Nifurtimox-Eflornithine Combination Therapy for Second-Stage *Trypanosoma brucei gambiense* Sleeping Sickness: A Randomized Clinical Trial in Congo

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(See the editorial commentary by Chappuis on pages 1443–5)

Background. Human African trypanosomiasis caused by *Trypanosoma brucei gambiense* is a fatal disease. Current treatment options for patients with second-stage disease are either highly toxic or impracticable in field conditions. We compared the efficacy and safety of the nifurtimox-eflornithine drug combination with the standard eflornithine regimen for the treatment of second-stage disease.

Methods. A randomized, open-label, active-control, phase III clinical trial comparing 2 arms was conducted at the Sleeping Sickness Treatment Center, which was run by Médecins Sans Frontières, in Nkayi, Bouenza Province, Republic of Congo. Patients were screened for inclusion and randomly assigned to receive eflornithine alone (400 mg/kg per day given intravenously every 6 h for 14 days) or eflornithine (400 mg/kg per day given intravenously every 12 h for 7 days) plus nifurtimox (15 mg/kg per day given orally every 8 h for 10 days). Patients were observed for 18 months. The study's outcomes were cure and adverse events attributable to treatment.

Results. A total of 103 patients with second-stage disease were enrolled. Cure rates were 94.1% for the eflornithine group and 96.2% for the nifurtimox-eflornithine group. Drug reactions were frequent in both arms, and severe reactions affected 25.5% of patients in the eflornithine group and 9.6% of those in the nifurtimox-eflornithine group, resulting in 2 and 1 treatment suspensions, respectively. There was 1 death in the eflornithine arm and no deaths in the nifurtimox-eflornithine arm.

Conclusions. The nifurtimox-eflornithine combination appears to be a promising first-line therapy for second-stage sleeping sickness. If our findings are corroborated by ongoing findings from additional sites (a multicenter extension of this study), the new nifurtimox-eflornithine combination therapy will mark a major and multifaceted advance over current therapies.

Human African trypanosomiasis (HAT), or sleeping sickness, remains a public health challenge in sub-Saharan Africa, with an estimated 50,000–70,000 new cases per year, of which ~20,000 are detected and reported [1]. The disease is caused by the protozoan parasite *Trypanosoma brucei gambiense,* which is transmitted by the tsetse fly (*Glossina* species), and it progresses from the hemolymphatic first stage to the meningoencephalitic second stage. It is invariably fatal without appropriate treatment. Since 1949, melarsoprol is the most commonly used treatment for second-stage HAT. This arsenical derivative is associated with severe toxic effects—in particular, reactive encephalopathy, which is fatal in 10%–70% of cases and affects 5%–10% of treated patients [2, 3]. Moreover, increasing melarsoprol failure rates (up to 30%) have been reported in several countries [4–6].

Eflornithine (diethylfluoromethylornitihine), the only new drug registered in 58 years for the treatment of second-stage HAT, is a trypanostatic that inhibits ornithine decarboxylase, an enzyme essential for cell multiplication and differentiation [7–9]. It is better tolerated than melarsoprol, and its toxic effects—mainly seizures, gastrointestinal disorders, and myelosuppression—are reversible if well managed. Its efficacy is comparable to that of melarsoprol. However, a major disadvantage of eflornithine is the mode of administration, requiring 1 slow infusion every 6 h for 14 days (56 infusions in total), a regimen imposed by its short half-life of 1.5–5 h [10, 11]. The difficulty in administering eflornithine in resource-poor settings explains why melarsoprol continues to be the first-line treatment.

Nifurtimox is an orally administered drug used in the treatment of Chagas disease (American trypanosomiasis) at dosages of 8–20 mg/kg per day for 90–120 days. Although it has not been approved for treatment of HAT, nifurtimox is used for

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compassionate treatment of relapsed disease. Its toxicity, which has been poorly documented, includes mainly neurological (headache, sleep disorders, agitation, and confusion) and gastrointestinal (anorexia, nausea/vomiting, and dyspepsia) dysfunctions [12, 13], some of which increase with the duration of intake [14, 15]. In the 1970s and 1980s, nifurtimox was tested empirically in several HAT case series, and the results were conflicting [14–17]. These studies, which applied different treatment regimens and evaluation criteria, are difficult to compare.

