New WHO guidelines for treating rhodesiense human African trypanosomiasis: expanded indications for fexinidazole and pentamidine

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Human African trypanosomiasis is a neglected tropical disease that is usually fatal without treatment. WHO has revised its rhodesiense human African trypanosomiasis treatment guidelines on the basis of an independent systematic literature review and following the GRADE methodology. This Review reports on the decision-making process and summarises the new recommendations and their potential implications for health-care professionals and policy makers. Due to data scarcity, all recommendations are conditional and based on very low certainty of evidence. Fexinidazole replaces suramin and melarsoprol as the first-line therapy in individuals aged 6 years and older with a bodyweight of 20 kg or more. As fexinidazole is effective in both stages of rhodesiense human African trypanosomiasis, a lumbar puncture for staging is no longer required. In settings in which first-choice drugs are not readily available, immediate interim treatment with pentamidine is suggested. The introduction of oral fexinidazole represents an advancement in the management of rhodesiense human African trypanosomiasis considering the life-threatening adverse reactions individuals can have to melarsoprol. However, children below the age or weight limits remain ineligible for treatment with fexinidazole.

Introduction

Human African trypanosomiasis (HAT), also known as sleeping sickness, is a neglected tropical disease that commonly affects low-income populations in rural environments in sub-Saharan Africa.[1] Flagellated protozoans of the species *Trypanosoma brucei*, which are transmitted by the bite of infected tsetse flies (*Glossina* spp), cause the disease. Two subspecies of the parasite lead to different forms of disease.[2] Gambiense HAT, caused by *Tb gambiense*, is prevalent in west and central Africa. This form of the disease is characterised by a chronic course in which the first haemolymphatic stage progresses over months to years and is followed by the second meningoencephalitic stage. In contrast, rhodesiense HAT, caused by *Tb rhodesiense*, is endemic to east and southern Africa (figure 1), and is an acute disease with a rapid progression over weeks or months. Uganda is the only country in which both gambiense and rhodesiense HAT are endemic (but each in distinct regions). Gambiense HAT is primarily anthroponotic, whereas rhodesiense HAT is a zoonosis.

HAT caused devastating epidemics throughout the 20th century, continuing a pattern of outbreaks from earlier times. Since the beginning of the 21st century, there has been a concerted effort to control the disease, resulting in a historically low number of reported cases. All HAT cases should be reported both within national reporting systems and to WHO to continuously assess the epidemiological situation. Since 2018, fewer than 1000 cases have been reported annually.[4] Rhodesiense HAT occurs less frequently than gambiense HAT, accounting for a proportion of cases ranging between 2% and 5% of all HAT cases, with occasional peaks of more than 10%, such as in 2019 and 2020.[5] The target to eliminate HAT as a public health problem by 2020 has been met.[4,6] In the WHO road map for neglected tropical diseases for the period 2021–30,[7] the target for rhodesiense HAT is the continued elimination of the disease as a public health concern, whereas for gambiense HAT, the target is the elimination of transmission (ie, obtaining zero new cases) by 2030. The interruption of

Key messages

- WHO has revised its treatment guidelines for rhodesiense human African trypanosomiasis (HAT) on the basis of an independent systematic review of the literature. A single-arm, non-randomised study of 45 individuals from Uganda and Malawi provided new evidence on fexinidazole treatment for rhodesiense HAT.
- Fexinidazole replaces suramin and melarsoprol as the first-line therapy in individuals aged 6 years and older with a bodyweight of 20 kg and above; as fexinidazole is effective in both stages of rhodesiense HAT, a lumbar puncture for staging is no longer required.
- Considering the life-threatening side-effects of melarsoprol, fexinidazole represents long-awaited progress in the treatment of rhodesiense HAT; as an oral treatment with fewer side-effects and no requirement for a lumbar puncture, fexinidazole can be administered at the primary care level, provided that specially trained health staff directly observe each intake for 10 days.
- As fexinidazole has only been evaluated in a small number of individuals with rhodesiense HAT, all treated patients must be closely evaluated clinically for relapse, at least at the end of treatment and at 1, 3, 6, and 12 months after treatment.
- Children younger than 6 years or with a bodyweight of less than 20 kg continue to require treatment with suramin or melarsoprol as fexinidazole has not been studied in clinical trials in this patient group.
- Given the usually rapid progression of rhodesiense HAT, in settings in which first-line drugs are not readily available, immediate initiation of pentamidine, if available, is recommended; as soon as first-line drugs become available, treatment should be switched to them.

