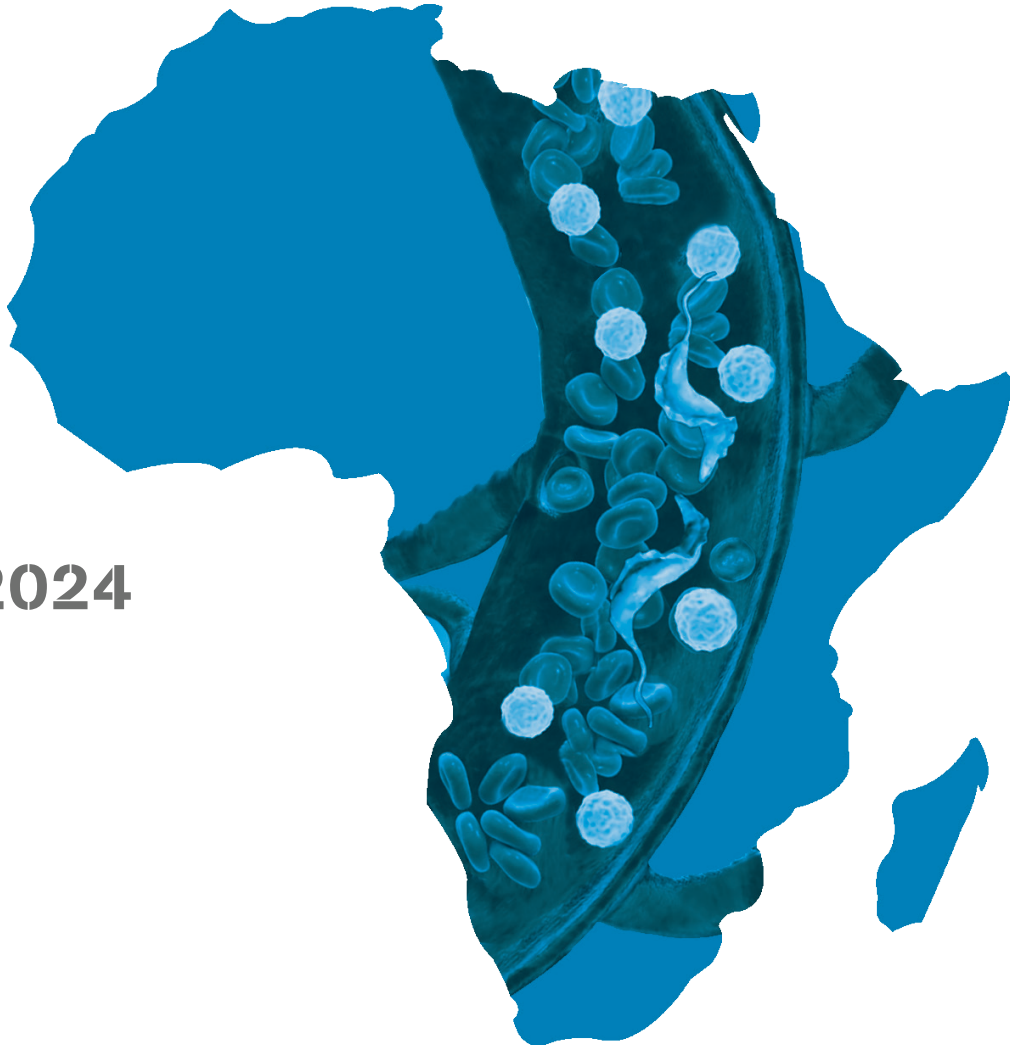
Guidelines

for the treatment of human African trypanosomiasis



June 2024

World Health Organization

Guidelines for the treatment of human African trypanosomiasis

June 2024

World Health Organization

Guidelines for the treatment of human African trypanosomiasis

ISBN 978-92-4-009603-5 (electronic version)

ISBN 978-92-4-009604-2 (print version)

Suggested citation. Guidelines for the treatment of human African trypanosomiasis. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at https://iris.who.int/.

Contents

Acknowledgements

The World Health Organization (WHO) is sincerely grateful to the many professionals from a range of backgrounds and specialties who contributed their time and expertise to the development of this guidance.

Guideline development group members

Andreas Lindner (Institute of Tropical Medicine and International Health, Berlin, Germany), Andrew Edielu (MRC/UVRI and LSHTM Uganda Research Unit, Entebbe, Uganda), Christopher Pasi (Harare Central Hospital, Harare, Zimbabwe), Jorge Seixas (Instituto de Higiene e Medicina Tropical, Lisbon, Portugal), Lucas Matemba (National Institute for Medical Research, Dodoma, United Republic of Tanzania), Lucille Blumberg (National Institute for Communicable Diseases, Johannesburg, South Africa), Michael Barrett (University of Glasgow, Glasgow, United Kingdom of Great Britain and Northern Ireland), Pere Perez Simarro (Consultant, Spain), Rebecca Chancey (Centers for Disease Control and Prevention, Atlanta, United States of America), Salome Bukachi (University of Nairobi, Nairobi, Kenya), Tapunda Phiri (Rumphi District Hospital, Rumphi, Malawi), Tihitina Mesha (Selamber Primary Hospital, Selambar, Ethiopia), Veerle Lejon (Institut de Recherche pour le Développement, Montpellier, France), Victor Mwanakasale (Copperbelt University School of Medicine, Ndola, Zambia)

Guideline methodologist

Elie Akl (American University of Beirut, Beirut, Lebanon)

WHO Secretariat

Augustin Kadima Ebeja (WHO Regional Office for Africa, Brazzaville, Congo), Gerardo Priotto (WHO Global Neglected Tropical Diseases Programme (WHO/NTD), Geneva, Switzerland), Jose Ramon Franco Minguell (WHO/NTD).

External peer reviewers

Philippe Büscher (Institute of Tropical Medicine, Antwerp, Belgium), Charles Wamboga (Ministry of Health, Kampala, Uganda), Vincent Jamonneau (Institut de Recherche pour le Développement, Montpellier, France).

Systematic evidence reviewers

The systematic reviews were conducted by the following researchers from the Cochrane Response group (London, United Kingdom), who developed the evidence profiles and GRADE tables: Gemma Villanueva (senior systematic reviewer and lead reviewer), Hanna Bergman (systematic reviewer), Katrin Probyn (systematic reviewer), Nicholas Henschke (senior systematic reviewer), and Brian Buckley, Elise Cogo, Jennifer Petkovic, Meghan Sebastianski, Yanina Sguassero (Cochrane Infectious Diseases Group, United Kingdom).

Overall coordination

Gerardo Priotto and Jose Ramon Franco Minguell (WHO/NTD).

WHO steering committee

Augustin Kadima Ebeja (WHO Regional Office for Africa, Brazzaville, Congo), Gerardo Priotto (WHO/NTD), Jose Ramon Franco Minguell (WHO/NTD), Daniel Dagne WHO/NTD), Annette Kuesel (WHO Special Programme for Research and Training in Neglected Diseases, Geneva, Switzerland), Marie Valentin (WHO Regulation and Safety, Geneva, Switzerland) and Hye Lynn Choi (WHO Medicines Assessment, Geneva, Switzerland).

The guidelines were drafted by Gerardo Priotto and Jose Ramon Franco Minguell (WHO/NTD). Drafts were reviewed, and input provided by the members of the Guideline Development Group, peer reviewers and the WHO Secretariat.

Financial support

Funding for the development of these guidelines was provided by WHO.

Abbreviations and acronyms

CSF	cerebrospinal fluid
DOT	directly observed treatment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HAT	human African trypanosomiasis
LP	lumbar puncture
NECT	nifurtimox–eflornithine combination therapy
PICO	population, intervention, comparator and outcome
WBC	white blood cell
WHO	World Health Organization

Executive summary

Human African trypanosomiasis (HAT), or sleeping sickness, is a parasitic infection that is endemic in sub-Saharan Africa and is almost invariably fatal unless treated.

The infection is transmitted to humans through the bite of an infected tsetse fly. The parasite multiplies in the lymph and blood, causing unspecific symptoms and signs (first-stage or haemo-lymphatic stage) and, over time, crosses the blood–brain barrier to infect the central nervous system (second-stage or meningo-encephalitic stage). Brain involvement causes various neurological disturbances, including sleep disorders (hence the name "sleeping sickness"), progression to coma and, ultimately, death.

The disease has two forms: the slowly progressing form (gambiense HAT), caused by infection with *Trypanosoma brucei gambiense*, found in western and central Africa (92% of cases in 2018–2022); and the more rapidly progressive form (rhodesiense HAT), caused by infection with *T. b. rhodesiense*, in eastern and southern Africa (responsible for the remainder of cases). All age groups and both sexes are at risk of both forms of HAT, although prevalence is higher in adults than in children.

The incidence of the disease has strongly declined in response to intensive surveillance and control interventions in endemic areas. As a result, HAT is among the neglected tropical diseases targeted for elimination by the World Health Organization (WHO).

The remarkable progress in the control of gambiense HAT has relied on case-finding and curative treatment, which interrupts transmission by depleting the reservoir of parasites in humans. This has been combined in some areas with vector control activities. In contrast to gambiense HAT, treatment of rhodesiense HAT patients has little impact on disease transmission, but it is certainly life-saving.

The *WHO interim guidelines for the treatment of gambiense HAT*, issued in 2019 added as a therapeutic option the new medicine fexinidazole. Thanks to its recent extension of indication, fexinidazole is now also recommended for treatment of rhodesiense HAT. The present guidelines incorporate all these changes, leading to a substantial reconfiguration of therapeutic choices for both disease forms.

HAT is a serious, life-threatening disease and the efficacy of fexinidazole depends on swallowing the medicine after an appropriate intake of food as well as on completing the full 10-day treatment schedule. Therefore, the recommendations regarding fexinidazole administration are considered key elements that must be carefully followed. When the conditions listed in these guidelines are not met for any individual patient, the alternative available treatments should be prescribed.

Methodology: The guidelines were developed in accordance with the recommendations of the WHO Guidelines Review Committee. A WHO steering committee defined their scope and formulated the questions to be addressed in PICO (population, intervention, comparator and outcome) format. A specialized team was externally commissioned to conduct a systematic review of the literature and to rate the evidence following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology. A guideline development group comprising experts with pertinent knowledge and experience, relevant geographical representation and without conflicts of interest met in Geneva, Switzerland, to scrutinize the available evidence and formulate recommendations based on the GRADE approach. Evidence-to-decision tables were built with the following elements: balance between desirable and undesirable effects, certainty of the evidence, resource implications, equity, acceptability and feasibility. The draft guideline was critically reviewed via remote collaboration by members of the guideline development group, the WHO steering committee, the guideline methodologist and the peer reviewers before submission to the WHO Guidelines Review Committee. The same methodology was followed for both the 2019 interim guidelines and the present 2024 guidelines update.

Summary of WHO recommendations for the treatment of gambiense HAT

Patient stratification	WHO recommendations	Strength	Certainty
Patients who can be managed without lumbar puncture (LP)	Patients aged ≥ 6 years and weighing ≥ 20 kg who meet both of the following conditions: • low index of suspicion of severe disease based on clinical judgement; and • high confidence that the patient will have appropriate follow-up to detect relapse early, will not require LP stratification and may be treated preferentially with fexinidazole.	Conditional	Very low
Patients requiring lumbar puncture (LP)	Patients who do not meet the above criteria will require LP stratification. Patients who require LP stratification but do not receive LP, and those whose LP results are unreliable, will be treated preferentially with NECT. Patients who reject or do not tolerate fexinidazole may need a LP to decide between pentamidine and NECT.	Conditional	Very low
Type of patient	**WHO recommendations**		
Patients aged ≥ 6 years and body weight ≥ 20 kg **AND** in first-stage or non-severe second-stage (WBC < 100/µL CSF)	Use fexinidazole over pentamidine in patients with first-stage HAT and over NECT in patients with second-stage HAT with WBC in CSF < 100/µL.	Conditional	Very low (first-stage), Low (second-stage)
Patients in severe second-stage (WBC ≥ 100/µL CSF)	Use NECT in preference to fexinidazole.	Conditional	Low
Children aged < 6 years or body weight < 20 kg	Use pentamidine in first-stage and NECT in second-stage.	Conditional	Very low
Pregnant women	Former WHO recommendations apply.[a] Fexinidazole can be given after the first trimester.	Conditional	Very low

Fexinidazole administration	WHO recommendations		
Food intake: For fexinidazole to be absorbed in therapeutic levels, it must be taken in a fed condition (i.e. after a substantial meal). As a condition for prescribing fexinidazole, the prescriber must have confidence in the availability of food for the patient, which will be eaten directly before the drug administration daily.		Conditional	Low
Directly observed treatment (DOT): Each intake of fexinidazole must be supervised by a trained health staff who must ensure that the patient is in a fed condition.		Conditional	Low
Outpatient administration (under daily supervision) can be decided in consultation with the patient, his/her family and clinicians, taking into account the following factors: • convenience to the patient and the family (e.g. distance and costs); • development of side-effects interfering with treatment compliance; • existing comorbidities; and • capacity of the health care system for supervised administration as an outpatient. Hospitalization should be mandatory in the following cases: • patients with psychiatric disorders; • children with body weight < 35 kg; • patients with ≥ 100 WBC treated (exceptionally) with fexinidazole; and • risk of poor compliance with treatment.		Conditional for either inpatient or outpatient	Very low

