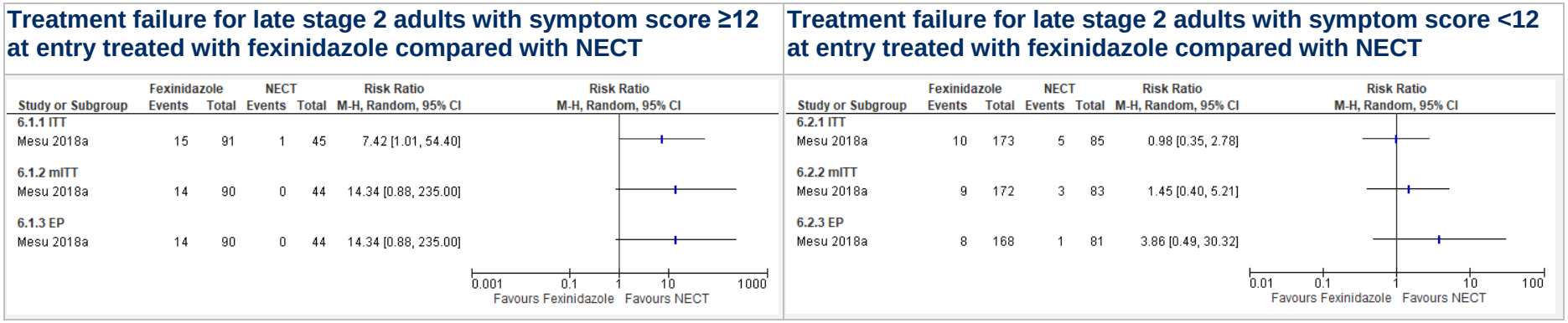
a. Non-randomised studies start at low certainty evidence, downgraded one more level for study design: post hoc analysis from two single arm non-comparative studies and the intervention arm of an RCT.

4.3. Accuracy of clinical predictors to predict treatment failure - results by test

Below we summarise the prognostic accuracy of the different clinical predictors to predict treatment outcomes.

4.3.1. Predictor: symptom score ≥12 or <12 at entry (requires no lumbar puncture)

Figure 6. Treatment failure for late stage 2 adults with symptom score ≥12 or 12 at entry treated with fexinidazole compared with NECT



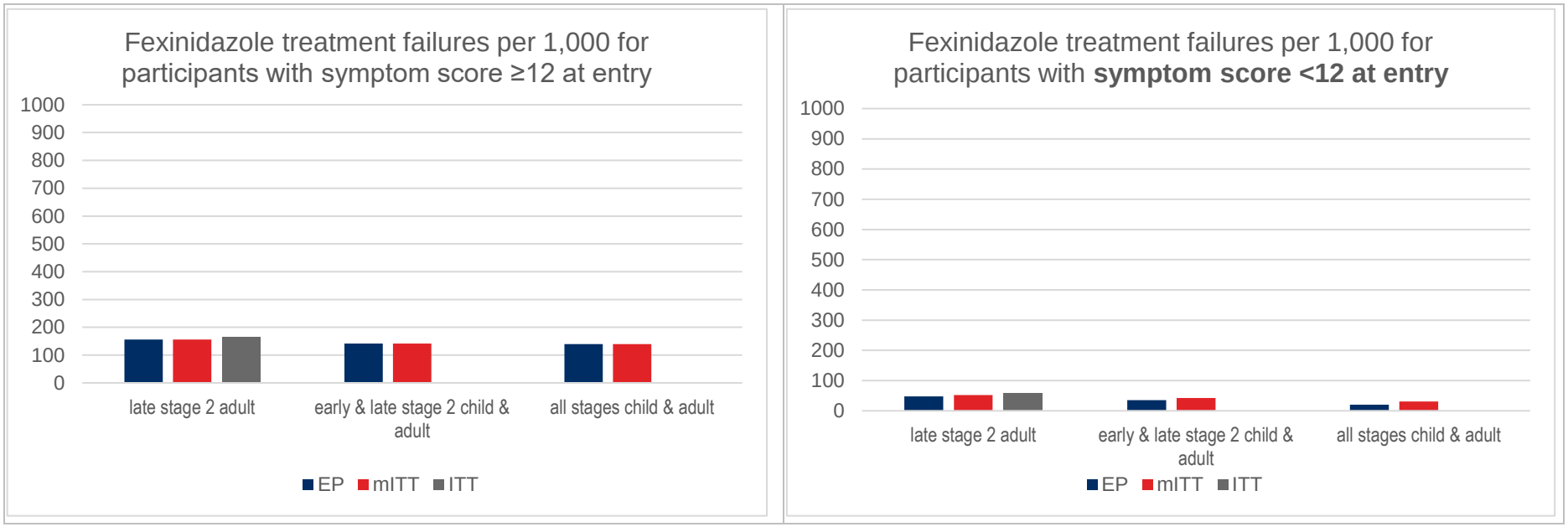
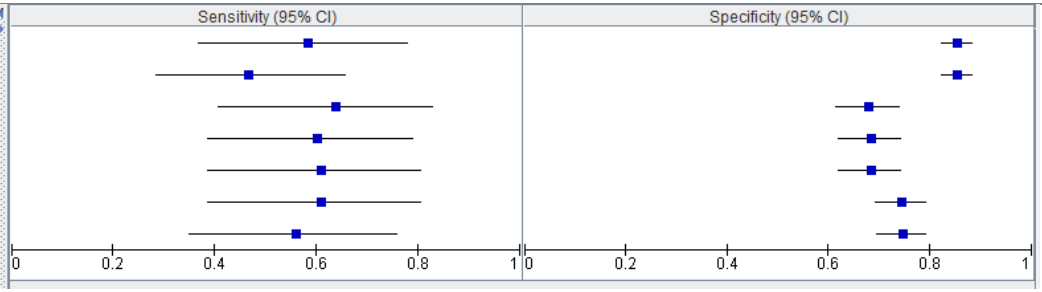


Figure 7. Sensitivity and specificity for symptom score ≥12

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
all stages adults/child- EP	14	86	10	498	0.58 [0.37, 0.78]	0.85 [0.82, 0.88]
all stages adults/child- mITT	14	86	16	501	0.47 [0.28, 0.66]	0.85 [0.82, 0.88]
late stage 2 adults- EP	14	76	8	160	0.64 [0.41, 0.83]	0.68 [0.61, 0.74]
late stage 2 adults- ITT	15	76	10	163	0.60 [0.39, 0.79]	0.68 [0.62, 0.74]
late stage 2 adults- mITT	14	76	9	163	0.61 [0.39, 0.80]	0.68 [0.62, 0.74]
stage 2 adults/child- EP	14	85	9	246	0.61 [0.39, 0.80]	0.74 [0.69, 0.79]
stage 2 adults/child- mITT	14	85	11	249	0.56 [0.35, 0.76]	0.75 [0.70, 0.79]



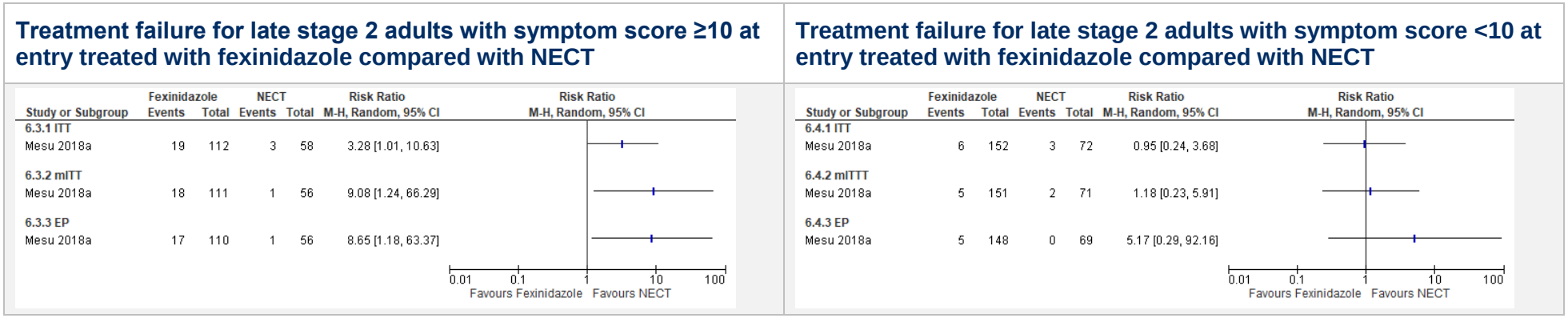
Predictive values (mITT populations)