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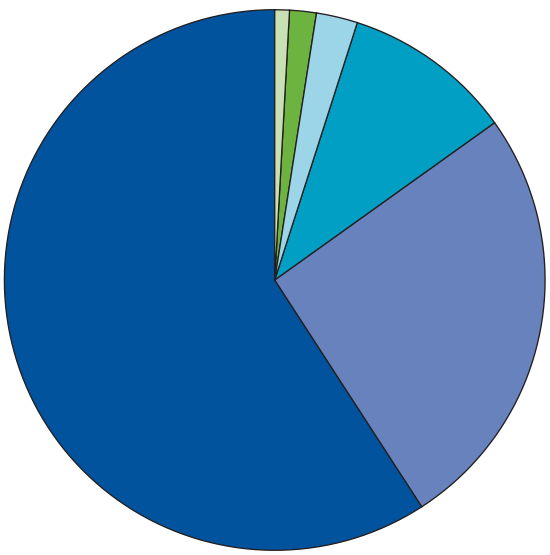

Figure 1: **Distribution of cases (N=683) of rhodesiense human African trypanosomiasis by country, 2013–22**
n=cumulative number of cases over the 10-year period.[3]

	Phase	Dosage	Duration
≥35 kg	Loading phase	1800 mg (three tablets)	4 days
≥35 kg	Maintenance phase	1200 mg (two tablets)	6 days
20–34 kg	Loading phase	1200 mg (two tablets)	4 days
20–34 kg	Maintenance phase	600 mg (one tablet)	6 days

Fexinidazole tablets must be administered once per day for a period of 10 days with a loading dose over the initial 4 days and a maintenance dose over the final 6 days. Doses must accompany a meal for sufficient absorption.

Table 1: **Dosing of fexinidazole in adults and children aged 6 years or older with a bodyweight of 20 kg or more**

transmission of rhodesiense HAT is more complex and currently not feasible as *Tb rhodesiense* mainly circulates in animals. The remarkable progress in the control of gambiense HAT has been achieved through the implementation of case-finding strategies and treatment. In some areas, vector control activities have also been integrated into this approach.[8]

For the diagnosis of rhodesiense HAT, because of the high parasitaemia, trypanosomes are usually readily detected in either stained thin or thick films or wet preparations of blood. Trypanosomes can also be visualised in lymph node fluid, chancre aspirate, or cerebrospinal fluid (CSF). Contrary to gambiense HAT, there are no rapid tests for the diagnosis of rhodesiense HAT.[9] Treatment failures can occur; thus in the weeks or months following treatment, the presence of symptoms and signs suggestive of a relapse should prompt a blood examination and lumbar puncture.[9] A definition of treatment success is a patient who is alive without the presence of trypanosomes in any bodily fluid at the end of hospitalisation and during the follow-up period and with a CSF white blood cell count that evolves to healthy by 6 months of follow-up.

Since 2001, drugs for HAT treatment have been donated by the manufacturers and distributed to endemic countries free of charge by WHO. In addition, WHO has established strategic emergency depots of HAT drugs in various non-endemic countries, thus facilitating more rapid access to treatment in the event of imported cases.[9] Treatment for gambiense HAT is based on five drugs: fexinidazole, pentamidine, eflornithine, nifurtimox, and, in rare cases, melarsoprol.[10] In 2018, the European Medicines Agency (EMA) provided a positive opinion regarding the use of fexinidazole in the treatment of gambiense HAT.[11] The 2019 WHO interim treatment guidelines enabled the use of fexinidazole in gambiense HAT, which resulted in a substantial simplification of clinical practice.[10,12] Fexinidazole is administered orally once per day for a period of 10 days, with a loading dose of 4 days followed by a maintenance dose of 6 days (table 1). Due to its effectiveness in both stages of the disease, a lumbar puncture for CSF examination can be avoided in individuals who, on the basis of clinical examination, are not suspected of having severe meningoencephalitic-stage HAT. Treatment with injectables—with intramuscular pentamidine for first-stage HAT and intravenous eflornithine in combination with oral nifurtimox for second-stage gambiense HAT—is only required in specific groups of patients, including children younger than 6 years or with a bodyweight of less than 20 kg and individuals with severe meningoencephalitic-stage HAT with a CSF white blood cell count of 100 white blood cells per µl or more.

Rhodesiense HAT must be treated without delay due to its rapid progression. Until mid-2024, the first-line therapy for first-stage rhodesiense HAT has been intravenous suramin. For second-stage rhodesiense HAT, the therapy has been intravenous melarsoprol.[13] Patients with first-stage rhodesiense HAT have occasionally received intramuscular pentamidine.[14] Therapy with melarsoprol is particularly problematic due to the high frequency of severe and life-threatening adverse effects.[15] The efficacy of fexinidazole in rhodesiense HAT was recently evaluated in a phase 2/3 clinical trial in Malawi and Uganda (NCT03974178).[16] In December, 2023, the EMA extended the indication of fexinidazole to include the treatment of rhodesiense HAT, under the EU-M4all procedure (previously called Article 58), a regulatory framework designed for medications intended for use outside the EU.[11,17] The EMA has indicated that fexinidazole should be used in accordance with official recommendations.

