WHO interim guidelines for the treatment of gambiense human African trypanosomiasis

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The changes to recommendations were discussed and validated conceptually with the directors or focal points of national sleeping sickness control programmes of the following disease-endemic countries: Benin, Burkina Faso, Cameroon, Congo, Côte d'Ivoire, Gabon, Ghana, Guinea, Equatorial Guinea, Mali, Nigeria, South Sudan, Central African Republic, Democratic Republic of the Congo, Chad and Togo.

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Abbreviations and acronyms

CSF	cerebrospinal fluid
DOT	directly observed treatment
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EtD	Evidence to Decision tables
GDG	Guideline Development Group
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 outcomes
STAG	Strategic and Technical Advisory Group
WBC	white blood cell
WHO	World Health Organization

Executive summary

Human African trypanosomiasis (HAT), or sleeping sickness, is a parasitic infection that is almost invariably fatal unless treated. It is a neglected tropical disease that occurs in sub-Saharan Africa.

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 (currently 98% of cases); and the faster progressing 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 is declining in response to intensive surveillance and control in endemic areas. As a result, HAT is among the neglected tropical diseases targeted by the World Health Organization (WHO) for elimination. WHO maintains exhaustive records of all declared cases; in 2018, a historically low number of cases (< 1000) was reported.

The remarkable progress in the control of gambiense HAT has relied on case-finding and curative treatment, a strategy that interrupts transmission by depleting the reservoir of parasites in humans. This has been combined occasionally with vector control activities. The subject of these guidelines, therefore, is of utmost importance for the continuation of progress to eliminate HAT.

Methodology: The guidelines were developed in accordance with the recommendations of the WHO Guidelines Review Committee.[1] A WHO steering committee defined the scope of the guidelines and formulated the questions to be addressed in PICO (population, intervention, comparator and outcomes) 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 in December 2018 to scrutinize the available evidence and formulate recommendations based on the GRADE approach. The following elements were considered: the balance between desirable and undesirable effects, certainty of the evidence, resource implications, equity, acceptability and feasibility. These elements were used to build the evidence-to-decision tables. 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 recent approval of a new medicine (fexinidazole) for the treatment of gambiense HAT has opened new possibilities for the management of cases and thus warrants the new WHO recommendations contained herein. While studies of fexinidazole and other therapies are ongoing, these guidelines are considered interim guidelines until new information becomes available.[2]

This document focuses on the management of patients affected by gambiense HAT and constitutes an update to the WHO therapeutic guidance issued in 2013.

The main changes in recommendations concern the criteria and methods for deciding the treatment among the new set of therapeutic options and the particular conditions that apply to treatment with fexinidazole, as outlined below. Because HAT is a serious, life-threatening disease and because 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, 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.

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[1] Handbook for guideline development, 2nd edition. Geneva: World Health Organization; 2014. (http://apps.who.int/medicinedocs/documents/s22083en/s22083en.pdf, accessed June 2019).

[2] Interim guidelines are produced when WHO is asked to provide guidance when the available data and information are most certainly incomplete, especially if additional data are anticipated in the near future.