Drug combinations can potentially avert or delay the emergence of drug-resistant organisms. Dosage reductions of each drug combined may reduce the overall toxicity while maintaining good efficacy. Combinations may also allow for a simpler administration of treatment, improving the feasibility of therapy in remote areas with logistic and staffing limitations.

A first attempt to assess various combinations for the treatment of second-stage HAT in Uganda was interrupted because of excess fatality in the melarsoprol-nifurtimox arm. Although the results were inconclusive, the trial showed promising safety and efficacy results with the nifurtimox-eflornithine combination [18]. Assessment of this combination was therefore extended to a case study of 31 patients that yielded similar results [19].

In 2003, Médecins Sans Frontières and Epicentre, in collaboration with the Ministry of Health, initiated a randomized, open-label clinical trial in Nkayi, Republic of Congo, to evaluate the efficacy and toxicity of the nifurtimox-eflornithine combination with doses equal to those in the 2 previous studies, with additional simplification of the administration schedule. In 2005, the study was extended to the Democratic Republic of Congo and Uganda, in partnership with the Drugs for Neglected Diseases initiative, the World Health Organization Special Program for Training and Research in Tropical Diseases, the Swiss Tropical Institute, and national HAT programs.

METHODS

To facilitate external comparability, the study methodology was similar to the methodologies in previous clinical trials involving second-stage HAT [18–22].

Participants. Study participants were identified among persons with cases diagnosed at the treatment center or during active screening. Inclusion criteria were as follows: confirmed second-stage infection, with trypanosomes detected in specimens of blood, lymph, or CSF, with >20 leukocytes/μL in CSF specimens. Exclusion criteria were as follows: age, <15 years; pregnancy; history of second-stage HAT treated during the preceding 36 months; severe comorbidities likely to lead to early death during the follow-up period; hemoglobin concentration, <5 g/dL; or inability to complete 18 months of follow-up for other reasons.

Three ethics committees approved the study protocol and protocol amendments: (1) the Médecins Sans Frontières Ethical Review Board, (2) Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale (Saint-Germain-en-Laye, France), and (3) the World Health Organization Research Ethics Review Committee (Geneva, Switzerland). The Congolese Ministry of Health issued authorization. All participants provided written informed consent.

A data safety monitoring board consisting of 4 independent experts was formed before study initiation. The data safety monitoring board received regular reports and issued recommendations for the study continuation.

Interventions. Participants were randomized into 1 of 2 arms: the eflornithine arm or the nifurtimox-eflornithine arm. A scientific committee established the dosages on the basis of published and unpublished evidence. The investigational arm received eflornithine (400 mg/kg per day given intravenously every 12 h for 7 days) plus nifurtimox (15 mg/kg per day given in oral tablets every 8 h for 10 days), and the active comparator arm received eflornithine (400 mg/kg per day given intravenously every 6 h for 14 days). Eflornithine was infused over a 2-h period and was diluted in 250 mL of normal saline. Nifurtimox doses were repeated if vomiting occurred within 30 min. All doses were directly administered and observed by the medical staff. Before commencement of treatment, all patients with malaria (as determined by microscopic evaluation and rapid diagnostic testing) received arthemeter-lumefantrine for 3 days; study treatment was started at least 1.5 days after the last dose of antimalarial therapy. The administration of drugs for all other concomitant conditions was postponed until the end of the hospitalization, unless the clinical need warranted immediate treatment. Patients and attendants received a food ration of at least 2100 kcal/day each.

All patients were examined daily and hospitalized for 7 days after the end of treatment (or longer, if deemed necessary). A lumbar puncture was performed on the day after the patient received his or her last dose, and CSF specimens were examined for trypanosomes. Laboratory studies, including lumbar puncture examinations and examinations of blood and lymph specimens, were performed at 3, 6, 12, and 18 months. At each follow-up visit, the CSF specimen was examined for parasites after double-centrifugation, a parallel CSF leukocyte count was determined, and IgM titers in CSF were determined using the Latex/IgM reagent (Institut de Médecine Tropicale) [23], which aimed at increasing the sensitivity of detection of relapses. Blood samples were examined by capillary tube centrifugation and quantitative buffy coat [24]. Lymph was aspirated from any palpable posterior cervical lymph node.