The WHO guideline development group on HAT treatment convened in February, 2024, and elaborated on

	Intervention or comparator	Recommendation	Strength of recommendation	Certainty of evidence	Key considerations
Patients with first-stage rhodesiense HAT	Fexinidazole or suramin	Use of fexinidazole over suramin	Conditional	Very low	Children aged <6 years or with a bodyweight <20 kg should receive suramin, as fexinidazole is not approved for this patient group
Patients with second-stage rhodesiense HAT	Fexinidazole or melarsoprol	Use of fexinidazole over melarsoprol	Conditional	Very low	Children aged <6 years or with a bodyweight <20 kg should receive melarsoprol, as fexinidazole is not approved for this patient group
Patients without timely access to treatment with the recommended drugs	Immediate interim treatment with pentamidine or delayed treatment with the recommended drugs	Immediate interim treatment with pentamidine; switch to the recommended treatment as soon as it becomes available	Conditional	Very low	Pentamidine might be more rapidly available in non-endemic countries, as it is also used to treat pneumonia caused by *Pneumocystis jirovecii*

HAT=human African trypanosomiasis. PICO=Population, Intervention, Comparison, Outcomes.

Table 2: **PICO questions and the related WHO recommendation, strength of recommendation, certainty of evidence, and key considerations of the new HAT treatment guidelines for rhodesiense HAT in different target populations**

and updated evidence-based treatment recommendations for policy makers and health-care professionals. These recommendations are accessible in detail on the WHO website.[18–20] This Review reports on the decision-making process, summarises the new recommendations, and provides complementary information on and discusses their implications.

Methods

The Guidelines for the Treatment of Human African Trypanosomiasis[18] were developed by WHO with the methodology outlined in the *WHO Handbook for Guideline Development*.[21] The WHO Secretariat formed a guideline development group that included professionals with recognised expertise in the fields of HAT treatment, public health, and national control programmes. A content expert and a guideline methodologist co-chaired the group.

During the initial prioritisation process, a WHO steering committee developed the key questions for the guidelines in the Population, Intervention, Comparison, Outcomes (PICO) format, with a focus on patient-relevant and setting-relevant outcomes.[22] The following key questions about rhodesiense HAT treatment were identified: whether fexinidazole or suramin should be used as first-line treatment for first-stage rhodesiense HAT; whether fexinidazole or melarsoprol should be used as first-line treatment for second-stage rhodesiense HAT; and in settings in which the recommended drugs for rhodesiense HAT are not readily available, whether immediate interim treatment with pentamidine or delayed treatment with the recommended drugs should be used.

A systematic review was externally commissioned from the Cochrane Response review team to synthesise and rate the evidence relevant to the PICO questions.[23] Details of this review are outlined in the full version of the guidelines, including the search strategy, study selection, data extraction, risk of bias, data analysis, and rating of the certainty of evidence processes.[19] The GRADE methodology was used to rate the certainty of evidence.[24,25] For each question, the systematic review team developed a so-called summary of findings table, which presented the certainty of the evidence and relevant statistical information for each outcome.[24,26]

The guideline development group formulated the recommendations and graded their strength as either strong or conditional following the GRADE methodology and Evidence to Decision tables.[25,27,28] The factors considered during the grading process were the desirable and undesirable effects (ie, benefits and harms) of the intervention relative to its comparator, the overall certainty of the evidence, the extent to which people value the main outcomes, the balance between desirable und undesirable effects, the effect on health equity, the resources needed, the acceptability of the intervention to key stakeholders, and the feasibility of the intervention.

Results

The recommendations for the three PICO questions, with their corresponding strength, certainty of supporting evidence, and key considerations, are shown in table 2. The Evidence to Decision tables, available on the WHO website, provide detailed judgements on the factors considered in grading these recommendations.[20]

PICO 1: fexinidazole or suramin for the treatment of first-stage rhodesiense HAT

The guideline development group suggests fexinidazole instead of suramin in individuals with first-stage rhodesiense HAT (conditional recommendation, very low certainty of evidence).