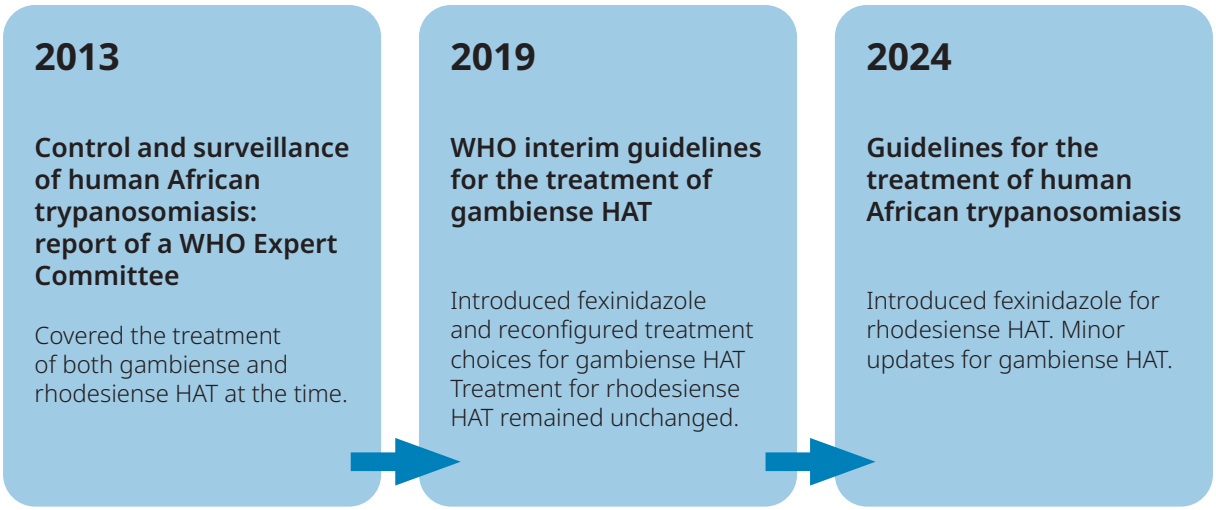
CSF, cerebrospinal fluid; LP, lumbar puncture; NECT, nifurtimox–eflornithine combination therapy; WBC, white blood cells.

[a] WHO Technical Report Series, no. 984 (2013).

Summary of WHO recommendations for the treatment of rhodesiense HAT

Type of patient	WHO recommendations	Strength	Certainty
Patients aged ≥ 6 years and body weight ≥ 20 kg in first-stage	Use fexinidazole over suramin.	Conditional	Very low
Patients aged ≥ 6 years and body weight ≥ 20 kg in second-stage	Use fexinidazole over melarsoprol. Melarsoprol may be preferred in patients who are: unable to swallow; with fexinidazole contraindication; with persistent vomiting; with oral absorption considered questionable.	Conditional	Very low
Children aged < 6 years or body weight < 20 kg	Use suramin in first-stage and melarsoprol in second-stage.	Conditional	Very low
When recommended medicines are not readily available	Immediate interim treatment with pentamidine. Switch to the recommended treatment as soon as it becomes available.	Conditional	Very low
Pregnant women	Given the rapid clinical evolution of rhodesiense HAT, treatment usually cannot be delayed. Clearly explain benefit–risk to patient and relatives. Fexinidazole and pentamidine are preferred. Suramin and melarsoprol may become necessary as rescue treatment.	Conditional	Very low
Fexinidazole administration	**WHO recommendations**		
Food intake: For fexinidazole to be absorbed in therapeutic levels, it must be taken in a fed condition (i.e. after a substantial meal). As a condition for prescribing fexinidazole, the prescriber must have confidence in the availability of food for the patient, which will be eaten directly before the drug administration daily.		Conditional	Low
Directly observed treatment (DOT): Each intake of fexinidazole must be supervised by a trained health staff who must ensure that the patient is in a fed condition.		Conditional	Very low
Hospitalization is preferred and should be mandatory in patients presenting: • neuropsychiatric disorders (considering both the risk of neuropsychiatric adverse effects of fexinidazole and the risk of poor compliance with treatment); • history of alcohol use disorder, due to the risk of Antabuse® (disulfiram) effect, and the risk of poor compliance. • body weight < 35 kg; to ensure full treatment compliance. • vomiting following administration of fexinidazole		Conditional	Very low

Timeline of WHO guidance for the treatment of human African trypanosomiasis



© B.Marquet

A technician from a mobile team belonging to the National programme of the fight against human African trypanosomiasis analyses samples of villagers that might be suffering from sleeping sickness, Mpata, Democratic Republic of the Congo.

1. Introduction and general aspects

The approval in 2018 of a new medicine (fexinidazole) for the treatment of gambiense HAT and the extension of its indication to rhodesiense HAT in 2023 opened new therapeutic possibilities for both forms of the disease and led to a revision of the previous recommendations for their treatment.

This guideline covers the management of patients affected by both gambiense and rhodesiense HAT and updates the previous WHO guidance and recommendations, namely:

- WHO (2013). Treatment. In: Control and surveillance of human African trypanosomiasis: report of a WHO Expert Committee. Geneva: World Health Organization (WHO Technical Report Series, no. 984);150–188 *(1)* ;
- WHO (2015). Medicines for the treatment of 1st stage African trypanosomiasis. In: The selection and use of essential medicines: report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization (WHO Technical Report Series, no. 994);437 *(2)*; and
- WHO (2019). WHO interim guidelines for the treatment of gambiense human African trypanosomiasis *(3)*.

1.1 Goal

The goal of these guidelines is to provide updated evidence-based recommendations on therapeutic choices to ensure the best possible treatment for individuals infected with *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, taking into account the current therapeutic options and the different epidemiological, clinical and operational scenarios.

1.2 Target audience

These guidelines are primarily targeted at policy-makers in ministries of health working in countries where HAT is endemic[1] to assist in updating national HAT policies and treatment guidelines. They are intended also as a resource for medical staff caring for patients with HAT infection. The guidelines take into consideration the fact that HAT mostly occurs in remote areas and is managed in health facilities with limited resources, by lesser trained medical staff (e.g. clinical officers, nurses, nursing aids).

1.3 Guiding principles

The objective of WHO is the attainment by all peoples of the highest possible level of health. The present guidelines have been developed in accordance with this principle and that of the United Nations Universal Declaration of Human Rights *(4)*. People infected with *T. b. gambiense* or *T. b. rhodesiense* may come from vulnerable or marginalized groups with poor access to health care and may be subject to discrimination and stigmatization. It is therefore essential that these guidelines and the policies derived therein incorporate basic human rights and equity, including the right to confidentiality and informed decision-making when considering whether to be screened and treated for HAT.

---

[1] Countries historically endemic for gambiense HAT: Angola, Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of the Congo, Côte d'Ivoire, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Niger, Nigeria, Senegal, Sierra Leone, South Sudan, Togo, Uganda. Countries historically endemic for rhodesiense HAT: Botswana, Burundi, Eswatini, Ethiopia, Kenya, Malawi, Mozambique, Namibia, Rwanda, Uganda, United Republic of Tanzania, Zambia, Zimbabwe.

High-quality care and treatment for persons with HAT require adequate supplies of medication and specially trained staff to ensure complete and correct administration of the appropriate medicine. Case management depends on the sub-species of causative trypanosome and on case presentation, and may require access to appropriate laboratory facilities for disease staging and assessment of the response to treatment. Observance of the fundamental ethical principles of good clinical practice (respect for persons, beneficence and justice) should extend to all health personnel caring for HAT patients.

1.4 Methodology and process of developing the guidelines

These guidelines were developed following the process recommended by the WHO Guidelines Review Committee *(5)*. A WHO steering committee defined the scope of the guidelines and the questions to be addressed in PICO (population, intervention, comparator and outcome) format. A specialized team was externally commissioned to conduct a systematic review of the literature and to rate the evidence following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology.

A guideline development group comprising experts with pertinent knowledge and experience, and geographical and gender balance, was formed; the geographical distribution of the experts was attentive to the specific geography of rhodesiense HAT, including experts from eight East African endemic countries; conflicts of interest were declared and confidentiality agreements were signed prior to the discussions. Meeting in Geneva, Switzerland, the experts scrutinized the available evidence and formulated recommendations based on the GRADE approach. Evidence-to-decision tables were built evaluating the following elements: desirable versus undesirable effects, certainty of the evidence, resource implications, equity, acceptability and feasibility. The draft guideline was critically reviewed via remote collaboration by the guideline development group members, the WHO steering committee, the guideline methodologist and the peer reviewers before submission to the WHO Guidelines Review Committee. The same methodology was followed for both the 2019 interim guidelines and the present 2024 guidelines update. Details of the methodology are provided in the Annex.

1.5 Background

1.5.1 Epidemiology and burden

HAT, or sleeping sickness, is a parasitic infection that is almost invariably fatal unless treated. Throughout the 20th century the disease caused devastating epidemics. However, as a result of sustained and coordinated efforts over the past 30 years, the number of reported cases has fallen to historically low levels (< 1000/year since 2018). HAT is a neglected tropical disease that is endemic in sub-Saharan Africa, within the distributional limits of its vector, the tsetse fly.

Two forms of the disease exist: the slowly progressing form, caused by infection with *T. b. gambiense*, found in western and central Africa (gambiense HAT); and the more rapidly progressive form, caused by *T. b. rhodesiense* infection, in eastern and southern Africa (rhodesiense HAT).

After a human is bitten by an infected fly (both male and female tsetse can transmit HAT infection), the parasite multiplies in the lymph and the blood, causing unspecific symptoms and signs such as headache, fever, weakness, joint and muscle pain and lymphadenopathy (first-stage or haemo-lymphatic stage). Over time, the parasite crosses the blood–brain barrier and infects the central nervous system (second-stage or meningo-encephalitic stage). Brain involvement causes various neurological changes, including sleep disorders (hence the name "sleeping sickness"), deep sensory disturbances, abnormal tone and mobility, ataxia, psychiatric disorders, seizures and coma. In infections with *T. b. rhodesiense* parasitaemia is usually much higher than with *T. b. gambiense*, causing multiple organ and systems damage that may lead to death, even before the central nervous system is affected.

Although the geographical area infested with tsetse flies is very large, HAT has a markedly focal distribution that results from complex and as yet incompletely understood interactions between the parasite, the vector, the host and the environment. The disease usually occurs in rural areas where human–tsetse contact is frequent, but periurban areas can also be affected. People become infected while farming, fishing, hunting, collecting water or wood, or during other activities that expose them to tsetse flies. All age groups and both sexes are at risk, although prevalence is higher in adults than in children. Sex distribution varies in relation to gender-specific at-risk activities.

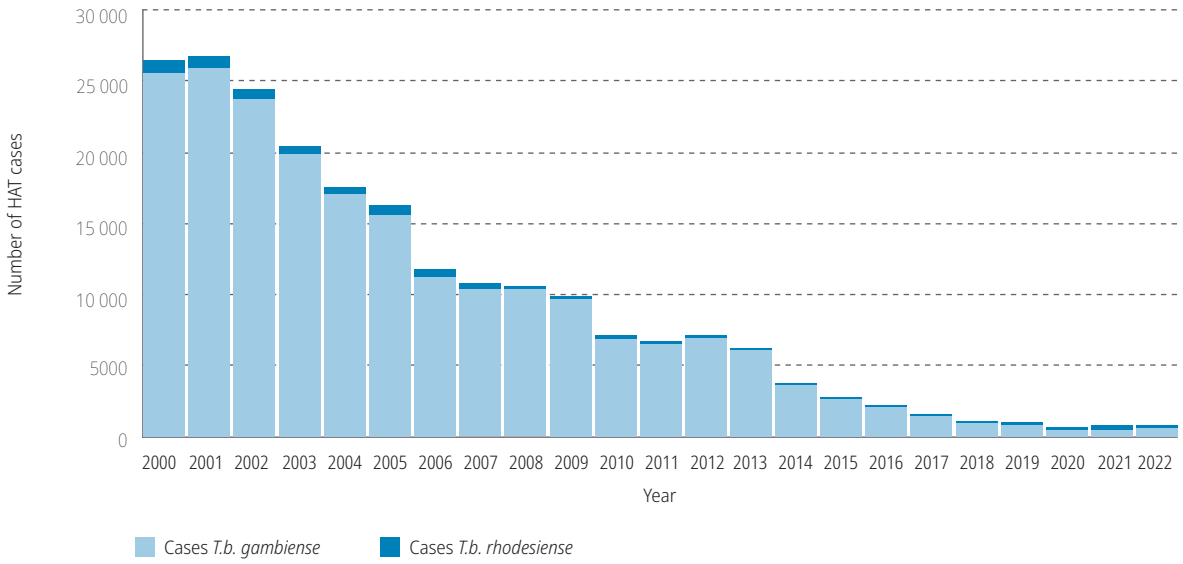
Humans are the main reservoir of *T. b. gambiense*, while domestic and wild animals constitute the reservoir for *T. b. rhodesiense*. Although domestic and wild animals can also host *T. b. gambiense*, their epidemiological role appears minor in comparison with the human reservoir.