The study follow-up period was set at 18 months, as recommended by the Informal Consultation on the Conduct of Clinical Trials in HAT (World Health Organization, 2004) on

the basis of data that suggested that 70%–90% of relapses occur ≤18 months after the completion of treatment. Although the study end point was determined at 18 months, the national protocol required a last follow-up visit at 24 months for all patients.

The definition of relapse is not currently standardized. Relapse was diagnosed if trypanosomes were seen in body fluid specimens or if CSF leukocyte counts increased twice consecutively by at least 20 cells/μL any time after the completion of treatment. Patients who presented with a single increase were reexamined 1 month later. At the month 18 examination, relapse was diagnosed if the CSF leukocyte count was ≥20 cells/μL, regardless of previous counts. Distinction between relapse and reinfection was not made. The probability of reinfection was considered to be minimal, because disease transmission had been substantially reduced after 3 years of intensive disease-control activities by Médecins Sans Frontières.

Safety was assessed with the international Common Toxicity Criteria [25], which grade adverse events by intensity from 1 to 4 (for mild, moderate, severe, and very severe, respectively), drug-event relationship (unrelated, unlikely, possible, probable, and definite), and outcome (complete recovery, still present, sequelae, and death). All patients had a blood sample taken before and after treatment; the sample was examined for hemoglobin concentration, total and differential leukocyte counts, total bilirubin level, creatinine level, and alanine aminotransferase level.

Anemia was defined as a hemoglobin concentration <13 g/dL for male patients and <11 g/dL for female patients that had decreased by >20%. Leukopenia was defined as a leukocyte count <4000 cells/μL that had decreased by >30%. Neutropenia as a neutrophil count <2000 cells/μL that had decreased by >30%.

Alanine aminotransferase, bilirubin, and creatinine levels were measured by a colorimetric method (Randox) in a subgroup of patients. The reagents for alanine aminotransferase were different (Human) for the last 39 patients because of logistical constraints. Abnormal values were defined as follows: bilirubin, >17 μmol/L, with a >1.5-fold increase; alanine aminotransferase, >12 IU/L (as determined for 43 patients using the Randox reagents) or >32 IU/L (for female subjects) and >42 IU/L (for male subjects, as determined for 39 patients using the Human reagents), with a >2.5-fold increase; and creatinine, >80 μmol/L (for female subjects) and >97 μmol/L (for male subjects), with a >1.5-fold increase.

Pharmacokinetic analysis of plasma and CSF drug concentrations was performed in an ancillary study related to the clinical trial. The methodology and results will be reported elsewhere.

Outcomes. The primary outcome was cure. The following end points were regarded as therapeutic failures: (1) death in temporal relation to treatment (i.e., ≤30 days after the commencement of treatment), and (2) relapse of HAT or death compatible with HAT within the 18 months of follow-up. Deaths due to disease without clearly established alternative causality were regarded as compatible with HAT. Secondary outcomes were the adverse events in temporal relation to treatment, particularly the major adverse events graded as severe (grade 3) and very severe (grade 4).

Sample size. The sample size to test noninferiority in cure rates for the complete multicenter study was set at 280 subjects. This report analyzes the data of the 103 patients enrolled in Nkayi.

The randomization list (in blocks of 10) was electronically generated. The list and the block size were concealed from the field team. Participants were enrolled in the same order in which they received diagnoses. Sealed and numbered opaque envelopes containing the treatment allocation were opened in strict numeric sequence. Blinding was unfeasible owing to the different drug administration modes.

Data management. Data were collected in purposely designed patient charts. Trial-specific data were extracted onto case report forms. These data were double-entered electronically with EpiData, version 3.0 (The EpiData Association), and were analyzed with Stata, version 9.0 (Stata). No statistical comparisons were performed, because interim analysis would alter the statistical power of the overall trial.

RESULTS

Participants. Of 630 patients who had HAT diagnosed during the trial period, 261 had cases that were in the second stage, of whom 103 met the entry criteria and were enrolled in the study (figure 1). The main reasons for ineligibility were relapsed status, young age, and/or low CSF leukocytes count. All enrolled patients were treated: 51 were treated with eflornithine, and 52 were treated with nifurtimox-eflornithine.