The systematic review did not identify any clinical trial with a direct comparison between fexinidazole and suramin. Data about fexinidazole treatment in patients with rhodesiense HAT originate from one single-arm, non-randomised trial.[17] The primary objective of this study was to show that the fatality rate (disease-related or treatment-related death) at the end of hospitalisation in patients with second-stage rhodesiense HAT was lower than the 8·5% fatality rate observed in a previous study with melarsoprol.[17] At the time the WHO treatment guidelines were established, the trial data had not yet been published. The data have now been shared with WHO by the Drugs for Neglected Diseases initiative under a confidential agreement and are also accessible via the EMA assessment report.[17] This study included 45 participants with rhodesiense HAT from Uganda (n=2) and Malawi (n=43); ten participants had first-stage rhodesiense HAT and 35 had second-stage HAT. All ten patients in the first stage had treatment success at the end of their hospitalisation and at their 12-month follow-up evaluation. Serious adverse events did not occur in any participants with first-stage HAT. The data on non-serious adverse events were only available for the total study population, without separation of participants with first-stage and second-stage HAT. In the total study population (45 patients), 24 non-serious adverse events were observed, with 22 occurring during hospitalisation and two occurring during follow-up. The most common adverse event was vomiting (n=6), occurring within 2 hours of drug administration. In these patients, the daily dose of fexinidazole was readministered.

For suramin treatment in first-stage rhodesiense HAT, evidence came from seven single-arm studies (prospective and retrospective cohorts and case series) in a total of 415 children and adults.[14,29–33] These studies are of little use in terms of their comparability due to the heterogeneity of the study populations, the outcome criteria, and the observational periods. The overall mortality rate during the course of treatment and for a period of up to 5 weeks thereafter ranged from 0% to 5% across five studies.[29,30,32,33] In four studies that reported follow-up between 2 years and 3 years, the mortality ranged from 0% to 19%.[14,29,31] Three studies reported relapse rates ranging from 11% to 34% with follow-up from 2 years to 3 years.[14,29] In a case series of 19 patients, a treatment success rate of 95% (n=18) was observed at day 30.[33] The treatment success in studies with longer follow-up periods of more than 24 months were in the range of 39–68%.[14,29] Just one study reported on adverse events, with 2·1% of participants experiencing rash or urticaria, and 10·5% experiencing rigor or chills.[29] None of the seven studies reported any serious adverse events.

The evidence from included studies on fexinidazole and suramin was judged to be of very low certainty, as no clinical trial with a direct comparison between fexinidazole and suramin is available and only non-comparative observational studies were included.

The guideline development group judged the balance of desirable and undesirable effects as probably favouring fexinidazole treatment. The use of fexinidazole probably enhances health equity. As an oral treatment with fewer side-effects and no requirement for lumbar puncture, it can be administered at the primary care level. However, there is a shortage of data on special population groups, including children, pregnant or lactating individuals, and people with comorbidities, and on treatment outcomes beyond 12 months. Children younger than 6 years or with a bodyweight of less than 20 kg still require treatment with suramin—with a lumbar puncture for disease staging—as the safety and efficacy of fexinidazole in this age group has not been established in clinical trials.

PICO 2: fexinidazole or melarsoprol for the treatment of second-stage rhodesiense HAT

The guideline development group suggests fexinidazole instead of melarsoprol in patients with second-stage rhodesiense HAT (conditional recommendation, very low certainty of evidence).

A direct comparison between fexinidazole and melarsoprol in a clinical trial is missing from the evidence. The only study about fexinidazole treatment in people with rhodesiense HAT included 35 patients with second-stage HAT.[17] 33 (94%) of 35 participants were classified as having treatment success at the end of the 12-month follow-up period. One (3%) of the 35 participants relapsed at week 9 and was subsequently treated successfully with melarsoprol. One (3%) of the 35 participants died during the treatment phase as a consequence of an acute kidney injury. In the follow-up period, two additional serious adverse events (pneumonia and urinary tract infection) were documented, resulting in a total of 3 (9%) of 35 participants having serious adverse events. None of these serious adverse events were considered related to the fexinidazole treatment.

The evidence for melarsoprol monotherapy in second-stage rhodesiense HAT is derived from seven studies (prospective and retrospective cohorts and case series) involving 908 children and adults.[14,29,34–38] The comparability of these studies is low due to the heterogeneity of the study populations, the outcome criteria, and the observational periods, and the use of different melarsoprol regimens. A prospective cohort study with 107 participants showed a 92% (98 of 107) treatment success rate at the end of treatment or hospitalisation, with an 88% (94 of 107) success rate at 12 months of follow-up.[37,38] Additionally, this study found a 1% (1 of 107) 12-month relapse rate. Another case series with 33 participants documented a 12-month relapse rate of 18% (six of 33 participants).[34] Across four studies, the mortality rate during treatment and up to 30 days post treatment was between 6% and 8%, and the rate at 12 months of follow-up was between 9% and 11%.[29,34,36,38]