WHO maintains exhaustive records of all declared cases of HAT. Since 2018, less than 1000 cases have been reported annually, most of which are caused by infection with *T. b. gambiense* (Figure 1).

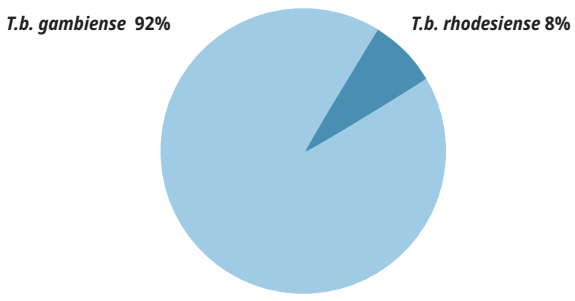
The remarkable progress in the control of gambiense HAT has relied on depleting the reservoir of parasites in humans, detecting cases and ensuring curative treatment, a strategy that has proven capable of interrupting transmission. These measures can be combined with vector control activities. For further progress towards gambiense HAT elimination, it is crucial that these guidelines are applied correctly in order to maximize the chances that every patient receives effective curative treatment.

For rhodesiense HAT, the link between treatment and disease control is less pronounced, because domestic and wild animals are the main reservoir, and infection of humans is infrequent but, importantly, without treatment it leads to death more rapidly than gambiense HAT. The interruption of transmission relies more heavily on One Health interventions connecting animal health and vector control to human health.

Figure 1. Progress in the elimination of HAT, by number of cases, 2000–2022



Distribution in 2018–2022 period



A few HAT cases are reported every year from nonendemic countries in all continents, most of whom are rhodesiense HAT cases in tourists visiting national parks and game reserves in eastern and southern Africa.

To encourage the pursuit of the efforts leading to the declining incidence, WHO has included HAT among the diseases targeted for elimination. As stated in the WHO road map for neglected tropical diseases 2021–2030 *(6)*, the 2030 target for rhodesiense HAT is the elimination as a public health problem, while for gambiense HAT it is the elimination of transmission (i.e. zero cases).

1.5.2 Case management prior to these guidelines

Treatment for gambiense HAT relies on five medicines (fexinidazole, eflornithine, melarsoprol, nifurtimox and pentamidine) and for rhodesiense HAT, until 2024, on three medicines (melarsoprol, pentamidine and suramin) *(7)*. These medicines are donated by manufacturers and distributed by WHO free of charge to ensure that all HAT patients worldwide have access to the most effective treatment available.

The choice of treatment has depended on the sub-species of causative trypanosome (*T. b. gambiense* or *T. b. rhodesiense*) and on the stage of the disease (first-stage: ≤ 5 WBC/μL and no trypanosomes in cerebrospinal fluid (CSF); second-stage: > 5 WBC/μL and/or trypanosomes in CSF). The medicines available prior to the 2019 and 2024 guidelines to treat first-stage (haemo-lymphatic) disease (pentamidine and suramin) generally do not cure second-stage (meningo-encephalitic) disease; and the medicines used to treat the meningo-encephalitic stage (elornithine, nifurtimox, melarsoprol), although effective, cannot be justified for treatment of the haemo-lymphatic stage because they tend to be more toxic and more difficult to administer. In 2019, this changed significantly for gambiense HAT because fexinidazole was introduced to treat first and second stage, except for severe cases (≥ 100 WBC/μL of CSF) and children aged < 6 years or body weight < 20 kg. The treatment for rhodesiense HAT remained unchanged until 2024.

1.5.3 Changes in case management established in these guidelines

This document updates the *WHO interim guidelines for the treatment of gambiense human African trypanosomiasis* (2019) and recommends a revised therapeutic protocol to include fexinidazole as first-line treatment for rhodesiense HAT. This is a substantial improvement in the management of rhodesiense HAT, especially because most patients in second stage will no longer be exposed to melarsoprol, a treatment with a poor safety profile. Another advantage is removing the need for lumbar punctures for staging and the need for injectable treatments in most rhodesiense HAT patients.

The present guidelines incorporate all the new data and new tools since the 2013 WHO guidelines, in a substantial reconfiguration of therapeutic choices for both disease forms.

The main characteristics of fexinidazole are given in section 2.2, and the supporting evidence is described in detail in Web Annex A (Systematic evidence review report and evidence summaries), as well as in the public assessment report of the European Medicines Agency published in December 2023 *(8)*.

The recommendations of the WHO guideline development group are presented in this document's Executive summary and can be consulted in full in Web Annex B (in the evidence-to-decision tables).

Summary of efficacy and safety data supporting the introduction of fexinidazole

- For first-stage gambiense HAT, in two open-label, single-arm studies in adults and children aged ≥ 6 years, respectively, fexinidazole treatment success rates at 18 months were 97.9% and 98.6%, mortality rates 1.6% and 1.4%, adverse event rates 93.1% and 88.4%, and serious adverse event rates 9.0% and 7.2%. These outcomes appear to be more favourable than those reported for pentamidine, although the length of follow-up differed and adverse events were of different types.

- For second-stage gambiense HAT, data from a randomized clinical trial comparing fexinidazole with nifurtimox–eflornithine combination therapy (NECT) showed that in patients with > 100 WBC/μL of CSF (severe second-stage), the treatment success rates at 18 months were 86.9% with fexinidazole versus 98.7% with NECT, significantly in favour of NECT. In patients with ≤ 100 WBC/μL of CSF, success rates were 98% with fexinidazole and 95.9% with NECT, with no significant difference. The overall safety data for both treatments were similar.
- For first-stage and second-stage rhodesiense HAT, in an open-label, single-arm study in adults and children aged ≥ 6 years, fexinidazole treatment success at 12 months was 100% in first-stage and 94.3% in second-stage, and mortality rates were 0 and 2.9% respectively. The mortality in second-stage rhodesiense HAT was substantially lower in comparison with historical data on melarsoprol.

Regarding the possibility of emergence of drug resistance, although cross-resistance of fexinidazole with nitro-containing medicines including nifurtimox can theoretically develop, this risk is estimated to be low given the current incidence of HAT resulting in low drug pressure. Moreover, nifurtimox is only given in combination with eflornithine (NECT), which averts the emergence of resistance to either molecule. Cross-resistance between fexinidazole and metronidazole, a more commonly used nitro-imidazole, is unlikely to develop due to differences in metabolic pathways required for its activity.

1.5.4 Relevance of older guidelines

For aspects other than the treatment of HAT patients, such as HAT control and surveillance, the guidelines published by WHO in 2013 remain relevant *(1)*.

2. Treatment of gambiense HAT

2.1 Case definitions, assessment of gambiense HAT patients and treatment choice

Clinical symptoms and signs, such as prolonged fever, swollen lymph nodes or neurological signs, can raise suspicion of HAT but are not sufficient to establish a diagnosis. Relatively simple, reliable antibody tests exist for screening populations at risk of *T. b. gambiense* infection. As clinical symptoms and signs or serological tests are not sufficiently specific, parasitological confirmation by observation of trypanosomes in body fluids is generally required.

2.1.1 Case definitions for gambiense HAT treatment

Cases of gambiense HAT have been categorized for treatment according to the above considerations as:

Confirmed case: An individual with epidemiological risk of gambiense HAT in whom trypanosomes have been observed.

Case suspected by serological findings: An individual with epidemiological risk of gambiense HAT in whom anti-trypanosomal antibodies have been detected with a serological test but in whom trypanosomes have not been observed.

All confirmed cases require treatment. Cases suspected by serological findings may be treated or not, depending on the national protocol, which usually sets specific conditions, such as plasma titration, other more specific serological tests (such as trypanolysis, enzyme-linked immunosorbent assay), and clinical and epidemiological parameters.

The following sections 2.1.2 and 2.1.3 apply in situations where treatment with fexinidazole is available and technically feasible.

2.1.2 Disease categorization for gambiense HAT treatment

HAT has been categorized classically as first-stage or second-stage disease for the main practical purpose of guiding therapeutic choices[1] (see section 1.5.2).

Currently, with the introduction of fexinidazole which is effective for both disease stages with a limit established at CSF WBC counts ≥ 100/µL, a new sub-category is proposed, as follows:

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

2.1.3 Categorization of gambiense HAT patients: clinical examination and situations where CSF examination is needed

Once a patient has been defined as a gambiense HAT case to be treated, a detailed clinical assessment must be carried out by a health professional who has training and capacity to establish the presence or absence of symptoms and signs that can raise suspicion of severe meningo-encephalitic disease.

---

[1] The historically firmer criterion for staging has been the 5 WBC/µL in CSF cut-off, discriminating the first and second stages. However, depending on the risk–benefit of the available therapeutic options over time, different cut-offs were used for gambiense HAT, sometimes defining three disease stages (e.g. first, intermediate, and second stage).

The main symptoms and signs consistent with severe meningo-encephalitic gambiense HAT are: mental confusion, abnormal behaviour, logorrhea, anxiety, ataxia, tremor, motor weakness, speech impairment, abnormal gait, abnormal movements and seizures. Although sleep disorder is very common in severe HAT, it is also frequent in non-severe HAT, and thus this feature alone is not sufficient for a suspicion of severe gambiense HAT. A summary, field-adapted description is provided in the box below:

Box: Symptoms and signs consistent with severe gambiense HAT

After a patient has been diagnosed with gambiense HAT, a detailed clinical assessment must be carried out by health staff to establish the presence or absence of symptoms and signs which can raise suspicion of severe HAT (i.e. ≥ 100 CSF WBC/µL). The objective of the clinical assessment is not to "diagnose" severe HAT, but rather to direct the patient to further laboratory examinations (i.e. lumbar puncture) which can determine the severity of the disease more precisely and guide treatment decisions. Conversely, in patients not presenting with these clinical features, a lumbar puncture may be avoided and treatment with fexinidazole can be initiated.

The symptoms and signs raising a suspicion of severe gambiense HAT in a patient are:

Mental confusion: disorientation in time and/or space, inattention, slowed thought processes, memory problems.

Abnormal behaviour: manifestly abnormal, inappropriate and/or unusual behaviour for that patient, such as disinhibition, excitement, euphoria, aggressiveness or indifference.

Logorrhea: excessive, incontrollable or incoherent speech.

Anxiety: constant anxiety, nervousness and worry about everything occurring in the patient's life.

Ataxia: loss of muscle control in the arms and legs, which may lead to a lack of balance and coordination and, possibly, a disturbance of gait. Ataxia may affect the fingers, hands, arms, legs, body, speech and even eye movements.

Tremor: involuntary twitching movements of one or more body parts.

Motor weakness: weakness in one or more muscle groups, usually the limbs and/or trunk.

Speech impairment: inability to speak and articulate words normally.

Abnormal gait: the patient cannot walk normally.

Abnormal movements: uncontrollable and abnormal movements which can affect the limbs, trunk, face or neck, such as facial grimacing, tremor, chorea and/or athetosis in the limbs, which may also be observed during walking or on clinical examination.

Seizures: uncontrolled shaking movements involving much of the body with loss of consciousness (tonic-clonic seizure), or shaking movements involving only part of the body with variable levels of consciousness (focal seizure).

Note: Sleep disorder is also frequently present in non-severe HAT. Therefore, this feature alone cannot determine the need for a lumbar puncture

A patient who does NOT present with any of the above symptoms and signs is assumed at low probability to be in the severe meningo-encephalitic stage and a lumbar puncture is not needed to guide the choice of treatment.

A gambiense HAT patient who presents with any of the above symptoms and signs may potentially be in the severe meningo-encephalitic stage and requires a lumbar puncture and a CSF examination in order to categorize the meningo-encephalitic stage and establish the best treatment option. If the lumbar puncture is not done for any reason (e.g. the patient refuses) or

the results cannot be interpreted (e.g. presence of red blood cells > 100/µL), then the first-choice treatment is NECT.

A patient for whom fexinidazole is not indicated (i.e. aged < 6 years or body weight < 20 kg) must undergo a lumbar puncture and a CSF examination to determine the treatment choice.

2.1.4 First-choice treatment

The first-choice treatment of gambiense HAT is determined by a two-step assessment as described in the algorithm shown in Figure 2. The first step is the clinical examination and the second step is the CSF examination (via lumbar puncture), which is required only for patients with clinical symptoms and signs suggestive of severe meningo-encephalitic stage. For patients undergoing lumbar puncture, the possible treatment scenarios are:

For gambiense HAT patients aged ≥ 6 years and body weight ≥ 20 kg:

- < 100 WBC/µL CSF ---> fexinidazole
- ≥ 100 WBC/µL CSF ---> NECT
- CSF WBC not available ---> NECT

For gambiense HAT patients aged < 6 years or body weight < 20 kg:

- ≤ 5 WBC/µL AND no trypanosomes in CSF ---> pentamidine
- > 5 WBC/µL OR trypanosomes in CSF ---> NECT
- CSF WBC not available ---> NECT

Fexinidazole is therefore the first-choice treatment in gambiense HAT patients aged ≥ 6 years and body weight ≥ 20 kg presenting without clinical features consistent with severe meningo-encephalitic HAT or presenting with < 100 WBC/µL in CSF. It is recommended that fexinidazole be prescribed only when there is high confidence that the patient will have appropriate follow-up to detect relapse early.

