MAJOR ARTICLE

Nifurtimox-Eflornithine Combination Therapy for Second-Stage Gambiense Human African Trypanosomiasis: Médecins Sans Frontières Experience in the Democratic Republic of the Congo

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Background. Existing diagnostic and treatment tools for human African trypanosomiasis (HAT) are limited. The recent development of nifurtimox-eflornithine combination therapy (NECT) has brought new hopes for patients in the second stage. While NECT has been rolled out in most endemic countries, safety data are scarce and derive only from clinical trials. The World Health Organization (WHO) coordinates a pharmacovigilance program to collect additional data on NECT safety and efficacy. We report here the results of 18 months of experience of NECT use in treatment centers run by Médecins Sans Frontières in the Democratic Republic of the Congo (DRC).

Methods. This cohort study included 684 second-stage HAT patients (including 120 children) treated with NECT in Doruma and Dingila hospitals, northeastern DRC, between January 2010 and June 2011. All treatment-emergent adverse events (AEs) were recorded and graded according to the Common Terminology Criteria for Adverse Events version 3.0. Safety and efficacy data were retrieved from the WHO pharmacovigilance forms and from Epitryps, a program monitoring database.

Results. Eighty-six percent of the patients experienced at least 1 AE during treatment. On average, children experienced fewer AEs than adults. Most AEs were mild (37.9%) or moderate (54.7%). Severe AEs included vomiting (n = 32), dizziness (n = 16), headache (n = 11), and convulsions (n = 11). The in-hospital case fatality rate was low (0.15%) and relapses were rare (n = 14).

Conclusions. In comparison with previous treatments, NECT was effective, safe, and well tolerated in nontrial settings in DRC, further supporting the roll-out of NECT as first-line treatment in second-stage *Trypanosoma brucei gambiense* HAT. Tolerance was particularly good in children.

Keywords. Democratic Republic of Congo; safety; NECT; human african trypanosomiasis; pharmacovigilance.

Human African trypanosomiasis (HAT), also known as sleeping sickness, is a vector-borne disease transmitted to humans by tsetse flies in sub-Saharan Africa [1]. It thrives among impoverished populations, mostly in remote rural areas and conflict zones. HAT is caused by 1 of 2 subspecies of a protozoan parasite. *Trypanosoma brucei (T.b.) gambiense* occurs in Western and Central Africa and is responsible for the majority of HAT cases, while *T.b. rhodesiense* is found in Eastern and Southern Africa [2].

The incidence of reported HAT cases has drastically decreased in recent years, from >26 000 in 2000 to <7200 in 2010. However, the true number of cases may be underestimated by a factor of 4 to 5 [3, 4].

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"Hot spots" still occur in areas of conflict or instability, and large areas in endemic countries have not been surveyed for decades. In July 2007, Médecins Sans Frontières (MSF) began population screening for HAT in the districts of Haut-Uélé and Bas-Uélé in northeastern Democratic Republic of the Congo (DRC), close to the borders with South Sudan and the Central African Republic [5].This region is subjected to sustained instability and conflict due to the presence of the Lord's Resistance Army, a revolutionary group from Uganda. Through early 2009, screening activities revealed an overall HAT prevalence rate of 3.4%, reaching 10% in some villages.

HAT due to *T.b. gambiense* occurs in 2 stages [6]. The hemolymphatic infection (first stage) is characterized by fever, headache, and joint pain. Transition to the meningoencephalitic stage (second stage) occurs after the parasite crosses the blood-brain barrier. Patients present with neuropsychiatric symptoms, including sensory motor deficit, walking difficulties, and psychotic behavior, leading to coma and death in the absence of treatment [7]. Treatment options for HAT are few and stage-specific. Of the 5 existing drugs, 3 are active in second-stage *T.b. gambiense* HAT [8]: melarsoprol, eflornithine, and nifurtimox; all present drawbacks.