Enrollment started in August 2003 and was closed in December 2004 as a result of a decrease in the disease prevalence in the area, resulting in a low enrollment rate. Patient characteristics were similar in the 2 groups (table 1). Four patients (2 in each arm) had CSF leukocyte counts of 5–20 cells/μL and were wrongly enrolled. Because these 4 patients had trypanosomes in the CSF, they were kept in the study. All patients received complete treatment in accordance with the protocol.

Outcomes and estimation. One patient died in temporal relation to the treatment regimen and was considered to have experienced treatment failure. The large majority of patients (98 [95.1%] of 103) completed the 18-month follow-up period or reached the study end point earlier, and the rest (5 [4.9%]) underwent partial follow-up. Of the 5 patients who underwent partial follow-up, all had demonstrated decreasing CSF leukocyte counts and IgM titers at their last follow-up visit. One

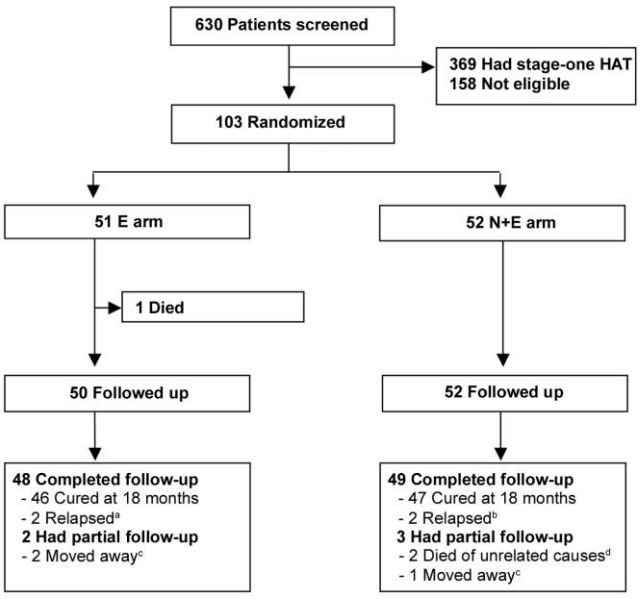

Figure 1. Trial profile. E, eflornithine; HAT, human African trypanosomiasis; N+E, nifurtimox-eflornithine. [a]Relapses were detected at 12 months in one patient and 18 months in the other. [b]Relapses were detected both at 18 months. [c]Condition was controlled at 12 months, with favorable evolution; patient moved away later. [d]One patient had controlled disease at 3 and 6 months, with favorable evolution; the patient later died of cerebral malaria. The other patient had controlled disease at 3, 6, and 12 months, with favorable evolution; the patient later died of ovarian cancer.

died of cerebral malaria (last follow-up visit was at month 6), another died after ovarian cancer surgery (last follow-up visit was at month 12), and 3 moved away after the month 12 follow-up visits. There were 4 relapses in total (2 per arm). All 4 patients who experienced relapse had increasing CSF leukocyte counts without detected trypanosomes; 1 patient had relapse at 12 months, and 3 had relapse at 18 months. Cure rates were 94.1% (48 of 51 patients) in the eflornithine arm and 96.2% (50 of 52) in the nifurtimox-eflornithine arm. If patients with partial follow-up are excluded from analysis, the cure rates are 93.3% (46 of 49 patients) in the eflornithine arm and 95.9% (45 of 49) in the nifurtimox-eflornithine arm.

Paired before-after treatment CSF IgM titers were available for 88 patients. Blood contamination of CSF (6% of specimens) and other constraints (1% of specimens) explain the missing measurements. Lumbar puncture was performed 12 h after the last dose of eflornithine and revealed that the titers decreased in 40 (46%) of 88 patients, stayed unchanged in 38 patients (43%), and increased in 10 patients (11%). The evolution of the IgM titer values during follow-up ($n = 102$) showed a consistent decrease over time. Only in patients who experienced relapse did increases in IgM titers accompany increases in CSF leukocyte counts.

