Web Annex A.

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

Commissioned by WHO

Cochrane Response

February 2024

Katrin Probyn, Brian Buckley, Elise Cogo, Hanna Bergman, Jennifer Petkovic, Meghan Sebastianski, Yanina Sguassero, Nicholas Henschke, Gemma Villanueva

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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

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 (accounting for 93% of HAT cases); and, the faster progressing form, caused by *Trypanosoma brucei rhodesiense*, found in eastern and southern Africa. The disease eventually affects the central nervous system, resulting in severe neurological symptoms. Without treatment, death is inevitable.

Rhodesiense HAT is primarily a zoonosis that only occasionally affects humans. Wild and domestic animals are the main reservoir for *T. b. rhodesiense* infection. *Trypanosoma brucei rhodesiense* is endemic in 13 countries but in the last 15 years cases have been declared in 7 countries (1) in eastern and southern Africa. This form represents under 7% of all reported cases of HAT and causes an acute infection. First signs and symptoms are observed a few days or weeks after infection. The disease develops rapidly affecting vital organs and invading the central nervous system.

Rhodesiense HAT is a truly neglected disease that for a long time has not received attention for research and development of diagnostic or therapeutic tools. The current treatments are over 100 years old (suramin, discovered in 1920) and 73 years old (melarsoprol, discovered in 1949). Hence, scientific literature is limited. This is compounded by several factors that play against the realization of studies:

- Very low number of cases (mean of 64 per year in the last 5 years), scattered in different areas, of sporadic occurrence and therefore difficult to predict
- Remoteness of most cases, in areas of difficult access
- Acute disease with rapid evolution and high lethality

Therefore, the strength of the available evidence is expected to be low, which justifies considering a large spectrum of sources.

The update proposed at this time concerns only rhodesiense HAT.

In 2019, WHO issued interim guidelines for treatment of gambiense HAT(2): Gambiense HAT can be treated with oral fexinidazole in first-stage and also non-severe second-stage, with some limitations of age and body weight and following some important specific rules to ensure efficacy. In first-stage, intramuscular pentamidine can be also used, and in second-stage nifurtimox–eflornithine combination therapy (NECT).

For treatment of rhodesiense HAT, the former WHO guidelines from 2013 (3) remain valid to date:

- Rhodesiense HAT must be treated without delay, because it can provoke multi-organ failure and progress to second-stage within a few weeks.
- In first-stage, the treatment is intravenous suramin. Suramin is the currently recommended first line treatment of the first-stage of *T. b. rhodesiense*. It provokes certain undesirable effects, including nephrotoxicity and allergic reactions.
- In second-stage of the disease, melarsoprol is currently recommended as first-line treatment as the only available treatment. Derived from arsenic and has many undesirable side effects, the most dramatic of which is reactive encephalopathy (encephalopathic syndrome) which can be fatal (3% to 10%).

- In particular situations, pentamidine is given either as an initial treatment phase or as full course. This happens when suramin is not rapidly available and starting treatment without delay can be life-saving, and also as alternative treatment when suramin provokes severe adverse events in a given patient.

Fexinidazole, the first all-oral drug for sleeping sickness is currently only indicated as a treatment for gambiense sleeping sickness, in the WHO human African Trypanosomiasis treatment interim guidelines from 2019(2). A non-randomised, single arm trial (https://dndi.org/research-development/portfolio/fexinidazole-tb-rhodesiense/; NCT03974178) assessing the efficacy and safety of Fexinidazole in stage-2 patients with HAT due to trypanosoma brucei rhodesiense has been conducted and results are now available and considered in this evidence review.

2 Objectives

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

The objective of this review is to provide evidence for the GDG to formulate recommendations on the treatment of rhodesiense HAT including fexinidazole and pentamidine. The systematic review is focused on the therapeutic protocols for rhodesiense HAT, considering the introduction of oral fexinidazole, and pentamidine as alternative treatment compared with the current therapies. Fexinidazole is an oral drug is included in 2019 in the WHO Essential medicines list and currently recommended only for the treatment of gambiense Human African Trypanosomiasis in the WHO Human African Trypanosomiasis interim treatment guidelines.

3 Methods

3.1. Review questions

This systematic review was carried out to inform the following questions:

- Should fexinidazole be recommended as first line treatment for first-stage rhodesiense HAT?
- Should pentamidine be recommended as alternative treatment of first-stage rhodesiense HAT in particular circumstances (e.g. to avoid treatment delays if alternative treatments are not available)?
- Should fexinidazole be recommended as first line treatment for second-stage rhodesiense HAT?
- 1. First-stage – fexinidazole vs suramin (current first line)

- 2. First-stage - fexinidazole vs pentamidine (current 2nd line when suramin is not available)
- 3. Second-stage – fexinidazole vs melarsoprol (current first line)

3.2. Inclusion criteria

3.2.1. Population

People with a confirmed or suspected diagnosis of first- or second-stage rhodesiense HAT .

Sub-groups of interest:

- Adults and children
- First-stage and second-stage
- CSF WBC count, if available. The cut-off for severity is <100/uL vs. ≥100/uL)
- Patients excluded from the fexinidazole indication (<6 years or <20 kg body weight; unable to swallow tablets)

Diagnostic criteria:

For this review, we will use diagnosis of rhodesiense HAT as defined by the study authors. The certainty of the evidence may be downgraded, if the diagnostic criteria used in the study differ from the criteria accepted by WHO.

Current WHO guideline recommends the following case definition:

- Confirmed case: disease in an individual with an epidemiological risk for rhodesiense HAT and in whom trypanosomes have been observed microscopically in one or more body fluids;
- Case suspected by serological detection: disease in an individual with an epidemiological risk for rhodesiense HAT in whom anti-trypanosomal antibodies have been detected with a validated serological test but in whom trypanosomes are not observed microscopically in body fluids;
- Case suspected by molecular detection: disease in an individual with an epidemiological risk for rhodesiense HAT in whom trypanosome DNA or RNA has been detected in body fluids but in whom trypanosomes are not observed microscopically in body fluids.

Studies with indirect populations may be considered as supportive information (e.g., studies that evaluate safety in healthy adults)

3.2.2. Interventions

For first-stage disease:

- Fexinidazole, administered orally once daily for 10 days, and accompanied with a meal to achieve sufficient absorption.
- Suramin: currently recommended first line treatment of the first-stage of T. b. rhodesiense (intravenous, test dose of 4–5mg/kg on day 1, followed by five injections of 20 mg/kg every 7 days, but other schedules are possible)

- Pentamidine (given intramuscularly once daily for 7-10 days. Given often when suramin is not readily available, while waiting to obtain it, or also as alternative treatment when suramin presents as problematic for a given patient.

For second-stage disease:

- Fexinidazole, administered orally once daily for 10 days, and accompanied with a meal to achieve sufficient absorption
- Melarsoprol: It is currently recommended as first-line treatment (only available treatment) in rhodesiense HAT (intravenous, lately 2.2 mg/kg per day for 10 days, formerly with different schedules).

Indirect evidence:

Gambiense HAT(g-HAT) is out of the scope of this review. However, we provide the following: the safety data of melarsoprol in g-HAT, taken from the already reviewed and published data by the Cochrane group on chemotherapy for second-stage g-HAT (6) and 2) the safety data of fexinidazole in g-HAT, taken from our previous work conducted in 2018-2019 and the Cochrane systematic review on fexinidazole for second-stage g-HAT(7) and (3) the safety data of pentamidine in g-HAT, taken from the already reviewed and published data by the Cochrane group on chemotherapy for second-stage g-HAT (6). An additional search or full systematic review was no conducted.

3.2.3. Comparison

- Treatments compared to each other
- Different formulations or treatment regimens of the same drug

Given the anticipated limited of evidence, studies with no comparison group were also considered for inclusion.

3.2.4. Outcomes

The following outcomes were included in the review:

Critical outcomes

- Overall mortality (for any reason, including HAT and treatment toxicity) up to 1 month after the last drug administration.
- 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, leucopenia, thrombocytopenia
  - Nephrotoxicity
  - Gastrointestinal symptoms: diarrhoea, nausea and vomiting
  - Skin reactions
  - Infections

- Cardiotoxicity

Important outcomes

- Death likely to be due to r-HAT, up to one month after the last drug administration.
- Death likely to be due to the treatment, up to one month after the last drug administration.
- Relapse during follow up: trypanosomes detected in any body compartment (blood, lymph, or CSF) at any follow-up examination (between 1 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)
- Adherence to treatment
- Withdrawals

3.2.5. Types of studies

All study designs, including case reports.

We included published and unpublished full-text studies, conference abstracts, irrespective of language.

3.3. Search strategy

An electronic search was conducted in April 2023 in the following databases: Medline OVID, Embase OVID, the Cochrane Library and Web of Science. No date, publication status (published, unpublished, in press, and in progress) or language restrictions were used. The searches were kept sensitive to include non-RCTs, and nor miss old studies which are poorly indexed.

In addition, we searched the ClinicalTrials.gov and the WHO Trials Registry.

Unpublished confidential data from the fexinidazole trial was considered as it became available from the WHO in December 2023.

3.4. Selection of studies

Screening was conducted using DistillerSR (5). 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. We checked to ensure that all included studies were independent.

3.5. Data extraction

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 planned to use the Cochrane Risk of Bias tool for RCTs (8).

For observational studies with a control group we planned use the Cochrane Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) (9).

There were no relevant studies in rhodesiense HAT that were either RCTs or observational studies with a relevant control group to be included this review.

We assessed the risk of bias for the included single arm studies (any observational studies with no control group) that report on monotherapies of Fexinidazole, Pentamidine, Suramin and Melarsoprol. We assessed and summarised the following sources of bias: bias due to confounding (we consider the most important confounders to be diagnostic or treatment delay, severity of disease (clinical observation of organs and function affected; CSF WBC count), co-morbidity, age, sex, malnutrition, country and treatment site), selection bias, and bias due to missing data. The results of the quality assessments are summarised and provide an evaluation of the overall quality of the included studies. They also assisted with GRADEing the evidence on an outcome basis.

3.7. Data analysis

There were not enough studies evaluating the same intervention for the same population to enable pair-wise meta-analysis and no relevant comparative data. We have therefore presented data from single-arm studies or studies with irrelevant comparison groups in tables.

3.8. Summarizing and interpreting results

3.8.1. GRADE

We used the GRADE approach to interpret findings and create a 'Summary of findings' table for each PICO following the GRADE handbook (10). The tables provide the effect estimate and the associated certainty of evidence for each outcome of interest. It also allows us to judge the overall certainty of evidence for the PICO question. The Summary of Findings tables were created using GRADEpro (11).

Certainty of evidence starts at high quality, but may be downgraded it to moderate, low or very low for the following reasons: limitations in study design or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision, or publication bias. We did not assess publication bias by testing for asymmetry in a funnel plot because there were less than 10 studies for each outcome.

3.8.2. Evidence to decision framework

This evidence review focussed on the benefits and harms of fexinidazole and pentamidine, suramin and melarsoprol in rhodesiense HAT.

In order to facilitate moving from the empirical evidence to the recommendation during the panel meeting, we aimed to collect information regarding to other contextual factors included in the Evidence to Decision framework (12), although a full systematic review of qualitative studies was not conducted.

This framework includes the following domains:

- Desirable and undesirable effects
- Certainty of the evidence
- Values
- Balance between desirable and undesirable effects
- Resource use
- Equity
- Acceptability
- Feasibility

4 Results

4.1. Results of the search

We retrieved 2032 records (after removal of duplicates) and identified 21 more studies through other sources. We assessed 2053 references. Title and abstract screening eliminated 1690 references and full-text screening eliminated another 254. references. 109 references were included, of which 23 references (21 studies) were single arm studies and 86 were case reports (see Appendix 2 for PRISMA flow diagram).

Studies excluded from full-text screening are listed in Appendix 4 with reasons for exclusion. No relevant ongoing studies were identified.

4.2. Characteristics of included studies

We included one single arm non-randomised trial on fexinidazole in 45 rhodesiense HAT patients (children and adults (Matovu 2023) - DNDI-FEX-07-HAT). 10 of these were stage 1, 35 of these were stage 2 patients. Safety data are only reported for the overall population (see Appendix 5). This trial was carried out in Uganda and Malawi, Lwala Hospital (Uganda) and Rumphi District Hospital (Malawi) from 29 September 2019 (first patient enrolled) to 12 October 2022 (last patient last visit). The final follow-up was at 12 months.

The primary objective of the study was to show that the fatality rate (r-HAT or treatment-related death) at the end of hospitalisation (EoH) in patients with stage 2 r-HAT treated with fexinidazole was smaller than a threshold of unacceptable rate of 8.5%, The rate had been established by study authors in a meta-analysis of Melarsoprol data.

Study treatment was Fexinidazole; formulation: 600 mg tablets administered orally with food.

Dose regimen by body weight:

- Body weight ≥35 kg: 1800 mg (3 x 600 mg tablets), once daily for 4 days (Day 1 to Day 4), followed by 1200 mg (2 x 600 mg tablets), once daily for 6 days (Day 5 to Day 10)
- Body weight ≥20 kg and <35 kg, 1200 mg (2 x 600 mg tablets), once daily for 4 days (Day 1 to Day 4), followed by 600 mg (1 x 600 mg tablets), once daily for 6 days (Day 5 to Day 10)

Of 46 patients screened, 45 were enrolled in the study and treated. The study population included 9 patients aged <12 years (20.0%) and a higher proportion of male than female patients (68.9% versus 31.1%). The median age was 24.0 years, ranging from 7.0 to 69.0 years, and median body mass index (BMI) was 18.7 kg/m^2, ranging from 12.8 to 29.5 kg/m^2.

One female patient was pregnant. Four patients (8.9%) had previously been treated for r-HAT and had a relapse or became re-infected.

All 45 patients presented with trypanosomes in the blood, except 1 patient who only had trypanosomes detected in the CSF. Lymph node aspirate was not performed in any patient. A total of 34 patients had trypanosomes in the CSF and 1 patient was trypanosome-negative in the CSF but had a CSF WBC count >5 cells/µL, making a total of 35 patients (77.8%) with stage 2 r-HAT. The remaining 10 patients (22.2%) were diagnosed with stage 1 r-HAT. At baseline, 42 patients (93.3%) were in altered or bad general health and 11 patients (24.4%) had a Karnofsky score of 50% or 60% (i.e., needing occasional to considerable assistance).

We included 20 single arm studies (reported in 22 papers), see Appendix 3 Summary of included studies reporting on either Suramin, Melarsoprol or Pentamidine.

Studies were conducted in 1950-2018 and consist of retrospective cohort studies, prospective cohort studies, case series and outbreak studies and non- comparative trials. Included studies report on Suramin, Melarsoprol, Pentamidine either as monotherapies or on combined schedules. Some studies report on additional drugs (Prednisolone, Tryparsamide).

Studies were conducted in the United Republic of Tanzania, Mozambique, Zambia, Kenya, Uganda, Malawi, Ethiopia (respectively cases evacuated from these countries in one study (Frean 2018).

Included participants all had rhodesiense HAT, either stage 1 or 2 or the stage was not reported, both children and adults were included in most studies (where the age was reported), one study included children from 0-13 years only (Buyst 1977), one case series reported on adults only (Frean 2018). See details of all included studies in Appendix 3 Summary of included studies)

Additionally, we included 86 case reports on rhodesiense HAT (see appendix 7 Summary of case reports of rhodesiense HAT).

4.2.1. Risk of bias in included single arm studies

The assessed risk of bias items in included studies reporting on monotherapies for Fexinidazole, Suramin, Pentamidine and Melarsorpol are summarised in Appendix 3 (table risk of bias assessment

4.3. Effects of interventions: efficacy and safety

4.3.1. Fexinidazole

Direct evidence

We included evidence from one single arm non-randomised trial on fexinidazole in 45 rhodesiense HAT patients (children and adults (Matovu 2023) - DNDI-FEX-07-HAT) presented separately for stage 1 and stage 2 patients. Of the included 10 stage 1 patients all had treatment success at end of hospitalisation and at 12 months follow up, with no relapsed cases.

Of the 35 stage 2 cases, one died in hospital during treatment, due to acute kidney injury unrelated to treatment or HAT. All remaining were successfully treated. Of the 34 remaining participants one had a relapse (at week 9) and was successfully treated with Melarsoprol.

44 patients fully completed treatment with fexinidazole. Treatment was permanently discontinued in 1 patient due to death during hospitalisation.

All patients took the treatment with a meal (administered within 30 minutes of a meal). Patients who vomited shortly after dosing (within 2 hours of study treatment administration) were to receive the daily dose of fexinidazole again. A total of 6 patients vomited doses within 2 hours after administration and all were re-administered.

In total 24 adverse events were reported: 22 during hospitalisation, two in the FU period. Specific adverse events reported comprised: During hospitalisation: vomiting n=6, Extrapyramidal disorder n=1, Epilepsy n=1, Anaemia n=1',Thrombocytopenia n=1, : Acute kidney injury n=1, Chromaturia n=1, Dysphagia n=1, gastritis n=1, Nausea n=2, , Hypothermia n=1, inflammation n=1, Malaria n=2, Bacteraemia n=1; Sinus tachycardia n=1. During follow up period: pneumonia n=1, urinary tract infection n=1. Among these three were serious adverse events (all in stage 2 patients): 1 during hospitalisation acute kidney injury that lead to death; two in the follow up period: pneumonia and urinary tract infection.

In addition, there is one case report on Fexinidazole in a stage 2 rhodesiense-HAT patient (Helleberg 2023), The patient received 1800 mg once a day for 4 days, followed by 1200 mg once a day for 6 days. He experienced no side-effects and showed no sign of relapse during a 6-month follow-up. The patient is still being regularly monitored.

See single arm data on r-HAT and case reports (see Appendices 5 and 7) for details on outcomes and results.

Indirect evidence

Indirect evidence from an RCT and single arm trials conducted with children and adults with first-stage and second-stage gambiense HAT and healthy adults is presented in Appendix 6. This evidence derives from the WHO interim guidelines for the treatment of gambiense human African trypanosomiasis (6) including safety data on healthy adults.

4.3.2. Suramin

Direct evidence

Six studies (one retrospective cohort study (De Andrade Silva 1957) in 36 stage 1 participants, one study consisting of a retrospective and prospective cohort (Wellde 1989a, Wellde 1989b) in 95 and 152 stage 1 participants, one retrospective cohort in 17 stage 1 participants (Kato 2015), one retrospective cohort in 47 stage 1 participants (McLean 2010), one retrospective cohort in 49 stage 1 participants (Veeken 1989) and one case series in 17 stage 1 participants (Frean 2018) reported on Suramin monotherapy. One additional study reported on Suramin+ Tryparsamide in stage 2 patients (De Andrade Silva 1957). The reported outcomes were overall mortality, death likely due to HAT, treatment success, relapse during follow up, and specific adverse events.

See single arm data on r-HAT and case reports (see Appendices 5 and 7) for details on outcomes and results.

Indirect evidence

No indirect evidence is included for Suramin.

4.3.3. Pentamidine

Direct evidence

One retrospective cohort reported on Pentamidine monotherapy in 46 stage 1 patients (De Andrade Silva 1957), additionally this study also reports on Pentamidine+ Tryparsamide in stage 2 patients. The outcomes reported are overall mortality, treatment success, death likely due to HAT, relapse during follow-up.

See single arm data on r-HAT and case reports (see Appendices 5 and 7) for details on outcomes and results.

Indirect evidence

Indirect evidence from single arm trials and observational studies conducted with children and adults with first-stage g-HAT is presented in Appendix 6. This evidence derives from the WHO interim guidelines for the treatment of gambiense human African trypanosomiasis (2).

4.3.4. Melarsoprol

Direct evidence

We included 7 studies reporting on Melarsoprol monotherapies in different schedules: Apted 1953/ Apted 1957, case series in 33 and 176 stage 2 patients, De Andrade Silva 1954, a case series in 130 stage 2 patients, De Andrade Silva 1957 a retrospective cohort study in 272 stage 2 patients and 34 stage 2 relapsed patients, One prospective cohort in 107 stage 2 patients that received Melarsoprol without Suramin pretreatment (Kuepfer 2011/2012, called IMPAMEL III), and one study (Wellde 1989b reporting on a retrospective cohort in 156 stage 2 patients. All studies included children and adults, or age was not reported. The outcomes reported were overall mortality, relapse during follow-up, treatment success, death likely due to treatment, death likely due to HAT, adverse events Arroz 1987, a case series (stage not reported) reported on adverse events only (encephalopathy) in 183 and 200 included patients with different Melarsoprol regimens. De Andrade Silva additionally reported on 21 stage 2 patients receiving Melarsoprol+ Tryparsamide and on 12 stage 1 patients receiving Melarsoprol.

See single arm data on r-HAT and case reports (Appendices 5 and 7) for details on outcomes and results.

Indirect evidence

Indirect evidence on people with second-stage g-HAT is presented in Appendix 6 – additional analysis. This evidence derives from the Cochrane review on Chemotherapy for second-stage Human African trypanosomiasis (Lutje 2013).

4.3.5. Suramin+Melarsoprol

We included 15 studies reporting on either combined schedules of Suramin and Melarsoprol, on a schedule of Melarsoprol following Suramin or report outcomes for Suramin in stage 1 patients and Melarsoprol in stage 2 patients together. One study additionally reported on Prednisolone in addition to Suramin+Melarsoprol. The included studies were Bales 1989, a retrospective cohort in 46 stage 1 and 2 patients, Buyst 1975 a case series in 231 stage 1 and 2 patients, Fèvre 2008, an outbreak study in 568 stage 1 and 2 patients, Foulkes 1975 a non-randomised trial reporting on 18 stage 2 patients receiving either Suramin+Melarsoprol or additional Prednisolone; Harrison 1997 a case series reporting on 28 stage 2 cases receiving Suramin+Melarsoprol, Kagira 2011 , a retrospective cohort reporting on 31 stage 1 and 2 patients receiving Suramin or Suramin+Melarsoprol, Kato 2015, a retrospective cohort reporting on 257 stage 1+stage 2 patients together and 240 stage 2 patients receiving Suramin+Melarsoprol, Kuepfer 2011/2012 a prospective cohort, reporting on the IMPAMEL III program, on 138 stage 2 cases receiving Suramin followed by Melarsoprol , MacLean 2010 , a retrospective cohort, reporting on 275 stage 1 and 2cases receiving Suramin and Melarsoprol , Matemba 2010, a retrospective cohort reporting on 143 stage 1 and 2 cases receiving Suramin+ Melarsoprol respectively, Veeken 1989, a retrospective cohort reporting on 158 stage 1 and 2 cases receiving either Suramin only (stage 1) or Suramin +Melarsorpol, Wellede 198a reporting on a prospective cohort study in 208 stage 1 and 2 patients receiving Suramin followed by Melarsoprol, Buyst 1977, a case series in 73 children (stage not reported) receiving Suramin followed by Melarsoprol, Hutchinson 1971, a case series, reporting on 220 stage 1 and 2 patients receiving suramin only (stage 1) or Suramin+Melarsoprol (stage 2). Robertson 1963, a case series in 89 patients (stage not reported) receiving Suramin followed by Melarsoprol. Outcomes reported were overall mortality, treatment success, death likely due to treatment, death likely due to HAT, relapse during follow up, adverse events.

See single arm data on r-HAT and case reports (see Appendices 5 and 7) for details of outcomes and results.

4.4. GRADE summary of findings tables

Summary of findings 1. Fexinidazole compared to Suramin for first stage rhodesiense HAT

Summary of findings:

Fexinidazole compared to Suramin for first stage rhodesiense HAT (PICO 1)

Patient or population: first stage rhodesiense HAT (PICO 1)
Setting: rHAT endemic countries
Intervention: Fexinidazole
Comparison: Suramin

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Overall mortality (for any reason, including HAT and treatment toxicity): Death during treatment	<u>Fexinidazole:</u> 1 study reports on overall mortality/death during treatment in children >6 years and adults at end of hospitalisation • **0/10** (Matovu 2023, single-arm trial) <u>Suramin:</u> 5 studies report on overall mortality/death during treatment up to 5 weeks in children and adults • **1/95** (1%) (Wellde 1989a, prospective cohort) • **0/17** (Kato 2015, retrospective cohort) • **2/49** (4%) (Veeken 1989, retrospective cohort) • **4/152** (3%) (Wellde 1989b retrospective cohort) • **1/19** (5%) (Frean 2018, case series)	(6 non-randomised studies)[a]	⨁◯◯◯ Very low[b]

Summary of findings:

Fexinidazole compared to Suramin for first stage rhodesiense HAT (PICO 1)

Patient or population: first stage rhodesiense HAT (PICO 1)
Setting: rHAT endemic countries
Intervention: Fexinidazole
Comparison: Suramin

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Overall mortality (for any reason, including HAT and treatment toxicity)	Fexinidazole: 1 study reports on overall mortality up to 12 months in children >6 years and adults • **0/10** (Matovu 2023, single-arm trial) Suramin: 4 studies report on overall mortality up to 3 years/> 2 years in children and adults • **1/95** (1%) (Wellde 1989a, prospective cohort) • **0/47** (MacLean 2010, retrospective cohort, FU time not reported) • **19/152 (**12.5%) (Wellde 1989b, retrospective cohort) • **7/36** (19%) (De Andrade Silva 1957, retrospective cohort), 12 of 36 (33%) not accounted for with reported outcomes	(5 non-randomised studies)[c]	⨁◯◯◯ Very low[b]
Death likely to be due to rHAT	Fexinidazole: 1 study reports on this outcome in children >6 years and adults, follow-up 12 months • 0/10 (Matovu 2023, single-arm trial) Suramin: 1 study reports on this outcome (age not reported) (follow-up not reported) • **2/36** (6%) (De Andrade Silva 1957, retrospective cohort 12 of 36 (33%) not accounted for with reported outcomes	(2 non-randomised studies)[d]	⨁◯◯◯ Very low[b]
Death likely to be due to the treatment	Fexinidazole: One study reported on death likely due to treatment in children >6 years and adults at 12 months follow-up • **0/10** (Matovu 2023, single-arm trial) Suramin: no studies reported on this outcome	(1 non-randomised study)[e]	⨁◯◯◯ Very low[b]

Summary of findings:

Fexinidazole compared to Suramin for first stage rhodesiense HAT (PICO 1)

Patient or population: first stage rhodesiense HAT (PICO 1)
Setting: rHAT endemic countries
Intervention: Fexinidazole
Comparison: Suramin

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Relapse during follow up: trypanosomes detected in any body compartment (blood, lymph, or CSF) at any follow-up examination	Fexinidazole: 1 study reported on this outcome in children >6 years and adults up to 12 months follow-up • **0/10** (Matovu 2023, single arm trial) Suramin: 3 studies report on this outcome with follow up >2 years or up to 3 years (age not reported) • **32/95** (34%) (Wellde 1989a, prospective cohort) • **4/36** (11%) (De Andrade Silva 1957, retrospective cohort), 12 of 36 (33%) not accounted for with reported outcomes • **30/152** (20%) (Wellde 1989b, retrospective cohort) Comment: De Andrade Silva 1957: One of the patients with CSF relapse had 8 cells/uL at baseline.	(4 non-randomised studies)[f]	⨁◯◯◯ Very low[b]
Treatment success: alive, no trypanosomes, no rescue medication, CSF WBC count below threshold follow-up: 30 days	Fexinidazole: 1 study reported on this outcome in children >6 years and adults at end of hospitalization • **10/10** (100%) (Matovu 2023, single-arm trial) Suramin: 1 study reported on this outcome in adults at 30 days follow-up: • **18/19** (95%) (Frean 2018, case series)	(2 non-randomised studies)[g]	⨁◯◯◯ Very low[b]

Summary of findings:

Fexinidazole compared to Suramin for first stage rhodesiense HAT (PICO 1)

Patient or population: first stage rhodesiense HAT (PICO 1)
Setting: rHAT endemic countries
Intervention: Fexinidazole
Comparison: Suramin

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Treatment success: alive, no trypanosomes, no rescue medication, CSF WBC count below threshold follow-up: range 6 to 12 months	Fexinidazole: 1 study reports on this outcome in children >6 years and adults at 12 months follow-up • **10/10** (100%) (Matovu 2023, single-arm trial) Suramin: 1 study reports on this outcome (age not reported) • **5/36** (14%) (De Andrade Silva 1957, retrospective cohort), 12 of 36 (33%) not accounted for with reported outcomes	(2 non-randomised studies)[d]	⨁◯◯◯ Very low[b]
Treatment success: alive, no trypanosomes, no rescue medication, CSF WBC count below threshold follow-up: 2 years	Fexinidazole: no studies reported on this outcome Suramin: 1 study reports on this outcome (age not reported) • **8/36** (22%) (De Andrade Silva 1957, retrospective cohort), 12 of 36 (33%) not accounted for with reported outcomes	(2 non-randomised studies)[d]	⨁◯◯◯ Very low[b]
Treatment success: alive, no trypanosomes, no rescue medication, CSF WBC count below threshold follow-up: range 2 to >2 years	Fexinidazole: no studies reported on this outcome Suramin: 3 studies report on this outcome at >2 years or 3 years follow up in children and adults • **62/95** (65%) (Wellde 1989 a, prospective cohort) • **14/36** (39%) (De Andrade Silva 1957, retrospective cohort), 12 of 36 (33%) not accounted for with reported outcomes • **103/152** (68%) (Wellde 1989b, retrospective cohort)	(3 non-randomised studies)[f]	⨁◯◯◯ Very low[b]
Serious adverse events	Fexinidazole: 1 study reports on SAE up to 12 months follow up in children >6 years and adults • **0/10** (Matovu 2023, single-arm trial) Suramin: No studies reported on this outcome	(1 non-randomised study)[e]	⨁◯◯◯ Very low[b]

Adverse events	Fexinidazole: 1 study reported on overall adverse events in the total study population (n=45 stage 1 and 2 patients) *Indirect evidence for stage 1 patients: reported only for overall study population:* at 12 months follow-up • 24/45 (53%) 24 adverse events (n=22 during hospitalisation, and n=2 in the follow-up period). During hospitalisation, 22 patients (48.9%) had 40 TEAEs . A total of 5 patients (11.1%) reported treatment-related TEAEs. The most frequently reported TEAEs were vomiting (6 patients, 13.3%), hypertension, electrocardiogram U-wave abnormality and hypoalbuminemia (each in 3 patients, 6.7%), and nausea, electrocardiogram QT prolonged, and malaria (each in 2 patients, 4.4%). Specific AEs: • 2/45 Nervous system disorders • 2/45 Blood and lymphatic system disorders (anaemia, Thrombocytopenia) • 2/45 Renal and urinary disorders • 10/45 Gastrointestinal disorders • 2/45 General and administration site conditions • 5/45 Infections and infestations • 1/45 Cardiac disorders There were no TEAEs leading to treatment discontinuation. Suramin: 2 studies reported on specific adverse events up to 30 days follow-up • **10/95** (11%) **Rigour and chills** (Wellde 1989 a, prospective cohort) • **2/95** (2%) **Rash and urticaria** (Wellde 1989 a, prospective cohort) • **1/19** (5%) **Myocarditis** (Frean 2018, case series)	(3 non-randomised studies)[h]	⨁◯◯◯ Very low[b]
Adherence to treatment	Fexinidazole: 1 study reported on this outcome in children >6 years and adults • 10/10 (Matovu 2023, single-arm trial) "All patients received their treatment under hospitalisation. Fexinidazole was to be administered within 30 minutes of a meal. A study nurse monitored study treatment intake to make sure that the patients had eaten sufficiently (a meal equivalent to a dose of Plumpy'Nut; if not, the	(1 non-randomised study)[e]	⨁◯◯◯ Very low[b]

Summary of findings:

Fexinidazole compared to Suramin for first stage rhodesiense HAT (PICO 1)

Patient or population: first stage rhodesiense HAT (PICO 1)
Setting: rHAT endemic countries
Intervention: Fexinidazole
Comparison: Suramin

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
	patient was to be provided with a bag of Plumpy'Nut) and fexinidazole was swallowed. All 10 patients fully completed treatment with fexinidazole. All patients took the treatment with a meal. Of the total patient group of 45 stage 1 and 2 participants: Patients who vomited shortly after dosing (within 2 hours of study treatment administration) were to receive the daily dose of fexinidazole again. A total of 6 patients vomited doses within 2 hours after administration and all were re-administered". Suramin: No studies reported on this outcome		
Withdrawals	Fexinidazole: 1 study reported on this outcome in children >6 years and adults (Matovu 2023, single-arm trial) • All patients completed the treatment, and all follow up visits (wk 9, 6,12 months) Suramin: no studies reported on this outcome	(1 non-randomised study)[e]	⨁◯◯◯ Very low[b]

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

Explanations
a. Matovu 2023, Wellde 1989a, Kato 2015, Veeken 1989, Wellde 1989a, prospective cohort, Wellde 1989, Frean 2018
b. downgraded one more level for study design: single arm non-comparative study
c. Matovu 2023, Wellde 1989a, MacLean 2010, Wellde 1989b, De Andrade Silva 1957
d. Matovu 2023, De Andrade Silva 1957
e. Matovu 2023
f. Matovu 2023, Wellde 1989a, De Andrade Silva 1957, Wellde 1989b
g. Matovu 2023, Frean 2018
h. Matovu 2023, Wellde 1989 a, Frean 2018

Summary of findings 2. Fexinidazole compared melarsoprol for second stage rhodesiense HAT

Summary of findings:

Fexinidazole compared to Melarsoprol for second stage rhodesiense HAT (PICO 2)

Patient or population: second stage rhodesiense HAT (PICO 2)
Setting: rHAT endemic countries
Intervention: Fexinidazole
Comparison: Melarsoprol

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Overall mortality (for any reason) during treatment	Fexinidazole 1 study • **1/35** (3%) (Matovu 2023, single arm trial, children >6 years and adults). One patient died during treatment due to reasons unrelated to treatment or HAT Melarsoprol 2 studies • **9/107** (8%) (Kuepfer 2011/2012, prospective cohort, children and adults). During treatment, 1 death was due to advanced HAT and 8 deaths due to encephalopathic syndrome. • **9/156** (6%) (Wellde 1989b, retrospective cohort, children and adults)	(3 non-randomised studies)[a]	⨁◯◯◯ Very low[b]
Overall mortality (for any reason) follow-up: 12 months	Fexinidazole 1 study • **1/35** (3%) at 12 months follow-up (1 single-arm trial; children >6 years and adults). One patient died during treatment due to reasons unrelated to treatment or HAT Melarsoprol 2 studies • **12/107** (11%) at 12 months (Kuepfer 2011/2012, prospective cohort, children and adults). During treatment, 1 death was due to advanced HAT and 8 deaths due to encephalopathic syndrome. During follow up, 1 death at 9 months was not related to HAT, and 2 others for unknown/unreported reasons. • **3/33** (9%) at 12 months (Apted 1953, case series, age not reported) (2/33 at 6 months)	(3 non-randomised studies)[c]	⨁◯◯◯ Very low[b]

Summary of findings:

Fexinidazole compared to Melarsoprol for second stage rhodesiense HAT (PICO 2)

Patient or population: second stage rhodesiense HAT (PICO 2)
Setting: rHAT endemic countries
Intervention: Fexinidazole
Comparison: Melarsoprol

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Overall mortality (for any reason) follow-up: 4 years	Fexinidazole No studies reported on this outcome Melarsoprol 5 studies • **19/156** at 3 years (12%) (Wellde 1989b retrospective cohort, children and adults) • **5/26** at 30-48 months (19%) (Apted 1953, case series, age not reported), available cases, 7 of 33 LTFU · • **21/136** at 6 months to 4 years (15%) (Apted 1957, case series, age not reported) available cases, 40 of 176 LTFU • **19/130** at 6-16 months (15%) (de Andrade Silva 1954, case series, age not reported), available cases, 61(46%) of 130 not accounted for with reported outcomes • **44/272** at >2 years (16%) (de Andrade Silva 1957, retrospective cohort, age not reported) 61of 272 (22%) not accounted for with reported outcomes	(5 non-randomised studies)[d]	⨁◯◯◯ Very low[b]
Death likely to be due to rHAT	Fexinidazole 1 study • **0/35** (1 single-arm trial, children >6 years and adults) at 12 months follow-up Melarsoprol 3 studies • **1/107** (1%) at 10 days (Kuepfer 2011/2012, prospective cohort, children and adults) • **14/136** (10%) at 6 months to 4 years (Apted 1957, case series, age not reported) available cases, 40 of 176 LTFU • **7/272** (3%) follow-up not reported (De Andrade Silva 1957, retrospective cohort, age not reported) 61 of 272 (22%) not accounted for with reported outcomes	(4 non-randomised studies)[e]	⨁◯◯◯ Very low[b]

