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Chemotherapy for second-stage human African trypanosomiasis: drugs in use (Review)

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[Intervention Review]

Chemotherapy for second-stage human African trypanosomiasis: drugs in use

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ABSTRACT

Background

Human African trypanosomiasis, or sleeping sickness, is a severe disease affecting people in the poorest parts of Africa. It is usually fatal without treatment. Conventional treatments require days of intravenous infusion, but a recently developed drug, fexinidazole, can be given orally. Another oral drug candidate, acoziborole, is undergoing clinical development and will be considered in subsequent editions.

Objectives

To evaluate the effectiveness and safety of currently used drugs for treating second-stage *Trypanosoma brucei gambiense* trypanosomiasis (gambiense human African trypanosomiasis, g-HAT).

Search methods

On 14 May 2021, we searched the Cochrane Infectious Diseases Group Specialized Register, the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, Latin American and Caribbean Health Science Information database, BIOSIS, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform. We also searched reference lists of included studies, contacted researchers working in the field, and contacted relevant organizations.

Selection criteria

Eligible studies were randomized controlled trials that included adults and children with second-stage g-HAT, treated with anti-trypanosomal drugs currently in use.

Data collection and analysis

Two review authors extracted data and assessed risk of bias; a third review author acted as an arbitrator if needed. The included trial only reported dichotomous outcomes, which we presented as risk ratio (RR) or risk difference (RD) with 95% confidence intervals (CI).

Main results

We included one trial comparing fexinidazole to nifurtimox combined with eflornithine (NECT). This trial was conducted between October 2012 and November 2016 in the Democratic Republic of the Congo and the Central African Republic, and included 394 participants. The study reported on efficacy and safety, with up to 24 months' follow-up. We judged the study to be at low risk of bias in all domains except

blinding; as the route of administration and dosing regimens differed between treatment groups, participants and personnel were not blinded, resulting in a high risk of performance bias.

Mortality with fexinidazole may be higher at 24 months compared to NECT. There were 9/264 deaths in the fexinidazole group and 2/130 deaths in the NECT group (RR 2.22, 95% CI 0.49 to 10.11; 394 participants; low-certainty evidence). None of the deaths were related to treatment.

Fexinidazole likely results in an increase in the number of people relapsing during follow-up, with 14 participants in the fexinidazole group (14/264) and none in the NECT group (0/130) relapsing at 24 months (RD 0.05, 95% CI 0.02 to 0.08; 394 participants; moderate-certainty evidence).

We are uncertain whether there is any difference between the drugs regarding the incidence of serious adverse events at 24 months. (31/264 with fexinidazole and 13/130 with NECT group at 24 months). Adverse events were common with both drugs (247/264 with fexinidazole versus 121/130 with NECT), with no difference between groups (RR 1.01, 95% CI 0.95 to 1.06; 394 participants; moderate-certainty evidence).

Authors' conclusions

Oral treatment with fexinidazole is much easier to administer than conventional treatment, but deaths and relapse appear to be more common. However, the advantages or an oral option are considerable, in terms of convenience, avoiding hospitalisation and multiple intravenous infusions, thus increasing adherence.

PLAIN LANGUAGE SUMMARY

Medicines for second-stage human African trypanosomiasis

What is the aim of this review?

Gambiense human African trypanosomiasis (g-HAT), or sleeping sickness, is a severe disease transmitted through the bite of infected tsetse flies found in rural parts of sub-Saharan Africa. Sleeping sickness has two clinical stages. This review only examines treating the second-stage, where people develop symptoms caused by invasion of the central nervous system (CNS), resulting in changes in the nervous system. Death is inevitable without treatment. Drugs for treatment are few, often require intravenous infusion every day over several weeks, and have serious side effects. In this review we aimed to compare the effects of current drugs for gambiense sleeping sickness and we examined nifurtimox-eflornithine combination (NECT) with a new drug, fexinidazole, that can be taken orally.

Key messages

Whilst fexinidazole cures some people, deaths from any cause and treatment failure rates are higher than with conventional treatment. Adverse events were common in both groups. Fexinidazole is more practical to give, and means less time in hospital for intravenous treatment infusion.

What was studied in this review?

We looked at the evidence about the benefits and harms of current drugs used in people with second stage g-HAT. We searched for randomized trials, which provide robust evidence about the various treatments. We aimed to determine whether any drug provides a definite advantage over the other, measured in terms of clinical outcomes and in relation to the severity of adverse effects.

What are the main results of the review?

We only identified one suitable trial, which included 394 people and was conducted in the Democratic Republic of the Congo and the Central African Republic. The trial showed that deaths from any cause at 24 months may be higher with fexinidazole compared with NECT. Nine of the 264 people who took fexinidazole died, compared with two of the 130 people who took NECT. Fexinidazole probably increases the number of people who relapse during two years. Fourteen people in the fexinidazole group relapsed, and none in the NECT group. Adverse events were very common in both groups over the two years, and there is not likely to be much difference between the two drugs (247/264 in the fexinidazole group and 121/130 in the NECT group). We do not know about the effect of fexinidazole on serious adverse events, as the evidence is very uncertain. There were 31/264 serious adverse events in the fexinidazole group and 13/130 in the NECT group at 24 months.

How up to date is this review?

The evidence is current to 14 May 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings table 1

Fexinidazole compared to NECT for second-stage human African trypanosomiasis

Patient or population: ≥ 15-year-old people with late second stage human African gambiense trypanosomiasis (trypanosomes in blood or nymph node fluid and WBC > 20 cells/µL or trypanosomes in CSF)

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

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

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with NECT	Risk with fexinidazole				
All-cause mortality Follow up: 24 months	15 per 1000	34 per 1000 (8 to 156)	RR 2.22 (0.49 to 10.11) (NNTH = 25)	394 (1 RCT)	⊕⊕⊖⊖ LOW[a,b]	Mortality with fexinidazole may be higher compared with NECT.
Relapse[c] Follow up: 24 months	<1%[d]	5 %[d]	RD 0.05 (0.02 to 0.08) (NNTH = 20)	394 (1 RCT)	⊕⊕⊕⊖ MODERATE[a,e]	Relapse is probably more common with fexinidazole compared with NECT.
Serious adverse events Follow up: 24 months	100 per 1000	117 per 1000 (64 to 217)	RR 1.17 (0.64 to 2.17) (NNTH = 51)	394 (1 RCT)	⊕⊖⊖⊖ VERY LOW[b,e]	We do not know whether or not serious adverse events with fexinidazole or NECT are different.

Adverse events Follow up: 24 months	931 per 1000	940 per 1000 (884 to 987)	RR 1.01 (0.95 to 1.06) (NNTH = 107)	394 (1 RCT)	⊕⊕⊕⊖ MODERATE[f]	More than 90% of participants experience adverse events in both groups, and there is little or no difference in these high levels between fexinidazole and NECT.

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

CI: confidence interval; **CSF**: cerebrospinal fluid;**IV**: intravenous; **NECT**: nifurtimox combined with eflornithine; **NNTH:** number needed to treat for an additional harmful outcome; **RCT**: randomized controlled trial; **RD**: risk difference; **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

[a]Not downgraded for risk of bias. Whilst the trial is open-label, this objective outcome is not subject to bias.
[b]Downgraded by two levels for very serious imprecision: few events and wide CIs that include both appreciable benefit and appreciable harm, as well as no effect.
[c]Relapse was defined as either rescue treatment use as a consequence of trypanosomes detected in any body compartment (blood, lymph, or CSF) at any follow-up examination; or CSF leukocyte count > 50 WBC/µL CSF, or doubled from previous count, at any follow-up examination; or CSF leukocyte count between 20 WBC/µL and 49 WBC/µL CSF, together with symptoms strongly suggestive of relapse (worsened clinical condition since previous examination, with long-lasting headache, mental or neurological disturbances, increased somnolence, recurrent fever, etc.).
[d]The risk in the intervention group is based on the number of events and participants in the intervention group; anticipated absolute effects could not be calculated as there were no events reported in the control group. We have therefore provided an estimate based on actual numbers in the trial.
[e]Downgraded by one level for serious imprecision: very few events and no events reported in the control group.
[f]Downgraded by one level for serious risk of bias: open label trial and consequently risk of performance and detection bias for outcomes that could be influenced by exposure to other factors apart from the intervention of interest.

BACKGROUND

Description of the condition

Human African trypanosomiasis (HAT), or sleeping sickness, is a disease caused by the protozoan parasite *Trypanosoma brucei* that is transmitted through the bite of infected tsetse flies. The eco-distribution of tsetse flies is determined by the climate, presence of water, vegetation, and their requirement for blood meals (human or animals), but they are mostly found in rural and forested areas. Essential human activities, such as collecting water from natural sources, washing, farming, collecting wood, hunting and fishing, can increase contact between humans and tsetse flies and contribute to the spread of the disease (Büscher 2017; Pépin 2001).

Two subspecies of *Trypanosoma brucei* can infect humans. *T b gambiense* causes a generally chronic form of sleeping sickness in West and Central Africa, in which humans are the principal reservoir of the parasite. *T b rhodesiense*, found in Eastern and Southern Africa, generally causes a more acute form of the disease, in which animals are the principal reservoir of the parasite and humans are occasionally affected. Gambiense HAT (g-HAT) caused more than 98% of reported cases of sleeping sickness in west and central Africa, but between 2000 and 2018 the number of cases decreased by 96%, with 953 cases in total in 2018 (Franco 2020). Rhodesiense HAT is present in eastern and southern Africa, representing about 2% of reported cases (24 cases in 2018; (Franco 2020)). In both forms, the disease is characterized by two clinical stages related to the propagation of the parasite in the infected host. In the first stage, when trypanosomes multiply in the haemolymphatic system, infected individuals experience intermittent fever and develop lymphadenopathy and other non-specific signs, such as hepatosplenomegaly and pruritus (Kennedy 2019; Stich 2002). In the second stage of the disease, trypanosomes reach the central nervous system, resulting in a severe meningoencephalitis with headaches and extensive and diverse neuropsychiatric disorders, typically including sleep disturbances resembling narcolepsy, and resulting in convulsions, coma, and death (Kennedy 2019; Stich 2002).

Sleeping sickness is usually fatal without adequate treatment; treatment of infected individuals is crucial for reducing the trypanosome reservoir in humans and consequently for controlling the disease. The mostly rural distribution of the disease, civil unrest occurring in many of the affected regions, the financial and social constraints experienced by endemic countries, and the difficulties in case finding, diagnosing and effectively treating people with HAT, have all contributed to making it one of the hardest diseases to control in sub-Saharan Africa (Brun 2010).

Incidence

The incidence of HAT has undergone several fluctuations through the last 100 years. Between the 1960s and the 1990s, the gradual breakdown of control programs, aggravated by economic hardship, war, and civil strife in most endemic countries, resulted in an alarming resurgence of the disease, with epidemics in the Democratic Republic of the Congo, Angola, Sudan, Uganda, and the Central African Republic (Brun 2010; Seed 2001). But in the last 20 years, the reported number of new cases of the chronic form of gambiense human African trypanosomiasis (g-HAT) fell by 97%, from 27,862 in 1999 to 953 cases in 2018 (Franco 2017; Franco 2020; WHO 2019). This was the result of enhanced control and surveillance activities, brought forward at the beginning of the century by the World Health Organization (WHO) and its partners when the number of infected people was reaching alarming levels. These activities were co-ordinated and implemented by National Sleeping Sickness Control Programs (NSSCPs), supported by the WHO, and involved a long-standing public-private partnership with Sanofi and Bayer (allowing the free availability of drugs), as well as the work of non-governmental organizations (NGOs) and other stakeholders (Franco 2014). As a result, the goal of eliminating sleeping sickness as a public health problem by 2020 was included by the WHO in its Neglected Tropical Diseases (NTD) roadmap in 2012 (WHO 2012), and the goal of complete interruption of transmission for g-HAT was set for 2030 (Franco 2018; WHO 2013).