Drug reactions. Only 1 patient, who was in the eflornithine group, died within 30 days after the start of treatment; this death was attributed to septic shock following severe neutropenia. Of a total of 261 adverse events, 14 were classified as unrelated to treatment, and 247 were regarded as drug reactions (table 2). Noteworthy differences in overall toxicity included fever, hypertension, and diarrhea, all of which were less common in the nifurtimox-eflornithine arm. On the other hand, the combination more frequently provoked nausea and vomiting, which tended to appear $\geqslant$1 h after the simultaneous administration of both drugs (for the first daily dose) and less frequently when the drugs were administered at different times.

There were 14 major drug reactions (i.e., those of grades 3 and 4) in the eflornithine arm and 6 such reactions in the nifurtimox-eflornithine arm, and the proportions of patients who experienced major reactions were 25.5% and 9.6% per arm, respectively (table 2). Treatment was suspended because of severe complications for 2 patients in the eflornithine arm and 1 patient in the nifurtimox-eflornithine arm. These interruptions were made as a result of seizures (1 patient in each arm) and arrhythmia (1 in the eflornithine arm). The 6 major adverse events observed in the nifurtimox-eflornithine arm were seizures (4 patients), fever (1 patient), and neutropenia (1 patient), all of which resolved favorably.

Before-and-after treatment hematologic data were available for all patients. Neutropenia and anemia were the most common biological adverse events, appearing 3 times more frequently in the eflornithine arm. Grade 3 neutropenia (i.e., a neutrophil count <1000 cells/μL) developed in 6 patients in the eflornithine arm, compared with only 1 patient in the nifurtimox-eflornithine arm. Abnormal biochemical values were rare and mild.

DISCUSSION

The results obtained with the nifurtimox-eflornithine combination are similar to those obtained with standard eflornithine treatment, even showing a trend of superiority in the safety parameters. These data confirm the observations made in our earlier studies from Uganda [18, 19]. With nearly complete follow-up data for patients (100% reviewed at least 2 times and 95% with complete follow-up), the high cure rates are reassuring.

The fact that 3 of the 4 relapses were detected at the month 18 visit, having been controlled at 12 months, suggests that the follow-up in clinical studies should be no shorter than 18 months. The lower occurrence of major drug reactions in the nifurtimox-eflornithine arm suggests a better safety profile of the combination.

Neutropenia occurred more frequently among recipients of eflornithine alone than among recipients of combination treat-

Table 1. Baseline characteristics of trial participants, by treatment arm.

Characteristic	Eflornithine arm (n = 51)	Nifurtimox-eflornithine arm (n = 52)
Demographic characteristics		
Female sex	23 (45.1)	26 (50.0)
Age, mean years (range)	36.1 (15–70)	33.1 (15–69)
Weight, mean kg ± SD	53.1 ± 7.2	51.7 ± 7.4
Mean body mass index[a] ± SD	19.7 ± 2.2	19.1 ± 2.0
Body mass index[a] <18.5	15 (29.4)	22 (42.3)
Parasitologic findings		
Case detected by active screening	29 (56.9)	31 (59.6)
Presence of trypanosomes		
In lymph nodes	40 (78.4)	36 (69.2)
In blood	47 (92.2)	42 (80.8)
In CSF	37 (72.6)	30 (57.7)
Leukocyte count in CSF		
5–20 cells/μL	2 (3.9)	2 (3.9)
21–99 cells/μL	10 (19.6)	19 (36.5)
⩾100 cells/μL	39 (76.5)	31 (59.6)
IgM titer in CSF >1:128 [b]	28 (57.1)	20 (40.8)
Clinical characteristics		
Mean Karnofsky score ± SD	84.6 ± 9.6	80.9 ± 15.9
Mean Glasgow coma score ± SD	15.0 ± 0.1	14.8 ± 0.8
Hemoglobin concentration, mean g/dL ± SD	12.7 ± 1.9	13.0 ± 1.8
Presence of malaria parasites	14 (27.5)	11 (21.2)
Lymphadenopathy	40 (78.4)	36 (69.2)
Hepatomegaly	2 (3.9)	5 (9.6)
Splenomegaly	14 (27.5)	11 (21.2)
Headache	35 (68.6)	38 (73.1)
Fever[c]	13 (25.5)	2 (3.8)
Pruritus	33 (64.7)	33 (63.5)
Daytime somnolence	35 (68.6)	32 (61.5)
Insomnia	18 (35.3)	16 (30.8)
History of seizures	5 (9.8)	4 (7.7)
Psychiatric signs	25 (49.0)	21 (40.4)
Speech disorder	8 (15.7)	9 (17.3)
Impotence or amenorrhea	15 (29.4)	19 (36.5)
Tremors	20 (39.2)	18 (34.6)
Anorexia	6 (11.8)	12 (23.1)
Duration of symptoms, mean months (range)	9.8 (1–72)	8.7 (0–24)

NOTE. Data are no. (%) of patients, with the percentages indicating proportion of the entire cohort, unless otherwise indicated.