	Late stage 2 adults	All stages children and adults	Early and late stage 2 children and adults
PPV	15.56% (11.22% to 21.16%)	14.00% (9.58% to 20.01%)	14.14% (10.01% to 19.61%)
NPV	94.77% (91.53% to 96.81%)	96.91% (95.72% to 97.77%)	95.77% (93.54% to 97.25%)

LR+	1.91 (1.31 to 2.79)	3.19 (2.07 to 4.89)	2.20 (1.49 to 3.26)
LR-	0.57 (0.34 to 0.96)	0.62 (0.45 to 0.87)	0.59 (0.38 to 0.92)
Predictive values (EP populations)			
	Late stage 2 adults	**All stages children and adults**	**Early and late stage 2 children and adults**
PPV	15.56% (11.33% to 20.99%)	14.00% (9.92% to 19.39%)	14.14% (10.16% to 19.34%)
NPV	95.24% (91.95% to 97.22%)	98.03% (96.87% to 98.77%)	96.47% (94.24% to 97.86%)
LR+	1.98 (1.37 to 2.85)	3.96 (2.68 to 5.85)	2.37 (1.63 to 3.45)
LR-	0.54 (0.31 to 0.94)	0.49 (0.30 to 0.79)	0.53 (0.32 to 0.88)

4.3.2. Predictor: symptom score ≥10 or <10 at entry (requires no lumbar puncture)

Figure 8. Treatment failure for late stage 2 adults with symptom score ≥10 or 10 at entry treated with fexinidazole compared with NECT



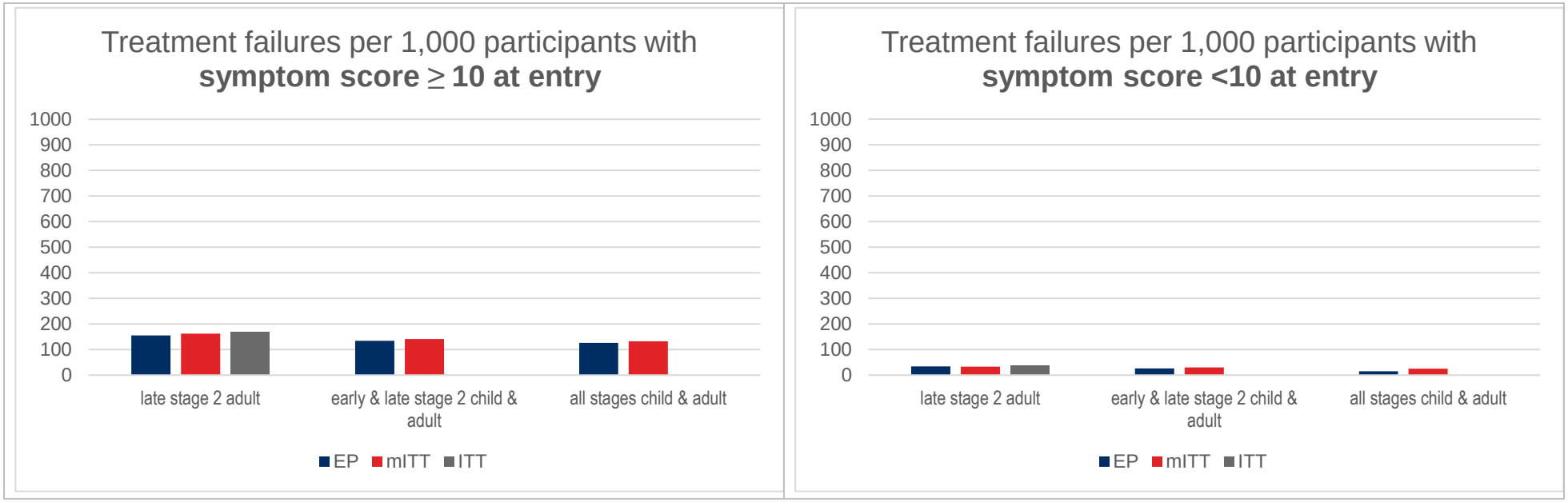
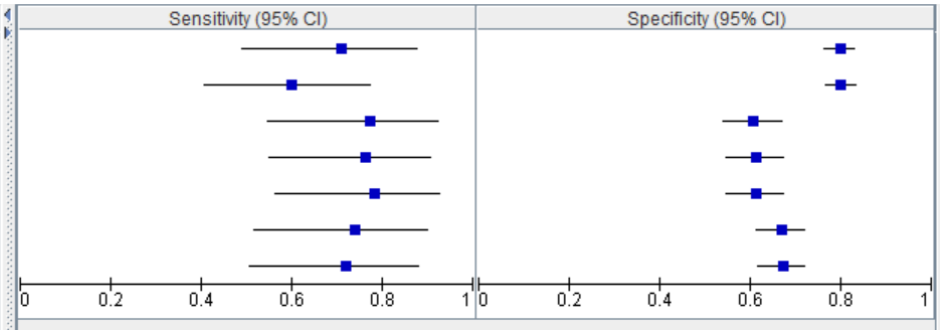


Figure 9. Sensitivity and specificity for symptom score ≥10

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
all stages adults/child- EP	17	118	7	466	0.71 [0.49, 0.87]	0.80 [0.76, 0.83]
all stages adults/child- mITT	18	118	12	469	0.60 [0.41, 0.77]	0.80 [0.76, 0.83]
late stage 2 adults- EP	17	93	5	143	0.77 [0.55, 0.92]	0.61 [0.54, 0.67]
late stage 2 adults- ITT	19	93	6	146	0.76 [0.55, 0.91]	0.61 [0.55, 0.67]
late stage 2 adults- mITT	18	93	5	146	0.78 [0.56, 0.93]	0.61 [0.55, 0.67]
stage 2 adults/child- EP	17	110	6	221	0.74 [0.52, 0.90]	0.67 [0.61, 0.72]
stage 2 adults/child- mITT	18	110	7	224	0.72 [0.51, 0.88]	0.67 [0.62, 0.72]



Predictive values (mITT populations)

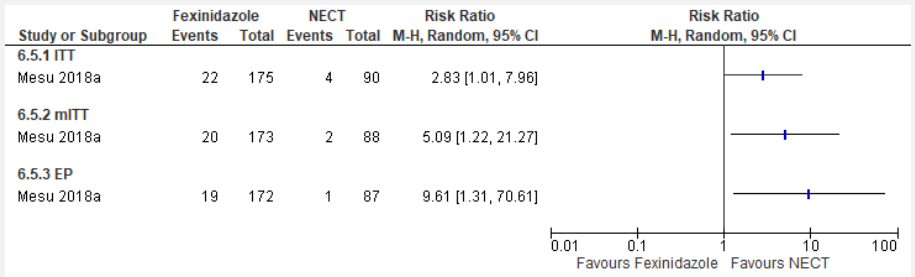
	Late stage 2 adults	All stages children and adults	Early and late stage 2 children and adults
PPV	16.22% (12.90% to 20.19%)	13.24% (9.85% to 17.56%)	14.06% (10.92% to 17.92%)
NPV	96.69% (93.04% to 98.46%)	97.51% (96.18% to 98.38%)	96.97% (94.44% to 98.37%)

LR+	2.01 (1.54 to 2.63)	2.98 (2.14 to 4.17)	2.19 (1.64 to 2.92)
LR-	0.36 (0.16 to 0.78)	0.50 (0.32 to 0.78)	0.42 (0.22 to 0.79)
Predictive values (EP populations)			
	Late stage 2 adults	**All stages children and adults**	**Early and late stage 2 children and adults**
PPV	15.45% (12.18% to 19.42%)	12.59% (9.62% to 16.32%)	13.39% (10.39% to 17.07%)
NPV	96.62% (92.93% to 98.42%)	98.52% (97.27% to 99.20%)	97.36% (94.85% to 98.66%)
LR+	1.96 (1.49 to 2.59)	3.51 (2.59 to 4.75)	2.22 (1.67 to 2.96)
LR-	0.38 (0.17 to 0.82)	0.37 (0.20 to 0.68)	0.39 (0.20 to 0.78)

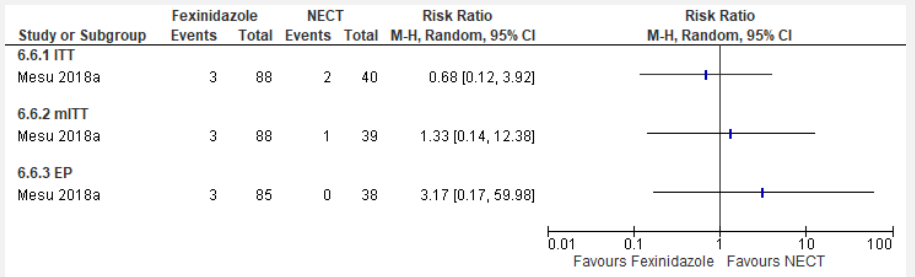
4.3.3. Predictor: trypanosomes or not in CSF at entry