Since 1949, melarsoprol intravenous injections have been the mainstay therapy for second-stage HAT [9]. The drug, an arsenic derivative, is very toxic. It is associated with severe reactive encephalopathies in 5%–10% of the cases and kills 3%–5% of patients [10, 11]. Studies have also shown an increase in treatment failure rates over recent years [12–14].

Eflornithine (D, L, α-difluoromethyleflornithine, DFMO) was shown to be active against *T.b. gambiense* in the 1980s [15]. Although better tolerated than melarsoprol, eflornithine also produces several side effects, including gastrointestinal problems, fever, hypertension, and convulsions [16]. The treatment involves 56 intravenous infusions over 14 days, therefore requiring complex logistics and trained health staff. The potential for resistance when used in monotherapy is an additional concern. Several studies have compared the safety and efficacy of melarsoprol and eflornithine. Mortality was found to be significantly lower in patients treated with eflornithine compared to those treated with melarsoprol [17–19].

Nifurtimox, which is registered for the treatment of Chagas disease, has shown some, albeit limited, efficacy against second-stage HAT [20–22]. In recent years, combination regimens of the above-mentioned drugs have been evaluated in second-stage *T.b. gambiense* HAT. Nifurtimox-eflornithine combination therapy (NECT: oral nifurtimox 15 mg/kg/day for 10 days plus eflornithine infusions 400 mg/kg/day for 7 days) proved to be the best combination in terms of both safety and efficacy [23–25]. The low mortality (0.7%) and high cure rates (97.7% at 18 months) reported with NECT prompted the World Health Organization (WHO) to add the combination to its Essential List of Medicines in 2009 [26]. However, the population exposed to NECT during clinical trials was limited (n = 191), and the WHO set up a pharmacovigilance system to monitor the safety of NECT after its roll-out in endemic countries. In parallel, the Drug for Neglected Diseases initiative launched a pragmatic trial (NECT-FIELD) to document the use of NECT as first-line therapy for second-stage HAT under field conditions [27].

Since December 2009, MSF has implemented NECT as first-line treatment in all of its programs, including the challenging region of Haut-Uélé and Bas-Uélé in DRC. Here we present a retrospective analysis of 684 patients treated with NECT in the Uélé districts and discuss the safety and feasibility of this treatment in remote, conflict-torn areas.

METHODS

Study Setting

This retrospective cohort study was conducted in the Zones De Santé of Doruma and Dingila, in the Province Orientale, northeastern DRC. All second-stage HAT patients diagnosed on site or by mobile teams were hospitalized in wards set up by MSF in the reference hospitals (equivalent to district hospitals) of Doruma (Haut-Uélé) or Dingila (Bas-Uélé), both run by the DRC Ministry of Health.

Participants and Procedures

All second-stage HAT patients treated with NECT between 1 January 2010 and 30 June 2011 were included in the analysis. Patients were mainly Congolese, with a high proportion of displaced people from neighboring areas owing to rampant insecurity.

Second-stage HAT was defined by the presence of trypanosomes in the cerebrospinal fluid (CSF) or a CSF leukocyte count >5 cells/μL in patients with trypanosomes found in lymph or blood, or in patients with positive high (1:16) card agglutination *Trypanosoma* test (CATT) titer. The CATT is an agglutination method based on the detection of circulating antibodies against *T.b. gambiense* [28]. Parasites detection in the lymph or blood relied on microscopic examination of samples. Cervical lymph nodes, when present, were punctured and the fluid was directly observed under microscope for the presence of motile trypanosomes. Prior to microscopy, blood samples were subjected to capillary tube centrifugation [29] or mini-anion exchange centrifugation [30] techniques. CSF was examined immediately after lumbar puncture, leukocytes were counted, and trypanosomes were searched for after single centrifugation. Positive laboratory results and CSF leukocyte counts were confirmed by 2 independent laboratory technicians.