[a] Body mass index was calculated as weight in kilograms divided by the square of height in meters. A body mass index <18.5 was considered to indicate thinness.

[b] IgM titer data were available for 98 patients (49 in the eflornithine arm and 49 in the nifurtimox-eflornithine arm).

[c] Temperature, ⩾37.5°C, axillary.

ment, which contains half as much eflornithine. Patients with grade 3 neutropenia are vulnerable to bacterial infection, which explains the frequent infectious complications emerging during or after treatment, as well as the only death in our cohort. The combination clearly offers improved safety over melarsoprol, which causes reactive encephalopathy in 5%–10% of recipients, with a high fatality rate. There were no clinical data to support theoretical concerns about toxicity related to drug interactions with the combination therapy.

Nkayi presented unusual advantages in comparison to most

Table 2. Clinical and biological drug reactions during hospitalization.

	No. (%) of events			
	Eflornithine arm (n = 51)		Nifurtimox-eflornithine arm (n = 52)	
Event	All	Major	All	Major
Treatment-related death	1 (2.0)	…	0 (0.0)	…
Neurologic reactions				
Seizures	2 (3.9)	2	4 (7.7)	4
Confusion	0 (0.0)	…	1 (1.9)	…
Anxiety and/or agitation	4 (7.8)	…	2 (3.8)	…
Dizziness	1 (2.0)	…	1 (1.9)	…
Insomnia	1 (2.0)	…	2 (3.8)	…
Gastrointestinal reactions				
Anorexia	0 (0.0)	…	1 (1.9)	…
Abdominal pain	11 (21.6)	…	10 (19.2)	…
Diarrhea	4 (7.8)	…	0 (0.0)	…
Constipation	0 (0.0)	…	2 (3.8)	…
Nausea and/or vomiting	8 (15.7)	…	26 (50.0)	…
Cardiovascular reactions				
Arrythmia	3 (5.9)	…	1 (1.9)	…
Hypertension	8 (15.7)	1	1 (1.9)	…
Edema	4 (7.8)	…	0 (0.0)	…
Infection				
Tissue infection	1 (2.0)	…	1 (1.9)	…
Septic shock (neutropenic)	1 (2.0)	1	0 (0.0)	…
Other infection	2 (3.9)	1	3 (5.8)	…
Other clinical events				
Fever[a]	13 (25.5)	2	5 (9.6)	1
Headache	15 (29.4)	…	13 (25.0)	…
Cough	3 (5.9)	…	0 (0.0)	…
Pruritus	7 (13.7)	…	3 (5.8)	…
Skin rash	3 (5.9)	…	0 (0.0)	…
Chest pain	3 (5.9)	…	0 (0.0)	…
Myalgia and/or arthralgia	3 (5.9)	…	3 (5.8)	…
Other	2 (3.9)	…	4 (7.7)	…
Biological reactions				
Anemia	11 (21.6)	1	4 (7.7)	0
Leukopenia	1 (2.0)	0	2 (3.8)	0
Neutropenia	29 (56.9)	6	11 (21.2)	1
Abnormal bilirubin level[b]	1 (2.0)	…	2 (3.8)	…
Abnormal alanine aminotransferase level[c]	0 (0.0)	…	0 (0.0)	…
Abnormal creatinine level[c]	0 (0.0)	…	1 (1.9)	…
Weight loss ⩾5%	0 (0.0)	…	3 (5.8)	…
Total no. of events[d]	141	14	106	6
No. (%) of patients who experienced major events	…	13 (25.5)	…	5 (9.6)
Treatment interruption	2 (3.9)	…	1 (1.9)	…
Treatment suspension	2 (3.9)	…	1 (1.9)	…
Treatment termination	0 (0.0)	…	0 (0.0)	…

NOTE. Percentages indicate the proportion of the entire cohort. "Major" indicates an event of grade 3 or 4 using the National Cancer Institute Common Toxicity Criteria [25].