Figure 10. Treatment failure for late stage 2 adults with trypanosomes or not in CSF at entry treated with fexinidazole compared with NECT

Treatment failure for late stage 2 adults with trypanosomes in CSF at entry treated with fexinidazole compared with NECT



Treatment failure for late stage 2 adults with no trypanosomes in CSF at entry treated with fexinidazole compared with NECT



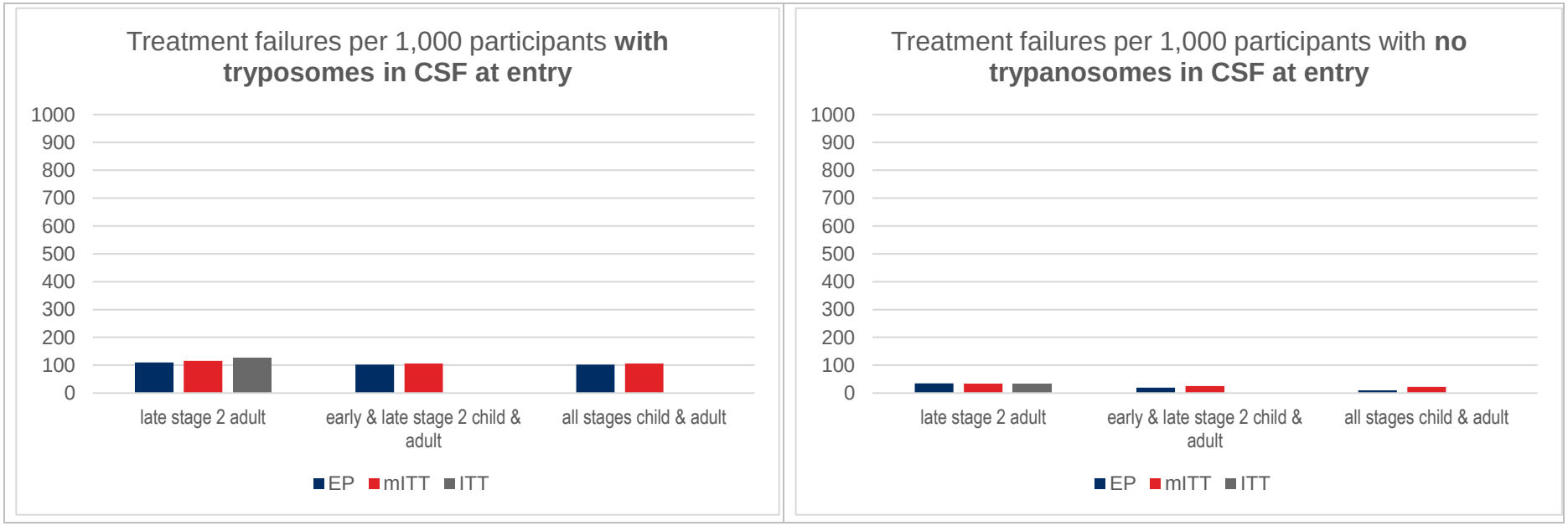
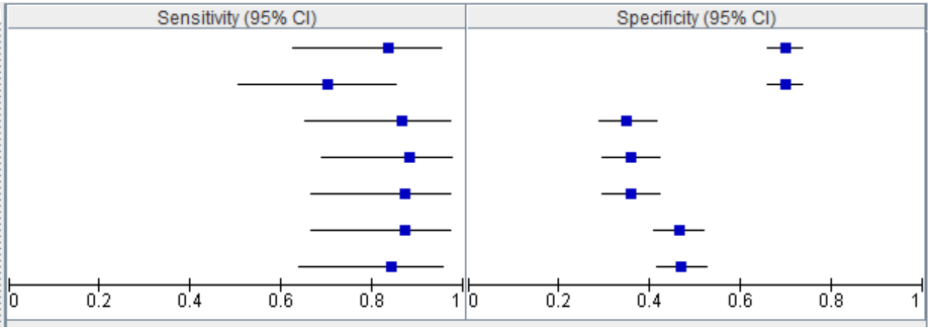


Figure 11. Sensitivity and specificity for trypanosomes in CSF

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
all stages adults/child- EP	20	177	4	406	0.83 [0.63, 0.95]	0.70 [0.66, 0.73]
all stages adults/child- mITT	21	177	9	409	0.70 [0.51, 0.85]	0.70 [0.66, 0.73]
late stage 2 adults- EP	19	153	3	82	0.86 [0.65, 0.97]	0.35 [0.29, 0.41]
late stage 2 adults- ITT	22	153	3	85	0.88 [0.69, 0.97]	0.36 [0.30, 0.42]
late stage 2 adults- mITT	20	153	3	85	0.87 [0.66, 0.97]	0.36 [0.30, 0.42]
stage 2 adults/child- EP	20	177	3	153	0.87 [0.66, 0.97]	0.46 [0.41, 0.52]
stage 2 adults/child- mITT	21	177	4	156	0.84 [0.64, 0.95]	0.47 [0.41, 0.52]



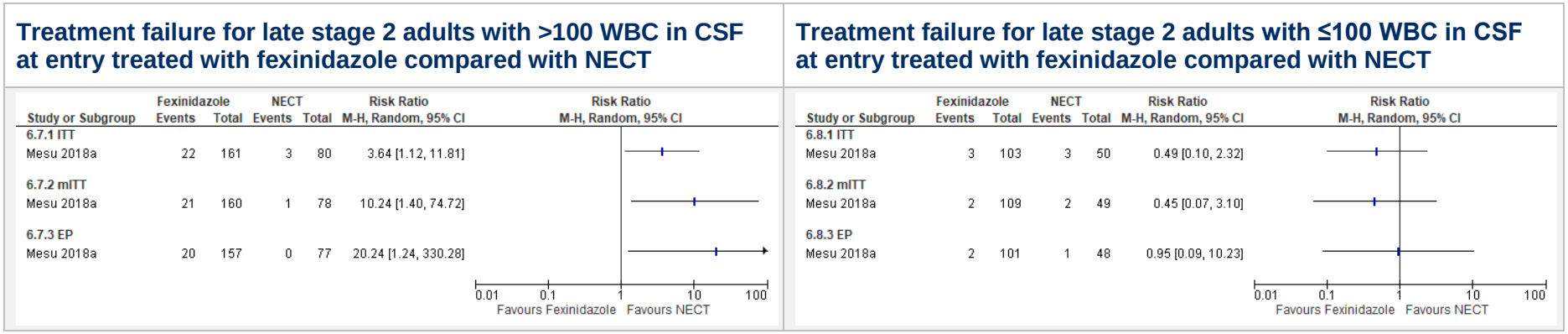
Predictive values (mITT populations)

	Late stage 2 adults	All stages children and adults	Early and late stage 2 children and adults
PPV	11.56% (9.80% to 13.58%)	10.61% (8.35% to 13.39%)	10.61% (8.87% to 12.64%)
NPV	96.59% (90.68% to 98.80%)	97.85% (96.33% to 98.75%)	97.50% (94.04% to 98.97%)

LR+	1.35 (1.12 to 1.63)	2.32 (1.78 to 3.02)	1.58 (1.30 to 1.93)
LR-	0.37 (0.13 to 1.06)	0.43 (0.25 to 0.74)	0.34 (0.14 to 0.84)
Predictive values (EP populations)			
	Late stage 2 adults	**All stages children and adults**	**Early and late stage 2 children and adults**
PPV	11.05% (9.31% to 13.06%)	10.15% (8.34% to 12.31%)	10.15% (8.57% to 11.99%
NPV	96.47% (90.40% to 98.76%)	99.02% (97.64% to 99.60%)	98.08% (94.64% to 99.33%)
LR+	1.33 (1.10 to 1.61)	2.74 (2.21 to 3.41)	1.62 (1.34 to 1.96)
LR-	0.39 (0.13 to 1.13)	0.24 (0.10 to 0.59)	0.28 (0.10 to 0.81)

4.3.4. Predictor: ≤100 or >100 WBC in CSF at entry

Figure 12. Treatment failure for late stage 2 adults with ≤100 or >100 WBC in CSF at entry treated with fexinidazole compared with NECT