Diagnosis and stage determination of HAT are problematic and cannot be based on clinical signs alone (Kennedy 2019; Lejon 2005). The presence of parasites has to be demonstrated in body fluids, and, according to the WHO, diagnosis of second-stage HAT should be based on an examination of cerebrospinal fluid (CSF) for the presence of trypanosomes, increased white blood cell count (WBC) in CSF, and increased total protein concentration (WHO 2004; WHO 2013). People with up to 5 WBC/µL in CSF are diagnosed with first-stage HAT. There is some controversy about the correct stage classification of people with 6 WBC/µL to 20 WBC/µL in CSF, as many people in this 'grey zone' do not display typical symptoms of second-stage HAT and can be cured with drugs that do not reach therapeutic levels in the brain (Lejon 2005). A WBC over 20 cells/µL in CSF is recommended as a cut-off point for inclusion of participants in clinical trials for treatment of second-stage HAT (WHO 2004; WHO 2013). However, changes in the classification of disease stages are being introduced with the use of fexinidazole (see Discussion).

Description of the intervention

Treatment for both stages of the disease is complex. In this review we will focus on the active area of clinical research, which includes the drugs currently recommended as first choice for the treatment of second-stage g-HAT (fexinidazole and NECT (nifurtimox combined with eflornithine)), and drugs in development (currently acoziborole).

The previous version of this Cochrane Review analyzed drugs that were previously used to treat second-stage g-HAT: melarsoprol, eflornithine or nifurtimox monotherapy, and adjunctive treatments such as steroids (Lutje 2013). Monotherapy with eflornithine is still included as second-choice treatment (after NECT) in children, and melarsoprol is still considered as a rescue medication in severe second-stage HAT if both fexinidazole and NECT have failed (WHO 2019).

Nifurtimox-eflornithine combination (NECT)

The combination of nifurtimox and eflornithine (NECT), two drugs that were previously used separately to treat second stage g-HAT (Lutje 2013), was approved by the Expert Committee on the Selection and Use of Essential Medicines at its 17th meeting on 30 April 2009, and was included in the WHO Essential List of Medicines for the treatment of human African trypanosomiasis (WHO 2010). Using NECT in people with second-stage HAT removed the need for melarsoprol and the significant risk of encephalopathic syndromes and other severe adverse events (Priotto 2009). Despite this advantage, NECT requires the administration of two

separate drugs, used for several days, involving specialized health personnel. Under field conditions, NECT has displayed a tolerability profile similar to that described in the initial clinical trials, and it has proved effective against g-HAT, since only a low number of relapses were reported during the analysis period (Alirol 2013; Franco 2012; Schmid 2012).

Fexinidazole

Fexinidazole is a 5-nitroimidazole, and in experimental studies was found to be active against both *T b gambiense* and *T b rhodesiense*, to have a favourable safety profile, and to be orally active (Torreele 2010). Tarral 2014 assessed dosage, tablet versus suspension formulation, and food effect for fexinidazole in healthy volunteers. The researchers concluded that oral fexinidazole up to 3600 mg/day was safe and well-tolerated; food intake increased drug absorption and plasma concentrations of fexinidazole and its two metabolites by approximately 200% (Tarral 2014). These findings led to a pivotal randomized non-inferiority trial comparing fexinidazole to NECT in people with late-stage g-HAT (Mesu 2018). Fexinidazole received a positive scientific opinion by the European Medicines Agency (EMA) in November 2018 (Assessment report Fexinidazole Winthrop EMA 2018, see Mesu 2018), and in July 2019, it was added to the WHO's Essential Medicines Lists for adults and children aged over six years with a body weight over 20 kg, for the treatment of both stages of g-HAT. Fexinidazole is now included as a new therapeutic protocol in the recently updated WHO interim guidelines for treatment of this form of HAT (WHO 2019).

Other candidate compounds

Another oral drug candidate, an oxaborole-6-carboxamide, acoziborole (SCYX-7158) is currently in phase 2/3 clinical trials promoted by the Drugs for Neglected Diseases Initiative (DNDi); it has the advantage of being administered as a single oral dose and has shown a favourable safety profile (Barrett 2018; Jones 2015). It is hoped that acoziborole can provide an effective one-day, one-dose stage-independent treatment option, which would improve patient adherence and support current efforts to eliminate the disease.

How the intervention might work

The use of anti-trypanosomal drugs is complicated by multiple factors, including logistics, availability, and patient adherence to treatment. NECT is an effective drug, but the eflornithine has to be administered intravenously in hospital. To cover the resources needed, the WHO designed a NECT kit containing the drug and all materials needed for intravenous injections, such as sterile water, catheters etc. Each box weights 39 kg and its transport to local health centres, often remote, can represent a logistical challenge (Eperon 2014). Fexinidazole has been shown to be safe and well-tolerated after oral administration in healthy volunteers (Tarral 2014), but optimal absorption requires food intake that has to be supervised. In this version of the review, we examine the safety and effectiveness of fexinidazole in people with second stage g-HAT.

Why it is important to do this review

The first published version of this review (Lutje 2010), and the updated review (Lutje 2013), examined drugs historically used up to that point for treating second-stage g-HAT. They included nine RCTs, with the most recent ones assessing the use of NECT. The discussion stated that "considering that none of the current therapeutic options for HAT is optimal in terms of adverse events and ease of administration, it is essential that new anti-trypanosomal compounds are developed and tested in experimental and clinical studies".

As the incidence of the disease is declining, following intensive surveillance and control activities in endemic areas, HAT has been included in the neglected tropical diseases targeted by the WHO for elimination. The approval of fexinidazole, an oral compound, active in both stages of the gambiense form of the disease, presents a new opportunity for better management of HAT and reduced burden on health systems. Other oral compounds, such as acoziborole, are undergoing field clinical trials.

In this new version of the review, we only consider comparisons between drugs currently used, or in development, for treating second-stage g-HAT (NECT, fexinidazole, and acoziborole), aiming to examine whether any of them provides a definite advantage over the others, measured in terms of clinical outcomes and in relation to the severity of adverse effects.

OBJECTIVES

To evaluate the effectiveness and safety of currently used drugs for treating second-stage gambiense HAT.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

We included adults and children with a primary diagnosis of second-stage g-HAT, that is, having evidence of trypanosomal infection and a CSF analysis showing a WBC count of more than 5 cells/µL, with no upper limit, or the presence of trypanosomes. Adults and children relapsing after treatment for second-stage g-HAT were also eligible. We excluded studies in people with *T b rhodesiense*.

Types of interventions

Intervention

We included drugs currently in use or under investigation for treating second-stage *T b gambiense* trypanosomiasis (gambiense human African trypanosomiasis, g-HAT): NECT, fexinidazole, acoziborole.

Control

We compared the eligible intervention drugs against drugs currently in use for treating second-stage *T b gambiense* trypanosomiasis (gambiense human African trypanosomiasis, g-HAT).

Types of outcome measures

Primary outcomes

- Overall mortality (for any reason, including HAT and treatment toxicity) up to 24 months 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 one 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 WBC/µL and 49 WBC/µL CSF, together with symptoms strongly suggestive of relapse (worsened clinical condition since previous examination, with long lasting headache, mental or neurological disturbances, increased somnolence, recurrent fever, etc.)

Secondary outcomes

- Treatment failure, up to 24 months of follow-up

Adverse events

- Adverse events that led to discontinuation of treatment
- Serious adverse events
- Any adverse events
- Specific adverse events

Search methods for identification of studies

We attempted to identify all relevant trials, regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

We searched the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register (14 May 2021); the Cochrane Central Register of Controlled Trials (Issue 5 of 12, May 2021); MEDLINE (Pubmed; 1966 to 14 May 2021); Embase (Ovid; 1974 to 14 May 2021); LILACS (Latin American and Caribbean Health Science Information database; Bireme; 1982 to 14 May 2021); BIOSIS (Web of Science; 1926 to 14 May 2021). We also searched Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (www.who.int/ictrp/search/en/), both on 14 May 2021.

Searching other resources

We screened the reference lists of included studies to identify any additional trials.

Researchers, organizations, and pharmaceutical companies

We attempted to locate unpublished and ongoing trials by contacting individual researchers working in the field; and organizations including Médecins sans Frontières, Epicentre, Malteser, WHO, DNDi, and WHO Special Programme for Research and Training in Tropical Diseases (TDR).

Data collection and analysis

Selection of studies

We uploaded all trials identified through systematic literature searches into Covidence. Two review authors (VL, GV) independently screened each title and abstract identified in the search. We retrieved full texts for potentially relevant references, and two review authors again (VL, GV) screened them independently, resolving disagreements by discussion.

Data extraction and management

For this review, we extracted data in Covidence. We created forms for data collection, which were piloted and then revised after the review author team's discussion. For previous versions of this review, we used Microsoft Word data collection forms.

Two review authors (HB, KP) independently extracted the data, and resolved disagreements by referring to the trial report or by consulting a third review author (GV).

We extracted the following data.

- Trial design, including setting, method of participant selection, sample size, method of blinding of participants and personnel.
- Participants, including, population characteristics; inclusion and exclusion criteria, withdrawals and loss to follow-up.
- Intervention: description of intervention (active ingredient, dose, formulation, method, frequency and timing of application)
- Outcomes: definition of outcome, number of events, number of participants, time point at which outcome was assessed, incomplete outcomes or missing data.

All outcomes were dichotomous, and we extracted the number of participants experiencing each outcome and the number of participants in each treatment group.

One review author entered the data into Review Manager 5 (RevMan 2020).

Assessment of risk of bias in included studies

Two review authors (HB, KP) independently assessed the risk of bias of each trial, using the Cochrane risk of bias tool (Higgins 2017), which addresses six specific domains: sequence generation; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data; selective outcome reporting; and other potential sources of bias. We categorized these judgements as ‘low', ‘high', or ‘unclear' risk of bias per outcome. We resolved disagreements through discussion with a third review author (GV). We created plots of risk of bias assessment in Review Manager 5 (RevMan 2020).

Measures of treatment effect

All outcomes were dichotomous. We analysed dichotomous data by calculating the risk ratio (RR) or the risk difference (RD) for each trial (expressed using blue squares in forest plots) with the uncertainty in each result expressed using 95% confidence intervals (CIs). We planned to use RDs in outcomes with no events in either of the intervention or control groups. For each outcome presented in the summary of findings table, we calculated the number needed to treat for an additional beneficial outcome (NNTB) or for an additional harmful outcome (NNTH) from the RR or RD, according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). The NNTB or NNTH expresses the estimated number of people who need to be treated with the intervention rather than the control treatment for one additional person to benefit or be harmed, respectively (Altman 1998).

Unit of analysis issues

The included trial did not have unit of analysis issues. Had included studies had multiple treatment arms and we considered it suitable,

we would have grouped the trial arms. We would have excluded irrelevant trial arms. We would have pooled cluster-RCT data that had been adjusted for clustering with data from trials that randomly assigned individuals. To do this, we would have used a logarithmic scale and the generic inverse variance method (Higgins 2019).

Dealing with missing data

We based all analyses on the intention-to-treat (ITT) population, with no events assumed for missing participants. Additionally, we undertook sensitivity analyses based on available cases per outcome, to test the robustness of assumptions made in the main analyses.