Relapse cases were defined as patients with (1) history of HAT treatment and (2) presence of trypanosomes in lymph,

blood, or CSF, or CSF leukocyte count >20 cells/μL, increased compared with previous count or associated with clinical features consistent with HAT. All patients who did not meet this definition at 6 or 12 months were considered cured.

Second-stage HAT patients were pretreated with albendazole, and those testing positive for malaria also received oral artesunate and amodiaquine. All patients received 3 meals per day (2100 kcal/day for adult patients). NECT (nifurtimox per oral 5 mg/kg every 8 hours for 10 days and eflornithine intravenous 200 mg/kg every 12 hours for 7 days) was administrated to all second-stage HAT patients except pregnant women (treated with pentamidine intramuscular 4 mg/kg/day for 7 days with NECT administered after delivery) and patients with signs of hepatic insufficiency (treated with eflornithine intravenous 400 mg/kg/day for 14 days). Eflornithine was diluted in distilled water and infused over 2 hours. Nifurtimox intake was directly observed, administered outside meals, and readministered if vomiting occurred within 30 minutes. Patients remained hospitalized during the entire treatment period. All patients were asked to return for follow-up visits 6, 12, 18, and 24 months after discharge. For patients diagnosed and treated between 1 January 2010 and 31 December 2010, treatment outcomes at 6 and 12 months could be assessed. For patients diagnosed and treated between 1 January 2011 and 30 June 2011, only the treatment outcome at 6 months was collected. NECT relapses were treated with a combination of melarsoprol (intravenous 1.2 mg/kg/day) and nifurtimox (per oral 15 mg/kg/day) for 10 days.

Data Collection

Baseline demographic and clinical characteristics, diagnostic and treatment data, adverse events, and laboratory follow-up data were entered in the Epitryps (Epicentre, France) database. In addition, all treatment-emergent adverse events (AEs) were recorded in pharmacovigilance forms designed by WHO. AEs were graded based on the Common Terminology Criteria for Adverse Events version 3.0. The causality between AE and NECT was assessed by the treating physician as either not related, unlikely to be related, possibly related, probably related, definitely related, or unknown. The start date and total duration of each AE were recorded together with the action taken and the outcome of the AE. Relapses were documented in WHO relapse forms.

Statistical Analysis

Results are presented with medians and interquartile ranges (IQRs) for numerical variables, which were compared with the Student *t* test. Mann-Whitney *U* test or Kruskal-Wallis test was used for nonnormally distributed values. Categorical variables were compared with χ^2 test or Fisher exact test as appropriate. Logistic regression was used for univariate and multivariate analysis of risk factors. Only variables that showed a significant association ($P < .05$) in the univariate analysis were included in the multivariate model.

Ethics

The data were collected as part of a routine pharmacovigilance program. As for most a posteriori studies, individual informed consent was not deemed necessary in accordance with MSF Ethics Committee rules [31].

RESULTS

Between 1 January 2010 and 30 June 2011, 1481 HAT patients were diagnosed and treated by MSF in Doruma and Dingila (Figure 1). Among 690 second-stage patients, 684 received NECT, 5 pregnant women were treated with pentamidine, and 1 patient with clinical signs of hepatic insufficiency received eflornithine monotherapy. The NECT group composed the study cohort. Patients treated with NECT had a median age of 36 years (IQR, 20–50 years) and 324 (47.4%) were females. The cohort included 120 children: 21 (3.1%) <5 years of age and 99 (14.5%) aged 5–15 years. Patients diagnosed by active screening represented 37.1% (n = 254) of the cohort. Among all patients treated with NECT, 23 were relapse cases. Table 1 shows the demographic and clinical characteristics of the cohort.

Adverse Events

Among 684 patients treated with NECT, most (n = 590 [86%]) experienced at least 1 AE during treatment. AEs occurred in 82 of 120 children (67.5%).