Regarding the side-effects of melarsoprol treatment, the prospective study with 107 participants is the most informative.[37,38] It reports adverse events in 70 (66%) of the 107 participants and serious adverse events in 27 (25%) of the participants, including an encephalopathic syndrome during treatment in eight (7%) of the participants.[37,38] In addition, a case series comprising 383 participants (stage not reported) exhibited a 6% encephalopathy rate (21 of 383 participants).[39] Deaths attributed to melarsoprol treatment were reported in 3–8% of cases.[35,37,38]

The evidence from included studies on fexinidazole and melarsoprol was judged to be of very low certainty; only non-comparative observational studies were included and no clinical trial with a direct comparison between fexinidazole and melarsoprol was available.

The guideline development group judged the balance of desirable and undesirable effects as probably favouring treatment with fexinidazole, largely because of the undesirable effects of melarsoprol and the much less undesirable effects of fexinidazole. The use of fexinidazole probably enhances health equity among individuals with second-stage HAT for the same reasons discussed for PICO 1. Its use is considered acceptable to key stakeholders. Considering the resources required for treatment, moderate financial savings are expected with fexinidazole, which requires fewer resources from the patient and the hospital and has lower costs from treatment-related side-effects.

Melarsoprol might be the preferred option in cases in which the patient presents with a contraindication to fexinidazole, is unable to swallow, has persistent vomiting despite antiemetic therapy, or is in a critical condition that raises concerns about the oral absorption of fexinidazole. Given that fexinidazole is not approved for use in children younger than 6 years or with a bodyweight less than 20 kg, performing a systematic lumbar puncture for staging is necessary in such children, as is administering melarsoprol if they have second-stage HAT.

In consideration of the scarce evidence probably favouring fexinidazole over suramin and melarsoprol and the improbability of further studies being conducted, the guideline development group formulated comprehensive recommendations for the follow-up of all individuals with rhodesiense HAT who receive fexinidazole. The systematic collection of safety and efficacy data in every patient who receives fexinidazole is planned to generate valuable additional data that will allow reassessment of this recommendation.

PICO 3: in settings in which the recommended drugs for rhodesiense HAT are not readily available, should immediate interim treatment with pentamidine be used over delayed treatment with the recommended drugs?

The guideline development group suggests immediate interim treatment with pentamidine instead of delayed treatment with other recommended drugs for rhodesiense HAT in settings in which other recommended treatments are not readily available (conditional recommendation, very low certainty of evidence).

One retrospective cohort study reported on pentamidine monotherapy in 46 individuals with first-stage rhodesiense HAT with a follow-up period of more than 24 months.[14] The mortality rate was 15% (seven of 45 participants, mainly for unknown reasons), the relapse rate was 9% (four of 46), the treatment success rate at 24 months was 46% (21 of 46), and 15 (30%) of 46 participants could not be accounted for with respect to the reported outcome. This study did not report on adverse events.

In addition, we identified 17 case reports on the use of pentamidine monotherapy (mostly for international travellers): 15 reported treatment success, one reported clinical improvement, and one did not report on the outcome.[19] The most commonly reported adverse events were renal toxicity, renal insufficiency, and diabetes.

The evidence from the one non-comparative observational study was judged to be of very low certainty; only one non-comparative observational study was included. Given the rapid clinical evolution of rhodesiense HAT, treatment in a timely manner is of utmost importance. Pentamidine might be more rapidly available in non-endemic countries, as it is also used to treat pneumonia caused by *Pneumocystis jirovecii*. As soon as first-line drugs become available, treatment should be switched to them.

Discussion

The new evidence-based treatment recommendations for rhodesiense HAT (figure 2) can be summarised as follows: fexinidazole replaces suramin as the first-line treatment for people with first-stage disease; fexinidazole also replaces melarsoprol as the first-line treatment for people with second-stage disease; as fexinidazole is effective in both disease stages, a lumbar puncture and CSF examination to discriminate between the first and second stage is no longer required in individuals aged 6 years and older and with a bodyweight of 20 kg or more; children younger than 6 years or with a bodyweight of less than 20 kg continue to require treatment with suramin or melarsoprol (and therefore a lumbar puncture for disease staging) as fexinidazole has not been studied in this patient group in clinical trials.

Given the usually rapid progression of rhodesiense HAT, rapid initiation of treatment is of particular importance. In settings in which first-choice drugs are not readily available, the guidelines recommend that immediate interim treatment with pentamidine, if available, be initiated. As soon as the first-choice drugs become available, treatment should be switched to them. Such situations will probably occur in non-endemic countries, as pentamidine is also used to treat other diseases, such as pneumonia caused by *P jirovecii*.