Assessment of heterogeneity

We planned to assess heterogeneity in the results of the trials by inspecting the graphical presentations and by calculating the Chi^2 test for heterogeneity. However, we were aware of the fact that the Chi^2 test has a poor ability to detect statistically significant heterogeneity among studies. We therefore also planned to quantify the impact of heterogeneity in the meta-analysis using a measure of the degree of inconsistency in the studies' results (Higgins 2003). This measure (the I^2 statistic) describes the percentage of total variation across studies that is due to heterogeneity rather than to the play of chance (Higgins 2003). The I^2 statistic values lie between 0% and 100%, and a simplified categorization of heterogeneity could be low, moderate, and high for I^2 statistic values of 25%, 50%, and 75% respectively (Higgins 2003).

Assessment of reporting biases

If there were 10 or more trials included in each meta-analysis, we intended to investigate reporting biases (such as publication bias) using funnel plots. We planned to assess funnel plot asymmetry both visually and using formal tests (Harbord 2006), and explore possible reasons for asymmetry.

Data synthesis

We analysed data using Review Manager 5 (RevMan 2020). Included trials only reported dichotomous outcomes.

We had intended to use a fixed-effect model, unless we found statistically significant heterogeneity ($P < 0.10$) for a specific outcome, in which case we would have used the random-effects model. However, we did not perform a meta-analysis. We presented results in forest plots and tables, and we planned to stratify analyses by comparisons and by doses/regimens of the drugs.

Subgroup analysis and investigation of heterogeneity

Only one study qualified for inclusion, therefore we did not perform any subgroup analysis or investigation of heterogeneity. We reported on post hoc subgroup analyses that were carried out by the study investigators (Table 1).

Sensitivity analysis

We undertook sensitivity analyses based on available cases per outcome, to test the robustness of assumptions made in the main analyses (where, based on the ITT population, we assumed no events for missing participants).

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of evidence using the GRADE approach (Guyatt 2011). We used GRADEpro GDT to import data from RevMan 2020 and to create summary of findings tables. These tables provide outcome-specific information concerning the overall certainty of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rated as critical to care of people with HAT and for decision-making.

We presented the following outcomes in the summary of findings tables, as we considered them to be the most critical for decision-making:

- Overall mortality
- Relapse
- Serious adverse events
- Adverse events

RCTs started as high-certainty evidence, but we downgraded the certainty of the evidence if there were valid reasons within the following five categories: risk of bias, imprecision, inconsistency, indirectness, and publication bias. We interpreted the different levels of certainty that result from GRADEing the evidence as follows.

- 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.
- 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.

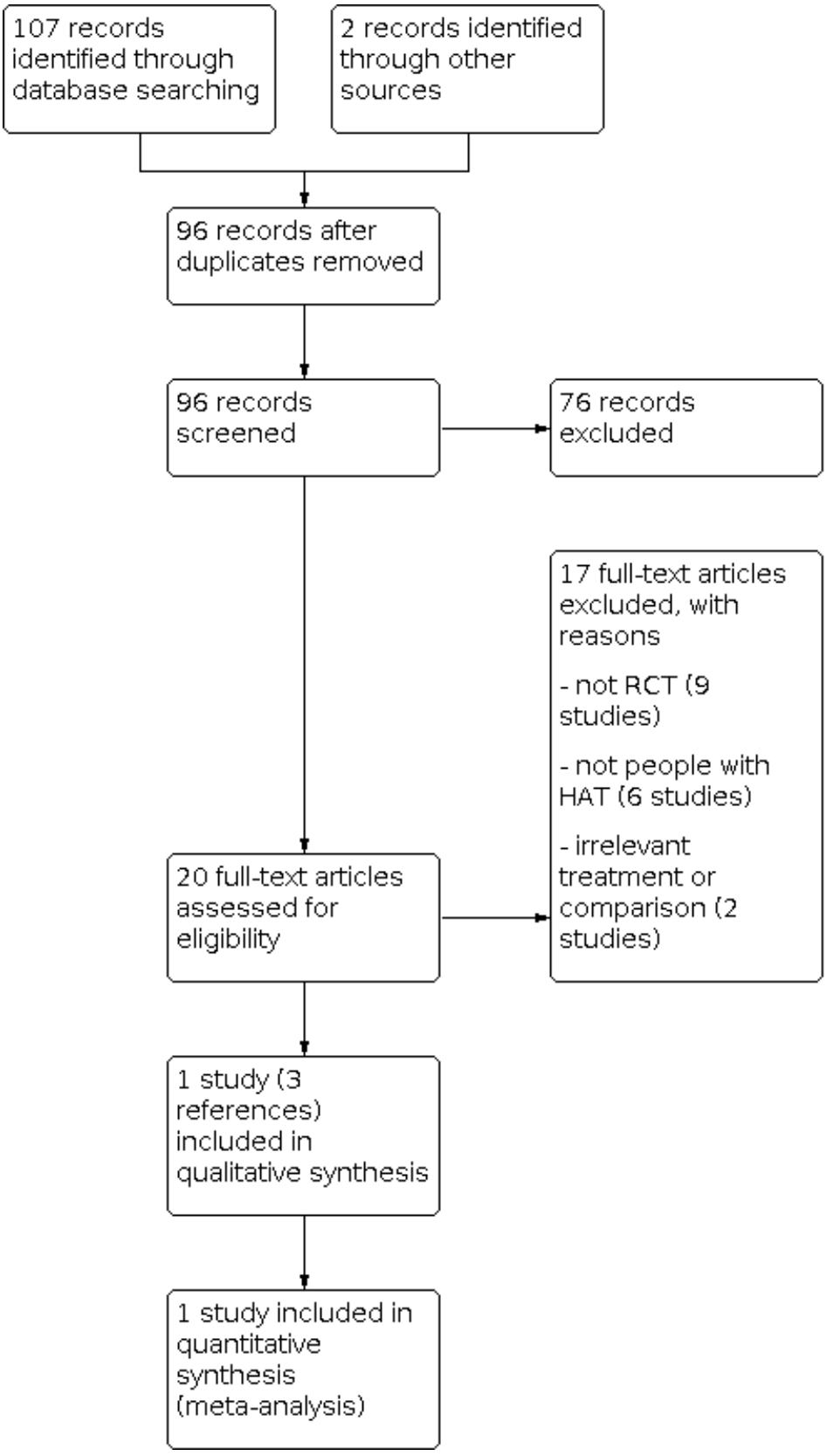
RESULTS

Description of studies

Results of the search

Our searches identified a total of 109 reports. After deduplication, we screened 96 records and considered 76 to be irrelevant. We retrieved the full texts of the remaining 20 records. Of these, one trial met the inclusion criteria (Mesu 2018). We found three references for this trial: one published article, one European Medicines Agency report that was available online, and one unpublished clinical study report (CSR) that was shared with us by the trialists. See Figure 1 for a flow diagram of the selection process.

Figure 1. Study flow diagram.



We reported reasons for excluding studies in the Characteristics of excluded studies table.

Ongoing studies

We identified one ongoing study (NCT03087955), a prospective study on oral drug candidate acoziborole (SCYX-7158).

Included studies

See Characteristics of included studies.

We identified one trial (Mesu 2018), which compared the new drug fexinidazole with current first-line treatment with NECT in people with second-stage HAT. This trial was conducted in 394 inpatients, aged 15 years or over, at 10 sites in the Democratic Republic of the Congo and the Central African Republic. Fexinidazole was given orally once a day with food (1800 mg, 3 × 600 mg tablets) on days one to four, followed by 1200 mg (2 × 600 mg tablets) once a day on days five to 10. Participants in the comparator arm received nifurtimox tablets three times a day at a dose of 15 mg/kg per day for 10 days (days 1 to 10), with eflornithine given twice a day as a two-hour intravenous infusion at a total dose of 400 mg/kg for seven days (days one to seven).

The trial reported on the following outcomes: mortality (overall, death during treatment), treatment success, treatment failure, withdrawals, relapse, adverse events, and serious adverse events. Parameters were collected at 18 months and 24 months. We collected data at 24 months' follow-up from the unpublished CSR.

Excluded studies

We excluded 17 studies (Figure 1) because they:

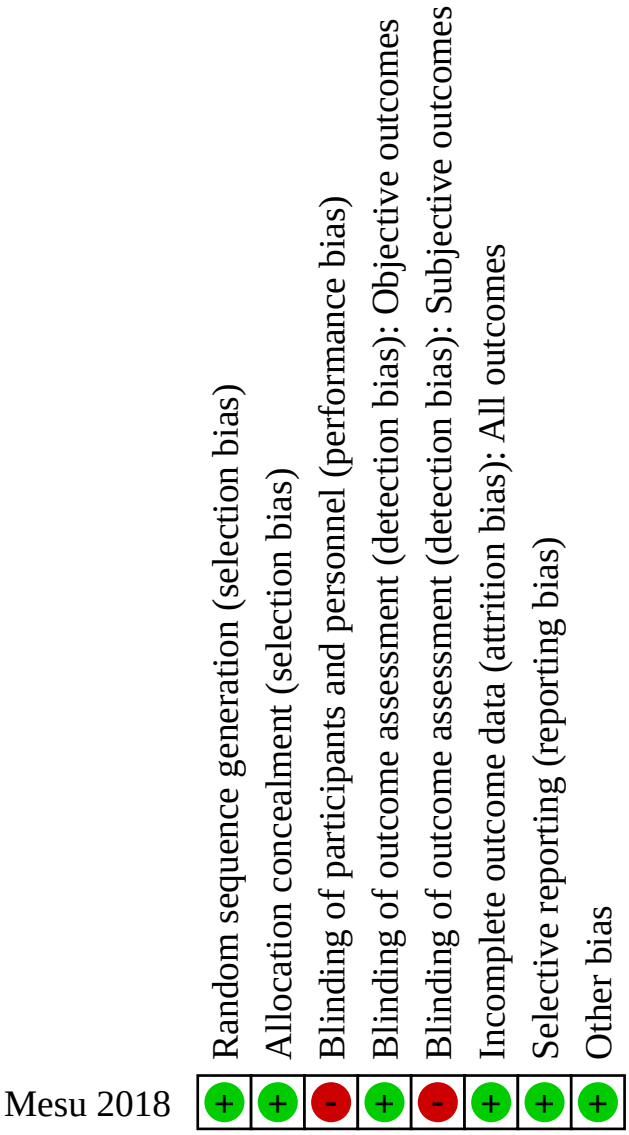
- were not RCTs (Alirol 2013; Chappuis 2018; Kazumba 2018; Mord 2013; Pelfrene 2019; Pollastri 2018; Schmid 2012, Valverde 2015; Watson 2019);
- did not include people with HAT (NCT00982904; NCT01483170; NCT01340157; NCT02571062, Tarral 2011; Tarral 2014); and
- did not include a relevant comparison (Jansson-Löfmark 2015; Kansiime 2018).

We described the reasons for excluding studies in the Characteristics of excluded studies table.

Risk of bias in included studies

We included one RCT. See Characteristics of included studies table for details, and also Figure 2 for the risk of bias assessments.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

There was a low risk of selection bias, with adequate random sequence generation. Participants were randomly assigned (2:1) on day one to receive either fexinidazole or nifurtimox eflornithine combination therapy, according to a predefined randomization list stratified by site. Allocation concealment was also adequate (randomization was centralized to avoid selection bias).

Blinding

There was a high risk of performance bias due to participants and personnel not being blinded, as this was an open-label study. As the route of administration and dosing regimens differed between treatment groups, a double-dummy study was not feasible and would have required placebo infusions.

