Web Annex B.
PICO questions, EtD tables, GDG recommendations

WHO Guidelines for the Treatment of Human African Trypanosomiasis

World Health Organization

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Web Annex B. PICO questions, EtD tables, GDG recommendations

- WHO guidelines for the treatment of human African trypanosomiasis, 2024 -

PICO questions and their framework

There were three PICO questions:

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

The Framework for the PICO questions was:

- **Population:** Adults and Children with rhodesiense HAT infection. Patients in first-stage versus in second-stage. Special groups (children <6 years old, pregnant and lactating women, comatose patients, etc.).
- **Intervention:** oral fexinidazole, administered once daily for 10 days, with one dosage in the first 4 days, and a lower dosage in the last 6 days, accompanied with a meal, to treat both stages of the disease. Pentamidine IM , once daily x 7 days, given when suramin is not readily available, or as an alternative when suramin is unsuitable for a given patient.
- **Comparison:** First-stage treatment with suramin IV (test dose of 4–5mg/kg on day 1, followed by five injections of 20 mg/kg every 7 days). Second-stage treatment with melarsoprol IV, 2.2 mg/kg per day for 10 days. For pentamidine, it depends on the situation: when suramin is not readily available, the comparator is "delaying the treatment"; when suramin is unsuitable for a given patient, the comparator is suramin.
- **Outcomes:** Critical for decision-making: Efficacy; Safety. Other important outcomes: Need for post-therapeutic follow-up. Need for lumbar puncture for staging. Adherence. Treatment-related adverse events leading to discontinuation of therapy. Management of adverse events. Workload of healthcare staff. Cost-effectiveness. Context of use (outpatients, hospitalized).

Evidence-to-decision tables

PICO 1 Question

Should Fexinidazole vs. Suramin be used for first stage rhodesiense HAT ?	
POPULATION:	First stage rhodesiense HAT (PICO 1)
INTERVENTION:	Fexinidazole
COMPARISON:	Suramin

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't	See also Summary of Findings in Web Annex A All evidence presented in this summary comes from stage 1 patients unless otherwise indicated and derives from one single arm trial in n=10 participants (children aged >6 and adults with stage 1 r-HAT treated with fexinidazole and 7 single arm prospective cohorts/retrospective cohorts/case series with n range	• Whether data from stage 2 (as indirect evidence) is informative for stage 1: likely yes • Patients in suramin trials might have been staged

know

between 17-152 participants in children and adults with stage 1 r-HAT treated with suramin. See also evidence report for additional evidence from case reports in people with r-HAT and indirect evidence from people with g-HAT

Outcome Overall certainty	N of studies	Impact
Overall mortality during treatment ⊕◯◯◯ Very low	Fexinidazole: • 1 single-arm trial, N = 10 children >6y and adults Suramin • 3 retrospective cohorts and 1 case series, follow- up to 5 weeks, N ranging between 17 and 152 adults and children	0% (0/10) 3-5%
Overall mortality at 12 months ⊕◯◯◯ Very low	Fexinidazole: • 1 single-arm trial, N = 10 children >6y and adults Suramin: • 3 retrospective cohorts and 1 prospective cohort with N ranging between 47 and 152 children and adults, overall mortality up to 3 years follow-up	0% (0/10) 1-19%
Death likely due to treatment ⊕◯◯◯ Very low	Fexinidazole: • 1 single-arm trial, N = 10 children >6y and adults Suramin: No studies reported on this outcome	0% (0/10)
Death likely due to rHAT ⊕◯◯◯ Very low	Fexinidazole: • 1 single-arm trial, N = 10 children >6y and adults, follow-up 12 months Suramin: • 1 retrospective cohort, N=36 adults and children, follow-up not reported	0% (0/10) 6% (2/36)
Relapse ⊕◯◯◯ Very low	Fexinidazole: • 1 single-arm trial, N = 10 children >6y and adults, follow-up 12 months Suramin: • 2 retrospective cohorts, 1 prospective cohort, N ranging between 36 and 152 adults and children, follow up >2 years or 3 years	0% (0/10) 11-34%
Treatment success/clinical cure at end of treatment ⊕◯◯◯ Very low	Fexinidazole: • 1 single-arm trial, N = 10 children >6y and adults Suramin: • 1 case series, n=19 adults	100% (10/10) 95% (18/19)
Treatment success/clinical cure at 12 months ⊕◯◯◯ Very low	Fexinidazole: • 1 single-arm trial, N = 10 children >6y and adults, follow-up 12 months Suramin: • 1 retrospective cohort reported on this outcome, N 36 adults and children ○ at 6-12 months ○ 2 years ○ >2 years	100% (10/10) 14% (5/36) 22% (8/36)