A total of 1878 events occurred during hospital stay, with a mean of 3.2 AEs per patient (range, 1–7). On average, adults experienced more AEs than children (mean difference = 1.19 AEs per patient; 95% confidence interval [CI], .904–1.475; $P < .001$). Most AEs were considered mild (grade 1) (n = 711 [37.9%]) or moderate (grade 2) (n = 1027 [54.7%]) by the physicians. Severe (grade 3) and very severe (grade 4) AEs were less frequent (n = 130 [6.9%] and n = 8 [0.4%], respectively). These included vomiting (n = 32), dizziness (n = 16), headache (n = 11), and convulsions (n = 11). AEs were considered related (certainly, probably, or possibly) to NECT in 94.3% (n = 1771) of cases by the physicians. All severe and very severe AEs were considered related to NECT. The in-hospital case fatality rate was low: 0.15% (n = 1). The patient who died during hospitalization presented with features of reactive encephalopathy, and the physician in charge considered it to be related to NECT.

Gastrointestinal AEs were the most frequently reported AEs (Table 2). Most AEs occurred early during treatment course. Among children treated with NECT, vomiting (49.2%), abdominal/stomach pain (28.3%), and anorexia (18.3%) were the

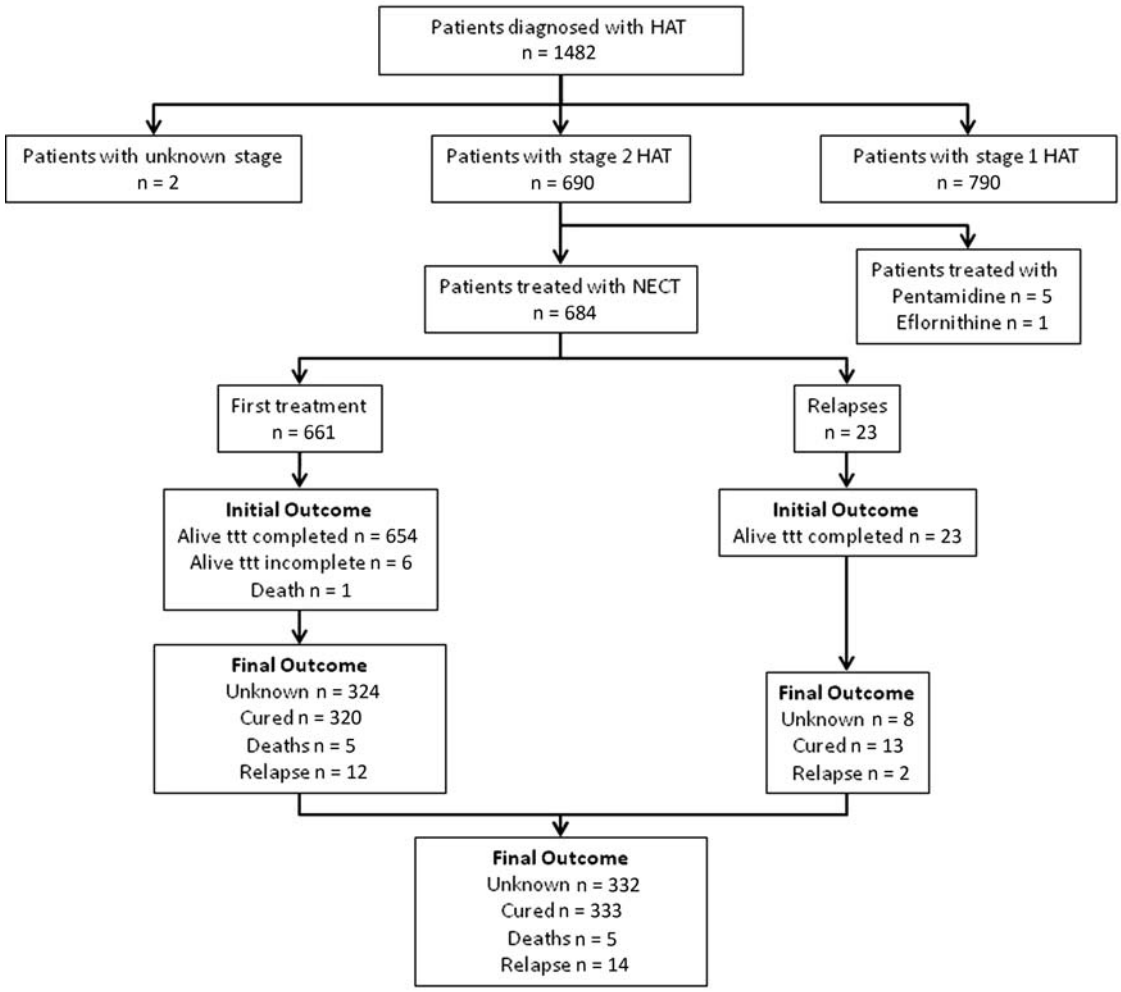

Figure 1. Flowchart of human African trypanosomiasis patients included in the study. Abbreviations: HAT, human African trypanosomiasis; NECT, nifurtimox-eflornithine combination therapy; ttt, treatment.

most frequent AEs. Among young (0–4 years) children (n = 21), vomiting was frequently reported (62%), but none presented with insomnia or anorexia, and no AE was graded as very severe.

When compared with the 94 patients who did not experience AEs, age >15 years increased the probability of having 1 or more AEs by 3.7-fold (Table 3). Presenting with fever on admission doubled the chances of AE occurrence, while being diagnosed by active screening decreased the chances by 1.7-fold. None of the other baseline characteristics included in the multivariate analysis affected the risk of developing AEs during treatment.