The funder, data management personnel, and statisticians (except the independent statistician in charge of the interim analysis) were masked to treatment until the primary analysis at 18 months. It

was unclear whether outcome assessors were blinded. 'All-cause mortality' and 'death during treatment' are observer-reported outcomes not involving judgement, so we assessed these to be at low risk of detection bias. 'Relapse', 'adverse events that lead to treatment discontinuation', 'death likely to be due to HAT', 'adherence to treatment', 'treatment failure', 'adverse events', and 'serious adverse events' involve some measure of judgement and could be affected by knowledge of intervention receipt. We assessed these outcomes to be at high risk of detection bias.

Incomplete outcome data

There was a low risk of attrition bias, as there were < 10% missing data for all outcomes at 18 and 24 months.

Selective reporting

There was a low risk of reporting bias, as all outcomes listed in the online trial record were reported (clinicaltrials.gov/ct2/show/NCT01685827), and the 24-month follow-up clinical study report was made available.

Other potential sources of bias

There was a low risk of other bias. Similar demographic characteristics were noted in the primary analysis population in both treatment groups.

Effects of interventions

See: **Summary of findings 1** Summary of findings table 1

Fexinidazole compared to NECT

See Summary of findings 1. There was one trial included in the analyses, with 264 participants in the fexinidazole group and 130 participants in the NECT group.

Overall mortality

During treatment up to the last drug administration, two people (2/264) died in the fexinidazole group and there were no deaths during treatment (0/130) in the NECT group (RD 0.01, 95% CI -0.01 to 0.02; 394 participants; Analysis 1.1).

Mortality with fexinidazole (9/264) compared with NECT (2/130) may be higher at 24 months' follow-up, ranging from eight fewer deaths to 140 more deaths per 1000 people compared to NECT (RR 2.22, 95% CI 0.49 to 10.11; 394 participants; low-certainty evidence; Analysis 1.2). At 18 months, there had been six deaths in the fexinidazole group (6/264) and two deaths (2/130) in the NECT group (RR 1.48, 95% CI 0.30 to 7.22; 394 participants).

Sensitivity analyses based on available cases at 18 and 24 months' follow-up (excluding those lost to follow-up and consent withdrawals) did not result in a change in the magnitude or direction of effect (18 months: RR 1.45, 95% CI 0.30 to 7.10; 386 participants; 24 months: RR 2.20, 95% CI 0.48 to 10.02; 384 participants; analyses not shown).

None of the 11 deaths that occurred during the 24 months' follow-up were considered related to treatment. However, causes of death were not reported.

Relapse

Fexinidazole likely results in an increase in the number of people relapsing during follow-up compared with NECT, with 14 participants relapsing in the fexinidazole group (14/264) and none in the NECT group (0/130) at 24 months' follow-up (RD 0.05, 95% CI 0.02 to 0.08, 394 participants; moderate-certainty evidence; Analysis 1.3). At 18 months, 15/264 people relapsed in the fexinidazole group and 0/130 in the NECT group (RD 0.06, 95% CI 0.03 to 0.09; 364 participants).

Relapse was defined as either: rescue treatment use as a consequence of trypanosomes detected in any body compartment (blood, lymph, or CSF) at any follow-up examination; or CSF leukocyte count > 50 WBC/µL CSF, or doubled from previous count, at any follow-up examination; or CSF leukocyte count between 20 WBC/µL and 49 WBC/µL CSF, together with symptoms strongly suggestive of relapse (worsened clinical condition since previous examination, with long-lasting headache, mental or neurological disturbances, increased somnolence, recurrent fever, etc.).

Sensitivity analyses based on available cases at 18 and 24 months' follow-up (excluding withdrawals due to death, those lost to follow-up, and consent withdrawals) did not result in a change in the magnitude or direction of effect (18 months: RD 0.06, 95% CI 0.03 to 0.09; 378 participants; 24 months: RD 0.06, 95% CI 0.03 to 0.09; 373 participants; analyses not shown).

Treatment failure

There were 27/264 events in the fexinidazole group and 3/130 events in the NECT group at 24 months' follow-up (RR 4.43, 95% CI 1.37 to 14.34; 394 participants; Analysis 1.4). At 18 months' follow-up, there were 23/264 events in the fexinidazole group and 3/130 events in the NECT group (RR 3.78, 95% CI 1.15 to 12.34; 394 participants).

In this study, treatment failure was a composite outcome of rescue treatment, death, CSF WBC > 20 cells/µL, trypanosomes in any body fluid, loss to follow-up, need for rescue treatment, refusal to comply with assessment, and consent withdrawal.

Adverse events

Adverse events that led to discontinuation of treatment

All participants completed treatment, except two people in the fexinidazole group who died during treatment (RD 0.01, 95% CI -0.01 to 0.02; 394 participants; Analysis 1.5). The Data Safety Monitoring Board of the trial concluded that these deaths were unrelated to treatment.

Serious adverse events

We do not know about the effect of fexinidazole on serious adverse events at 24 months compared with NECT (RR 1.17, 95% CI 0.64 to 2.17; 394 participants; very low-certainty evidence; Analysis 1.6). There were 31/264 events in the fexinidazole group and 13/130 events in the NECT group at 18 months. There were no additional serious adverse events reported from 18 months to 24 months.

Sensitivity analyses based on available cases at 18 and 24 months' follow-up (excluding withdrawals due to death, those lost to follow-up, and consent withdrawals) did not result in a change in the magnitude or direction of effect (18 months: RR 1.16, 95% CI 0.63 to

2.14; 378 participants; 24 months: RR 1.19, 95% CI 0.64 to 2.19; 373 participants; analyses not shown).

Any adverse events

Adverse events were very common in both groups. At 24 months' follow-up, there were 247/264 adverse events with fexinidazole and 121/130 adverse events with NECT, ranging from 47 fewer to 56 more adverse events per 1000 people. There is likely to be little to no difference between groups for this outcome (RR 1.01, 95% CI 0.95 to 1.06; 394 participants; moderate-certainty evidence; Analysis 1.7). At 18 months, there had been 247/264 adverse events in the fexinidazole groups and 120/130 in the NECT group (RR 1.01, 95% CI 0.96 to 1.08; 394 participants) .

Sensitivity analyses based on available cases at 18 and 24 months' follow-up (excluding withdrawals due to death, those lost to follow-up, and consent withdrawals) did not result in a change in the magnitude or direction of effect (18 months: RR 1.00, 95% CI 0.97 to 1.04; 378 participants; 24 months: RR 1.02, 95% CI 0.99 to 1.05; 373 participants; analyses not shown).

Specific adverse events

When looking at specific adverse events, there were 158/264 central nervous system adverse events (neurological and psychiatric disorders) in the fexinidazole group and 64/130 events in the NECT group (RR 1.22, 95% CI 0.99 to 1.49; 394 participants). With fexinidazole there were 157/264 gastrointestinal symptoms (diarrhoea, nausea, and vomiting) compared with 64/130 gastrointestinal symptoms in the NECT group (RR 1.21, 95% CI 0.99 to 1.48; 394 participants). Regarding the occurrence of bone marrow toxicity (anaemia, neutropenia, thrombocytopenia) there were 29/264 events with fexinidazole compared to 18/130 with NECT (RR 0.79, 95% CI 0.46 to 1.37; 394 participants). There were 22/264 skin reactions with fexinidazole compared to 8/130 with NECT (RR 1.35 95% CI 0.62 to 2.96; 394 participants). Infections occurred in 22/264 participants with fexinidazole compared to 8/130 with NECT (RR 1.35, 95% CI 0.62 to 2.96; 394 participants). Cardiotoxicity-related adverse events occurred in 18/264 participants with fexinidazole and in 7/130 with NECT (RR 1.27, 95% CI 0.54 to 2.95; 394 participants) (Analysis 1.8).

DISCUSSION

Summary of main results

See Summary of findings 1.

The main comparison is between the effectiveness and safety of fexinidazole compared to NECT for second-stage human African trypanosomiasis.

One trial compared fexinidazole with NECT (nifurtimox tablets combined with intravenous eflornithine). Overall mortality at 24 months may be higher with fexinidazole compared with NECT (low-certainty evidence). Fexinidazole probably increases the number of people relapsing during follow-up (moderate-certainty evidence). We do not know the effect of fexinidazole on serious adverse events at 24 months (very low-certainty evidence). Although adverse events were very common in both groups, there is likely to be little to no difference in adverse events between the drugs at 24 months (moderate-certainty evidence).

Overall completeness and applicability of evidence

We only identified one randomized trial for inclusion, and this may reduce the completeness of the evidence.

Additional data from a post hoc analysis of the Mesu 2018 trial included a subgroup of participants with severe second-stage HAT (CSF WBC count ≥ 100 cells/µL), and showed that fexinidazole efficacy was inferior to NECT (Table 1); it was not possible to establish reliable clinical score-based predictive criteria, and lumbar punctures were required to identify these participants (Pelfrene 2019). Having > 400 CSF WBC/100 /µL was even more predictive of treatment failure in participants receiving fexinidazole, compared to those treated with NECT (Mesu 2018). However, people without clinical suspicion of severe second stage HAT can receive fexinidazole without the need for a lumbar puncture, which represents a significant change in clinical practice and an advantage in view of the invasive and painful characteristics of the feared lumbar puncture (Chappuis 2018; Lindner 2020).

Two non-randomized studies without direct comparators, run concomitantly to Mesu 2018, provided additional information on the usefulness and applicability of fexinidazole in different participant populations not included in the pivotal RCT: a single-arm cohort study (Mesu 2021) showed high response to treatment with fexinidazole at 12 and 18 months in participants older than 15 years with early stage two g-HAT or stage one g-HAT. Another concomitant study to the main fexinidazole trial, reported in the European Medicines Agency Assessment report for fexinidazole (Mesu 2018), provided supportive data for the efficacy of fexinidazole in children at least six years old and weighing over 20 kg.

One outcome of relevance to HAT management that we did not examine in the review was participants' adherence to treatment, because participants in the included study were kept in hospital for up to 18 days (10 days of treatment plus an observation period), to ensure compliance. As fexinidazole needs to be taken after food, trained health personnel were needed to confirm that the participants were in a fed state, also in view of potential gastrointestinal adverse effects. Availability of food and confirmed ingestion of the drug are potential issues for fexinidazole outpatients managed in health centres or in their villages.

Quality of the evidence

The overall certainty of the evidence ranged from very low to moderate. Most results were downgraded for imprecision, due to sample size being too small to assess rare outcomes, few reported events, wide confidence intervals, or a combination of these. In addition, we also downgraded two outcomes due to risk of bias, as this was an open-label trial with high risk of performance and detection bias.

At the review level, some aspects of methodological quality were related to the characteristics of the treatments under investigation. The different routes of administration (oral and intravenous) would not have allowed blinding of participants and medical personnel. Allocation concealment and randomization methods were adequate and well-described.

Inconsistency could not be assessed as we only included one study. We did not downgrade due to indirectness, but it is important to note that fexinidazole was administered in the hospital, and the

results may be different when this treatment is administered in outpatients.

Potential biases in the review process

The strict inclusion criterion to only include trials evaluating current treatments resulted in the review examining only one trial comparing fexinidazole with NECT. Studies comparing NECT with other treatments were already included in the previous versions of this review (Lutje 2010; Lutje 2013).