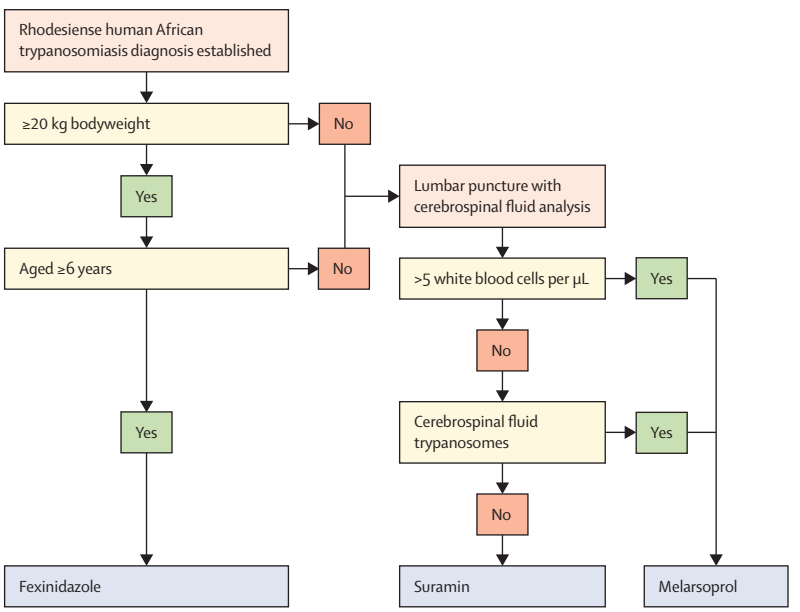

Figure 2: **Algorithm of WHO guidelines for the management of patients with rhodesiense human African trypanosomiasis**

	First-choice treatment	Second-choice treatment	Rescue treatment
Aged <6 years or with a bodyweight <20 kg			
CSF count ≤5 white blood cells per µL; no trypanosomes	Suramin	Pentamidine	Fexinidazole*
CSF count >5 white blood cells per µL or presence of trypanosomes	Melarsoprol	..	Fexinidazole*
Aged ≥6 years and with a bodyweight ≥20 kg			
Lumbar puncture not needed	Fexinidazole	Lumbar puncture needed; suramin or pentamidine (first-stage disease) or melarsoprol (second-stage disease)	Lumbar puncture needed; suramin (first-stage disease) or melarsoprol (second-stage disease)

CSF=cerebrospinal fluid. *Compassionate treatment.

Table 3: **Summary of treatment choices for patients with rhodesiense HAT**

However, especially in rhodesiense HAT endemic countries, pentamidine availability is likely to be poor and the drug difficult to access.

Although fexinidazole has not been studied in children younger than 6 years or with a bodyweight less than 20 kg, it could be considered a compassionate rescue treatment when other treatment options have failed (table 3). In such exceptional cases, consultation with a medical specialist regarding dosage and administration is advisable.

The interim guidelines for the treatment of gambiense HAT, which were established in 2019 by a guideline development group, have remained unchanged.[40] The new WHO Guidelines for the Management of Human African Trypanosomiasis, which follow from the recommendations formulated by the guideline development group, contain detailed guidelines for policy makers and medical staff managing patients.[18–20] Fexinidazole must always be administered with food, during or immediately after the main meal of the day. The bioavailability is substantially reduced when administered without food and the active metabolites might not reach therapeutic levels.[41] In cases in which a patient is in a critical condition and oral absorption of fexinidazole is uncertain, or when a patient is unable to swallow, suramin or melarsoprol might be the preferred option depending on the stage of the disease. The feasibility of crushing fexinidazole tablets is currently under investigation.[42]

Considering the 10-day duration of fexinidazole treatment, the risk of non-compliance is high, given that nausea and vomiting are common side-effects, and concomitant food intake is necessary for full drug absorption. Therefore, trained health staff are needed to directly observe each drug intake to ensure correct administration.

The introduction of fexinidazole as a treatment for rhodesiense HAT represents an important advancement, particularly in the context of the severe and life-threatening adverse reactions associated with the use of melarsoprol.[15,43] As an oral treatment, fexinidazole offers logistical and safety advantages over other HAT treatment options that necessitate labour-intensive intravenous or intramuscular injections, which carry a risk of catheter-related or needle-related infection and necessitate systematic hospitalisation. Furthermore, oral treatment results in cost savings for the health system in terms of accessory supplies and logistics. Additionally, patients might be able to access treatment at a shorter distance from their homes—a more convenient and affordable option.