wrongly (considering suramin is not effective in stage 2); fexinidazole efficacy is not stage dependent

- Data from mouse models is supportive of the efficacy of fexinidazole in r-HAT
- Even in terms of adverse effects fexinidazole is more desirable (less AEs).
- Lumbar puncture could be avoided with fexinidazole (not required for treatment decisions), so avoiding complications of lumbar puncture.
- No injection-associated complications with oral fexinidazole

	• 2 additional retrospective cohorts, N ranging between 95 and 152 children and adults reported on this outcome at 3 years follow up	39% (14/36) 65-68%	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	See also Summary of Findings in Web Annex A	Vomiting and nausea can be significant with fexinidazole

Outcome Overall certainty	N of studies	Impact
Serious adverse events at 12 months ⊕◯◯◯ Very low	Fexinidazole: • 1 single-arm trial, N =10 children >6y and adults Suramin: No studies reported on this outcome	0% (0/10)
Adverse events at 12 months ⊕◯◯◯ Very low	Fexinidazole: • 1 single-arm trial, N = 45 children >6y and adults with stage 1 and 2 r-HAT Suramin: • 1 prospective cohort, N=95, adults and children: 11% experienced rigour and chills, 2% experienced rash and urticaria • 1 case series, n=19 adults 5% experienced myocarditis	53% (24/45)

Suramin has major complications such as anaphylaxis, and CNS side effects

50% small/50% trivial

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence from included studies on fexinidazole and suramin across all outcomes was judged as very low certainty, only non-comparative observational studies were included.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know		Perspective: from the point of view of the patients, their families, hospital Resources needed: • cost of the medication (at this point, both drugs are available for free through donation) • cost of food (particularly with fexinidazole); there is also the cost of food for the companions • staff (12 days hospitalization with fexinidazole; 2-3 days for suramin); duration of hospitalization will depend on the severity of the illness • staff must invest time for the directly observed treatment • cost and effort for training staff Cost for patient vs. hospital perspective • fexinidazole: might be less costly for the patient, more costly for the hospital; Suramin: might be the opposite • varies across context and across patients within the same context

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies		

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know		Favors fexinidazole: fewer and less severe side effects (and can be handled at the primary care level) and no injections; might improve availability at lower level hospitals. Does not favor fexinidazole: less information on special groups (pediatrics, pregnancy, lactating women, comorbidities); excludes those below 6 years, and below 20 kg. However, their proportion among r-HAT patients is low.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Fexinidazole is more likely to be acceptable given it is orally administered Lumbar puncture could be avoided with fexinidazole (more acceptable to patients and clinicians)

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Summary of judgements

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know

	JUDGEMENT						
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation

WHO suggests fexinidazole over suramin for first stage rhodesiense HAT (conditional recommendation based on very low certainty evidence)

Remarks:

Suramin may be the preferred option if
- there is a contraindication for fexinidazole according to the manufacturer's instructions;
- the patient is in a critical condition and oral absorption of fexinidazole may be questionable; and
- the patient is unable to swallow. Whether fexinidazole tablets can be crushed is currently the subject of investigation and cannot be recommended at present.

With fexinidazole treatment, lumbar puncture (LP) and CSF microscopy can be avoided in most patients.
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 choice of treatment (suramin vs. melarsoprol).