Summary of findings:

Fexinidazole compared to Melarsoprol for second stage rhodesiense HAT (PICO 2)

Patient or population: second stage rhodesiense HAT (PICO 2)
Setting: rHAT endemic countries
Intervention: Fexinidazole
Comparison: Melarsoprol

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Death likely to be due to the treatment	Fexinidazole 1 study • **0/35** (1 single-arm trial, children >6 years and adults) at 12 months follow-up Melarsoprol 4 studies • **8/107** (7%) at 10 days (Kuepfer 2011/2012, prospective cohort, children and adults) • **4/136** (3%) at 6 weeks (Apted 1957, case series, age not reported) available cases, 40 of 176 LTFU • **11/130** (8%) at 6-16 months (De Andrade Silva 1954, case series, age not reported) 61 of 130 (46%) not accounted for with reported outcomes • **5/183** (3%) **and 7/200** (4%) after last dose (Arroz1987, case series, age not reported, stage not reported)	(5 non-randomised studies)[f]	⨁◯◯◯ Very low[b]

Summary of findings:

Fexinidazole compared to Melarsoprol for second stage rhodesiense HAT (PICO 2)

Patient or population: second stage rhodesiense HAT (PICO 2)
Setting: rHAT endemic countries
Intervention: Fexinidazole
Comparison: Melarsoprol

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Relapse during follow up: trypanosomes detected in any body compartment (blood, lymph, or CSF) at any follow-up examination follow-up: 12 months	Fexinidazole 1 study • **1/34** (3%) (available cases), (single-arm trial, children >6 years and adults) at 12 months follow-up. One patient relapsed during follow up. The relapse was detected at W9, when the patient was trypanosome-positive and received rescue treatment the next day (successful recovery). Melarsoprol 2 studies • **1/107** at 12 months (1%) (Kuepfer 2011/2012, prospective cohort, children and adults) • **6/33** at 12 months (18%) (Apted 1953, case series, age not reported) (3/33 at 6 months)	(3 non-randomised studies)[c]	⨁◯◯◯ Very low[b]
Relapse during follow up: trypanosomes detected in any body compartment (blood, lymph, or CSF) at any follow-up examination follow-up: 4 years	Fexinidazole no studies reported on this outcome Melarsoprol 4 studies • **1/26** (4%) status at last follow-up (Apted 1953, case series, age not reported) 7/26 (27%) relapsed during FU period, available cases, 7 of 33 LTFU • **13/136** (10%) at 6 months to 4 years (Apted 1957, case series, age not reported), available cases, 40 of 176 LTFU • **8/272** (3%) at >2 years (De Andrade Silva 1957, retrospective cohort, age not reported), (61 of 272 (22%) not accounted for with reported outcomes • **6/156** (4%) at >2 years (Wellde 1989b, retrospective cohort, children and adults)	(4 non-randomised studies)[g]	⨁◯◯◯ Very low[b]

Summary of findings:

Fexinidazole compared to Melarsoprol for second stage rhodesiense HAT (PICO 2)

Patient or population: second stage rhodesiense HAT (PICO 2)
Setting: rHAT endemic countries
Intervention: Fexinidazole
Comparison: Melarsoprol

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Treatment success: alive, no trypanosomes, no rescue medication, CSF WBC count below threshold/ End of treatment/hospitalisation	Fexinidazole 1study • **34/35** (97%) at end of hospitalization (Matovu 2023, single arm trial, children >6 years and adults) Melarsoprol 1 study • **98/107** (92%) at end of hospitalization (Kuepfer 2011/2012, prospective cohort, children and adults)	(2 non-randomised studies)[h]	⨁◯◯◯ Very low[b]
Treatment success: alive, no trypanosomes, no rescue medication, CSF WBC count below threshold follow-up: 12 months	Fexinidazole 1 study • **33/35** (94%) at 12 months (Matovu 2023, single arm trial, children> 6 years and adults) Melarsoprol 2 studies • **94/107** (88%) at 12 months (Kuepfer 2011/2012, prospective cohort, children and adults) • **36/272** (13%) at 6-12 months (De Andrade Silva 1957, retrospective cohort, age not reported), (61 of 272 (22%) not accounted for with reported outcomes	(3 non-randomised studies)[i]	⨁◯◯◯ Very low[b]
Treatment success: alive, no trypanosomes, no rescue medication, CSF WBC count below threshold follow-up: 2 years	Fexinidazole no studies reported on this outcome Melarsoprol 2 studies • **50/130** (39%) at 6-16 months (De Andrade Silva 1954, case series, age not reported), 61 of 130 (46%) not accounted for with reported outcomes • **97/272** (36%) at 2 years (De Andrade Silve 1957, retrospective cohort, age not reported), 61 of 272 (22%) not accounted for with reported outcomes	(2 non-randomised studies)[j]	⨁◯◯◯ Very low[b]

Summary of findings:

Fexinidazole compared to Melarsoprol for second stage rhodesiense HAT (PICO 2)

Patient or population: second stage rhodesiense HAT (PICO 2)
Setting: rHAT endemic countries
Intervention: Fexinidazole
Comparison: Melarsoprol

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Treatment success: alive, no trypanosomes, no rescue medication, CSF WBC count below threshold follow-up: 4 years	Fexinidazole no studies reported on this outcome Melarsoprol 4 studies • **131/156** (84%) at 3 years (Wellde 1889b, retrospective cohort, children and adults) • **160/272** (59%) at >2years (De Andade Silva1957 , retrospective cohort, age not reported) 61 of 272(22%) not accounted for with reported outcomes • **102/136** (76%) at 6 months to 4 years (Apted 1957, case series, children and adults), available cases, 40 of 176 (23%) LTFU • **20/26** (77%) at 2.5-4 years (Apted 1953, case series, age not reported), available cases, 7 of 33 (21%) LTFU	(4 non-randomised studies)[g]	⨁◯◯◯ Very low[b]

Summary of findings:

Fexinidazole compared to Melarsoprol for second stage rhodesiense HAT (PICO 2)

Patient or population: second stage rhodesiense HAT (PICO 2)
Setting: rHAT endemic countries
Intervention: Fexinidazole
Comparison: Melarsoprol

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Serious adverse events	Fexinidazole 1 study • **3/35** at 12 months (9%) (1 single-arm trial single arm trial, children >6 years and adults) One during hospitalisation (acute kidney injury) and two in the follow-up period: pneumonia n=1, urinary tract infection n=1) Melarsoprol 1 study • **27/107** at 34 days (25%) (Kuepfer 2011/2012, prospective cohort, children and adults). 33.3% (9/27) of the SAEs were fatal and included one death due to advanced HAT and 8 deaths due to ES. 14.8% (4/27) SAEs were life threatening events (non-fatal ES). 22.2% (6/27) SAEs were based on prolonged hospitalizations of patients who were kept for observation due to general weakness. 29.6% (8/27) SAEs were medical events and included treatment of malaria, severe vomiting, severe headache, cardiac arrhythmia and psychosis at end of treatment.	(2 non-randomised studies)[h]	⨁◯◯◯ Very low[b]

Adverse events follow-up: 34 days	Fexinidazole 1 study *Indirect evidence for stage 1 patients: reported only for overall study population n=45 stage 1 and 2 patients:* at 12 months follow-up • 24/45 (53%) 24 adverse events (n=22 during hospitalisation, and n=2 in the follow-up period). During hospitalisation, 22 patients (48.9%) had 40 TEAEs . A total of 5 patients (11.1%) reported treatment-related TEAEs. The most frequently reported TEAEs were vomiting (6 patients, 13.3%), hypertension, electrocardiogram U-wave abnormality and hypoalbuminemia (each in 3 patients, 6.7%), and nausea, electrocardiogram QT prolonged, and malaria (each in 2 patients, 4.4%). Specific AEs: • 2/45 Nervous system disorders • 2/45 Blood and lymphatic system disorders (anaemia, Thrombocytopenia) • 2/45 Renal and urinary disorders • 10/45 Gastrointestinal disorders • 2/45 General and administration site conditions • 5/45 Infections and infestations • 1/45 Cardiac disorders There were no TEAEs leading to treatment discontinuation. Melarsoprol 2 studies • **65.5%** had adverse event (Kuepfer 2011/2012, prospective cohort) Specific AEs: • **8/107** (7%) Encephalopathic syndrome during treatment (Kuepfer 2011/2012, prospective cohort) • **11/183** (6%) Encephalopathy after last dose (Arroz 1987, case series) • **10/200** (5%) Encephalopathy after last dose (Arroz 1987, case series) Comment: Kuepfer 2011/2012: “35.5% the patients had an event-free treatment.” [27/107 had an SAE. Other adverse events reported included febrile reactions (37%), headache (22%), vomiting (13%), dizziness (9%), skin reactions (6.5%), nausea (5.6%) and diarrhoea (4%)]	(3 non-randomised studies)[k]	⨁◯◯◯ Very low[b]

Summary of findings:

Fexinidazole compared to Melarsoprol for second stage rhodesiense HAT (PICO 2)

Patient or population: second stage rhodesiense HAT (PICO 2)
Setting: rHAT endemic countries
Intervention: Fexinidazole
Comparison: Melarsoprol

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Adherence to treatment	Fexinidazole "All patients received their treatment under hospitalisation. Fexinidazole was to be administered within 30 minutes of a meal. A study nurse monitored study treatment intake to make sure that the patients had eaten sufficiently (a meal equivalent to a dose of Plumpy'Nut; if not, the patient was to be provided with a bag of Plumpy'Nut) and fexinidazole was swallowed. 34 patients fully completed treatment with fexinidazole. Treatment was permanently discontinued in 1 patient due to death during hospitalisation. The death was unrelated to r-HAT and/or study treatment). For this patient, treatment duration was 7 days. All patients took the treatment with a meal. Of the total patient group of 45 stage 1 and 2 participants: Patients who vomited shortly after dosing (within 2 hours of study treatment administration) were to receive the daily dose of fexinidazole again. A total of 6 patients vomited doses within 2 hours after administration and all were re-administered" Melarsoprol No studies reported on this outcome	(1 non-randomised study)[l]	⨁◯◯◯ Very low[b]
Withdrawals	Fexinidazole All 34 patients that finished the treatment course could be followed up at all follow up visits (wk 9,6, 12 months) Melarsoprol No studies reported on this outcome.	(1 non-randomised study)[l]	⨁◯◯◯ Very low[b]

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

Explanations
a. Kuepfer 2011/2012, Wellde 1989b
b. downgraded one more level for study design: single arm non-comparative study
c. Matovu 2023, Kuepfer 2011/2012, Apted 1953
d. Wellde 1989b, Apted 1953, Apted 1957, de Andrade Silva 1954, de Andrade Silva 1957
e. Matovu 2023, Apted 1957, De Andrade Silva 1957, Kuepfer 2011/2012
f. Matovu 2023, Kuepfer 2011/2012, Apted 1957, De Andrade Silva 1954, Arroz 1987
g. Wellde 1989b, Apted 1953, Apted 1957, de Andrade Silva 1957
h. Matovu 2023, Kuepfer 2011/2012
i. Matovu 2023, Kuepfer 2011/2012, De Andrade Silva 1957
j. de Andrade Silva 1954, de Andrade Silva 1957
k. Matovu, 2023, Kuepfer 2011/2012, Arroz 1987
l. Matovu 2023

Summary of findings 3. Pentamidine compared to delayed treatment for first stage rhodesiense HAT

Summary of findings:

Pentamidine compared to delayed treatment for first stage rhodesiense HAT (PICO 3)

Patient or population: first stage rhodesiense HAT (PICO 3)
Setting: rHAT endemic countries
Intervention: Pentamidine
Comparison: delayed treatment

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Overall mortality (for any reason, including HAT and treatment toxicity) follow-up: 2 years	• **7/46** (15%) (De Andrade Silva 1957, retrospective cohort) Comment: - 15 of 46 (33%) not accounted for with reported outcomes - Details of those 7 deaths: n=1 TB, n=1 bad condition, n =5 died of unknown reasons at their village, after being followed up at 2 and 6 months post treatment, without signs of disease.	(1 non-randomised study)[a]	⨁◯◯◯ Very low[b]
Death likely to be due to rHAT (follow-up not reported)	• **2/46** (4%) (De Andrade Silva 1957, retrospective cohort) Comment: 15 of 46 (33%) not accounted for with reported outcomes	(1 non-randomised study)[a]	⨁◯◯◯ Very low[b]
Death likely to be due to the treatment	not reported	-	-

Summary of findings:

Pentamidine compared to delayed treatment for first stage rhodesiense HAT (PICO 3)

Patient or population: first stage rhodesiense HAT (PICO 3)
Setting: rHAT endemic countries
Intervention: Pentamidine
Comparison: delayed treatment

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Relapse (follow-up: >2 years)	• **4/46** (9%) (De Andrade Silva 1957, retrospective cohort) (1/46 Parasitological relapse; 3/46 (CSF relapse definite) Comments: - 15 of 46 (33%) not accounted for with reported outcome - One of these cases had 9 cells/uL before treatment (in 2nd stage)	(1 non-randomised study)[a]	⨁◯◯◯ Very low[b]
Treatment success follow-up: range 6 to 12 months	• **7/46** (15%) (De Andrade Silva 1957**,** retrospective cohort) Comment: 15 of 46 (33%) not accounted for with reported outcomes	(1 non-randomised study)[a]	⨁◯◯◯ Very low[b]
Treatment success follow-up: 2 years	• **15/46** (33%) (De Andrade Silva 1957**,** retrospective cohort) Comment: 15 of 46 (33%) not accounted for with reported outcomes	(1 non-randomised study)[a]	⨁◯◯◯ Very low[b]
Treatment success (follow-up: >2 years)	• **21/46** (46%) (De Andrade Silva 1957**,** retrospective cohort) Comment: 15 of 46 (33%) not accounted for with reported outcomes	(1 non-randomised study)[a]	⨁◯◯◯ Very low[b]
Serious adverse events	not reported	-	-
Adverse events	not reported	-	-
Adherence to treatment	not reported	-	-
Withdrawals	not reported	-	-

Summary of findings:

Pentamidine compared to delayed treatment for first stage rhodesiense HAT (PICO 3)

Patient or population: first stage rhodesiense HAT (PICO 3)
Setting: rHAT endemic countries
Intervention: Pentamidine
Comparison: delayed treatment

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)

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

Explanations
a. De Andrade Silva 1957
b. downgraded one more level for study design: single arm non-comparative study

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unpublished trial report

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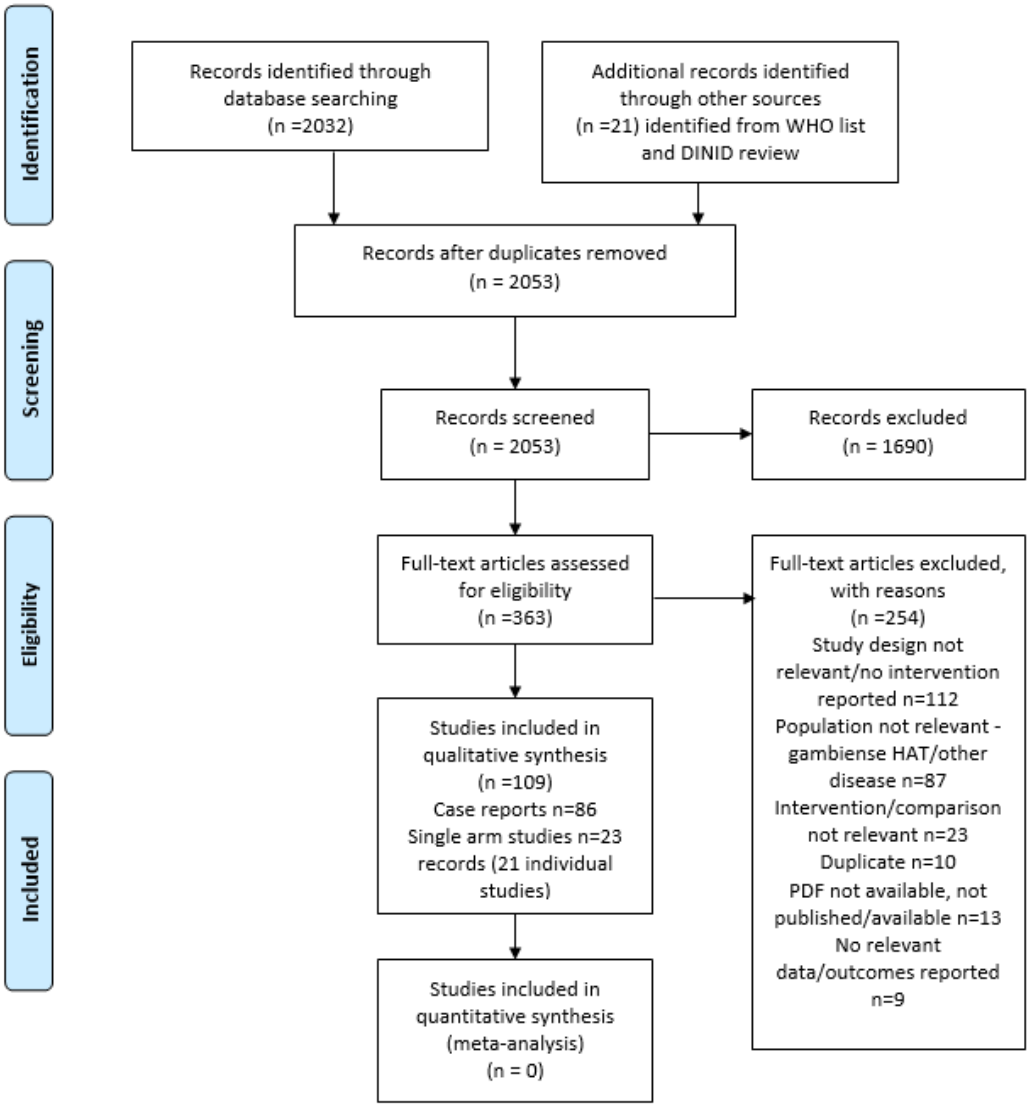
Appendix 1. Search strategy

3 Ovid Databases: Embase Classic+Embase 1947 to 2023 May 25, MEDLINE(R) ALL 1946 to May 25, 2023, EBM Reviews - Cochrane Central Register of Controlled Trials April 2023:

1. Trypanosomiasis, African/
2. Trypanosoma brucei rhodesiense/
3. African trypanosom*.mp.
4. (HAT or Nagana).mp.
5. sleeping sickness*.mp.

6. (rhodesi* adj3 (trypanosom* or brucei or "T. b." or "T.b.")).mp.
7. or/1-6
8. melarsoprol/ or pentamidine/ or suramin/ or Eflornithine/
9. (Fexinidazole or Eflornithine).mp.
10. (Suramin or Pentamidine or Melarsoprol or Lomidine or Diamidine).mp.
11. (Nebupent or Pentacarinat or Pentam or Germanin or Naganin or Naganol or Naphuride or Moranil or moranyl).mp.
12. (Mel B or Melars* or Arsobal or specia or trypamidium or tryparsamide).mp.
13. or/8-12
14. 7 and 13
15. limit 7 to "therapy (maximizes specificity)"
16. 14 or 15
17. exp animals/ not humans/
18. 16 not 17
19. (comment or editorial or newspaper article).pt.
20. 18 not 19
21. African trypanosomiasis/
22. trypanosoma brucei rhodesiense/
23. or/3-6,21-22
24. 13 and 23
25. limit 23 to "therapy (maximizes specificity)"
26. 24 or 25
27. editorial.pt.
28. 26 not 27
29. (animal experiment/ or exp animal/) not (human experiment/ or exp human/)
30. 28 not 29
31. 20 use medall
32. 30 use emczd
33. 14 use cctr
34. 31 or 32 or 33
35. remove duplicates from 34

Appendix 2. PRISMA flowchart



Appendix 3. Summary of included studies and risk of bias

Study characteristics table

Study ID Study design Trial registry Study dates Country/setting	Population (N, Stage) age, sex, included/excluded characteristics)	Intervention (manufacturer) Schedule	Outcomes	Comments Study aim Funding COI
Apted 1953, Apted 1957 Case series Follow-up: up to 4 years 1951-1955 Tanzania, Sleeping Sickness Medical Department, Tanganyika	33 rHAT cases (stage not formally reported, but all advanced disease) and 181 rHAT cases (stage 1 n=5 and stage 2 n=176, confirmed in CSF before treatment) Age and sex not reported	**Mesarsoprol *Mel B* (Dr Friedheim) and *Arsobal* (Specia Laboratories, Paris)** Schedule: 2 series, 2 weeks apart, of 4 daily IV doses of 1.8 mg/kg OR 2 series, 2 weeks apart, of 3 IV daily doses of 3.6 mg/kg **Mesarsoprol *Melarsen oxide/BAL* (Messrs. May and Baker Ltd.), *Mel B* (Dr Friedheim) and ' *Arsobal* (Specia Laboratories, Paris)** Schedule: 4 x 1.8 mg/kg days 1-4 followed by 4 x 1.8 mg/kg days 19-22; OR 3 x 1.8 mg/kg days 1-3 followed by 3 x 3.6 mg/kg days 18-20; OR 1 x 1.8 mg/kg day 1, 2 x 3.6 mg/kg days 2-3 followed by 3 x 3.6 mg/kg days 18-20; OR 3 x 3.6 mg/kg days 1-3; OR 4 x 3.6 mg/kg days 1-4; OR 3 x 2.5 ml days 1-3 followed by 3 ml day 11, 4 ml day	<u>n=33 stage 2 cases</u> Longest FU: 2.5-4 years reported for n=26, 7 lost to final follow up, reasons not reported 5/26 deaths 1/26 relapsed at last FU 20/26 'well' at last FU <u>n=176 Stage 2 cases</u> Longest FU: 6 months reported for n=136, 40 "not traced", timepoint last seen not known 21/136 deaths 4/136 deaths due to treatment 14/136 death due to HAT 13/136 relapsed 102 well at last FU <u>n=5 stage 1 cases:</u> 5/5 well at last FU	Cases of rHAT admitted to a single center in present-day Tanzania Aim: Safety/efficacy of intervention Funding: not reported Conflict of interest: not reported

		12, 5 ml day 13 followed by 3 x 5 ml days 21-23; OR 0.5 ml rising very gradually, not according to any fixed scheme but depending on the patient's condition and response, injections being given daily, on alternate days, or every third day or: A single injection of 3.6 mg./kg. (maximum dose 5 ml.)		
Arroz 1987 Case series Follow-up: a few days after final dose 1959-1985 Mozambique, Tete Provincial Hospital, C.P. 28, Tete, Mozambique	383 rHAT cases (stage not reported) Age and sex not reported	**Melarsoprol** 3 series of 3 x daily progressively increasing IV doses (preceded by 2 or 3 Suramin IV doses and accompanied by corticosteroids) Single series of 4 x daily IV doses 3.6 mg/kg (sometimes preceded by Suramin, and sometimes with Tryparsamide)	Outcomes reported for N=200 and n=183 for two different melarsoprol regimens separately Follow up: A few days after last dose Reports on encephalopathy due to melarsoprol and resulting deaths (treatment related deaths only. Treatment success, relapses and overall mortality not reported LTFU not reported	Case series from a single centre spanning two different treatment regimens. Aim: Safety/efficacy of intervention Funding: not reported Conflict of interest: not reported
Bales 1988 Retrospective cohort Follow-up: not reported November 1983- not reported Kenya, Human Treatment Facility, Kenya Trypanosomiasis Research Institute	46 rHAT cases (stage 1 and 2 classified with CSF examination) Age: not reported Sex: 41.3% female, 58.7% male	**Suramin+ Melarsoprol** (manufacturer not reported) Schedule: not reported, treatment not fully described	Follow up time not reported 5/46 deaths (2 due to treatment) 3/46 relapses Treatment success not reported as outcome	Comment: Abstract only; Forty-six cases of human African trypanosomiasis (Rhodesian type) treated since November 1983 at the Human Treatment Facility of the Kenya Trypanosomiasis Research Institute (KETRI) at Alupe,

(KETRI), Alupe, Kenya				Kenya, are reviewed. Aim: Safety/efficacy of intervention Funding: not reported Conflict of interest: not reported
Buyst 1975 Case series Follow-up: 6-18 months April 1972 - August 1973 Zambia, Isoka District Hospital, Muchinga Province, Zambia	229 new rHAT cases and 2 suramin relapse cases (CSF leucocyte counts in 214 of 231 patients showed "many of them to be in a very advanced stage of the disease") Age: 190 adults, 41 children Sex: Adults: 51% male 49% female,; children unknown All included patients also received chloroquine/proguanil malaria treatment	**Melarsoprol after preliminary Suramin** (manufacturer not reported) Schedule: Days 1-5 = Suramin: Day 1 1/4 full dose, Day 3 1/2, Day 5 full dose. Days 7-36 = Melarsoprol: Day 7 1/10 full dose, Day 8 2/10, Day 9 3/10, Day 16 4/10, Days 17&18 5/10, Day 25 5-6/10, Day 26 7-8/10, Day 27 9/10, Days 34, 35& 36 full dose. Full doses: Suramin = 20 mg per Kg body weight (maximum 1 g); Melarsoprol = 3.6 mg per Kg body weight or 0.1 ml of a 3.6% solution per kg (maximum 180 mg or 5 ml).	Reports outcomes on n=231 13 of originally 244 patients were excluded: 3 who discharged themselves before treatment completion, 1 who died before commencement, and 9 because of different treatment scheme Follow-up: 4 days after treatment completion: 14/231 death 3/231 death due to HAT 7/231 death due to treatment Relapses and treatment successes not reported LTFU not reported Adverse events reported for 36 days post treatment: 12/231 CNS reactions 62/231 Diarrhoea	New and relapse cases admitted to a single hospital between April 1972 and August 1973. Aim: Safety/efficacy of intervention Funding: not reported Conflict of interest: not reported
Buyst 1977 Case series Follow-up: 7 weeks August 1971-July 1974 Zambia, Isoka District Hospital,	73 children with rHAT (stage not reported) Of the 64 participants diagnosed at hospital 64.1% had trypanosomes in CSF Of the 64 participants diagnosed at hospital	**Preliminary Suramin followed by Melarsoprol** (manufacturer not reported) Schedule: 4 interrupted 3-day courses with gradually	N=78, 5 lost to follow-up/ excluded, 73 analysed: 3 lost to follow up reported as self-discharge before commencement (n=1) or completion (n=1) of treatment, died before commencement	Comment: Series of child cases diagnosed over 3 years Aim: Safety/efficacy of intervention

Luangwa valley, Muchinga Province, Zambia	64.1% had trypanosomes in CSF Age 0-13 years	increasing doses over 36 days, calculated according to weight	(n=1), no reason reported (n=2) Follow up 7 weeks Reports on deaths, deaths due to treatment, and death due to HAT 6/73 deaths 1/73 death due to HAT 2/73 deaths due to treatment 3/73 AEs: encephalopathy Treatment success and relapse not reported as outcome	Funding: not reported Conflict of interest: not reported
De Andrade Silva 1954 Case series 6-16 months follow-up 1950-1953 Mozambique, setting not reported	130 rHAt cases (stage 1 and 2) Age and sex not reported	**Melarsoprol** (manufacturer not reported) 3.6 mg/kg; 2 courses x 4 daily IV doses, separated by 7-14 days; 3.6 mg/kg; 1 course x 4 daily IV doses; 3.6 mg/kg; 4 x IV doses 3 days apart. 3 cases also received **suramin or pentamidine + tryparsamide**	Reports on deaths (due to treatment) and treatment success at 6-16 months FU 130 reported as denominator, 61 of 130 not accounted for with reported outcomes, relapse not reported as outcome, LTFU not reported, no reasons reported 19/130 deaths 50/130 treatment success	Comment: Series of mainly grade 2 rHAT cases treated with melarsoprol Aim: Safety/efficacy of intervention Funding: not reported Conflict of interest: not reported
De Andrade Silva 1957 Retrospective cohort Follow-up: >2 years 1942-1955 Mozambique, treatment centre unclear	1346 rHAT cases (stage 1 and 2 classified with CSF examination) Age and sex not reported	<u>Stage 1</u> **Suramin *Antrypol* (Bayer)** Schedule: 3-10 grs, usual dose 1.0=1.5 grs in adults **Pentamidine** (manufacturer not reported) Schedule: From 1 x 26 mg + 7 x 52 mg to 1 x 100 mg + 10 x 200 mg	Reports outcomes for different drug regimens separately Longest FU>2 years, Reports on deaths (overall, due to treatment and HAT), relapses and treatment success <u>Pentamidine Stage 1 cases at >2 years</u> 14 of 46 not accounted for with reported outcome at longest FU(>2 years),	Comment: This paper records our observations in Mozambique and deals with the T. Rhodesiense sleeping sickness from 1942 up to the end of 1955. Aim: Safety/efficacy of intervention Funding: not reported

		Melarsoprol (manufacturer not reported) Schedule: From 1 x 3.6 mg to 3 x 3.6 mg <u>Stage 2</u> **Suramin *Antrypol* (Bayer);+ Tryparsamide** (manufacturer not reported) Schedule: From 1 course of < 20 gms to 4 courses of > 100 gms **Pentamidine+ Tryparsamide** (manufacturer not reported) Schedule: Pentamidine: From 1 x 26 mg + 7 x 52 mg to 1 x 100 mg + 10 x 200 mg. Tryparsamide: From 1 course of < 20 gms to 4 courses of > 100 gms **Melarsoprol** (manufacturer not reported) Schedule: From 3 x 3.6 mg to 4 courses of 4 x 3.6 mg **Melarsoprol + Tryparsamide** (manufacturer not reported) Schedule: Melarsoprol: From 3 x 3.6 mg to 2 courses of 4 x 3.6 mg/3 courses of 3 x 3.6 mg. Tryparsamide: 4 injections, 0.04 g / Kg	LTFU not reported, reasons not reported 7/46 death 21/46 treatment success 4/46 relapses <u>Pentamidine+Trysamide for 2 Stage</u> 56 of 222 not accounted for with reported outcomes in longest FU >2 years, LTFU not reported, no reasons reported. 72/222 deaths 84/222 treatment success 10/222 relapse <u>Melarsoprol Stage 1</u> 11/12 treatment success 1/12 death Melarsoprol Stage 2 60 of 272 not accounted for with reported outcomes, LTFU not reported, reasons not reported 44/272 deaths 160/272 treatment success 8/272 relapse <u>Suramin Stage 1</u> 11 of 36 not accounted for with reported outcomes, LTU not reported, reasons not reported 7/36 deaths 14/36 treatment success 4/36 relapse	Conflict of interest: not reported

		Tryparsamide Relapses: **Melarsoprol** (manufacturer not reported) Schedule: From 1 x 3.6 mg to 3 courses of 4 x 3.6 mg	Suramin + Tryparsamide Stage 2 146 of 737 not accounted for with reported outcomes at longest FU >2 years, LTFU not reported, reasons not reported 313/737 deaths 240/737 treatment success 38/737 relapse Melarsoprol + Tryparsamide 6 of 21 not accounted for for with reported outcomes , LTFU not reported, reasons not reported Reports 1/21 death 0/21 relapses at >2 year 14/21 treatment success at 2 years Melarsoprol in relapsed cases 10 of 34 not accounted for with reported outcomes at >2 years, LTFU not reported, reasons not reported 3/34 deaths 17/34 treatment success 4/34 relapse	
Fèvre 2008 Retrospective cohort	568 rHAT cases (stage 1 and 2 diagnosis in blood and CSF examination)	**Suramin+ Melarsoprol** (manufacturer not reported)	Reports on overall mortality only at approx. 2 months FU	Comment: Outbreak study; We identified the unique characteristics

Follow-up: approx.. 2 months 1999-2005 Uganda, Serere health centre	Age and sex not reported	Schedule: first-stage patients received Suramin and second-stage patients Melarsoprol, details not reported	27/568 LTFU not reported	affecting the burden of rhodesiense HAT such as age, severity, level of under- reporting and duration of hospitalisation, and use field data and empirical estimates of these to model the burden imposed by this and other important diseases in this study population. While we modelled DALYs using standard methods, we also modelled uncertainty of our parameter estimates through a simulation approach. HAT control. Aim: To estimate the burden of rhodesiense sleeping sickness during an outbreak in Serere, eastern Uganda Funding: public/non-profit: Animal Health Programme (AHP) of the UK Department for International Development (DFID) and the World Health Organization (WHO) Conflict of interest: none
Foulkes 1975 Non-randomized trial	36 rHAT cases (stage 2, "all cases were meningoencephlitic")	**Suramin + Melarsoprol + Prednisolone**	Reports on different schedules separately Longest FU at 3 months,	Comment: Every other patient suffering from T. rhodesiense was given prednisolone

Follow-up: 3 months after treatment Study dates not reported Zambia, Mukinge Hospital, Kasempa, Zambia	Age and sex not reported	(manufacturer not reported) Schedule: Suramin 0.25 gm day 1, 0.25 gm day 3, 0.5 gm day 5; Melarsoprol 37.5 cl over 4 weeks (proportionally less for children); Prednisolone 10 mg 3/day from diagnosis until 1 week after end of melarsoprol treatment **Suramin + Melarsoprol** (manufacturer not reported), Schedule: Suramin 0.25 gm day 1, 0.25 gm day 3, 0.5 gm day 5; Melarsoprol 37.5 cl over 4 weeks (proportionally less for children)	<u>Suramin + Melarsoprol + Prednisolone:</u> 2/18 deaths at 4 weeks 9/11 treatment success 7 LTFU at 3 months, no reasons reported. <u>Suramin+Melarsoprol</u> 4/18 death at 4 weeks 8/12 treatment success 6 LTFU at 3 months, no reasons reported	(in addition to rHAT treatment) from the day of diagnosis to one week after the last melarsoprol injection. Aim: Safety/efficacy of intervention Funding: not reported Conflict of interest: not reported
Frean 2018 Case series 2004-2018 Follow-up: 10 months South Africa (evacuated cases originating from Zambia, Malawi, Zimbabwe, Tanzania, and Uganda)	21 adult rHAT cases (stage 1 and 2) Age: 26-69 years Sex: 19% female; 81% male	<u>Stage 1:</u> **Suramin** test dose followed by 5 mg/kg by slow IV infusion on day 1, 10 mg/kg on day 3, and then 20 mg/kg on days 5, 11, 17, 23, and 30, to a maximum cumulative dose of 10 g. <u>Stage 2:</u> **Suramin+Melarsoprol** 2mg/kg intravenously 3 x courses of 3 x daily doses at weekly intervals,	Reports on deaths and treatment success: Suramin stage 1: 18/19 treatment success 1/19 deaths	Aim: Safety/efficacy of intervention Funding: not reported Conflict of interest: not reported

		combined with prednisolone 60 mg daily (25 days).		
Harrison 1997 Case series Follow-up: 45 months 1984-1985 Kenya. The Kenya Trypanosomiasis Research Institute, Alupe, Kenya	28 children and adult rHAT cases (stage 2, all had trypanosomes in the spinal fluid and some symptoms of meningoencephalopathy); Age: 5-73 years Sex: 68% male, 32% female	**Suramin + Melarsoprol** (manufacturer not reported) Initial dosing: suramin on days 1 (5 mg/kg), 2 (10 mg/kg), and 4 (10 mg/kg); followed by IV melarsoprol 3 courses of 3 consecutive daily doses at increasing concentrations, 7 days between courses 1 and 2 and 6 days between 2 and 3 (Day 5 1.8 mg/kg, Day 6 2.16 mg/kg, Day 7 2.52 mg/kg, Day 14 2.52 mg/kg, Day 15 2.88 mg/kg, Day 16 3.24 mg/kg, Day 23 3.6 mg/kg, Day 24 3.6 mg/kg, Day 25 3.6 mg/kg)	Reports on deaths, treatment success and relapse at 2.5-45 months 4 of 28 LTFU, reasons not reported 2/24 death 2/24 relapse 20/24 treatment success 1 of 24 not accounted for with reported outcomes, LTFU to reported, no reasons reported	Aim: Safety/efficacy of intervention Funding: public/non-profit: This work was supported in part by a grant from the United States Army Medical Research and Material Command and by Fitzsimons Army Medical Center. Conflict of interest: not reported
Hutchinson 1971 Case series October 1968 – March 1970 Follow-up: 10 months Ethiopia, Gambela district, Illubabor province, SW Ethiopia	220 rHAT cases (Stage 1 and 2) Age and sex not reported	<u>Stage 1</u> **Suramin** (manufacturer not reported) <u>Stage 2</u> **Suramin + melarsoprol** (manufacturer not reported) Suramin test dose and 5-6 IV injections of 20mg/kg, 5 day intervals after first two doses (on alternate days) Melarsoprol 2 courses of 4 daily injections, courses separated by 1	12 of original 232 not included in mortality extraction because both drugs were not available, so the adequate treatment regimen was not possible. Denominator overall 220, for AEs only reported for n=150, for relapses only reported for n=125 LTFU and reason for missing data not reported 27/220 death 9/150 death due to treatment 5/125 relapses	Comment: Account of the emergence of the disease in Ethiopia For this extraction cases were excluded for whom Suramin and Melarsoprol were not both available (and thus they could not be treated adequately according to the treatment strategy reported). Aim: Safety/efficacy of intervention Funding: Wellcome trust

		week. dose starts at 1.8 mg/kg then works up to full dose of 3.6 mg/kg by dose 3 or 4. Some patients received a 3rd course of melarsoprol, 3 patients received orally	Treatment success not reported as outcome	Conflict of interest: not reported
Kagira 2011 Retrospective cohort Follow-up: 2 months 2000-2009 Kenya. National Sleeping Sickness Referral Hospital (NSSRH) in Alupe, Kenya	31 children and adult rHAT cases (stage 1 and 2 defined according to WHO criteria) Age: 14–57 years Sex: 38.7% female; 41.3% male 100% Malaria co-infected, Helminthiasis 65%, 13% HIV coinfected, 23%Thyphoid, 3% Tuberculosis, 16% UTI	**Suramin+ Melarsoprol** (Manufacturer not reported) Early-stage disease was treated using 5 injections of suramin at a dosage of 20 mg/kg body weight (a maximum of 1 g/injection) at intervals of 5–7 days. Late-stage disease was treated using Melarsoprol (3.6 mg/kg repeated every 7 days for 4 weeks).	Reports on deaths and treatment success at 2 months FU 2/31 deaths 29/31 treatment success	Comment: Retrospective data from National Sleeping Sickness Referral Hospital (NSSRH) in Alupe, Kenya, were used in this study. The patients are normally referred to the hospital by other health centres or can report directly to the hospital once they have signs associated with the disease. The hospital records of the HAT patients were also examined for data on sex, age, area of origin, parasites/coinfections, and disease stage. The patients are normally screened for HAT and other tropical diseases including malaria, typhoid, and helminthiasis using standard parasitological methods. Aim: The current study was aimed at establishing the infections which are associated with HAT in Kenya.