Summary of WHO recommendations for the treatment of gambiense HAT

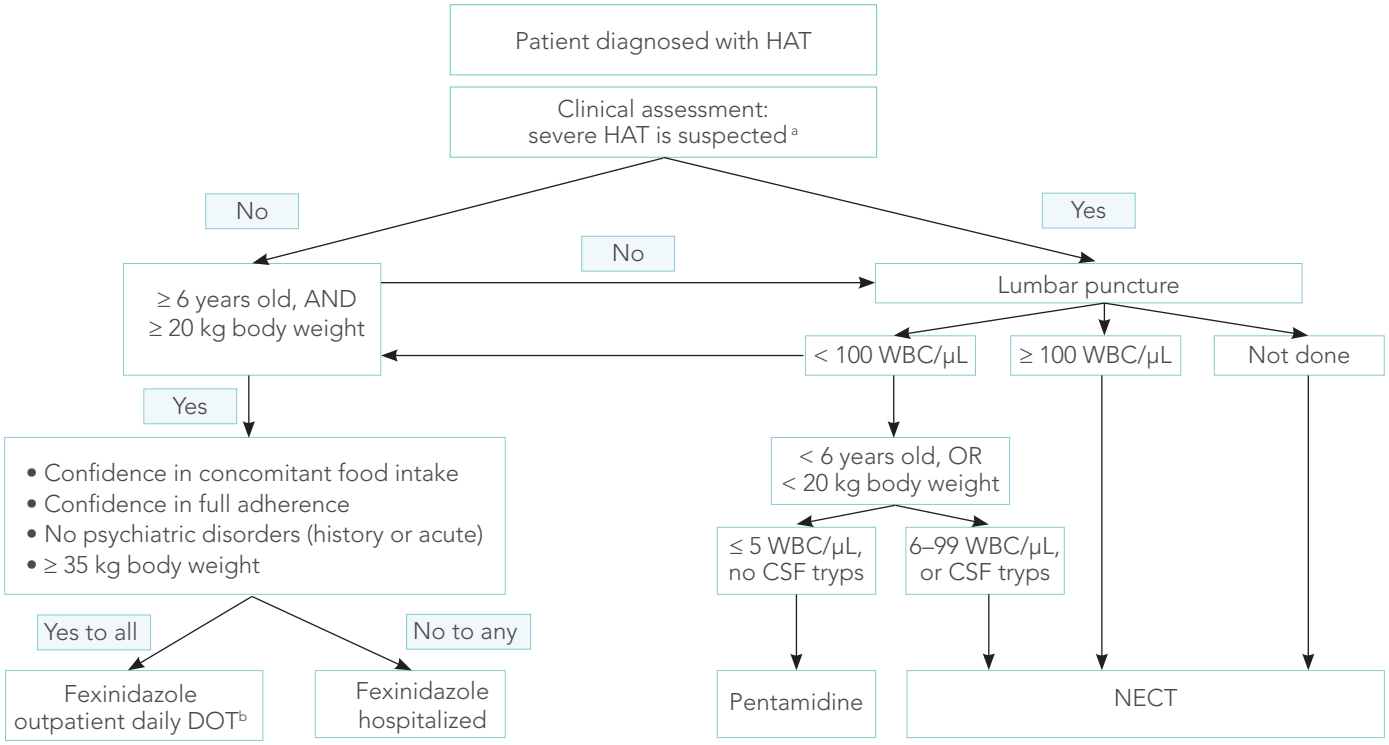
Patient stratification	WHO recommendations	Strength of recommendation	Quality of evidence
Patients who can be managed without lumbar puncture (LP)	Patients aged ≥ 6 years and weighing ≥ 20 kg who meet both of the following conditions: ▪ low index of suspicion of severe disease based on clinical judgement; 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**	**Strength of recommendation**	**Quality of evidence**
Patients aged ≥ 6 years and body weight ≥ 20 kg AND in first-stage or non-severe second-stage (WBC in CSF < 100/µL)	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 in CSF ≥ 100/µL)	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. Fexinidazole can be given after the 1st trimester.	Conditional	Very low

Fexinidazole administration WHO recommendations	Strength of recommendation	Quality of evidence
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: 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
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 healthcare 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 treatment; WBC, white blood cell

This new set of recommendations is integrated into a new algorithm for the management of gambiense HAT, as represented in the figure below.

Algorithm of WHO recommendations for the management of 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 Annex 1.
b If the health facility has capacity for supervised administration as an outpatient.

1. Introduction

The approval in 2018 of a new medicine (fexinidazole) for the treatment of gambiense HAT opens new possibilities for the management of cases and thus warrants updating of the existing recommendations for treatment of HAT. While studies of fexinidazole and other drugs are ongoing, the present guidelines are considered interim guidelines until new information becomes available.

This document focuses on the management of patients affected by gambiense HAT and constitutes an update and a complement to the existing 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]

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*, 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[3] 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).

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[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://apps.who.int/iris/bitstream/handle/10665/95732/9789241209847_eng.pdf, accessed June 2019).

[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://apps.who.int/iris/bitstream/handle/10665/189763/9789241209946_eng.pdf, accessed June 2019).

[2] Countries 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.

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.

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 thus requires access to appropriate laboratory facilities for disease staging and to assess the response to treatment. Observance of the fundamental ethical principles of good clinical practice (respect for persons, beneficence and justice) should therefore extend to all health personnel caring for HAT patients.

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

2. Methodology and process of developing the guidelines

These WHO guidelines were developed following the process recommended by the WHO Guidelines Review Committee, including systematic evidence reviews, rating of evidence following the GRADE methodology, use of formal procedures and rules for selection of experts, management of conflicts of interest and the GRADE methodology for decision-making and to formulate recommendations. Details of the methodology are provided in **Annex 2**.

3. Background

3.1. Epidemiology and burden

Human African trypanosomiasis (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 25 years, the number of reported cases has fallen to historically low levels (< 1000 in 2018). HAT is a neglected tropical disease that occurs in sub-Saharan Africa, within the distributional limits of its vector, the tsetse fly.

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). People who become infected may or may not show noticeable signs of illness immediately, but 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, coma and, ultimately, death.

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 faster progressing form, caused by *T. b. rhodesiense* infection, in eastern and southern Africa (rhodesiense HAT).

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 parasite, vector, 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.

Human beings 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.