Agreements and disagreements with other studies or reviews

We did not identify other current systematic reviews examining the use of fexinidazole for HAT, probably because this is a new treatment which was only recently tested, and added to the WHO's Essential Medicines Lists and the WHO guidelines for the treatment of g-HAT (WHO 2019). A recent paper by the European Medicines Agency comments on the lower efficacy estimate for fexinidazole as compared with NECT as being within the prespecified non-inferiority margin (Pelfrene 2019), and considered acceptable in view of the easier administration route of fexinidazole and potential advantages in patient compliance and product distribution, in comparison with NECT.

AUTHORS' CONCLUSIONS

Implications for practice

Choice of therapy for second stage gambiense human African trypanosomiasis (g-HAT) in the next few years will continue to be dictated by local conditions of availability and logistical difficulties. Fexinidazole has the advantages expected of an oral treatment, such as removal of the need for infusions and systematic hospitalisation, as well as reduced costs. It has been included in the World Health Organization (WHO) Essential List of Medicines for African trypanosomiasis, and included in the WHO guidelines for the treatment of g-HAT (Lindner 2020; WHO 2019). The observed inferiority of fexinidazole versus nifurtimox combined with eflornithine (NECT) in people with more than 100 white blood cells (WBC)/µL in cerebrospinal fluid (CSF) has led to changes in the classification of disease stages:

- haemo-lymphatic stage (first-stage): ≤ 5 WBC/µL and no trypanosomes in CSF;
- meningo-encephalitic stage (second-stage): > 5 WBC/µL with or without trypanosomes in CSF; and
- severe meningo-encephalitic stage (severe second-stage): ≥ 100 WBC/µL with or without trypanosomes in CSF (WHO 2019).

In our review we have only assessed treatment for second stage g-HAT, defined as > 5 WBC/µL with or without trypanosomes in CSF, but future review updates may have to take into account this new classification of disease severity. The presence of signs and symptoms indicating severe second-stage disease and requiring a lumbar puncture is described in the WHO guidelines (Lindner 2020), which will guide drug treatment choice including the use of fexinidazole for individual g-HAT patients.

Implications for research

We feel it necessary to mention that trials of treatment for sleeping sickness have often encountered logistic, organizational and clinical difficulties that have to be taken into consideration when assessing trial design, the number of studies, and methodological quality. The number of drugs for HAT treatment in use or under consideration has always been limited; their routes of administration are potentially painful or difficult to secure under field conditions, and drug toxicity has often been high. In this respect, an oral drug such as fexinidazole is a true game changer. Even a well-designed trial such as Mesu 2018 took four years to complete, including the long follow-up period; more than half a million people were screened to identify study participants. The practical implications of the latest HAT trials go beyond their clinical results to also include a framework for planning and executing trials in resource-poor settings. It is likely that randomized trials for HAT treatments which have already been approved will not be repeated, and pragmatic longitudinal studies may be conducted to examine burden of treatment and adherence in real-life situations. Furthermore, the present low or very low incidence of the disease observed in many endemic areas that resulted from control efforts (and also as a consequence of the screening activities to recruit participants for clinical trials) will render the execution of adequately-powered RCTs virtually impossible in the near future. As an example, the ongoing acoziborole pivotal trial is designed as an open-label single-group assignment study, and aims to enrol 260 participants.

It is essential that future research continues the development of anti-trypanosomal compounds that are effective for both stages of the disease and are easy to administer. Acoziborole SCYX-7158, a new product with oral administration that is active in both stages of HAT, has completed phase I studies (NCT01533961). A pivotal phase II/III clinical trial in adults with stage one and stage two g-HAT is currently ongoing (NCT03087955).

Parasite resistance to the drugs (as well as the drugs' effectiveness and safety), needs to be carefully monitored in correctly designed and implemented pharmacovigilance activities and phase IV studies. This will increase knowledge about special groups (such as children of all ages, pregnant and lactating women, and people with poor nutritional status or chronic diseases), especially for fexinidazole, for which this evidence is not yet available. Developments in new diagnostic tools, and combinations of diagnostic tests and diagnostic algorithms, are necessary to identify people in need of treatment (and to determine disease stage) without the need to perform a lumbar puncture under unsafe conditions.

After several decades of scarce attention, the past decade has seen a new impetus in the fight against HAT, due in good part to an efficient co-ordination and collaboration between different agencies, researchers, and national trypanosomiasis programmes; capacity building activities; and the free provision of diagnostics, reagents, and medicines. The number of recorded cases of g-HAT has been steadily declining, and the goal of complete interruption of transmission for g-HAT has been set for 2030. Treatment of all people infected with *T b gambiense* is the essential component of the elimination strategy. The new oral drugs fexinidazole and possibly acoziborole, effective in both stages of the disease, will play a critical role in attaining elimination (Franco 2018; WHO 2013).

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REFERENCES

References to studies included in this review

Mesu 2018 *{published and unpublished data}*

DNDi. Follow-up abbreviated clinical study report DNDiFEX004 - fexinidazole. 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: a pivotal, non-inferiority, randomised, open-label, multicentre study. Data on file Unpublished clinical study report received from Drs Olaf Valverde Mordt and Antoine Tarral (DNDi) July 2019.

European Medicines Agency Committee for Medicinal Products for Human Use. Assessment report fexinidazole winthrop; 2018. www.ema.europa.eu/en/documents/medicine-outside-eu/fexinidazole-winthrop-assessment-report_en-0.pdf (accessed 16 November 2018).

* Mesu VK, Kalonji WM, Bardonneau C, Mordt OV, Blesson S, Simon F, et al. Oral fexinidazole for late-stage African Trypanosoma brucei gambiense trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial. *Lancet* 2018;**391**(10116):144-54.

References to studies excluded from this review

Alirol 2013 *{published data only}*

Alirol E, Schrumpf D, Amici Heradi J, Riedel A, de Patoul C, Quere M, et al. Nifurtimox-eflornithine combination therapy for second-stage gambiense human African trypanosomiasis: Medecins Sans Frontieres experience in the Democratic Republic of the Congo. *Clinical Infectious Diseases* 2013;**56**(2):195-203.

Chappuis 2018 *{published data only}*

Chappuis F. Oral fexinidazole for human African trypanosomiasis. *Lancet* 2018;**391**(10116):100-2.

Jansson-Löfmark 2015 *{published data only}*

Jansson-Löfmark R, Na-Bangchang K, Björkman S, Doua F, Ashton M. Enantiospecific reassessment of the pharmacokinetics and pharmacodynamics of oral eflornithine against late-stage Trypanosoma brucei gambiense sleeping sickness. *Antimicrobial Agents and Chemotherapy* 2015;**59**(2):1299-307.

Kansiime 2018 *{published data only}*

Kansiime F, Adibaku S, Wamboga C, Idi F, Kato CD, Yamuah L, et al. A multicentre, randomised, non-inferiority clinical trial comparing a nifurtimox-eflornithine combination to standard eflornithine monotherapy for late stage Trypanosoma brucei gambiense human African trypanosomiasis in Uganda. *Parasites & Vectors* 2018;**11**(1):105.

Kazumba 2018 *{published data only}*

Kazumba LM, Kaka JT, Ngoyi DM, Tshala-Katumbay D. Mortality trends and risk factors in advanced stage-2 Human African Trypanosomiasis: a critical appraisal of 23 years of experience in the Democratic Republic of Congo. *PLOS Neglected Tropical Diseases* 2018;**12**(6):e0006504.

Mord 2013 *{published data only}*

Mord OV, Bernhard S, Ghabri S, Kande V, Mutombo W, Ilunga M, et al. NECT feld phase IIIb trial: final effectiveness in adults and children results. *Tropical Medicine & International Health* 2013;**18**(Suppl 1):59-60.

NCT00982904 *{published data only}*

NCT00982904. 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]. clinicaltrials.gov/ct2/show/NCT00982904 (first posted 23 September 2009).

NCT01340157 *{published data only}*

NCT01340157. Fexinidazole (1200mg) bioavailability under different food intake conditions [Randomized, open study to assess the impact of two different types of food on the relative bioavailability of fexinidazole tablets after single oral dose in healthy male volunteers]. clinicaltrials.gov/ct2/show/NCT01340157 (first posted 22 April 2011).

NCT01483170 *{published data only}*

NCT01483170. 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]. clinicaltrials.gov/ct2/show/NCT01483170 (first posted 1 December 2011).

NCT02571062 *{published data only}*

NCT02571062. 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]. clinicaltrials.gov/ct2/show/NCT02571062 (first posted 8 October 2015).

Pelfrene 2019 *{published data only}*

Pelfrene E, Harvey Allchurch M, Ntamabyaliro N, Nambasa V, Ventura FV, Nagercoil N, et al. The European Medicines Agency's scientific opinion on oral fexinidazole for human African trypanosomiasis. *PLOS Neglected Tropical Diseases* 2019;**13**(6):e0007381.

Pollastri 2018 *{published data only}*

Pollastri MP. Fexinidazole: a new drug for African sleeping sickness on the horizon. *Trends in Parasitology* 2018;**34**(3):178-9.

Schmid 2012 *{published data only}*

Schmid C, Kuemmerle A, Blum J, Ghabri S, Kande V, Mutombo W, et al. In-hospital safety in field conditions of nifurtimox eflornithine combination therapy (NECT) for T. b. gambiense sleeping sickness. *PLOS Neglected Tropical Diseases* 2012;**6**(11):e1920.

Tarral 2011 *{published data only}*

Tarral A, Valverde O, Blesson S, Strub-Wourgaft N, Hosvepian L, Evene E. Single-dose safety, pharmacokinetics (PK) and pharmacodynamics (PD) of fexinidazole in healthy subjects. 7th European Congress on Tropical Medicine & International Health. 2011. www.dndi.org/media-centre/events/events-2011/216-media-centre/events/980-barcelona.html(DW note: authors please check link as it's no longer valid. Do you mean https://dndi.org/wp-content/uploads/2011/10/Fexi%20Antoine%20FINAL.pdf?) (accesssed dd Month yyyy).

Tarral 2014 *{published data only}*

Tarral A, Blesson S, Mordt OV, Torreele E, Sassella D, Bray MA, et al. Determination of an optimal dosing regimen for fexinidazole, a novel oral drug for the treatment of human African trypanosomiasis: first-in-human studies. *Clinical Pharmacokinetics* 2014;**53**(6):565-80.

Valverde 2015 *{published data only}*

Valverde Mordt O, Bernhard S, Ghabri S, Kande V, Mutombo W, Ilunga M, et al. Nifurtimox eflornithine combination therapy phase IIIb field trial (NECT Field): final effectiveness and safety results. *Tropical Medicine & International Health* 2015;**20**(Suppl 1):325.

Watson 2019 *{published data only}*

Watson JA, Strub-Wourgraft N, Tarral A, Ribeiro I, Tarning J, White NJ. Pharmacokinetic-pharmacodynamic assessment of the hepatic and bone marrow toxicities of the new trypanoside fexinidazole. *Antimicrobial Agents and Chemotherapy* 2019;**63**(4):e02515-8.

References to ongoing studies

NCT03087955 *{published and unpublished data}*

NCT03087955. Prospective study on efficacy and safety of acoziborole (SCYX-7158) in patients infected by human African trypanosomiasis due to T. b. gambiense (OXA002) [Efficacy and safety study of acoziborole (SCYX-7158) in patients with human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense: a multicentre, open-label, prospective study]. clinicaltrials.gov/ct2/show/NCT03087955 (first posted 23 March 2017).

Additional references

Altman 1998

Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998;**317**(7168):1309-12. [DOI: 10.1136/bmj.317.7168.1309]

Barrett 2018

Barrett MP. The elimination of human African trypanosomiasis is in sight: report from the third WHO stakeholders meeting on elimination of gambiense human African trypanosomiasis. *PLOS Neglected Tropical Diseases* 2018;**12**(12):e0006925.