[a] Temperature, ⩾37.5°C, axillary.

[b] Data were available for 83 patients (41 in the eflornithine arm and 42 in the nifurtimox-eflornithine arm).

[c] Data were available for 82 patients (41 in each arm).

[d] In the eflornithine arm, there were 2.8 adverse events per patient and 0.3 major adverse events per patient; in the nifurtimox-eflornithine arm, there were 2.0 adverse events per patient and 0.1 major adverse events per patient.

other HAT foci, including sociopolitical stability, the supply of electricity, the availability of internet communication, daily flights to the capital, good hospital infrastructure, and qualified medical staff. The study did not achieve the planned sample size of 280 subjects in Nkayi because of bureaucratic delays that resulted in the bulk of patients being detected and treated by Médecins Sans Frontières before enrollment could begin. There were, however, some advantages to this situation: the smaller caseload facilitated good medical supervision and eased laboratory work. With a decreased prevalence of disease, the probability of reinfection during follow-up was also minimized.

Limitations. As a result of the insufficient number of patients recruited at this site, we have not yet performed the noninferiority analysis designed in the protocol; this will only be possible when the studies from additional sites are completed. Therefore, these data should not be regarded as definitive proof.

Overall evidence. In the face of unsatisfactory therapeutic options for second-stage sleeping sickness, the need to identify new, safe, feasible, and effective therapies is urgent [3]. Research is hampered by the fact that foci with high caseloads that can sustain good enrollment rates are often affected by conflict and located in isolated and impoverished parts of Africa. Gathering the minimal elements for quality research projects (e.g., qualified personnel, infrastructure, communications, and stable and functional logistics) at such sites represents a challenge that very few researchers are willing to assume.

Even if, at this first study site, we did not attain the complete sample size, we believe that our data are of crucial interest because of the promising efficacy and safety results of the nifurtimox-eflornithine combination, which was tested here for the first time with a simpler (twice-daily) eflornithine administration schedule.

The short half-life of eflornithine theoretically requires shorter administration intervals for effective therapy, and this was one of the key issues addressed in this study. We hypothesize that this adverse pharmacokinetic profile may be balanced by the long-lasting pharmacodynamic effect on trypanosomes, explained by the long time (18–19 h) needed by *T. brucei gambiense* to replenish their ornithine decarboxylase after inhibition by eflornithine [26]. This would give sufficient opportunity for trypanocydal nifurtimox to eliminate the parasites. Our data seem to confirm that the 12-h intervals are possible if the agent is combined with nifurtimox.

The simplified regimen in this nifurtimox-eflornithine schedule, which involves 4-fold fewer eflornithine infusions (i.e., 14 infusions instead of 56), represents an important advance in terms of access to safer and effective treatment. Most treatment centers are located near disease transmission foci, in remote areas where logistical means and trained staff are scarce, and most patients need treatment for second-stage disease. The twice-per-day infusions are key because they fit well in the routine of rural health facilities. Another important advantage is the cost reduction coming from the shorter hospitalization durations and from the 4-fold reduction in the number of intravenous infusions, requiring fewer infusion materials and logistics and less staffing.

A degree of protection against the development of drug resistance can also be expected from combination versus monotherapy, as is the case for drug combinations in use for other infectious diseases. In the context of increasing parasite resistance to melarsoprol, and because eflornithine is the only alternative agent for second-stage HAT, the availability of a combination treatment regimen is urgent, to avert the development of eflornithine resistance as well.

Because these new data reinforce the evidence in favor of the nifurtimox-eflornithine combination, timely completion of the additional sites and ensuring good follow-up of patients are essential. It will also be necessary to organize field studies with simpler—but sound—methodology to assess the administration of treatment in more-realistic situations. Studies of children will also be needed. For all this to be possible, the continued production and availability of nifurtimox must be ensured. If our findings are corroborated by ongoing studies from additional sites (i.e., from a multicenter extension of this study), the new nifurtimox-eflornithine combination therapy will mark a major and multifaceted advance over current therapies.

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