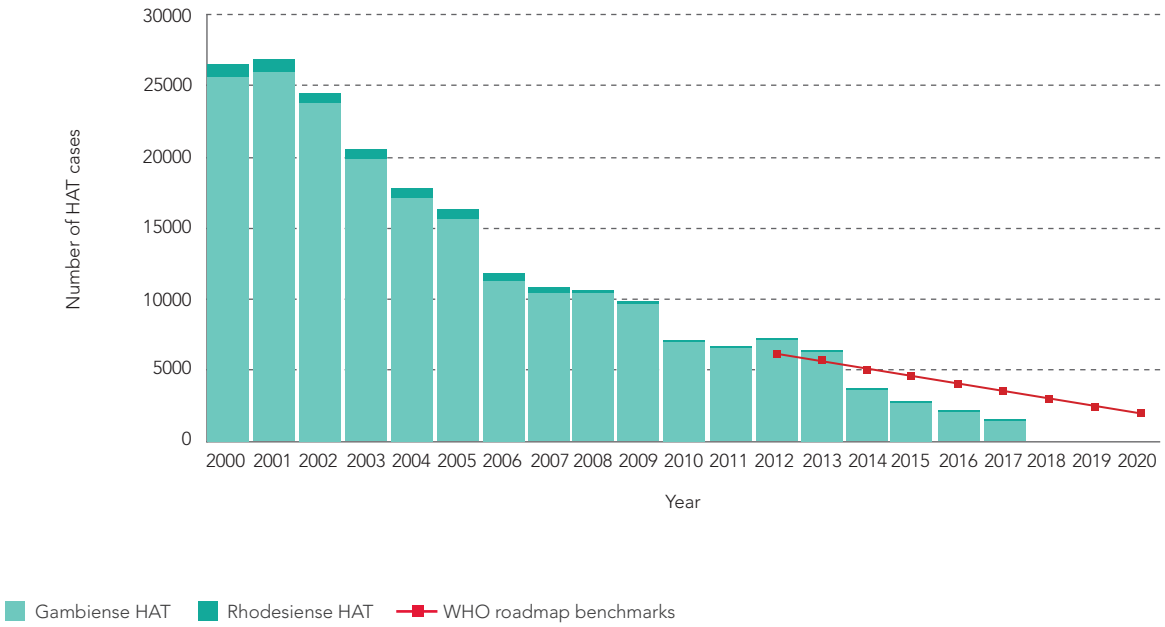
The World Health Organization (WHO) maintains exhaustive records of all declared cases. In 2018, a historically low number of cases (< 1000) was reported, most of which were caused by infection with *T. b. gambiense* (**Figure 1**). In response to the declining incidence of HAT, WHO has included the disease among those targeted for elimination

as a public health problem by 2020, as stated in the WHO roadmap for control, elimination and eradication of neglected tropical diseases.[1] A further target is to fully eliminate the occurrence of gambiense HAT (i.e. zero cases) by 2030.

At its tenth meeting in 2017, the Strategic and Technical Advisory Group for Neglected Tropical Diseases[2] defined the "elimination of HAT as a public health problem" with two main indicators:

- reduction of the total number of new cases reported worldwide < 2000 by 2020; and
- 90% reduction of the total area at risk reporting ≥ 1 case/10 000 people per year by 2020, from the 2004 baseline levels.

Figure 1. Progress in the elimination of HAT, by number of cases, 2000–2020



The process of validation of the elimination of HAT was established according to the *Generic framework for control, elimination and eradication of neglected tropical diseases.*[3]

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. This has been combined occasionally with vector control activities.

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[1] Accelerating work to overcome the global impact of neglected tropical diseases: a roadmap for implementation. Geneva: World Health Organization; 2012 (https://www.who.int/neglected_diseases/NTD_RoadMap_2012_Fullversion.pdf, accessed June 2019).

[2] 10th meeting of the Strategic and Technical Advisory Group for Neglected Tropical Diseases. Geneva: World Health Organization; 2017 (http://www.who.int/neglected_diseases/NTD_STAG_report_2017.pdf, accessed June 2019).

[3] Generic framework for control, elimination and eradication of neglected tropical diseases. Geneva: World Health Organization; 2015 (http://www.who.int/neglected_diseases/resources/NTD_Generic_Framework_2015.pdf, accessed June 2019).

Therefore, for progress towards HAT elimination to continue, it is crucial that these guidelines are applied correctly in order to maximize the chances that every patient receives effective curative treatment.

3.2. Case management until now

To date, treatment for gambiense HAT has relied on four medicines (eflornithine, melarsoprol, nifurtimox and pentamidine) and for rhodesiense HAT three medicines (melarsoprol, pentamidine and suramin).[1] The drugs 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 CSF; second-stage: > 5 WBC/μL and/or trypanosomes in CSF). The medicines available to treat first-stage (haemo-lymphatic) disease generally do not cure second-stage (meningo-encephalitic) disease. Although effective, the medicines used to treat the meningo-encephalitic stage cannot be justified for treatment of the haemo-lymphatic stage because they tend to be more toxic and more cumbersome to administer.

