New WHO guidelines for treatment of gambiense human African trypanosomiasis including fexinidazole: substantial changes for clinical practice

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Human African trypanosomiasis caused by *Trypanosoma brucei gambiense* is a parasitic infection that usually progresses to coma and death unless treated. WHO has updated its guidelines for the treatment of this infection on the basis of independent literature reviews and using the Grading of Recommendations Assessment, Development and Evaluation methodology. The first-line treatment options, pentamidine and nifurtimox–eflornithine combination therapy, have been expanded to include fexinidazole, an oral monotherapy given a positive opinion from the European Medicines Agency. Fexinidazole is recommended for individuals who are aged 6 years and older with a bodyweight of 20 kg or more, who have first-stage or second-stage gambiense human African trypanosomiasis and a cerebrospinal fluid leucocyte count less than 100 per µL. Nifurtimox–eflornithine combination therapy remains recommended for patients with 100 leucocytes per µL or more. Without clinical suspicion of severe second-stage disease, lumbar puncture can be avoided and fexinidazole can be given. Fexinidazole should only be administered under supervision of trained health staff. Because these recommendations are expected to change clinical practice considerably, health professionals should consult the detailed WHO guidelines. These guidelines will be updated as evidence accrues.

Introduction

Human African trypanosomiasis (HAT), or sleeping sickness, is a neglected tropical disease that affects populations in rural sub-Saharan Africa, where the tsetse fly vector transmits the parasite. Two forms of the disease exist, the usually slower progressing form known as gambiense HAT (caused by *Trypanosoma brucei gambiense*), which is endemic in western and central Africa, and the usually faster progressing form known as rhodesiense HAT (caused by *Trypanosoma brucei rhodesiense*), which is endemic in eastern and southern Africa.

After devastating epidemics in the 20th century, sustained and coordinated control efforts over the past 20 years led to a historically low number of 1446 reported cases in 2017, the majority of which were gambiense HAT (98%). Rhodesiense HAT is mainly a zoonosis that occasionally affects humans. The target of eliminating HAT as a public health problem by 2020, with fewer than 2000 cases per year and 90% reduction of the areas at risk (reporting ≥1 case per 10 000 people per year), has therefore nearly been met.[1,2] This remarkable progress has relied on case finding and treatment, a strategy that reduces transmission by depleting the parasite reservoir in humans, and has been occasionally complemented with vector control activities such as targets and traps.

The treatment of gambiense HAT is dependent on the stage of the disease, until now requiring all patients to undergo a systematic lumbar puncture and cerebrospinal fluid (CSF) examination to discriminate between first (haemolymphatic) and second (meningoencephalitic) stages.[3] Pentamidine is the recommended first-line treatment of first-stage gambiense HAT (≤5 white blood cells [WBC] per µL and no trypanosomes in CSF). Pentamidine is given intramuscularly once a day for 7 days and can be administered at the primary health-care level. The first-line treatment of second-stage gambiense HAT (>5 WBC per µL or trypanosomes in CSF, or both) is a combination therapy of nifurtimox (given orally, three times a day for 10 days) and eflornithine (given intravenously in two infusions a day for 7 days).[3] Nifurtimox–eflornithine combination therapy is a major improvement compared with its predecessors, melarsoprol or eflornithine monotherapy.[4] However, nifurtimox–eflornithine combination therapy requires patient hospitalisation, intensive nursing, and complex drug transport logistics.[5]

Fexinidazole is an effective oral monotherapy against gambiense HAT.[6] In November, 2018, the European Medicines Agency (EMA) issued a positive opinion for fexinidazole treatment of gambiense HAT under Article 58, a mechanism designed for drugs intended for use outside the EU.[7,8] In December, 2018, marketing authorisation was given for this treatment in the Democratic Republic of the Congo, which has the most cases of this parasitic infection in Africa.

Fexinidazole is administrated orally once a day for 10 days (4 days at a loading dose and 6 days at a maintenance dose), and evidence supports its effectiveness in both disease stages.[6] These features will allow for significant modifications in the clinical management of gambiense HAT, such as circumventing systematic lumbar puncture and removing the need for injectable treatment in specific groups of patients. However, this new drug also has limitations. First, patients with severe central nervous system involvement are at higher risk of treatment failure.[7] Second, fexinidazole tablets should be taken with a meal because bioavailability is substantially compromised in the unfed state.[9]

The EMA stated that fexinidazole should be used in line with official recommendations.[7] In December, 2018, the WHO Guideline Development Group on the treatment

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of HAT met in Geneva, Switzerland, to provide updated evidence-based recommendations on therapeutic choices for policy makers and medical staff. The detailed treatment guidelines on gambiense HAT, which resulted from this meeting, are accessible on the WHO website.[10] The objective of this Review is to document the decision process, to provide complementary information, to summarise the updated WHO recommendations, and to discuss their implications for clinical practice.

Methods

WHO developed guidelines using the methodology outlined in the WHO handbook for guideline development.[11] The WHO Secretariat formed a guidelines development group that included individuals with recognised expertise in the field of treatment of HAT, public health, and national control programmes. The group was co-chaired by a disease expert and a guideline methodologist.

In an initial prioritisation process, key questions were formulated pertaining to gambiense HAT treatment and outcomes judged important to patients within the context of the disease and its setting. The questions, structured in Population, Intervention, Comparison, Outcome (PICO) format were:[12] should fexinidazole or pentamidine be used for first-stage gambiense HAT? Should fexinidazole or nifurtimox–eflornithine combination therapy be used for second-stage gambiense HAT? Should clinical stratification, or lumbar puncture stratification, or no stratification be used in the treatment of gambiense HAT? Should inpatient administration or outpatient administration under supervision be used for the treatment with fexinidazole?