Pentamidine is the first-choice treatment in gambiense HAT patients aged < 6 years or body weight < 20 kg presenting with ≤ 5 WBC/µL and no trypanosomes in CSF.

NECT is the first-choice treatment in gambiense HAT patients presenting clinical features consistent with severe meningo-encephalitic HAT and with ≥ 100 WBC/µL in CSF or where CSF data are unavailable. It is also the first choice of treatment for patients aged < 6 years or body weight < 20 kg presenting with > 5 WBC/µL or trypanosomes in CSF.

2.1.5 Second-choice and rescue treatments

A second-choice treatment is the alternative treatment recommended in cases where the first-choice treatment is not available or is not appropriate for a particular patient for other reasons. It should not be confused with rescue treatment, which is given in cases of treatment failure (see section 2.9).

The second choice to fexinidazole is pentamidine (if ≤ 5 WBC/µL and no trypanosomes in CSF) or NECT (if > 5 WBC/µL or trypanosomes in CSF).

The second choice to NECT is eflornithine monotherapy if aged < 6 years or body weight < 20 kg; or fexinidazole above those thresholds.

Treatment choices are summarized in Table 1.

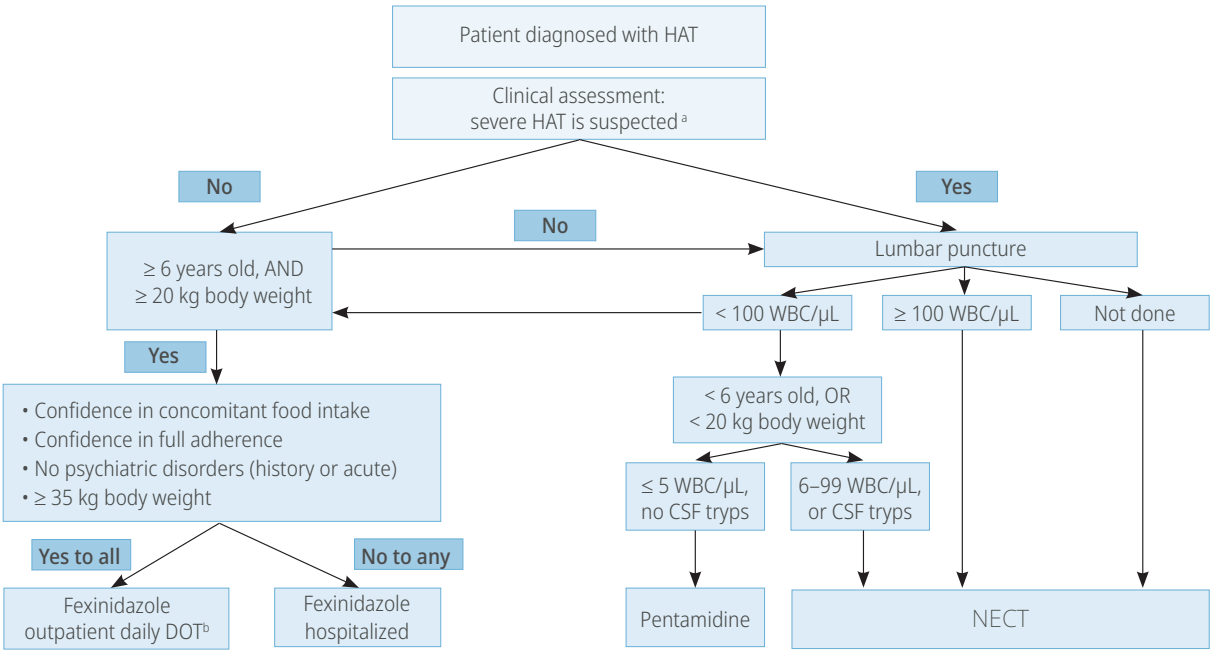
Table 1. Summary of treatment choices for patients with gambiense HAT

Age, body weight	Clinical examination	CSF findings	Treatment		
			1st choice	2nd choice	Rescue[a]
< 6 years or < 20 kg		≤ 5 WBC/µL, no trypanosomes	pentamidine	–	NECT
		> 5 WBC/µL, or trypanosomes	NECT	eflornithine	NECT-long or melarsoprol
≥ 6 years and ≥ 20 kg	No suspicion of severe HAT	LP not needed	fexinidazole	– LP needed – pentamidine (first-stage) or NECT (second-stage)	NECT or NECT long
	Suspicion of severe HAT	< 100 WBC/µL	fexinidazole	pentamidine (first-stage) or NECT (second-stage)	NECT or NECT long
		≥ 100 WBC/µL or failed LP	NECT	fexinidazole	NECT-long or melarsoprol

LP: lumbar puncture; NECT-long: nifurtimox (15 mg/kg per day) in three doses for 10 days; eflornithine (400 mg/kg per day) in two infusions for 14 days; WBC, white blood cells.

[a] See section 2.9 for more details.

Figure 2. Algorithm of WHO recommendations on the management of persons with gambiense HAT



CSF, cerebrospinal fluid; DOT, directly observed treatment; NECT, nifurtimox–eflornithine combination therapy; WBC, white blood cell

[a] Presence of symptoms and signs consistent with severe second-stage HAT, as detailed in Box in section 2.1.3.
[b] If the health facility has capacity for supervised administration as an outpatient.

2.2 Fexinidazole

As an oral treatment, fexinidazole has important advantages over other treatment options that require labour-intensive intravenous or intramuscular injections, which carry a risk of catheter or needle-related infection and generally necessitate hospitalization. In addition, oral treatment implies cost reductions both for the health system in terms of accessory materials and logistics and for some patients who may be able to access treatment at shorter distances from their home.

When taken correctly for 10 days, fexinidazole presents, in gambiense HAT, equivalent efficacy to pentamidine in first-stage and to NECT in second-stage with CSF WBC counts < 100/µL. The efficacy is inferior to NECT in the severe second-stage, defined by a CSF WBC count ≥ 100 /µL (8).

If fexinidazole is not taken at the right dosage for the full course of treatment, or without the appropriate concomitant food intake, its efficacy is unknown and probably lower than that reported in clinical trials.[1]

The medicine is a nitroimidazole derivative and it is suggested that it acts through bioactivation by parasite nitroreductase enzymes to generate reactive amines and/or other metabolites that exert toxic effects on the trypanosomes. Fexinidazole is rapidly absorbed, and food intake markedly increases its bioavailability. It is metabolized to two active metabolites (fexinidazole sulfoxide (M1) and fexinidazole sulfone (M2)). Most of the M1 and M2 are excreted in the faeces within the first 48 and 120 hours after dosage, respectively. Only a small fraction (< 3%) of the dose administered is recovered in the urine.

2.2.1 Presentation

Fexinidazole (Fexinidazole Winthrop) is supplied as pale-yellow biconvex tablets containing 600 mg of active compound. The full treatment is included in a wallet, of which there are two types: a wallet containing 14 tablets for children (aged ≥ 6 years and body weight 20–34 kg); and a wallet with 24 tablets for adults (body weight ≥ 35 kg).

2.2.2 Dosage

Fexinidazole must be taken once daily for 10 days, with a loading dose over the first four days and a maintenance (lower) dose over the last six days (Table 2). Tablets must be taken with food, during or immediately after the main meal of the day, and preferably at the same time each day.

The dosage varies according to the patient's body weight, determining two categories (cut-off 35 kg), that receive a different number of tablets. All tablets contain 600 mg of the active ingredient.

Table 2. Dosage of fexinidazole in adults and children aged ≥ 6 years

Body weight	No. of tablets (600 mg) to be taken once daily with food		Duration
≥ 35 kg	Loading phase	3 tablets (1800 mg)	4 days
	Maintenance phase	2 tablets (1200 mg)	6 days
20–34 kg	Loading phase	2 tablets (1200 mg)	4 days
	Maintenance phase	1 tablet (600 mg)	6 days

If the treatment schedule is interrupted or the patient vomits after swallowing fexinidazole, the trained health care staff responsible for the treatment should decide how to continue the treatment based on the time point of the interruption within the 10-day schedule or the timing of the vomiting. The following general rules apply.

[1] Current data are limited to oral fexinidazole taken during 10 days under strict supervision in clinical trial settings.

Missed doses: For the treatment to be considered acceptable (although not ideal), a minimum of 7 doses must be correctly taken, including the complete loading phase (D1–D4), plus at least 3 doses during the maintenance phase (D5–D10).

If a dose is missed (i.e. not taken on the assigned day), normal dosing should resume the following day until the full course (10 days) is complete.

- If a dose is missed during the loading phase (D1–D4), and > 1 day has passed, the treatment must re-start from zero.
- If a dose is missed during the maintenance phase (D5–D10), the rule is to ensure that a minimum of 3 doses (out of the 6 doses of the maintenance phase) are correctly taken.

If a second dose is missed (i.e. the patient does not attend for directly observed treatment, does not swallow the tablets, or does not present in a fed condition), the patient should be considered unreliable to take oral fexinidazole and an alternative treatment should be established.

Vomiting: If a first event of vomiting occurs after receiving fexinidazole, do not re-dose the same day. Consider giving anti-emetics (e.g. domperidone or metoclopramide) if available.

- If the vomiting happened less than 2 hours after fexinidazole intake, there is risk of incomplete absorption. Repeat the same dose the following day. The treatment will be 1 day longer (using tablets from an extra treatment wallet).
- If the vomiting happened more than 2 hours after fexinidazole intake, that dose is considered valid and assumed to be sufficiently absorbed.

If a second event of vomiting occurs after administration of any other dose, with or without the use of an antiemetic, consider the possibility of changing to an alternative treatment. Again, the timing (2 hours after medicine intake) defines the validity of the dose taken.

The health care staff responsible for the treatment should ensure that a minimum of 7 doses, including all during the loading phase (D1–D4), plus at least 3 doses during the maintenance phase (D5–D10) are completed correctly.

2.2.3 Food concomitant with fexinidazole

Fexinidazole must always be taken with food in the stomach (i.e. the patient must be in a "fed condition"). Taken without food, its absorption is insufficient and the active metabolites do not reach therapeutic levels, especially in the central nervous system (where the bioavailability is three-fold lower). Therefore, a dose taken without food is equal to a dose missed.

The tablets must be swallowed during or immediately after the main meal of the day, within 30 minutes of that meal.

The amount of food taken is more important than the type of food (fat content, etc.); however, liquid food is proscribed because it would drastically decrease fexinidazole absorption. The amount considered necessary is defined as a standard breakfast or lunch (as a reference, a minimum volume of 250 mL of solid food).

2.2.4 Directly observed treatment

Fexinidazole should be administered to all eligible patients only under the strict supervision of trained health staff who must confirm that the patient is in a fed condition and who must directly observe each drug intake. Treatment can be directly observed on an outpatient or inpatient basis, depending on the characteristics of the patient, as outlined below.

2.2.4.1 Outpatient: daily DOT by trained health staff

Outpatient administration of fexinidazole is possible in patients with a low expected risk of poor compliance with treatment. Treatment should be directly observed in hospitals or peripheral health facilities and can, in particular situations, be directly observed at home, but always under the strict supervision of trained health staff who must ensure daily compliance of drug intake with food, for the total duration of treatment (10 days).

Fexinidazole can ONLY be given on an outpatient basis when all of the following conditions are met:

- confidence in concomitant food intake;
- confidence in full adherence to treatment;
- absence of psychiatric disorders (history or acute); and
- body weight ≥ 35 kg.

The decision to administer fexinidazole as an outpatient (under daily supervision) should be taken in consultation between the patient, his/her family and clinicians, taking the above factors into account.

2.2.4.2 Inpatient: daily DOT at the hospital bedside

Patients should be hospitalized to receive fexinidazole when the above conditions are NOT met.

2.2.5 Special populations

Elderly: No dose adjustment is required in patients aged ≥ 65 years.

Renal impairment: No dose adjustment is required for patients with renal impairment.

Hepatic impairment: Contraindicated (see below).

Malnutrition or diarrhoea/vomiting: The patient should receive potassium-rich foods or potassium chloride tablets in order to compensate for potential hypokalemia.

2.2.6 Contraindications and warnings

Patients should not be treated with fexinidazole if any one of the following conditions is present:

- hypersensitivity to fexinidazole, to any agent of the nitroimidazole class (e.g. metronidazole, tinidazole), or to any of the excipients; or
- jaundice, generalized oedema, bleeding or other clinical signs of hepatic insufficiency (e.g. due to liver cirrhosis); or
- risk of QT interval prolongation: patients with congenital prolongation of QT interval, uncorrected electrolyte abnormalities (e.g. hypokalemia or hypomagnesaemia), history of symptomatic cardiac arrhythmia, clinically relevant bradycardia, severe congestive cardiac failure, family history of sudden death or patients with concomitant use of medicinal products that prolong QT interval or induce bradycardia or hypokalemia.
- Cockayne syndrome[1]: fexinidazole should be used only if no alternative is available, and patients hospitalized for close monitoring and timely halting treatment if needed.

Alcohol should not be consumed during treatment with fexinidazole or within 48 hours of the last dose due to the risk of a disulfiram-like reaction (antabuse effect, as with other nitroimidazoles) characterized by flushing, rash, peripheral oedema, nausea and headache. If alcohol is consumed concomitantly with fexinidazole, severe and potentially fatal cardiorespiratory and neurological reactions may occur.