Until now, the first-line treatment for gambiense HAT was pentamidine for first-stage disease and nifurtimox–eflornithine combination therapy (NECT) for second-stage disease. Eflornithine and melarsoprol monotherapies, the second- or third-line alternatives, were rarely used.

3.3. Changes in case management established in these guidelines

These guidelines present a revised therapeutic protocol to include fexinidazole, a new medicine that received regulatory approval for treatment of gambiense HAT in 2018.[2] The characteristics of this new therapeutic alternative open the way for significant modifications in the management of gambiense HAT cases, such as removing the need for systematic lumbar punctures for staging and also the need for injectable treatments in specific groups of patients.

The main characteristics of fexinidazole are given in section 5, and the supporting evidence is described in detail in Web appendix 1 (Systematic Evidence Review), as well as in the public assessment report of the European Medicines Agency published in November 2018.[3]

The recommendations of the WHO Guideline Development Group are summarized in the Executive Summary and can be consulted in full in Web appendix 2 (Evidence to Decision tables).

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[1] See: 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://apps.who.int/iris/bitstream/handle/10665/95732/9789241209847_eng.pdf, accessed June 2019).

[2] Positive scientific opinion of the European Medicines Agency (EMA) in November 2018 and marketing authorization in the Democratic Republic of the Congo in December 2018.

[3] Product information 15/11/2018: fexinidazole Winthrop H-W-2320. Amsterdam: European Medicines Agency; 2019 (https://www.ema.europa.eu/en/fexinidazole-winthrop-h-w-2320, accessed June 2019).

Summary efficacy and safety data supporting the changes

- For first-stage 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 HAT, data from a randomized clinical trial comparing fexinidazole with 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 were not substantially different for both treatments.

3.4. Relevance of older guidelines

The present guidelines deal with case management and treatment of gambiense HAT patients only. For rhodesiense HAT, the management of patients is still covered by the guidelines published by WHO in 2013 which remain relevant also for other aspects of HAT control and surveillance.

4. Case definitions, assessment of 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.

4.1. Case definitions for treatment

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

Confirmed case: An individual in whom trypanosomes have been observed.

Case suspected by serological findings: An individual with an epidemiological risk for 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 serology may be treated or not, depending on the national protocol, which usually sets specific conditions, such as plasma titration, other more specific serological tests (trypanolysis), and clinical and epidemiological parameters.

The following sections (4.2–4.5) apply in situations where treatment with fexinidazole is available and technically feasible.

4.2. Disease categorization for 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 3.2).

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

[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).

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

4.3. Categorization of patients: clinical examination and situations where CSF examination is needed

Once a patient has been defined as a 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 which can raise suspicion of severe meningo-encephalitic HAT.

The main symptoms and signs consistent with severe meningo-encephalitic 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 considered sufficient for a suspicion of severe HAT. A summary, field-adapted description is provided in **Annex 1**.

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 patient who presents with any of the above symptoms and signs, as described in Annex 1, is considered potentially to be in the severe meningo-encephalitic stage and a lumbar puncture followed by a CSF examination are required 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 aged < 6 years or body weight < 20 kg (i.e. a patient for whom fexinidazole is not indicated) must undergo a lumbar puncture and a CSF examination to determine the treatment choice.

4.4. First-choice treatment

The first-choice treatment 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 (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 patients aged ≥ 6 years and body weight ≥ 20 kg:

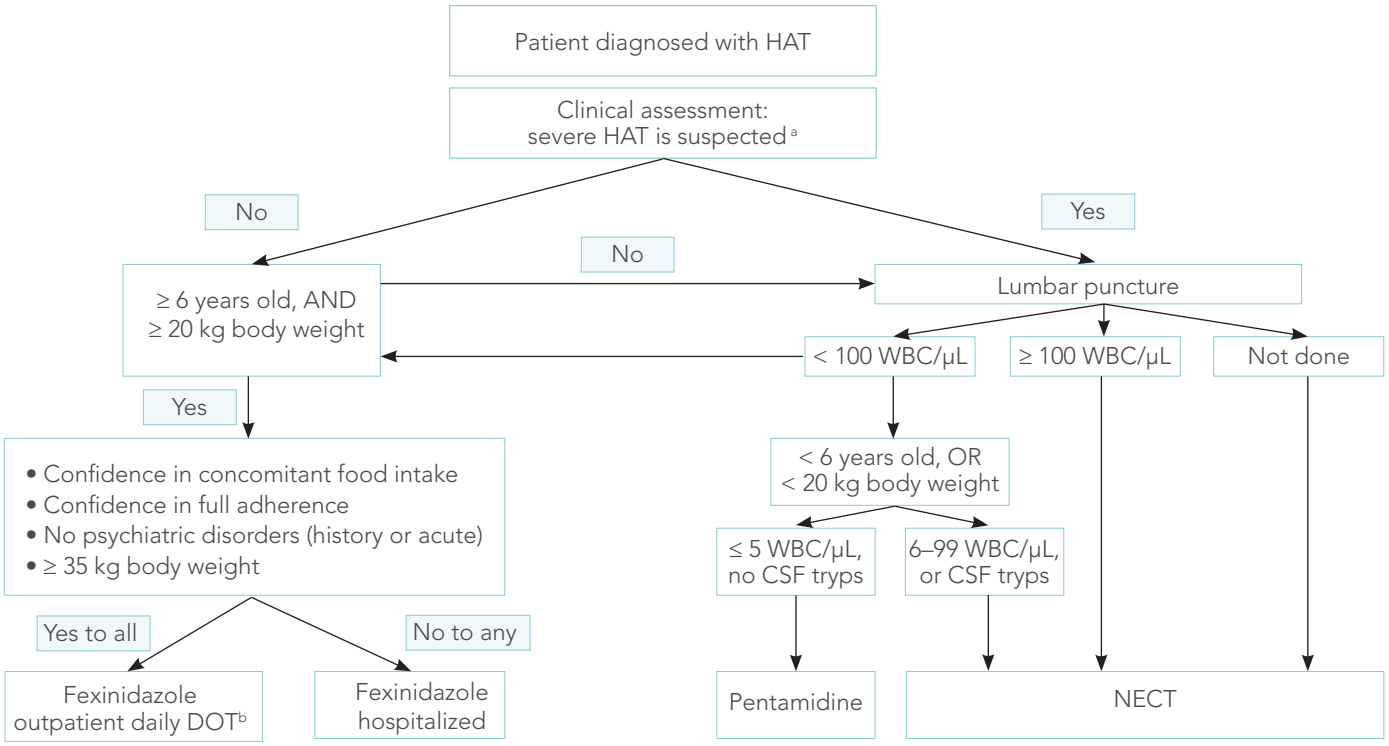
- < 100 WBC/µL CSF **-->** fexinidazole
- ≥ 100 WBC/µL CSF **-->** NECT
- CSF WBC not available **-->** NECT

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

- ≤5 WBC/µL CSF, no trypanosomes **-->** pentamidine
- > 5 WBC/µL CSF or trypanosomes **-->** NECT
- CSF WBC not available **-->** NECT.

Fexinidazole is therefore the first-choice treatment in 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.

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 Annex 1.
b If the health facility has capacity for supervised administration as an outpatient.

Pentamidine 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.

NECT is the first-choice treatment in patients presenting clinical features consistent with severe meningo-encephalitic HAT 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.

4.5. 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 12).

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

Second choice to NECT: fexinidazole.

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
≥ 6 years and ≥ 20 kg	No suspicion of severe HAT	LP not needed	fexinidazole	– LP needed – pentamidine (first-stage) or NECT (second-stage)	NECT
	Suspicion of severe HAT	< 100 WBC/μL	fexinidazole	pentamidine (first-stage) or NECT (second-stage)	NECT
		≥ 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 cell

a See section 12 for more details

5. Fexinidazole

As an oral treatment, fexinidazole has important advantages over other treatment options that require labour-intensive intravenous or intramuscular infusions, which carry a risk of catheter or needle-related infection and necessitate systematic 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,[1] fexinidazole presents equivalent efficacy to pentamidine in first-stage HAT and to NECT in second-stage HAT 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.[2]

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

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 the 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.

5.1. Presentation

Fexinidazole (Fexinidazole Winthrop) is supplied as pale-yellow 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).

5.2. Posology

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. 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.

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[1] Current data are limited to oral fexinidazole taken during 10 days under strict supervision in clinical trials settings.
[2] Product information 15/11/2018: fexinidazole Winthrop H-W-2320. Amsterdam: European Medicines Agency; 2019 (https://www.ema.europa.eu/en/fexinidazole-winthrop-h-w-2320, accessed June 2019).

Table 2. Posology 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	1800 mg (3 tablets)	4 days
	Maintenance phase	1200 mg (2 tablets)	6 days
20–34 kg	Loading phase	1200 mg (2 tablets)	4 days
	Maintenance phase	600 mg (1 tablet)	6 days

The tablets should not be broken or crushed, i.e. they should be swallowed whole.

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:

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 come, 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 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.

5.3. 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, the 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).

5.4. 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.

5.4.1. 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 conditions into account.