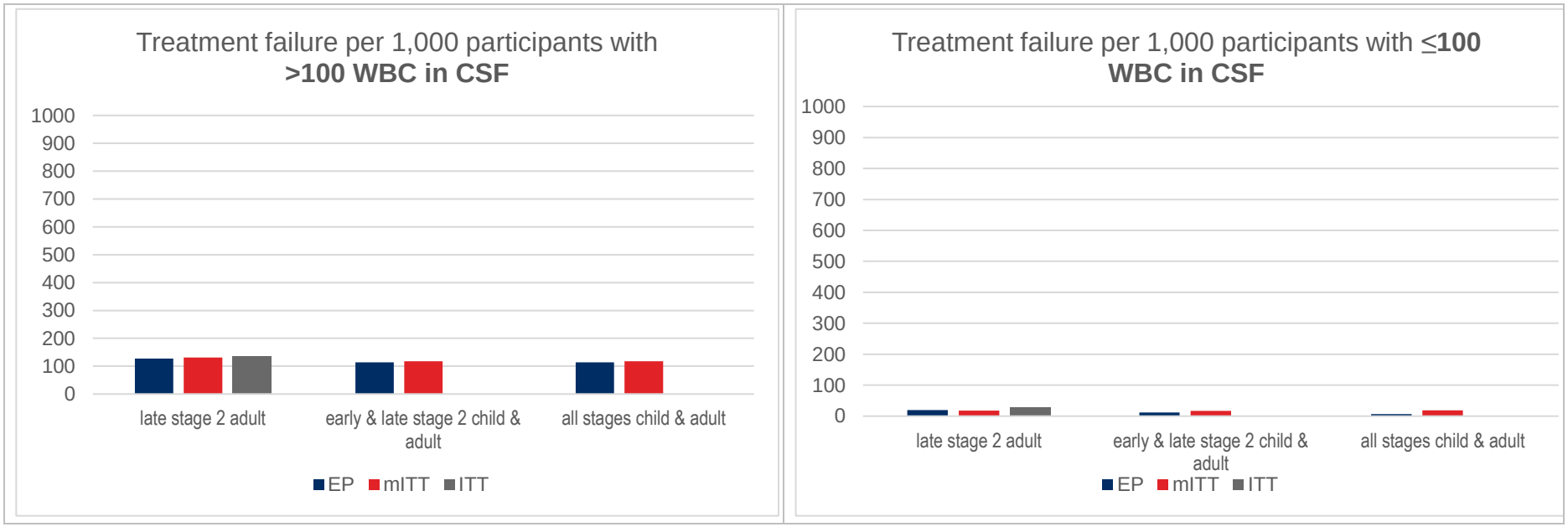
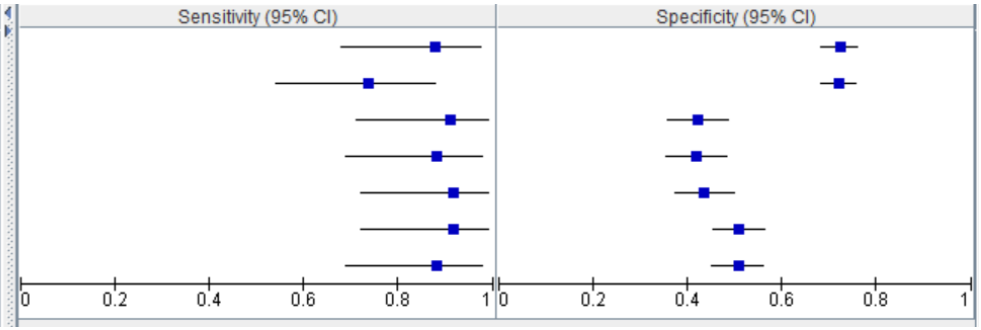


Figure 13. Sensitivity and specificity for >100 WBC in CSF at entry

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
all stages adults/child- EP	21	163	3	421	0.88 [0.68, 0.97]	0.72 [0.68, 0.76]
all stages adults/child- mITT	22	165	8	422	0.73 [0.54, 0.88]	0.72 [0.68, 0.75]
late stage 2 adults- EP	20	137	2	99	0.91 [0.71, 0.99]	0.42 [0.36, 0.49]
late stage 2 adults- ITT	22	139	3	100	0.88 [0.69, 0.97]	0.42 [0.36, 0.48]
late stage 2 adults- mITT	21	139	2	107	0.91 [0.72, 0.99]	0.43 [0.37, 0.50]
stage 2 adults/child- EP	21	163	2	168	0.91 [0.72, 0.99]	0.51 [0.45, 0.56]
stage 2 adults/child- mITT	22	165	3	169	0.88 [0.69, 0.97]	0.51 [0.45, 0.56]



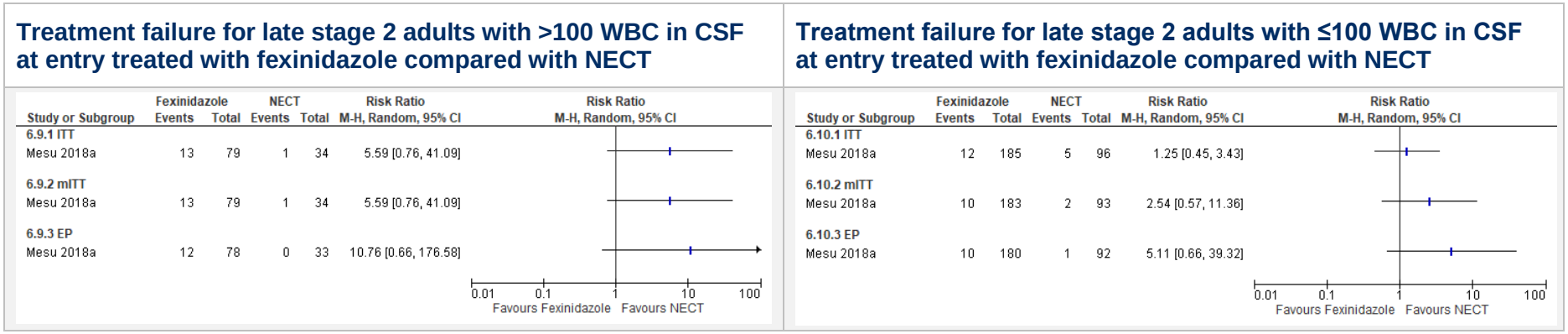
Predictive values (mITT populations)

	Late stage 2 adults	All stages children and adults	Early and late stage 2 children and adults
PPV	13.12% (11.33% to 15.15%)	11.76% (9.39% to 14.64%)	11.76% (10.01% to 13.78%)
NPV	98.17% (93.39% to 99.51%)	98.14% (96.68% to 98.97%)	98.26% (95.09% to 99.39%)

LR+	1.62 (1.37 to 1.91)	2.61 (2.03 to 3.36)	1.78 (1.49 to 2.13)
LR-	0.20 (0.05 to 0.76)	0.37 (0.20 to 0.67)	0.24 (0.08 to 0.69)
Predictive values (EP populations)			
	Late stage 2 adults	**All stages children and adults**	**Early and late stage 2 children and adults**
PPV	12.74% (10.96% to 14.76%)	11.41% (9.54% to 13.59%)	11.41% (9.83% to 13.21%)
NPV	98.02% (92.90% to 99.47%)	99.29% (97.99% to 99.75%)	98.82% (95.70% to 99.69%)
LR+	1.57 (1.32 to 1.86)	3.13 (2.57 to 3.83)	1.85 (1.57 to 2.19)
LR-	0.22 (0.06 to 0.82)	0.17 (0.06 to 0.50)	0.17 (0.05 to 0.65)

4.3.5. Predictor: ≤400 or >400 WBC in CSF at entry

Figure 14. Treatment failure for late stage 2 adults with ≤400 or >400 WBC in CSF at entry treated with fexinidazole compared with NECT