A systematic review was externally commissioned to synthesise the evidence relevant to the PICO questions.[13] The full version of the guidelines provides the details of the review, including the search strategy, study selection, data extraction, and data analysis.[14] The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was followed to rate the certainty of the evidence for each outcome as high, moderate, low, or very low.[15,16] The evidence was then summarised by outcome using the so-called summary of findings tables.[15] The tables provide outcome-specific information concerning the certainty of evidence and the relevant statistical information.[15,17]

Using the GRADE methodology, the guideline development group shaped the recommendations and graded their strength as either strong or conditional.[18] The grading considered the following factors: the desirable and undesirable effects of the intervention relative to its comparator, the overall certainty of the evidence, the values attached to the main outcomes, the balance between desirable and undesirable effects, the resource requirements, the effect on health equity, the acceptability of the intervention to key stakeholders, and the feasibility of the intervention.

Results

The table provides a summary of recommendations addressing the four PICO questions, their strength, the certainty of the supporting evidence, and key considerations. Detailed judgements on various factors considered when grading the recommendations are provided in the Evidence to Decision tables accessible on the WHO website.[10]

PICO 1: fexinidazole or pentamidine for the treatment of first-stage gambiense HAT

The guideline development group suggests using fexinidazole in favour of pentamidine in patients with first-stage gambiense HAT (conditional recommendation, very low certainty of evidence; table).

To date, no clinical trial has compared fexinidazole with pentamidine. Data about fexinidazole treatment of first-stage patients originate from two prospective, open-label, single-arm studies in adults (n=189; DNDiFEX005) and children (≥6 years old and ≥20 kg; n=69; DNDiFEX006). At 18 months the treatment failure rates were 2·1% (adult study) and 1·4% (child study), the mortality rates were 1·6% (adult study) and 1·4% (child study), adverse event rates were 93·1% (adult study) and 88·4% (child study), and serious adverse event rates were 9·0% (adult study) and 7·2% (child study).[14]

For pentamidine treatment of first-stage gambiense HAT, evidence came from the comparator group of two randomised clinical trials[19,20] and nine observational studies[21–29] that in total included 6722 treated children and adults. The comparability of these studies is limited because of the heterogeneity of study populations, outcome criteria, and observation periods. The range of treatment failure rates was 3·9–4·6%. Adverse events occurred in 17·6–98·5% of treated patients and serious adverse events in 2·4–17·5% of treated patients.[14]

The balance of desirable and undesirable effects appears to favour fexinidazole. Adverse event rates seem to be similar, but the events are of different types. Fexinidazole causes gastrointestinal events, mainly vomiting and nausea, as well as headache, insomnia, tremor, and dizziness. The main adverse event for pentamidine is hypotension, with occasionally nausea, vomiting, and pain at the injection site. Information was insufficient to compare the direct costs of both treatments. However, the indirect costs in terms of human resources are probably lower for oral fexinidazole treatment than for intramuscular injection with pentamidine. Children younger than 6 years or with a bodyweight less than 20 kg should receive pentamidine because the safety and efficacy of fexinidazole in this age group has not been established in clinical trials.

PICO 2: fexinidazole or nifurtimox–eflornithine combination therapy for the treatment of second-stage gambiense HAT

The guideline development group suggests using fexinidazole in favour of nifurtimox–eflornithine combination therapy in patients with second-stage gambiense HAT and

	Intervention or comparator	Recommendation	Strength of recommendation (certainty of evidence)	Key considerations
Patients with first-stage gambiense HAT	Fexinidazole or pentamidine	Use fexinidazole	Conditional (very low)	Children <6 years old or weighing <20 kg should receive pentamidine because fexinidazole is not approved for this group
Patients with second-stage gambiense HAT if CSF <100 WBC per µL	Fexinidazole or nifurtimox–eflornithine combination therapy	Use fexinidazole	Conditional (low)	Children <6 years old or weighing <20 kg should receive nifurtimox–eflornithine combination therapy because fexinidazole is not approved for this group
Patients with second-stage gambiense HAT if CSF ≥100 WBC per µL (severe second stage)	Fexinidazole or nifurtimox–eflornithine combination therapy	Use nifurtimox–eflornithine combination therapy	Conditional (low)	In severe second-stage gambiense HAT the risk of treatment failure is higher with fexinidazole
Patients diagnosed with gambiense HAT, prior to treatment	Stratification by clinical examination or CSF examination or no stratification	A lumbar puncture with CSF examination in case of clinical signs and symptoms raising suspicion of severe second-stage gambiense HAT; no lumbar puncture in the absence of such clinical suspicion	Conditional (very low)	In the absence of clinical suspicion of severe second-stage gambiense HAT, a lumbar puncture can be avoided and fexinidazole preferentially be given in case of high confidence in appropriate follow-up to detect relapse early; there are no validated clinical scores for patient stratification and their development is a research priority; children <6 years old or weighing <20 kg require a lumbar puncture because fexinidazole is not approved for this group
Patients requiring fexinidazole administration	Inpatient or outpatient administration of fexinidazole	Fexinidazole to be given in an outpatient setting when all of the following conditions are met: confidence in concomitant food intake, confidence in full adherence, absence of psychiatric disorders (history or acute), and bodyweight ≥35 kg	Conditional for either inpatient or outpatient (very low)	Outpatient administration should be done in hospitals or peripheral health facilities and in particular situations, at home, but always under the strict supervision of trained health staff to ensure daily compliance of drug intake with food (because of insufficient drug absorption without food)

CSF=cerebrospinal fluid. HAT=human African trypanosomiasis. WBC=white blood cells.