Brun 2010

Brun R, Blum J, Chappuis F, Burri C. Human African trypanosomiasis. *Lancet* 2010;**375**(9709):148-59.

Büscher 2017

Büscher P, Cecchi G, Jamonneau V, Priotto G. Human African trypanosomiasis. *Lancet* 2017;**390**(10110):2397-409.

Covidence [Computer program]

Veritas Health Innovation Covidence. Melbourne, Australia: Veritas Health Innovation, accessed 10 January 2017. Available at covidence.org.

Eperon 2014

Eperon G, Balasegaram M, Potet J, Mowbray C, Valverde O, Chappuis F. Treatment options for second-stage gambiense human African trypanosomiasis. *Expert Review of Anti-infective Therapy* 2014;**12**(11):1407-17.

Franco 2012

Franco JR, Simarro PP, Diarra A, Ruiz-Postigo JA, Samo M, Jannin JG. Monitoring the use of nifurtimox-eflornithine combination therapy (NECT) in the treatment of second stage gambiense human African trypanosomiasis. *Research and Reports in Tropical Medicine* 2012;**3**:93-101.

Franco 2014

Franco JR, Simarro PP, Diarra A, Ruiz-Postigo JA, Jannin JG. The journey towards elimination of gambiense human African trypanosomiasis: not far, nor easy. *Parasitology* 2014;**141**(6):748-60.

Franco 2017

Franco JR, Cecchi G, Priotto G, Paone M, Diarra A, Grout L, et al. Monitoring the elimination of human African trypanosomiasis: update to 2014. *PLOS Neglected Tropical Diseases* 2017;**11**(5):e0005585.

Franco 2018

Franco JR, Cecchi G, Priotto G, Paone M, Diarra A, Grout L, et al. Monitoring the elimination of human African trypanosomiasis: update to 2016. *PLOS Neglected Tropical Diseases* 2018;**12**(12):e0006890.

Franco 2020

Franco JR, Cecchi G, Priotto G, Paone M, Diarra A, Grout L, et al. Monitoring the elimination of human African trypanosomiasis

at continental and country level: update to 2018. *PLOS Neglected Tropical Diseases* 2020;**14**(5):e0008261.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), accessed before 23 November 2021. Available at gradepro.org.

Guyatt 2011

Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *Journal of Clinical Epidemiology* 2011;**64**(4):380-2.

Harbord 2006

Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**(20):3443-57.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency is preferable to testing for heterogeneity in meta-analysis. *BMJ* 2003;**327**(7414):557-60.

Higgins 2017

Higgins JP, Altman DG, Sterne JA, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017). Cochrane, 2017. Available from training.cochrane.org/handbook.

Higgins 2019

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions. 2nd edition. Chichester (UK): John Wiley & Sons, 2019.

Jones 2015

Jones DC, Foth BJ, Urbaniak MD, Patterson S, Ong HB, Berriman M, et al. Genomic and proteomic studies on the mode of action of oxaboroles against the African trypanosome. *PLOS Neglected Tropical Diseases* 2015;**9**(12):e0004299.

Kennedy 2019

Kennedy PG, Rodgers J. Clinical and neuropathogenetic aspects of human African trypanosomiasis. *Frontiers in Immunology* 2019;**10**:39.

Lejon 2005

Lejon V, Büscher P. Review Article: cerebrospinal fluid in human African trypanosomiasis: a key to diagnosis, therapeutic decision and post-treatment follow-up. *Tropical Medicine & International Health* 2005;**10**(5):395-403.

Lindner 2020

Lindner AK, Lejon V, Chappuis F, Seixas J, Kazumba L, Barrett MP, et al. New WHO guidelines for treatment of gambiense human African trypanosomiasis including fexinidazole: substantial changes for clinical practice. *Lancet Infectious Diseases* 2020;**20**(2):e38-46.

Mesu 2021

Mesu VK, Kalonji WM, Bardonneau C, Mordt OV, Digas NT, Blesson S, et al. Oral fexinidazole for stage 1 or early stage 2 African *Trypanosoma brucei gambiense* trypanosomiasis: a prospective, multicentre, open-label, cohort study. *Lancet Global Health* 2021;**9**(7):e999-1008. [DOI: 10.1016/S2214-109X(21)00208-4]

NCT01533961

NCT01533961. Human African trypanosomiasis: first in man clinical trial of a new medicinal product, the SCYX-7158 [Randomized, double-blind, placebo-controlled sequential study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of SCYX-7158 after single oral ascending doses in healthy male volunteers]. clinicaltrials.gov/ct2/show/NCT01533961 (first posted 16 February 2012).

Pépin 2001

Pépin J, Méda HA. The epidemiology and control of human African trypanosomiasis. *Advances in Parasitology* 2001;**49**:71-132.

Priotto 2009

Priotto G, Kasparian S, Mutombo W, Ngouama D, Ghorashian S, Arnold U, et al. Nifurtimox-eflornithine combination therapy for second-stage African Trypanosoma brucei gambiense trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. *Lancet* 2009;**374**(9683):56-64.

RevMan 2020 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.4. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2020.

Seed 2001

Seed JR, Boykin DW. Chemotherapy of African trypanosomiasis. In: Black SJ, Seed JR, editors(s). The African trypanosomes. Series: World Class Parasites, Vol. 1. Boston: Kluwer Academic Publishers, 2001:65-78.

Stich 2002

Stich A, Abel PM, Krishna S. Human African trypanosomiasis. *BMJ* 2002;**325**(7357):203-6.

Torreele 2010

Torreele E, Bourdin Trunz B, Tweats D, Kaiser M, Brun R, Mazué G, et al. Fexinidazole--a new oral nitroimidazole drug candidate entering clinical development for the treatment of sleeping sickness. *PLOS Neglected Tropical Diseases* 2010;**4**(12):e923.

WHO 2004

World Health Organization. Recommendations of the informal consultation on issue for clinical product development for human African trypanosomiasis; Geneva, Switzerland. 9-10 September 2004. Available at www.who.int/neglected_diseases/mediacentre/Final

%20Clinical_products_for_trypanosomiasis%20November%2007.pdf. [WHO/CDS/NTD/IDM/2007.1]

WHO 2010

World Health Organization. WHO model list of essential medicines, 16th list (updated); March 2010. Available at www.who.int/medicines/publications/essentialmedicines/Updated_sixteenth_adult_list_en.pdf.

WHO 2012

World Health Organization. Accelerating work to overcome neglected tropical diseases: a roadmap for implementation; 2012. Available at www.who.int/neglected_diseases/NTD_RoadMap_2012_Fullversion.pdf.

WHO 2013

World Health Organization. Report of a WHO meeting on elimination of African trypanosomiasis (Trypanosoma brucei gambiense); 2013. who.int/publications/i/item/WHO-HTM-NTD-IDM-2013.4.

WHO 2019

World Health Organization. WHO interim guidelines for the treatment of gambiense human African trypanosomiasis; 2019. apps.who.int/iris/bitstream/handle/10665/326178/9789241550567-eng.pdf?ua=1.

References to other published versions of this review

Lutje 2006

Lutje V, Seixas J. Chemotherapy of second-stage Human African trypanosomiasis. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No: CD006201. [DOI: 10.1002/14651858.CD006201]

Lutje 2010

Lutje V, Seixas J, Kennedy A. Chemotherapy for second stage Human African trypanosomiasis. *Cochrane Database of Systematic Reviews* 2010, Issue 8. Art. No: CD006201. [DOI: 10.1002/14651858.CD006201.pub2]

Lutje 2013

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

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Mesu 2018

Study characteristics	
Methods	**Study design:** randomized controlled trial **Study dates:** recruitment between October 2012 and November 2016 **Length of follow-up:** up to 24 months **Subgroup analyses - post hoc:** treatment failure at 18 months for those with 1) presence or absence of trypanosomes in CSF at entry; 2) ≥ 100 or < 100 WBC/µL and ≥ 400 or < 400 WBC/µL in CSF at entry; or 3) ≥ 12 or < 12 and ≥ 10 or < 10 score on clinical signs and symptoms score at entry
Participants	**Participants:** n = 394 randomized **Age (mean):** fexinidazole: 34.5 (SD 12.6) years; NECT: 35.3 (SD 13.2) years **Sex:** fexinidazole: 161 (61.0%) male; NECT: 80 (61.5%) male **Weight:** mean bodyweight was 50.6 kg (IQR 45 to 56), mean BMI was 19.2 kg/m^2, with 75% of participants having a BMI lower than 20.7 kg/m^2 **Diagnosis:** parasitologically confirmed late-stage g-HAT infection: 1) parasites in at least one body fluid (blood, lymph node fluid, or CSF), and 2) CSF > 20 WBC/µL or trypanosomes in the CSF. **Symptoms:** most commonly reported clinical signs and symptoms of g-HAT included headache (281 (71%)), pruritus (228 (57%)), sleepiness (218 (55%)), weight loss (217 (55%)), and asthenia (216 (55%)) **Comorbidities:** nervous system disorders: fexinidazole: 67 (25%), NECT: 34 (26%)

Mesu 2018 *(Continued)*

	Inclusion criteria: people aged 15 years or older with parasitologically confirmed late-stage g-HAT infection **Exclusion criteria:** clinically significant laboratory test abnormalities, pregnancy, unstable abnormalities on electrocardiogram (ECG), QT interval corrected using Fridericia's formula (QTcF) of at least 450 ms (on automatic reading on two successive ECGs in resting position, done 10 min to 20 min apart), and people not tested for malaria or not having received appropriate treatment for malaria or for soil-transmitted helminthiasis.
Interventions	**Intervention characteristics** Experimental drug: fexinidazole (N randomized = 264) • Treatment regimen: oral fexinidazole once a day with food (1800 mg, 3 × 600 mg tablets) on days 1 to 4, followed by 1200 mg (2 × 600 mg tablets) once a day on days 5 to 10 Active Comparator: NECT (N randomized = 130) • Treatment regimen: nifurtimox tablets three times a day at a dose of 15 mg/kg per day for 10 days (days 1 to 10) with eflornithine given twice a day as a 2-h intravenous infusion at a total dose of 400 mg/kg for 7 days (days 1 to 7) **Co-intervention for both groups:** participants who tested positive for malaria received antimalarial treatment and had a recovery period of at least 3 days before starting study treatment for g-HAT. All participants received treatment for soil-transmitted helminthiasis.
Outcomes	Mortality (overall mortality, death during treatment), treatment success, treatment failure, withdrawals, relapse, adverse events, serious adverse events. Time points: end of treatment, 18 months, 24 months
Identification	**Funding:** Drugs for Neglected Diseases initiative (DNDi) **Setting and Country:** inpatients in the Central African Republic (Batangafo), and in The Democratic Republic of the Congo (Bagata Hospital, Bagata, Bandundu; Masi Manimba Hospital, Masi Manimba, Bandundu; Vanga Hospital, Vanga, Bandundu; HGR (General Reference Hospital)Mushie Hospital, Mushie, Bandundu; CRT (Centre de Réference et de Traitement) Dipumba, Dipumba General Hospital, Mbuji Mayi, East Kasai; HS Katanda hospital, Katanda, Kasaï Oriental; HGR Isangi Hospital, Isangi, Province Orientale; HGR Bandundu, Bandundu; Dingila Hospital, Province Bas Uelé, Democratic Republic of Congo). **Study IDs:** NCT01685827, DNDiFEX004
Notes	We used published and unpublished data from this study in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned (2:1) on day 1 to receive either fexinidazole or nifurtimox eflornithine combination therapy according to a predefined randomisation list stratified by site."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was centralised to avoid selection bias and occurred in blocks of six patients."
Blinding of participants and personnel (performance bias)	High risk	There was a high risk of performance bias due to participants and personnel not being blind, as this was an open-label study. The route of administration and dosing regimens differed between treatment groups, so a double-dummy study was not feasible and would have required placebo infusions.