				Funding: The HAT drugs were provided for free by World Health Organization (WHO). Other treatment was paid by the Government of Kenya. Conflict of interest: not reported
Kato 2015 Retrospective cohort Follow-up: 1 months 2005-2012 Uganda, Lwala hospital, Kaberamaido district, North Eastern Uganda	257 children and adult rHAT cases (stage 1 and 2 according to WHO diagnostic criteria)* <u>Stage 1: n=17</u> Age: mean age 28.6 years (0.1–85) Sex: 53% female; 47% male <u>Stage 2: n=240</u> Age: mean age 28.6 years (0.1–85) Sex: 52% female; 48% male *Patient without complete medical records were excluded	<u>Stage 1</u> **Suramin** (manufacturer not reported) Schedule not reported <u>Stage 2</u> **Melarsoprol** (manufacturer not reported) Schedule: initial dose of suramin followed by a daily dose of melarsoprol	Reports on deaths, relapses and reactive encephalopathy (AE) for the overall group on n=257 at 1 month FU. And death by stage 0/17 stage 1 27/240 stage 2 Overall: 27/257 deaths 7/257 death due to treatment 10/257 relapses 19/257 reactive encephalopathy (AE) LTFU not reported, treatment success not reported as outcome	Comment: This was a retrospective study in which all data analyzed was recovered from that routinely collected as a requirement for HAT diagnosis and treatment following national guidelines Aim: To describe the clinical presentation, co-infections and disease outcome of rHAT cases Funding: public/non-profit: This work was funded by the Wellcome Trust Conflict of interest: none
Kuepfer 2011, Kuepfer 2012 The IMPAMEL III program ISRCTN40537886 Prospective cohort Follow-up: 12 months August 2006-August 2008	138 (107) children and adult rHAT cases (stage 2 confirmed in blood and CSF) Age: 6-85 years Sex: 42.8% female ; 57.2% male Patients with first-stage infections, pregnant women and moribund or unconscious patients were excluded	**Suramin Antrypol (Bayer)** + **Melarsoprol (Sanofi-aventis)** Suramin: Tanzania: IV suramin 5 mg/kg (day 1), full dose 20 mg/kg (day 3); Uganda: IV suramin 5 mg/kg. Followed by Melarsoprol or Melarspoprol only:	138 originally included FU time not reported: Surmin followed by Melarsoprol: 15/138 deaths 123/138 treatment success Melarsoprol only N=107: total 138 recruited, 30 were excluded that had received centre-	Comment: Sequential conduct of a proof-of-concept trial (n = 60) and a utilization study (n = 78) using historic controls as comparator. The study also reports on encephalitis and mortality outcomes in historic controls, but with no

Tanzania, Uganda. The Kaliua Health Centre (KHC) in Tanzania (Urambo District) and the Lwala Hospital in Uganda (Kaberamaido District)	41% malaria positive on admission BMI mean (SD): 18.5 (3.4) BMI <16.5: n=26 (24.3%)	Melarsoprol treatment for all patients: 2.2 mg/kg of melarsoprol IV for 10 consecutive days as a 3.6% solution in propylene glycol, maximally 5 ml a day.	specific Suramin treatments in the proof-of-concept stage of the study, and 1 excluded who died before initiation of treatment. At 12 months FU: 12/107 deaths 94/107 treatment success 1/107 relapse Also reports death due to treatment (due to encephalopathy): 8/107 Death due to HAT: 1/107 Adverse events: Encephalopathic syndrome during treatment: 8/107 SAEs during 34 days 27/107 Any AEs: 64.5%	information on treatments received. Not extracted as there is no real comparison. Aim: safety/efficacy of intervention Funding: public/non profit: "The clinical trial program was funded by the Swiss Agency for Development and Cooperation and the Swiss Tropical and Public Health Institute Conflict of interest: none
MacLean 2010 Retrospective cohort Follow up: not reported October 1998-July 2003 Uganda, Kenya, Malawi. Livestock Health Research Institute (LIRI) hospital SE Uganda, Serere Health Centre E Uganda, Nkhotakota hospital Central Malawi	275 children and adult rHAT cases (stage 1and 2 defined according to WHO criteria). Age: 2-85 years Sex: Uganda: 41.8% female adults; 31.9% male adults; 26.3% children. Malawi: 60.0% female adults; 27.9% male adults; 11.6% children. Individuals diagnosed with malaria, filariasis or schistosomiasis were excluded	**Suramin *Antrypol*** (Bayer) **Suramin *Antrypol* (Bayer) + Melarsoprol *Arsobal* (Rhone-Poulenc)** <u>Uganda</u> early stage patients were given Suramin 20 mg/kg Uganda: late stage cases were initially given suramin 20 mg/kg followed by four series of melarsoprol 3.6 mg/kg <u>Malawi</u> early stage cases were given four	Reports deaths overall (FU not reported) separately for different schedules/stages/settings LTFu not reported, no other outcomes reported Deaths 17/275 overall 0/47 early stage early stage rHAT, Uganda 14/ 185 late stage Uganda 2/36 early stage rHAT, Malawi 1/9 late stage rHAT, Malawi	Comment: All HAT cases diagnosed during the defined study periods were recruited (with the exception of 10 cases due to co-infections). Observation bias is minimised as all individuals are confirmed HAT cases (this is an absolute diagnosis not prone to bias), and clinical parameters are recorded on a standardised patient recruitment form. Aim: To report clinical presentations of

		doses of suramin followed by one series of MelB late stage patients were given two doses of suramin followed by three series of MelB.		rHAT cases in 3 geographical foci. Funding: public/non-profit: This work was funded by the Wellcome Trust Conflict of interest: none
Matemba 2010 Retrospective cohort Follow-up: average 25 days January 2004 - December 2004 Tanzania, Kaliua Health Centre, Urambo district	143 children and adult rHAT cases diagnosed in 2004 (Stage 1 and 2 diagnosis in blood and CSF examination, n=22 patients without staging data assumed stage 1) Age: 0-4 years = 3.5%, 5-14 = 10.5%, 15-29 = 34.3%, 30-44 = 23.8%, 45-59 = 16.1%, 60-69 = 6.3%, 70-79 = 3.5%, 80+ = 2.1% Sex: not reported	<u>Stage 1 (n=30)</u> **Suramin** (manufacturer not reported) Schedule not reported <u>Stage 2 (n=113)</u> **Melarsoprol** (manufacturer not reported) Schedule not reported	Reports deaths at an average of FU 2 months; No other outcomes reported, LTFU not reported Death reported overall 7/143 And death reported by age groups: 0/5 aged 0-4 1/15 aged 5-14 3/49 aged 15-29 1/34 aged 30-44 1/23 aged 45-59 1/9 aged 60-69 0/8 aged 70-80+	Comment: This study aimed to estimate the public health burden of rhodesiense HAT in terms of DALYs and financial costs in a highly disease endemic area of Tanzania using hospital records. Data was obtained from 143 patients admitted in 2004 for treatment for HAT at Kaliua Health Centre, Urambo District. The direct medical and other indirect costs incurred by individual patients and by the health services were calculated. DALYs were estimated using methods recommended by the Global Burden of Disease Project as well as those used in previous rhodesiense HAT estimates assuming HAT under reporting of 45%, a figure specific for Tanzania. Funding: public/non/profit: Animal Health Programme (AHP) of the UK

				Department for International Development (DIFD) and the World Health Organization (WHO) Conflict of interest: none
Matovu 2023 DNDI-FEX-07-HAT NCT03974178 Non-randomized trial Follow-up: 12 months 29 September 2019- 21 September 2021 Uganda , Malawi. Lwala Hospital (Uganda) and Rumphi District Hospital (Malawi)	45 children and adult rHAT cases (Stage 1 and 2 classified according to WHO criteria) Age: age range 7- 69 years, median age: 24, mean (SD): 27 (16) Sex: 31.1% female, 68.9% male 1 woman was pregnant 42 patients (93.3%) were in altered or bad general health and 11 patients (24.4%) had a Karnofsky score of 50% or 60% (i.e., needing occasional to considerable assistance).	**Fexinidazole** (Aptuit, Verona, Italy) Body weight ≥35 kg 1800 mg (3 x 600 mg tablets), once daily for 4 days (Day 1 to Day 4), followed by 1200 mg (2 x 600 mg tablets), once daily for 6 days (Day 5 to Day 10)• Body weight ≥20 kg and <35 kg 1200 mg (2 x 600 mg tablets), once daily for 4 days (Day 1 to Day 4), followed by 600 mg (1 x 600 mg tablets), once daily for 6 days (Day 5 to Day 10). Fexinidazole was administered within 30 minutes of the main meal and the total duration of treatment was 10 days.	Reports on outcomes at EoH, 6, 9, 12, moths. No patient LTFU, all patients accounted for with reported outcomes. 44/45 patients adhered to treatment for 10 days. (One patient died in hospital) <u>Safety data reported for stage 1 and 2 patients together:</u> Any AEs 24/45 SAEs 3/45 Specific AEs: 2/45 Nervous system disorders 2/45 Blood and lymphatic system disorders (anaemia, Thrombocytopenia) 2/45 Renal and urinary disorders 10/45 Gastrointestinal disorders 2/45 General and administration site conditions 5/45 Infections and infestations 1/45 Cardiac disorders	Comment: strictly confidential data received from DNDI Multicentre, phase II/III, open-label, non-randomised clinical trial Aim: Safety/efficacy of intervention Funding: mixed: funded by European and Developing Countries Clinical Trials Partnership Association (EDCTP2) programme supported by the European Union; Fundação para a Ciência e a Tecnologia from Portugal; Swiss Agency for Development and Cooperation (SDC), from Switzerland; Médecins Sans Frontières International; and UK International Development, United Kingdom; and other private foundations and individuals.

			Mortality/efficacy data reported by stage: <u>Stage 1</u> 0/10 overall mortality 0/10 treatment failure 0/10 relapse during follow up 10/10 treatment success at EoH and 12 months follow up <u>Stage 2</u> 1/35 overall mortality 1/34 relapse during follow up 1/35 treatment failure at EoH (one death) 2/35 treatment failure at 12 months (1 death during hospitalisation, 1 relapse during follow up) 34/35 treatment success at EoH 33/35 treatment success at 12 months	
Robertson 1963 Case series Follow-up: 30 days Study dates not reported Uganda, South-east Uganda	89 rHAT cases (stage not reported) Age and sex not reported	**Suramin followed by Melarsoprol** (manufacturer not reported) Schedule A: Days 1, 2 and 3 - 2.0, 2.5 and 3.0 ml., respectively. Days 10, 11 and 12 - 3.5, 4.0 and 5.0 ml., respectively. Days 19, 20 and 21 - 5.0 ml. on each day. Total : 35.0 ml. Schedule B: Days 1, 3 and 5 - 0.5, 1.0 and 1.5 ml.,	Reports on reactions observed during treatment at 1 months FU only LTFU not reported, no other outcomes reported 1/89 Erythema nodosum leprosum 1/89 Agranulocytosis	wo case series of patients with T. rhodesiense or T. gambiense. (only rHAT cases extracted) Aim: Safety/efficacy of intervention Funding: not reported Conflict of interest: not reported

		respectively. Days 10, 11 and 12 - 2.5 ml. each day. Days 19, 20 and 21 - 2.5 or 3.0, 3.5 or 4.0 and 4.0 or 5.0 ml., respectively. Days 28, 29 and 30 - 5.0 ml. each day. Total : 35.5-37.5 ml.)		
Veeken 1989 Retrospective cohort Follow-up: 21 months January 1985-September 1986 Tanzania, Kabanga Hospital, Kigoma Region, Tanzania	158 children and adult cases of rHAT (Stage 1 and 2 classified diagnosis in blood and CSF examination) Age: < 2 yr = 1.9%; 2-15 yr = 13.9%; 16-40 = 63.3%; >40 yr = 20.9% Sex: 24.7% female; 75.3% male	Stage 1 **Suramin** (manufacturer not reported) Stage 2 **Suramin + melarsoprol** (manufacturer not reported) 20 mg/kg IV (max 1 g) on days 1 & 3. Lumbar puncture (LP) day 4 – if normal suramin days 7, 14 & 21. LP repeated day 21. If LP either abnormal, Melarsoprol started. 36 g/L, 3 daily IV doses, 1 week interval, 3 daily IV doses; doses increasing beginning 72-180 mg/day, maximum 1242 mg.	Reports on all-cause mortality overall stage 1 and 2 at 5 weeks: 19/158 Longest FU 3-9 months in 83 cases 75/158 LTFU, reasons not reported 19/83 deaths 49/83 treatment success 15/83 relapses Also reports on AEs (up to 5 weeks) 3 =3 LTFU In 155 participants 1/155 Allergic rash 5/155 Fever, shivering 1/155 Convulsions 1/155 Psychosis In stage 2: Encephalopathy due to Melarsporol: 19/106 Death due to treatment (encephalopathy): 10/106 Mortality by stage in 155 participants at 5 weeks : 3 =3 LTFU Stage 1 2/49	Comment: A retrospective analysis was done of the management and the results of treatment in 158 trypanosomiasis patients seen in a rural hospital in Tanzania during 1985. Aim: Safety/efficacy of intervention Funding and conflict of interest not reported

			Stage 2 17/106	
Wellde 1989 Prospective and retrospective cohorts 1966-June 1987 Follow-up: three years (prospective cohort) Kenya. Kisii and Homa Bay Hospitals, Lambwe, Kenya	208 primary rHAT cases (stage 1 and 2, classified with CSF examination) Children and adults age and sex not reported	**Suramin *Antrypol*** (Bayer) (1966-1979) 1966-71: 1 g days 1, 3, 6, 9, & 15. 1971-72: extended treatment, 7.5 g total with 0.5 g test dose. 1972-77: 1 g every 5 days to 4.5-12.0 g total with 0.5 g test dose. 1978-19: 5 weekly 1 g doses with 0.2 g test dose (all IV) (1980-1984) Suramin test dose 0.2g day 1; followed by 1 g (0.5 for children) day 2. Lumbar puncture day 3; CSF ≤5 leucocytes/mcl subsequently treated with 4 more weekly injections 1 g (0.5 for children). **Suramin *Antrypol* (Bayer) + Melarsoprol *Arsobal* (Specia Laboratories, Paris)** (1966-1979) 1966-67: 1.5 rising to 3.5 mL days 1-4; 4.0 rising to 5.0 mL days 11-14. 1968-76: 2.0 rising to 3.0 days 1-3; 3.5 rising to 5.0 mL days 12-14; 5.0 ml days 23-35. 1978-79: 1.5 rising to 2.5 mL days 1, 3 & 5; 3.0 rising to 4.0 mL days 12-14; 4.5	Reports on different schedules for stage 1 and 2 separately Longest FU 3 years Suramin only: (1980-1984) n=95 1/95 death 32/95 relpase 62/95 treatment success Suramin only: (1966-1979) N=152 19/152 deaths 30/152 relapse 103/152 treatment success Suramin+Melaroprol (1980-1984): n=113 11/113 deaths 7/113 relapse 95/113 treatment sucess Melarsoprol (1966-1979): n=156 19/156 deaths 6/156 relapse 131/156 treatment success	Comment: Retrospective cohort: An extensive effort was made to trace all former sleeping sickness patients from the Lambwe area identified from hospital records. The homes of former patients were identified and the households were questioned with regards to the status of previous sleeping sickness patients. (1966-1979): Patients with incomplete records or whose whereabouts could not be traced were excluded from the analysis. Prospective cohort: A follow up of all patients treated from 1980 onwards in the study area was initiated in 1981, with about three-monthly intervals between visits. Patients from outside the Lambwe Valley area were visited less often. The most recent follow up was in June 1987. A follow up period of three years was decided upon since Apted reported relapses at 24 to 27

		rising to 5.0 mL days 21-23 (all IV) (1980-1984) Suramin test dose 0.2g day 1; followed by 1 g (0.5 for children) day 2. Lumbar puncture day 3; CSF leucocytes/mcl >5 leucocytes/mcl treated with melarsoprol, 3 courses of 3 injections every other day, 1 week between each course; doses rising from 0.5 mL to 5.0 mL.		months post treatment. Aim: Safety/efficacy of intervention Funding: not reported Conflict of interest: not reported

Risk of bias assessment

Study ID	Risk of bias due to confounding					Selection Bias
	Malnutrition	Age and sex	Comorbidities	HAT stage/diagnostic criteria	Setting/Location	
Apted 1953	not reported	Age not reported, sex not reported	not reported	Stage not formally reported, but all advanced disease	Tanzania: Sleeping Sickness Medical Department, Tanganyika	Inclusion and exclusion crite not reported
Apted 1957	not reported	Age not reported, sex not reported	not reported	Stage 2- CSF before treatment	Tanzania: Sleeping Sickness Medical Department, Tanganyika	Inclusion and exclusion crite not reported
Arroz 1987	not reported	Age not reported, sex not reported	not reported	Stage not reported - Diagnostic criteria not reported	Mozambique: Tete Provincial Hospital, C.P. 28, Tete, Mozambique	Inclusion and exclusion crite not reported
Kuepfer 2011/2012	Nutrition status (mean (SD): 18.6 +- 3.5; Severe Malnutrition	Adults and chidren:6-72 years; 42.8% female ; 57.2% male	41% malaria positive on admission	Stage 2-Diagnosis of HAT was made in blood and in the cerebrospinal fluid (CSF). Blood was examined using	Tanzania, Uganda: The Kaliua Health Centre (KHC) in Tanzania (Urambo District) and the Lwala Hospital in	Patients with confirmed second-stage T.b. rhodesien HAT; minimum age of 6 years

	(BMI <16.5: n=26 (24.3%)			microscopy and/or the haematocrit centrifugation technique (WOO test). If trypanosomes were present, a lumbar puncture was performed for disease staging. Analysis of the CSF was done by direct microscopy and/or single modified centrifugation technique and white blood cell (WBC) count using counting chambers. Second-stage infections were confirmed by the presence of trypanosomes and/or ≥5 WBC/mm3 in the CSF.	Uganda (Kaberamaido District)	were included. Pregnant women; unconscious o moribund patients were excluded
MacLean 2010	not reported	Adults and children: age 2-85, Uganda: 41.8% female adults; 31.9% male adults; 26.3% children.	not reported	Stage 1-HAT staging criteria. Stage of trypanosome infection was determined in accordance with WHO criteria, late stage infection diagnosed when trypanosomes are detected in the cerebrospinal fluid (CSF) or when present in blood and CSF white blood cell (WBC) count >5/mm3.	Uganda (Suramin only): Livestock Health Research Institute (LIRI) hospital SE Uganda	all HAT cases diagnosed dur the defined stu periods were recruited (with the exception 10 cases due to co-infections) they represent Individuals diagnosed with malaria, filaria or schistosomias were excluded
Veeken 1989	not reported	Adults and childen: < 2 yr = 1.9%; 2-15 yr = 13.9%; 16-40 = 63.3%; >40 yr = 20.9%; 24.7% F; 75.3% M	not reported	Stage 1-Trypanosomiasis was diagnosed by demonstrating trypanosomes in blood or cerebrospinal fluid (CSF) and in a few cases on clinical suspicion in combination with	Tanzania: Kabanga Hospital, Kigoma Region, Tanzania	All cases presented to hospital includ

				elevated cells and protein in the CSF while no trypanosomes were seen. Trypanosomes in blood were identified in thick smears, no concentration method was used. Lymphnode aspiration was not performed, as lymphadenopathy was usually not a striking feature of the disease. Cerebral involvement indicating the meningoencephalitic (ME) stage was diagnosed in case of an abnormal CSF. A normal CSF was defined as having not more than 6 leucocytes/mm3, up to 40 mg/di of total protein, and the absence of trypanosomes. Trypanosomcs in the CSF were examined by the direct method only. Double centrifugation of the CSF was not performed due to lack of electricity.		
Wellde 1989a and b	not reported	Adults and children: age not reported, sex not reported	not reported	Stage 1 and 2-CSF analysis	Kenya: Kisii and Homa Bay Hospitals, Lambwe, Kenya	Includes: prim rHAT cases; patients with incomplete records or wh whereabouts could not be traced were excluded from the analysis. A extensive effo was made to trace all forme sleeping

						sickness patien from the Lambwe area identified from hospital record
Kato 2015	not reported	Adults and children: mean age 28.6 years (0.1–85); 53% F; 47% M	The overall prevalence of co-infections was 37.2% (90/242). Among the co-infections, malaria was significantly more prevalent (28.9%; followed by urinary tract infections (4.2%). Co-infections were present in 14.3% of in-hospital deaths, 38.5% of which were recorded as Malaria. Malaria was significantly more common in patients under 18 years (45.5%; and was reported in 60% of the fatal cases in this age group	Stage 1- The routine diagnosis of suspected HAT patients, was done by microscopic examination of wet and thick blood films from finger prick blood. If trypanosomes were present in the blood smear, or the patient presented with highly suspicious HAT signs, a lumbar puncture was performed following WHO disease staging guidelines. Analysis of cerebrospinal fluid for trypanosomes and White blood cell (WBC) counts was done microscopically using the Neubauer Haemocytometer method. Late stage infection was confirmed by the presence of trypanosomes in the CSF and/or a White blood cell count of ≥5 cells/mm3.	Uganda: Lwala hospital, Kaberamaido district, North Eastern Uganda A significantly high number of cases were from Kaberamaido district (165/239; 69%; p< 0.0001), followed by Dokolo district with 54 cases (22.6%). Alebtong had 13 (5.4%), Soroti 5 (2.1%), Lira and Kole each with 1 (0.4%; see Table 1). Data on district of residence for 19 patients was not recorded. Within Kaberamaido, the majority of cases were from Alwa (25.7%) and Otuboi (24.3%) sub-counties.	Included: Sleeping sickn patients reporting to Lwala hospital between 2005 and 2012. Patients witho complete medical record only
De Andrade Silva 1957	not reported	Age not reported, sex not reported	not reported	Stage 1 and 2 - All cases were carefully classified with CSF examination before the commencement of treatment.	Mozambique; Setting location: Unclear	Inclusion and exclusion crite not reported

Matovu, 2023	median body mass index (BMI) was 18.7 kg/m², ranging from median body mass index (BMI) was 18.7 kg/m², ranging from 12.8 to 29.5 kg/m²	Adults and childen: range 7.0 t-69.0 years, median age: 24, mean (SD): 27 (16); 68.9% male, 31.1% female	At baseline, 42 patients (93.3%) were in altered or bad general health and 11 patients (24.4%) had a Karnofsky score of 50% or 60% (i.e., needing occasional to considerable assistance	Stage 1 and 2 – Patients without trypanosomes in the cerebrospinal fluid (CSF) but with trypanosomes in the blood and/or lymph and CSF white blood cells (WBC) ≤5 cells/µL were classified as stage 1. Patients with trypanosomes in the CSF (and/or in blood/lymph) and/or CSF WBC >5 cells/µL were classified as stage 2	Uganda , Malawi: Two centres screened patients: 1 in Uganda (Lwala Hospital) and 1 in Malawi (Rumphi District Hospital)	Inclusion crite ≥6 years old, ≥ kg body weigh Ability to inges at least one complete mea per day (or at least one Plumpy'Nut® sachet), Karnofsky inde ≥40 , parasitologic confirmed of T brucei rhodesiense infection Exclusions: • Active clinicall relevant medic conditions oth than HAT that could jeopardi patient's safet or, at the Investigator's discretion, cou interfere with participation i the study (e.g., patients at risk QT prolongatio Compromised general health severely deteriorated general condition, such as severe malnutrition, cardiovascular shock, respiratory distress, or terminal illnes • Patients with severe hepatic impairment (e clinical signs o cirrhosis or jaundice)

						• Known hypersensitivit to fexinidazole to any nitroimidazole drugs (e.g., metronidazole tinidazole), or any of the excipients • Patients previously enrolled in the study or havin already receive fexinidazole.
De Andrade Silva 1954	not reported	Age not reported, sex not reported	not reported	Stage 2- Blood tests for trypanosomes, lumbar punctures	Mozambique- Setting location: Not reported	Inclusion and exclusion crite not reported
Frean 2018	not reported	Adults only, 26-69 years, 19% F; 81% M	not reported	Stage 1: Laboratory confirmation of the diagnosis by microscopic examination of Giemsa-stained blood films; lumbar puncture	South Africa Evacuated cases originating from Zambia, Malawi, Zimbabwe, Tanzania, and Uganda. "With few exceptions, they were admitted to private hospitals in Johannesburg and Pretoria."	The cases of Ea African trypanosomias patients evacuated to South Africa, fo whom cases of East African trypanosomias patients evacuated to South Africa, fo whom diagnos and clinical management advice was provided over the years 2004 2018

Appendix 4. Excluded studies

Ref ID	Bibliography	Reason for exclusion
1	2005. Efficacy - Safety of Eflornithine-Nifurtimox Combination Versus Eflornithine to Treat Human African Trypanosomiasis Clinical Study Comparing the Nifurtimox-Eflornithine Combination With the Standard Eflornithine Regimen for the Treatment of Trypanosoma Brucei Gambiense Human African	Population not relevant -gambiense HAT

	Trypanosomiasis in the Meningoencephalitic Phase, #volume#(#issue#): #Pages#.	
2	2005. Assessing three day pentamidine for early stage human African trypanosomiasis (Angola) #journal#, #volume#(#issue#): #Pages#.	Study design not relevant (no interventional study)
5	2008. Trial of DB289 for the Treatment of Stage I African Trypanosomiasis Phase II b Trial of DB289 for the Treatment of Stage I African Trypanosomiasis, #volume#(#issue#): #Pages#.	Study design not relevant (no interventional study)
6	2009. Human African Trypanosomiasis: first in Man Clinical Trial of a New Medicinal Product, the Fexinidazole Randomized, Double-blind, Placebo-controlled Study of the Tolerability, and Pharmacokinetics of Fexinidazole After Single and Repeated Oral Ascending Doses, Completed by a Comparative Bioavailability Study of an Oral Suspension Versus a Tablet and an Exploratory Assessment of Food Effect, in Healthy Male Volunteers, #volume#(#issue#): #Pages#.	Population not relevant- other disease
7	2011. Multiple Dose Study to Evaluate Security, Tolerance and Pharmacokinetic of Fexinidazole (Drug Candidate for Human African Trypanosomiasis) Administered With a Loading Dose and With Food Double-blind, Placebo Controlled, Randomized Multiple Ascending Dose Study in Fed Conditions for Ten Days Dosing Regimen With a Loading Dose to Evaluate the Safety, the Tolerability and the Pharmacokinetics of Oral Fexinidazole in 36 Healthy Male Sub-Saharan Volunteers, #volume#(#issue#): #Pages#.	Population not relevant- other disease
8	2012. Pivotal Study of Fexinidazole for Human African Trypanosomiasis in Stage 2 Efficacy and Safety of Fexinidazole Compared to Nifurtimox-Eflornithine Combination Therapy (NECT) in Patients With Late-stage Human African Trypanosomiasis (HAT) Due to T.b. Gambiense: pivotal, Non-inferiority, Multicentre, Randomised, Open-label Study, #volume#(#issue#): #Pages#.	Study design not relevant (no interventional study)
9	2015. Bioequivalence Study - Reference Clinical Fexinidazole Tablet Versus Proposed Market Formulation A Bioequivalence Study of the Reference Clinical Fexinidazole Tablet vs Proposed Market Formulation in Healthy Male Volunteers of African Sub-Saharan Origin: an Open-label,Randomized,Two-treatment,Single Dose,Replicate Design,Fed Condition, #volume#(#issue#): #Pages#.	Not published - Not available
13	Abaru, D. E., Liwo, D. A., Isakina, D., Okori, E. E. 1984. Retrospective long-term study of effects of berenil by follow-up of patients treated since 1965 Tropenmedizin und Parasitologie, 35(3): 148-50.	Population not relevant- other disease
19	Abel, Paulo M., Kiala, Godi, Loa, Vanda, Behrend, Markus, Musolf, Jens, Fleischmann, Hanne, Theophile, Josenando, Krishna, Sanjeev, Stich, August 2004. Retaking sleeping sickness control in Angola Tropical medicine & international health : TM & IH, 9(1): 141-8.	Population no relevant -gambiense HAT
23	Acres, I. S. 1950. A study of sleeping sickness in an endemic area of the Belgian Congo over a period of ten years Transactions of the Royal Society of Tropical Medicine and Hygiene, 44(1): 77-92.	Population no relevant -gambiense HAT
30	Adriaenssens, K. 1960. Side effects of melarsoprol in sleeping sickness due to trypanosoma rhodesiense Annales de la Societe Belge de Medecine Tropicale, 40(4): 701-704.	PDF not available
31	Adriaenssens, K. 1962. Furaltadone in the treatment of Rhodesian sleeping sickness Tropical and Geographical Medicine, 14(2): 171-182.	Intervention/ comparison not relevant

39	Aiyedun, B. A., Amodu, A. A. 1976. Mel B toxicity in human trypanosomiasis in the Gboko endemic area of Nigeria Acta tropica, 33(1): 96-100.	Population no relevant -gambiense HAT
76	Ancelle, T., Barret, B., Flachet, L., Moren, A. 1994. [2 epidemics of arsenical encephalopathy in the treatment of trypanosomiasis, Uganda, 1992-1993] Etude de deux epidemies d'encephalopathies arsenicales dans le traitement de la trypanosomiase, Ouganda, 1992-1993., 87(5): 341-6.	Study design not relevant (no interventional study)
85	Anonymous 1979. Chemotherapy of sleeping sickness The Central African journal of medicine, 25(11): 251.	Study design not relevant (no interventional study)
88	Anonymous 1991. A new drug for the treatment of sleeping sickness Schweizerische Apotheker Zeitung, 129(6): 163-164.	Study design not relevant (no interventional study)
90	Anonymous 1992. New chances to heal sleeping sickness TW Neurologie Psychiatrie, 6(4): 199-200.	Study design not relevant (no interventional study)
92	Anonymous 1998. Eflornithine trial results TDR news, #volume#(57): 1-2.	Study design not relevant (no interventional study)
93	Anonymous 2000. Cytotoxic - melarsoprol Manufacturing Chemist, 71(10): 39.	Study design not relevant (no interventional study)
101	Anonymous 2021. Fexinidazole American Journal of Health-System Pharmacy, 78(22): 2005-2008.	Study design not relevant (no interventional study)
109	Apted, F. I. C. 1960. Nitrofurazone in the treatment of sleeping sickness due to trypanosoma rhodesiense Transactions of the Royal Society of Tropical Medicine and Hygiene, 54(3): 225-228.	Intervention/ comparison not relevant
110	Apted, F. I. C. 1973. Human African trypanosomiasis Medecine et Hygiene, 31(1067): 1194-1195.	Study design not relevant (no interventional study)
118	Arroe, M., Willumsen, L., Tvede, M., Bennike, T. 1985. [Acute African trypanosomiasis imported into Denmark] Akut afrikansk trypanosomiasis importeret til Danmark., 147(37): 2915-6.	Duplicate
123	Authie, E., Bringaud, F., Bakalara, N., Tetaud, E., Baltz, T. 1999. Human and animal trypanosomiasis: Sleeping disease and Nagana Annales de l'Institut Pasteur/Actualites, 10(1): 27-50.	Study design not relevant (no interventional study)
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1847	Williamson, J. 1976. Chemotherapy of African trypanosomiasis Transactions of the Royal Society of Tropical Medicine and Hygiene, 70(2): 117-9.	Duplicate
1851	Willyard, C. 2011. Putting sleeping sickness to bed Nature Medicine, 17(1): 14-17.	Study design not relevant (no interventional study)
1860	Woodrow, C. J., Abel, P. M., Krishna, S. 2007. Randomized, controlled trial of treatments for second-stage sleeping sickness [5] Journal of Infectious Diseases, 196(4): 650-657.	Study design not relevant (no interventional study)
1864	Wu, S. H. 1985. African human trypanosomiasis in southern Sudan. Report of 77 cases Chinese medical journal, 98(1): 37-41.	Population no relevant -gambiense HAT
1869	Yagnik, Kruti J., Pezo-Salazar, Alonso, Rosenbaum, David, Jaso, Jesse Manuel, Cavuoti, Dominick, Nelson, Benjamin, Chancey, Rebecca J., McKenna, Megan L., Castellino, Laila M. 2021. A Wandering Missionary's Burden: Persistent Fever and Progressive Somnolence in a Returning Traveler Open forum infectious diseases, 8(8): ofab377.	Population no relevant -gambiense HAT
1897	Zumbuhl, O. 1984. Trypanosomiasis: Sleeping sickness and Chagas' disease Schweizerische Apotheker-Zeitung, 122(16): 842-848.	Study design not relevant (no interventional study)
1903	Abaru, D. E., Matovu, F. S. 1983. Berenil in the treatment of early stage human trypanosomiasis cases #journal#, #volume#(#issue#): 194-198.	Intervention/ comparison not relevant

1927	Buyst, H. 1976. The use of antimalarials during treatment of T. rhodesiense sleeping sickness East African Medical Journal (Special Number), 53(8): 506-507.	PDF not available
1933	Damper, P. D. W. 1975. Pentamidine transport in brucei-subgroup trypanosomes Dissertation Abstracts International, 36B(#issue#): 2067-2068.	PDF not available
1940	Doua, F., Boa, F. Y. 1994. Current chemotherapy for African trypanosomiasis Bulletin de la Société de Pathologie Exotique, 87(5, bis 5): 337-340.	Study design not relevant (no interventional study)
1956	Janssens, P. G., Muynck, A. de 1977. Malignant Rhodesian trypanosomiasis Annales de la Societe Belge de Medecine Tropicale, 57(6): 589-592.	Study design not relevant (no interventional study)
1965	Knuttgen, H. J. 1980. The diagnosis and therapy of acute Trypanosoma rhodesiense infections with high parasitaemias #journal#, #volume#(#issue#): 134-136.	PDF not available
1971	Lowenthal, M. N., Jones, I. G., Kouchner, G. A., Desai, M., Chimbayo, W. A. S., Rajappan, C. 1977. Nitrofurazone as primary therapy for trypanosomal meningo-encephalitis #journal#, 71(#issue#): 88-89.	Study design not relevant (no interventional study)
1984	Muhammad, Ayub, S. Aamir, Shah, Muhammad, Irfan, Junaid Afsar, Khan, Shuaib N, Hashmi 2011. <A> case of human African trypanosomiasis during United Nation mission in Liberia #journal#, 61(#issue#): 149-151.	Population no relevant -gambiense HAT
2000	Robins-Browne, R. M., Schneider, J. 1977. Coagulation disturbances in African trypanosomiasis #journal#, #volume#(#issue#): 565-572.	PDF not available
2004	Sayer, P. D., Onyango, J. D., Gould, S. S., Waitumbi, J. N., Raseroka, B. H., Akol, G. W. O., Ndung'u, J. M., Njogu, A. R. 1988. Treatment of African trypanosomiasis with combinations of drugs with special reference to suramin and nitroimidazoles Publication - International Scientific Council for Trypanosomiasis Research and Control, #volume#(No. 144): 205-210.	PDF not available
2026	Wood, L., Miller, D., Jacobs, P., Mansvelt, E. 2002. Trypanosomiasis - an unusual cause of reversible multiple organ dysfunction in South Africa #journal#, 92(#issue#): 527-528.	Population not relevant- gambiense HAT
2033	World Health Organization 2019. WHO interim guidelines for the treatment of gambiense human African trypanosomiasis #journal#, #volume#(#issue#): #Pages#.	Population not relevant- other disease
2034	World Health Organization #year#. Global Health Observatory. Number of new reported cases of human African trypanosomiasis (T. b. rhodesiense) 2021 [updated 21 July 2022. #journal#, #volume#(#issue#): #Pages#.	Intervention/ comparison not relevant
2035	World Health Organization 2022. Report of the fourth WHO stakeholders meeting on gambiense and rhodesiense human African trypanosomiasis elimination, Virtual meeting, 1–3 June 2021 #journal#, #volume#(#issue#): #Pages#.	Study design not relevant (no interventional study)
2036	World Health Organization 2015. Report of the first WHO stakeholders meeting on rhodesiense human African trypanosomiasis. Geneva, 20–22 October 2014. #journal#, #volume#(#issue#): #Pages#.	Study design not relevant (no interventional study)
2037	MSF Médecins Sans F 2021. MSF Médecins Sans F. Clinical guidelines - Diagnosis and treatment manual. April 2021. Chapter 6. Parasitic diseases. Human African trypanosomiasis (sleeping sickness). 2021 April 2021 #journal#, #volume#(#issue#): #Pages#.	Study design not relevant (no interventional study)

2038	Gao JM, Qian ZY, Hide G, Lai DH, Lun ZR, Wu ZD 2020. uman African trypanosomiasis: the current situation in endemic regions and the risks for non-endemic regions from imported cases Parasitology, 147(9): 922-31.	Study design not relevant (no interventional study)
2039	World Health Organization 2020. Report of the third WHO stakeholders meeting on rhodesiense human African trypanosomiasis. 10–11 April 2019 #journal#, #volume#(#issue#): #Pages#.	Study design not relevant (no interventional study)
2040	World Health Organization 2017. Report of the second WHO stakeholders meeting on rhodesiense human African trypanosomiasis, Geneva, 26–28 April 2017 #journal#, #volume#(#issue#): #Pages#.	Intervention/ comparison not relevant
2043	Apted FI, Smyly DP, Ormerod WE, Stronach BW 1963. A comparative study of the epidemiology of endemic Rhodesian sleeping sickness in different parts of Africa Trop Med Hyg, 66(#issue#): 1-16.	Study design not relevant (no interventional study)
2049	Madanitsa M, Chisi J, Ngwira B 2009. The epidemiology of trypanosomiasis in Rumphi district, Malawi: a ten year retrospective study Malawi Medical Journal, 21(1): 22-27.	no relevant data reported
2051	Berrang-Ford, L., Wamboga, C., Kakembo, A.S.L. 2012. Trypanososma brucei rhodesiense sleeping sickness, Uganda Emerg Infect Dis, #volume#(18): 1686–1687.	Study design not relevant (no interventional study)
2052	Onyango, R., Bailey, N., Okach, R., Mwangi, E., Ogada, T. 1969. Encephalopathy during treatment of human trypanosomiasis #journal#, #volume#(#issue#): #Pages#.	Study design not relevant (no interventional study)

Appendix 5. Data and analyses (direct evidence)

Analysis 1.1 Fexinidazole in people with first-stage r-HAT

Study included: Matovu, 2023 - DNDI-FEX-07-HAT

Outcome *Definition in the study*	Cases/N	FU time	Narrative results
Overall mortality	0/10	12 months	No deaths occurred in stage 1 patients during the 12 months follow-up.
Treatment failure *Presence of trypanosomes in any body fluid at EoT, or Death possibly related to r-HAT or treatment, according to DSMB, at EoH, or Absence of clinical improvement leading to the use of rescue medication* *+ death due to any causes*	0/10	12 months	No deaths, withdrawals or treatment failures occurred in stage 1 patients during the 12 months follow-up
Treatment success *Trypanosome-negative patient with ≤20 WBC/µL in CSF in non-haemorrhagic sample*	10/10	12 months	All included stage 1 patients were successfully treated with fexinidazole without relapses up to 12 months follow-up.