Table: **Summary of recommendations by patient population for the treatment of gambiense HAT**

fewer than 100 CSF WBC per µL (conditional recommendation, low certainty of evidence). In patients with second-stage gambiense HAT and 100 CSF WBC per µL or more, the guideline development group suggests using nifurtimox–eflornithine combination therapy in favour of fexinidazole (conditional recommendation, low certainty of evidence; table).

In one randomised, non-inferiority trial, 264 patients aged 15 years or older with second-stage gambiense HAT and more than 20 WBC per µL or trypanosomes in CSF were given fexinidazole, and 130 patients were given nifurtimox–eflornithine combination therapy.[6] Treatment failure at 24 months occurred in 27 (10·3%) of 262 patients in the fexinidazole group versus three (2·4%) of 127 patients in the group treated with nifurtimox–eflornithine combination therapy (risk ratio [RR] 4·36 [95% CI 1·35–14·11]).[14] At 18 months, adverse events occurred in 247 (93·6%) of 264 patients in the fexinidazole group versus 121 (93·1%) of 130 patients given nifurtimox–eflornithine combination therapy (1·01 [0·95–1·06]) and serious adverse events in 31 (11·7%) of 264 patients in the fexinidazole group versus 13 (10·0%) of 130 patients given nifurtimox–eflornithine combination therapy (1·17 [0·64–2·17]).[14] The most frequently reported adverse events were gastrointestinal (60%), headache, insomnia, asthenia, tremor and dizziness, which occurred in a higher proportion of patients on fexinidazole, with the exception of vomiting. The EMA report[7] highlighted that in this trial, the treatment failure rate at 18 months in patients with second-stage gambiense HAT and with 100 CSF WBC per µL or more was significantly higher for fexinidazole (21 [13·1%] of 160 patients) than for nifurtimox–eflornithine combination therapy (one [1·3%] of 78 patients). By contrast, in the group with fewer than 100 CSF WBC per µL, the treatment failure rate with fexinidazole was two (2·0%) of 102 patients and with nifurtimox–eflornithine combination therapy was two (4·1%) of 49 patients.[7] Furthermore, data about fexinidazole treatment of patients with second-stage gambiense HAT aged 15 years or older with 20 CSF WBC per µL or less originated from a single-arm study (n=41; DNDiFEX005), with 2·4% treatment failure at 18 months.[14] The single-arm study of children aged 6–15 years with second-stage gambiense HAT (n=56; DNDiFEX006) showed 1·8% treatment failure.[14] In both studies, similar adverse events—gastrointestinal and CNS

***Panel*: Symptoms or signs to raise suspicion of severe second-stage gambiense human African trypanosomiasis (ie, cerebrospinal fluid white blood cells ≥100 per µL)**

Mental confusion
Disorientation in time or space, inattention, slowed thought processes, or memory problems.

Abnormal behaviour
Manifestly inappropriate or unusual behaviour for that patient such as disinhibition, excitement, euphoria, aggressiveness, or indifference.

Logorrhoea
Excessive, uncontrollable, or incoherent speech.

Speech impairment
Inability to speak and articulate words normally.

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

Tremor
Involuntary twitching movements of one or more body parts.

Motor weakness
Weakness in one or more muscles groups, usually the limbs or trunk.

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

Abnormal gait
Patient cannot walk normally.

Abnormal movements
Uncontrollable and abnormal movements that can affect the limbs, trunk, face, or neck, such as facial grimacing, tremor, chorea, or athetosis in the limbs. Abnormal movements might 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).

related—were observed as in the randomised controlled trial.

Based on the EMA results, the guideline development group decided to consider the patient group with severe second-stage gambiense HAT with 100 WBC per µL or more separately and to split the PICO 2 question on the basis of this cutoff. The balance of desirable and undesirable effects does not favour either fexinidazole or nifurtimox–eflornithine combination therapy if CSF WBC is less than 100 per µL and favours nifurtimox–eflornithine combination therapy if CSF WBC is 100 per µL or more. However, fexinidazole outpatient treatment was judged more feasible, requiring relatively little resources, and allowing financial savings, being about five to ten times less costly than nifurtimox–eflornithine combination therapy. Nifurtimox–eflornithine combination therapy requires hospitalisation and complex logistics, to deliver the comparatively large volume of drugs and accessory materials required for use (such as sterile water for injection). Oral treatment allows patients to be treated closer to their home, including in remote or insecure settings, which accrues fewer expenses, thus increasing health equity. Oral treatment with fexinidazole in non-severe HAT is expected to be the preferred treatment option (from the feasibility standpoint) for both the patients and the health system; although, some patients might perceive intravenous treatment as a better option in serious illness in general.[30] Children younger than 6 years or with a bodyweight less than 20 kg, or both, should receive nifurtimox–eflornithine combination therapy because fexinidazole is not approved for this group.

PICO 3: clinical stratification, lumbar puncture stratification, or no stratification for the treatment of gambiense HAT

The guideline development group suggests doing a lumbar puncture with CSF examination in favour of not doing a lumbar puncture (conditional recommendation, very low certainty of evidence; table). Without clinical suspicion of severe second-stage gambiense HAT, a lumbar puncture can be avoided and fexinidazole preferentially given.