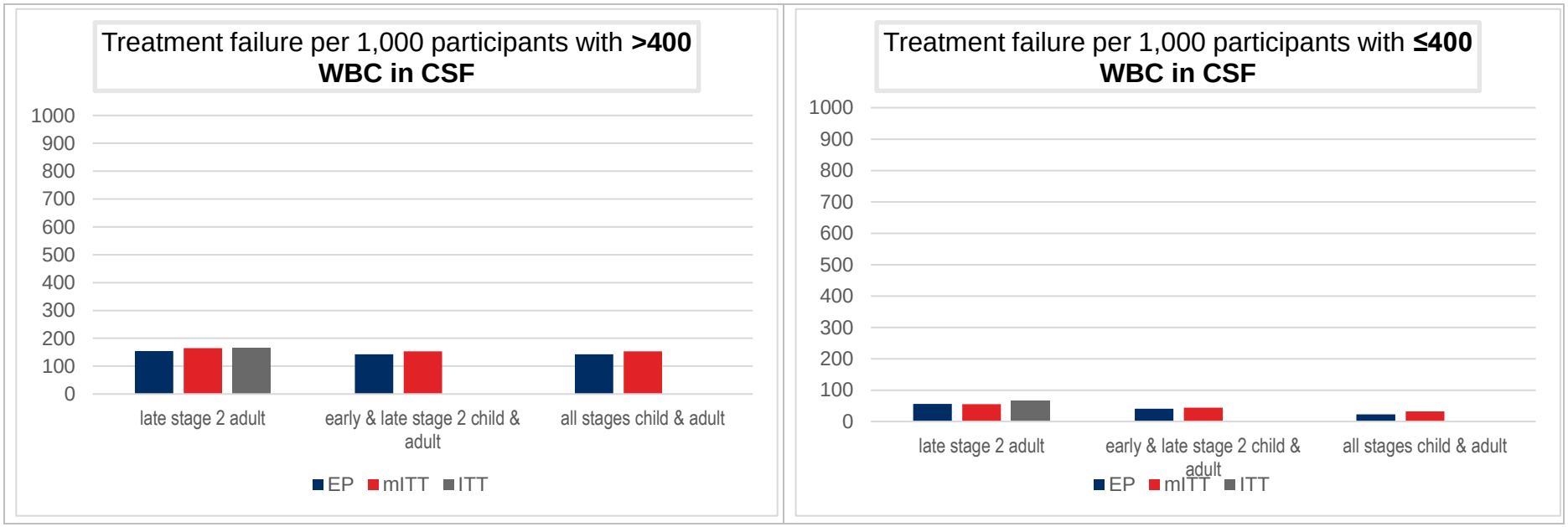
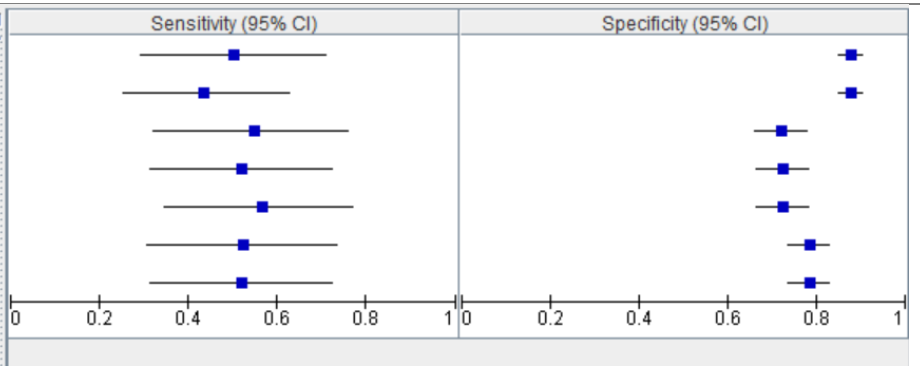


Figure 15. Sensitivity and specificity for >400 WBC in CSF at entry

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
all stages adults/child- EP	12	72	12	512	0.50 [0.29, 0.71]	0.88 [0.85, 0.90]
all stages adults/child- mITT	13	72	17	515	0.43 [0.25, 0.63]	0.88 [0.85, 0.90]
late stage 2 adults- EP	12	66	10	170	0.55 [0.32, 0.76]	0.72 [0.66, 0.78]
late stage 2 adults- ITT	13	66	12	173	0.52 [0.31, 0.72]	0.72 [0.66, 0.78]
late stage 2 adults- mITT	13	66	10	173	0.57 [0.34, 0.77]	0.72 [0.66, 0.78]
stage 2 adults/child- EP	12	72	11	259	0.52 [0.31, 0.73]	0.78 [0.73, 0.83]
stage 2 adults/child- mITT	13	72	12	262	0.52 [0.31, 0.72]	0.78 [0.74, 0.83]



Predictive values (mITT populations)			
	Late stage 2 adults	**All stages children and adults**	**Early and late stage 2 children and adults**
PPV	16.46% (11.53% to 22.94)	15.29% (10.21% to 22.29%)	15.29% (10.52% to 21.70%)
NPV	94.54% (91.51% to 96.52%)	96.80% (95.68% to 97.65%)	95.62% (93.53% to 97.06%)
LR+	2.05 (1.35 to 3.09)	3.53 (2.22 to 5.61)	2.41 (1.57 to 3.70)
LR-	0.60 (0.37 to 0.96)	0.65 (0.47 to 0.88)	0.61 (0.41 to 0.92)
Predictive values (EP populations)			
	Late stage 2 adults	**All stages children and adults**	**Early and late stage 2 children and adults**
PPV	15.38% (10.55% to 21.89%)	14.29% (9.56% to 20.80%)	14.29% (9.68% to 20.58%)
NPV	94.44% (91.44% to 96.44%)	97.71% (96.62% to 98.46%)	95.93% (93.87% to 97.31%)
LR+	1.95 (1.27 to 3.01)	4.06 (2.57 to 6.39)	2.40 (1.54 to 3.73)
LR-	0.63 (0.40 to 1.00)	0.57 (0.38 to 0.85)	0.61 (0.40 to 0.94)

4.4. Accuracy of clinical predictors to predict treatment outcome failure - results by population

Figure 16. Treatment failure - all predictors per subgroups (mITT population)

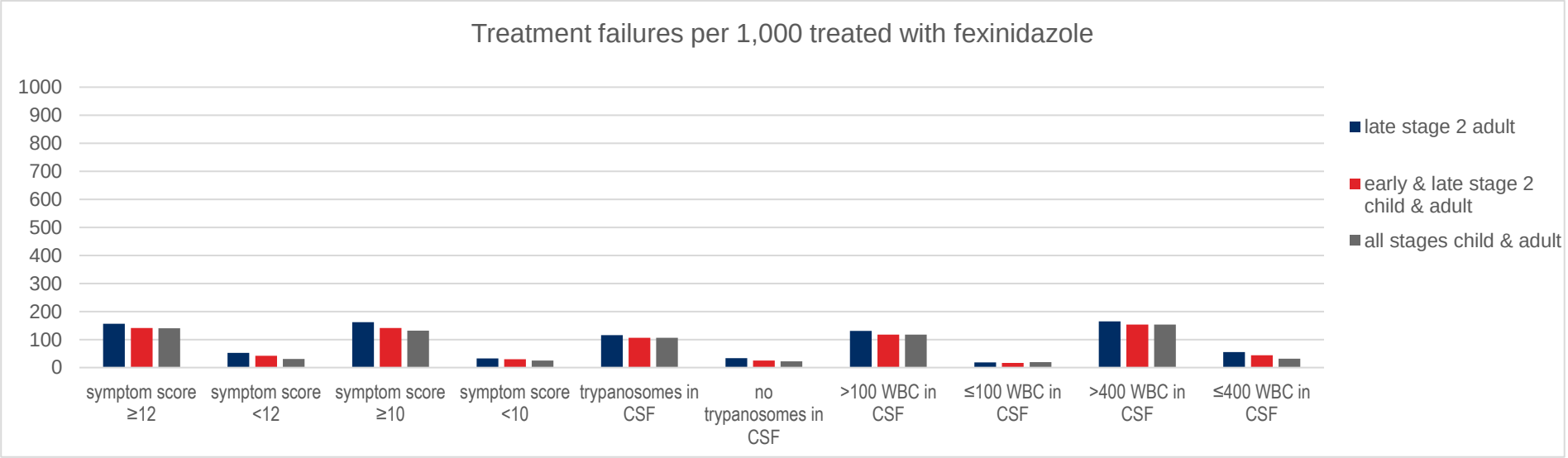


Figure 17. Treatment failure - all predictors per subgroups (EP population)