Adherence to Treatment and Follow-up

Six hundred seventy-seven of 684 patients completed their treatment. Reasons for discontinuation included death during treatment (n = 1), treatment toxicity (n = 4), or patient default (n = 2). Six months of follow-up data were available for 336 of 684 patients (49.1%), and 12 months of follow-up data were available for 106 of 305 patients (34.8%). At 6 months, 9 patients (2.7%) were considered to have relapsed (5 had trypanosomes in the CSF), 4 had died, and 323 (96.1%) were considered cured. At 12 months, 5 patients (4.8%) were considered to have relapsed (2 had trypanosomes in the CSF), and 101 (95.2%) were considered cured. The overall cure rate was 94.6% (333/352 patients for whom a final outcome was available).

DISCUSSION

NECT showed a relatively good safety profile and good efficacy among 684 patients with second-stage *T.b. gambiense* HAT treated in 2 hospitals supported by MSF in northeastern

Table 1. Demographic and Clinical Characteristics of 684 Patients Treated With Nifurtimox-Eflornithine Combination Therapy in Doruma and Dingila, Democratic Republic of the Congo

Patient Characteristics	All Patients (N = 684)
Age, y, median (IQR)	36 (20–50)
Age >15 y	564 (82.5)
Female	324 (47.4)
Diagnosed by active screening	254 (37.1)
BMI, kg/m^2, median (range)[a]	19.6 (17.5–21.7)
Body temperature on admission, °C, median (range)	36.2 (35–38.5)
Malaria coinfection	185 (27)
Karnofsky score[b], median (range)	90 (10–100)
Symptoms on admission	
Headache	462 (67.5)
Arthralgia	351 (51.3)
Pruritus	318 (46.5)
Somnolence	206 (30.1)
Fever	199 (29.1)
Amenorrhea/impotence	166 (24.3)
Behavioral changes	113 (16.5)
Insomnia	35 (5.1)
Convulsion	5 (0.7)
Presence of trypanosomes in CSF	137 (20)
Leukocytes in CSF	
6–20 cells/μL	502 (73.4)
21–99 cells/μL	164 (24)
≥100 cells/μL	18 (2.6)

Data are presented as No. (%) unless otherwise specified.

Abbreviations: BMI, body mass index; CSF, cerebrospinal fluid; IQR, interquartile range.