Further details regarding pharmacology, interactions with other products, warnings and adverse reactions appear in the manufacturer's notice provided in each box.

---

[1] Cockayne syndrome is a rare and fatal inherited disorder in which people are hypersensitive to sunlight, have short stature, and have the appearance of premature aging.

2.2.7 Adverse reactions

The most frequent adverse reactions to fexinidazole reported in clinical trials were vomiting (38% of patients), nausea (33%), asthenia (20%), decreased appetite (17%), headache (16%), insomnia (15%), tremor (14%) and dizziness (14%). Vomiting was more frequent in children than in adults.

Neuropsychiatric adverse reactions (insomnia, hallucination, agitation, logorrhea, abnormal behaviour, anxiety, psychotic disorder, suicidal ideation) are more frequent with fexinidazole than with NECT. Caution should be exercised when using fexinidazole in patients with psychiatric disorders (historical or acute) and these patients should be hospitalized during the 10-day treatment period. Patients and their relatives should be advised to contact the treating clinician immediately if they notice signs of suicidal thoughts.

QT interval prolongation (average increase of 15.4 ms) may increase the risk for ventricular arrhythmias when certain conditions coexist (see sections 2.2.5 and 2.2.6).

Neutropenia may occur in patients receiving fexinidazole. Therefore, fexinidazole should be used with caution in patients with evidence, or history, of blood dyscrasia. Patients should return to the clinic if they develop a fever or clinical signs of suspected infection within 3 months of the end of treatment.

2.3 Pentamidine

Pentamidine remains the first-choice treatment for first-stage gambiense HAT (CSF WBC ≤ 5/μL) in children aged < 6 years or body weight < 20 kg, or in other patients in first-stage who cannot receive fexinidazole. The cure rate with pentamidine in first-stage gambiense HAT is 93–98% and has not decreased for decades. Pentamidine is usually given as a deep intramuscular injection because of the frequent occurrence of severe hypotension after intravenous administration.

2.3.1 Presentation

Pentamidine is supplied in vials with 300 mg of pentamidine isethionate powder, to be reconstituted with 10 mL of water for injection.

2.3.2 Dosage and administration

The dosage is 4 mg/kg once daily for 7 days, administered by intramuscular injection.

The 300 mg pentamidine vial should be diluted in water for injection (10 mL) using a syringe (see below), to obtain a final concentration of 30 mg/mL. The dose is calculated according to body weight (Table 3).

Note that the capacity of the vial of pentamidine is smaller than 10 mL. The recommended procedure is:

- Draw up 10 mL of water for injection into a syringe of 10 mL.
- Inject 3 mL into the pentamidine vial, keep the syringe and mix well. Take this dilution into the syringe (mixing it with the remaining water) and repeat the process twice until the pentamidine is completely diluted. Finally, draw up the entire preparation into the syringe.
- Adjust the volume in the syringe according to the weight of the patient by discarding the excess.

Pentamidine is administered intramuscularly (in the gluteal region), with strict respect for antiseptic technique and on alternate sides (left–right) each day.

Patients should be given a source of sugar (e.g. a sweet drink, water with sugar and/or biscuits, bananas, mangos) before injection to prevent hypoglycaemia.

Patients should lie down for at least 1 h after injection to prevent orthostatic hypotension.

Vital signs should be checked again 1 h after injection and monitored if the patient is unwell.

Table 3. Reference table for pentamidine dosage according to body weight

Weight	Dose/day (mg)	mL to inject
5 kg	20 mg	0.7 mL
10 kg	40 mg	1.3 mL
15 kg	60 mg	2.0 mL
20 kg	80 mg	2.7 mL
25 kg	100 mg	3.3 mL
30 kg	120 mg	4.0 mL
35 kg	140 mg	4.7 mL
40 kg	160 mg	5.3 mL
45 kg	180 mg	6.0 mL
50 kg	200 mg	6.7 mL
55 kg	220 mg	7.3 mL
60 kg	240 mg	8.0 mL
65 kg	260 mg	8.7 mL
70 kg	280 mg	9.3 mL
75 kg	300 mg	10.0 mL

2.3.3 Adverse reactions

Pentamidine is generally well tolerated, although minor adverse reactions are common. Possible immediate reactions include hypotension in about 10% of patients, with dizziness and sometimes collapse and shock; after intravenous injection, hypotension can be as frequent as 75%. Occasional adverse reactions are nausea or vomiting and pain at the injection site. Sterile abscesses or necrosis may occur at the site of intramuscular injection. Systemic reactions reported include azotaemia due to nephrotoxicity, leukopenia, thrombocytopenia, anaemia, raised liver function enzymes, hypoglycaemia and hyperglycaemia. Persistent diabetes is a rare but feared event. Rare cardiac disorders such as QT prolongation and arrhythmia have been reported. Severe adverse events such as anaphylaxis and acute pancreatitis are extremely rare.

Further details regarding pharmacology, interactions with other products, warnings and adverse reactions appear in the manufacturer's notice provided in each box.

2.4 NECT

Nifurtimox–eflornithine combination therapy, or NECT, is highly effective against second-stage gambiense HAT, with documented cure rates of 95–98% and fatality rates of < 1%. As a drug combination, NECT is believed to avoid selection of drug resistance by the parasite. It remains the first-choice treatment for meningo-encephalitic stage gambiense HAT with > 100 WBC/μL in CSF and for all children aged < 6 years or body weight < 20 kg with second-stage gambiense HAT (> 5 WBC/μL in CSF).

NECT consists of oral nifurtimox and intravenous eflornithine (α-difluoromethylornithine or DFMO): nifurtimox 15 mg/kg per day orally in three doses for 10 days; eflornithine 400 mg/kg per day intravenously in two 2-hour infusions (each dose diluted in 250 mL of water for injection) for 7 days. In children weighing < 10 kg, it should be diluted in 50 mL of water for injection. If water for injection is unavailable, eflornithine can be diluted in 5% dextrose or in normal saline.

A variation of NECT used occasionally as rescue treatment is the schedule called NECT-long, which extends eflornithine (at the same dose) for 14 days. Nifurtimox is given for 10 days.

2.4.1 Presentation

The NECT kit (comprising medicines and materials for four adults) is distributed by WHO to ensure access to treatment for patients affected by gambiense HAT. Each kit contains:

- eflornithine hydrochloride (Ornidyl) 50 mL (200 mg/mL), 2 boxes of 30 glass vials (total 60 vials);
- nifurtimox (Lampit) tablets 120 mg, 3 bottles with 100 tablets each (total of 300 tablets);
- sterile water for injection, 60 plastic bags of 250 mL each;
- infusion giving set "Y" Luer lock, with air inlet, sterile, 1 box of 60 sets (50 drops per mL);
- catheter, intravenous, single use 20G (1.0 x 32 mm) pink, 1 box with 50 catheters;
- catheter top, Luer male, sterile, 1 box with 100 tops;
- needle, single use, Luer IV, 19G (1.1 x 40 mm), cream, 2 boxes of 100 needles (total 200 needles);
- syringe, single use, Luer 20 mL, 1 box with 160 syringes;
- syringe, single use, Luer 2 mL, 1 box with 100 syringes;
- compress gauze hydrophilic, sterile 10 cm, 120 compresses;
- bandage, extensible, 7 cm x 4 m, 1 box with 20 bandages;
- adhesive tape, zinc oxide, perforated 10 cm x 5 m, 1 roll;
- cotton wool 500 g, 1 roll;
- povidone iodine 10% 200 mL, 1 bottle;
- examination gloves, single use, size large, 1 box with 100 gloves;
- examination gloves, single use, size medium, 1 box with 100 gloves;
- tourniquet 100 x 1.8 cm, 2 tourniquets; and
- leaflet, Trypano NECT kit, in French and English.

2.4.2 Dosage and administration of eflornithine

Dosage

Eflornithine is administered by intravenous infusion every 12 hours for 7 days. The infusion must extend over 2 hours. Ornidyl is hypertonic and must be diluted prior to infusion with sterile water for injection. The dose is calculated according to the patient's body weight: 200 mg/kg every 12 hours (Table 4).

Further details regarding pharmacology, interactions with other products, warnings and adverse reactions appear in the manufacturer's notice provided in each box.

Table 4. Reference table for eflornithine dosage according to body weight, given every 12 hours

Patient body weight (kg)	Eflornithine dose (mg)	Ornidyl to be diluted (mL)	Sterile water for injection (mL)	Total volume of solution to be administered (mL)
5	1000	5	50	55
10	2000	10	50	60
15	3000	15	100	115
20	4000	20	100	120
25	5000	25	100	125
30	6000	30	250	280
35	7000	35	250	285
40	8000	40	250	290
45	9000	45	250	295
50	10 000	50	250	300
55	11 000	55	250	305
60	12 000	60	250	310
65	13 000	65	250	315
70	14 000	70	250	320

Administration

The eflornithine solution must be administered starting within the hour after preparation, by intravenous infusion where the total infusion time should be around 2 hours.

The solution must be administered every 12 hours for 7 days to complete the treatment. The following practical steps should be taken:

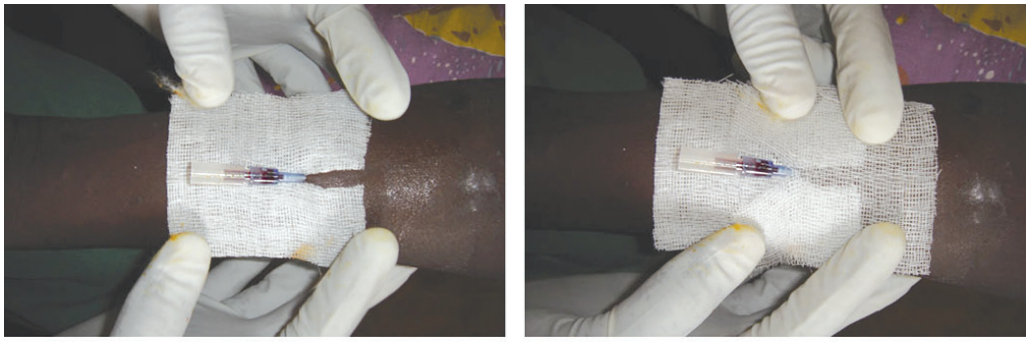
- Label the sterile water for injection bag by writing the name of the patient and/or the number of the bed on the adhesive tape that should be fixed on the bag.
- Write down on the water-for-injection bag the dose of eflornithine in mL.
- Using the 20 mL syringe, extract the quantity of eflornithine (mL) written on the sterile water-for-injection bag and inject that amount of eflornithine into the bag.
- Assemble the drip set; let a small quantity of solution flow through to remove the air bubbles.
- Verify there is no phlebitis.
- Remove the top from the catheter and throw it away (the kit has a box with sterile tops).
- Connect the drip set to the catheter.
- Verify the patency of the catheter. At times between administrations, the catheter can be blocked by a small blood clot. If the solution does not flow, lock the drip set and press the rubber. Usually this action will be enough to remove the clot. If this fails, use 1 mL of sodium chloride with a 2 mL syringe to flush the small blood clots.

- Adjust the infusion rate (drops per minute) for a total time of 2 hours.
- Regularly check the drip rate.
- When the infusion is finished (after 2 hours) stop the drip set and remove it, then cover the catheter with a new sterile top. Tick the drug administration sheet.
- Ensure that the catheter is protected (Figure 3).
- Discard the drip set and the bag in the litter bin.

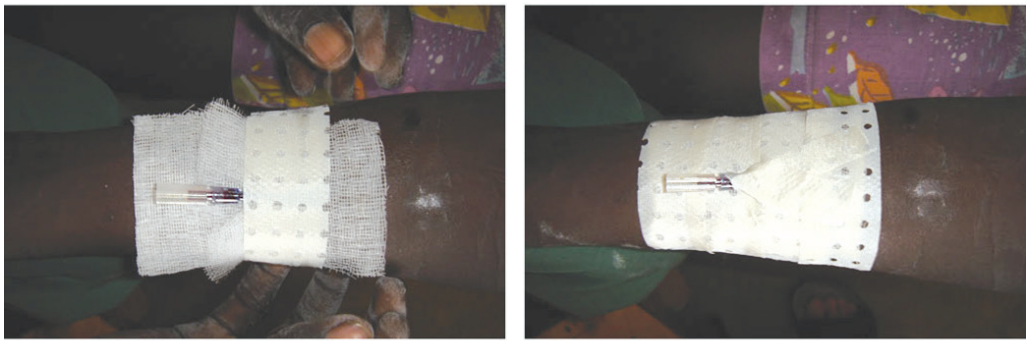
Replace the cannula for infusion at least every 48 hours. The cannulas should be placed following strict asepsis and kept covered by a sterile gauze and fixed with a gauze bandage.