Mesu 2018 *(Continued)*

Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	'All-cause mortality' and 'death during treatment' are outcomes not involving judgement.
Blinding of outcome assessment (detection bias) Subjective outcomes	High risk	Although the funder, data management personnel, and statisticians were masked to treatment until the final analysis at 18 months, 'Relapse', 'adverse events that lead to treatment discontinuation', 'death likely to be due to HAT'; 'adherence to treatment', treatment failure, adverse events and serious adverse events involve some measure of judgement and could be affected by knowledge of intervention receipt.
Incomplete outcome data (attrition bias) All outcomes	Low risk	For all outcomes and all time points missing data is < 10%.
Selective reporting (reporting bias)	Low risk	All outcomes listed in online trial record were reported (clinicaltrials.gov/ct2/show/NCT01685827), and 24 month follow-up clinical study report was made available
Other bias	Low risk	Quote: "Table 1 shows the baseline characteristics of trial participants. Similar demographic characteristics were noted in the primary analysis population in both treatment groups." Judgement Comment: No other risk of biases were detected. Baseline characteristics were balanced between groups

BMI: body mass index; CSF: cerebrospinal fluid; g-HAT: gambiense human African trypanosomiasis; IQR: interquartile range; NECT: nifurtimox eflornithine combination therapy; SD: standard deviation; WBC: white blood cell count

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

Study	Reason for exclusion
Alirol 2013	Not an RCT
Chappuis 2018	Not an RCT
Jansson-Löfmark 2015	Irrelevant treatment: eflornithine
Kansiime 2018	Irrelevant comparison treatment: eflornithine
Kazumba 2018	Not an RCT
Mord 2013	Not an RCT
NCT00982904	Irrelevant population: healthy male volunteers
NCT01340157	Irrelevant population: healthy male volunteers
NCT01483170	Irrelevant population: healthy volunteers
NCT02571062	irrelevant population: healthy volunteers
Pelfrene 2019	Not an RCT
Pollastri 2018	Not an RCT

Study	Reason for exclusion
Schmid 2012	Not an RCT
Tarral 2011	irrelevant population: healthy male volunteers
Tarral 2014	Irrelevant population: healthy male volunteers
Valverde 2015	Not an RCT
Watson 2019	Not as RCT

RCT: randomized controlled trial

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

NCT03087955

Study name	Prospective study on efficacy and safety of acoziborole (SCYX-7158) in patients infected by human African trypanosomiasis due to *T b gambiense* (OXA002)
Methods	Phase 2/phase 3 trial; intervention model: single group assignment; masking: none (open-label)
Participants	Adults (15 years or older) with *T b gambiense* HAT
Interventions	Acoziborole (SCYX-7158)
Outcomes	Success or failure for people in late stage HAT (18 months' follow-up)
Starting date	11 October 2016
Contact information	Drugs for Neglected Diseases
Notes	

HAT: human African trypanosomiasis

DATA AND ANALYSES

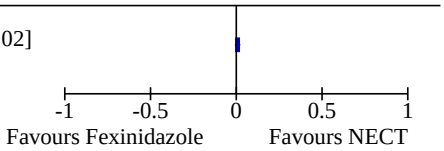
Comparison 1. Fexinidazole versus NECT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Death during treatment, up to the last drug administration	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
1.2 Overall mortality (up to 24 months)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.2.1 18 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.2.2 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Relapse (up to 24 months)	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
1.3.1 18 months	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
1.3.2 24 months	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
1.4 Treatment failure (up to 24 months)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4.1 18 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4.2 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.5 Adverse events that lead to treatment discontinuation	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
1.6 Serious adverse events (up to 24 months)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.6.1 18 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.6.2 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.7 Adverse events (up to 24 months)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.7.1 18 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.7.2 24 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.8 Adverse events (up to 24 months) (specific)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.8.1 Adverse events - central nervous system	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.8.2 Adverse events - gastrointestinal symptoms	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.8.3 Adverse events - bone marrow toxicity	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.8.4 Adverse events - skin reactions	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.8.5 Adverse events - infections	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.8.6 Adverse events - cardiotoxicity	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

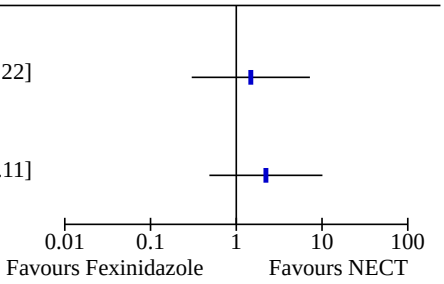
Analysis 1.1. Comparison 1: Fexinidazole versus NECT, Outcome 1: Death during treatment, up to the last drug administration

Study or Subgroup	Fexinidazole Events	Fexinidazole Total	NECT Events	NECT Total	Risk Difference M-H, Fixed, 95% CI
Mesu 2018	2	264	0	130	0.01 [-0.01 , 0.02]



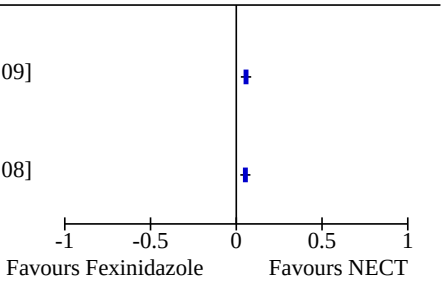
Analysis 1.2. Comparison 1: Fexinidazole versus NECT, Outcome 2: Overall mortality (up to 24 months)

Study or Subgroup	Fexinidazole Events	Fexinidazole Total	NECT Events	NECT Total	Risk Ratio M-H, Fixed, 95% CI
1.2.1 18 months					
Mesu 2018	6	264	2	130	1.48 [0.30 , 7.22]
1.2.2 24 months					
Mesu 2018	9	264	2	130	2.22 [0.49 , 10.11]



Analysis 1.3. Comparison 1: Fexinidazole versus NECT, Outcome 3: Relapse (up to 24 months)

Study or Subgroup	Fexinidazole Events	Fexinidazole Total	NECT Events	NECT Total	Risk Difference M-H, Fixed, 95% CI
1.3.1 18 months					
Mesu 2018 (1)	15	264	0	130	0.06 [0.03 , 0.09]
1.3.2 24 months					
Mesu 2018 (2)	14	264	0	130	0.05 [0.02 , 0.08]



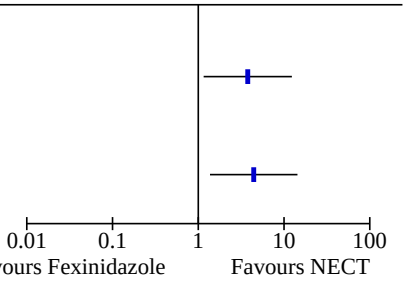
Footnotes

(1) Relapse includes rescue treatment, CSF WBC > 20 cells/microL, trypanosomes in the blood.

(2) The discrepancy between 18 and 24 months is due to an additional death after 18 months.

Analysis 1.4. Comparison 1: Fexinidazole versus NECT, Outcome 4: Treatment failure (up to 24 months)

Study or Subgroup	Fexinidazole Events	Fexinidazole Total	NECT Events	NECT Total	Risk Ratio M-H, Fixed, 95% CI
1.4.1 18 months					
Mesu 2018 (1)	23	264	3	130	3.78 [1.15 , 12.34]
1.4.2 24 months					
Mesu 2018	27	264	3	130	4.43 [1.37 , 14.34]

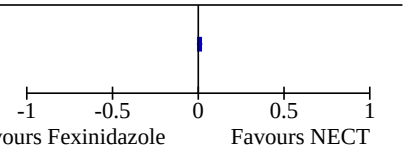


Footnotes

(1) incl. rescue treatm., death, CSF WBC > 20 cells/µl, trypanosomes in blood, lost to follow-up, consent withdrawal

Analysis 1.5. Comparison 1: Fexinidazole versus NECT, Outcome 5: Adverse events that lead to treatment discontinuation

Study or Subgroup	Fexinidazole Events	Fexinidazole Total	NECT Events	NECT Total	Risk Difference M-H, Fixed, 95% CI
Mesu 2018 (1)	2	264	0	130	0.01 [-0.01 , 0.02]

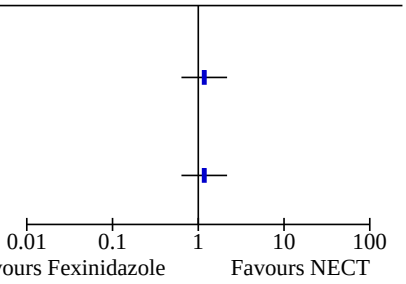


Footnotes

(1) Two people in the fexinidazole group died during treatment.

Analysis 1.6. Comparison 1: Fexinidazole versus NECT, Outcome 6: Serious adverse events (up to 24 months)

Study or Subgroup	Fexinidazole Events	Fexinidazole Total	NECT Events	NECT Total	Risk Ratio M-H, Fixed, 95% CI
1.6.1 18 months					
Mesu 2018 (1)	31	264	13	130	1.17 [0.64 , 2.17]
1.6.2 24 months					
Mesu 2018 (1)	31	264	13	130	1.17 [0.64 , 2.17]

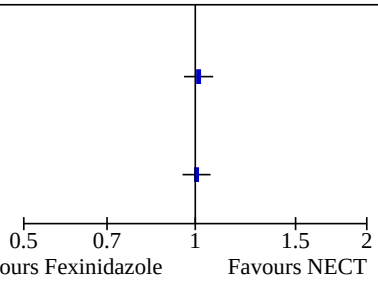


Footnotes

(1) Active monitoring of SAE during observation period (day 1 to 18); continued to be collected up to end of follow-up.

Analysis 1.7. Comparison 1: Fexinidazole versus NECT, Outcome 7: Adverse events (up to 24 months)

Study or Subgroup	Fexinidazole Events	Fexinidazole Total	NECT Events	NECT Total	Risk Ratio M-H, Fixed, 95% CI
1.7.1 18 months					
Mesu 2018 (1)	247	264	120	130	1.01 [0.96 , 1.08]
1.7.2 24 months					
Mesu 2018 (1)	247	264	121	130	1.01 [0.95 , 1.06]

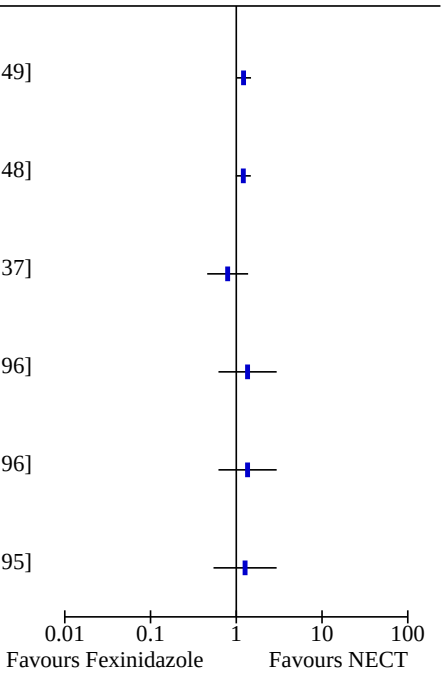


Footnotes

(1) Active monitoring of AE during observation period (day 1 to 18); continued to be collected up to end of follow-up.