[a] BMI was calculated only for patients >5 years of age.

[b] The Karnofsky performance status score is a quantification of a patient's general well-being and activities of daily living [32].

DRC, a region characterized by poor health infrastructures, remoteness, and insecurity. The in-hospital mortality rate was very low (0.15%), confirming previous findings [23–25]. This figure corresponds to the lowest case fatality rate ever observed in HAT programs conducted by MSF, a nongovernmental organization that has treated approximately 50 000 *T.b. gambiense* HAT patients since 1986. Although the majority of patients (86%) developed at least 1 AE during treatment, most events were mild or moderate. Major events (grade 3 and grade 4) were relatively uncommon (7.4%). These figures are lower than those reported by Priotto et al [25] and Checchi et al [23], who observed major events in 14% and 25%, respectively, of NECT-treated patients. In addition, in contrast with previous publications, the frequency of seizures among patients with major AEs remained low (15% [11 of 70 events]) in our study. Vomiting, on the other hand, was the most common major AE (45.7% [32 of 70 events]). These differences could be explained by the interobserver variability in grading AEs.

Strikingly, NECT was better tolerated in children than in adults. Adults had 4 times more chances to develop 1 or more AEs, and on average, experienced more events than children. This may be related to the better safety profile of nifurtimox in children [33–35], or to a better general condition of children on admission, as reflected by the better mean Karnofsky score. Most AEs occurred early during treatment, which suggests that NECT-related AEs do not depend on cumulative doses. Digestive symptoms were the most common events in both adults and children. Abdominal pain (40.6%), vomiting (38.7%), and headache (29.9%) were most frequently observed, similar to what was reported by others [23–25]. Conversely, fever was less frequent in our cohort (1.5%; 10 of 684 patients) as were infections (2.2%; 15 of 684 patients) and diarrhea (7.2%; 49 of 684 patients). This is likely to be due to the high proportion (73%) of patients with early second-stage disease (6–20 cells/μL in the CSF) in our cohort, as this category of patients was not included in the largest previous report [25]. The pattern of treatment-emergent AEs noted in the present study is overall consistent with that of nifurtimox and eflornithine monotherapies, although the incidence and severity of specific AEs appears lower, most likely due to the shorter treatment duration [16, 36].

The overall cure rate was high (95.1%), and comparable to the figures reported earlier [23–25]. Only 14 relapses were reported, of which 9 were diagnosed at the 6-month follow-up visit, and 5 at the 12-month follow-up visit. We observed a higher relapse rate when NECT was given for HAT relapse (7.1%) than in first-time treated patients (1.8%). The previous treatments administered in the 23 relapse patients were pentamidine (n = 18), eflornithine (n = 5), and unknown (n = 1). The low number of relapses treated with NECT in our cohort prevents any definite conclusion, but this issue should be studied in larger cohorts.

With only 14 infusions over a week, NECT is much easier to administer than eflornithine monotherapy, entails a decreased workload for medical staff, shortens the duration of hospitalization, and significantly reduces costs. Yun et al estimated that the cost of treatment, excluding drug costs, is reduced from €107 to €39 per patient [37]. Theoretically, NECT may also prevent the emergence of resistance. The relative ease of administration allowed a rapid roll-out of NECT in endemic countries. In 2008, half of stage 2 HAT patients were still receiving melarsoprol as first-line treatment; in 2010 this figure was reduced to 10% [38]. This shift in treatment use is most welcome, and should be further encouraged by the finding that NECT is well tolerated in the field setting.