Until now, selecting treatment for gambiense HAT has required a systematic lumbar puncture and CSF examination for staging. Fexinidazole is effective in both disease stages. However, as stated earlier, in severe second-stage gambiense HAT (≥100 CSF WBC per µL) the risk of treatment failure is significantly higher with fexinidazole than with nifurtimox–eflornithine combination therapy.[7,14] The guideline development group therefore had to consider the potential benefit of avoiding systematic lumbar puncture versus the risk of treatment failure in patients with severe second-stage infection.

The guideline development group concluded that in the case of any clinical sign and symptom that raises suspicion of severe second-stage gambiense HAT, lumbar puncture and CSF examination should be done. In the absence of a validated clinical tool for stratification, an ad-hoc group of clinicians and neurologists identified symptoms and signs that could be used for selection of patients likely to be in severe second-stage gambiense HAT. The following symptoms and signs, correlating with severe meningo-encephalitic gambiense HAT and assessable in peripheral health facilities, were identified:[31,32] mental confusion, abnormal behaviour, logorrhoea, speech impairment, anxiety, tremor, motor weakness, ataxia, abnormal gait, abnormal movements, and seizures (see the panel for further descriptions of symptoms and signs). The presence of any of these symptoms or signs should raise suspicion of severe second-stage gambiense HAT. Although sleep disorder is very common in severe HAT, it is also frequent in non-severe cases, thus this feature alone was not considered sufficient to be indicative. Without clinical suspicion of severe second-stage gambiense HAT, lumbar puncture can be avoided and fexinidazole preferentially

given, on condition of having high confidence in appropriate follow-up to detect relapse early. Avoiding systematic lumbar puncture in a subgroup of patients for treatment stratification was judged to allow for moderate savings of human and material resources. Because fexinidazole is not approved for children younger than 6 years or with a bodyweight less than 20 kg, they require systematic lumbar puncture for disease staging.

PICO 4: inpatient or outpatient administration of fexinidazole under supervision

The guideline development group concluded that either inpatient or outpatient administration under supervision should be decided according to specific criteria (conditional recommendation, very low certainty of evidence; table).

In the previously mentioned clinical trials, fexinidazole was administered as an inpatient treatment. Taken without food, fexinidazole bioavailability is 2·5–3·0 times lower than with food and the active metabolites do not reach therapeutic concentrations, in the central nervous system and elsewhere..[9] Incomplete adherence to unsupervised oral treatments is commonly reported. The efficacy of fexinidazole as outpatient treatment risks being impaired through non-adherence or sub-therapeutic drug concentrations if taken without a meal. Therefore, an independent, non-systematic search was done on adherence to oral malaria treatment (predominantly a 3 day course) as a proxy of the expected adherence to the 10 day fexinidazole oral regimen. Four systematic reviews encompassing 133 studies reported high variability of adherence to malaria treatment, ranging from 1·5% to 100%. Only one review[33] (25 studies) calculated a pooled prevalence, yielding a 69·8% adherence.[33–36] Vomiting, other adverse events, non-supervised first dose, lower education or income level, being male, and belief in traditional medicine were among the factors associated with non-adherence to oral malaria treatment.

Adults treated with fexinidazole reported a higher frequency of psychiatric adverse reactions (103 [39%] of 264 patients)—most mild to moderate in severity—than those treated with nifurtimox–eflornithine combination therapy (23 [18%] of 130 patients).[6] One of the most frequent adverse reactions reported in adults treated with fexinidazole was vomiting (reported in 75 [28%] of 264 patients in one study[6] and 97 [42%] of 230 patients in another[14]), mostly mild to moderate without permanent treatment discontinuation under clinical trial conditions in hospitalised patients.[6,14] Vomiting was more frequent in children (86 [69%] of 125 patients) than in adults.[14] These adverse drug reactions were recognised as additional threats to the compliance with the 10 day fexinidazole course.

Therefore, administration of fexinidazole should be done under the strict supervision of trained health staff, who must confirm that the patient has eaten a meal and who must directly observe each drug intake. The guideline development group suggested administering fexinidazole in outpatient settings only if there is confidence in concomitant food intake, confidence in full adherence, absence of psychiatric disorders (history or acute), and if bodyweight is 35 kg or more (below 35 kg the dose is smaller and drug exposure margins are narrower). This patient treatment, always under the strict supervision of trained health staff, can be done in hospitals or peripheral health facilities, and, in particular situations, at home. Outpatient versus inpatient treatment should be a shared decision between the patient, their family, and the health staff involved. The preference of the patient (eg, in regard to treatment-related costs for travel and hospitalisation), existing comorbidities, the risk of developing side-effects interfering with compliance, and the capacity of the health-care system for supervised administration in the outpatient setting should be considered.

Discussion

The updated evidence-based recommendations on therapeutic choices for gambiense HAT can be summarised as follows: fexinidazole replaces pentamidine as first-line treatment in patients with first-stage gambiense HAT, and replaces nifurtimox–eflornithine combination therapy as first-line treatment in patients with second-stage gambiense HAT with fewer than 100 CSF WBC per µL. Patients younger than 6 years or with a bodyweight less than 20 kg are excluded because the safety and efficacy of fexinidazole in this age group has not been established in the clinical trials and consequently, fexinidazole is not approved for this group. For patients with severe second-stage gambiense HAT, defined by 100 CSF WBC per µL or more, nifurtimox–eflornithine combination therapy treatment is recommended. Without clinical suspicion of severe second-stage HAT, lumbar puncture can be avoided and fexinidazole given. Administration of fexinidazole should be done under the strict supervision of trained health staff.