Analysis 1.8. Comparison 1: Fexinidazole versus NECT, Outcome 8: Adverse events (up to 24 months) (specific)

Study or Subgroup	Fexinidazole Events	Fexinidazole Total	NECT Events	NECT Total	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Adverse events - central nervous system					
Mesu 2018	158	264	64	130	1.22 [0.99 , 1.49]
1.8.2 Adverse events - gastrointestinal symptoms					
Mesu 2018	157	264	64	130	1.21 [0.99 , 1.48]
1.8.3 Adverse events - bone marrow toxicity					
Mesu 2018	29	264	18	130	0.79 [0.46 , 1.37]
1.8.4 Adverse events - skin reactions					
Mesu 2018	22	264	8	130	1.35 [0.62 , 2.96]
1.8.5 Adverse events - infections					
Mesu 2018	22	264	8	130	1.35 [0.62 , 2.96]
1.8.6 Adverse events - cardiotoxicity					
Mesu 2018	18	264	7	130	1.27 [0.54 , 2.95]



ADDITIONAL TABLES

Table 1. Post hoc subgroup analyses of treatment failure at 18 months' follow-up

Criterion	Subgroup	Analysis	Fexinidazole	NECT	RR (95% CI)	Test for subgroup differences[a]
Signs and symptoms score* ≥	Symptom score ≥ 12	ITT	15/91	1/45	7.42 (1.01 to 54.40)	P = 0.08, I^2 = 67.8%

Table 1. Post hoc subgroup analyses of treatment failure at 18 months' follow-up *(Continued)*

12 at entry (no lumbar puncture required)	Symptom score < 12		10/173	5/85	0.98 (0.35 to 2.78)	
	Symptom score ≥ 12	mITT	14/90	0/44	14.34 (0.88 to 235.00)	P = 0.14, I^2 = 53.2%
	Symptom score < 12		9/172	3/83	1.45 (0.40 to 5.21)	
	Symptom score ≥ 12	EP	14/90	0/44	14.34 (0.88 to 235.00)	P = 0.46, I^2 = 0%
	Symptom score < 12		8/168	1/81	3.86 (0.49 to 30.32)	
Signs and symptoms score* ≥ 10 at entry (no lumbar puncture required)	Symptom score ≥10	ITT	19/112	3/58	3.28 (1.01 to 10.63)	P = 0.18, I^2 = 45.6%
	Symptom score < 10		6/152	3/72	0.95 (0.24 to 3.68)	
	Symptom score ≥10	mITT	18/111	1/56	9.08 (1.24 to 66.29)	P = 0.12, I^2 = 59.1%
	Symptom score < 10		5/151	2/71	1.18 (0.23 to 5.91)	
	Symptom score ≥10	EP	17/110	1/56	8.65 (1.18 to 63.37)	P = 0.77, I^2 = 0%
	Symptom score < 10		5/148	0/69	5.17 (0.29 to 92.16)	
Presence of trypanosomes in CSF at entry	With trypanosomes in CSF	ITT	22/175	4/90	2.83 (1.01 to 7.96)	P = 0.17, I^2 = 46.9%
	No trypanosomes in CSF		3/88	2/40	0.68 (0.12 to 3.92)	
	With trypanosomes in CSF	mITT	20/173	2/88	5.09 (1.22, 21.27)	P = 0.32, I^2 = 0%
	No trypanosomes in CSF		3/88	1/39	1.33 (0.14 to 12.38)	
	With trypanosomes in CSF	EP	19/172	1/87	9.61 (1.31 to 70.61)	P = 0.54, I^2 = 0%
	No trypanosomes in CSF		3/85	0/38	3.17 (0.17 to 59.98)	
Presence of > 100 WBC/µL in CSF at entry	WBC > 100 cells/µL	ITT	22/161	3/80	3.64 (1.12 to 11.81)	P = 0.04, I^2 = 75.5%
	WBC ≤ 100 cells/µL		3/103	3/50	0.49 (0.10 to 2.32)	
	WBC > 100 cells/µL	mITT	21/160	1/78	10.24 (1.40 to 74.72)	P = 0.03, I^2 = 79.5%
	WBC ≤ 100 cells/µL		2/109	2/49	0.45 (0.07 to 3.10)	
	WBC > 100 cells/µL	EP	20/157	0/77	20.24 (1.24 to 330.28)	P = 0.10, I^2 = 62.6%
	WBC ≤ 100 cells/µL		2/101	1/48	0.95 (0.09 to 10.23)	
Presence of > 400 WBC/µL in CSF at entry	WBC > 400 cells/µL	ITT	13/79	1/34	5.59 (0.76 to 41.09)	P = 0.19, I^2 = 42.3%
	WBC ≤ 400 cells/µL		12/185	5/96	1.25 (0.45 to 3.43)	

Table 1. Post hoc subgroup analyses of treatment failure at 18 months' follow-up *(Continued)*

WBC > 400 cells/μL	mITT	13/79	1/34	5.59 (0.76 to 41.09)	P = 0.53, I^2 = 0%
WBC ≤ 400 cells/μL		10/183	2/93	2.54 (0.57 to 11.36)	
WBC > 400 cells/μL	EP	12/78	0/33	10.76 (0.66 to 176.58)	P = 0.67, I^2 = 0%
WBC ≤ 400 cells/μL		10/180	1/92	5.11 (0.66 to 39.32)	

*Five significant signs and symptoms, based on the standard list of HAT warning symptoms: sleepiness, pruritus, tremor, asthenia, and recurrent headache with respectively 5, 4, 3, 2, and 1 points.
[a]Analysis not shown.
CI: confidence interval; CSF: cerebrospinal fluid; EP: evaluable population; g-HAT: gambiense human African trypanosomiasis; ITT: intention-to-treat; mITT: modified intention-to-treat; NECT: nifurtimox combined with eflornithine; RR: risk ratio; WBC: white blood cell count

APPENDICES

Appendix 1. Search strategies

MEDLINE (PubMed)

Search	Query
#1	Search "human african trypanos*"
#2	Search "sleeping sickness"
#3	Search "Trypanosomiasis, African"[Mesh]
#4	Search HAT
#5	Search (((#4) OR #3) OR #2 OR #1
#6	Search "drug therapy" [Subheading]
#7	Search NECT
#8	Search fexinidazole
#9	Search melarsoprol
#10	Search eflornithine
#11	Search nifurtimox
#12	Search (((#11) OR #10) OR #9 OR #8 OR #7 OR 6
#13	Search #12 Filters: Clinical Trial
#14	Search "Randomized Controlled Trial" [Publication Type] OR "Controlled Clinical Trial" [Publication Type]

(Continued)

#15	Search randomized or placebo or randomly or trial or groups Field: Title/Abstract
#16	Search (#14) OR #15
#17	Search (animals[MeSH Terms]) NOT humans[MeSH Terms]
#18	Search (#16) NOT #17
#19	Search (#18) AND #12
#20	Search #19 OR #13
#21	Search #5 AND #20

Database: Embase (OVID)

Search Strategy:

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1 African trypanosomiasis/ or human african trypanosom*.mp.

2 "sleeping sickness".mp.

3 1 or 2

4 drug therapy/

5 fexinidazole.mp. or fexinidazole/

6 melarsoprol.mp. or melarsoprol/

7 eflornithine.mp. or eflornithine/

8 nifurtimox.mp. or NECT.mp or nifurtimox/

9 4 or 5 or 6 or 7 or 8

10 3 and 9

11 randomized controlled trial.mp. or randomized controlled trial/

12 controlled clinical trial.mp. or controlled clinical trial/

13 (randomized or randomly or placebo).mp.

14 11 or 12 or 13

15 10 and 14

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#1 (Human African trypanosom*): ti, ab, kw

#2 MeSH descriptor: [Trypanosomiasis, African] explode all trees

#3 (sleeping sickness): ti, ab, kw

#4 #1 or #2 or #3

Search History BIOSIS

#7	#6 AND #5
#	**6 TOPIC:** ("randomized trial") *OR***TOPIC:** ("clinical trial") *OR***TOPIC:** (placebo or "single blind*" or "double blind*")
#5	#4 OR #3
#4	**TOPIC:** (fexinidazole or eflornithine or melarsoprol or nifurtimax) *OR***TOPIC:** ("drug therapy" or chemotherapy) *AND***TOPIC:** ("sleeping sickness")
#3	#2 AND #1
#2	**TOPIC:** (fexinidazole or eflornithine or melarsoprol or nifurtimax) *OR***TOPIC:** ("drug therapy" or chemotherapy)
#1	**TOPIC:** (african trypanosom*)

WHO International Clinical Trials Registry Platform (WHO ICTRP), Clinicaltrials. Gov: African Trypanosomiases, Sleeping sickness

CONTRIBUTIONS OF AUTHORS

VL contributed to literature searches, search results screening, and review writing.

KP contributed to data extraction, risk of bias assessment, analysis, GRADE, and review writing.

JS contributed to review writing.

HB contributed to data extraction, risk of bias assessment, analysis, GRADE, and review writing.

GV contributed to screening, analysis, GRADE, and review writing.

All authors read and approved the final version of the review.

DECLARATIONS OF INTEREST

VL has no known conflicts of interest. VL works as an independent consultant conducting literature searches for various research groups. None of them has any potential relevance to the submitted work.

KP received payment for work on this review from Cochrane Response, an evidence services unit operated by the Cochrane Collaboration. Cochrane Response was contracted by the WHO to produce a systematic review upon which a part of this review update is based (see ‘Sources of support').

JS has participated as an expert in the WHO guideline development group for the use of fexinidazole; collaborates in the WHO network for Human African Trypanosomiasis Elimination Group; is designated chairman of the subgroup 'Integration of new tools into national and global policies' of the aforementioned WHO Group; is designated member of the WHO Human African Trypanosomiasis Elimination Technical Advisory Group (HAT-e-TAG); and participated in 2018 as an expert in the Scientific Advisory Group meeting on Fexinidazole Winthrop, promoted by the Committee for Medicinal Products for Human Use of the European Medicines Agency.

HB received payment for work on this review from Cochrane Response, an evidence services unit operated by the Cochrane Collaboration. Cochrane Response was contracted by the WHO to produce a systematic review upon which a part of this review update is based (see ‘Sources of support').

GV received payment for work on this review from Cochrane Response, an evidence services unit operated by the Cochrane Collaboration. Cochrane Response was contracted by the WHO to produce a systematic review upon which a part of this review update is based (see ‘Sources of support').

SOURCES OF SUPPORT

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This is a split review from Lutje 2013.

For this review, we changed the author team and we only included trials of currently used drugs against second stage *T b gambiense*. As we only included one trial, we did not perform meta-analysis, subgroup analysis, investigation of heterogeneity, or sensitivity analysis.

We have added RD as en effect measure for outcomes with no events in the control group. To aid interpretation of results, we also added the measure of NNTB for the primary outcomes.

We included a post hoc subgroup analysis, obtained from an additional data source (Table 1). This analysis was not specified in the protocol (Lutje 2006), and we obtained the data from an additional study identified as grey literature (Mesu 2018).

INDEX TERMS

Medical Subject Headings (MeSH)

*Antiprotozoal Agents [adverse effects]; Nifurtimox [adverse effects]; *Pharmaceutical Preparations; Randomized Controlled Trials as Topic; Trypanosoma brucei gambiense; *Trypanosomiasis, African [drug therapy]

MeSH check words

Animals; Humans