5.4.2. Inpatient: daily DOT at the hospital bedside

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

5.5. 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.

5.6. 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.

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) characterized by flushing, rash, peripheral oedema, nausea and headache. If alcohol is consumed concomitant to fexinidazole, severe and potentially fatal cardiorespiratory and neurological reactions may occur.

5.7. 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) 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.

QT interval prolongation (average increase of 15.4 ms), which may increase the risk for ventricular arrhythmias when certain conditions coexist (see sections 5.5. and 5.6).

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.

6. Pentamidine

Until now, pentamidine has been the first-choice treatment for first-stage gambiense HAT (CSF WBC ≤ 5/μL) and it remains so for children aged < 6 years or body weight < 20 kg, or in other patients with CSF WBC count ≤ 5 /μL who cannot receive fexinidazole. The cure rate with pentamidine in first-stage 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.

6.1. Presentation

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

6.2. Posology 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 (4 mg/kg).

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 symptomatic 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

6.3. 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, raised liver function enzymes, hypoglycaemia and hyperglycaemia. Persistent diabetes is a rare but feared event. Severe adverse events such as anaphylaxis and acute pancreatitis are extremely rare.

7. 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-h 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 saline.

7.1. 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) 100 mL (200 mg/mL), 3 boxes of 12 glass vials (total 36 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, French and English.

7.2. Posology 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

7.2.1. Eflornithine

Dosage

Eflornithine is administered by intravenous infusion every 12 h for 7 days. The infusion must extend over 2 h. The presentation of 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 h (**Table 4**).

Further details regarding pharmacology, safety 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)	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 at 50 drops per min. The total time should be around 2 h.

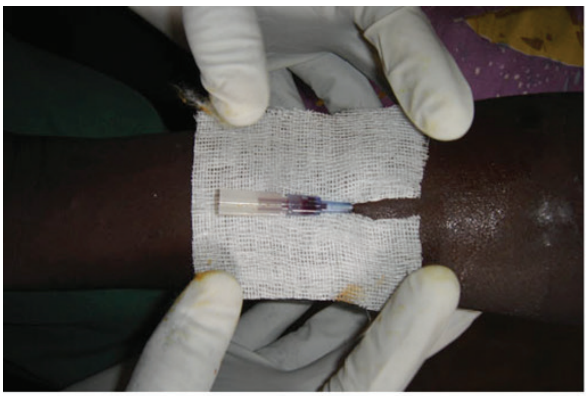
The solution must be administered every 12 h for 7 days to complete the treatment. The following practical steps should be taken:

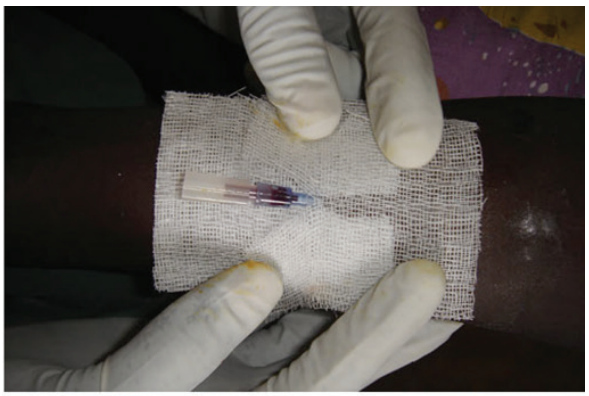
- Label the sterile water for injection bag by writing the name of the patient and/or the number of the bed on the adhesive tape that should be fixed on the bag.
- Write down on the water-for-injection bag the dose of eflornithine in mL.
- Using the 20 mL syringe, extract the quantity of eflornithine (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 the set 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 to 50 drops per min.
- Regularly check the drip rate.
- When the infusion is finished (after 2 h) stop the drip set and remove, 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 h. The cannulas should be placed following strict asepsis and maintained covered by a sterile gauze and fixed with a gauze bandage.