Table 2. Description of Adverse Events During Nifurtimox-Eflornithine Combination Therapy in 684 Patients With Second-Stage Human African Trypanosomiasis in Doruma and Dingila Hospitals, Democratic Republic of the Congo

Adverse Event	No. of Events	No. (%) of Patients	No. (%) of Children (<15 y)	Severity Grade[a], No. (% of all events)				Time of Onset, Median d (IQR)	Duration of AE, Median d (IQR)
				1	2	3	4		
Stomach/abdominal pain	309	278 (40.6%)	34 (28.3%)	110 (35.6%)	196 (63.4%)	3 (1%)		2 (1–5)	2 (1–3)
Vomiting	265	265 (38.7%)	59 (49.2%)	100 (37.7%)	133 (50.2%)	30 (11.3%)	2 (0.8%)	2 (1–4)	2 (1–3)
Headache	205	205 (29.9%)	14 (11.6%)	97 (47.3%)	97 (47.3%)	11 (5.4%)		2 (1–4)	2 (1–4)
Musculoskeletal pain	204	168 (24.6%)	11 (9.1%)	71 (34.8%)	126 (61.8%)	7 (3.4%)		1.5 (0–4)	1 (1–3)
Anorexia[b]	144	144 (21.1%)	22 (18.3%)	72 (50%)	67 (46.5%)	4 (2.8%)		5 (3–6)	2 (1–5)
Dizziness	136	136 (19.9%)	3 (2.5%)	50 (36.7%)	70 (51.4%)	16 (11.7%)		5 (2.25–7)	2 (1–4)
Insomnia	82	82 (11.9%)	1 (0.1%)	39 (47.6%)	40 (48.8%)	3 (3.7%)		5 (3–7)	2 (1–3)
Fatigue	76	76 (11.1%)	4 (3.3%)	17 (22.4%)	51 (67.1%)	8 (10.5%)		5 (3–8)	2 (1–3)
Mood/behavior change	61	56 (8.2%)	2 (1.7%)	18 (29.5%)	33 (54.1%)	9 (14.8%)	1 (1.6%)	6 (4–7)	2 (1–1.75)
Nausea	52	52 (7.6%)	1 (0.1%)	29 (55.8%)	21 (40.4%)	2 (3.9%)		2 (1–4)	2 (1–3)
Diarrhea	50	49 (7.2%)	6 (5%)	13 (26%)	30 (60%)	7 (14%)		5 (2–7)	2 (1–3)
Tremor	46	46 (6.7%)	0 (0%)	19 (41.3%)	25 (54.3%)	2 (4.3%)		6 (4–8)	2 (1–3)
Pruritus	30	30 (4.4%)	2 (1.7%)	11 (36.7%)	16 (53.3%)	3 (1%)		4.5 (2.75–6.25)	2 (2–4)
Convulsion	28	28 (4.1%)	2 (1.7%)	6 (21.4%)	11 (39.3%)	10 (35.7%)	1 (3.6%)	5 (2.25–6)	1 (1–2)
Psychosis	20	20 (2.9%)	0 (0%)	3 (15%)	11 (55%)	4 (20%)	2 (10%)	6 (4–7)	2.5 (1–6.25)

Abbreviations: AE, adverse event; IQR, interquartile range..

[a] Severity was graded from 1 (mild) to 5 (fatal) according to the Common Terminology Criteria for Adverse Events version 3.0.

[b] Missing value = 1.

Table 3. Risk Factors for Developing 1 or More Adverse Events Among 684 Second-Stage Human African Trypanosomiasis Patients Treated With Nifurtimox-Eflornithine Combination Therapy in Doruma and Dingila Hospitals, Democratic Republic of the Congo