These recommendations introduce important changes into clinical practice. Detailed guidelines for policy makers and medical staff for managing patients, which follow from the four recommendations formulated by the guideline development group, can be found in the WHO guidelines for the treatment of gambiense HAT.[10] The algorithm shown in the figure summarises these recommendations. Once a patient has been diagnosed with gambiense HAT, a detailed clinical assessment by a health professional who has adequate training and capacity to raise suspicion of severe second-stage gambiense HAT has a decisive role. An association of neurological signs and symptoms with increasing CSF WBC count—especially with 100 or more WBC per µL—has been shown.[31] A patient not presenting with any of these suggestive symptoms and signs is assumed to have a low probability of being at the severe meningoencephalitic stage and a lumbar puncture can be avoided, with the

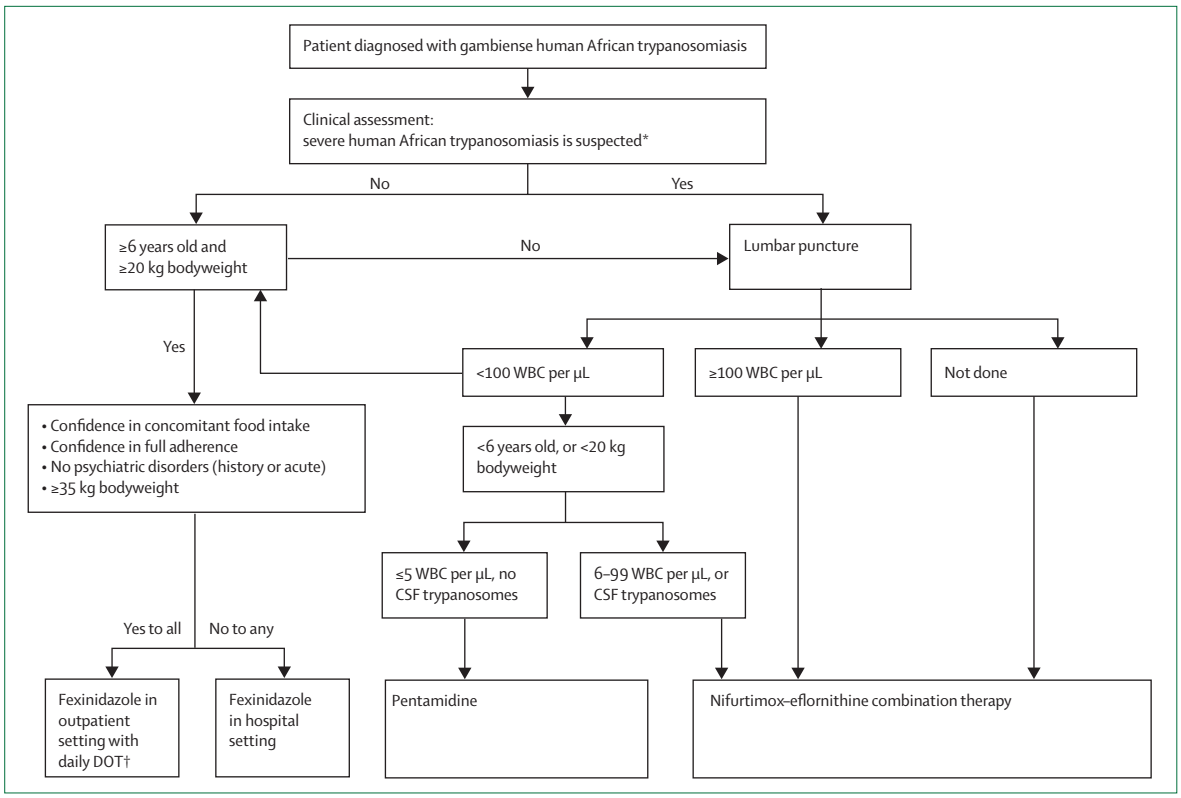

Figure: **Algorithm of WHO guidelines for the management of patients with gambiense human African trypanosomiasis**
WBC=white blood cell. CSF=cerebrospinal fluid. DOT=directly observed therapy. *Presence of any symptom or sign consistent with severe second-stage gambiense human African trypanosomiasis, described in the panel. †If the health facility has capacity for supervised administration in the outpatient setting.

exception of patients younger than 6 years or with a bodyweight less than 20 kg. Patients who do not need a lumbar puncture are treated with fexinidazole when there is high confidence in appropriate follow-up to detect relapse early. In the other patients, a CSF examination is required to establish the best treatment indication (figure). Based on the results of the CSF examination, the recommendations favour: fexinidazole for patients (≥6 years and ≥20 kg) with fewer than 100 WBC per µL CSF; nifurtimox–eflornithine combination therapy for patients with 100 WBC per µL CSF or more, for children (<6 years or <20 kg) with more than 5 CSF WBC per µL or trypanosomes in CSF, or if the lumbar puncture is not done or if the CSF results are not interpretable; or pentamidine for children (<6 years or <20 kg) with fewer than 5 WBC per µL CSF and no trypanosomes in CSF. Fexinidazole treatment should be given in the outpatient setting only when there is confidence in concomitant food intake and full adherence, no psychiatric disorders, and the patient weighs 35 kg or more.[7] As new relevant evidence emerges, the WHO guidance will be updated and completed.[3,10,37]

These WHO guidelines for gambiense HAT treatment have several strengths. Although previous HAT treatment guidelines relied more strongly on expert opinion and on non-systematic reviews of the evidence,[3] this update followed the stricter methodology now mandatory by WHO.[11] Decision making was based on externally commissioned independent systematic reviews, and recommendations were formulated using the GRADE framework.[15,17] The reviewers, methodologists, and panel members all appreciated the use of the more rigorous approach as constructive.