Figure 3. Protection of the catheter

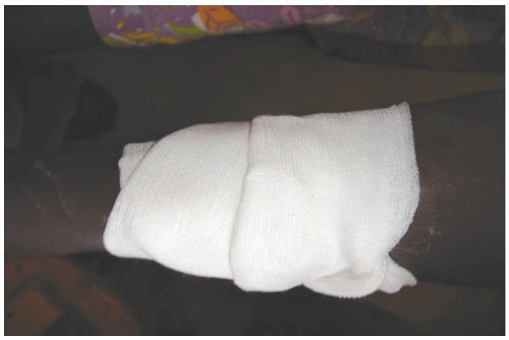
3a. Protect the open end of the catheter with sterile gauze



3b. Fix the catheter



3c. Protect the catheter between two doses



Photos: F. Chappuis

2.4.3 Dosage and administration of nifurtimox

Dosage

Nifurtimox is administered orally every 8 hours for 10 days (Table 5). The dose is calculated according to the patient's weight: 5 mg/kg every 8 hours (total daily dose of 15 mg/kg). Tablets may be cut to obtain the correct dose or, if needed, crushed and diluted into food or water with sugar to facilitate their intake.

Administration

Nifurtimox must be administered under strict supervision to ensure that the patient swallows the tablets, preferably after a meal, and to check if vomiting occurs. If vomiting occurs within 30 minutes after swallowing the tablets, the same dose must be repeated. If it occurs 30–60 minutes after the intake, a half dose should be administered. If it occurs 1 hour after the medicine was taken, then it is considered that the medicine has been fully absorbed. If intense nausea or vomiting persists, consider giving domperidone or metoclopramide before subsequent nifurtimox administrations.

Table 5. Reference table for nifurtimox dosage according to body weight, given every 8 hours

Body weight (kg)	No. of tablets/8 h		
6–7	¼	¼	¼
8–9	½	¼	¼
10–11	½	½	¼
12	½	½	½
13–14	¾	½	½
15–16	¾	¾	½
17–18	¾	¾	¾
19–20	1	¾	¾
21–22	1	1	¾
23–24	1	1	1
25–26	1¼	1	1
27–28	1¼	1¼	1
29–31	1¼	1¼	1¼
32–33	1½	1¼	1¼
34–35	1½	1½	1¼
36–37	1½	1½	1½
38–39	1¾	1½	1½
40–41	1¾	1¾	1½
42–43	1¾	1¾	1¾

Body weight (kg)	No. of tablets/8 h		
44–45	2	1¾	1¾
46–47	2	2	1¾
48–49	2	2	2
50–51	2¼	2	2
52–53	2¼	2¼	2
54–55	2¼	2¼	2¼
56–57	2¼	2¼	2½
58–59	2½	2¼	2½
60–61	2½	2½	2½
62–63	2¾	2½	2½
64–65	2¾	2¾	2½
66–67	2¾	2¾	2¾
68–69	3	2¾	2¾
70–71	3	3	2¾
72–73	3	3	3
74–75	3¼	3	3
76–77	3¼	3¼	3
78–79	3¼	3¼	3¼
80–81	3½	3¼	3¼

2.4.4 Stopping and resuming treatment with NECT

- If treatment was interrupted for 24 hours or less (≤ 2 doses of eflornithine or ≤ 3 doses of nifurtimox), the missing doses should be added at the end of the treatment. The patient will therefore receive the total of 14 doses of eflornithine and 30 doses of nifurtimox that were initially planned.
- If treatment was suspended for more than 24 hours (> 2 doses of eflornithine or > 3 doses of nifurtimox), nifurtimox should still be administered until a total of 30 doses is reached. ONLY eflornithine will be adjusted as follows:
    - If the patient received < 6 doses of eflornithine, then a new course of 14 doses should be started.
    - If the patient received 6–12 doses, 4 additional doses of eflornithine should be added at the end of the treatment, so that a total of 18 doses are administered.
    - If the patient already received > 12 doses of eflornithine, then the treatment should be continued with nifurtimox only.

2.4.5 Adverse reactions

Adverse reactions after treatment with NECT are similar to those of monotherapy with eflornithine (see section 2.5.3) and nifurtimox but are generally better tolerated than those associated with eflornithine monotherapy. NECT is better tolerated in children than in adults. The most common adverse reactions are abdominal pain, nausea, vomiting and headache. There is a risk of seizures, and occasionally psychotic reactions and hallucinations. Diarrhoea and vomiting are frequent (> 50% of treated patients) but do not warrant cessation of treatment. Other described adverse effects are: tremor (5–10%), headache, bone marrow suppression (anaemia, leucopenia), vertigo and ear troubles.

2.5 Eflornithine monotherapy

Eflornithine is given as a monotherapy for second-stage gambiense HAT when NECT is not feasible because the companion drug nifurtimox is unavailable or contraindicated and when, additionally, fexinidazole cannot be given. Cure rates are 90–95% and fatality rates < 2%. Eflornithine is both cytostatic (i.e. it affects the host's cells) and trypanostatic (i.e. it affects trypanosome metabolism preventing cell division). An active immune system is required to achieve cure: in patients who are immunocompromised, parasite elimination might not be complete with eflornithine alone.

2.5.1 Presentation

Eflornithine hydrochloride (Ornidyl) is supplied in 50 mL vials (200 mg/mL), packed in boxes of 30 vials.

2.5.2 Dosage and administration

As monotherapy, eflornithine is administered as a slow intravenous infusion every 6 hours for 14 days (56 infusions in total). The dosage is 400 mg/kg per day intravenously, divided into four 2-hour infusions (each dose diluted, preferably in 100 mL of water for injection) for 14 days. In children weighing < 10 kg, it is diluted in 50 mL of water for injection. In children weighing 10–25 kg, it is diluted in 100 mL of water for injection. If water for injection is unavailable, eflornithine can be diluted in 5% dextrose or in normal saline.

The dose is calculated according to the patient's weight: 100 mg/kg every 6 hours (Table 6).

Table 6. Reference table for eflornithine dosage according to body weight, given every 6 hours[a]

Body weight (kg)	Eflornithine dose (mg)	Ornidyl to be diluted (mL)	Sterile water for injection (mL)	Total volume of solution to be administered (mL)
5	500	2.5	50	52.5
10	1000	5	50	55
15	1500	7.5	100	107.5
20	2000	10	100	110
25	2500	12.5	100	112.5
30	3000	15	100	115
35	3500	17.5	100	117.5
40	4000	20	100	120
45	4500	22.5	100	122.5
50	5000	25	100	125
55	5500	27.5	100	127.5
60	6000	30	100	130
65	6500	32.5	100	132.5
70	7000	35	100	135

[a] For details regarding administration, see section 2.4.2.

2.5.3 Adverse reactions

Adverse reactions are frequent and similar to those of other cytostatics (including diarrhoea and neutropenia). The main adverse reactions are fever, pruritus, hypertension, nausea, vomiting, diarrhoea, abdominal pain, headaches, myelosuppression (anaemia, leucopenia, thrombocytopenia) and, more rarely, seizures that are generally isolated and respond to treatment.

2.6 Melarsoprol

Another treatment option is melarsoprol, which has variable efficacy (due to parasite resistance) and a high fatality rate (about 6% in gambiense HAT, but higher in rhodesiense HAT). Given the high frequency of severe, life-threatening adverse reactions, the only remaining indication in gambiense HAT is the treatment of recurrent relapse after first-line and rescue treatments (including NECT, NECT-long, fexinidazole or eflornithine monotherapy, as appropriate).

See section 3.4 (rhodesiense HAT) for dosage and administration, adverse reactions and monitoring of patients.

2.7 Gambiense HAT treatment in pregnancy

Recommendations for anti-trypanosomal treatment during pregnancy and lactation are based on clinical practice rather than on solid evidence. Fexinidazole and pentamidine can be given after the first trimester. Melarsoprol, eflornithine and nifurtimox are all theoretically contraindicated, and their use and treatment timing (stage of pregnancy) depend on the general condition of the mother. If her general condition allows for watchful waiting, regular (at least monthly) clinical assessment is advised. Fexinidazole or pentamidine should be administered, with the main objective of reducing the risk of vertical transmission of the disease. NECT should be administered after delivery. If the general condition of the pregnant woman is moderately or severely altered,

treatment with fexinidazole, eflornithine alone or NECT must be administered with the main objective of saving her life. The benefits and risks must be clearly explained to the patient and her relatives. After delivery, the newborn should be examined clinically and checked for the presence of circulating trypanosomes in the blood. Breastfeeding should continue during HAT treatment.

2.8 Follow-up after gambiense HAT treatment

The assessment of treatment outcome requires following up the patient for up to 24 months, as relapses may occur more than a year after treatment.

In patients treated with pentamidine and NECT, systematic and active follow-up is not recommended, owing to the high efficacy of these therapies, where good compliance with the full schedule is guaranteed because of being injectable. Instead, patients are to be advised to come for check-up if symptoms reappear (see WHO Technical Report Series, No. 984, 2013 *(1)*).

Because oral fexinidazole presents the risk of insufficient compliance with the full treatment schedule and/or with the concomitant food intake, which is essential for drug absorption, the desirability of systematic follow-up is high. In gambiense HAT patients treated with fexinidazole, relapses may occur late, even 12–24 months after treatment. Therefore, it is recommended that these patients be asked to attend for general examination at 6, 12, 18 and 24 months after treatment, or at any time if symptoms reappear. If signs or symptoms suggest a possibility of relapse, laboratory examinations of body fluids, including CSF, should be performed in order to detect trypanosomes and/or CSF leukocytosis.

A relapse will be defined by the presence of trypanosomes in any body fluid or tissue. When trypanosomes are not seen, a high WBC count in CSF (regardless of counts at first diagnosis) will be considered a relapse according to the following criteria:

- 3 months post-treatment (0–4-month window):
  - the WBC count in CSF does not provide reliable information; diagnosis of relapse is based only on the observation of parasites
- 6 months post-treatment (5–9-month window):
  - 6–49 WBC/µL of CSF: The evolution is uncertain. Rescue treatment could be considered by the clinician if clinical features suggest relapse. Otherwise, a new follow-up at 12 months is strongly recommended.
  - ≥ 50 WBC/µL of CSF: Relapse; rescue treatment needed.
- 12 months post-treatment or later (10–24-month window):
  - ≥ 20 WBC/µL of CSF: Relapse; rescue treatment needed.

2.9 Treatment of gambiense HAT relapses

A summary of rescue treatments after relapse is shown in Table 1 (section 2.1.5).

If a patient treated with fexinidazole relapses, then NECT should be given.

If a patient treated with pentamidine relapses, fexinidazole or NECT should be administered depending on the patient's age/weight and the CSF WBC count.

If after NECT the patient relapses, the first rescue treatment should be NECT-long, which comprises eflornithine infusions (400 mg/kg per day in two infusions) for a total of 14 days. Nifurtimox is given for 10 days, exactly as in the NECT schedule. The treatment alternatives are eflornithine monotherapy at 100 mg/kg every 6 hours (400 mg/kg per day) for 14 days, or fexinidazole if age/weight appropriate and WBC in CSF < 100 cells (compassionate use).

If the patient relapses after the above rescue treatments, then melarsoprol should be considered as a final treatment option due to its toxicity.

3. Treatment of rhodesiense HAT

3.1 Case definitions, assessment of rhodesiense HAT patients and treatment choice

Clinical symptoms and signs, such as prolonged fever, trypanosomal chancre, swollen lymph nodes or neurological signs, can raise suspicion of HAT but are not sufficient to establish a diagnosis. Serological rapid tests for screening populations at risk of *T. b. rhodesiense* infection do not exist. As clinical symptoms and signs are not sufficiently specific, parasitological confirmation is required. Trypanosomes are usually readily detected in stained thin or thick blood films or in wet preparations of blood or chancre exudate. Concentration methods of blood (capillary tube centrifugation, mini-anion exchange centrifugation technique) or of CSF (modified single centrifugation) offer higher sensitivity. All confirmed cases require immediate treatment.

3.1.1 Categorization of rhodesiense HAT patients, and situations where CSF examination is needed

HAT has been categorized classically as first-stage or second-stage disease for the main practical purpose of guiding therapeutic choices, via CSF examination as follows:

- haemo-lymphatic stage (first-stage): ≤ 5 WBC/µL AND no trypanosomes in CSF; and
- meningo-encephalitic stage (second-stage): > 5 WBC/µL OR trypanosomes in CSF.

With the introduction of fexinidazole, which is effective for both disease stages of rhodesiense HAT, the CSF examination is needed to guide the choice of treatment only for patients that fall outside the fexinidazole indication: aged < 6 years or body weight < 20 kg or who have contraindications for the use of fexinidazole. Prior to a lumbar puncture, a dose of suramin is often administered to reduce parasitaemia and minimize the theoretical risk (if a blood vessel is pierced) of iatrogenic introduction of trypanosomes into the CSF, and also of misinterpretation of red cells and parasites seen in the CSF.

3.1.2 First-choice treatment of rhodesiense HAT

The first-choice treatment (algorithm in Figure 4 and Table 7) is determined first by the patient's age and body weight, and by the CSF examination (lumbar puncture) only for children < 6 years old or body weight < 20 kg.

Fexinidazole is the first-choice treatment in rhodesiense HAT patients aged ≥ 6 years and body weight ≥ 20 kg.