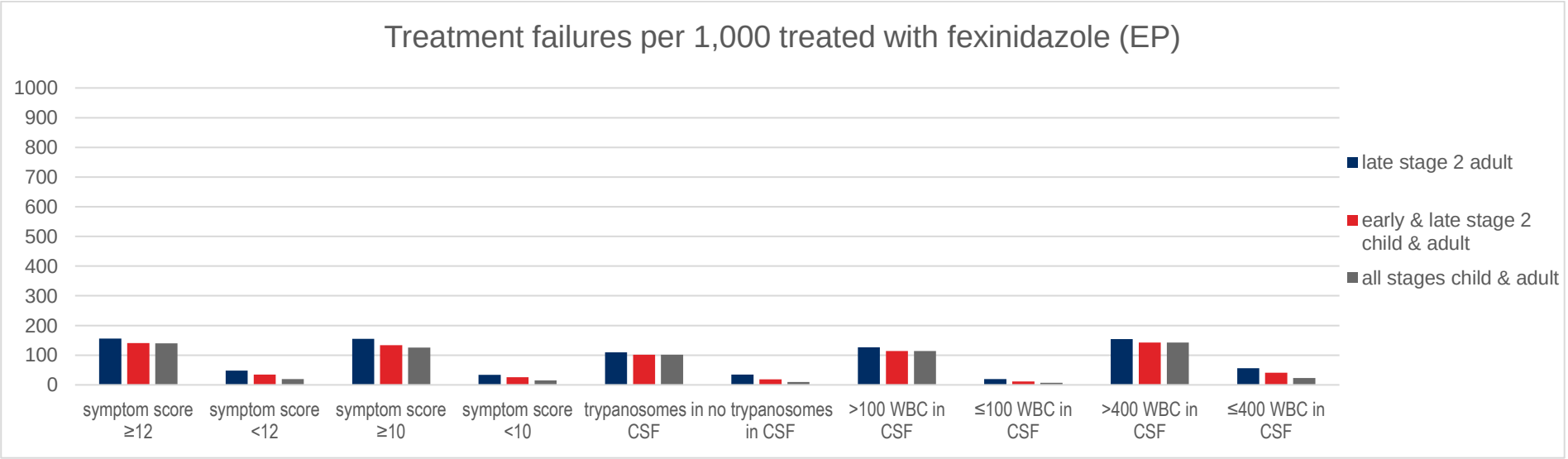


Figure 18. Number of treatment failures per 1,000 for (A) above threshold predictors, and (B) below threshold predictors (mITT population)

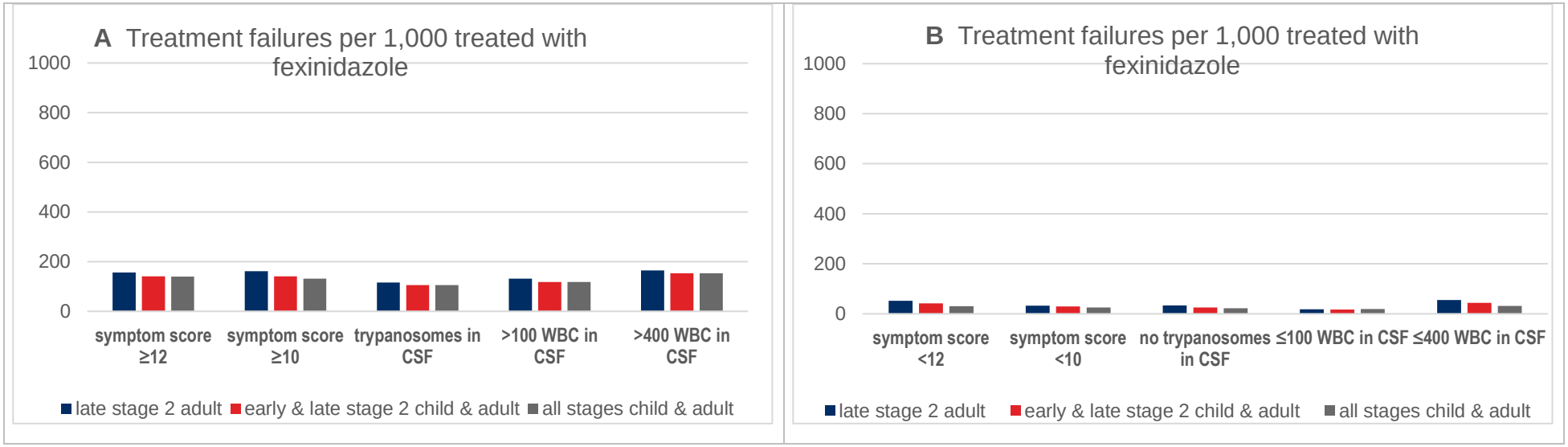


Figure 19. Number of treatment failures per 1,000 for (A) above threshold predictors, and (B) below threshold predictors (EP population)

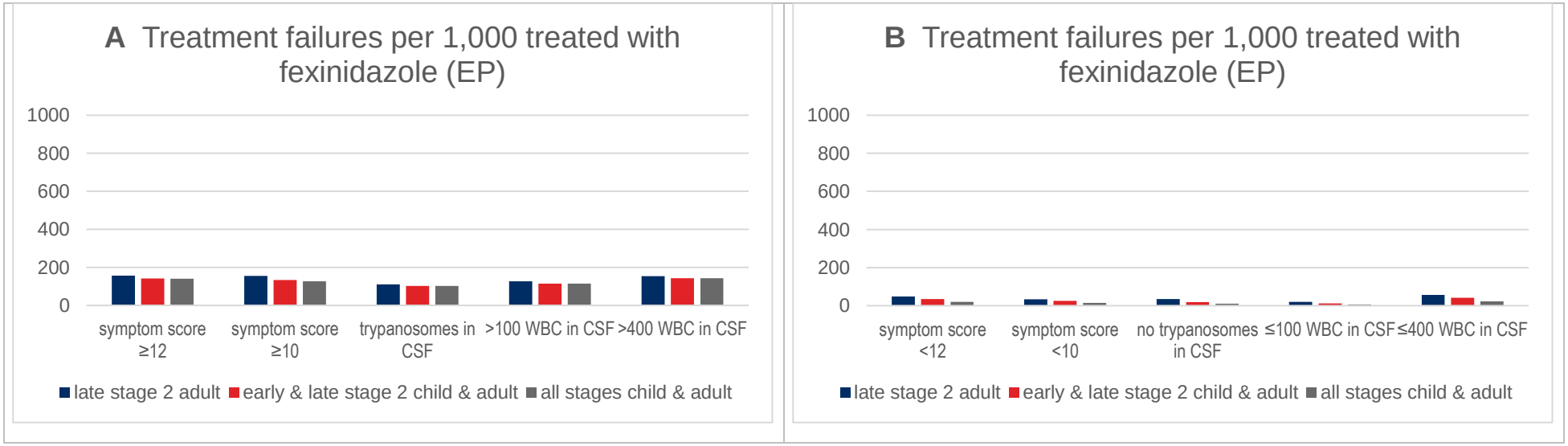


Figure 20. Sensitivity and specificity all stages children and adults (mITT population)

Test	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
1 Symptom score >=12	14	86	16	501	0.47 [0.28, 0.66]	0.85 [0.82, 0.88]
2 Symptom score >=10	18	118	12	469	0.60 [0.41, 0.77]	0.80 [0.76, 0.83]
3 Trypanosomes in CSF	21	177	9	409	0.70 [0.51, 0.85]	0.70 [0.66, 0.73]
4 >100 WBC in CSF	22	165	8	422	0.73 [0.54, 0.88]	0.72 [0.68, 0.75]
5 >400 WBC in CSF	13	72	17	515	0.43 [0.25, 0.63]	0.88 [0.85, 0.90]

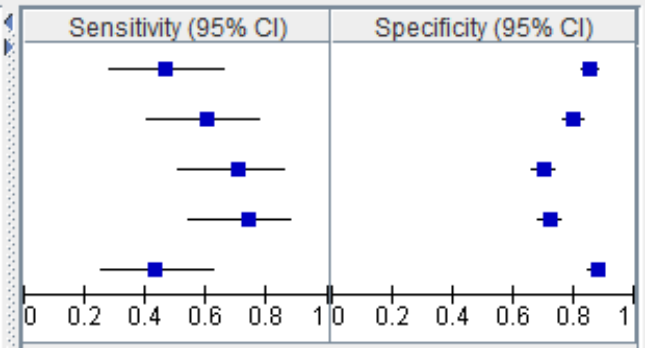


Figure 21. Sensitivity and specificity all stages children and adults (EP population)

Test	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
1 Symptom score >=12	14	86	10	498	0.58 [0.37, 0.78]	0.85 [0.82, 0.88]
2 Symptom score >=10	17	118	7	466	0.71 [0.49, 0.87]	0.80 [0.76, 0.83]
3 Trypanosomes in CSF	20	177	4	406	0.83 [0.63, 0.95]	0.70 [0.66, 0.73]
4 >100 WBC in CSF	21	163	3	421	0.88 [0.68, 0.97]	0.72 [0.68, 0.76]
5 >400 WBC in CSF	12	72	12	512	0.50 [0.29, 0.71]	0.88 [0.85, 0.90]

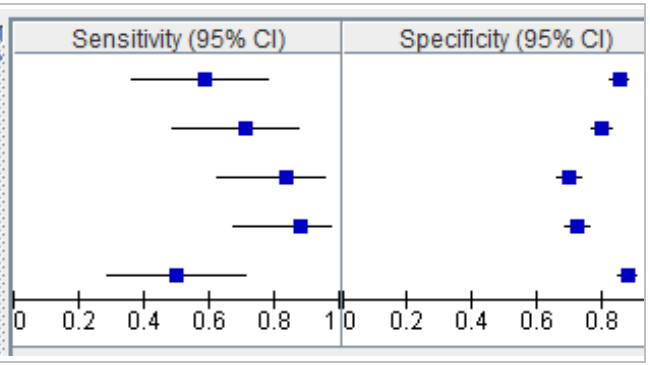


Figure 22. Sensitivity and specificity: late stage 2 adults (mITT population)