There are some limitations that remain.[38] Studies evaluating treatment modalities for HAT are particularly challenging.[39,40] Because of the progressive decrease in cases of gambiense HAT, trials cannot enrol large patient groups and have low statistical power.[2] The trials have to be done in remote areas in sub-Saharan Africa with a long follow-up of 24 months. For PICO 4, adherence to oral malaria treatment was used as a proxy of the expected adherence to fexinidazole. Accordingly, the certainty of evidence supporting the recommendations were rated as either very low certainty (PICO 1, PICO 3, and PICO 4), or low certainty (PICO 2).

Regarding the question on stratification (PICO 3), the guideline development group had to judge how much the potential benefit of avoiding lumbar puncture outweighs the inferior efficacy of fexinidazole, particularly in severe second-stage HAT. On one hand, the EMA pointed out that the decision regarding the best treatment is complex and should still rely on a combination of clinical and CSF data

because currently no other equivalent method exists.[7] Fexinidazole data are so far limited to a modest number of patients (619 patients in the three main studies DNDiFEX004–006), and there are uncertainties around factors associated with relapse, hindering proposals for less invasive stratification. On the other hand, avoiding a lumbar puncture and CSF microscopy has other positive implications for patients and the health-care system.[41] Lumbar puncture is relatively safe, even in low-resource hospitals in rural Africa, but is painful, requires adequate material and know how, and might induce headache, back pain, confusion, and in rare cases cerebral herniation.[42] Fear of lumbar puncture represents a barrier to HAT screening and for seeking treatment after HAT diagnosis.[43,44] The step-wise approach chosen exploits the advantages of fexinidazole. A primary clinical assessment followed by lumbar puncture only in cases of suspected severe second-stage HAT will identify patients with high CSF leucocytosis who should receive nifurtimox–eflornithine combination therapy to reduce the risk of treatment failure. Indeed, neurological and psychiatric symptoms increase significantly with CSF WBCs and indicate disease progression.[31]

Even with the introduction of fexinidazole, systematic treatment of patients testing antibody positive in screening tests, such as the card agglutination test for trypanosomiasis for *Tb gambiense* (CATT/*Tb gambiense*) or in rapid diagnostic tests, but in whom no trypanosomes are detected in blood or lymph is not justified. Considering the low positive predictive value of such serological tests at low prevalence, the national protocols set specific conditions for treating these patients, such as plasma titration, additional serological tests, and clinical and epidemiological parameters. The national protocol might also require lumbar puncture or continued follow-up with additional parasitological examinations of patients who are seropositive. Once a patient is parasitologically confirmed or is considered to have gambiense HAT on the basis of additional criteria, the present treatment guidelines should be followed.

Fexinidazole is a new drug that has been tested only in clinical trial settings. Because this drug is a 10-day oral treatment, frequently causes nausea and vomiting, and requires concomitant food intake for full drug absorption, there is risk of non-compliance. Hence, the need for systematic patient follow-up is high, even if follow-up is made challenging by limited resources. Additionally, relapses with fexinidazole might occur late, up to 12–24 months after treatment.[7] Therefore, contrary to the situation with nifurtimox–eflornithine combination therapy and pentamidine, for which systematic follow-up is currently not recommended,[3] patients treated with fexinidazole should return for general examination at 6, 12, 18, and 24 months after treatment, or at any time if symptoms reappear. When signs or symptoms suggest a possibility of relapse, laboratory examinations of body fluids, including CSF, should be done to look for trypanosomes and CSF leucocytosis.

To date, resistance to nifurtimox–eflornithine combination therapy has not been identified; however, resistance to eflornithine and nifurtimox has been selected in the laboratory. Eflornithine resistance emerges when an amino acid transporter that carries the drug into the cell is lost.[45] Nifurtimox resistance is associated with diminished activity of a nitroreductase enzyme required to activate the drug.[46] The same enzyme is responsible for activation of fexinidazole, and its diminished activity might cause cross-resistance between nifurtimox and fexinidazole.[47] Therefore, there is a theoretical risk of resistance to nifurtimox being selected, rendering parasites cross-resistant to fexinidazole, or the inverse. However, to date, the fitness of nitroreductase-deficient parasites to be transmitted by tsetse flies has not been assessed. Given the mitochondrial localisation of that enzyme and the prominent role of the mitochondrion in the tsetse fly stages of the parasites, whether parasites with diminished nitroreductase activity could be transmitted by tsetse flies is unknown. Furthermore, with relatively few doses of therapy currently given to patients with HAT and low gambiense parasitaemias, the risk of resistance, and hence emergence of cross-resistance, although theoretically possible, seems low.

Considering the novelty of fexinidazole to treat gambiense HAT, some open questions and research priorities remain. The algorithm to decide which drug to use is relatively complicated due to the higher risk for relapse observed with fexinidazole if the patient has a CSF WBC of 100 per µL or more, and because of age and bodyweight limitations. Risk factors for relapse after fexinidazole treatment remain poorly characterised. In this context, the development and validation of clinical scores for treatment stratification is a research priority. An ongoing study on implementation, particularly on home-based treatment and adherence, will yield further information on the potential of fexinidazole in the future (NCT03025789). Considering that in-vitro and in-vivo studies have shown that fexinidazole kills *Tb rhodesiense*[48] and that the only treatment for second-stage rhodesiense HAT is the highly toxic melarsoprol, a clinical trial testing efficacy of fexinidazole to treat this form of HAT has started (NCT03974178). Further studies in children younger than 6 years or with a bodyweight less than 20 kg are needed to improve treatment in this group.