Patient Characteristic on Admission	Univariate OR (95% CI)	*P* Value	Multivariate OR (95% CI)	*P* Value
Age >15 y				
No	1			
Yes	3.965 (2.467–6.372)	<.001	3.681 (2.146–6.315)	<.001
Sex				
Male	1			
Female	1.459 (.936–2.275)	.095	…	
Detected by active screening				
No	1			
Yes	0.420 (.271–.653)	<.001	0.579 (.358–.937)	.026
Malaria coinfection				
No	1			
Yes	1.352 (.842–2.169)	.212	…	
Symptoms on admission				
Amenorrhea/impotence				
No	1			
Yes	1.102 (.652–1.862)	.716	…	
Arthralgia				
No	1			
Yes	1.741 (1.115–2.719)	.015	0.895 (.533–1.505)	.677
Fever				
No	1			
Yes	2.610 (1.44–4.729)	.002	2.191 (1.164–4.123)	.015
Headache				
No	1			
Yes	1.562 (.997–2.448)	.052	…	
Insomnia				
No	1			
Yes	2.645 (.624–11.218)	.187	…	
Pruritus				
No	1			
Yes	1.884 (1.158–3.067)	.011	1.462 (.858–2.492)	.163
Psychiatric symptoms				
No	1			
Yes	1.767 (.886–3.523)	.106	…	
Somnolence				
No	1			
Yes	1.392 (.842–2.301)	.197	…	
Trypanosomes in CSF				
No	1			
Yes	2.506 (1.224–5.130)	.012	1.939 (.922–4.078)	.081
Leukocytes in CSF				
$\leq 20 \times 10^9$ cells/L	1			
$21–99 \times 10^9$ cells/L	2.335 (.808–6.749)	.117	…	
$\geq 100 \times 10^9$ cells/L	3.120 (.996–9.771)	.051	…	

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; OR, odds ratio.

However, NECT cannot yet be considered as an ideal treatment. The requirement for 7 days of intravenous administration still represents a definite obstacle for use in the primary healthcare setting. Despite the overall good tolerance, some AEs are troublesome. Vomiting is frequent and may cause insufficient bioavailability of nifurtimox, requiring frequent use

of antiemetics and occasional readministration of nifurtimox. Psychotic behavior and convulsions are less frequent but are a source of distress for patients and relatives, and can be a source of rumors within local populations. In addition, NECT is unlikely to be effective against second-stage *T.b. rhodesiense* HAT, with melarsoprol left as the only drug option. To overcome NECT shortcomings, the development of an oral drug such as fexinidazole holds great promise [39]. In the meantime, NECT provides a safe and effective treatment option.

This study bears some limitations. First, heterogeneity in the reporting of AEs occurred. The number and nature of the AEs captured in the pharmacovigilance forms varied between the 3 reporting clinicians during the study period. In addition, as laboratory investigations were limited, diagnosis relied mainly on clinical assessment, impeding conclusive diagnosis of AEs and cause of death. In particular, hematological abnormalities such as neutropenia, which is a common side effect of eflornithine, could not be assessed. Also, causality assessment of AEs is highly observer-dependent, and the absence of a comparative control group in our study makes it difficult to ascertain the relationship between the AEs observed and NECT. Hospitalized patients with second-stage HAT usually have numerous AEs, regardless of the regimen used. In most cases, it cannot be conclusively established if the AEs are due to the treatment, to the disease itself, or to concurrent illnesses. The high proportion of patients with early second-stage disease may also limit the external validity of our findings. Finally, the efficacy of NECT is likely to be overestimated as 6 and 12 months of follow-up data were available only for a fraction of patients, and none were followed up until 24 months. A substantial proportion of relapses can indeed occur after 12 months following treatment [25].

Nevertheless, this study provides crucial information and complements the existing safety data generated by the only randomized controlled trial conducted so far [25]. Of note, our cohort included 120 children <15 years of age, in whom NECT was particularly well tolerated, as well as 23 relapse cases. The population assessed during clinical trials is subjected to specific inclusion and exclusion criteria, and patients with comorbidities, pregnant women, children, and the elderly are systematically excluded. It is therefore particularly important to continue assessing the safety of new treatments after their large-scale introduction in the general population. Pharmacovigilance programs such as that deployed by WHO are particularly important. As MSF is one of the main treatment providers for several neglected tropical diseases, its participation in pharmacovigilance activities provides crucial complementary safety data on newly developed therapies such as NECT. Such involvement makes particular sense, as MSF initiated and participated in the development of NECT and other new therapies.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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