Death likely to be due to r-HAT *Only deaths possibly related to r-HAT or treatment according to DSMB were considered. In case of death, the WHO verbal autopsy questionnaire was to be used since anatomopathological techniques were not available at the study sites (unless the death occurred at the hospital, in which case the Investigator was present).*	0/10	EoH; 12 months	No deaths occurred in stage 1 patients during the 12 months follow-up.
Death likely to be due to the treatment *Only deaths possibly related to r-HAT or treatment according to DSMB were considered. In case of death, the WHO verbal autopsy questionnaire was to be used since anatomopathological techniques were not available at the study sites (unless the death occurred at the hospital, in which case the Investigator was present).*	0/10	EoH, 12 months	No deaths occurred in stage 1 patients during the 12 months follow-up.
Relapse *Trypanosomes detected in any body fluid; Earliest time to detect a relapse from EoT to M12: Presence of trypanosomes in any body fluid, or The date of death if attributable to r-HAT or treatment administration, according to the DSMB, or The administration of rescue medication.*	0/10	12 months	No relapses occurred during the 12 months follow-up period in the included stage 1 patients.
Serious adverse events *"An SAE was defined as any AE that: • Resulted in death • Was life-threatening • Required in-patient hospitalisation or prolongation of existing hospitalisation • Resulted in persistent or significant disability or incapacity • Was a congenital anomaly or birth defect • Was an important medical event.".*	0/10	12 months	No serious adverse events occurred in stage 1 participants

Analysis 1.2 Fexinidazole in second-stage r-HAT

Study included: Matovu, 2023 - DNDI-FEX-07-HAT

Outcome *Definition in the study*	cases	FU time	Narrative results
Overall mortality	1/35	12 months	One patient died during treatment due to reasons unrelated to treatment or HAT
Treatment failure	1/35	End of hospitalisation	One death in a stage 2 patient occurred during hospitalisation.

Presence of trypanosomes in any body fluid at EoT, or Death possibly related to r-HAT or treatment, according to DSMB, at EoH, or Absence of clinical improvement leading to the use of rescue medication *+ death due to any causes*			The reason for death was unrelated to treatment or HAT (1 SAE of acute kidney injury which led to the patient's death at Day 8; the cause of death was considered unrelated to r-HAT and/or study treatment) Note: In the study definition unrelated deaths are not counted as treatment failure, in our review definition deaths due to any reasons are counted as treatment failure.
Treatment failure *Presence of trypanosomes in any body fluid at EoT, or Death possibly related to r-HAT or treatment, according to DSMB, at EoH, or Absence of clinical improvement leading to the use of rescue medication* *+ death due to any causes*	2/35	12 months	One death during hospitalisation, one treatment failure during follow-up (week 9), successful rescue treatment with melarsoprol.
Treatment success *Trypanosome-negative patient with ≤20 WBC/µL in CSF in non-haemorrhagic sample*	34/35	End of hospitalisation	One death during hospitalisation
Treatment success *Trypanosome-negative patient with ≤20 WBC/µL in CSF in non-haemorrhagic sample*	33/35	12 months	One death during hospitalisation, one treatment failure during follow-up (week 9), successful rescue treatment with melarsoprol
Death likely to be due to r-HAT *Only deaths possibly related to r-HAT or treatment according to DSMB were considered. In case of death, the WHO verbal autopsy questionnaire was to be used since anatomopathological techniques were not available at the study sites (unless the death occurred at the hospital, in which case the Investigator was present).*	0/35	12 months	One patient died during treatment due to reasons unrelated to treatment or HAT
Death likely to be due to the treatment *Only deaths possibly related to r-HAT or treatment according to DSMB were considered. In case of death, the WHO verbal autopsy questionnaire was to be used since anatomopathological techniques were not available at the study sites (unless the death occurred at the hospital, in which case the Investigator was present).*	0/35	12 months	One patient died during treatment due to reasons unrelated to treatment or HAT
Relapse *Trypanosomes detected in any body fluid; Earliest time to detect a relapse from EoT to*	1/34 (available cases)	12 months	One patient relapsed during follow up. The relapse was detected at W9, when the patient was trypanosome-positive and received

M12: Presence of trypanosomes in any body fluid, or The date of death if attributable to r-HAT or treatment administration, according to the DSMB, or The administration of rescue medication.			rescue treatment the next day (successful recovery)
Serious adverse events *"An SAE was defined as any AE that: • Resulted in death • Was life-threatening • Required in-patient hospitalisation or prolongation of existing hospitalisation • Resulted in persistent or significant disability or incapacity • Was a congenital anomaly or birth defect • Was an important medical event.".*	3/35	12 months	N=1 severe kidney injury (leading to death), no related to treatment or HAT during hospitalisation, n=1 pneumonia, n=1 urinary tract infection, both unrelated to treatment and HAT during follow-up period

Analysis 1.3 Fexinidazole in first and second-stage r-HAT – safety and adherence

Study included: Matovu, 2023 - DNDI-FEX-07-HAT

Outcome	Participants with at least one AE in the category:	FU time	Narrative results
Any adverse events *Occurrence of all AEs (including abnormal laboratory or ECG findings) during the observation period (until the EoH scheduled up to 7 days after EoT) and occurrence of AEs considered as serious or as possibly related to fexinidazole until the end of the follow-up period (M12). An AE was defined as any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product, and which did not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.*	24/45	12 months	22 during hospitalisation, 2 in the FU period
Specific AEs *Nervous system disorders*	2/45	12 months	During hospitalisation: Extrapyramidal disorder n=1, Epilepsy n=1
Specific AEs: Bone marrow toxicity: anaemia, leucopenia, thrombocytopenia *Blood and lymphatic system disorders (anaemia, Thrombocytopenia)*	2/45	12 months	During hospitalisation: Anaemia n=1',Thrombocytopenia n=1

Specific AEs: Nephrotoxicity *Renal and urinary disorders*	2/45	12 months	During hospitalisation: Acute kidney injury n=1, Chromaturia n=1
Specific AEs: Gastrointestinal symptoms: diarrhoea, nausea and vomiting *Gastrointestinal disorders*	10/45	12 months	During hospitalisation: Dysphagia n=1, gastritis n=1, Nausea n=2, vomiting n=6
Specific AEs: Skin reactions *General and administration site conditions*	2/45	12 months	During hospitalisation: Hypothermia n=1, inflammation n=1
Specific AEs: Infections *Infections and infestations*	5/45	12 months	During hospitalisation: Malaria n=2, Bacteraemia n=1; During follow up period: pneumonia n=1, urinary tract infection n=1
Specific AEs: Cardiotoxicity *Cardiac disorders*	1/45	12 months	During hospitalisation: Sinus tachycardia n=1
Adherence to treatment *Treatment compliance*		End of hospitalisation	"All patients received their treatment under hospitalisation. Fexinidazole was to be administered within 30 minutes of a meal. A study nurse monitored study treatment intake to make sure that the patients had eaten sufficiently (a meal equivalent to a dose of Plumpy'Nut; if not, the patient was to be provided with a bag of Plumpy'Nut) and fexinidazole was swallowed 44 patients fully completed treatment with fexinidazole. Treatment was permanently discontinued in 1 patient due to death during hospitalisation. The death was unrelated to r-HAT and/or study treatment). For this patient, treatment duration was 7 days. All patients took the treatment with a meal. Patients who vomited shortly after dosing (within 2 hours of study treatment administration) were to receive the daily dose of fexinidazole again. A total of 6 patients vomited doses within 2 hours after administration and all were re-administered"

Analysis 2. Suramin in people with first-stage r-HAT

Overall mortality

Population	Study Study design	Outcome in the study, timepoint	Treatment/ Schedule	Events / participants	Comments
Stage 1 **Children and adults**	Kato 2015 (retrospective cohort)	Death in hospital 1 month	Suramin[1]	0/17	
Stage 1 **Children and adults**	MacLean 2010 (retrospective cohort)	Death Follow-up not reported	Suramin[2]	0/47	
Stage 1 **Children and adults**	Veeken 1989 (retrospective cohort)	All cause death 5 weeks	Suramin[3]	2/49	
Stage 1 **Children and adults**	Wellde 1989a (prospective cohort)	Mortality during treatment 4 weeks	Suramin[4]	1/95	
Stage 1 **Children and adults**	Wellde 1989a (prospective cohort)	Mortality to 3 years	Suramin[4]	1/95	
Stage 1 **Children and adults**	Wellde 1989b (retrospective cohort)	Mortality during treatment 4 weeks	Suramin[5]	4/152	
Stage 1 **Children and adults**	Wellde 1989b (retrospective cohort)	Mortality to 3 years	Suramin[5]	19/152	
Stage 1 **Adults**	Frean 2018 (case series)	Death during treatment 30 days	Suramin[6]	1/19	
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Deaths to 2 years and over	Suramin[7]	7/36	
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Deaths to 2 years and over	Suramin+ Tryparsamide[8]	313/737	Indirect evidence

[1]Schedule not reported

[2]Uganda: early stage patients were given Suramin (Antrypol: Bayer: 20 mg/kg), schedule not reported

[3]20 mg/kg IV (max 1 g) on days 1 & 3, 7, 14 & 21

[4](1980-1984): Suramin test dose 0.2g day 1; followed by 1 g (0.5 for children) day 2. Lumbar puncture day 3; CSF ≤5 leucocytes/mcl subsequently treated with 4 more weekly injections 1 g (0.5 for children).

[5](1966-1979): 1966-71: Suramin 1 g days 1, 3, 6, 9, & 15. 1971-72: extended treatment, 7.5 g total with 0.5 g test dose. 1972-77: 1 g every 5 days to 4.5-12.0 g total with 0.5 g test dose. 1978-19: 5 weekly 1 g doses with 0.2 g test dose (all IV)

[6]Suramin (stage 1): test dose followed by 5 mg/kg by slow IV infusion on day 1, 10 mg/kg on day 3, and then 20 mg/kg on days 5, 11, 17, 23, and 30, to a maximum cumulative dose of 10 g

[7]Data for all treatment schedules combined: 13-10 grs, usual dose 1.0=1.5 grs in adults

[8]Data for all treatment schedules combined: Suramin: From 1 course of < 20 gms to 4 courses of > 100 gms Tryparsamide: 4 injections, 0.04 g / Kg

Death likely to be due to HAT

Population	Study Study design	Outcome in the study, timepoint	Treatment Schedule	Events/ participants	Narrative results
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort) (	Deaths due to trypanosomiasis Follow-up unclear	Suramin[1]	2/36	
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Deaths due to trypanosomiasis Follow-up unclear	Suramin+ Tryparsamide[2]	*/737	Indirect evidence

[1] Data for all treatment schedules combined: 13-10 grs, usual dose 1.0=1.5 grs in adults

[2] Data for all treatment schedules combined: Suramin: From 1 course of < 20 gms to 4 courses of > 100 gms Tryparsamide: 4 injections, 0.04 g / Kg

Treatment success, cure

Population	Study Study design	Outcome in the study, timepoint	Treatment Schedule	Events / participants	Comments
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Favourable evolution with no signs of disease At 6 -12 months	Suramin[1]	5/36	
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Favourable evolution with no signs of disease At 2 years	Suramin[1]	8/36	
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Favourable evolution with no signs of disease >2 years	Suramin[1]	14/36	

Stage 1 **Adults and children**	Wellde 1989a (prospective cohort)	Survival without relapse 3 years	Suramin[2]	62/95	
Stage 1 **Adults and children**	Wellde 1989b (retrospective cohort)	Survival without relapse 3 years	Suramin[3]	103/152	
Stage 1 **Adults**	Frean 2018 (case series)	"Recovered" 30 days	Suramin[4]	18/19	
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Favourable evolution with no signs of disease At 6-12 months	Suramin+ Tryparsamide[5]	68/737	Indirect evidence
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Favourable evolution with no signs of disease At 2 years	Suramin+ Tryparsamide[5]	113/737	Indirect evidence
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Favourable evolution with no signs of disease >2 years	Suramin+ Tryparsamide[5]	240/737	Indirect evidence

[1] Data for all treatment schedules combined: 13-10 grs, usual dose 1.0=1.5 grs in adults

[2] (1980-1984): Suramin test dose 0.2g day 1; followed by 1 g (0.5 for children) day 2. Lumbar puncture day 3; CSF ≤5 leucocytes/mcl subsequently treated with 4 more weekly injections 1 g (0.5 for children).

[3]1966-1979): 1966-71: Suramin 1 g days 1, 3, 6, 9, & 15. 1971-72: extended treatment, 7.5 g total with 0.5 g test dose. 1972-77: 1 g every 5 days to 4.5-12.0 g total with 0.5 g test dose. 1978-19: 5 weekly 1 g doses with 0.2 g test dose (all IV)

[4] Suramin (stage 1): test dose followed by 5 mg/kg by slow IV infusion on day 1, 10 mg/kg on day 3, and then 20 mg/kg on days 5, 11, 17, 23, and 30, to a maximum cumulative dose of 10 g

[5] Data for all treatment schedules combined: Suramin: From 1 course of < 20 gms to 4 courses of > 100 gms Tryparsamide: 4 injections, 0.04 g / Kg

Relapse during follow-up

Population	Study Study design	Outcome in the study, timepoint	Treatment Schedule	Events / participants	Comments
Stage 1 **Age not reported**	De Andrade Silva 1957	Parasitological relapse	Suramin[1]	1/36	One of the patients with CSF relapse had 8

	(retrospective cohort)	CSF relapse (definite) >2 years		3/36	cells/uL at baseline.
Stage 1 **Age not reported**	Wellde 1989a (prospective cohort)	Parasitological or clinical relapse 3 years	Suramin[2]	32/95	
Stage 1 **Age not reported**	Wellde 1989b (retrospective cohort)	Parasitological or clinical relapse 3 years	Suramin[3]	30/152	
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Parasitological relapse >2 years	Suramin+ Tryparsamide[4]	38/737	Indirect evidence

[1] Data for all treatment schedules combined: 13-10 grs, usual dose 1.0=1.5 grs in adults

[2] (1980-1984): Suramin test dose 0.2g day 1; followed by 1 g (0.5 for children) day 2. Lumbar puncture day 3; CSF ≤5 leucocytes/mcl subsequently treated with 4 more weekly injections 1 g (0.5 for children).

[3]1966-1979): 1966-71: Suramin 1 g days 1, 3, 6, 9, & 15. 1971-72: extended treatment, 7.5 g total with 0.5 g test dose. 1972-77: 1 g every 5 days to 4.5-12.0 g total with 0.5 g test dose. 1978-19: 5 weekly 1 g doses with 0.2 g test dose (all IV)

[4] Data for all treatment schedules combined: Suramin: From 1 course of < 20 gms to 4 courses of > 100 gms Tryparsamide: 4 injections, 0.04 g / Kg

Specific adverse events

Population	Study Study design	Outcome in the study, timepoint	Treatment Schedule	Events / participants	Comments
Stage 1 **Adults and children**	Wellde 1989a (prospective and retrospective cohort)	Rigours and chills 4 weeks	Suramin[1]	10/95	
Stage 1 **Adults and children**	Wellde 1989b (prospective and retrospective cohort)	Rash and urticaria 4 weeks	Suramin[1]	2/95	
Stage1 **Adults**	Frean 2018 (case series)	Myocarditis 30 days	Suramin[2]	1/19	

[1] (1980-1984): Suramin test dose 0.2g day 1; followed by 1 g (0.5 for children) day 2. Lumbar puncture day 3; CSF ≤5 leucocytes/mcl subsequently treated with 4 more weekly injections 1 g (0.5 for children).

[2]Suramin (stage 1): test dose followed by 5 mg/kg by slow IV infusion on day 1, 10 mg/kg on day 3, and then 20 mg/kg on days 5, 11, 17, 23, and 30, to a maximum cumulative dose of 10 g

Analysis 3. Pentamidine in people with first-stage r-HAT

Overall mortality

Population	Study ID Study design	Outcome in the study, timepoint	Treatment Schedule	Events / participants	Comments
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Deaths to 2 years and over	Pentamidine monotherapy[1]	7/46[a]	
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Deaths to 2 years and over	Pentamidine + Tryparsamide[2]	72/222[b]	Indirect evidence

[a]Available cases; Missing data: 15 participants not accounted for in reported outcomes and no reason for missingness reported;

[b]Available cases; Missing data: 56 participants not accounted for in reported outcomes and no reason for missingness reported.

[1]All schedules combined: Pentamidine monotherapy: From 1 x 26 mg + 7 x 52 mg to 1 x 100 mg + 10 x 200 mg

[2]All schedules combined Pentamidine + Tryparsamide: From 1 course of < 20 gms to 4 courses of > 100 gms

Clinical cure

Defined as: treatment success: alive, no trypanosomes, no rescue medication, CSF WBC count below threshold

Population	Study ID Study design	Outcome in the study, timepoint	Treatment Schedule	Events / participants	Comments
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Favourable evolution with no signs of disease 6-12 months	Pentamidine monotherapy[1]	7/46[a]	
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Favourable evolution with no signs of disease 2 years	Pentamidine monotherapy[1]	15/46[a]	
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Favourable evolution with no signs of disease >2 years	Pentamidine monotherapy[1]	21/46[a]	
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Favourable evolution with no signs of disease 6-12 months	Pentamidine + Tryparsamide[2]	39/222[b]	Indirect evidence

Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Favourable evolution with no signs of disease 2 years	Pentamidine + Tryparsamide[2]	61/222[b]	Indirect evidence
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Favourable evolution with no signs of disease >2 years	Pentamidine + Tryparsamide[2]	84/222[b]	Indirect evidence

[a] Available cases; Missing data: 15 participants not accounted for in reported outcomes and no reason for missingness reported;

[b] Available cases; Missing data: 56 participants not accounted for in reported outcomes and no reason for missingness reported.

[1]All schedules combined: Pentamidine monotherapy: From 1 x 26 mg + 7 x 52 mg to 1 x 100 mg + 10 x 200 mg

[2]All schedules combined Pentamidine + Tryparsamide: From 1 course of < 20 gms to 4 courses of > 100 gms

Death likely due to HAT

Population	Study ID Study design	Outcome in the study, timepoint	Treatment Schedule	Events / participants	Comments
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Deaths due to trypanosomiasis Timepoint unclear	Pentamidine monotherapy[1]	2/46[a]	
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Deaths due to trypanosomiasis Timepoint unclear	Pentamidine + Tryparsamide[2]	*/222[a]	Indirect evidence

[a]Available cases

[1]All schedules combined: Pentamidine monotherapy: From 1 x 26 mg + 7 x 52 mg to 1 x 100 mg + 10 x 200 mg

[2]All schedules combined Pentamidine + Tryparsamide: From 1 course of < 20 gms to 4 courses of > 100 gms

Relapse during follow up

Population	Study ID Study design	Outcome in the study, timepoint	Treatment/Schedule	Events / participants	Comments
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Parasitological relapse CSF relapse (definite) >2 years	Pentamidine monotherapy[1]	1/46[a] 3/46 [a]	
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Parasitological relapse >2 years	Pentamidine + Tryparsamide[2]	10/222 [a]	Indirect evidence

[a]Available cases

[1]All schedules combined: Pentamidine monotherapy: From 1 x 26 mg + 7 x 52 mg to 1 x 100 mg + 10 x 200 mg

[2]All schedules combined Pentamidine + Tryparsamide: From 1 course of < 20 gms to 4 courses of > 100 gms

Analysis 4. Melarsoprol in people with second-stage r-HAT

Overall mortality

Population	Study/	Outcome in the study, timepoint	Treatment/Schedule	Events / participants	Comments
Stage 2 **Age not reported**	Apted 1953 (case series)	Deaths at 6 months	Melarsoprol [1]	2/33	
Stage 2 **Age not reported**	Apted 1953 (case series)	Deaths at 12 months	Melarsoprol [1]	3/33	
Stage 2 **Age not reported**	Apted 1953 (case series)	Deaths at 30-48 months	Melarsoprol [1]	5/26[a]	
Stage 2 **Age not reported**	Apted 1953 (case series)	Deaths at 2.5-4 years	Melarsoprol [1]	5/26[a]	
Stage 2 **Age not reported**	Apted 1957 (case series)	Died at 6 months to 4 years	Melarsoprol[2]	21/136[b]	
Stage 2 **Age not reported**	De Andrade Silva 1954 (case series)	Deaths 6-16 months	Melarsoprol[3]	19/130	
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Deaths 2 years and over	Melarsoprol[4]	44/272	
Stage 2 **Adults and children**	Kuepfer 2011/2012 (prospective cohort)	Death during treatment 10 days	Melarsoprol[6]	9/107[c]	
Stage 2 **Adults and children**	Kuepfer 2011/2012	Total mortality 12 months	Melarsoprol[6]	12/107[cd]	
Stage 2 **Adults and children**	Wellde 1989b (retrospective cohort)	Mortality during treatment 4 weeks	Melarsoprol[7]	9/156	
Stage 2 **Adults and children**	Wellde 1989b (retrospective cohort)	Mortality Up to 3 years	Melarsoprol[7]	19/156	
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Deaths 2 years and over	Melarsoprol[8]	1/12	Indirect evidence

Stage 2 relapses **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Deaths 2 years and over	Melarsoprol[9] "Old nervous cases previously treated with tryparsamide" (stage 2 relapses)"	3/34	Mixed population
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Deaths 2 years and over	Melarsoprol+ Tryparsamise[11]	1/21	Indirect evidence

[a]Available cases, 7 of 33 lost to final follow up, reasons not reported

[b] 40 of 176 "not traced", timepoint last seen not known

[c]Of total 138 recruited, 30 were excluded that had received centre-specific Suramin treatments in the proof-of-concept stage of the study, and 1 excluded who died before initiation of treatment.

[d]During treatment, 1 death was due to advanced HAT and 8 deaths due to encephalopathic syndrome. During follow up, 1 death at 9 months was not related to HAT, and 2 others for unknown/unreported reasons.

[1] Dr Friedheim (Mel B), Specia Laboratories, Paris (Arsobal).2 series, 2 weeks apart, of 4 daily IV doses of 1.8 mg/kg OR 2 series, 2 weeks apart, of 3 IV daily doses of 3.6 mg/kg

[2] Melarsen oxide/BAL (Messrs. May and Baker Ltd.), Mel B ' (Friedheim) and ' Arsobal ' (Specia). 4 x 1.8 mg/kg days 1-4 followed by 4 x 1.8 mg/kg days 19-22; OR 3 x 1.8 mg/kg days 1-3 followed by 3 x 3.6 mg/kg days 18-20; OR 1 x 1.8 mg/kg day 1, 2 x 3.6 mg/kg days 2-3 followed by 3 x 3.6 mg/kg days 18-20; OR 3 x 3.6 mg/kg days 1-3; OR 4 x 3.6 mg/kg days 1-4; OR 3 x 2.5 ml days 1-3 followed by 3 ml day 11, 4 ml day 12, 5 ml day 13 followed by 3 x 5 ml days 21-23; OR 0.5 ml rising very gradually, not according to any fixed scheme but depending on the patient's condition and response, injections being given daily, on alternate days, or every third day.

[3]Melarsoprol all schedules combined: 3.6 mg/kg; 2 courses x 4 daily IV doses, separated by 7-14 days; Melarsoprol 3.6 mg/kg; 1 course x 4 daily IV doses; Melarsoprol 3.6 mg/kg; 4 x IV doses 3 days apart. 3 cases also received suramin or pentamidine + tryparsamide

[4] Data for all treatment schedules combined: From 3 x 3.6 mg to 4 courses of 4 x 3.6 mg

[6]Melarsoprol (without suramin pre-treatment): 2.2 mg/kg of melarsoprol IV for 10 consecutive days as a 3.6% solution in propylene glycol, maximally 5 ml a day

[7](1966-1979) 1966-67: 1.5 rising to 3.5 mL days 1-4; 4.0 rising to 5.0 mL days 11-14. 1968-76: 2.0 rising to 3.0 days 1-3; 3.5 rising to 5.0 mL days 12-14; 5.0 ml days 23-35. 1978-79: 1.5 rising to 2.5 mL days 1, 3 & 5; 3.0 rising to 4.0 mL days 12-14; 4.5 rising to 5.0 mL days 21-23 (all IV)

[8] Data for all treatment schedules combined: From 1 x 3.6 mg to 3 x 3.6 mg

[10] Data for all treatment schedules combined: From 1 x 3.6 mg to 3 courses of 4 x 3.6 mg

[11] Data for all treatment schedules combined: Melarsoprol: From 3 x 3.6 mg to 2 courses of 4 x 3.6 mg/3 courses of 3 x 3.6 mg. Tryparsamide: 4 injections, 0.04 g / Kg

Relapse during follow up

Population	Study Study design	Outcome in the study, timepoint	Treatment/ Schedule	Events / participants	Comments
Stage 2	Apted 1953	Relapse	Melarsoprol [1]	3/33	

Age not reported	(case series)	at 6 months			
Stage 2 **Age not reported**	Apted 1953 (case series)	Relapse at 12 months	Melarsoprol [1]	6/33	
Stage 2 **Age not reported**	Apted 1953 (case series)	Relapse at 30-48 months	Melarsoprol [1]	7/26[a]	
Stage 2 **Age not reported**	Apted 1953 (case series)	Relapse at 2.5-4 years	Melarsoprol [1]	1/26[a]	
Stage 2 **Age not reported**	Apted 1957 (case series)	Relapse at 6 months to 4 years	Melarsoprol[2]	13/136[b]	
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Parasitological relapse CSF relapse (definite) >2 years	Melarsoprol[3]	1/272 7/272	
Stage 2 **Adults and children**	Kuepfer 2011/2012 (prospective cohort)	Relapse 12 months	Melarsoprol[5]	1/107[c]	
Stage 2 **Adults and children**	Wellde 1989b (retrospective cohort)	Parasitological or clinical relapse Up to 3 years	Melarsoprol[5]	6/156	
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Parasitological relapse CSF relapse (definite) >2 years	Melarsoprol[6]	0/12 0/12	Indirect evidence
Stage 2 relapses **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Parasitological relapse CSF relapse (definite) >2 years	Melarsoprol[7] "Old nervous cases previously treated with tryparsamide" (stage 2 relapses)	2/34 2/34	Mixed population
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort)	Parasitological relapse CSF relapse (definite) >2 years	Melarsoprol+ Tryparsamide[8]	0/21 0/21	Indirect evidence

[a]Available cases, 7 lost to final follow up, reasons not reported

[b]40 of 176 "not traced", timepoint last seen not known

[c]Of total 138 recruited, 30 were excluded that had received centre-specific Suramin treatments in the proof-of-concept stage of the study, and 1 excluded who died before initiation of treatment.

[1] Dr Friedheim (Mel B), Specia Laboratories, Paris (Arsobal).2 series, 2 weeks apart, of 4 daily IV doses of 1.8 mg/kg OR 2 series, 2 weeks apart, of 3 IV daily doses of 3.6 mg/kg

[2] Melarsen oxide/BAL (Messrs. May and Baker Ltd.), Mel B ' (Friedheim) and ' Arsobal ' (Specia). 4 x 1.8 mg/kg days 1-4 followed by 4 x 1.8 mg/kg days 19-22; OR 3 x 1.8 mg/kg days 1-3 followed by 3 x 3.6 mg/kg days 18-20; OR 1 x 1.8 mg/kg day 1, 2 x 3.6 mg/kg days 2-3 followed by 3 x 3.6 mg/kg days 18-20; OR 3 x 3.6 mg/kg days 1-3; OR 4 x 3.6 mg/kg days 1-4; OR 3 x 2.5 ml days 1-3 followed by 3 ml day 11, 4 ml day 12, 5 ml day 13 followed by 3 x 5 ml days 21-23; OR 0.5 ml rising very gradually, not according to any fixed scheme but depending on the patient's condition and response, injections being given daily, on alternate days, or every third day

[3]Data for all treatment schedules combined: From 3 x 3.6 mg to 4 courses of 4 x 3.6 mg

[4]Melarsoprol (without suramin pre-treatment): 2.2 mg/kg of melarsoprol IV for 10 consecutive days as a 3.6% solution in propylene glycol, maximally 5 ml a day

[5](1966-1979) 1966-67: 1.5 rising to 3.5 mL days 1-4; 4.0 rising to 5.0 mL days 11-14. 1968-76: 2.0 rising to 3.0 days 1-3; 3.5 rising to 5.0 mL days 12-14; 5.0 ml days 23-35. 1978-79: 1.5 rising to 2.5 mL days 1, 3 & 5; 3.0 rising to 4.0 mL days 12-14; 4.5 rising to 5.0 mL days 21-23 (all IV)

[6] Data for all treatment schedules combined: From 1 x 3.6 mg to 3 x 3.6 mg

[7]Data for all treatment schedules combined From 1 x 3.6 mg to 3 courses of 4 x 3.6 mg

[8] Data for all treatment schedules combined: Melarsoprol: From 3 x 3.6 mg to 2 courses of 4 x 3.6 mg/3 courses of 3 x 3.6 mg. Tryparsamide: 4 injections, 0.04 g / Kg

Clinical cure/treatment success

Population	Study Study design	Outcome in the study, timepoint	Treatment/ Schedule	Events / participants	Comments
Stage 2 **Age not reported**	Apted 1953 (case series)	"Well at last follow-up 2.5 to 4 years	Melarsoprol[1]	20/26[a]	
Stage 2 **Adults and children**	Apted 1957 (case series)	"Well at last follow-up" 6 months to 4 years	Melarsoprol[2]	102/136[b]	
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort study	Favourable evolution with no signs of disease 6-12 months	Melarsoprol[3]	36/272	
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort study)	Favourable evolution with no signs of disease At 2 years	Melarsoprol[3]	97/272	
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort study)	Favourable evolution with no signs of disease >2 years	Melarsoprol[3]	160/272	

Stage 2 **Adults and children**	Kuepfer 2011/2012 (prospective cohort study)	Cure *(parasitological & clinical)* 10 days	Melarsoprol[4]	98/107[c]	
Stage 2 **Adults and children**	Kuepfer 2011/2012 (prospective cohort study)	Cure *(parasitological & clinical)* 12 months	Melarsoprol[4]	94/107[c]	
Stage 2 **Adults and children**	Wellde 1989b (retrospective cohort study)	Survival without relapse Up to 3 years	Melarsoprol[5]	131/156	
Stage 2 **Age not reported**	De Andrade Silva 1954 (case series)	Both blood and CSF free from trypanosomes after treatment and at follow up 6-16 months	Melarsoprol[6]	50/130	
Stage 2 relapses **Age not reported**	De Andrade Silva 1957 (retrospective cohort study)	Favourable evolution with no signs of disease 6-12 months	Melarsoprol[7] "Old nervous cases previously treated with tryparsamide" (stage 2 relapses)	4/34	Mixed population
Stage 2 relapses **Age not reported**	De Andrade Silva 1957 (retrospective cohort study)	Favourable evolution with no signs of disease At 2 years	Melarsoprol[7] "Old nervous cases previously treated with tryparsamide" (stage 2 relapses)	14/34	Mixed population
Stage 2 relapses **Age not reported**	De Andrade Silva 1957 (retrospective cohort study)	Favourable evolution with no signs of disease >2 years	Melarsoprol[7] "Old nervous cases previously treated with tryparsamide" (stage 2 relapses)	17/34	Mixed population
Stage 1 **Adults and children**	Apted 1957 (case series)	“Well at last follow-up” 6 months to 4 years	Melarsoprol[8]	5/5	Indirect evidence
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort study)	Favourable evolution with no signs of disease 6-12 months	Melarsoprol[9]	3/12	Indirect evidence
Stage 1 **Age not reported**	De Andrade Silva 1957	Favourable evolution with no signs of disease	Melarsoprol[9]	7/12	Indirect evidence

	(retrospective cohort study)	At 2 years			
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort study)	Favourable evolution with no signs of disease >2 years	Melarsoprol[9]	11/12	Indirect evidence
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort study)	Favourable evolution with no signs of disease 6-12 months	Melarsoprol +Tryparsamise[10]	5/21	Indirect evidence
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort study)	Favourable evolution with no signs of disease At 2 years	Melarsoprol +Tryparsamise[10]	14/21	Indirect evidence
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort study)	Favourable evolution with no signs of disease >2 years	Melarsoprol +Tryparsamise[10]	*/21	Indirect evidence

[a] 7/33 lost to follow up, reasons not reported

[b] 40 "not traced", timepoint last seen not known

[c] Of total 138 recruited, 30 were excluded that had received centre-specific Suramin treatments in the proof-of-concept stage of the study, and 1 excluded who died before initiation of treatment.