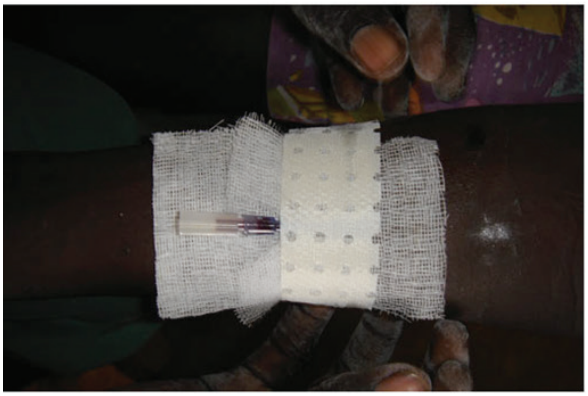
Figure. 3. Protection of the catheter

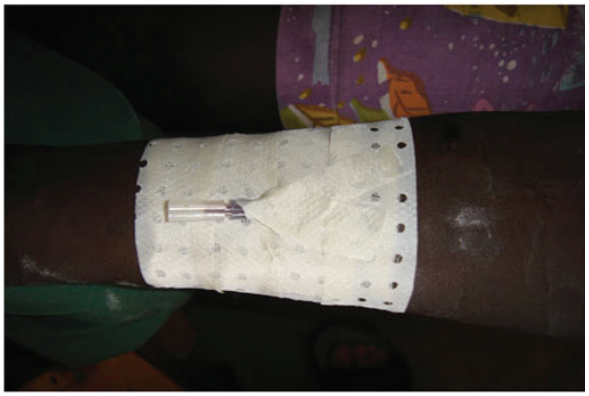
3a. Protect the open end of the catheter with sterile gauze



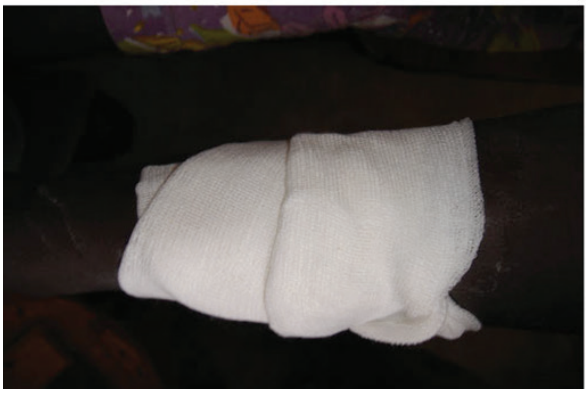


3b. Fix the catheter





3c. Protect the catheter between two doses



Photos: courtesy of F. Chappuis

7.2.1. Nifurtimox

Dosage

Nifurtimox is administered orally every 8 h for 10 days. The dose is calculated according to the patient's weight: 5 mg/kg every 8 h (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.

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

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 min after swallowing the tablets, the same dose must be repeated. If it occurs 30–60 min after the intake, a half dose should be administered. If it occurs 1 h 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.

7.3. Stopping and resuming treatment with NECT

- If treatment was interrupted for 24 h 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 h (> 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.

7.4. Adverse reactions

Adverse reactions after treatment with NECT are similar to those of monotherapy with eflornithine (see section 8.3) 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.

8. 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.

8.1. Presentation

Eflornithine hydrochloride (Ornidyl) is supplied in 100 mL vials (200 mg/mL), packed in boxes of 12 vials.

8.2. Posology and administration

As monotherapy, eflornithine is administered as a slow intravenous infusion every 6 h for 14 days (56 infusions in total). The dosage is 400 mg/kg per day intravenously, divided into four 2-h 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 saline.

The dose is calculated according to the patient's weight: 100 mg/kg every 6 h (**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)	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	250	265
35	3500	17.5	250	267.5
40	4000	20	100	120
45	4500	22.5	100	123.5
50	5000	25	100	127
55	5500	27.5	100	130.5
60	6000	30	100	134
65	6500	32.5	100	137.5
70	7000	35	100	141

a For details regarding administration, see section 7.1.s

8.3. 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.

9. Melarsoprol

Another treatment option is melarsoprol, which has variable efficacy (due to parasite resistance) and a fatality rate of about 6%. 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).

9.1. Posology 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 7**).

Table 7. 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

The medicine should be administered with oral prednisolone 1 mg/kg per day (maximum dose 50 mg) for 12 days, tapering the dosage in the last 3 days (**Table 8**).

Melarsoprol cannot be prepared with water, or come into contact with water, which may cause precipitation. If conditions are appropriate (i.e. good sterilization procedures are followed), 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). A few brands of plastic syringes 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 8. 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	

9.2. Adverse reactions

The most important serious reaction 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 thought to be a component of the encephalopathic syndrome. The encephalopathic syndrome usually occurs 7–14 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 or headache, or both, 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 complications, such as exfoliative dermatitis, occur in fewer than 1% of cases. Cardiac failure is common and can be fatal, but it might be attributable to HAT itself.

10. Treatment in pregnancy

Recommendations for anti-trypanosomal treatment during pregnancy and lactation are based on clinical practice rather than on solid evidence. Pentamidine and fexinidazole 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 generally 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.

11. Follow-up after 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).

Because fexinidazole is a new medicine, and given the risk of insufficient compliance with the full treatment schedule and/or with the concomitant food intake which is essential for drug absorption, the interest of systematic follow-up is high. In 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, 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:

- 0–4 months post-treatment:
  - 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 and a new follow-up at 12 months is strongly recommended. Rescue treatment could be considered by the clinician if clinical features suggest relapse.
  - ≥ 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.