In conclusion, fexinidazole has the potential to simplify diagnosis and treatment of gambiense HAT and to change clinical practice in that direction. The next steps include the incorporation of the WHO guidelines into national treatment guidelines, appropriate training of health personnel, and field implementation, as well as putting in place a pharmacovigilance system. Because fexinidazole will be deployed in areas poorly served by standard pharmacovigilance systems, proactive data collection is required that is adapted to the local field

constraints. Considering the limited evidence, and the ongoing additional studies on fexinidazole and on acoziborole, a new single-dose oral compound for treatment of all stages of gambiense HAT (NCT03087955), these WHO guidelines will be updated once new results become available.

Contributors

AKL and VL led the writing of the manuscript and contributed equally. GP and JRFM coordinated the guidelines development and led the writing of the full guidelines. EA functioned as guidelines methodologist and co-chair. GV and HB presented the systematic reviews, evidence profiles, and GRADE tables. All authors contributed to the development of the New WHO Interim Guidelines for the Treatment of Human African Trypanosomiasis.

Declaration of interests

HB and GV report personal fees from WHO Department of Control of Neglected Tropical Diseases during the conduct of the work. VL reports personal fees from Drugs for Neglected Diseases Initiative, outside the submitted work. EAA, MPB, FC, AKE, OE, JRFM, LK, AKL, EM, GP, JS, and PS declare no competing interests.

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References

1 WHO. Accelerating work to overcome the global impact of neglected tropical diseases—a roadmap for implementation. Geneva: World Health Organization, 2012.

2 Franco JR, Cecchi G, Priotto G, et al. Monitoring the elimination of human African trypanosomiasis: update to 2016. *PLoS Negl Trop Dis* 2018; **12:** e0006890.

3 WHO. Control and surveillance of human African trypanosomiasis. Technical Report Series 984. Geneva: World Health Organization, 2013.

4 Priotto G, Kasparian S, Mutombo W, et al. Nifurtimox–eflornithine combination therapy for second-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. *Lancet* 2009; **374:** 56–64.

5 Eperon G, Balasegaram M, Potet J, Mowbray C, Valverde O, Chappuis F. Treatment options for second-stage gambiense human African trypanosomiasis. *Expert Rev Anti Infect Ther* 2014; **12:** 1407–17.

6 Mesu VKBK, Kalonji WM, Bardonneau C, et al. Oral fexinidazole for late-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial. *Lancet* 2018; **391:** 144–54.

7 European Medicines Agency Committee for Medicinal Products for Human Use. Assessment report fexinidazole winthrop. 2018. https://www.ema.europa.eu/en/documents/medicine-outside-eu/fexinidazole-winthrop-assessment-report_en-0.pdf (accessed Aug 8, 2019).

8 Pelfrene E, Harvey Allchurch M, Ntamabyaliro N, et al. The European Medicines Agency's scientific opinion on oral fexinidazole for human African trypanosomiasis. *PLoS Negl Trop Dis* 2019; **13:** e0007381.

9 Tarral A, Blesson S, Mordt OV, et al. Determination of an optimal dosing regimen for fexinidazole, a novel oral drug for the treatment of human African trypanosomiasis: first-in-human studies. *Clin Pharmacokinet* 2014; **53:** 565–80.

10 WHO. WHO interim guidelines for the treatment of gambiense human African trypanosomiasis. 2019. https://www.who.int/neglected_diseases/news/WHO-publishes-guidelines-treatment-sleeping-sickness/en/ (accessed Aug 8, 2019).

11 WHO. Handbook for guideline development, 2nd edn. Geneva: World Health Organization, 2014.

12 Huang X, Lin J, Demner-Fushman D. Evaluation of PICO as a knowledge representation for clinical questions. *AMIA Annu Symp Proc* 2006; **2006:** 359–63.

13 Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions version 5.1.0. 2011. http://handbook-5-1.cochrane.org/ (accessed Aug 8, 2019).

14 Bergman H, Probyn K, Villanueva G, et al. Evidence summary: systematic review of oral fexinidazole as first line treatment for gambiense human African trypanosomiasis. Appendix of the WHO interim guidelines for the treatment of gambiense human African trypanosomiasis. 2019. https://www.who.int/trypanosomiasis_african/resources/ISBN978-92-4-155056-7-Appendix-1.pdf?ua=1 (accessed Aug 8, 2019).

15 Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction–GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; **64:** 383–94.

16 Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol* 2011; **64:** 407–15.

17 Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; **64:** 401–06.

18 Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol* 2013; **66:** 719–25.

19 Burri C, Yeramian PD, Allen JL, et al. Efficacy, safety, and dose of pafuramidine, a new oral drug for treatment of first stage sleeping sickness, in a phase 2a clinical study and phase 2b randomized clinical studies. *PLoS Negl Trop Dis* 2016; **10:** e0004362.

20 Pohlig G, Bernhard SC, Blum J, et al. Efficacy and safety of pafuramidine versus pentamidine maleate for treatment of first stage sleeping sickness in a randomized, comparator-controlled, international phase 3 clinical trial. *PLoS Negl Trop Dis* 2016; **10:** e0004363.

21 Balasegaram M, Harris S, Checchi F, Hamel C, Karunakara U. Treatment outcomes and risk factors for relapse in patients with early-stage human African trypanosomiasis (HAT) in the Republic of the Congo. *Bull World Health Organ* 2006; **84:** 777–82.