[1] Dr Friedheim (Mel B), Specia Laboratories, Paris (Arsobal).2 series, 2 weeks apart, of 4 daily IV doses of 1.8 mg/kg OR 2 series, 2 weeks apart, of 3 IV daily doses of 3.6 mg/kg

[2] Melarsen oxide/BAL (Messrs. May and Baker Ltd.), Mel B ' (Friedheim) and ' Arsobal ' (Specia). 4 x 1.8 mg/kg days 1-4 followed by 4 x 1.8 mg/kg days 19-22; OR 3 x 1.8 mg/kg days 1-3 followed by 3 x 3.6 mg/kg days 18-20; OR 1 x 1.8 mg/kg day 1, 2 x 3.6 mg/kg days 2-3 followed by 3 x 3.6 mg/kg days 18-20; OR 3 x 3.6 mg/kg days 1-3; OR 4 x 3.6 mg/kg days 1-4; OR 3 x 2.5 ml days 1-3 followed by 3 ml day 11, 4 ml day 12, 5 ml day 13 followed by 3 x 5 ml days 21-23; OR 0.5 ml rising very gradually, not according to any fixed scheme but depending on the patient's condition and response, injections being given daily, on alternate days, or every third day

[3] Data for all treatment schedules combined: From 3 x 3.6 mg to 4 courses of 4 x 3.6 mg

[4] Melarsoprol (without suramin pre-treatment): 2.2 mg/kg of melarsoprol IV for 10 consecutive days as a 3.6% solution in propylene glycol, maximally 5 ml a day

[5] (1966-1979) 1966-67: 1.5 rising to 3.5 mL days 1-4; 4.0 rising to 5.0 mL days 11-14. 1968-76: 2.0 rising to 3.0 days 1-3; 3.5 rising to 5.0 mL days 12-14; 5.0 ml days 23-35. 1978-79: 1.5 rising to 2.5 mL days 1, 3 & 5; 3.0 rising to 4.0 mL days 12-14; 4.5 rising to 5.0 mL days 21-23 (all IV)

[6] Melarsoprol all schedules combined: 3.6 mg/kg; 2 courses x 4 daily IV doses, separated by 7-14 days; Melarsoprol 3.6 mg/kg; 1 course x 4 daily IV doses; Melarsoprol 3.6 mg/kg; 4 x IV doses 3 days apart. 3 cases also received suramin or pentamidine + tryparsamide

[7] Data for all treatment schedules combined From 1 x 3.6 mg to 3 courses of 4 x 3.6 mg

[8] Melarsen oxide/BAL (Messrs. May and Baker Ltd.), Mel B ' (Friedheim) and ' Arsobal ' (Specia). A single injection of 3.6 mg./kg. (maximum dose 5 ml.)

[9] Data for all treatment schedules combined: From 1 x 3.6 mg to 3 x 3.6 mg

[10] Data for all treatment schedules combined: Melarsoprol: From 3 x 3.6 mg to 2 courses of 4 x 3.6 mg/3 courses of 3 x 3.6 mg. Tryparsamide: 4 injections, 0.04 g / Kg

Death likely to be due to treatment

Population	Study/	Outcome in the study, timepoint	Treatment/Schedule	Events / participants	Comments
Stage 2 **Age not reported**	Apted 1957 (case series)	Death definitely or possibly due to treatment At 6 weeks	Melaroprol[1]	4/136[a]	
Stage 2 **Age not reported**	De Andrade Silva 1954 (case series)	Deaths due to toxic encephalopathy 6-16 months	Melarsoprol[2]	11/130	
Stage 2 **Adults and children**	Kuepfer 2011/2012 (prospective cohort study)	Deaths due to encephalopathic syndrome 10 days	Melarsoprol[3]	8/107[b]	
Stage 2 relapses **Age not reported**	De Andrade Silva 1957 (retrospective cohort study)	Deaths due to Arsenical encephalopathy Follow-up unclear	Melarsoprol[4] Old nervous cases previously treated with tryparsamide" (stage 2 relapses)	3/34	Mixed population
Stage not reported **Age not reported**	Arroz 1987 (case series)	Encephalopathy resulting in death A few days after last dose	Melarsoprol[5]	5/183	Unclear population
Stage not reported **Age not reported**	Arroz 1987 (case series)	Encephalopathy resulting in death A few days after last dose	Melarsoprol[6]	7/200	Unclear population

[a]40 "not traced", timepoint last seen not known

[b]Of total 138 recruited, 30 were excluded that had received centre-specific Suramin treatments in the proof-of-concept stage of the study, and 1 excluded who died before initiation of treatment.

[1]Melarsen oxide/BAL (Messrs. May and Baker Ltd.), Mel B ' (Friedheim) and ' Arsobal ' (Specia). 4 x 1.8 mg/kg days 1-4 followed by 4 x 1.8 mg/kg days 19-22; OR 3 x 1.8 mg/kg days 1-3 followed by 3 x 3.6 mg/kg days 18-20; OR 1 x 1.8 mg/kg day 1, 2 x 3.6 mg/kg days 2-3 followed by 3 x 3.6 mg/kg days 18-20; OR 3 x 3.6 mg/kg days 1-3; OR 4 x 3.6 mg/kg days 1-4; OR 3 x 2.5 ml days 1-3 followed by 3 ml day 11, 4 ml day 12, 5 ml day 13 followed by 3 x 5 ml days 21-23; OR 0.5 ml rising very gradually, not according to any fixed scheme but depending on the patient's condition and response, injections being given daily, on alternate days, or every third day

[2]Melarsoprol all schedules combined: 3.6 mg/kg; 2 courses x 4 daily IV doses, separated by 7-14 days; Melarsoprol 3.6 mg/kg; 1 course x 4 daily IV doses; Melarsoprol 3.6 mg/kg; 4 x IV doses 3 days apart. 3 cases also received suramin or pentamidine + tryparsamide

[3]Melarsoprol (without suramin pre-treatment): 2.2 mg/kg of melarsoprol IV for 10 consecutive days as a 3.6%

[4]Data for all treatment schedules combined From 1 x 3.6 mg to 3 courses of 4 x 3.6 mg

[5]Melarsopral 3 series of 3 x daily progressively increasing IV doses (preceded by 2 or 3 Suramin IV doses and accompanied by corticosteroids)

[6] Melarsoprol single series of 4 x daily IV doses 3.6 mg/kg (sometimes preceded by Suramin, and sometimes with Tryparsamide)

Death likely to be due to HAT

Population	Study Study design	Outcome in the study, timepoint	Treatment/ Schedule	Events / participants	Comments
Stage 2 **Age not reported**	Apted 1957 (case series)	occurred following a "failure to respond to treatment" 6 months to 4 years	Melaroprol[1]	14/136[a]	
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort study)	Deaths due to trypanosomiasis Follow-up unclear	Melarsoprol[2]	7/272	
Stage 2 **Adults and children**	Kuepfer 2011/2012 (prospective cohort study)	Death during treatment due to severe r-HAT 10 days	Melarsoprol[3]	1/107[b]	
Stage 1 **Age not reported**	De Andrade Silva 1957 (retrospective cohort study)	Deaths due to trypanosomiasis Follow-up unclear	Melarsoprol[4]	0/12	Indirect evidence
Stage 2 **Age not reported**	De Andrade Silva 1957 (retrospective cohort study)	Deaths due to trypanosomiasis Follow-up unclear	Melarsoprol+ Tryparsamise[5]	0/21	Indirect evidence

[a] 40 of originally 176 "not traced", timepoint last seen not known

[b] Of total 138 recruited, 30 were excluded that had received centre-specific Suramin treatments in the proof-of-concept stage of the study, and 1 excluded who died before initiation of treatment.

[1] Melarsen oxide/BAL (Messrs. May and Baker Ltd.), Mel B ' (Friedheim) and ' Arsobal ' (Specia). 4 x 1.8 mg/kg days 1-4 followed by 4 x 1.8 mg/kg days 19-22; OR 3 x 1.8 mg/kg days 1-3 followed by 3 x 3.6 mg/kg days 18-20; OR 1 x 1.8 mg/kg day 1, 2 x 3.6 mg/kg days 2-3 followed by 3 x 3.6 mg/kg days 18-20; OR 3 x 3.6 mg/kg days 1-3; OR 4 x 3.6 mg/kg days 1-4; OR 3 x 2.5 ml days 1-3 followed by 3 ml day 11, 4 ml day 12, 5 ml day 13 followed by 3 x 5 ml days 21-23; OR 0.5 ml rising very gradually, not according to any fixed scheme but depending on the patient's condition and response, injections being given daily, on alternate days, or every third day

[2] Data for all treatment schedules combined: From 3 x 3.6 mg to 4 courses of 4 x 3.6 mg

[3] Melarsoprol (without suramin pre-treatment): 2.2 mg/kg of melarsoprol IV for 10 consecutive days as a 3.6% solution in propylene glycol, maximally 5 ml a day

[4] Data for all treatment schedules combined: From 1 x 3.6 mg to 3 x 3.6 mg

[5] Data for all treatment schedules combined: Melarsoprol: From 3 x 3.6 mg to 2 courses of 4 x 3.6 mg/3 courses of 3 x 3.6 mg. Tryparsamide: 4 injections, 0.04 g / Kg

Adverse events

Population	Study Study design	Outcome in the study, timepoint	Treatment/Schedule	Events / participants	Comments
Stage 2 **Adults and children**	Kuepfer 2011/2012 (prospective cohort study)	Encephalopathic syndrome during treatment 10 days	Melarsoprol[1]	8/107[a]	
Stage 2 **Adults and children**	Kuepfer 2011/2012 (prospective cohort study)	SAEs 34 days	Melarsoprol[1]	27/107[ab]	
Stage 2 **Adults and children**	Kuepfer 2011/2012 (prospective cohort study)	Any AEs 34 days	Melarsoprol[1]	65.5%[ab]	"35.5% the patients had an event-free treatment." [27/107 had an SAE. Other adverse events reported included febrile reactions (37%), headache (22%), vomiting (13%), dizziness (9%), skin reactions (6.5%), nausea (5.6%) and diarrhoea (4%)]
Stage not reported **Age not reported**	Arroz 1987 (case series)	Encephalopathy A few days after last dose	Melarsoprol[2]	11/183	Unclear population
Stage not reported **Age not reported**	Arroz 1987 (case series)	Encephalopathy A few days after last dose	Melarsoprol[3]	10/200	Unclear population

[a]Of total 138 recruited, 30 were excluded that had received centre-specific Suramin treatments in the proof-of-concept stage of the study, and 1 excluded who died before initiation of treatment.

[b]Follow-up for SAEs not explicitly reported, but all SAEs were during treatment or involved prolongation of hospitalisation subsequent to treatment. Maximum hospitalisation period was 34 days, so this is extracted as the timepoint. 33.3% (9/27) of the SAEs were fatal and included one death due to advanced HAT and 8 deaths due to ES. 14.8% (4/27) SAEs were life threatening events (non-fatal ES). 22.2% (6/27) SAEs were based on prolonged hospitalizations of patients who were kept for observation due to general weakness. 29.6% (8/27) SAEs were medical events and included treatment of malaria, severe vomiting, severe headache, cardiac arrhythmia and psychosis at end of treatment.

[1]Melarsoprol (without suramin pre-treatment): 2.2 mg/kg of melarsoprol IV for 10 consecutive days as a 3.6% solution in propylene glycol, maximally 5 ml a day

[2]Melarsopral 3 series of 3 x daily progressively increasing IV doses (preceded by 2 or 3 Suramin IV doses and accompanied by corticosteroids)

[3] Melarsoprol single series of 4 x daily IV doses 3.6 mg/kg (sometimes preceded by Suramin, and sometimes with Tryparsamide)

Analysis 5. Suramin+Melarsoprol in people with second-stage r-HAT

Overall mortality

Population	Study Study design	Outcome in the study, timepoint	Treatment/Schedule	Events / participants	Comments
Stage 1 and 2[1] **Age not reported**	Bales 1989	"died either before, during or after therapy with melarsoprol" FU time not reported	Suramin+Melarsoprol [2]	5/46[a]	Mixed population
Stage 1 and 2 [4] **Adults and children**	Buyst 1975 (case series)	Mortality during or immediately after treatment Up to 4 days after treatment	Suramin+Melarsoprol[5]	14/231[b]	Mixed population
Stage 1 and 2 **Age not reported**	Fèvre 2008 (outbreak study)	Deaths reported Approx.2 months	Suramin (Stage1) or Melarsoprol (Stage 2)[7]	27/568[c]	Mixed population
Stage 2 **Adults and children**	Foulkes 1975	Expiration in hospital Up to 4 weeks	Suramin + Melarsoprol + Prednisolone[8]	2/18	Additional treatment
Stage 2 **Adults and children**	Foulkes 1975	Expiration in hospital Up to 4 weeks	Suramin + Melarsoprol[9]	4/18	
Stage 1 and 2[10] **Adults and children**	Harrison 1997	Non-survival 2.5 to 45 months	Suramin followed by Melarsoprol[11]	2/24[d]	Mixed population
Stage 1 and 2 **Children and adults**	Kagira 2011	Died 2 months	Suramin (stage 1) or Melarsoprol (stage 2)[12]	2/31	Mixed population
Stage 2 **Adults and children**	Kato 2015 (retrospective cohort)	Death in hospital 1 month	Suramin followed by Melarsoprol[13]	27/240	
Stage 1 and 2 **Adults and children**	Kato 2015	Death in hospital 1 month	Suramin or Suramin followed by Melarsoprol[13]	27/257	Mixed population

Stage 1 **Adults and children**	MacLean 2010	Death Follow-up not reported	Suramin followed by Melarsoprol[15]	2/34	Mixed population
Stage 2 **Adults and children**	MacLean 2010	Death Follow-up not reported	Suramin followed by Melarsoprol[16]	14/185	
Stage 2 **Adults and children**	MacLean 2010	Death Follow-up not reported	Suramin followed by Melarsoprol[17]	1/9	
Stage 1 and 2 **Adults and children**	MacLean 2010	Death Follow-up not reported	Suramin (stage 1) or Suramin followed by Melarsoprol (stage 1 and 2) [18]	17/275	Mixed population
Stage 1 and 2[g] **Adults and children**	Matemba 2010	Reported deaths Follow-up: average 25 days	Suramin (stage 1) or Melarsoprol (stage 2) [19]	7/143[h]	Mixed population
Stage 2 **Adults and children**	Veeken 1989	All cause death 5 weeks	Suramin+Melarsoprol[20]	17/106	
Stage 1 and 2 **Adults and children**	Veeken 1989	All cause death 5 weeks	Suramin (stage 1) or Suramin followed by Melarsoprol (stage 2) [21]	19/158	Mixed population
Stage 1 and 2 **Adults and children**	Veeken 1989	All cause death 3-9 months	Suramin (stage 1) or Suramin followed by Melarsoprol (stage 2) [21]	19/83[i]	Mixed population
Stage 2 **Adults and children**	Wellde 1989a	Mortality during treatment 4 weeks	Suramin followed by Melarsoprol [22]	5/113	
Stage 2 **Adults and children**	Wellde 1989a	Mortality Up to 3 years	Suramin followed by Melarsoprol [22]	11/113	
Stage not reported **Children**	Buyst 1977	Death 7 weeks	Suramin followed by Melarsoprol[23]	6/73[j]	Stage not reported
Stage 1 and 2 **Adults and Age not reported**	Hutchinson 1971	All-cause mortality during treatment 1.5 months	Suramin (Stage 1) or Suramin+Melarsoprol (Stage 2)[24]	27/220[k]	Mixed population

[1]Forty cases were late stage, CNS disease, with six early stage, peripheral disease.

[2]Treatment details not reported

[a] Five died either before (2), during (2) or after (1) therapy with melarsoprol. The two that died during therapy with melarsoprol are considered to represent toxic encephalopathy.

[4] CSF leucocyte counts in 214 of 231 patients showed "many of them to be in a very advaced stage of the disease. All 231 included patients also received chloroquine/proguanil malaria treatment.

[5] Days 1-5 = Suramin: Day 1 1/4 full dose, Day 3 1/2, Day 5 full dose. Days 7-36 = Melarsoprol: Day 7 1/10 full dose, Day 8 2/10, Day 9 3/10, Day 16 4/10, Days 17&18 5/10, Day 25 5-6/10, Day 26 7-8/10, Day 27 9/10, Days 34, 35& 36 full dose. Full doses: Suramin = 20 mg per Kg body weight (maximum 1 g); Melarsoprol = 3.6 mg per Kg body weight or 0.1 ml of a 3.6% solution per kg (maximum 180 mg or 5 ml).

[b] One death not included as a study death has been included in all-cause mortality extraction (patient discharged apparently cured and died at a drinks party 3 days later). Causes of death included: r-HAT (2), unknown cause at a beer party (1), measles (1), malaria (1), treatment-related encephalopathy (6), arsenical enteritis (1), trypanosomal myocarditis (1), abdominal crisis, probably of reactive origin (1).

[7]Schedule not reported; suramin (stage 1) or Melarsoprol (stage 2)

[c]Mortality not extractable by drug / stage

[8]Suramin 0.25 gm day 1, 0.25 gm day 3, 0.5 gm day 5; Melarsoprol 37.5 cl over 4 weeks (proportionally less for children); Prednisolone 10 mg 3/day from diagnosis until 1 week after end of melarsoprol treatment

[9]Suramin 0.25 gm day 1, 0.25 gm day 3, 0.5 gm day 5; Melarsoprol 37.5 cl over 4 weeks (proportionally less for children)

[10]All had trypanosomes in the spinal fluid and some symptoms of meningoencephalopathy

[11] Initial dosing: suramin on days 1 (5 mg/kg), 2 (10 mg/kg), and 4 (10 mg/kg); followed by IV melarsoprol 3 courses of 3 consecutive daily doses at increasing concentrations, 7 days between courses 1 and 2 and 6 days between 2 and 3 (Day 5 1.8 mg/kg, Day 6 2.16 mg/kg, Day 7 2.52 mg/kg, Day 14 2.52 mg/kg, Day 15 2.88 mg/kg, Day 16 3.24 mg/kg, Day 23 3.6 mg/kg, Day 24 3.6 mg/kg, Day 25 3.6 mg/kg)

[d]Lost to follow-up: n=4 of 28 reasons not reported

[12]Early-stage disease was treated using 5 injections of suramin at a dosage of 20 mg/kg body weight (a maximum of 1 g/injection) at intervals of 5–7 days, while late-stage disease was treated using Melarsoprol (3.6 mg/kg repeated every 7 days for 4 weeks).

[13]Initial dose of Suramin followed by a daily dose of melarsoprol

[14]Tanzania: IV suramin 5 mg/kg (day 1), full dose 20 mg/kg (day 3). Uganda: IV suramin 5 mg/kg. Melarsoprol treatment for all patients: 2.2 mg/kg of melarsoprol IV for 10 consecutive days as a 3.6% solution in propylene glycol, maximally 5 ml a day.

[15]Early stage cases, Malawi. Early stage cases were given four doses of suramin followed by one series of MelB

[16] Late stage cases, Uganda. Late stage cases were initially given suramin followed by four series of melarsoprol (MelB) (Arsobal: Rhone-Poulenc: 3.6 mg/kg).

[17] Late stage cases, Malawi. Late stage patients were given two doses of suramin followed by three series of MelB.

[18] Stage 1 Uganda: Suramin, Stage1 Malawi and stage 2 Uganda and Malawi, different schedules of Suramin, followed by Melarsoprol

[g] 30 early and 113 late stage cases

[19] “first-stage patients receive Suramin and second-stage patients Melarsoprol". Schedule not reported

[h] Deaths also reported by age: 0-4 years: 0/5; 5-14 years: 1/15; 15-29 years: 3/49; 30-44 years: 1/34; 45-59 years: 1/23; 60-69 years: 1/9; 70-80+years: 0/8

[20] Suramin: 20 mg/kg IV (max 1 g) on days 1 & 3. Lumbar puncture (LP) day 4 If LP abnormal, Melarsoprol started. 36 g/L, 3 daily IV doses, 1 week interval, 3 daily IV doses; doses increasing beginning 72-180 mg/day, maximum 1242 mg.

[21]Suramin 20 mg/kg IV (max 1 g) on days 1 & 3. Lumbar puncture (LP) day 4 – if normal suramin days 7, 14 & 21. LP repeated day 21. If LP abnormal, Melarsoprol started. 36 g/L, 3 daily IV doses, 1 week interval, 3 daily IV doses; doses increasing beginning 72-180 mg/day, maximum 1242 mg.

[i]Lost to follow up: 75/158 at 3-9 months

[22] (1980-1984) Suramin test dose 0.2g day 1; followed by 1 g (0.5 for children) day 2. Lumbar puncture day 3; CSF leucocytes/mcl >5 leucocytes/mcl treated with melarsoprol, 3 courses of 3 injections every other day, 1 week between each course; doses rising from 0.5 mL to 5.0 mL.

[23]Preliminary Suramin. Melarsoprol: 4 interrupted 3-day courses with gradually increasing doses over 36 days, calculated according to weight

[j]Deaths: Severity of r-HAT = 1, Measles = 3, Encephalopathy = 2

[24]Early cases; Suramin. Late cases: Suramin + melarsoprol; Suramin test dose and 5-6 IV injections of 20mg/kg, 5 day intervals after first two doses (on alternate days); Melarsoprol 2 courses of 4 daily injections, courses separated by 1 week. dose starts at 1.8 mg/kg then works up to full dose of 3.6 mg/kg by dose 3 or 4. Some patients received a 3rd course of melarsoprol, 3 patients received orally.

[k]12 of originally included 232 not included in mortality extraction because both drugs were not available, so the adequate treatment regimen was not possible.

Death likely due to treatment

Population	Study/	Outcome in the study, timepoint	Treatment/ Schedule	Events / participants	Comments
Stage 1 and 2[1] **Age not reported**	Bales 1989	"Death due to toxic encephalopathy" FU time not reported	Suramin+Melarsoprol [2]	2/46	Mixed population
Stage 1 and 2[3] **Adults and children**	Buyst 1975	Treatment-related mortality during or immediately after treatment Up to 4 days after treatment	Suramin+Melarsoprol[4]	7/231[a]	Mixed population
Stage 2 Adults and children	Foulkes 1975	Expiration in hospital due to reactive encephalopathy Up to 4 weeks	Suramin + Melarsoprol + Prednisolone[5]	2/18	Additional treatment
Stage 2 Adults and children	Foulkes 1975	Expiration in hospital due to reactive encephalopathy Up to 4 weeks	Suramin + Melarsoprol[6]	0/18	
Stage 2 Adults and children	Kato 2015	Death following Reactive Encephalopathy 1 month	Suramin or Suramin followed by Melarsoprol[7]	7/257	

Stage 2 **Adults and children**	Veeken 1989	Developed encephalopathy while receiving melarsoprol and died 5 weeks	Suramin+Melarsoprol[9]	10/106	
Stage not reported **Children**	Buyst 1977	Death due to Encephalopathy 7 weeks	Suramin followed by Melarsoprol[10]	2/73	Stage not reported
Stage 2 **Age not reported**	Hutchinson 1971	Deaths due to AEs (Encephalopathy, intractable diarrhea, chest pain, jaundice) 1.5 months	Suramin+Melarsoprol[11]	9/150	

[1]Forty cases were late stage, CNS disease, with six early stage, peripheral disease.

[2] Treatment details not reported.

[3]CSF leucocyte counts in 214 of 231 patients showed "many of them to be in a very advanced stage of the disease. All 231 included patients also received chloroquine/proguanil malaria treatment.

[4]Days 1-5 = Suramin: Day 1 1/4 full dose, Day 3 1/2, Day 5 full dose. Days 7-36 = Melarsoprol: Day 7 1/10 full dose, Day 8 2/10, Day 9 3/10, Day 16 4/10, Days 17&18 5/10, Day 25 5-6/10, Day 26 7-8/10, Day 27 9/10, Days 34, 35& 36 full dose. Full doses: Suramin = 20 mg per Kg body weight (maximum 1 g); Melarsoprol = 3.6 mg per Kg body weight or 0.1 ml of a 3.6% solution per kg (maximum 180 mg or 5 ml).

[a] Causes of death included: treatment-related encephalopathy (6), abdominal crisis, probably of reactive origin (1).

[5]Suramin 0.25 gm day 1, 0.25 gm day 3, 0.5 gm day 5; Melarsoprol 37.5 cl over 4 weeks (proportionally less for children); Prednisolone 10 mg 3/day from diagnosis until 1 week after end of melarsoprol treatment

[6]Suramin 0.25 gm day 1, 0.25 gm day 3, 0.5 gm day 5; Melarsoprol 37.5 cl over 4 weeks (proportionally less for children)

[7]Initial dose of Suramin followed by a daily dose of melarsoprol

[9]Suramin: 20 mg/kg IV (max 1 g) on days 1 & 3. Lumbar puncture (LP) day 4 If LP abnormal, Melarsoprol started. 36 g/L, 3 daily IV doses, 1 week interval, 3 daily IV doses; doses increasing beginning 72-180 mg/day, maximum 1242 mg.

[10]Preliminary Suramin. Melarsoprol: 4 interrupted 3-day courses with gradually increasing doses over 36 days, calculated according to weight

[11]Suramin + melarsoprol; Suramin test dose and 5-6 IV injections of 20mg/kg, 5 day intervals after first two doses (on alternate days); Melarsoprol 2 courses of 4 daily injections, courses separated by 1 week. dose starts at 1.8 mg/kg then works up to full dose of 3.6 mg/kg by dose 3 or 4. Some patients received a 3rd course of melarsoprol, 3 patients received orally.

Death likely due to HAT

Population	Study/	Outcome in the study, timepoint	Treatment/ Schedule	Events / participants	Comments
Stage 1 and 2 [1] **Adults and children**	Buyst 1975	r-HAT-related mortality during	Suramin+Melarsoprol[2]	3/231[a]	Mixed population

		or immediately after treatment Up to 4 days after treatment			
Stage not reported **Children**	Buyst 1977	Death due to severity of HAT 7 weeks	Suramin followed by Melarsoprol[4]	1/73	Stage not reported

[1] CSF leucocyte counts in 214 of 231 patients showed "many of them to be in a very advanced stage of the disease. All 231 included patients also received chloroquine/proguanil malaria treatment.

[2]Days 1-5 = Suramin: Day 1 1/4 full dose, Day 3 1/2, Day 5 full dose. Days 7-36 = Melarsoprol: Day 7 1/10 full dose, Day 8 2/10, Day 9 3/10, Day 16 4/10, Days 17&18 5/10, Day 25 5-6/10, Day 26 7-8/10, Day 27 9/10, Days 34, 35& 36 full dose. Full doses: Suramin = 20 mg per Kg body weight (maximum 1 g); Melarsoprol = 3.6 mg per Kg body weight or 0.1 ml of a 3.6% solution per kg (maximum 180 mg or 5 ml).

[a]Causes of death included: r-HAT severity (2), trypanosomal myocarditis (1)

[4]Preliminary Suramin. Melarsoprol: 4 interrupted 3-day courses with gradually increasing doses over 36 days, calculated according to weight.

Relapse during follow-up

Population	Study	Outcome in the study, timepoint	Treatment/ Schedule	Events / participants	Comments
Stage 1 and 2[1] **Age not reported**	Bales 1989	"Relapse following therapy with suramin and melarsoprol" FU time not reported	Suramin+Melarsoprol[2]	3/46	Mixed population
Stage not reported[3] **Adults and children**	Harrison 1997	Relapse defined as determined by re-emergence of trypanosomes in CNS fluid 2.5 to 17 months	Suramin followed by Melarsoprol[4]	2/24	Stage not reported
Stage 1 and 2 **Adults and children**	Kato 2015	Relapse Up to 1 month	Suramin or Suramin followed by Melarsoprol[5]	10/257	Mixed population
Stage 2 **Adults and children**	Wellde 1989a	Parasitological or clinical relapse Up to 3 years	Suramin followed by Melarsoprol[6]	7/113	
Stage 2 **Age not reported**	Hutchinson 1971	Deaths due to AEs (Encephalopathy, intractable diarrhea, chest pain, jaundice)	Suramin+Melarsoprol[7]	9/125	

		1.5 months			
Stage 1 and 2 **Adults and children**	Veeken 1989	Relapsed at 3-9 months	Suramin (stage 1) or Suramin followed by Melarsoprol (stage 2) [9]	15/83[b]	Mixed population

[1]Forty cases were late stage, CNS disease, with six early stage, peripheral disease.

[2] Treatment details not reported

[3]All had trypanosomes in the spinal fluid and some symptoms of meningoencephalopathy

[4] Initial dosing: suramin on days 1 (5 mg/kg), 2 (10 mg/kg), and 4 (10 mg/kg); followed by IV melarsoprol 3 courses of 3 consecutive daily doses at increasing concentrations, 7 days between courses 1 and 2 and 6 days between 2 and 3 (Day 5 1.8 mg/kg, Day 6 2.16 mg/kg, Day 7 2.52 mg/kg, Day 14 2.52 mg/kg, Day 15 2.88 mg/kg, Day 16 3.24 mg/kg, Day 23 3.6 mg/kg, Day 24 3.6 mg/kg, Day 25 3.6 mg/kg)

[5]Initial dose of Suramin followed by a daily dose of melarsoprol

[6] (1980-1984) Suramin test dose 0.2g day 1; followed by 1 g (0.5 for children) day 2. Lumbar puncture day 3; CSF leucocytes/mcl >5 leucocytes/mcl treated with melarsoprol, 3 courses of 3 injections every other day, 1 week between each course; doses rising from 0.5 mL to 5.0 mL.

[7] Melarsoprol; Suramin test dose and 5-6 IV injections of 20mg/kg, 5 day intervals after first two doses (on alternate days); Melarsoprol 2 courses of 4 daily injections, courses separated by 1 week. dose starts at 1.8 mg/kg then works up to full dose of 3.6 mg/kg by dose 3 or 4. Some patients received a 3rd course of melarsoprol, 3 patients received orally.

[9]Suramin 20 mg/kg IV (max 1 g) on days 1 & 3. Lumbar puncture (LP) day 4 – if normal suramin days 7, 14 & 21. LP repeated day 21. If LP abnormal, Melarsoprol started. 36 g/L, 3 daily IV doses, 1 week interval, 3 daily IV doses; doses increasing beginning 72-180 mg/day, maximum 1242 mg

[b]Lost to follow up: 75/158 at 3-9 months, 15 15 discharged with HL trypanosomiasis, evidence for CNS involvement was found during FU, necessitation of melarsoprol treatment. Reinfection cannot be excluded.

Specific adverse events

Population	Study	Outcome in the study, timepoint	Treatment/ Schedule	Events / participants	Comments
Stage 1 and 2 [1] **Adults and children**	Buyst 1975	CNS reactions Up Treatment completion (day 36)	Suramin+Melarsoprol[2]	12/231	Mixed population
Stage 1 and 2 [1] **Adults and children**	Buyst 1975	Diarrhoea Up Treatment completion (day 36)	Suramin+Melarsoprol[2]	62/231	Mixed population
Stage 2 **Adults and children**	Foulkes 1975	Reactive encephalopathy up to 4 weeks	Suramin + Melarsoprol + Prednisolone[3]	3/18	
Stage 2 **Adults and children**	Foulkes 1975	Reactive encephalopathy up to 4 weeks	Suramin + Melarsoprol[4]	1/18	

Stage 2 **Adults and children**	Foulkes 1975	"Arsenical dermatitis up to 4 weeks	Suramin + Melarsoprol + Prednisolone[3]	0/18	
Stage 2 **Adults and children**	Foulkes 1975	Arsenical dermatitis up to 4 weeks	Suramin + Melarsoprol[4]	1/18	
Stage 2 **Adults and children**	Foulkes 1975	Severe febrile reaction up to 4 weeks	Suramin + Melarsoprol + Prednisolone[3]	0/18	
Stage 2 **Adults and children**	Foulkes 1975	Severe febrile reaction up to 4 weeks	Suramin + Melarsoprol[4]	1/18	
Stage 2 **Adults and children**	Foulkes 1975	Arsenical enteritis up to 4 weeks	Suramin + Melarsoprol + Prednisolone[3]	0/18	
Stage 2 **Adults and children**	Foulkes 1975	Arsenical enteritis up to 4 weeks	Suramin + Melarsoprol[4]	1/18	
Stage 1 and 2 **Adults and children**	Kato 2015	Reactive Encephalopathy 1 month	Suramin or Suramin followed by Melarsoprol[5]	19/257	Mixed population
Stage 2 **Adults and children**	Veeken 1989	Developed encephalopathy while receiving melarsoprol 5 weeks	Suramin+Melarsoprol[7]	19/106	
Stage 1 and 2 **Adults and children**	Veeken 1989	Allergic rash 5 weeks	Suramin (stage 1) or Suramin followed by Melarsoprol (stage 2) [8]	7/155	Mixed population
Stage 1 and 2 **Adults and children**	Veeken 1989	Fever, shivering 5 weeks	Suramin (stage 1) or Suramin followed by Melarsoprol (stage 2) [8]	5/155	Mixed population
Stage 1 and 2 **Adults and children**	Veeken 1989	Convulsions 5 weeks	Suramin (stage 1) or Suramin followed by Melarsoprol (stage 2) [8]	1/155	Mixed population
Stage 1 and 2 **Adults and children**	Veeken 1989	Psychosis 5 weeks	Suramin (stage 1) or Suramin followed by Melarsoprol (stage 2) [8]	1/155	Mixed population

Stage not reported **Children**	Buyst 1977	Encephalopathy 7 weeks	Suramin followed by Melarsoprol[9]	3/73	Stage not reported
Stage not reported **Age not reported**	Robertson 1963	Erythema nodosum leprosum 1 month	Suramin followed by Melarsoprol[10]	1/89	Stage not reported
Stage not reported **Age not reported**	Robertson 1963	Agranulocytosis 1 month	Suramin followed by Melarsoprol[10]	1/89	Stage not reported
Stage 2 **Age not reported**	Hutchinson 1971	Encephalopathy (Major toxic reactions following melarsoprol)	Suramin+Melarsoprol[11]	14/150	
Stage 2 **Age not reported**	Hutchinson 1971	Urticarial or morbilliform rash (Major toxic reactions following melarsoprol)	Suramin+Melarsoprol[11]	9/150	
Stage 2 **Age not reported**	Hutchinson 1971	Jaundice (Major toxic reactions following melarsoprol)	Suramin+Melarsoprol[11]	2/150	
Stage 2 **Age not reported**	Hutchinson 1971	Severe diarrhea (Major toxic reactions following melarsoprol)	Suramin+Melarsoprol[11]	4/150	
Stage 2 **Age not reported**	Hutchinson 1971	Chest pain (Major toxic reactions following melarsoprol)	Suramin+Melarsoprol[11]	1/150	

[1] CSF leucocyte counts in 214 of 231 patients showed "many of them to be in a very advaced stage of the disease. All 231 included patients also received chloroquine/proguanil malaria treatment.

[2]Days 1-5 = Suramin: Day 1 1/4 full dose, Day 3 1/2, Day 5 full dose. Days 7-36 = Melarsoprol: Day 7 1/10 full dose, Day 8 2/10, Day 9 3/10, Day 16 4/10, Days 17&18 5/10, Day 25 5-6/10, Day 26 7-8/10, Day 27 9/10, Days 34, 35& 36 full dose. Full doses: Suramin = 20 mg per Kg body weight (maximum 1 g); Melarsoprol = 3.6 mg per Kg body weight or 0.1 ml of a 3.6% solution per kg (maximum 180 mg or 5 ml).