Subgroup considerations

Pregnant women:

In view of the acute presentation and rapid clinical evolution of r-HAT, treatment usually cannot not be delayed until after delivery. Recommendations for anti-trypanosomal treatment during pregnancy and lactation are based on clinical practice rather than on solid evidence. Fexinidazole and pentamidine can be given after the first trimester. Suramin and melarsoprol are theoretically contraindicated, but their use may become necessary as rescue treatment. 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.

Implementation considerations

Implementation considerations when prescribing fexinidazole

- 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 that the patient has access to food, which must be eaten directly before the drug administration each day.
- Directly observed treatment: Each intake of fexinidazole must be supervised by a trained health worker who must ensure that the patient is in a fed condition.
- Hospitalization is preferred and should be mandatory in the following cases:
    - patients with neuropsychiatric disorders (considering both the risk of neuropsychiatric adverse effects of fexinidazole and the risk of poor compliance with treatment);
    - patients with history of alcohol use disorder (considering both the risk of the antabuse (disulfiram) effect (shared with other nitroimidazoles like fexinidazole) and the risk of poor compliance)
    - children and patients with body weight < 35 kg; risk of poor compliance with treatment.
    - consider early admission if vomiting occurs following administration of fexinidazole
- In exceptional circumstances, outpatient administration (under daily supervision) may be considered in the course of the treatment in consultation with the patient, his/her family and clinicians, taking into account the following factors:
    - the clinical condition;
    - existing comorbidities;
    - convenience to the patient and the family (e.g. distance and costs);
    - development of side-effects interfering with treatment compliance; and
    - capacity of the healthcare system for supervised administration as an outpatient.
- Patients should be asked to attend for general examination in the hospital where they were treated at least at the end of treatment (day 10), and at 1 and 3 months post-treatment. At 6 and 12 months post-treatment, a check-up is required. However, this can be done by the treating clinician by phone or other electronic communication, by a trained health professional, or by a health community worker, whichever is most suitable. A patient should return to the hospital at any time if symptoms reappear. If signs or symptoms suggest a possibility of relapse, laboratory examinations of body fluids, including CSF, should be performed in order to detect trypanosomes and/or CSF leukocytosis.

Monitoring and evaluation

Safety and efficacy monitoring for fexinidazole use is recommended (intensive pharmacovigilance), whereby the experience with fexinidazole PV in gambiense HAT can be built upon.

PICO 2 Question

Should Fexinidazole vs. Melarsoprol be used for second stage rhodesiense HAT?	
POPULATION:	Second stage rhodesiense HAT (PICO 2)
INTERVENTION:	Fexinidazole
COMPARISON:	Melarsoprol

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	All evidence presented in this summary is from people with second stage r-HAT (unless indicated otherwise). See full Summary of Findings in Web Annex A. See also evidence report for additional evidence from case reports in people with r-HAT and indirect evidence from people with g-HAT in Web Annex A, , Appendix 6.	• Question whether there is less chance of developing resistance with fexinidazole? possible but not proven • Data from mouse models is supportive of the efficacy of fexinidazole in r-HAT • In terms of adverse effects fexinidazole is more desirable (less AEs). • No injection-associated complications with oral fexinidazole • Potential of reduced efficacy in advanced disease • Patients who are severely ill might not be candidates for fexinidazole

Outcome Overall certainty	N of studies	Impact
Overall mortality during treatment ⊕◯◯◯ Very low	Fexinidazole: • 1 single-arm trial, N = 35 children >6y and adults Melarsoprol: • 1 prospective cohort study, N = 107 children and adults • 1 retrospective cohort, N = 156 children and adults	3% (1/35) 8% (9/107) 9/156 (6%)
Overall mortality at 12 months ⊕◯◯◯ Very low	Fexinidazole • 1 single-arm trial, N = 35 children >6y and adults Melarsoprol • 1 prospective cohort study, N = 107 children and adults • 1 case series, N = 33 patients with stage 2 r-HAT	3% (1/35) 11% (12/107) 9% (3/33)
Death due to treatment at up to 16 months ⊕◯◯◯ Very low	Fexinidazole • 1 single-arm trial, 12 months FU, N = 35 children >6y and adults Melarsoprol • 1 prospective cohort, 10 days FU, N = 107 children and adults • 3 additional non-randomised studies, follow-up to 16 months, N ranging between 130 and 183 patients	0% (0/35) 7% (8/107) 3-8%
Death due to r-HAT at up to 4 years ⊕◯◯◯ Very low	Fexinidazole, • 1 single-arm trial, 12 months FU, N = 35 children >6y and adults Melarsoprol • 1 prospective cohort, 10 days FU, N = 107 children and adults • 2 non-randomised studies, follow-up range up to 4 years, N ranging between 136 and 272	0% (0/35) 1% (1/107) 3-10%
Relapse at 12 months ⊕◯◯◯ Very low	Fexinidazole: • 1 single-arm trial, N = 35 children >6y and adults Melarsoprol: 2 studies	3% (1/34)