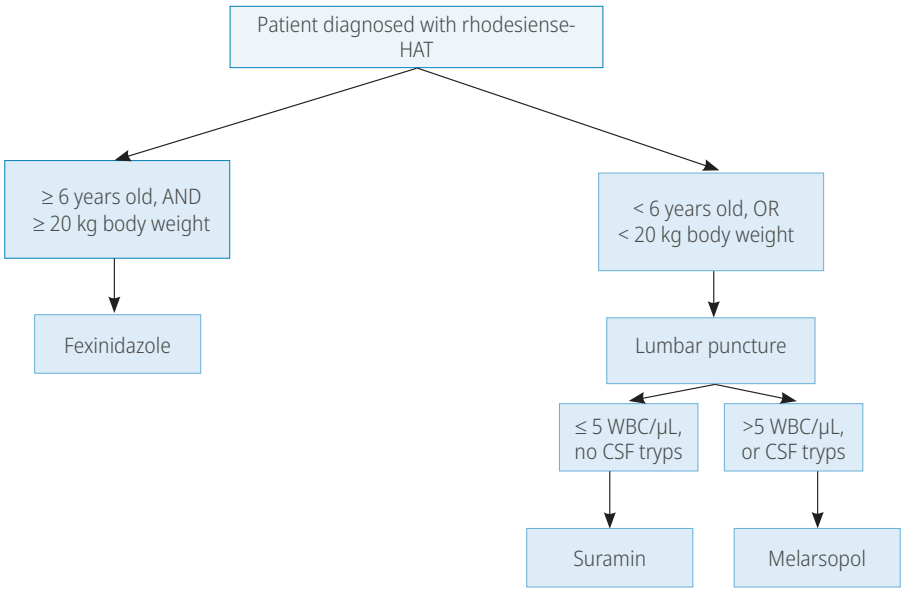
Because the efficacy evidence for fexinidazole in rhodesiense HAT is still limited, appropriate follow-up to detect a relapse early is essential.

Suramin is the first-choice treatment in patients aged < 6 years or body weight < 20 kg presenting with ≤ 5 WBC/µL in CSF and no trypanosomes in CSF.

Melarsoprol is the first-choice treatment in patients aged < 6 years or body weight < 20 kg presenting with > 5 WBC/µL or trypanosomes in CSF.

Pentamidine is recommended when the medicines mentioned above are not readily available, as an interim treatment, or when they present as problematic for a given patient.

Figure 4. Algorithm of WHO recommendations for the management of rhodesiense HAT



CSF: cerebrospinal fluid; WBC: white blood cells.

When recommended medicines are not readily available (e.g. in non-endemic countries), immediate interim treatment with pentamidine should be provided.

Exceptionally, outpatient treatment with daily directly observed treatment should be provided if: the health facility has capacity for supervised administration as an outpatient; it is justified by distance and costs; there is confidence in concomitant food intake; the patient is ≥ 35 kg body weight; the patient is in an acceptable clinical condition; the patient has no serious comorbidities; the patient has experienced no side-effects interfering with treatment compliance.

3.1.3 Second-choice and rescue treatments of rhodesiense HAT

A second-choice treatment is the alternative treatment recommended in cases where the first-choice treatment is not available or is not appropriate for a particular patient for other reasons. It should not be confused with rescue treatment, which is given in cases of treatment failure (see section 3.8).

The second choice to fexinidazole is suramin (if ≤ 5 WBC/µL and no trypanosomes in CSF) or melarsoprol (if > 5 WBC/µL or trypanosomes in CSF).

The second choice to suramin is pentamidine.

Table 7. Summary of treatment choices for patients with rhodesiense HAT

Age, body weight	CSF findings	Treatment		
		1st choice	2nd choice	Rescue[a]
< 6 years or < 20 kg	≤ 5 WBC/µL, no trypanosomes	suramin	pentamidine	Fexinidazole[b]
	> 5 WBC/µL, or trypanosomes	melarsoprol	–	Fexinidazole[b]
≥ 6 years and ≥ 20 kg	LP not needed	fexinidazole	– LP needed – suramin or pentamidine (first-stage) or melarsoprol (second-stage)	– LP needed – suramin (first-stage) or melarsoprol (second-stage)

LP: lumbar puncture; WBC: white blood cells.

When recommended medicines are not readily available, immediate interim treatment with pentamidine should be provided.

[a] See sections 3.1.3 and 3.8 for more details.

[b] Compassionate use.

3.2 Fexinidazole

Fexinidazole has the important advantages of an oral treatment over the options that require intravenous or intramuscular injections. It also reduces costs both for the health system and for the patients who may access treatment closer to their home.

3.2.1 Dosage

Fexinidazole must be taken once daily for 10 days, with a loading dose over four days and a lower maintenance dose over the last six days. Tablets must be taken with food, during or immediately after the main meal of the day, and preferably at the same time each day.

Two distinct dosages are given according to the patient's body weight, as portrayed in Table 8.

Table 8. Dosage of fexinidazole in adults and children aged ≥ 6 years

Body weight	No. of tablets (600 mg) to be taken once daily with food		Duration
≥ 35 kg	Loading phase	3 tablets (1800 mg)	4 days
	Maintenance phase	2 tablets (1200 mg)	6 days
20–34 kg	Loading phase	2 tablets (1200 mg)	4 days
	Maintenance phase	1 tablet (600 mg)	6 days

When taken correctly for 10 days[1] by rhodesiense HAT patients, fexinidazole presents similar efficacy to suramin in first-stage HAT and has better safety than melarsoprol in second-stage HAT. Given its lower case fatality, fexinidazole's overall efficacy is better than that of melarsoprol. The relapse rate with fexinidazole can be assessed further through its implementation.

For more detailed information such as pharmacological properties, presentation, rules in case of treatment interruption or vomiting, requirements of concomitant food, contraindications and warnings, see section 2.2 (gambiense HAT) of this guideline.

3.2.2 Directly observed treatment

Fexinidazole should be administered to all eligible patients only under the strict supervision of trained health staff who must confirm each time that the patient has eaten food and who must directly observe each drug intake. For the treatment of rhodesiense HAT, hospitalization is preferred and should be mandatory in patients presenting particular characteristics, as outlined below.

3.2.2.1 Rhodesiense HAT inpatient: daily DOT at the hospital bedside

Patients with rhodesiense HAT should preferably be hospitalized to ensure the correct administration of fexinidazole. Hospitalization is mandatory when the following conditions are present:

- neuropsychiatric disorders (considering both the risk of neuropsychiatric adverse effects of fexinidazole and the risk of poor compliance with treatment);
- history of alcohol use disorder, due to the risk of Antabuse® (disulfiram) effect, as well as the risk of poor compliance;
- body weight < 35 kg; to ensure full treatment administration;
- if vomiting occurs following administration of fexinidazole.

3.2.2.2 Rhodesiense HAT outpatient: daily DOT by trained health staff

In exceptional circumstances, outpatient administration (under daily supervision) may be considered in the course of the treatment in consultation with the patient, his/her family and clinicians, taking into account the following factors:

- the patient's clinical condition;
- existing comorbidities;
- convenience to the patient and the family (e.g. distance and costs);
- confidence in concomitant food intake;
- development of side-effects interfering with treatment compliance;
- capacity of the healthcare system for supervised administration as an outpatient.

3.2.3 Special populations

Elderly: No dose adjustment is required in patients aged ≥ 65 years.

Renal impairment: No dose adjustment is required for patients with renal impairment.

Hepatic impairment: Contraindicated (see 2.2.6).

Malnutrition or diarrhoea/vomiting: The patient should receive potassium-rich foods or potassium chloride tablets in order to compensate for potential hypokalemia.

---

[1] Current data are limited to oral fexinidazole taken during 10 days under strict supervision in clinical trials settings.

3.2.4 Adverse reactions in rhodesiense HAT patients

Fexinidazole data in rhodesiense HAT are limited, because only one small clinical trial (n=45) reported adverse reactions. The most frequent were vomiting (16% of patients), electrocardiogram abnormality (U-wave, QT prolonged) (11%) and nausea (4%).

More fexinidazole safety data are available in section 2.2 on gambiense HAT.

3.3 Suramin

Suramin (Germanin) was introduced in 1920 for the treatment of trypanosomiasis. It remains the first-choice treatment for rhodesiense HAT in children aged < 6 years or body weight < 20 kg who are in first-stage (CSF WBC ≤ 5/µL), and in older patients in first-stage who cannot receive fexinidazole.

Suramin does not pass the blood–brain barrier, and is therefore not effective for second-stage HAT.

Suramin binds extensively (99.7%) to plasma proteins and has a very long half-life. After a single 1-g dose it is detected in plasma for 5–8 days; after a full course of 5–6 doses the half-life is 44–54 days. Elimination is primarily renal.

3.3.1 Presentation

Suramin is supplied in vials with 1 g of suramin sodium powder, to be reconstituted with 10 mL of sterile water for injection. A suramin solution can be stored for 24 h after dilution at room temperature (up to 25 °C).

3.3.2 Dosage and administration

Suramin is given by slow intravenous injection. Intense local irritation appears when given intramuscularly or if there is extravasation.

Various dosing schedules are used, without particular differences described, probably due to the very long half-life of the drug. All schemes start by administering a test dose, to control for early hypersensitivity reactions, including urticaria and circulatory collapse, which are rare (2–5/10 000).

The most commonly used suramin dosage consists of five injections of 20 mg/kg (maximum 1 g) given weekly for 5 weeks (e.g. days 1, 8, 15, 22, 29). On the first day, suramin is initially administered as a test dose of 4–5mg/kg; a few hours later the rest of the dose is administered (Table 9). Completing the first full dose on day 1 allows for curative concentrations to be rapidly reached. In critically ill patients, a slower dose escalation may be considered.

Table 9. Reference table for suramin dosage according to body weight

Weight	Dose/day	Suramin solution to inject
5 kg	100 mg	1.0 mL
10 kg	200 mg	2.0 mL
15 kg	300 mg	3.0 mL
20 kg	400 mg	4.0 mL
25 kg	500 mg	5.0 mL
30 kg	600 mg	6.0 mL
35 kg	700 mg	7.0 mL
40 kg	800 mg	8.0 mL
45 kg	900 mg	9.0 mL
≥ 50 kg	1 g	10.0 mL

3.3.3 Contraindications and warnings

Suramin should be avoided in patients with severe renal disease (which among other causes can be due to severe rhodesiense HAT). Adapt the dosing schedule in patients with renal failure. Suramin is not removed by dialysis.

If possible, suramin should be administered in a high dependency setting due to the risk of anaphylaxis and cardiovascular adverse reactions.

In case of onchocerciasis coinfection, there is a risk of allergic reactions arising from the rapid killing of microfilaria. However, the general prevalence of onchocerciasis has substantially decreased in the past 2 decades and it is rare in areas endemic for rhodesiense HAT, even if it may affect other areas of the same countries.

3.3.4 Adverse reactions

The adverse reactions to suramin depend on the nutritional status, concomitant illnesses (especially onchocerciasis) and the general clinical condition of the patient. Adverse drug reactions are frequent but mostly mild and reversible; they include pyrexia, nephrotoxicity, peripheral neuropathy, agranulocytosis, haemolytic anaemia and thrombocytopenia. Vomiting, nausea and diarrhea can also occur. Hypersensitivity reactions such as urticaria and circulatory collapse (justifying the current practice of administering a test dose) or late hypersensitivity reactions like pruritus, exfoliative dermatitis, ulceration of the buccal mucosa are described.

Nephrotoxicity, due to suramin reaching higher concentrations in the kidneys than in other organs, is usually mild and reversible. The first manifestation is albuminuria; cylindruria and haematuria may occur later. Regular urine checks during the course of treatment are therefore strongly advised.

Uncommon life-threatening events have been described (< 1%).

Further details regarding pharmacology, interactions with other products, warnings and adverse reactions appear in the manufacturer's notice provided in each box.

3.4 Melarsoprol

Melarsoprol was introduced in 1949 and was the only effective treatment of rhodesiense HAT in second-stage until approval of fexinidazole for this condition. Since then, the only remaining indication of melarsoprol is in children aged < 6 years or body weight < 20 kg who are in second-stage rhodesiense HAT, and in older patients in second-stage who cannot receive fexinidazole, due to contraindications or inability to swallow.

3.4.1 Dosage and administration

Melarsoprol (Arsobal) is available in a 5 mL ampoule containing 180 mg of melarsoprol dissolved in propylene glycol (36 mg/mL). The dosage is 2.2 mg/kg per day (maximum: 5 mL) in slow intravenous injections once daily for 10 days (Table 10).

Table 10. Reference table for melarsoprol dosage according to body weight, given once daily

Body weight (kg)	Melarsoprol dose (mg)	Arsobal to inject (mL)
10	22	0.6
15	33	0.9
20	44	1.2
25	55	1.5
30	66	1.8
35	77	2.1
40	88	2.4
45	99	2.8
50	110	3.1
55	121	3.4
60	132	3.7
65	143	4.0
70	154	4.3
75	165	4.6
80	176	4.9
> 80	180	5.0

Concomitant oral prednisolone may reduce the risk of adverse reactions (see section 3.4.2), administered at 1 mg/kg per day (maximum dose 50 mg) for 9 days, tapering the dosage on days 10–12 (Table 11).

Melarsoprol cannot be prepared with water, or come into contact with water, as this may result in precipitation. If appropriate sterilization procedures are available, it is better to use sterile, dry glass syringes to draw up and inject melarsoprol. After use, these syringes must be washed, dried and sterilized. Care must be taken when using melarsoprol in plastic syringes; after drawing up the liquid (at the patient's bedside) it must be administered immediately (but slowly). Plastic syringes may show signs of deterioration when used with melarsoprol. It is best given intravenously via a micro-profuser (butterfly) as a SLOW push. The injection is very painful, and the subsequent local reaction means that another intravenous site and line must be used for the next dose. Melarsoprol should preferably be administered by health care personnel with experience in use of this drug and under careful supervision.