22 Bastide S, Priotto G, Echochard R, Etard J. Effectiveness of short vs long treatment schedules with pentamidine in first-stage HAT: a large field cohort study. *Trop Med Int Health* 2011; **16:** 68–69.

23 Doua F, Yapo FB. Human trypanosomiasis in the Ivory Coast: therapy and problems. *Acta Trop* 1993; **54:** 163–68.

24 Eperon G, Schmid C, Loutan L, Chappuis F. Clinical presentation and treatment outcome of sleeping sickness in Sudanese pre-school children. *Acta Trop* 2007; **101:** 31–39.

25 Ginoux PY, Bissadidi N, Frezil JL. Complications observed in the treatment of trypanosomiasis in the Congo. *Med Trop (Mars)* 1984; **44:** 351–55.

26 Jamonneau V, Solano P, Garcia A, et al. Stage determination and therapeutic decision in human African trypanosomiasis: value of polymerase chain reaction and immunoglobulin M quantification on the cerebrospinal fluid of sleeping sickness patients in Côte d'Ivoire. *Trop Med Int Health* 2003; **8:** 589–94.

27 Mumba Ngoyi D, Lejon V, Pyana P, et al. How to shorten patient follow-up after treatment for *Trypanosoma brucei gambiense* sleeping sickness. *J Infect Dis* 2010; **201:** 453–63.

28 Ruiz JA, Simarro PP, Josenando T. Control of human African trypanosomiasis in the Quiçama focus, Angola. *Bull World Health Organ* 2002; **80:** 738–45.

29 Tongue Kohagne L, Louis F, Dologuele N. Relapse after treatment with first stage drug in human African trypanosomiasis: contribution of molecular biology. *Int J Infect Dis* 2008; **12:** e383.

30 Anne Loes van Staa AH. Injection practices in the developing world—results and recommendations from field studies in Uganda and Indonesia—EDM Research Series No 020. Geneva: World Health Organization, 1996.

31 Blum J, Schmid C, Burri C. Clinical aspects of 2541 patients with second stage human African trypanosomiasis. *Acta Trop* 2006; **97:** 55–64.

32 Kennedy PG. Clinical features, diagnosis, and treatment of human African trypanosomiasis (sleeping sickness). *Lancet Neurol* 2013; **12:** 186–94.

33 Yakasai AM, Hamza M, Dalhat MM, et al. Adherence to artemisinin-based combination therapy for the treatment of uncomplicated malaria: a systematic review and meta-analysis. *J Trop Med* 2015; **2015:** 189232.

34 Banek K, Lalani M, Staedke SG, Chandramohan D. Adherence to artemisinin-based combination therapy for the treatment of malaria: a systematic review of the evidence. *Malar J* 2014; **13:** 7.

35 Bruxvoort K, Goodman C, Kachur SP, Schellenberg D. How patients take malaria treatment: a systematic review of the literature on adherence to antimalarial drugs. *PLoS One* 2014; **9:** e84555.

36 Fuangchan A, Dhippayom T, Kongkaew C. Intervention to promote patients' adherence to antimalarial medication: a systematic review. *Am J Trop Med Hyg* 2014; **90:** 11–19.

37 WHO. 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). WHO technical report series, no 994. Geneva: World Health Organization, 2015.

38 Norris SL, Ford N. Improving the quality of WHO guidelines over the last decade: progress and challenges. *Lancet Glob Health* 2017; **5:** e855–56.

39 WHO. Human African trypanosomiasis: update of the methodological framework for clinical trials. Report of the first meeting of the development of new tools subgroup. Geneva: World Health Organization, 2014.

40 WHO. Recommendations of the informal consultation on issues for clinical product development for human African trypanosomiasis. Geneva: World Health Organization, 2007.

41 Chappuis F. Oral fexinidazole for human African trypanosomiasis. *Lancet* 2018; **391:** 100–02.

42 Mukendi D, Kalo JL, Kayembe T, et al. Where there is no brain imaging: safety and diagnostic value of lumbar puncture in patients with neurological disorders in a rural hospital of Central Africa. *J Neurol Sci* 2018; **393:** 72–79.

43 Mpanya A, Hendrickx D, Vuna M, et al. Should I get screened for sleeping sickness? A qualitative study in Kasai province, Democratic Republic of Congo. *PLoS Negl Trop Dis* 2012; **6:** e1467.

44 Mpanya A, Hendrickx D, Baloji S, et al. From health advice to taboo: community perspectives on the treatment of sleeping sickness in the Democratic Republic of Congo, a qualitative study. *PLoS Negl Trop Dis* 2015; **9:** e0003686.

45 Vincent IM, Creek D, Watson DG, et al. A molecular mechanism for eflornithine resistance in African trypanosomes. *PLoS Pathog* 2010; **6:** e1001204.

46 Wilkinson SR, Taylor MC, Horn D, Kelly JM, Cheeseman I. A mechanism for cross-resistance to nifurtimox and benznidazole in trypanosomes. *Proc Natl Acad Sci USA* 2008; **105:** 5022–27.

47 Wyllie S, Foth BJ, Kelner A, Sokolova AY, Berriman M, Fairlamb AH. Nitroheterocyclic drug resistance mechanisms in *Trypanosoma brucei*. *J Antimicrob Chemother* 2016; **71:** 625–34.

48 Kaiser M, Bray MA, Cal M, Bourdin Trunz B, Torreele E, Brun R. Antitrypanosomal activity of fexinidazole, a new oral nitroimidazole drug candidate for treatment of sleeping sickness. *Antimicrob Agents Chemother* 2011; **55:** 5602–08.