	• 1 prospective cohort, n=107 , children and adults • 1 additional case series, n=33, age not reported	1% (1/107) 18% (6/33)
Treatment success/clinical cure at end of treatment ⊕◯◯◯ Very low	Fexinidazole: • 1 single-arm trial, N = 35 children >6y and adults Melarsoprol: • 1 prospective cohort, N = 107 children and adults	97% (34/35) 92% (98/107)
Treatment success/clinical cure at 12 months ⊕◯◯◯ Very low	Fexinidazole: • 1 single-arm trial, N = 35 children >6y and adults Melarsoprol: • 1 prospective cohort, N = 107 children and adults • 1 retrospective cohort, age not reported	94% (33/35) 88% (94/107) 13% (36/272)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	All evidence presented in this summary is from people with second stage rHAT (unless indicated otherwise). See full Summary of Findings in Web Annex A, See also evidence report for additional evidence from case reports in people with rHAT and indirect evidence from people with g-HAT in Web Annex A, Appendix 6.	Vomiting and nausea can be significant with fexinidazole CNS effects of fexinidazole, including (by decreasing frequency) insomnia, agitation, anxiety, psychotic disorder, abnormal behaviour, depression, logorrhoea, nightmare, personality change, and suicidal ideation.

Outcome Overall certainty	N of studies	Impact
Serious adverse events at 12 months ⊕◯◯◯ Very low	Fexinidazole: • 1 single-arm trial, N = 35 children >6y and adults Melarsoprol • 1 prospective cohort, N = 107 children and adults	9% (3/35) 25% (27/107)
Adverse events at 12 months ⊕◯◯◯ Very low	Fexinidazole: • 1 single-arm trial, N= 45 children >6y and adults, stage 1 and 2 r-HAT, follow-up: 12 months Melarsoprol • 1 prospective cohort, N=107 children and adults (7% experienced encephalopathic syndrome during treatment) • 1 case series reported ~6% encephalopathy cases (n=383)	53% (24/45) 65.5%

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence from included studies on fexinidazole and melarsoprol across all outcomes was judged as very low certainty, only non-comparative observational studies were included.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know		Perspective: from the point of view of the patients, their families, and hospital Resources needed: • cost of the medication (at this point, both drugs are available for free through donation) • cost of food (particularly with fexinidazole); there is also the cost of food for the companions • staff (12 days for hospitalization with fexinidazole; 10-12 days for melarsoprol); duration of hospitalization will depend on the severity of the illness • staff must invest time for the directly observed treatment • cost and effort for training staff • fexinidazole: is less costly for the patient, less costly for the hospital • part of the increased cost with melarsoprol is related to the associated side effects • varies across context and across patients within the same context

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No included studies	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know		Favors fexinidazole: fewer and less severe side effects (and can be handled at the primary care level) and no injections; might improve availability at lower level hospitals. Does not favor fexinidazole: less information on special groups (pediatrics, pregnancy, lactating women, commodities); excludes group of those who are below 6 years and below 20 kg. However, the proportion among r-HAT patients is low. Very severe cases may not be candidates for fexinidazole

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Fexinidazole is more acceptable in certain settings given the apprehension around lumbar puncture (LP) LP could be avoided with fexinidazole (more acceptable to patients and clinicians) Fexinidazole is more likely to be acceptable given it is orally administered

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Summary of judgements

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation

WHO suggests Fexinidazole over Melarsoprol for second stage rhodesiense HAT (conditional recommendation based on very low certainty evidence)

Remarks:

Melarsoprol may be the preferred option when the patient:

- has a contraindication to fexinidazole;
- is unable to swallow;
- has persistent vomiting despite antiemetic therapy;
- is in a critical condition and oral absorption of fexinidazole may be questionable.