For rhodesiense HAT, no data are available regarding reduced efficacy of fexinidazole in the severe meningoencephalitic stage of the disease (ie, with CSF white blood cell counts higher than 100 per µl), unlike for gambiense HAT. Even if the drug had reduced efficacy in severe rhodesiense HAT, treatment with fexinidazole is probably preferable over treatment with melarsoprol, which, in case of relapse, can still be given as rescue treatment. The guideline development group therefore considered lumbar puncture unnecessary for rhodesiense HAT management in adults. Avoiding a lumbar puncture and CSF microscopy has further positive implications for patients and health-care systems.[44] Although lumbar puncture is a safe procedure, even in low-resource hospitals in rural Africa, it is associated with considerable discomfort and necessitates the availability of appropriate materials and expertise.[45] The procedure can induce headache, back pain, confusion, and (in rare cases) cerebral herniation.[3,45] The fear of a lumbar puncture and superstition about negative consequences represent a substantial barrier to screening for HAT, and also to patients returning for follow-up.[3,46]

Given the scarce data on fexinidazole use in rhodesiense HAT, the guideline development group recommended that safety and efficacy monitoring, through intensive pharmacovigilance, are conducted with this new treatment. In this regard, the experience with fexinidazole pharmacovigilance in gambiense HAT can be built upon. As of June, 2024, WHO has collected pharmacovigilance data on 733 individuals with gambiense HAT who received fexinidazole in ten countries.[42] The preliminary results indicate that the safety profile of fexinidazole is consistent with that observed in clinical trials for gambiense HAT.[11] In addition to the frequent common adverse effects, such as vomiting (38% of patients) and nausea (33% of patients), attention should be paid to the occurrence of QT prolongation, neutropenia, and neuropsychiatric adverse reactions including psychotic disorder and suicidal ideation.[11,17]

The progression of rhodesiense HAT is typically more rapid than in gambiense HAT, and relapses can occur earlier, potentially within a few weeks or months following treatment.[37] Given that fexinidazole in rhodesiense HAT has been evaluated in only a small number of patients, there is a paucity of data on relapses. Consequently, the WHO guidelines have established follow-up recommendations for up to 12 months. These guidelines include a clinical evaluation in the treating hospital at least at the end of treatment and at 1 month and 3 months post treatment, and evaluations at 6 months and 12 months. In some circumstances, the 6-month and 12-month evaluations can be conducted by telephone or remotely by other health professionals.[18] In the event that signs or symptoms indicate a potential for relapse, laboratory examinations of bodily fluids, including CSF, are recommended in order to detect the presence of trypanosomes or CSF leukocytosis.

Fexinidazole enables treatment in peripheral health facilities in rural areas. HAT drugs are usually stored in various locations within the endemic countries to ensure their timely availability. The complexity of drug supply systems and the low number of HAT cases can be challenging. Fortunately, the shelf life of fexinidazole has been extended from 3 years to 5 years, which can mitigate this problem.[42]

The process of updating the WHO guidelines involved the application of a rigorous methodology that is mandatory within the organisation.[21] This methodology entailed the commissioning of an externally conducted independent systematic literature review, which informed the decision-making process and the formulation of recommendations following the GRADE framework.[24,26] However, evidence limitations remain due to the difficult context surrounding this disease. Trials evaluating treatment methods for HAT treatment are particularly challenging. Such trials are, by necessity, conducted in remote areas of sub-Saharan Africa, and for rhodesiense HAT in particular, case numbers are low and predicting where cases might be found is difficult. For example, the recruitment of 45 participants for the sole clinical study on fexinidazole use in rhodesiense HAT took more than 2 years.[17] For these guidelines, the evidence from the included studies for all outcomes was judged to be of very low certainty because only non-comparative observational studies were included. Furthermore, indirect evidence on the safety of HAT drugs in the treatment of gambiense HAT was considered in formulating these recommendations for rhodesiense HAT. Most studies did not report on the sex of participants, making it impossible to judge sex-specific aspects of the therapy.

Some members of the guideline development group were involved in support roles in the clinical trial of fexinidazole, for example as members of the data safety or project management boards. This overlap can be explained by the fact that the community engaged in research into HAT is small, and a high level of collaboration is required to develop improved tools for HAT control.