Table 11. Reference table for melarsoprol treatment schedule, with concomitant prednisolone

Day	Prednisolone (PO)	Melarsoprol (IV)
D1	1 mg/kg	2.2 mg/kg
D2	1 mg/kg	2.2 mg/kg
D3	1 mg/kg	2.2 mg/kg
D4	1 mg/kg	2.2 mg/kg
D5	1 mg/kg	2.2 mg/kg
D6	1 mg/kg	2.2 mg/kg
D7	1 mg/kg	2.2 mg/kg
D8	1 mg/kg	2.2 mg/kg
D9	1 mg/kg	2.2 mg/kg
D10	0.75 mg/kg	2.2 mg/kg
D11	0.5 mg/kg	STOP
D12	0.25 mg/kg	
D13	STOP	

IV: intravenous; PO: per os (oral route).

3.4.2 Adverse reactions

The most important serious reaction to melarsoprol is an encephalopathic syndrome that occurs in 5–18% of all treated cases and is fatal in 10–70% of affected patients. Co-administration of prednisolone might have a protective effect against the immune reaction that is thought to be a component of the encephalopathic syndrome. The encephalopathic syndrome usually occurs 3–10 days (mean 7 days) after the first injection and is characterized by fever and convulsions, rapid onset of neurological disorders, progressive coma or abnormal behaviour. Close monitoring of patients might allow detection of early signs, such as fever, headache or vomiting, prompting the cessation of melarsoprol and management with dexamethasone and diazepam. Other frequent adverse reactions include general malaise and gastrointestinal (nausea, vomiting and diarrhoea) and skin reactions (pruritus); severe and common complications include myocardial damage, albuminuria and hypertension. Cardiac failure is common and can be fatal, but it might be attributable to HAT itself. Exfoliative dermatitis occurs in fewer than 1% of cases.

Further details regarding pharmacology, interactions with other products, warnings and adverse reactions appear in the manufacturer's notice provided in each box.

3.5 Pentamidine in rhodesiense HAT

Used extensively for a long time in gambiense HAT, pentamidine treatment was reported in small numbers of rhodesiense HAT patients with seemingly acceptable results, although the evidence is of very low certainty. During the past decades, more evidence has accumulated from patients who were successfully treated with pentamidine in settings located outside endemic areas where first-choice medicines were not available.

Because rhodesiense-HAT has a rapid evolution affecting vital organs even before reaching the central nervous system, timely administration of trypanocides is crucial.

In settings where first-choice medicines are not readily available, immediate interim treatment with pentamidine is recommended. Treatment should be switched to the first-choice medicines as soon as they become available.

For detailed information on presentation, dosage, administration and adverse events, see section 2.3 (gambiense HAT) of this guideline.

3.6 Rhodesiense HAT treatment in pregnancy

In view of the acute presentation and rapid clinical evolution of rhodesiense HAT, treatment usually cannot be delayed. Recommendations for anti-trypanosomal treatment during pregnancy and lactation are based on clinical practice rather than on solid evidence.

Fexinidazole and pentamidine can be given after the first trimester. Suramin and melarsoprol are theoretically contraindicated, but their use may become necessary as a rescue treatment.

If the general condition of the pregnant woman is moderately or severely altered, treatment with fexinidazole must be administered immediately with the main objective of saving her life. The benefits and risks must be clearly explained to the patient and her relatives.

After delivery, the newborn should be examined clinically and checked for the presence of circulating trypanosomes in the blood. Breastfeeding should continue during HAT treatment.

3.7 Follow-up after treatment of rhodesiense HAT

Because fexinidazole in rhodesiense HAT has been evaluated on a small cohort, the occurrence and timing of relapses are not yet well known. Hence, follow up as explained below should be strictly applied.

As the progression of rhodesiense HAT is usually faster than in gambiense HAT, relapses after treatment may occur earlier, possibly after a few weeks or months.

Patients should be asked to attend for general examination in the hospital where they were treated at least at the end of treatment (day 10), and at 1 and 3 months post-treatment.

At 6 and 12 months post-treatment, a check-up is required. When not feasible at the hospital, this can be done by the treating clinician by telephone or other remote communication, by a trained health professional, or by a health community worker, whichever is most suitable.

A patient should return or be referred to the hospital at any time if symptoms reappear. If signs or symptoms suggest a possibility of relapse, laboratory examinations of body fluids, including CSF, should be performed in order to detect trypanosomes and/or CSF leukocytosis.

A relapse will be defined by the presence of trypanosomes in any body fluid or tissue. It is recommended to apply the most sensitive trypanosome detection techniques when relapse is suspected (i.e. mini-anion exchange centrifugation technique for blood, and modified single centrifugation of CSF). When trypanosomes are not seen, a high WBC count in CSF enhances the suspicion of relapse. However, without evidence-based data to interpret CSF WBC counts for treatment outcome assessment in rhodesiense HAT, the proposed criteria are largely based on those for gambiense HAT:

- 3 months post-treatment (0–4-month window):
  - the WBC count in CSF does not provide reliable information; diagnosis of relapse is based only on the observation of parasites
- 6 months post-treatment (5–9-month window):
  - 6–49 WBC/µL of CSF: The evolution is uncertain. Rescue treatment could be considered by the clinician if clinical features suggest relapse, otherwise, a new follow-up 1-3 months later is strongly recommended.
  - ≥ 50 WBC/µL of CSF: Relapse; rescue treatment needed.
- 12 months post-treatment or later (10–24-month window):
  - ≥ 20 WBC/µL of CSF: Relapse; rescue treatment needed.

3.8 Treatment of rhodesiense HAT relapses

A summary of rescue treatments after relapse is shown in Table 7.

If a patient relapses after treatment with fexinidazole, then a lumbar puncture is needed for staging, and suramin or melarsoprol should be given according to stage.

If the patient is a child < 6 years or < 20 kg who relapses after treatment with suramin, depending on the stage, pentamidine or melarsoprol should be given. In a post-melarsoprol relapse, a compassionate rescue treatment with fexinidazole can be considered.

Even though fexinidazole has not been studied in patients aged < 6 years or < 20 kg body weight, it may be considered as compassionate rescue treatment when other treatment options have failed. In such exceptional cases, a medical specialist should be consulted for dosage and administration.

References

1 Control and surveillance of human African trypanosomiasis: report of a WHO Expert Committee. Geneva: World Health Organization; 2013 (WHO technical report series; no. 984; (https://iris.who.int/handle/10665/95732).

2. The selection and use of essential medicines: report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization (WHO technical report series; no 994 (https://iris.who.int/handle/10665/189763).

3. WHO interim guidelines for the treatment of gambiense human African trypanosomiasis. Geneva: World Health Organization; 2019 (https://iris.who.int/handle/10665/326178).

4. Universal Declaration of Human Rights. Geneva: United Nations; 1948 (https://www.ohchr.org/EN/UDHR/Documents/UDHR_Translations/eng.pdf, accessed June 2019).

5. WHO handbook for guideline development, second edition. Geneva: World Health Organization; 2014 (https://iris.who.int/handle/10665/145714).

6. Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030. Geneva: World Health Organization; 2020 (https://iris.who.int/handle/10665/338565).

7. Control and surveillance of human African trypanosomiasis: report of a WHO Expert Committee. Geneva: World Health Organization; 2013 (WHO technical report series; no. 984; (https://iris.who.int/handle/10665/95732).

8. Product information 14/12/2023: fexinidazole Winthrop - opinion on medicine for use outside EU. Amsterdam: European Medicines Agency; 2024 (https://www.ema.europa.eu/en/opinion-medicine-use-outside-EU/human/fexinidazole-winthrop, accessed 27 May 2024).

Annex. Guideline development methods

These guidelines were developed in accordance with the recommendations of the *WHO handbook for guideline development (1)* following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework. A guideline development group (GDG) was created, including 14 experts with recognized work in the field of treatment of rhodesiense HAT and also in public health related issues, from different institutions. The group comprised experts from endemic countries in sub-Saharan Africa working in the national sleeping sickness control programmes and/or other institutions involved in health care, with vast experience in managing HAT cases. The members are affiliated to different institutions, both from endemic countries and from non-endemic countries. Geographical representation, gender balance and possible conflict of interests were also considerations in selecting members.

An independent guideline methodologist supervised the process and co-chaired the GDG meeting.

An initial scoping and planning process was used to formulate key questions about HAT treatment and determine patient-important outcomes. These questions were structured in PICO (population, intervention, comparator and outcome) format. The framework for the questions, comprising these four elements, were also defined in advance.

The PICO questions were:

1. Should fexinidazole be recommended as first line treatment for first-stage rhodesiense HAT?
2. Should fexinidazole be recommended as first line treatment for second-stage rhodesiense HAT?
3. Should pentamidine be recommended as an alternative treatment for rhodesiense HAT in particular circumstances (e.g. to avoid treatment delays or when suramin is unsuitable for a given patient)?

A systematic evidence review was commissioned externally to address the questions. Criteria for inclusion and exclusion of the literature reviewed (e.g. study design, sample size, duration of follow up) were based on the evidence needed to answer the PICO questions. Search strategies and summaries of evidence are reported in Web Annex A. The GRADE methodology was used to assess evidence certainty, which was categorized per outcome and per PICO question as high, moderate, low or very low, considering the following factors: risk of bias, indirectness, imprecision, inconsistency and publication bias.

The development of recommendations followed the GRADE methodology. For each question the GDG reviewed the available evidence and made judgements for each of the following aspects: desirable effects, undesirable effects, evidence certainty, values, balance of effects, resources required, impact on equity, acceptability and feasibility. Based on this judgement, the GDG decided on the direction (in favour vs against) and the strength (strong vs conditional) of the recommendation. The discussion was guided by the GRADE evidence-to-decision tables *(2)*. The GDG also used these tables to provide additional information, as needed, on: justification, subgroup considerations, monitoring and evaluation, and research priorities.

Decision-making mechanism: Discussions were facilitated by the chair and co-chair (guideline methodologist), with emphasis on giving equal voice to all panel members. An anonymous voting system was used to build the group's opinion on each element underlying the questions. The final recommendations were drafted by consensus (agreement by all members).

Consideration of potential harms and unintended consequences: The WHO steering committee considered potential harms and unintended consequences as part of the outcomes of interest for the PICO questions. Subsequently, the systematic reviewers searched, synthesized and rated the certainty of evidence about these aspects. The GDG reviewed the issues and the evidence following the evidence-to-decision tables' structure and made judgements about the "balance of desirable and undesirable effects". They also discussed how to mitigate the risks and unintended consequences. Those judgements contributed to the GDG's decision on the direction and strength of the recommendations.

Management of conflicts of interest: In accordance with WHO policy, all invited members of the GDG and peer reviewers completed and signed a WHO declaration of interests form, including any participation in consulting and advisory panels, research support and financial investments. The WHO Secretariat assessed the declarations submitted and, having observed no significant financial, commercial or intellectual conflicts of interests, concluded that no member should be excluded from actively taking part in formulating the recommendations (Web Annex C). For the peer review group, the WHO Secretariat found no conflict of interest leading to exclusion from the review process. Prior to the GDG meeting in February 2024, WHO posted summary biographies of GDG members for 14 days on the WHO webpage, calling for comments to be sent confidentially to WHO. At the meeting itself, all participants verbally disclosed to the rest of the group any interests in addition to those declared in written form. Hence, the GDG was aware of any existing interests among its members. The WHO Secretariat and the GDG methodologist judged that there were no commercial or financial interests present in the group. Also, they considered the disclosed non-remunerated participation as independent experts in advisory committees and as trainers of staff in the preparatory phase of the clinical trials, without involvement in the data generation itself, and judged that the risk of bias was not significant to prevent them from discussing the evidence and the formulation of recommendations. The evidence review team was contracted via the Cochrane Collaboration with specific terms of reference. The declaration of interests of researchers involved in the review were assessed and cleared by the WHO Secretariat for financial, commercial or intellectual conflicts of interests.

Dissemination plan: The publication plan, after approval by the WHO e-Pub system, includes disseminating hard copies of the guidelines and making them available online. The guidelines will be accessible on the WHO website, with links to other related websites, and translated into the official UN languages pertinent to the HAT field. Hard copies will be distributed through national HAT control programmes to health staff working on case management. The WHO Secretariat will work with the WHO regional offices to ensure dissemination to WHO country offices and health ministries as well as to key international and national collaborating centres. Additional tools will be developed to support country implementation.

Incorporation of these guidelines into the national treatment protocols and their implementation in the field will be monitored via the ongoing support activities, and through the annual WHO coordination meeting of HAT endemic countries.

References

1. WHO handbook for guideline development, second edition. Geneva: World Health Organization; 2014 (https://iris.who.int/handle/10665/145714).
2. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. BMJ. 2016;28:353.

Global Neglected Tropical Diseases Programme
World Health Organization
20 Avenue Appia
1211 Geneva 27
Switzerland

www.who.int/teams/control-of-neglected-tropical-diseases

9789240096035