[3]Suramin 0.25 gm day 1, 0.25 gm day 3, 0.5 gm day 5; Melarsoprol 37.5 cl over 4 weeks (proportionally less for children); Prednisolone 10 mg 3/day from diagnosis until 1 week after end of melarsoprol treatment

[4]Suramin 0.25 gm day 1, 0.25 gm day 3, 0.5 gm day 5; Melarsoprol 37.5 cl over 4 weeks (proportionally less for children)

[5]Initial dose of Suramin followed by a daily dose of melarsoprol

[7]Suramin: 20 mg/kg IV (max 1 g) on days 1 & 3. Lumbar puncture (LP) day 4 If LP abnormal, Melarsoprol started. 36 g/L, 3 daily IV doses, 1 week interval, 3 daily IV doses; doses increasing beginning 72-180 mg/day, maximum 1242 mg.

[8]Suramin 20 mg/kg IV (max 1 g) on days 1 & 3. Lumbar puncture (LP) day 4 – if normal suramin days 7, 14 & 21. LP repeated day 21. If LP abnormal, Melarsoprol started. 36 g/L, 3 daily IV doses, 1 week interval, 3 daily IV doses; doses increasing beginning 72-180 mg/day, maximum 1242 mg.

[9]Preliminary Suramin. Melarsoprol: 4 interrupted 3-day courses with gradually increasing doses over 36 days, calculated according to weight

[10] Preliminary Suramin followed by Melarsoprol (Schedule A: Days 1, 2 and 3 - 2.0, 2.5 and 3.0 ml., respectively. Days 10, 11 and 12 - 3.5, 4.0 and 5.0 ml., respectively. Days 19, 20 and 21 - 5.0 ml. on each day. Total : 35.0 ml. Schedule B: Days 1, 3 and 5 - 0.5, 1.0 and 1.5 ml., respectively. Days 10, 11 and 12 - 2.5 ml. each day. Days 19, 20 and 21 - 2.5 or 3.0, 3.5 or 4.0 and 4.0 or 5.0 ml., respectively. Days 28, 29 and 30 - 5.0 ml. each day. Total : 35.5-37.5 ml.)

[11]Suramin + melarsoprol; Suramin test dose and 5-6 IV injections of 20mg/kg, 5 day intervals after first two doses (on alternate days); Melarsoprol 2 courses of 4 daily injections, courses separated by 1 week. dose starts at 1.8 mg/kg then works up to full dose of 3.6 mg/kg by dose 3 or 4. Some patients received a 3rd course of melarsoprol, 3 patients received orally.

Clinical cure, treatment success

Population	Study/	Outcome in the study, timepoint	Treatment/Schedule	Events / participants	Narrative results
Stage 2 **Adults and children**	Foulkes 1975	*"Fit"* *at 3 month post-treatment*	Suramin + Melarsoprol + Prednisolone[1]	9/11[a]	
Stage 2 **Adults and children**	Foulkes 1975	*"Fit"* *at 3 month post-treatment*	Suramin + Melarsoprol[2]	8/12[b]	
Stage 1 and 2 **Adults and children**	Harrison 1997	*Survival with clear CNS fluid* *2.5 to 45 months*	Suramin followed by Melarsoprol[4]	20/24[c]	
Stage 1 and 2 **Children and adults**	Kagira 2011	*Successfully treated* *2 months*	Suramin (stage 1) or Merarsprol (stage 2)[5]	29/31[d]	
Stage 1 and 2 **Adults and children**	Veeken 1989	*Showed no abnormalities at follow-up* *3-9 months*	Suramin (stage 1) or Suramin followed by Melarsoprol (stage 2) [6]	49/83[e]	
Stage 2 **Adults and children**	Wellde 1989a	*Survival without relapse* *Up to 3 years*	Suramin followed by Melarsoprol [7]	95/113	

[a],7 LTFU at 3 months,

[b]6 LTFU at 3 months

[1]Suramin 0.25 gm day 1, 0.25 gm day 3, 0.5 gm day 5; Melarsoprol 37.5 cl over 4 weeks (proportionally less for children); Prednisolone 10 mg 3/day from diagnosis until 1 week after end of melarsoprol treatment

[2]Suramin 0.25 gm day 1, 0.25 gm day 3, 0.5 gm day 5; Melarsoprol 37.5 cl over 4 weeks (proportionally less for children)

[3]All had trypanosomes in the spinal fluid and some symptoms of meningoencephalopathy

[4] Initial dosing: suramin on days 1 (5 mg/kg), 2 (10 mg/kg), and 4 (10 mg/kg); followed by IV melarsoprol 3 courses of 3 consecutive daily doses at increasing concentrations, 7 days between courses 1 and 2 and 6 days between 2 and 3 (Day 5 1.8 mg/kg, Day 6 2.16 mg/kg, Day 7 2.52 mg/kg, Day 14 2.52 mg/kg, Day 15 2.88 mg/kg, Day 16 3.24 mg/kg, Day 23 3.6 mg/kg, Day 24 3.6 mg/kg, Day 25 3.6 mg/kg)

[c]Lost to follow-up: n=4/28 reasons not reported

[5]Early-stage disease was treated using 5 injections of suramin at a dosage of 20 mg/kg body weight (a maximum of 1 g/injection) at intervals of 5–7 days, while late-stage disease was treated using Melarsoprol (3.6 mg/kg repeated every 7 days for 4 weeks).

[d]Two cases (6.4%) which had co-infection with HIV resulted in death, while the rest were successfully treated."

[6]Suramin 20 mg/kg IV (max 1 g) on days 1 & 3. Lumbar puncture (LP) day 4 – if normal suramin days 7, 14 & 21. LP repeated day 21. If LP abnormal, Melarsoprol started. 36 g/L, 3 daily IV doses, 1 week interval, 3 daily IV doses; doses increasing beginning 72-180 mg/day, maximum 1242 mg.

[e]Lost to follow up: 75/158 at 3-9 months

[7] (1980-1984) Suramin test dose 0.2g day 1; followed by 1 g (0.5 for children) day 2. Lumbar puncture day 3; CSF leucocytes/mcl >5 leucocytes/mcl treated with melarsoprol, 3 courses of 3 injections every other day, 1 week between each course; doses rising from 0.5 mL to 5.0 mL.

Any adverse events

Population	Study/	Outcome in the study, timepoint	Treatment/Schedule	Events / participants	Narrative results
Stage 1 and 2[1] **Adults and children**	Harrison 1997	*Toxicity* *2.5 to 45 months*	Suramin followed by Melarsoprol[2]	3/24[a]	

[a]Lost to follow-up: n=4 reasons not reported

[1]All had trypanosomes in the spinal fluid and some symptoms of meningoencephalopathy

[2] Initial dosing: suramin on days 1 (5 mg/kg), 2 (10 mg/kg), and 4 (10 mg/kg); followed by IV melarsoprol 3 courses of 3 consecutive daily doses at increasing concentrations, 7 days between courses 1 and 2 and 6 days between 2 and 3 (Day 5 1.8 mg/kg, Day 6 2.16 mg/kg, Day 7 2.52 mg/kg, Day 14 2.52 mg/kg, Day 15 2.88 mg/kg, Day 16 3.24 mg/kg, Day 23 3.6 mg/kg, Day 24 3.6 mg/kg, Day 25 3.6 mg/kg)

Serious adverse events

Population	Study	Outcome in the study, timepoint	Treatment/ Schedule	Events / participants	Narrative results
Stage 1 and 2[1] Adults and children	Harrison 1997	*Severe toxicity* *2.5 to 45 months*	Suramin followed by Melarsoprol[2]	2/24[a]	

[1]All had trypanosomes in the spinal fluid and some symptoms of meningoencephalopathy

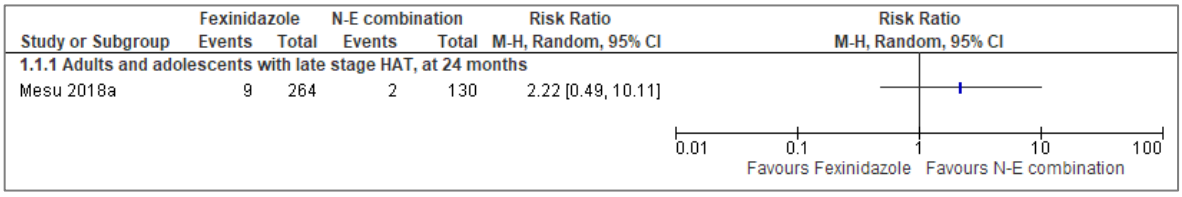
[2] Initial dosing: suramin on days 1 (5 mg/kg), 2 (10 mg/kg), and 4 (10 mg/kg); followed by IV melarsoprol 3 courses of 3 consecutive daily doses at increasing concentrations, 7 days between courses 1 and 2 and 6 days between 2 and 3 (Day 5 1.8 mg/kg, Day 6 2.16 mg/kg, Day 7 2.52 mg/kg, Day 14 2.52 mg/kg, Day 15 2.88 mg/kg, Day 16 3.24 mg/kg, Day 23 3.6 mg/kg, Day 24 3.6 mg/kg, Day 25 3.6 mg/kg)*Lost to follow-up: n=4 reasons not reported

[a]Lost to follow-up: n=4 reasons not reported

Appendix 6. Data and analyses (indirect evidence)

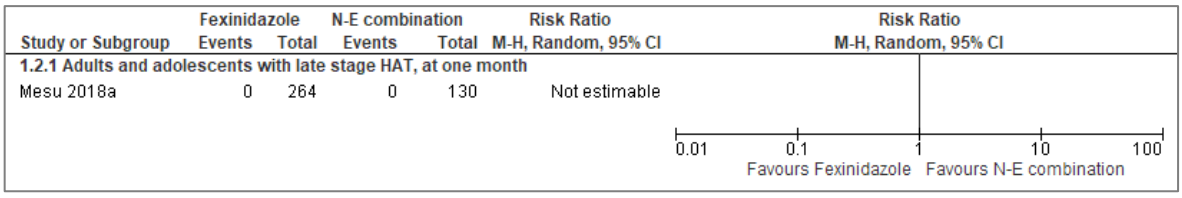
Fexinidazole (oral) versus nifurtimox-eflornithine (oral/IV) in second-stage g-HAT

1.1 Overall mortality, follow-up: 24 months

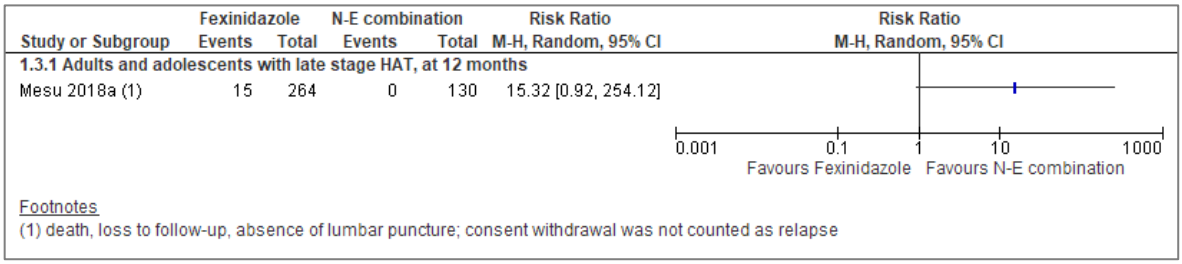


Causes of death: not reported

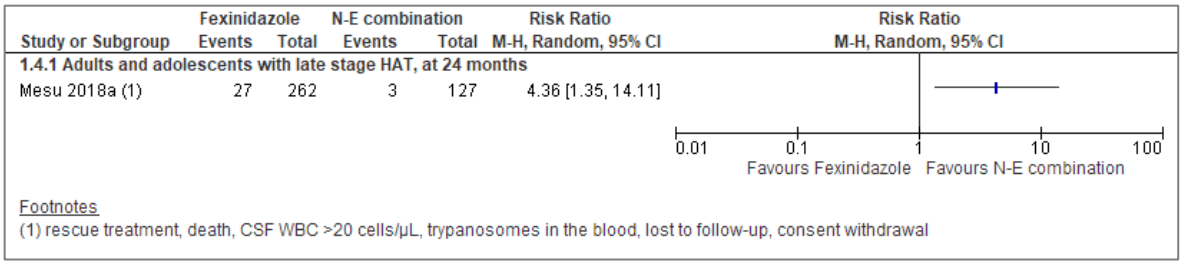
1.2 Death likely due to HAT, follow-up: 1 month



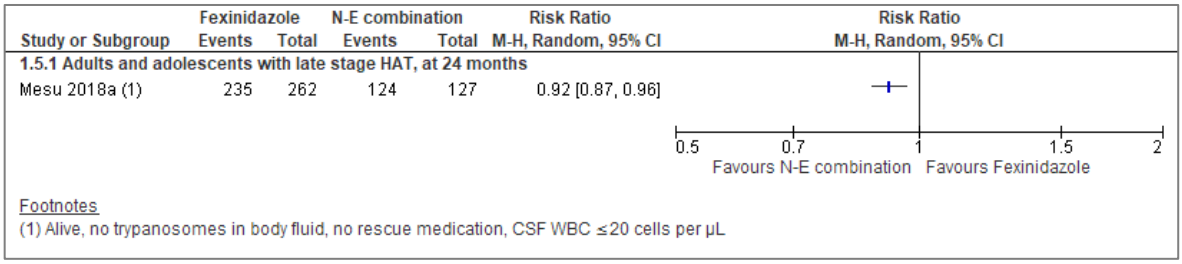
1.3 Relapse, follow-up: 12 months



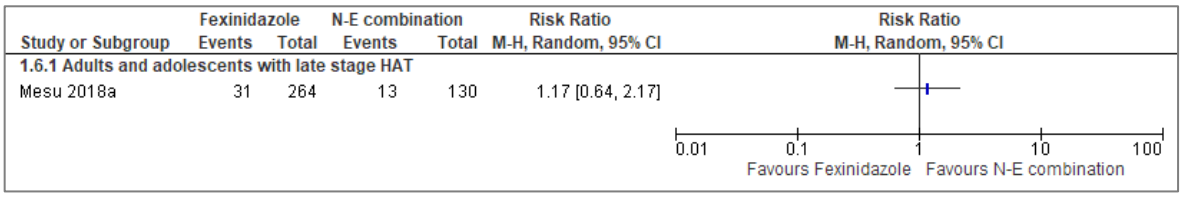
1.4 Treatment failure, follow-up: 24 months



1.5 Treatment success, follow-up: 24 months

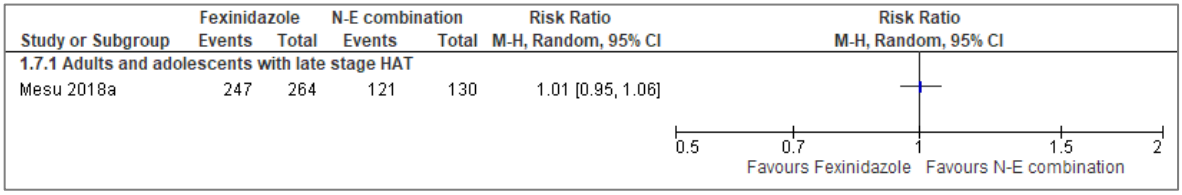


1.6 Serious adverse events, follow-up: 18 months

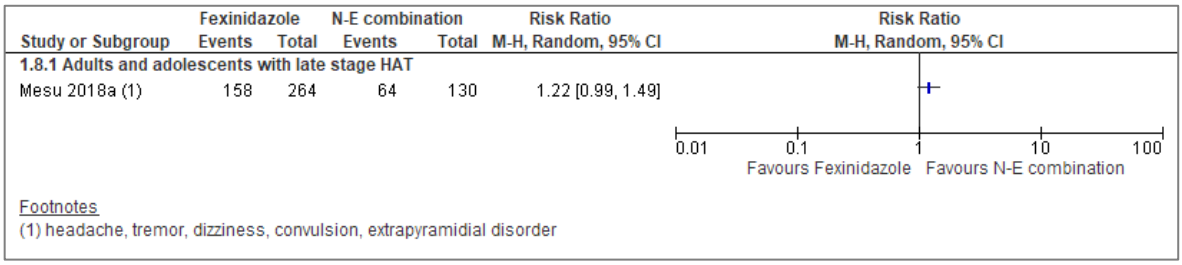


Four serious adverse events reported in three participants who received fexinidazole were considered possibly related to treatment: personality change, acute psychosis, and hyponatraemia. One patient with personality change died later from an unrelated serious adverse event following the use of traditional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

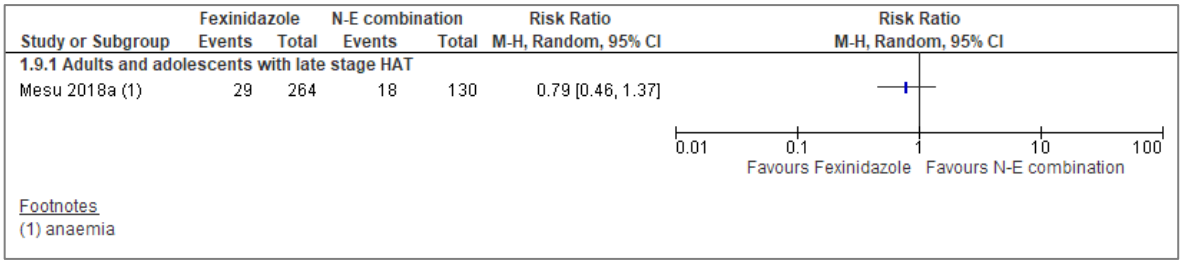
1.7 Adverse events, follow-up: 18 months



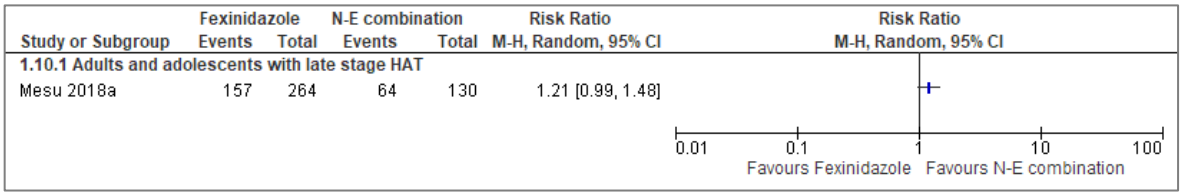
1.8 Adverse events: central nervous system, follow-up: 24 months



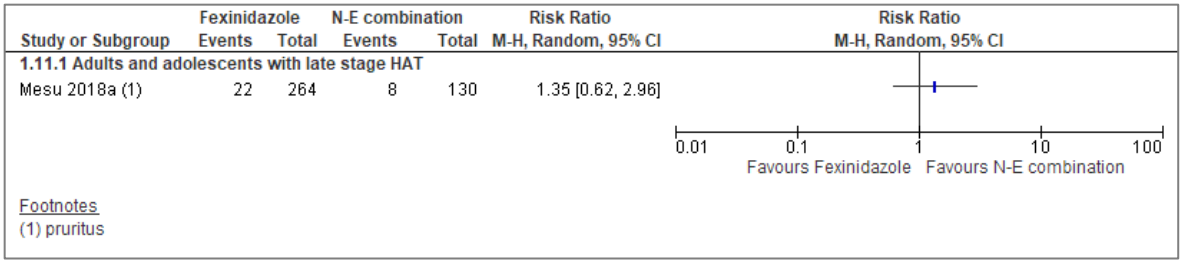
1.9 Adverse events: bone marrow toxicity, follow-up: 24 months



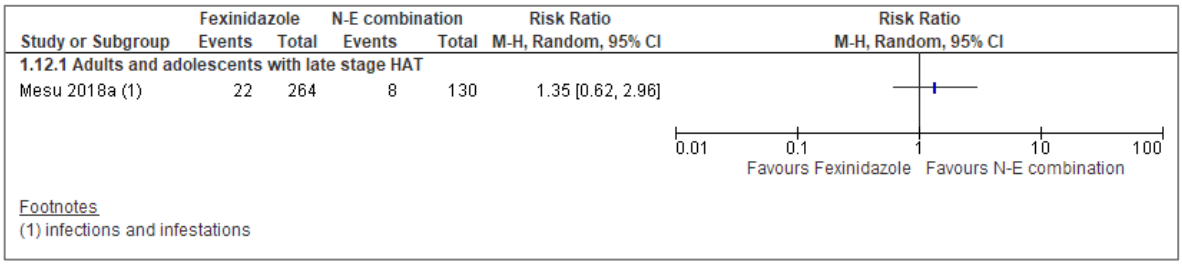
1.10 Adverse events: gastrointestinal symptoms, follow-up: 24 months



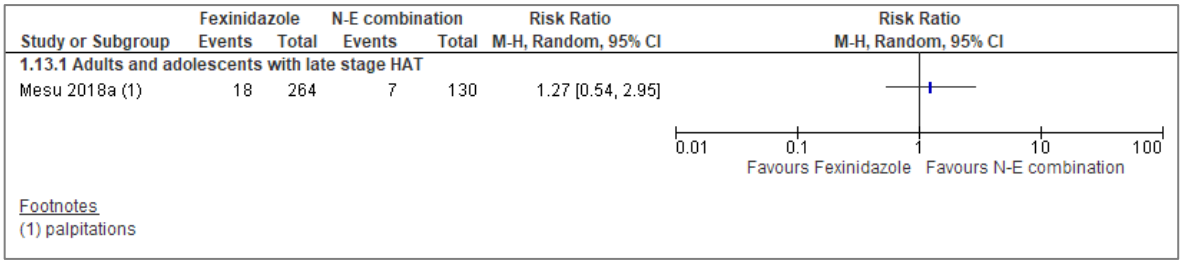
1.11 Adverse events: skin reactions, follow-up: 24 months



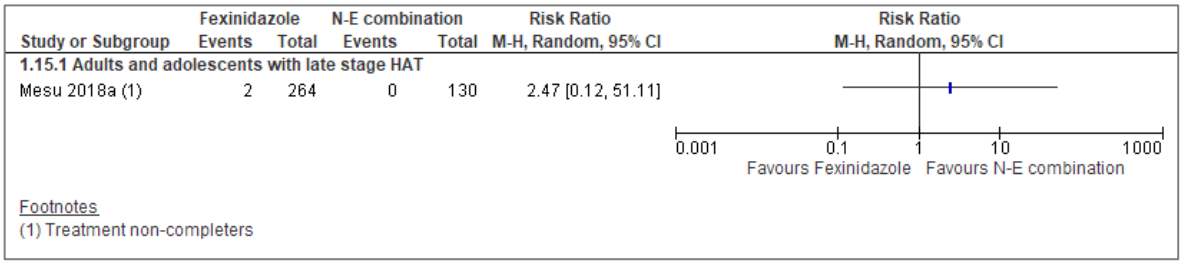
1.12 Adverse events: infections, follow-up: 24 months



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



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



Fexinidazole (oral) in adults and children with g-HAT 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 g-HAT	≥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 g-HAT	≥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 g-HAT	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 g-HAT	≥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 g-HAT	≥15 years	Mesu 2018b	1 / 41	24 per 1000	
	6-15 years	Mesu 2018c	0 / 19	0 per 1000	
Late stage 2 g-HAT	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 g-HAT	≥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 g-HAT	≥15 years	Mesu 2018b	40 / 41	977 per 1000	
	6-15 years	Mesu 2018c	19 / 19	1000 per 1000	
Late stage 2 g-HAT	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 g-HAT	≥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 g-HAT	≥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 g-HAT	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 g-HAT	≥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 g-HAT	≥15 years	Mesu 2018b	38 / 41	927 per 1000	
	6-15 years	Mesu 2018c	18 / 19	947 per 1000	
Late stage 2 g-HAT	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 g-HAT	≥15 years	Mesu 2018b	112 / 189 *	593 per 1000	

	6-15 years	Mesu 2018c	31 / 69 *	449 per 1000	Single arm extension studies to RCT Mesu 2018a
Early stage 2 g-HAT	≥15 years	Mesu 2018b	30 / 41 *	732 per 1000	
	6-15 years	Mesu 2018c	10 / 19 *	526 per 1000	
Late stage 2 g-HAT	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 g-HAT	≥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 g-HAT	≥15 years	Mesu 2018b	36 / 41	878 per 1000	
	6-15 years	Mesu 2018c	15 / 19	789 per 1000	
Late stage 2 g-HAT	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

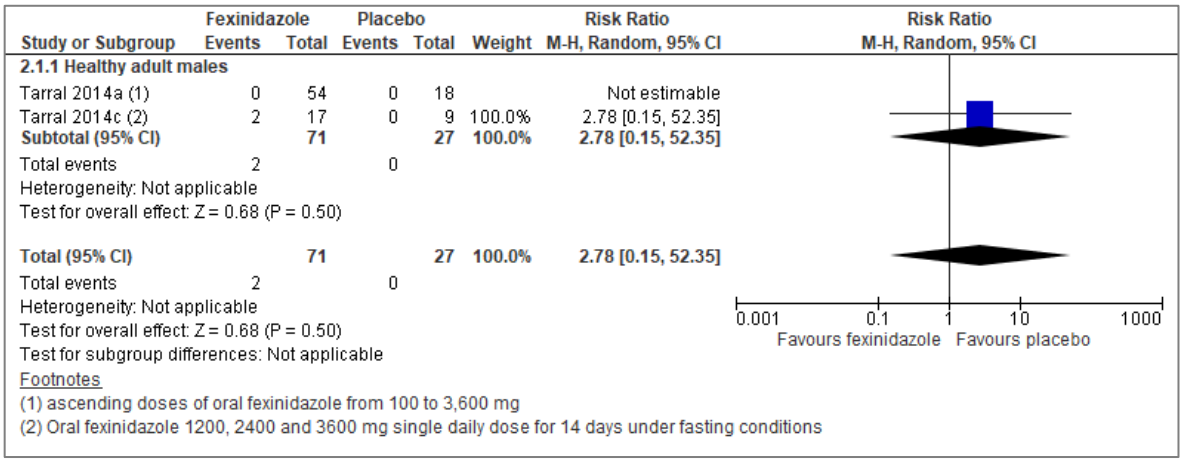
Population		Study	Events / participants	Rate per 1000	Comments
stage	age				
Stage 1	≥15 years	Mesu 2018b	0 / 189	0 per 1000	Single arm extension studies to RCT Mesu 2018a
	6-15 years	Mesu 2018c	0 / 69	0 per 1000	
Early stage 2	≥15 years	Mesu 2018b	0 / 41	0 per 1000	
	6-15 years	Mesu 2018c	0 / 19	0 per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

		Tarrall 2014d	1 / 12	83 per 1000	Single dose of 1200 mg
		Tarrall 2014e	7 / 30	233 per 1000	1200 mg to 2400 mg oral fexinidazole for 10d

*all patients were hospitalized during the treatment period

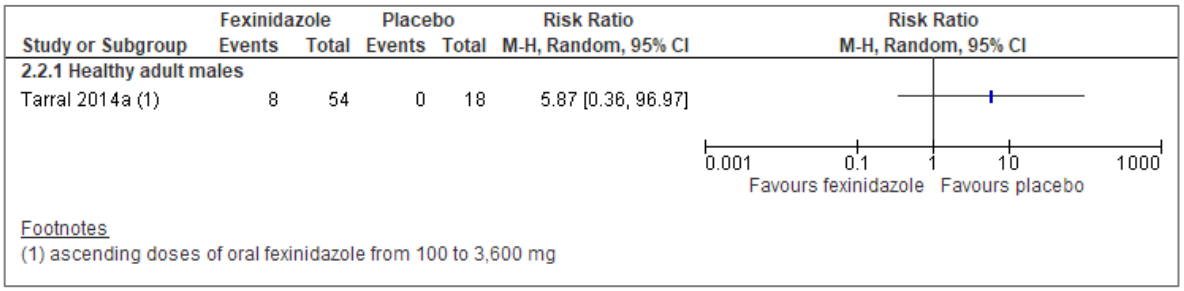
Fexinidazole (oral) versus placebo in healthy adult male volunteers

2.1 Serious adverse events, follow-up: not reported

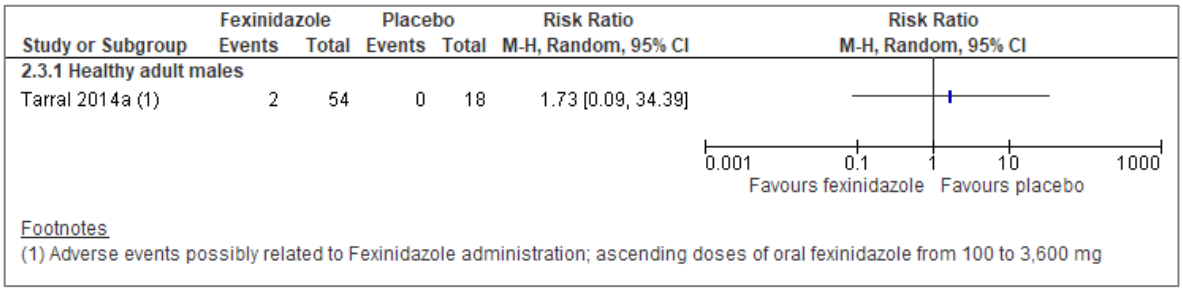


Two SAEs were reported by subjects who received fexinidazole: one subject (2,400 mg) asked to stop the study after 9 days of treatment due to intermittent headache, anxiety, vomiting, liquid stool episodes and myalgia of inferior limbs. Moderate anxiety had started the day preceding the first study drug 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.

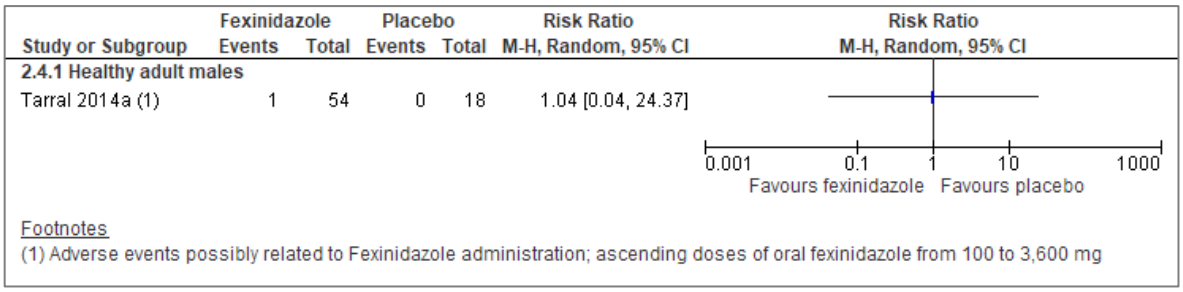
2.2 Adverse events, follow-up: not reported



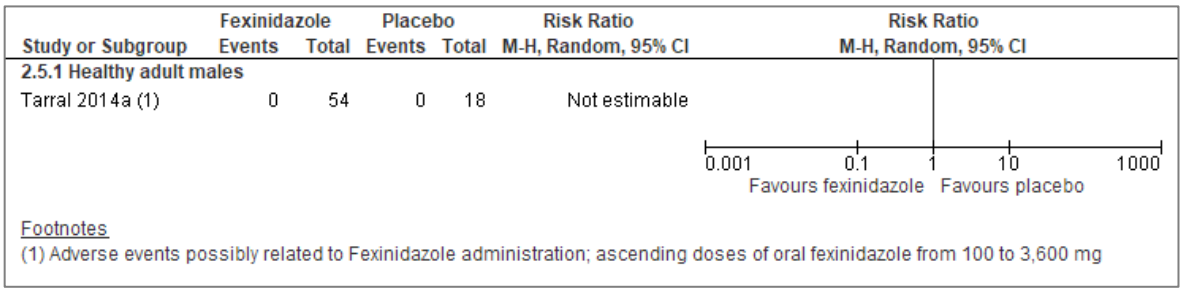
2.3 Adverse events: central nervous system, follow-up: not reported



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



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



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

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

Population age	Study	Events / participants	Rate per 1000	Causes of death
≥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 /mm^3 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	Study	Events / participants	Rate per 1000
age			
≥15 years	Pohlig 2016	23 / 137	168 per 1000

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

Population	Study	Events / participants	Rate per 1000	Comments
age				
≥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

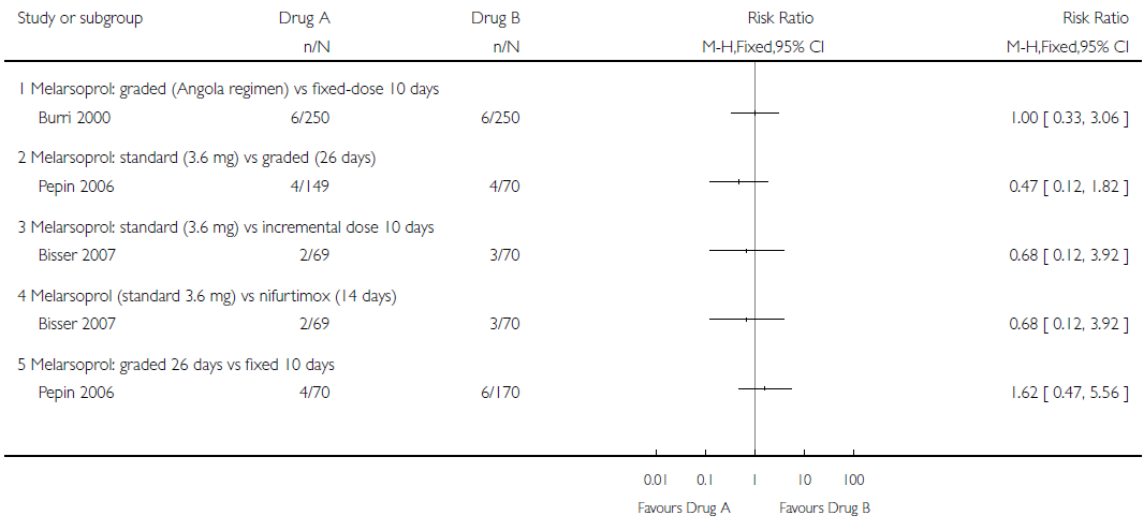
Population	Study	Events / participants	Rate per 1000	Comments
age				
≥12 years	Pohlig 2016	86 / 137	628 per 1000	blood pressure disorders, shock

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

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

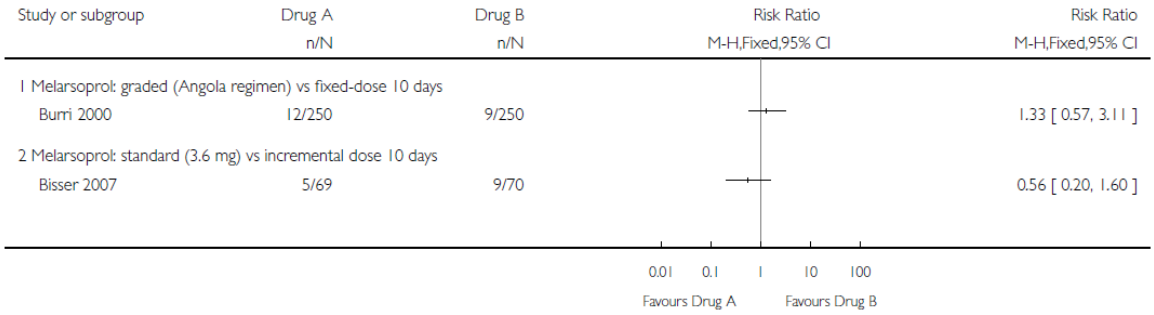
Melarsoprol monotherapy : different treatment regimens in people with second-stage g-HAT

Death during treatment



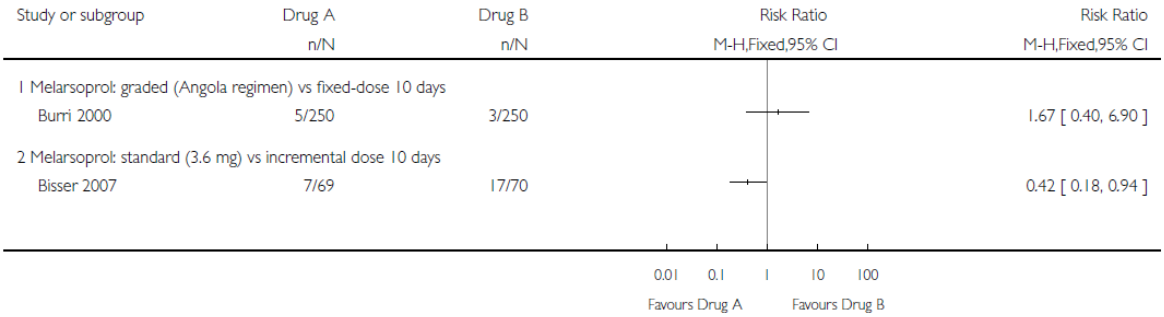
Source: Lutje V, Seixas J, Kennedy A. Chemotherapy for second-stage Human African trypanosomiasis. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD006201.