In accordance with WHO policy, all members of the guideline development group and peer reviewers completed and signed a WHO declaration of interests form. The form collected information regarding any participation in consulting and advisory panels, research support, and financial investments. The WHO Secretariat assessed the declarations submitted and observed no notable conflicts of interest. As a result, they concluded that no member should be excluded from actively taking part in formulating these recommendations.[47]

An important treatment gap remains for children younger than 6 years or weighing less than 20 kg, as fexinidazole has not yet been studied in this age group. There is no specific paediatric formulation. In general, very few clinical trials have focused on HAT treatment in children. Typically, young children are excluded from clinical trials, resulting in their exclusion from new drug labels. Dosages are often extrapolated from adult dosages, and specific paediatric formulations are frequently absent. Furthermore, the administration of intravenous medication is more problematic in children. The Global Accelerator for Paediatric Formulations is a network hosted by WHO that serves as a coordinating body for all partners, facilitating the identification and resolution of paediatric treatment.[48] Furthermore, the decreasing overall incidence of HAT will also hamper the establishment of paediatric studies.[5]

Acoziborole, a new single-dose, oral treatment for both stages of gambiense HAT, has shown high efficacy and a favourable safety profile in a multicentre, single-arm, phase 2/3 clinical trial.[49] An ongoing clinical trial aims to evaluate acoziborole in children aged between 1 year and 14 years (NCT05433350). Acoziborole also appears to be active against *Tb rhodesiense* on the basis of scarce preclinical data.[42] If proven effective, acoziborole could play

Search strategy and selection criteria

Searches of MEDLINE OVID, Embase OVID and CENTRAL (on May 29, 2023), Global Health (EBSCO) and Global Index Medicus (on June 4, 2023), and The Cochrane Infectious Diseases Group Specialised Register (on June 5, 2023) were conducted. The searches focused on African trypanosomiasis, with the related terms "*Trypanosoma brucei rhodesiense*", "African trypanosomiasis", "sleeping sickness", "HAT", and "Nagana". Treatment terms included "melarsoprol", "pentamidine", "suramin", "eflornithine", "fexinidazole", and their common brand names or abbreviations. Restrictions on date, publication status (ie, published, unpublished, in press, or in progress), or language were not used. The searches were sensitive enough to include non-randomised controlled trials and to not miss old, poorly indexed trials. In addition, on June 14, 2023, a search was conducted of ClinicalTrials.gov and the WHO Trials Registry. WHO provided supplementary references for consideration, and a reference list screening of the included reviews was conducted to identify additional relevant studies. At this time, trial data on fexinidazole treatment in people with rhodesiense human African trypanosomiasis were not yet published. The data were shared with WHO by the Drugs for Neglected Diseases initiative under a confidential agreement. Two authors (KP and GV) independently screened all citations and abstracts identified by the searches. Full reports for potentially eligible studies were obtained and independently assessed by two authors (KP and GV). Any disagreements were resolved by consensus or by involving WHO. All included studies were verified as being independent.

an important role in filling the treatment gap for children with both gambiense and rhodesiense HAT.

In conclusion, fexinidazole was considered by the guideline development group as an improvement in the management of rhodesiense HAT. The next steps include incorporating the WHO guidelines into national treatment guidelines, training health-care workers in fexinidazole use, and its implementation in the field (accompanied with active pharmacovigilance).

Contributors

AKL led the writing of the manuscript and chaired the guideline development group meeting. GP and JRFM coordinated the guidelines development and led the writing of the full guidelines. EAA functioned as the guidelines methodologist and co-chair. GV and KP contributed to the systematic reviews, evidence profiles, and Grading of Recommendations Assessment, Development, and Evaluation tables. All authors contributed to the development of the new WHO Guidelines for the Treatment of Human African Trypanosomiasis and the revision of the manuscript.

Declaration of interests

JS reports that the Instituto de Higiene e Medicina Tropical–Lisbon was a partner in the European & Developing Countries Clinical Trials Partnership (EDCTP2) HAT-r-ACC project (for a clinical trial on fexinidazole in rhodesiense human African trypanosomiasis [HAT]; NCT03974178), coordinated by the Drugs for Neglected Diseases initiative (DNDi), and funded by the EDCTP. JS had a non-remunerated role in training the clinical investigators of the field teams. LB was a member of the data and safety monitoring board for the clinical trial on fexinidazole in rhodesiense HAT. PPS was employed as an advisor at the DNDi until 2021. MPB participated in the scientific advisory committee of the DNDi that dealt with the fexinidazole trials, among other projects. VL reports that the Institut de Recherche pour le Développement was a partner in the HAT-r-ACC project (for a clinical trial on fexinidazole in rhodesiense HAT [NCT03974178]), coordinated by the DNDi. VL was responsible for training project health staff in the diagnosis of HAT (two trainings, one in Malawi and one in Uganda, in 2019). AE chaired the data and safety monitoring board for the clinical trial on fexinidazole in rhodesiense HAT. AE also participated in the scientific advisory committee of the DNDi. All other authors declare no competing interests.

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