12. Treatment of relapses

A summary of rescue treatments after relapse is shown in **Table 1** (section 4.5).

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, and nifurtimox given for 10 days, exactly as in the NECT schedule. The treatment alternatives are eflornithine monotherapy at 100 mg/kg every 6 h (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 last treatment option due to its toxicity.

Annexes

Annex 1: Symptoms and signs consistent with severe 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 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 HAT 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 muscles 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 a frequent clinical feature that is very common in severe HAT, but also frequently present in non-severe HAT. Therefore, this feature alone cannot determine the need for a lumbar puncture.

Annex 2: Guideline development methods

These WHO 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 experts with recognized work in the field of treatment of HAT and other similar and/or related pathologies, but 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 with vast experience in managing HAT cases. Geographical representation and gender balance were also considerations in selecting members. 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 outcomes) format.

The PICO questions were:

1	Should fexinidazole vs pentamidine be used for first-stage HAT?
2a	Should fexinidazole (oral) vs NECT (oral/intravenous) be used for people with HAT that have ≤ 100 WBC in CSF?
2b	Should fexinidazole (oral) vs NECT (oral/intravenous) be used for people with HAT that have > 100 WBC in CSF?
3	Should clinical stratification vs no stratification be used for people with HAT?
4	Should inpatient administration vs outpatient administration under supervision be used for people with HAT being treated with fexinidazole?

CSF, cerebrospinal fluid; NECT, nifurtimox–eflornithine combination therapy; WBC, white blood cell

Systematic evidence reviews were 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 appendix 1. 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 PICO 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

[1] WHO handbook for guideline development, 2nd edition. Geneva: World Health Organization; 2014 (http://apps.who.int/medicinedocs/documents/s22083en/s22083en.pdf, accessed June 2019).

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 (EtD).[1] 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. The final recommendations were drafted by consensus (full agreement by all members). When consensus was not reached, the GDG used anonymous voting, and the relevant discrepancies were noted in the EtD tables.

Consideration of potential harms and unintended consequences

When developing the PICO questions, the steering committee considered potential harms and unintended consequences as part of the outcomes of interest. Subsequently, the systematic reviewers searched for, synthesized and rated the certainty of evidence about potential consequences, which was included in the evidence profiles and EtD tables. The GDG reviewed that evidence and made judgements about the "undesirable effects" and later 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.

Recommended new procedure for choosing the treatment

The WHO panel suggested doing lumbar puncture (LP) stratification over not doing LP stratification in patients diagnosed with HAT, which is in line with the scientific opinion of the European Medicines Agency. However, it recommended a two-step stratification (first, clinical; second, LP) whereby LP is reserved for patients presenting clinical features leading to the suspicion of severe second-stage HAT, who should be evaluated via LP to ensure they receive the most appropriate treatment. A subgroup of patients not presenting such clinical features can be spared the LP and be treated with fexinidazole. This decision reduces the risk associated with LP in an important number of patients for whom it is considered that fexinidazole has similar efficacy to the current treatment. The only potential harm/unintended consequence identified is the possible error of clinical judgement in a disease presenting high variability of clinical manifestations, which would lead to the prescription of fexinidazole to patients for whom NECT is more appropriate. This risk was minimized by recommending LP when any neurological abnormality is observed, and by preparing a checklist of key neuropathy features to be assessed at field level. Moreover, it was also recommended that all medical staff treating HAT patients receive specific training. Finally, it was recommended that patients receiving fexinidazole should be followed up 6-monthly for 24 months post-treatment, in order to detect relapses early.

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[1] 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.

Management of conflicts of interest

In accordance with WHO policy, all members of the GDG and peer reviewers completed a WHO declaration of interests (DOI) 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. For the peer review group, the WHO Secretariat was satisfied that there had been a transparent declaration of interests, and no case necessitated exclusion from the review process. At the meeting of the GDG in December 2018, all participants verbally disclosed any interests declared to the rest of the group. Hence, the GDG was aware of any existing interests among its members. The evidence review team was contracted via the Cochrane Collaboration with specific terms of reference. Researchers involved in the review were also required to complete WHO DOI, which were assessed and cleared by the WHO Secretariat for financial, commercial or intellectual conflicts of interests.

Dissemination plan

A publication plan was approved in the WHO e-Pub system, including hard copies and availability 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 Secretariat will work with the WHO regional offices to ensure dissemination to WHO country offices and ministries of health, as well as 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 implementation in the field will be monitored via the ongoing support activities, and through the annual WHO coordination meeting of HAT endemic countries.

As stated in the introductory section, the present guidelines are considered interim guidelines because new information is expected in the near future from pharmacovigilance and ongoing studies, particularly on oral drugs. An update to these guidelines is therefore planned within a few years.

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