In patients with r-HAT who receive fexinidazole, LP is usually not required.

If fexinidazole is not used, LP is still required for disease staging and treatment decisions (suramin vs. melarsoprol) A lumbar puncture can be considered for diagnostic reasons when the presence of trypanosomes has not been confirmed in other body fluids while there is high r-HAT suspicion.

Subgroup considerations

Pregnant women: Same as in PICO 1

Implementation considerations

Same as in PICO 1

Monitoring and evaluation

Safety and efficacy monitoring for fexinidazole use is recommended (intensive pharmacovigilance), whereby the experience with fexinidazole PV in gambiense HAT can be built upon.

PICO 3 Question

Should immediate interim treatment with pentamidine be used over delayed treatment with other recommended agents for rhodesiense HAT in settings where those other recommended agents are not readily available ?	
POPULATION:	rhodesiense HAT in settings where recommended agents are not readily available (PICO 3)
INTERVENTION:	immediate interim treatment with pentamidine
COMPARISON:	delayed treatment with other recommended agents

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	All evidence presented in this summary is from people with first stage r-HAT receiving pentamidine monotherapy. See full Summary of Findings in Web Annex A. See also evidence report for additional evidence from case reports in people with r-HAT and indirect evidence from people with g-HAT in Web Annex A, Appendix 6.	Timeliness of treatment reduce progression of illness Extent of desirable effects might depend on the clinical condition at presentation

Outcome **Overall certainty**	**N of studies**	**Impact**
Overall mortality at 2 years ⊕◯◯◯ Very low	1 retrospective cohort study, N = 46	7/46 (15%)

Death likely due to r-HAT, follow-up not reported ⊕◯◯◯ Very low	1 retrospective cohort study, N = 46	2/46 (4%)
Death likely due to the treatment	Not reported	
Relapse at 2 years ⊕◯◯◯ Very low	1 retrospective cohort study, N = 46	4/46 (9%)
Treatment success • follow-up: 6 to 12 mo.	1 retrospective cohort study, N = 46	7/46 (15%)
• follow-up: 2 years	1 retrospective cohort study, N = 46	15/46 (33%)
• follow-up: >2 years ⊕◯◯◯ Very low	1 retrospective cohort study, N = 46	21/46 (46%)
Serious adverse events	Not reported	
Adverse events	Not reported	
Adherence to treatment	Not reported	
Withdrawals	Not reported	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know		Adverse effects of pentamidine

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The evidence from included studies on pentamidine across all outcomes was judged as very low certainty, only one non-comparative observational study was included.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or		

variability ○ No important uncertainty or variability		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		

Resources required

How large are the resource requirements (costs)?"

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		Perspective: from the point of view of the patients, their families, the hospital. Hospital has to procure pentamidine; pentamidine may not be easily available; procurement might be expensive Delayed treatment: longer hospital stay Varies by setting

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No included studies	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know		Concern about the need to procure; concern about the availability of pentamidine

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		Key stakeholders: patients, caregivers, clinicians Concern that it might not be acceptable to stock pentamidine

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		concerns: availability of pentamidine

Summary of judgements

	JUDGEMENT						
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		**Varies**	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

Conclusions

Recommendation

WHO suggests immediate interim treatment with pentamidine over delayed treatment with other recommended agents for rhodesiense HAT in settings where those other recommended agents are not readily available (conditional recommendation, based on very low certainty evidence)

Remarks:

- treatment should be switched to the recommended agent as soon as it becomes available
- key issue: availability of pentamidine