Overall mortality



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

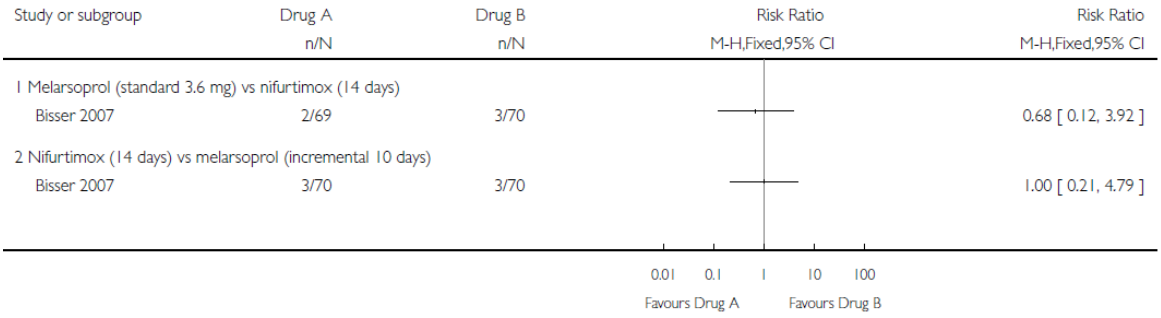
Relapse during follow-up



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

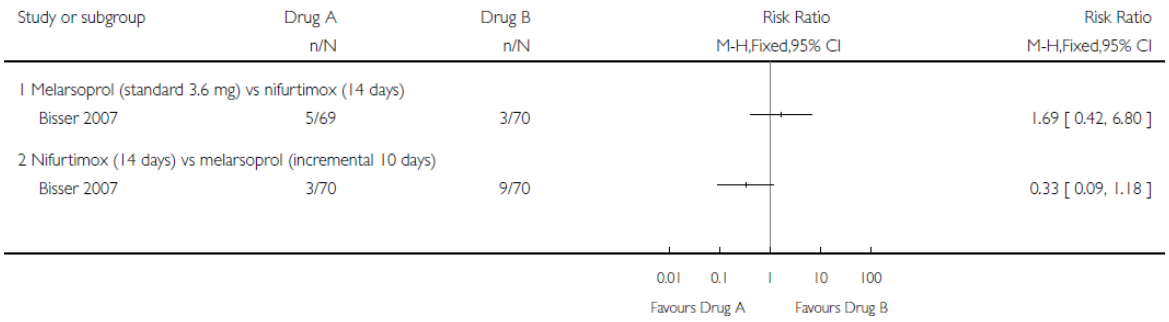
Melarsoprol monotherapy compared to other pharmacological treatment in people with second-stage g-HAT

Death during treatment



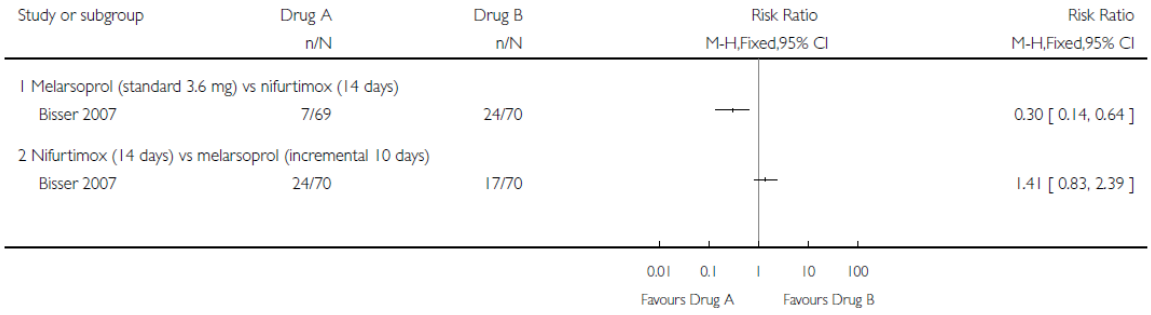
Source: Lutje V, Seixas J, Kennedy A. Chemotherapy for second-stage Human African trypanosomiasis. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD006201.

Overall mortality



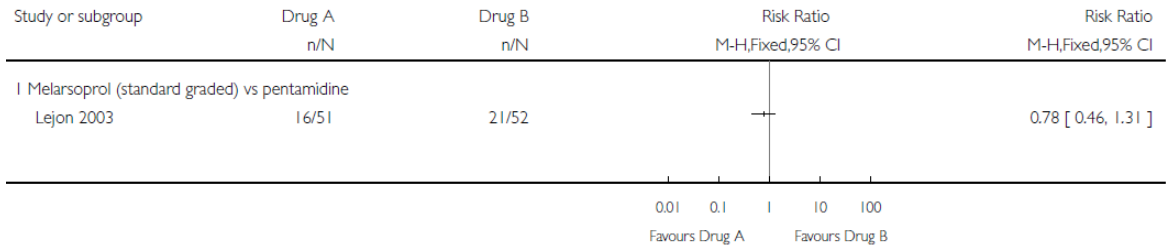
Source: Lutje V, Seixas J, Kennedy A. Chemotherapy for second-stage Human African trypanosomiasis. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD006201.

Relapse during follow-up



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

Relapse



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

Melarsoprol: adverse events in people with second-stage g-HAT

Table 2. Adverse events

Comparison (Drug A vs Drug B)	Trial	n/N[a]		Adverse event
		Drug A	Drug B	
Melarsoprol monotherapy				
Melarsoprol: graded (Angolan) vs fixed 10 days	Burri 2000	14/250	14/250	Encephalopathy
		17/250	18/250	Diarrhoea
		15/250	39/250	Skin reactions
Melarsoprol: standard 3.6 mg vs graded 26 days	Pepin 2006	7/149	7/70	Seizures
		10/149	3/70	Confusion
		1/149	0/70	Skin reactions
Melarsoprol: standard 3.6 mg vs incremental 10 days	Bisser 2007	4/69	5/70	Encephalopathy
		7/69	5/70	Diarrhoea
		14/69	11/70	Nausea and vomiting
		19/69	13/70	Infection (phlebitis)
Standard melarsoprol 3.6 mg vs fixed melarsoprol 10 days	Pepin 2006	10/149	6/170	Confusion
		7/149	4/170	Seizures
		1/149	6/170	Skin reactions
Graded melarsoprol 26 days vs fixed melarsoprol 10 days	Pepin 2006	3/70	6/170	Confusion
		7/70	4/170	Seizures
		0/70	6/170	Skin reactions

Comparisons between single drugs				C
Standard melarsoprol 3.6 mg vs nifurtimox 14 days	Bisser 2007	4/69	1/70	Encephalopathy
		7/69	10/70	Diarrhoea
		14/69	17/70	Nausea and vomiting
		19/69	0/70	Infection (phlebitis)
Melarsoprol incremental 10 days vs nifurtimox 14 days	Bisser 2007	5/70	1/70	Encephalopathy
		5/70	10/70	Diarrhoea
		11/70	17/70	Nausea and vomiting
		13/70	0/70	Infection (phlebitis)
Standard (graded) melarsoprol vs pentamidine	Lejon 2003	None recorded	None recorded	-

Appendix 7. Summary of case reports of rhodesiense HAT

Ordered alphabetically by treatment

DSR ID Author, year Number of cases	Patient details age, sex Country of exposure Year when case was detected Country where case was treated	Clinical features Diagnosis Stage	Drug Treatment details	Outcomes
Melarsoprol				
#1743 Uslan 2006 n=1	case 1 age not reported, female Country of exposure: Not reported Year when case was detected: not reported Country where case was treated: USA	Symptoms: plaque with central clearing from the left groin ascending to the trunk with multiple satellite patches Diagnosis: Blood Stage 2	Melarsoprol 108 mg of melarsoprol daily for 3 days (IV), week 2 - 144 mg of melarsoprol daily for 3 days; week 3 - 216 mg of melarsoprol daily for 3 days	treatment success
#1696 Taube 1958 n=11	case 11 ~ 45, male Country of exposure: Zimbabwe Year when case was detected: 1955 Country where case was treated: Zimbabwe	Symptoms: headache, fever, joint pain Diagnosis: Blood Stage not reported	Melarsoprol 2 courses, 4 x 2.5 ml on consecutive days with 14 days rest in between	treatment success
#1594 Sindato 2008 n=1	case 1 38, male Country of exposure: Tanzania Year when case was detected: 2007 Country where case was treated: Tanzania	Symptoms: fever ,headache, sleep disorder Diagnosis: Blood Stage 1, progressed to stage 2	Melarsoprol incremental doses to 3.6 mg/kg, in 3 series of 3 dailt doses, followed by 7 day rest period (Series 1=1.44, 1.8 and 2.16mg/kg/day; rest for seven days then Series 2= 2.52, 2.88 and 3.24mg/kg/day; rest for seven days then Series 3= 3.6	treatment success

			mg/kg/day for the last three injections	
#1696 Taube 1958 n=11	case 1 ~35, male Country of exposure: Zimbabwe Year when case was detected: 1952 Country where case was treated: Zimbabwe	Symptoms: fever, headache, weight loss Diagnosis: CSF Stage 2	Melarsoprol Mel B, 2 courses, 4 x 2.5 ml on consecutive days with 14 days rest in between after relapse 1: 2 courses, 4 x 4 ml on consecutive days with 14 days rest in between after relapse 2: 2 courses, 4 x 5 ml on consecutive days with 14 days rest in between	relapse
#1696 Taube 1958 n=11	case 2 ~ 40, male Country of exposure: Zimbabwe Year when case was detected: 1954 Country where case was treated: Zimbabwe	Symptoms: headache, general malaise, falling asleep Diagnosis: CSF Stage 2	Melarsoprol Mel B: 2 courses, 4 x 3 ml on consecutive days with 14 days rest in between	treatment success
#1696 Taube 1958 n=11	case 10 ~ 60, male Country of exposure: Zimbabwe Year when case was detected: 1955 Country where case was treated: Zimbabwe	Symptoms: headache, joint pain, weakness Diagnosis: Blood Stage not reported	Melarsoprol mel B: 2 courses, 4 x 3.5 ml on consecutive days with 14 days rest in between	not reported
#1696 Taube 1958 n=11	case 3 ~ 60, male Country of exposure: Zimbabwe Year when case was detected: 1954 Country where case was treated: Zimbabwe	Symptoms: headache, fever, generalized pain Diagnosis: CSF Stage 2	Melarsoprol mel B: 2 courses, 4 x 3ml on consecutive days with 14 days rest in between	treatment success
#1498 Sabbah 1997 n=1	case 1 30, male Country of exposure: Rwanda Year when case was detected: not	Symptoms: headache, weight loss, fever, eruptions on skin and mucosa, hepatosplenomegaly, lymphadenopathy	Melarsoprol melarsoprol - three 4-day courses at 10-day intervals	treatment success AEs : encephalopathy associated with sleepiness, pyramidal

	reported Country where case was treated: France	and petechial purpura Diagnosis: CSF Stage 2		syndrome, right hemiparaesis, static and dynamic bilateral cerebellar syndrome, and dysphagia
#1314 Oscherwitz 2003 n=1	case 1 56, male Country of exposure: Kenya Year when case was detected: 2001 Country where case was treated: USA	Symptoms: fever, chills, and swollen, red, bite areas, stomach cramps Diagnosis: Blood Stage 2	Melarsoprol no details	treatment success AEs : headache with delirium and periods of somnolence
#757 Hall 2020 n=1	case 1 age not reported, male Country of exposure: Zambia Year when case was detected: not reported Country where case was treated: Zambia	Symptoms: fever, arthralgia Diagnosis: Blood Stage not reported	Melarsoprol none	death due to treatment (melarsoprol-induced arsenic encephalopathy)
#34 Aggarwal, 2017 n=1	case 1 46, male Country of exposure: Zambia Year when case was detected: not reported Country where case was treated: India	Symptoms: Fever, pruritic rash, lethargy and weight loss over an eight month period Diagnosis: Blood Stage 2	Melarsoprol not reported	Death death due to treatment : fatal drug-related encephalopathy with right basal ganglion haemorrhage and massive cerebral oedema
#258 Boller, 1977 n=1	case 1 63, female Country of exposure: Botswana Year when case was detected: 1977 Country where case was treated: Switzerland	Symptoms: lesion, fever, lethargy , headache, nausea progressed rapidly; patient died after 11 days Diagnosis: Blood Stage 1, progressed to stage 2	Melarsoprol not reported	death : death due to mengingitis
#433 Coulaud 1975 n=2	case 2 age not reported, male Country of exposure: Burundi Year when case was detected: not reported	Symptoms: fever, asthenia, weight loss Diagnosis: not reported Stage not reported	Melarsoprol not reported	treatment success

	Country where case was treated: France			
#1180 Migchelsen 2011 case 23, table 2 (not in distiller, ref 43)	case 6 68, male Country of exposure: Tanzania Year when case was detected: 2002 Country where case was treated: South Africa	Symptoms: Fever, renal failure, acidosis, jaundice Diagnosis: not reported Stage 2	Melarsoprol not reported	treatment success
#1199 Montmayeur 1994 n=2	case 1 30, female Country of exposure: Rwanda Year when case was detected: not reported Country where case was treated: France	Symptoms: not reported Diagnosis: Blood Stage 2	Melarsoprol not reported, AEs occured between 2nd and 3rd treatments	AEs : acute encephalitic attach with pyramidal and cerebellar symptoms
#1199 Montmayeur 1994 n=2	case 2 27, male Country of exposure: Rwanda Year when case was detected: not reported Country where case was treated: France	Symptoms: not reported Diagnosis: Blood Stage 2	Melarsoprol not reported, received 1 session of melarsoprol	not reported
Pentamidine				
#117 Arroe, 1985 n=1	case 1 27, male Country of exposure: Tanzania Year when case was detected: 1985 Country where case was treated: Denmark	Symptoms: Trypanosomal chancre, fever, impaired renal function and heavy parasitaemia, but no CNS-involvement. Additional thrombocytopenia, anaemia and S. aureus septicaemia Diagnosis: not reported Stage 1	Pentamidine 10 day course	treatment success
#685 Gelfand 1954 n=3	case 3 age not reported, male Country of exposure: Zimbabwe Year when case was	Symptoms: he first developed pains in his legs. enlarged spleen and lymphatic glands, fever, oedema of	Pentamidine 300 mg /day IM for 10 days The blood pressure was recorded daily, the lowest reading	treatment success

	detected: 1952 Country where case was treated: Zimbabwe	ankles Diagnosis: Blood Stage 1	recorded was 110/70 at the beginning of the treatment. The fever lasted 4 days, after which the temperature returned to normal. We were able to keep this patient for only 1 month after his treatment was completed as he felt so well and refused to remain longer in hospital, but blood films taken at weekly intervals after treatment showed no trypanosomes, and animals inoculated with his blood remained free from trypanosomiasis	
#432 Coulaud 1975 n=1	case 1 30, male Country of exposure: Tanzania Year when case was detected: 1973 Country where case was treated: France	Symptoms: Fever, chills, suspected malaria, initial treatment with chloroquine. After diagnosis of trypanosomiasis treatment with pentamidine Diagnosis: Blood Stage not reported	Pentamidine 4 rounds of injections with pentamidine The total curative dose was close to 25 mg/kg, divided into 8 to 10 intramuscular injections of 2 to 3 mg/kg, given every other day.	treatment success AEs : renal toxicity
#685 Gelfand 1954 n=3	case 2 32, male Country of exposure: Zimbabwe Year when case was detected: 1952 Country where case was treated: Zimbabwe	Symptoms: very ill with fever, confusion, drowsiness, became delirious Diagnosis: Blood Stage 1	Pentamidine 400 mg. by intramuscular injection on the 1st day, 300 mg. on the 2nd, 300 mg. again on the 3rd, and thereafter 250 mg. daily for a further 6 days. Five days after treatment commenced, the glands in the axillae and neck were no longer palpable and his general	treatment success

			condition was much improved. The chancres, which took a longer time to resolve, had disappeared by about the 10th day. By then his appetite was returning and he began to take an interest in his surroundings. Subsequent to the completion of the treatment, lumbar puncture was performed twice, the last occasion being almost 2 months after his admission to hospital; the fluid was found to be normal in every respect. Repeated attempts to recover the trypanosomes all proved negative. The patient made an excellent recovery. He began to put on weight steadily and soon he was asking for his discharge. Six months after his treatment he was found to be in excellent health.	
#1180 Migchelsen 2011 case 15, table 2 (not in distiller, ref 59)	case 2 30, female Country of exposure: Tanzania Year when case was detected: 2000 Country where case was treated: Not reported (Australian nationality)	Symptoms: Fever, rigor, headache Diagnosis: Blood Stage 1	Pentamidine no details	treatment success
#1180 Migchelsen 2011 case 21,	case 4 44, female Country of exposure: Tanzania	Symptoms: lesion, fever Diagnosis: not	Pentamidine no details	treatment success

table 2 (not in distiller, ref 43)	Year when case was detected: 2002 Country where case was treated: not reported (British)	reported Stage 2		
#433 Coulaud 1975 n=2	case 1 age not reported, male Country of exposure: Kenya and Tanzania Year when case was detected: not reported Country where case was treated: France	Symptoms: suspected malaria, Asthenia, Precordial, weight loss Diagnosis: not reported Stage not reported	Pentamidine not reported	treatment success AEs : renal insufficiency, diabetes
#1340 Paul 2016 n=1	case 1 61, male Country of exposure: Uganda Year when case was detected: not reported Country where case was treated: Poland	Symptoms: high-grade fever, chills, bleeding from the gums and oral mucosa, haemorrhages at the sites of venipuncture, numerous ecchymoses, fine-spotted skin rash, tachycardia, hepatosplenomegaly, dehydration, jaundice, dyspnoea, hypoxaemia, generalised oedema and oliguria Diagnosis: Blood Stage 1	Pentamidine not reported	treatment success
#2053 Gautret 2009 n=3	case 3 61, male Country of exposure: Uganda, Queen Elizabeth national park Year when case was detected: 2009 Country where case was treated: Poland	Symptoms: Symptoms for 8 days before diagnosis: fever, jaundice, respiratory distress, bleeding (disseminated intravascular coagulation - DIC), oliguria, skin rash, hepatosplenomegaly Diagnosis: not reported Stage not reported	Pentamidine not reported	not reported

#1180 Migchelsen 2011 case 39, table 2 (not in distiller, ref 70)	case 11 61, male Country of exposure: Uganda, Rwanda Year when case was detected: 2009 Country where case was treated: not reported (Polish)	Symptoms: Fever, multi-organ failure, asthenia, lesion, chills, jaundice, respiratory distress, hepatosplenomegaly, mucosal haemorrhage Diagnosis: Blood Stage 1	Pentamidine not reported	treatment success
#181 Basson, 1977 n=4	case 2 "young men of the Defence Force" (age not reported), male Country of exposure: Botswana Year when case was detected: 1977 Country where case was treated: South Africa	Symptoms: no CSF involvement One week before the disappearance of the chancre he started feeling unwell. After the chancre had disappeared the patient developed headache, spikes of fever, rigors, generalized lymphadenopathy, hepatosplenomegaly and a morbilliform rash which tended to be petechial on the legs. Diagnosis: not reported Stage 1	Pentamidine Pentamidine for 20 days	treatment success
#181 Basson, 1977 n=4	case 3 "young men of the Defence Force" (age not reported), male Country of exposure: Botswana Year when case was detected: 1977 Country where case was treated: South Africa	Symptoms: no chancre The clinical picture on admission resembled that of case 2, but in contrast to the previous 2 patients, he was moribund, had marked generalized oedema, and was slightly jaundiced. Diagnosis: not reported Stage 1	Pentamidine Pentamidine for 20 days	treatment success
#181 Basson, 1977 n=4	case 1 "young men of the Defence Force" (age not reported), male	Symptoms: no CSF involvement Diagnosis: not	Pentamidine Pentamidine for 20 days Treatment was	there was marked clinical improvement

	Country of exposure: Botswana Year when case was detected: 1977 Country where case was treated: South Africa	reported Stage 1	started with pentamidine injection on alternate days	
#2041 Ripamonti 2002 n=2	case 2 30, male Country of exposure: Tanzania Year when case was detected: 2001 Country where case was treated: Italy	Symptoms: skin lesion, fever, jaundice, petechial exanthema Diagnosis: Blood Stage 1	Pentamidine pentamidine- IV 4mg/kg every 48 hours	treatment success
#1212 Mossop 1956 n=1	case 1 32, female Country of exposure: Zimbabwe Year when case was detected: 1955 Country where case was treated: Zimbabwe	Symptoms: tired, headache, vomiting, fever, rash Diagnosis: Blood Stage 1	Pentamidine pentamidine, 200 mg IM for 12 days	treatment success
#685 Gelfand 1954 n=3	case 1 27, male Country of exposure: Zimbabwe Year when case was detected: 1952 Country where case was treated: Zimbabwe	Symptoms: 17 days after exposure taken ill suddenly, with fever and severe headache, enlarged lymph node Diagnosis: Blood Stage 1	Pentamidine Pentamidine, 200 mg/day IM for 10 days Seven days after the commencement of treatment the glands in the neck were no longer palpable, and after a further interval of 5 days the glands elsewhere, which were previously palpable, could no longer be felt.	treatment success
#278 Bourgeade 1985 n=1	case 1 age not reported, male Country of exposure: Tanzania Year when case was detected: 1984 Country where case was treated: France	Symptoms: hepatic jaundice, thrombopenia, renal insufficiency, neutropenia with anaemia, lesions, fever, splenomegaly Diagnosis: CSF Stage 2	Pentamidine The first course of pentamidine, at a reduced dose, had to be uninterrupted due to renal failure. . After D. F. M. O, cure of the disease was obtained by a new course of pentamidine.	treatment success : the cure was effectuated by administration of pentamidine

Suramin				
#1472 Robertson 1980 n=1	case 1 22, male Country of exposure: Not reported (laboratory) Year when case was detected: same case as ref 1999 Country where case was treated: UK	Symptoms: headache, tired, fever, diarrhoea, vomiting, rash, Diagnosis: Blood Stage 1	Suramin 0.5 g on the 1st, 2nd days and 1.0 g on the 3rd, 7th, 14 and 21	treatment success
#472 Darby 2008 n=2	case 2 25 years, female; 31 years, male Country of exposure: Malawi Year when case was detected: 2007 Country where case was treated: Malawi, treatment continued in South Africa	Symptoms: fever, rigors, nausea, vomiting, and diarrhoea, generalized rash, headache, myalgia Diagnosis: Blood Stage 1	Suramin 1 g dose, 2 doses 2 days apart	treatment success
#418 Cochran 1983 n=1	case 1 72, male Country of exposure: Tanzania Year when case was detected: 1981 Country where case was treated: Kenya and USA	Symptoms: weakness, chills, delirium, Diagnosis: Blood Stage 1	Suramin 1 g during a five-minute period on the 1st, 3rd, 7th, and 14th	treatment success
#1204 Moore 2002 n=1	case 1 37, male Country of exposure: Kenya Year when case was detected: not reported Country where case was treated: Nepal (detected)/USA (treated)	Symptoms: fever, pain in left foot, chancre, headache, myalgia, dyspnoea Diagnosis: Blood Stage 1	Suramin 1 g of suramin on days 1, 3, 7, 14, and 21	treatment success
#1625 Squarre 2016 n=1	case 1 47, male Country of exposure: Zambia Year when case was detected: not reported Country where case was treated: Zambia	Symptoms: headache, fever, dizziness, body malaise, and erythematous skin rashes Diagnosis: Blood Stage 1	Suramin 1 gram (g) dissolved in 5 centimetre cubed (cm3) of sterile water was administered slowly and intravenously on days 1, 3, 5, 14, and 21	treatment success

#1936 Davis 2021 n=1	case 1 52, male Country of exposure: Zanzibar Year when case was detected: 2009 Country where case was treated: Canada	Symptoms: fever, headache, conjunctivitis, chancre Diagnosis: Blood Stage 1	Suramin 5 doses suramin a total of 1.5 g (16 mg/kg) on days 1, 3, 7, 14 and 21	AEs : rash, elevated liver enzyme levels and nephrotic range proteinuria
#1040 Limbos 1977 n=3	case 1 42, male Country of exposure: Rwanda Year when case was detected: 1973 Country where case was treated: Belgium	Symptoms: high fever, restlessness Diagnosis: Blood Stage 1	Suramin 5 injections of suramin	treatment success
#612 Faust 2004 n=2	cases 1 & 2 9 and 14, males Country of exposure: Tanzania Year when case was detected: 2003 Country where case was treated: England	Symptoms: fever and skin lesions, abdominal pain, Diagnosis: Blood Stage 1	Suramin 5 mg/kg on day 1, 10 mg/kg on day 3 and 20 mg/kg on days 5, 9, 16, 23 and 30	treatment success
#700 Ginsberg 1985 n=1	case 1 27, male Country of exposure: Tanzania Year when case was detected: not reported Country where case was treated: USA	Symptoms: fever, diarrhoea, weight loss Diagnosis: Blood Stage 1	Suramin 5g	treatment success
#680 Gear 1986 n=8	case 1 age not reported, male Country of exposure: Botswana Year when case was detected: not reported Country where case was treated: South Africa	Symptoms: marked primary lesion on his leg as sociated with regional lymphadenitis. Diagnosis: Blood Stage 1	Suramin After seven intravenous injections of Bayer 205, now known as Suramin, he was discharged from the private hospital in which he had been treated feeling well. There was no recurrence of the disease. His case was reported to the state health department and the	treatment success

			health of the other members of the party was checked.	
#723 Gopalakrishnan 2003 n=1	case 1 50, male Country of exposure: Kenya, Tanzania Year when case was detected: not reported Country where case was treated: India	Symptoms: fever, chills, nausea, jaundice, painless skin lesion Diagnosis: Blood Stage 1	Suramin five doses of 1g IV on days 1, 3, 7, 14 and 21	treatment success
#680 Gear 1986 n=8	case 4 60, male Country of exposure: Botswana Year when case was detected: 1982 Country where case was treated: Botswana and USA	Symptoms: On examination it was noted that he was somewhat confused, his temperature was 40Â°C(104Â°F),his blood pressure was 120/70, he had slight jaundice, and a healing sore below his right ear which was suspected to be the primary sore of tick bite fever. He had enlarged nontender cervical glands, but no neck stiffness, and a diffuse erythematous rash. His chest was clear, his abdomen soft and the spleen was palpable. His extremities were normal. Diagnosis: Blood Stage 1	Suramin He was treated with Suramin to which he responded and was discharged relatively well for his course of treatment to be continued in the United States.	treatment success
#680 Gear 1986 n=8	case 7 26, male Country of exposure: Botswana and Zimbabwe Year when case was detected: 1983 Country where case was treated: South Africa	Symptoms: Felt fatigues. He noticed a sore on his leg. On admission he looked ill and toxic, high fever (He was dyspnoeic and had faint crepitations with dullness at the base of his right lung. He had tachycardia with	Suramin In spite of the relatively long time that had elapsed since contracting the infection, he responded well to treatment with Suramin.	treatment success

		faint heart sounds but no murmurs. His abdomen was distended, and the liver and spleen were both enlarged but not tender. He had rash on his abdomen, a healing sore on his left leg. He developed blurring of vision associated with a retinal haemorrhage in one eye. Diagnosis: Blood Stage 1		
#1059 Loscher 1989 n=2	case 1 51, male Country of exposure: Rwanda Year when case was detected: 1987 Country where case was treated: Germany	Symptoms: lesion, high fever, myalgia, weakness Diagnosis: Blood Stage 1	Suramin Initial suramin in Rwanda, Suramin IV 1g /week for 6 weeks	treatment success AEs : reversible glucosuria and proteinuria
#1059 Loscher 1989 n=2	case 2 39, female Country of exposure: Rwanda Year when case was detected: 1987 Country where case was treated: Germany	Symptoms: lesion, high fever, myalgia, weakness Diagnosis: Blood Stage 1	Suramin Initial suramin in Rwanda, Suramin IV 1g /week for 6 weeks	treatment success
#1180 Migchelsen 2011 case 35, table 2, n=4 (not in distiller, ref 67)	case 8 not reported Country of exposure: Malawi Year when case was detected: 2007 Country where case was treated: not reported (Canadian, British, Australian)	Symptoms: Thrombocytopenia, hallucinations Diagnosis: Blood Stage 1	Suramin no details	not reported
#1180 Migchelsen 2011 case 38, table 2 (not	case 10 25, female Country of exposure: Tanzania Year when case was detected: 2009	Symptoms: Fever, lymphadenopathy, lesion, headache Diagnosis: Blood Stage 1	Suramin no details	treatment success

in distiller, ref 69)	Country where case was treated: not reported (Dutch)			
#901 Katsidzira 2010 n=1	case 1 28, male Country of exposure: Zimbabwe Year when case was detected: not reported Country where case was treated: Zimbabwe	Symptoms: fever, headache, night sweats, weight loss Diagnosis: Blood Stage 2	Suramin no details, suramin provided, melarsoprol obtained but not started	death due to HAT
#427 Conway-Klaassen 2002 n=1	case 1 18 year, male Country of exposure: Kenya or Tanzania Year when case was detected: not reported Country where case was treated: USA	Symptoms: high fever (39 to 41oC), elevated pulse and respiration, chills and rigors, along with a frontal headache, rash Diagnosis: Blood Stage 1	Suramin not reported	treatment success
#1168 Mendonca 2002 n=3	case 2 55, female Country of exposure: Tanzania Year when case was detected: Not reported Country where case was treated: Netherlands	Symptoms: fever, chills, malaise, lesion Diagnosis: Blood Stage 1	Suramin not reported	treatment success
#1180 Migchelsen 2011 case 16, table 2 (not in distiller, ref 60)	case 3 32, male Country of exposure: Tanzania Year when case was detected: 2001 Country where case was treated: Belgium	Symptoms: Fever, chancre, headache, jaundice, hepatosplenomegaly Diagnosis: Blood Stage 1	Suramin not reported	treatment success
#1180 Migchelsen 2011 case 22, table 2 (not in distiller, ref 43)	case 5 41, male Country of exposure: Tanzania Year when case was detected: 2002 Country where case was treated: not reported (Swedish)	Symptoms: lesion, fever Diagnosis: not reported Stage 1	Suramin not reported	treatment success

#1180 Migchelsen 2011 case 40, table 2 (not in distiller, ref 46)	case 12 30, female Country of exposure: Tanzania Year when case was detected: not reported Country where case was treated: not reported (Dutch)	Symptoms: fever, chancre, jaundice Diagnosis: Blood Stage 1	Suramin not reported	treatment success
#1586 Simarro 2011 case 17 from table 2 (not in distiller, ref 10)	case 1 34, female Country of exposure: Tanzania Year when case was detected: 2001 Country where case was treated: South Africa	Symptoms: not reported Diagnosis: Blood Stage 1	Suramin not reported	not reported
#1586 Simarro 2011 case 18 from table 2 (not in distiller, ref 10)	case 2 50, female Country of exposure: Tanzania Year when case was detected: 2001 Country where case was treated: USA	Symptoms: not reported Diagnosis: Blood Stage 1	Suramin not reported	not reported
#1586 Simarro 2011 case 19, table 2 (not in distiler, ref 10)	case 3 18, male Country of exposure: Tanzania Year when case was detected: 2001 Country where case was treated: USA	Symptoms: not reported Diagnosis: Blood Stage 1	Suramin not reported	not reported
#1586 Simarro 2011 case 20, table 2 (not in distiller, ref 10)	case 4 57, female Country of exposure: Tanzania Year when case was detected: 2001 Country where case was treated: USA	Symptoms: not reported Diagnosis: Blood Stage 1	Suramin not reported	not reported
#1586 Simarro 2011 case 21, table 2 (not in distiller, ref 10)	case 5 29, male Country of exposure: Tanzania Year when case was detected: 2001 Country where case	Symptoms: not reported Diagnosis: Blood Stage 1	Suramin not reported	not reported

	was treated: South Africa			
#2053 Gautret 2009 n=3	case 2 25, female Country of exposure: Tanzania- Serengeti National park Year when case was detected: 2009 Country where case was treated: Netherlands	Symptoms: Symptoms before diagnosis for 4 days: Fever, headache, cellulitis, red papule, lymphangitis Diagnosis: not reported Stage not reported	Suramin not reported	not reported
#1180 Migchelsen 2011 case 24, table 2 (not in distiller, ref 43)	case 7 27, female Country of exposure: Tanzania Year when case was detected: 2002 Country where case was treated: not reported (Norwegian)	Symptoms: lesion, fever Diagnosis: not reported Stage 1	Suramin not reported	treatment success
#1117 Manuelidis 1965 n=6 (one treated with Tryparsamide, not included)	case 6 58, male Country of exposure: Uganda Year when case was detected: 1958 Country where case was treated: Uganda	Symptoms: weak, headache, back/neck/knee pain, aching joints, fever Diagnosis: Lymph other, please specify : lymph node juice	Suramin suramin - 0.5mg IV mel B - 2.0ml IV day 2, 2.5mL IV day 3, 3.0 mL on day 4,	death due to treatment : haemorrhagic encephalopathy
#1167 Meltzer 2012 n=1	case 1 31, female Country of exposure: Tanzania Year when case was detected: not reported Country where case was treated: Israel	Symptoms: fever and headache, vomiting, cutaneous lesion Diagnosis: Blood Stage 1	Suramin suramin - complete course	treatment success
#1596 Sinha 1999 n=2	case 1 54, male Country of exposure: Tanzania Year when case was detected: not reported Country where case was treated: USA	Symptoms: fever, sweats, chills, myalgia Diagnosis: Blood Stage 1	Suramin Suramin - test dose 100 mg, 5 1g doses on days 0, 1, 7, 14, 21	treatment success AEs : diffuse macular rash,

#1596 Sinha 1999 n=2	case 2 49, male Country of exposure: Tanzania Year when case was detected: not reported Country where case was treated: USA	Symptoms: fever, malaise, daytime drowsiness and nighttime insomnia, chills, sweats, headache, myalgia, arthralgia, erythematous lesion Diagnosis: Blood Stage 1	Suramin Suramin - test dose 100 mg, 5 1g doses on days 0, 1, 7, 14, 21	treatment success AEs : diffuse macular rash
#416 Clerinx 2012 n=1	case 1 age not reported, male Country of exposure: Kenya Year when case was detected: 2012 Country where case was treated: Belgium	Symptoms: chancre Diagnosis: Blood Stage 1	Suramin suramin (1g) given once weekly for five weeks	AEs : papulopruriginous rash
#1998 Reijer 1981 n=1	case 1 35-40, female Country of exposure: Zambia Year when case was detected: 1980 Country where case was treated: Zambia	Symptoms: abdominal pain, distended abdomen, general malaise, amenorrhea Diagnosis: Paracentesis of the abdomen Stage 2	Suramin suramin 0.25g on day 1, 0.5 on day 3, 1.0g on day 5 (IV) melarsoprol: 3 days slowly increasing IV doses, 1 week rest, for 12 doses, 37 ml total	treatment success
#1999 Robertson 1980 n=1	case 1 22, male Country of exposure: Laboratory, original stock collected from Uganda Year when case was detected: 1974 Country where case was treated: UK	Symptoms: tired, headache, fever, diarrhoea, vomiting, rash, arthralgia Diagnosis: Blood Stage 1	Suramin suramin 0.5g IV on 1st and 2nd days, 1.0g IV on day 3, 7, 14, 21	treatment success
#1420 Quinn 1983 n=1	case 1 38, male Country of exposure: Sudan Year when case was detected: not reported Country where case was treated: USA	Symptoms: f fever, shaking chills, sweats, headaches, diarrhoea, dehydration, weight loss Diagnosis: Blood Stage 1	Suramin suramin 1.0 g IV on the 1st, 3rd, 7th, 14th, and 21st days	treatment success
#1858 Wolf 2012 n=1	case 1 62, male Country of exposure:	Symptoms: fever, chancres	Suramin suramin 1g infusion over 1 hour, then	treatment success