Test	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
1 Symptom score >=12	14	76	9	163	0.61 [0.39, 0.80]	0.68 [0.62, 0.74]
2 Symptom score >=10	18	93	5	146	0.78 [0.56, 0.93]	0.61 [0.55, 0.67]
3 Trypanosomes in CSF	20	153	3	85	0.87 [0.66, 0.97]	0.36 [0.30, 0.42]
4 >100 WBC in CSF	21	139	2	107	0.91 [0.72, 0.99]	0.43 [0.37, 0.50]
5 >400 WBC in CSF	13	66	10	173	0.57 [0.34, 0.77]	0.72 [0.66, 0.78]

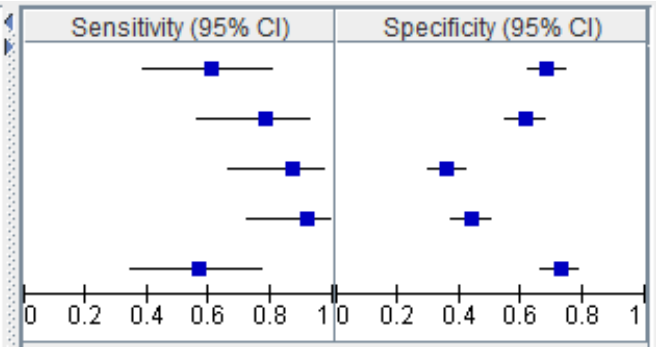


Figure 23. Sensitivity and specificity: late stage 2 adults (EP population)

Test	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
1 Symptom score >=12	14	76	8	160	0.64 [0.41, 0.83]	0.68 [0.61, 0.74]
2 Symptom score >=10	17	93	5	143	0.77 [0.55, 0.92]	0.61 [0.54, 0.67]
3 Trypanosomes in CSF	19	153	3	82	0.86 [0.65, 0.97]	0.35 [0.29, 0.41]
4 >100 WBC in CSF	20	137	2	99	0.91 [0.71, 0.99]	0.42 [0.36, 0.49]
5 >400 WBC in CSF	12	66	10	170	0.55 [0.32, 0.76]	0.72 [0.66, 0.78]

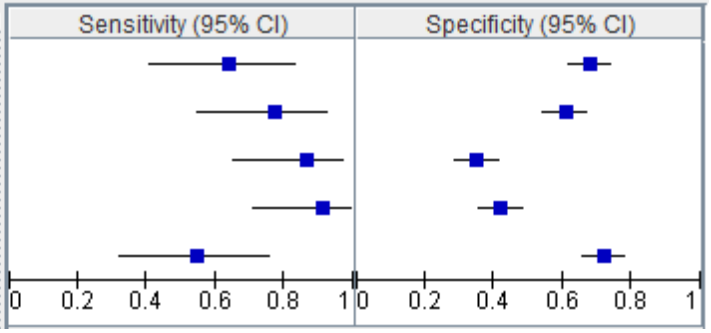


Figure 24. Sensitivity and specificity: early & late stage 2 children and adults (mITT population)

Test	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
1 Symptom score >=12	14	85	11	249	0.56 [0.35, 0.76]	0.75 [0.70, 0.79]
2 Symptom score >=10	18	110	7	224	0.72 [0.51, 0.88]	0.67 [0.62, 0.72]
3 Trypanosomes in CSF	21	177	4	156	0.84 [0.64, 0.95]	0.47 [0.41, 0.52]
4 >100 WBC in CSF	22	165	3	169	0.88 [0.69, 0.97]	0.51 [0.45, 0.56]
5 >400 WBC in CSF	13	72	12	262	0.52 [0.31, 0.72]	0.78 [0.74, 0.83]

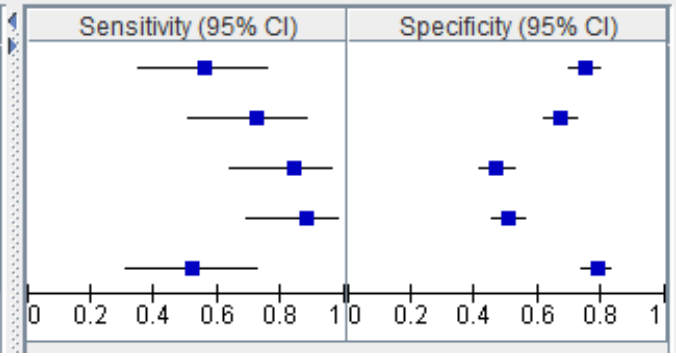
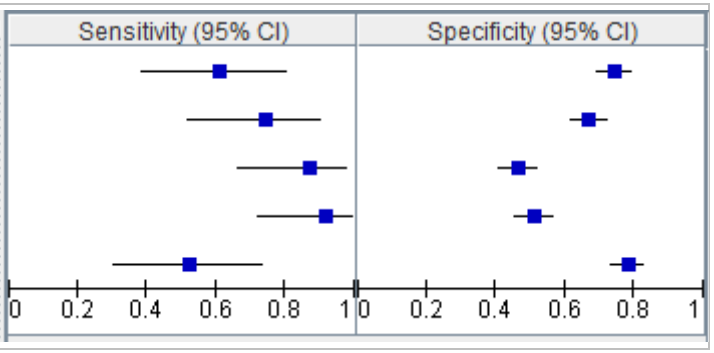


Figure 25. Sensitivity and specificity: early & late stage 2 children and adults (EP population)

Test	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
1 Symptom score >=12	14	85	9	246	0.61 [0.39, 0.80]	0.74 [0.69, 0.79]
2 Symptom score >=10	17	110	6	221	0.74 [0.52, 0.90]	0.67 [0.61, 0.72]
3 Trypanosomes in CSF	20	177	3	153	0.87 [0.66, 0.97]	0.46 [0.41, 0.52]
4 >100 WBC in CSF	21	163	2	168	0.91 [0.72, 0.99]	0.51 [0.45, 0.56]
5 >400 WBC in CSF	12	72	11	259	0.52 [0.31, 0.73]	0.78 [0.73, 0.83]



5 Summary of results

All results presented below are based on EP analysis.

5.1. Symptom score ≥12

Adults with late stage-2 HAT

Adults with late stage-2 HAT and with a symptom score ≥12 at entry who were treated with fexinidazole experienced a higher rate a treatment failure at 18 months, compared to those who were treated with NECT [RR 14.34 (95% CI 0.88 to 235.00); 1 RCT, N = 134] (very low certainty evidence).

For adults with late stage-2 HAT and with a symptom score <12 at entry there was little or no difference in treatment failure at 18 months between those who were treated with fexinidazole and those who were treated with NECT [RR 3.86 (95% CI 0.49 to 30.32); 1 RTC, N = 249] (very low certainty evidence).

The confidence intervals for the two subgroups overlap considerably, the test for subgroup differences is not significant ($Chi^2 = 0.55$, P = 0.46), and $I^2 = 0\%$.

For the fexinidazole group, the ≥12 threshold had a sensitivity of 63.64% and specificity of 67.80%.

Children and adults with early and late second stage HAT (all treated with fexinidazole)

Pooled results from 2 single arm trials and the intervention arm of 1 RCT showed that rates of treatment failure were higher in people with threshold ≥12 (n = 99) than in those with threshold <12 (n = 255) (141 *vs* 35 failures per 1000) (very low certainty evidence).

The ≥12 threshold had a sensitivity of 60.87% and a specificity of 74.32%.

Children and adults with any stage HAT (all treated with fexinidazole)

Pooled results from 2 single arm trials and the intervention arm of 1 RCT showed that rates of treatment failure were higher in people with threshold ≥12 (n = 100) than in those with threshold <12 (n = 517) (140 *vs* 20 failures per 1000) (very low certainty evidence).

The ≥12 threshold had a sensitivity of 58.33% and a specificity of 85.27%.

5.2. Symptom score of ≥10

Adults with late stage-2 HAT

Adults with late stage-2 HAT and with a symptom score ≥10 at entry who were treated with fexinidazole experienced a higher rate a treatment failure at 18 months, compared to those who were treated with NECT [RR 8.65 (95% CI 1.18 to 63.37); 1 RTC, N = 166] (very low certainty evidence).

For adults with late stage-2 HAT and with a symptom score <10 at entry there was little or no difference in treatment failure at 18 months between those who were treated with fexinidazole and those who were treated with NECT [RR 5.17 (95% CI 0.29 to 92.16); 1 RTC, N = 217] (very low certainty evidence).

The confidence intervals for the two subgroups overlap considerably, the test for subgroup differences is not significant ($Chi^2 = 0.08$, P = 0.77), and $I^2 = 0\%$.

For the fexinidazole group, the ≥10 threshold had a sensitivity of 77.27% and specificity of 60.59%.

Children and adults with early and late second stage HAT (all treated with fexinidazole)

Pooled results from 2 single arm trials and the intervention arm of 1 RCT showed that rates of treatment failure were higher in people with threshold ≥10 (n = 127) than in those with threshold <10 (n = 227) (134 *vs* 26 failures per 1000) (very low certainty evidence).

The ≥10 threshold had a sensitivity of 73.91% and a specificity of 66.77%.

Children and adults with any stage HAT (all treated with fexinidazole)

Pooled results from 2 single arm trials and the intervention arm of 1 RCT showed that rates of treatment failure were higher in people with threshold ≥10 (n = 135) than in those with threshold <10 (n = 473) (126 *vs* 15 failures per 1000) (very low certainty evidence).

The ≥10 threshold had a sensitivity of 70.83% and a specificity of 79.79%.

5.3. Presence of trypanosomes in CSF

Adults with late stage-2 HAT

Adults with late stage-2 HAT and presence of trypanosomes is CSF at entry who were treated with fexinidazole experienced a higher rate a treatment failure at 18 months, compared to those who were treated with NECT [RR 9.61 (95% CI 1.31 to 70.61); 1 RTC, N = 259] (very low certainty evidence).

For adults with late stage-2 HAT and no presence of trypanosomes is CSF at entry there was little or no difference in treatment failure at 18 months between those who were treated with fexinidazole and those who were treated with NECT [RR 3.17 (95% CI 0.17 to 59.98); 1 RTC, N = 123] (very low certainty evidence).

The confidence intervals for the two subgroups overlap significantly, the test for subgroup differences is not significant ($Chi^2 = 0.37$, P = 0.54), and $I^2 = 0\%$.

For the fexinidazole group, the presence of trypanosomes in CSF at entry showed a sensitivity of 86.36% and specificity of 34.89%.

Children and adults with early and late second stage HAT (all treated with fexinidazole)

Pooled results from 2 single arm trials and the intervention arm of 1 RCT showed that rates of treatment failure were higher in people with presence of trypanosomes in CSF at entry (n = 197) than in those without trypanosomes at entry (n = 156) (102 *vs* 19 failures per 1000) (very low certainty evidence).

The presence of trypanosomes in CSF at entry had a sensitivity of 86.96% and a specificity of 46.36%.

Children and adults with any stage HAT (all treated with fexinidazole)

Pooled results from 2 single arm trials and the intervention arm of 1 RCT showed that rates of treatment failure were higher in people with presence of trypanosomes in CSF at entry (n = 197) than in those without trypanosomes at entry (n = 410) (102 *vs* 10 failures per 1000) (very low certainty evidence).

The presence of trypanosomes in CSF at entry had a sensitivity of 83.33% and a specificity of 69.64%.

5.4. Presence of WBC in CSF at entry >100

Adults with late stage-2 HAT

Adults with late stage-2 HAT and presence of WBC in CSF at entry >100 who were treated with fexinidazole experienced a higher rate a treatment failure at 18 months, compared to those who were treated with NECT [RR 20.24 (95% CI 1.24 to 330.28); 1 RTC, N = 234] (very low certainty evidence).

For adults with late stage-2 HAT and presence of WBC in CSF at entry <100 there was little or no difference in treatment failure at 18 months between those who were treated with fexinidazole and those who were treated with NECT [RR 0.95 (95% CI 0.09 to 10.23); 1 RTC, N = 149] (very low certainty evidence).

The confidence intervals for the two subgroups partially overlap, the test for subgroup differences is not significant (Chi^2 = 2.67, P = 0.10), but heterogeneity is substantial I^2 = 62.6%.

For the fexinidazole group, the presence of WBC in CSF at entry >100 showed a sensitivity of 90.91% and specificity of 41.95%.

Children and adults with early and late second stage HAT (all treated with fexinidazole)

Pooled results from 2 single arm trials and the intervention arm of 1 RCT showed that rates of treatment failure were higher in people with presence of WBC in CSF at entry >100 (n = 184) than in those presence of WBC in CSF at entry ≤100 (n = 170) (114 *vs* 12 failures per 1000) (very low certainty evidence).

The presence of WBC in CSF at entry >100 had a sensitivity of 91.30% and a specificity of 50.76%.

Children and adults with any stage HAT (all treated with fexinidazole)

Pooled results from 2 single arm trials and the intervention arm of 1 RCT showed that rates of treatment failure were higher in people with presence of WBC in CSF at entry >100 (n = 184) than in those presence of WBC in CSF at entry ≤100 (n = 424) (114 *vs* 7 failures per 1000) (very low certainty evidence).

The presence of WBC in CSF at entry >100 had a sensitivity of 87.50% and a specificity of 72.09%.

5.5. Presence of WBC in CSF at entry >400

Adults with late stage-2 HAT

For adults with late stage-2 HAT and presence of WBC in CSF at entry >400 there was little or no difference in treatment failure at 18 months between those who were treated with fexinidazole and those who were treated with NECT [RR 10.76 (95% CI 0.66 to 176.58); 1 RTC, N = 111] (very low certainty evidence).

Likewise, for adults with late stage-2 HAT and presence of WBC in CSF at entry <400 there was little or no difference in treatment failure at 18 months between those who were treated with fexinidazole and those who were treated with NECT [RR 5.11 (95% CI 0.66 to 39.32); 1 RTC, N = 272] (very low certainty evidence).

The confidence intervals for the two subgroups overlap considerably, the test for subgroup differences is not significant (Chi^2 = 0.18, P = 0.67), and I^2 = 0%.

For the fexinidazole group, the presence of WBC in CSF at entry >400 showed a sensitivity of 54.55% and specificity of 72.03%.

Children and adults with early and late second stage HAT (all treated with fexinidazole)

Pooled results from 2 single arm trials and the intervention arm of 1 RCT showed that rates of treatment failure were higher in people with presence of WBC in CSF at entry >400 (n = 84) than in those presence of WBC in CSF at entry ≤400 (n = 270) (143 *vs* 41 failures per 1000) (very low certainty evidence).

The presence of WBC in CSF at entry >400 had a sensitivity of 52.17% and a specificity of 78.25%.

Children and adults with any stage HAT (all treated with fexinidazole)

Pooled results from 2 single arm trials and the intervention arm of 1 RCT showed that rates of treatment failure were higher in people with presence of WBC in CSF at entry >400 (n = 84) than in those presence of WBC in CSF at entry ≤400 (n = 524) (143 *vs* 23 failures per 1000) (very low certainty evidence).

The presence of WBC in CSF at entry >400 had a sensitivity of 50% and a specificity of 87.67%.

6 Limitations

The results presented here derived from a post hoc analysis conducted by the manufacturer at request from the EMA. It is known that post -hoc analysis may lack sufficient statistical power and may be subjected to bias, and this has been reflected in the GRADE ratings.

With regards to the clinical predictors, the results presented here are limited to those stated in the manufacturer's report. It was beyond the remit of this piece of work to conduct a formal systematic review to identify other existing predictor tools (if available).

It is important to note that the clinical signs and symptoms score described in the manufacturer's report has not been validated or tested outside the context of these trials, thus these preliminary results should be interpreted with caution (Hayden 2013).

The narrative results reported here are based on evaluable population analysis only (although calculations were made for ITT and mITT analysis were data was available) and may differ from the results presented in the manufacturer's report.

7 References

Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y. Chapter 10: Analysing and Presenting Results. In: Deeks JJ, Bossuyt PM, Gatsonis C (editors), Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0. The Cochrane Collaboration, 2010. Available from: http://srdta.cochrane.org/

[Unpublished report] CHMP D120 List of outstanding issues fexinidazole (HOE239). EMEA/H/W002320. Response to Agency request relative to clinical efficacy and safety aspects. Sanofi.

Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Annals of internal medicine. 2013 Feb 19;158(4):280-6.

Mesu VKBK, Kalonji WM, Bardonneau C, Mordt OV, Blesson S, Simon F, et al. Oral fexinidazole for late-stage African Trypanosoma brucei gambiense trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial. Lancet. 2018 Jan 13;391(10116):144-154.

Mesu 2018b - unpublished trial report

Mesu 2018c - unpublished trial report