	Keya Year when case was detected: 2012 Country where case was treated: Germany	Diagnosis: Blood Stage 1	followed on day 1, 3, 7, 14, 21	
#2041 Ripamonti 2002 n=2	case 1 33, male Country of exposure: Tanzania Year when case was detected: 2001 Country where case was treated: Italy	Symptoms: fever, headache, nausea, vomiting, skin lesion Diagnosis: Blood Stage 1	Suramin suramin 1g IV, 1g IV on day 9, then 1g IV once per week for 3 weeks after discharge	treatment success
#1268 Nieman 1999 n=1	case 1 58, female Country of exposure: Rwanda Year when case was detected: 1985 Country where case was treated: USA	Symptoms: fever, erythematous rash Diagnosis: Blood Stage 1	Suramin Suramin IV f 1 g on days I, 4, 7, 14, and 28 (beginning on the second hospital day)	treatment success
#1951 Harries 1988 n=1	case 1 42, male Country of exposure: Malawi Year when case was detected: not reported Country where case was treated: Malawi	Symptoms: painless lesion, fever, arthralgia, rash, unable to breathe, anaphylaxis Diagnosis: Blood Stage 1	Suramin suramin IV O.25 g on day 1, 0.5 g on day 3, 1.0 g on day 5, and 1.0 g weekly thereafter to a total of 5.75 g without ill effect	treatment success
#445 Croft 2006 n=2	case 1 26, male Country of exposure: Malawi Year when case was detected: 2005 Country where case was treated: Malawi and South Africa	Symptoms: chancre, regional lymphadenopathy, circinate erythema and a cyclical fever pattern Diagnosis: Blood Stage 1	Suramin Suramin IV on days 1 (test dose), 4, 7, 10 and 14	treatment success
#1378 Perera 1969 n=1	case 1 57, male Country of exposure: Zimbabwe, Botswana Year when case was detected: 1968 Country where case was treated: USA	Symptoms: fever, chills, lethargy, malaise, axillary lymphadenopathy, and a skin lesion Diagnosis: Blood Stage 1	Suramin suramin IV, 1 dose, then withheld for 2 weeks, then given for 4 weeks. total 3.4 g	treatment success AEs : oliguria, hyponatremia, and azotaemia

#1205 Moore 2002 n=2	case 1 51, male Country of exposure: Zambia Year when case was detected: 2000 Country where case was treated: UK	Symptoms: erythematous lesion, myalgia, abdominal discomfort, diarrhoea, vomiting, headache, fever, rigors, and sweats Diagnosis: Blood Stage 1	Suramin suramin IV, doses of 5, 10, and 20 mg/kg on days 1, 3, and 5, respectively (maximum 1.5 g/dose), 7 doses	AEs : dysesthesia of the fingertips
#1205 Moore 2002 n=2	case 2 30, male Country of exposure: Tanzania Year when case was detected: 2000 Country where case was treated: UK	Symptoms: skin lesion, fever, rigor, diarrhoea, vomiting Diagnosis: Blood Stage 1	Suramin suramin IV, doses of 5, 10, and 20 mg/kg on days 1, 3, and 5, respectively (maximum 1.5 g/dose), 7 doses	AEs : dysesthesia of the fingertips
#430 Cottle 2012 n=1	case 1 49, female Country of exposure: Zambia Year when case was detected: not reported Country where case was treated: UK	Symptoms: fever, malaise, headache, dizziness, abdominal discomfort, diarrhoea, and vomiting, jaundice, tachycardia Diagnosis: Blood Stage 1	Suramin Suramin IV: Test dose of 100 mg in 100 mL 0.9% saline over 30 min on day 0; and 5 doses of 20 mg/kg (maximum 1 g/dose) in 250 mL 0.9% saline over 3 h on days 1, 3, 7, 14, 21.	treatment success
#1241 Myrvang 2002 n=1	case 1 26, female Country of exposure: Tanzania Year when case was detected: 2002 Country where case was treated: Norway	Symptoms: fever, nausea and other symptoms, and had thrombocytopenia and pathological liver values Diagnosis: Blood Stage 1	Suramin suramin test dose then 1 g on days 1, 3, 7, 14 and 21.	treatment success
#1562 Shah 2022 n=1	case 1 36, female Country of exposure: Uganda Year when case was detected: 2020 Country where case was treated: India	Symptoms: fever, rigors, headache, nausea, vomiting, abdominal pain Diagnosis: Blood Stage 1	Suramin suramin test dose, then 1g inj suramin , and 4 doses every 7th day	treatment success
#2027 Wurapa 1984 n=1	case 1 56, male Country of exposure: Zambia Year when case was detected: 1982	Symptoms: sore eyes, no other symptoms Diagnosis: Blood Stage 1	Suramin suramin total 5.75 g	treatment success

	Country where case was treated: Zambia			
#1622 Spencer 1975 n=5	case 1 56, male Country of exposure: Botswana Year when case was detected: 1969 Country where case was treated: USA	Symptoms: malaise, confusion, anorexia, lethargy Diagnosis: Blood Stage 1	Suramin suramin: 1g IV days 1, 3, 7, 14, 21	treatment success
#1622 Spencer 1975 n=5	case 3 57, male Country of exposure: Rwanda Year when case was detected: 1970 Country where case was treated: USA	Symptoms: malaise, confusion, anorexia, lethargy Diagnosis: Blood Stage 1	Suramin suramin: 1g IV days 1, 3, 7, 14, 21	treatment success
#1622 Spencer 1975 n=5	case 4 19, male Country of exposure: Botswana Year when case was detected: 1970 Country where case was treated: USA	Symptoms: malaise, confusion, anorexia, lethargy Diagnosis: Blood Stage 1	Suramin suramin: 1g IV days 1, 3, 7, 14, 21	treatment success
#410 Claessen 2010 n=1	case 1 30, female Country of exposure: Tanzania Year when case was detected: not reported Country where case was treated: Netherlands	Symptoms: chancre on calf, pancytopenia (haemoglobin 6.6 mmol/l, leucocytes 2.2 x 109/l, thrombocytes 37 x 109/l), diffuse intravascular coagulation, metabolic acidosis, elevated bilirubin (212 µmol/l, conjugated fraction 0.66), ASAT (594 U/l) and ALAT (416 U/l), serum creatinine 55 µmol/l and a mild proteinuria Diagnosis: Blood Stage 1	Suramin suramin IV test dose of 200 mg and then 1000 mg on days 1, 3, 10, 17, 24 and 31	treatment success : clinical improvement AEs : dyspnoea, ARDS
#814 Huits 2018 n=1	case 1 53, female Country of exposure: Uganda	Symptoms: fever, headache, confusion, dyspnea, painful red lesion,	Suramin test dose of 100mg, then 1000 mg IV weekly for 5 weeks	treatment success AEs : transient painful paresthesias in hands, feet, scalp

	Year when case was detected: 2015 Country where case was treated: Belgium	cough Diagnosis: Blood Stage 1		
#1318 Otte 1995 n=1	case 1 49, male Country of exposure: Zimbabwe Year when case was detected: not reported Country where case was treated: Belgium	Symptoms: flu-like feeling with muscle pain, Cough, vomiting, diarrhoea and fever over 40°C. Diagnosis: Blood Stage 1	Suramin Treatment with suramin was carried out:100 mg intravenously on days 1, 3, 7, 14 and 2r. On the 4th day after at the start of treatment the blood was free of parasites. The course became complicated due to severe anaemia	treatment success
#680 Gear 1986 n=8	case 5 age not reported, male Country of exposure: Botswana Year when case was detected: 1982 Country where case was treated: Botswana and South Africa, USA	Symptoms: he developed a flu-like illness and it was noticed he had a sore on his scalp suggestive of a tick bite, a diagnosis which was supported by a positive Weil-Felix test. Chloramphenicol, 250 mg four times a day, was prescribed; complaining fever, headache, and nausea he became very ill and jaundiced and was Diagnosis: Blood Stage 1	Suramin Trypanosomes were found in his blood smear and he responded rapidly to treatment with Suramin. His treatment was continued after his discharge and return to the United States.	treatment success
#357 Callens 2003 n=1	case 1 28,male Country of exposure: Tanzania Year when case was detected: 2001 Country where case was treated: Netherlands	Symptoms: a three-day fever and muscle pain. muscle weakness, headache and vertigo. Clinical examination measured a temperature of 39.1°C, a pulse rate of 9<1/min and a	Suramin Two days after the start of intravenous suramin, the patient was afebrile. the laboratory values normalized after one month. For a total of 6 weeks, 1 g of suramin was	treatment success

		locomotive pressure of 110/85 mmHg. Inspection revealed patchy erythema over the entire body and various skin lesions on the feet, suggestive of insect bites. However, there was no clear inoculation problem present. The spleen was palpable, but there were no enlarged lymph nodes. The following abnormal laboratory results were noted: leukocyte count: 4.5 x ro9/1 (normal: 4.0-10.h) with lymphopenia of 0.4 x 109/1 (normal: 1.5-3.5): platelet count: 39 x w'' /1 (normal: 140-440): sodium: 129.5 mmol/1 (normal: 135-145): alanine aminotransferase: 97 U/1 (normal: 5-40): aspartate aminotransferase: 91 U/1 (normal: 5 - 37): lactate dehydrogenase: 1114 U/1 (normal: 240-480); Creatine phosphokinase: 989 U/l (normal: 24-195): C-active protein: 31.5 mg/l (normal: 5). There was no polyclonal hypergammaglobulinemia. Numerous trypanosomes were seen on thick drop. The lower cerebral spinal fluid result was normal. Diagnosis: CSF Stage 1	administered intravenously weekly, a treatment that was well tolerated by the patient.	

Combination of treatments				
#2046 Helleberg 2023 n=1	case 1 60, male Country of exposure: Zambia Year when case was detected: not reported Country where case was treated: Denmark	Symptoms: fever, headache, joint pain Diagnosis: Blood Stage 2	Pentamidine, Fexinidazole Pentamidine – 5 days intravenous, dose not reported Fexinidazole - 10 days oral treatment 1800 mg once a day for 4 days, 1200 mg once a day for 6 days	treatment success
#286 Braendli 1990 n=2	case 1 32, male Country of exposure: Rwanda Year when case was detected: 1988 Country where case was treated: Switzerland	Symptoms: Fever, headache, lesion Diagnosis: CSF Stage 2	Pentamidine,Melarsoprol after initial treatment for suspected malaria, treatment with pentamidine in Rwanda, then melarsoprol 3.6% and in Switzerland	treatment success
#1586 Simarro 2011 case 22, table 2 (not in distiller, ref 10)	case 6 40, male Country of exposure: Tanzania Year when case was detected: 2001 Country where case was treated: South Africa	Symptoms: not reported Diagnosis: Blood Stage 2	Pentamidine,Melarsoprol not reported	not reported
#1400 Ponce-de-Leon 1996 n=1	case 1 68, male Country of exposure: Kenya Year when case was detected: 1994 Country where case was treated: Mexio	Symptoms: fever, headache, skin lesion Diagnosis: Blood Stage 1, progressed to stage 2	Pentamidine,Melarsoprol pentamidine IV melarsoprol 3 cycles	AEs : peripheral neuropathy (melarsoprol?)
#181 Basson, 1977 n=4	case 4 "young men of the Defence Force" (age not reported), male Country of exposure: Botswana Year when case was detected: 1977 Country where case	Symptoms: severely jaundiced necrotic lesion Diagnosis: not reported Stage 2	Pentamidine,Melarsoprol The clinical course suggested either infection with pentamidine-resistant trypanosomal strains, or CNS involvement.	treatment success : relapsed with pentamidine, melarsoprol rescue treatment

	was treated: South Africa		Melarsoprol for 30 days	
#854 Jannsens 1960 n=1	case 1 age not reported, female Country of exposure: Democratic Republic of the Congo Year when case was detected: 1958 Country where case was treated: Democratic Republic of the Congo	Symptoms: complications with melarsoprol treatment and viral co infection Diagnosis: Blood Stage 1	Pentamidine,Melarsoprol treateded with pentamidine (8 daily IM injections) and relapsed after initial cure, treatment with melarsoprol 6 ml arsobal IV 3x	treatment success : after relapse AEs : encephalopathy with coxsackie virus B infection during melarsoprol treatment
#1117 Manuelidis 1965 n=6 (one treated with Tryparsamide, not included)	case 4 70, male Country of exposure: Uganda Year when case was detected: 1959 Country where case was treated: Uganda	Symptoms: initial disease not reported, relapse: prostrate, stuporous incontinent, headaches, chest pain Diagnosis: CSF Stage 2	Suramin,Melarsoprol Mel B: total of 34.5 ml at relapse: suramin - 0.25 g IV on Days 2 and 3; mel B - mel B 0.5ml IV day 3, 1.0mL IV day 4, and 1.5 ml IV day 5	death due to HAT relapse
#983 Kumar 2006 n=1	case 1 62, female Country of exposure: Kenya and Tanzania Year when case was detected: not reported Country where case was treated: USA	Symptoms: fever and rash Diagnosis: Blood Stage 2: CSF involvement detected	Suramin,Melarsoprol Melarsoprol IV: numbness, and a prickly burning sensation that started in both feet and progressed upwards, with bilateral leg pain and weakness	treatment success AEs : n=1: ascending paresthesias
#1180 Migchelsen 2011 case 37, table 2 (not in distiller, ref 35, 41)	case 9 44, female Country of exposure: Tanzania Year when case was detected: 2009 Country where case was treated: not reported (German)	Symptoms: Lesion, fever, myalgia, malaise, diarrhea, convulsions Diagnosis: Blood Stage 2	Suramin,Melarsoprol no details	death
#936 Kibiki 2006 n=1	case 1 age reported (middle aged), male Country of exposure: Tanzania Year when case was	Symptoms: numbness, and a prickly burning sensation that started in both feet and progressed	Suramin,Melarsoprol not reported	treatment success : n=1

	detected: not reported Country where case was treated: Tanzania	upwards, with bilateral leg pain and weakness Diagnosis: CSF Stage 2		
#1168 Mendonca 2002 n=3	case 3 52, female Country of exposure: Tanzania Year when case was detected: not reported Country where case was treated: South Africa (diagnosed in Malawi)	Symptoms: fever, headache, lesion Diagnosis: Blood Stage 2	Suramin,Melarsoprol not reported	death due to treatment AEs : tetraparesis, polyneuropathy
#2053 Gautret 2009 n=3	case 1 38, male Country of exposure: Namibia, Mozambique, Malawi (unknown reason, travel for 2.5 years) Year when case was detected: 2007 Country where case was treated: Europe (Britian)	Symptoms: Symptomns for 4 months before diagnosis: Fatigue, somnolence, headache, fever, lymph nodes, hepatomegaly, myalgia. One relapse episode. Diagnosis: not reported Stage not reported	Suramin,Melarsoprol not reported	not reported
#1696 Taube 1958 n=11	case 4 ~ 38, male Country of exposure: Zimbabwe Year when case was detected: 1954 Country where case was treated: Zimbabwe	Symptoms: not reported Diagnosis: Blood Stage not reported	Suramin,Melarsoprol received antrypol and tryparsamide, not details then antrypol 10 x 1 g mel B: 2 courses, 4 x 3.5 ml on consecutive days with 14 days rest in between	treatment success
#1238 Mwanakasale 2014 n=2	case 1 16, male Country of exposure: Zambia Year when case was detected: not reported Country where case was treated: Zambia	Symptoms: fever, dizziness, sleeping mainly during the day, and constipation Diagnosis: Blood Stage 2	Suramin,Melarsoprol suramin - five doses at 1g/day, given as a single dose, on days 2, 4, 7, 12 and 19. melarsoprol 126mg/day, given as a single dose, on	death due to HAT

			days 1, 2, 3, 11, 12, 13, 21, 22, and 23.	
#285 Braakman 2006 n=1	case 1 52, female Country of exposure: Tanzania Year when case was detected: not reported Country where case was treated: Netherlands	Symptoms: intermittent fever, headache, vomiting, diarrhea, drowsiness, and tremors Diagnosis: Blood Stage 2 : first detected in blood, later in CSF	Suramin,Melarsoprol Suramin (1 g/day IV on days 1, 3, 7, 14, and 21: total of 5 g); melarsoprol (2 mg/kg IV for 3 days, three times at weekly intervals combined with methylprednisolone); melarsoprol (3.6 mg/kg IV for 3 days, at three weekly intervals	death : death due to widespread lymphoplasmacytoid perivascular inflammation through the brainstem, cerebellum, and cerebrum
#1107 Malesker 1999 n=1	case 1 41, male Country of exposure: Tanzania Year when case was detected: 1996 Country where case was treated: USA	Symptoms: weakness, fever, chills, sweats, anorexia, weight loss Diagnosis: Blood Stage 2	Suramin,Melarsoprol suramin - 100 mg test dose, 1g IV melarsoprol - total 20 mg/kg, 4 doses over 4 weeks	treatment success
#1696 Taube 1958 n=11	case 5 ~36, female Country of exposure: Zimbabwe Year when case was detected: 1953 Country where case was treated: Zimbabwe	Symptoms: fever, headache, pains in arms and legs Diagnosis: Blood Stage 2	Suramin,Melarsoprol suramin (antrypol) 10 x 1 g tryparsamide 20 x 1.5 g	treatment success
#1117 Manuelidis 1963 n=6 (one treated with Tryparsamide, not included)	case 2 25, male Country of exposure: Uganda Year when case was detected: 1960 Country where case was treated: Uganda	Symptoms: dehydrated, wasted, bed sores, incontinence Diagnosis: CSF Stage 2	Suramin,Melarsoprol suramin 0.1 and 0.25 g IV on days 2 and 3; Mel W 30, 50, 100, 0100 mg IM on days 4, 5, 6, 7	death due to HAT
#1117 Manuelidis 1965 n=6 (one treated with Tryparsami	case 3 40, male Country of exposure: Uganda Year when case was detected: 1957 Country where case was treated: Uganda	Symptoms: headache, backache, join pain, mentally clouded, weak, emaciated Diagnosis: Blood Stage 2	Suramin,Melarsoprol suramin 0.25 g IV on day 1 and 3, 0.2g day 14 mel B 1.5 mL day 4 and 2 mL day 5, 2.5 mL on day 11	death due to HAT

de, not included)				
#1926 Buyst 1975 n=1	case 1 premature baby 2 days old, sex not reported Country of exposure: Zambia Year when case was detected: not reported Country where case was treated: Zambia	Symptoms: lethargic, slightly jaundiced and anaemic, eye infection Diagnosis: CSF Stage 2	Suramin,Melarsoprol suramin 10, 20 and 37.5 mg on days 7, 9, 11 (intramuscular) melarsoprol 0.1 ml of a 3.6 % solution was given on three consecutive days (total: 0.3 ml), was started on day 13. A second Mel B course totalled 0.6 ml and a third one 0.9 ‘ml. The interval between Mel B courses was approximately one week; the injections were given intravenously, using a scalp vein.	treatment success
#1238 Mwanakasale 2014 n=2	case 2 19, female Country of exposure: Zambia Year when case was detected: not reported Country where case was treated: Zambia	Symptoms: sleeping mainly during the day, heart palpitations, loss of weight, headache, body weakness, and feeling ‘blocked’ in the throat for 2 years Diagnosis: Blood Stage 2 : CSF also had typanosomes	Suramin,Melarsoprol suramin 1g/day intravenously on alternating days for 3 days then two doses of suramin at 1g/week melarsoprol 120mg/day intravenously 3 days after her first dose of suramin for 12 doses	treatment success
#1696 Taube 1958 n=11	case 6 ~ 40, male Country of exposure: Zimbabwe Year when case was detected: 1955 Country where case was treated: Zimbabwe	Symptoms: headache, joint pain, pyrexia, dizziness Diagnosis: Blood Stage 2	Suramin,Melarsoprol suramin 2 x 1g Mel B: 2 courses, 4 x 2.5 ml on consecutive days with 14 days rest in between	treatment success
#1622 Spencer 1975 n=5	case 2 24, female Country of exposure: Kenya Year when case was	Symptoms: malaise, confusion, anorexia, lethargy Diagnosis: CSF Stage 2	Suramin,Melarsoprol suramin: 1g IV on days 1, 3, 7, 14, 21 melarsoprol: 1.5, 2,	treatment success

	detected: 1970 Country where case was treated: USA		and 2.2 mg/kg followed after a 7-day interval by doses of 2.5, 3, and 3.6 mg/kg; finally a third 3-day course of one daily injection of 3.6 mg/kg was given	
#1622 Spencer 1975 n=5	case 5 74, male Country of exposure: Botswana Year when case was detected: 1971 Country where case was treated: USA	Symptoms: malaise, confusion, anorexia, lethargy Diagnosis: CSF Stage 2	Suramin,Melarsoprol suramin: 1g IV melarsoprol: 1.5, 2, and 2.2 mg/kg followed after a 7-day interval by doses of 2.5, 3, and 3.6 mg/kg; finally a third 3-day course of one daily injection of 3.6 mg/kg was given	treatment success
#680 Gear 1986 n=8	case 8 28, male Country of exposure: Botswana Year when case was detected: 1983 Country where case was treated: Zimbabwe	Symptoms: Symptoms for 6 months before diagnosis of HAT: fatigued; lymph nodes in his neck and an enlarged liver; it was not ed his spleen was palpable and the blood count at this time showed Hb 12.5 g, white cell count 3,600, neutrophils 50, monocytes 4, lymphocytes 45, eosinophils 0, and basophils 1 Diagnosis: Blood Stage 1, progressed to stage 2	Suramin,Melarsoprol Suramin treatment: The patient rapidly improved first, then it became clear that this patient had developed involvement of the central nervous system for which treatment with Suramin is not adequate. He was then given a full course of Mel B: 1.5, 2.0, 2.2 mg/kg daily then a seven day interval; 2.5, 3.0, 3.6 mg/kg then another seven-day interval; and a third course of3.6 mg/ kg/day for three days. During the first course he developed slight blurring of vision, however this cleared up and the course was completed	treatment success AEs : Melarsoprol: During the first course he developed slight blurring of vision

			without further complication, and his cure was complete.	
#680 Gear 1986 n=8	case 3 age not reported, male Country of exposure: Botswana Year when case was detected: not reported Country where case was treated: Botswana	Symptoms: After about two weeks in the swamps he became ill with cold shivers and high fever Diagnosis: not reported Stage 2	Suramin,Melarsoprol treated with the prescribed course ofthe then recently introduced drug Melarsoprol(Mel B) In the midst of the melarsoprol course he became stuporose and comatose and was flown down to Johannesburg for specialist treatment. It was noted he was deeply comatose and had very marked derma graphia indicative of a marked hypersensitivity state. He was started on a course of Suramin but died from encephalopathy	death due to treatment : encephalopathy
#156 Bales, 1989 n=3	case 1 35, female Country of exposure: Kenya Year when case was detected: 1981 Country where case was treated: Kenya	Symptoms: relapsed cases of stage 2 rHAT with weakness, headache,malaise, poor memory, trypanosomes in CSF Diagnosis: Blood Stage 2	Suramin,Melarsoprol,Difiuoromethylomithine Relaped after initial treatment with Mel B and Suramin high dose Mel-B, DFMO 400mg kg- 1 BW/day for 14 days IV infusion for 21 days, 300 mg kg/BEW/day orally for 14 days.	treatment success
#1334 Patel 2018 n=3 (1 r-HAT)	case 1 38, male Country of exposure: South Africa, Malawi, Mozambique and Namibia	Symptoms: fatigue, fever, headache and sleeplessness Diagnosis: Blood Stage 2	Suramin,Melarsoprol,Eflornithine suramin and melarsoprol first, eflornithine after relapse (2 weeks of treatment) followed	AEs : confused and suffered a generalised tonic-clonic seizure

	Year when case was detected: 2004 Country where case was treated: UK		by suramin and melarsoprol	
#395 Checkley 2007 n=1	case 1 38, male Country of exposure: Namibia, Mozambique, Malawi or South Africa Year when case was detected: 2004 Country where case was treated: South Africa and England	Symptoms: fatigue, sleeplessness, severe headache and fever,38.5 ◦C, posterior cervical and axillary lymphadenopathy and mild hepatomegaly Diagnosis: Blood Stage 2	Suramin,Melarsoprol,Eflornithine suramin every 3 days: 5 mg/kg, 10 mg/kg and 20 mg/kg, melarsoprol in incremental doses to 2 mg/kg or 3.6 mg/kg, in three series of three daily doses, each followed by a 7-day rest period, eflornithine 100 mg/kg four times a day i.v. for 14 day	Relapse AEs : confusion, apraxia, tonic-clonic seizures, post-treatment reactive encephalopathy
#639 Foulkes 1996 n=1	case 1 37, male Country of exposure: N/A Year when case was detected: 1992 Country where case was treated: Zambia	Symptoms: not reported Diagnosis: Blood Stage 2	Suramin,Melarsoprol,Metronidazole melarsoprol 1350 mg, metronidazole 1.5g orally every 6 hours for 7 days, one week off, 2 g every 6 hours for 6 days; suramin 1g IV on day 1 and weekly to 5 g	treatment success
#119 Arroz, 1988 n=1	case 1 30, male Country of exposure: Mozambique Year when case was detected: 1982 Country where case was treated: Mozambique	Symptoms: Condition deteriorated; Trypanosomes in CSF + + +, 133 cells/mm3, and protein 56 mg% Diagnosis: CSF Stage 1, progressed to stage 2	Suramin,Melarsoprol,Metronidazole,Nitrofurazone,Nifurtimox,Difiuoromethylomithine Intravenous suramin was given on days I (0·2g), 2 (0·5g), 3, 7, 14 and 21 (20 mg/kg) and oral metronidazole in a daily dose of 40 mg/kg for 10 d after failed treatment of: repeated courses of suramin and melarsoprol, as well as nitrofurazonc, nifurtimox (120 d) and difiuoromethylomithine.	treatment success relapse : relapse after three weeks

#156 Bales, 1989 n=3	case 3 20, male Country of exposure: Kenya Year when case was detected: 1982 Country where case was treated: Kenya	Symptoms: relapsed case of stage 2 rHAT with weakness, headache,malaise, poor memory, trypanosomes in CSF Diagnosis: CSF Stage 2	Suramin,Melarsoprol,Nifurtimox Relaped after initial treatment with Mel B and Suramin Suramin and Mel B; DFMO 800 mg for 21 days, IV, oral dose of 160 mg/BW/day for 14 days. Nifurtimox after	treatment success
#156 Bales, 1989 n=3	case 2 49, male Country of exposure: Kenya Year when case was detected: 1985 Country where case was treated: Kenya	Symptoms: relapsed case of stage 2 rHAT with weakness, headache,malaise, poor memory, trypanosomes in CSF Diagnosis: CSF Stage 2	Suramin,Melarsoprol,Nifurtimox,Difiuoromethylomithine Relaped after initial treatment with Mel B and Suramin Suramin and concurrent DFMO, Nifurtimox for 21 days	treatment success
#1117 Manuelidis 1965 n=6 (one treated with Tryparsamide, not included)	case 5 30, male Country of exposure: Uganda Year when case was detected: 1958 Country where case was treated: Uganda	Symptoms: initial: headache, backache, joint pain 2nd admission: facile, dull, weight loss 3rd admission: treat hemoyltic anemia 4th admission: somnolence, coarse tremor 5th admission: increase saliva, facile, restless 6th admission: facile, restless, increase saliva, athetosis 7th admission: N/A 8th admission: facile, pyrexia 9th admission: weakness, athetosis 10th admission: weight loss, weakness, coarse tremor Diagnosis: CSF Stage 2	Suramin,Melarsoprol,Nitrofurazone first admission: suramin - 0.5g; mel B - total 39.5ml 2nd admission: mel B - total 35 ml 3rd admission: mel B - total 35 ml 4th admission: mel W -total 2325mg; nitrofurazone - dose not reported; mel B - total 46 ml 5th admission: not reported 6th admission: none 7th admission: none 8th admission: nitrofurazone and mel W (no details reported) 9th admission: mel W - total dose 4050 mg 10th admission: mel B - total 10.5 ml	death : epileptiform attach with clonic spasms relapse AEs : hemolytic anemia, polyneuropathy (from nitrofurazone)

#1696 Taube 1958 n=11	case 9 ~ 45, male Country of exposure: Zimbabwe Year when case was detected: 1950 originally, 1953 relapse Country where case was treated: Zimbabwe	Symptoms: dull, dry skin, lethargic Diagnosis: not reported Stage 2	Suramin,Melarsoprol,tryparsamide no details on 1950 or 1952 treatment after relapse (1953) antrypol 5x1g tryparsamide 2x2g (to 22.5 g) after relapse 1954 - 2 courses, 4 x 3 ml on consecutive days with 14 days rest in between	Relapse AEs : from tryparsamide - deterioration of vision
#1696 Taube 1958 n=11	case 7 43, male Country of exposure: Zimbabwe Year when case was detected: 1952 Country where case was treated: zimbabwe	Symptoms: not reported Diagnosis: Blood Stage 2	Suramin,Melarsoprol,tryparsamide suramin 10x1g tryparsamide 15x2g mel B: 2 courses, 4 x 3 ml on consecutive days with 14 days rest in between	treatment success relapse
#286 Braendli 1990 n=2	case 2 age not reported, male Country of exposure: Rwanda Year when case was detected: 1988 Country where case was treated: Switzerland	Symptoms: fever, weakness, lesion Diagnosis: Blood Stage 1	Suramin,Pentamidine After initial treatment with pentamidine in Rwanda, treatment with Suramin in Switzerland.	treatment success
#1168 Mendonca 2002 n=3	case 1 57, male Country of exposure: Tanzania Year when case was detected: not reported Country where case was treated: Netherlands	Symptoms: fever, chills, lesion Diagnosis: Blood Stage 1	Suramin,Pentamidine details not provided	relapse : after suramin AEs : Non-insulin dependent diabetes (pentamidine)
#1040 Limbos 1977 n=3	case 2 17, female Country of exposure: Rwanda Year when case was detected: 1973 Country where case was treated: Belgium	Symptoms: primary inoculation lesions, high fever, restlessness Diagnosis: Blood Stage 1	Suramin,Pentamidine injection of 160 mg of Lomidine and the same dose the next day. The patient recieved 224 mg of Pentamidine (4 mg per kg) the next day,	treatment success AEs : vomiting occurred, accompanied by oliguria, agitation and elevation of the blood urea level, which reached the maximum figure of

			then three other injections, at the same dose, all both days. Suramin course after	210 mg/100 ml on the eighth day of hospitalization.
#1659 Baden 2016 n=1	case 1 62, female Country of exposure: Zimbabwe, Botswana Year when case was detected: not reported Country where case was treated: USA	Symptoms: fever, chills, myalgias, headache, and two pruritic areas on her back Diagnosis: Blood Stage 1	Suramin,Pentamidine IVpentamidine; five doses of suramin over a period of 3 weeks	treatment success
#1333 Pasternak 2013 n=1	case 1 age not reported, male Country of exposure: Zimbabwe Year when case was detected: not reported Country where case was treated: Brazil	Symptoms: fever, headache, muscle pain and asthenia, skin lesion Diagnosis: Blood Stage 1	Suramin,Pentamidine no details reported	treatment success
#1180 Migchelsen 2011 case 3, table 2 (not in Distiller, ref 53)	case 1 49, male Country of exposure: Tanzania, Kenya, Rwanda Year when case was detected: 1991 Country where case was treated: not reported (USA nationality)	Symptoms: Fever, lesion, lymphadenopathy, chills, sweat, anorexia, malaise, diarrhea Diagnosis: Blood Stage 1	Suramin,Pentamidine not reported	treatment success
#1840 Wijsman 2018 n=1	case 1 56, female Country of exposure: Tanzania and Kenya Year when case was detected: not reported Country where case was treated: Netherlands	Symptoms: nausea, vomiting, headache Diagnosis: Blood Stage 1	Suramin,Pentamidine Pentamidine - 300 mg; Suramin 100 mg followed by 400 mg the same day, 500 mg on day 2, 1000 mg on day 8, 15, 22	treatment success
#1243 Nadjm 2009 n=1	case 1 32, female Country of exposure: Tanzania Year when case was	Symptoms: fever, headache, and soft-tissue swelling of the forehead with severe regional	Suramin,Pentamidine pentamidine - 4 mg/kg (1 dose) suramin - 5 mg/kg	treatment success

	detected: not reported Country where case was treated: UK	adenopathy Diagnosis: Blood Stage 1	and increased over the next 2 doses up to 1 g	
#1755 van Genderen 2021 n=1	case 1 66, female Country of exposure: Malawi Year when case was detected: not reported Country where case was treated: Netherlands	Symptoms: chancre, shivers, headache, nausea Diagnosis: Blood Stage 1	Suramin,Pentamidine Pentamidine single dose - 4 mg/kg; suramin standard dose	treatment success
#719 Go´mez-Junyent 2017 n=1	case 1 49, female Country of exposure: Tanzania Year when case was detected: 2015 Country where case was treated: Spain	Symptoms: fever, malaise, joint pain, chancre Diagnosis: Blood Stage 1	Suramin,Pentamidine Pentamidine, 200 mg IV; suramin 5 doses on days 1, 3, 5, 14, and 21 (100 mg to start then 900 mg)	treatment success
#1047 Liu 2018 n=1	case 1 41, female Country of exposure: Kenya, Tanzania Year when case was detected: 2017 Country where case was treated: China	Symptoms: fever, dizziness, fatigue, rigors, red chancre, headache, cough, jaundice Diagnosis: Blood Stage 1	Suramin,Pentamidine pentamidine: 200 mg IV, 200 mg IM next 2 days suramin: test dose 200 mg IV; 1g IV on days 3, 7, 14, 21, 28	treatment success
#1929 Chen 2018 n=1	case 1 age not reported, male Country of exposure: Tanzania Year when case was detected: 2017 Country where case was treated: China	Symptoms: fever, lesion Diagnosis: Blood Stage 1	Suramin,Pentamidine Pentamidine: 4mg/kg×3d per day, intramuscular injection Suramin: test dose 4mg/kg, then 20 mg/kg on days 1, 3, 7, 14, 21	treatment success
#165 Barrett-Connor, 1972 n=1	case 1 19, male Country of exposure: Botswana Year when case was detected: 1970 Country where case was treated: USA	Symptoms: local reaction: persistent elevation of a bite site on the left thigh; fever, anorexia, and malaise, which was unchanged by a five-day course of ampicillin and	Suramin,Pentamidine regimen of pentamidine (no effect on the parasitemia within 24 hours).	Suramin treatment successful within 24 hours and

		chloramphenicol therapy; confused, somnolent, or manic, with evening hallucinations, severe headache Diagnosis: Blood Stage 1		
#1040 Limbos 1977 n=3	case 3 16, female Country of exposure: Rwanda Year when case was detected: 1973 Country where case was treated: Rwanda	Symptoms: primary inoculation lesions, high fever, restlessness Diagnosis: Blood Stage 1	Suramin,Pentamidine two injections of 160 mg of Pentamidine and in whom, for the same reasons as in the first case (proteinuria and presence of red blood cells in the urine), the treatment has Suramin was not undertaken and Pentamidine continued at the dose of 248 mg per injection. Surmin after	treatment success AEs : vomiting, kidney damage

Appendix 8. Summary of finding tables: indirect evidence

Fexinidazole for first-stage *gambiense* Human African Trypanosomiasis

Source: WHO interim guidelines for the treatment of gambiense human African trypanosomiasis. Available from: https://www.who.int/publications/i/item/9789241550567

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 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 6 [Mesu 2018b; Mesu 2018c]
Death likely due to HAT	No studies reported on this outcome			
Relapse	No studies reported on this outcome			
Treatment failure defined as: rescue treatment, death, CSF WBC >20 cells/µL, trypanosomes in the blood, lost to follow-up, consent withdrawal 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 6 [Mesu 2018b; Mesu 2018c]

Treatment success defined as: alive, no trypanosomes in body fluid, no rescue medication, CSF WBC ≤20 cells per µL 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 6 [Mesu 2018b; Mesu 2018c]
Serious adverse events 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 6 [Mesu 2018b; Mesu 2018c]
Adverse events 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 6 [Mesu 2018b; Mesu 2018c]
Adverse events: central nervous system 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 6 [Mesu 2018b; Mesu 2018c]
Adverse events: bone marrow toxicity 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 6 [Mesu 2018b; Mesu 2018c]
Adverse events: gastrointestinal symptoms 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 6 [Mesu 2018b; Mesu 2018c]
Adverse events: skin reactions 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 6 [Mesu 2018b; Mesu 2018c]

Adverse events: infections 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 6 [Mesu 2018b; Mesu 2018c]
Adverse events: cardiotoxicity 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 6 [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 6 [Mesu 2018b; Mesu 2018c]

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

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

Fexinidazole in healthy volunteers (RCTs, indirect evidence)

Source: WHO interim guidelines for the treatment of gambiense human African trypanosomiasis. Available from: https://www.who.int/publications/i/item/9789241550567

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				
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 6 [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 6 [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 6 [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 6 [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 6 [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

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.

Fexinidazole in healthy volunteers (single arm data, indirect evidence)

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
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 6 [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 6 [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 6 [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 6 [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 6 [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

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.