Research

Short-course eflornithine in Gambian trypanosomiasis: a multicentre randomized controlled trial

Jacques Pépin,[1] Nzambi Khonde,[2] Faustine Maiso,[3] Félix Doua,[4] Shabbar Jaffar,[5] Stéphane Ngampo,[6] Bokelo Mpia,[2] Dawson Mbulamberi,[7] & Felix Kuzoe[8]

Objective A randomized controlled trial was conducted to determine whether 7 days of intravenous eflornithine (100 mg/kg every 6 h) was as effective as the standard 14-day regimen in the treatment of late-stage *Trypanosoma brucei gambiense* trypanosomiasis.

Methods A total of 321 patients (274 new cases, 47 relapsing cases) were randomized at four participating centres in Congo, Côte d'Ivoire, the Democratic Republic of the Congo, and Uganda to one of these treatment regimens and followed up for 2 years.

Results Six patients died during treatment, one of whom was on the 7-day regimen, whereas the other five had been on the 14-day regimen ($P = 0.2$). The response to eflornithine differed markedly between Uganda and other countries. Among new cases in Uganda, the 2-year probability of cure was 73% on the 14-day course compared with 62% on the 7-day regimen (hazard ratio (HR) for treatment failure, 7-day versus 14-day regimen: 1.45, 95% CI: 0.7, 3.1, $P = 0.3$). Among new cases in Côte d'Ivoire, Congo, and the Democratic Republic of the Congo combined, the 2-year probability of cure was 97% on the 14-day course compared with 86.5% on the 7-day regimen (HR for treatment failure, 7-day vs 14-day: 6.72, 95% confidence interval (CI): 1.5, 31.0, $P = 0.003$). Among relapsing cases in all four countries, the 2-year probability of cure was 94% with 7 days and 100% with 14 days of treatment. Factors associated with a higher risk of treatment failure were: a positive lymph node aspirate (HR 4.1; 95% CI: 1.8–9.4), a cerebrospinal fluid (CSF) white cell count $\geqslant 100/mm^3$ (HR 3.5; 95% CI: 1.1–10.9), being treated in Uganda (HR 2.9; 95% CI: 1.4–5.9), and CSF trypanosomes (HR 1.9; 95% CI : 0.9–4.1). Being stuporous on admission was associated with a lower risk of treatment failure (HR 0.18; 95% CI: 0.02–1.4) as was increasing age (HR 0.977; 95% CI: 0.95–1.0, for each additional year of age).

Discussion The 7-day course of eflornithine is an effective treatment of relapsing cases of Gambian trypanosomiasis. For new cases, a 7-day course is inferior to the standard 14-day regimen and cannot be recommended.

Keywords: trypanosomiasis, African, drug therapy; *Trypanosoma brucei gambiense;* eflornithine, administration and dosage; eflorithine, adverse effects; trypanocidal agents; randomized controlled trials.

Bulletin of the World Health Organization, 2000, **78**: 1284–1295.

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Introduction

Trypanosoma brucei gambiense trypanosomiasis is re-emerging as a major public health problem in Central Africa, with an annual incidence of 35 000 cases in the Democratic Republic of the Congo, and of many thousand cases in Angola, Sudan, and Uganda (*1*, *2*). For the past 50 years, the only commercially available

[1] Director, Centre de santé internationale, Université de Sherbrooke, 3001, 12ème Avenue Nord, Sherbrooke, Québec, J1H 5N4, Canada (email: jpepin01@courrier.usherb.ca). Correspondence should be addressed to this author.

[2] Medical Officer, Zone de santé rurale de Nioki, Nioki, Democratic Republic of the Congo.

[3] Medical Officer, National Sleeping Sickness Control Programme, Jinja, Uganda.

[4] Director, Projet de Recherches Cliniques sur la Trypanosomiase, Daloa, Côte d'Ivoire.

[5] Lecturer, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, England.

[6] Director, Programme National de Lutte contre la Trypanosomiase, Brazzaville, Congo.

[7] Director, National Sleeping Sickness Control Programme, Jinja, Uganda.

[8] Manager, Product Development Team for African Trypanosomiasis Chemotherapy, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, World Health Organization, Geneva, Switzerland.

Ref. No. **99-0070**

drug for the treatment of late-stage Gambian trypanosomiasis has been melarsoprol, an arsenical, which is very effective but toxic; approximately 6% of melarsoprol-treated patients die of drug-induced encephalopathy (*3, 4*). Eflornithine, an inhibitor of polyamine synthesis, is effective and better tolerated than melarsoprol (*5*). However, its future availability is doubtful given the lack of a commercial market. The current cost of a 14-day regimen of eflornithine is US$ 508, a price that endemic countries cannot afford.

The standard regimen of eflornithine for late-stage Gambian trypanosomiasis is 100 mg/kg, given intravenously every 6 h for 14 days. The treatment was developed empirically, based on a murine *T.b. brucei* model, which suggested that 14 days of oral eflornithine in drinking-water was the minimum curative dose (*6*). However, *T.b. gambiense* is more sensitive to eflornithine than *T.b. brucei,* and much higher blood levels are achieved by intravenous than oral administration. Thus, the relevance of this model to the minimal duration of treatment needed to cure human African trypanosomiasis is questionable. Anecdotal data on a small number of patients in whom eflornithine had to be interrupted prematurely showed that cure could be achieved after just a few days of treatment. It was hypothesized that a shorter, cheaper, regimen would make this drug widely available to patients with late-stage Gambian sleeping sickness. To validate the efficacy of a shorter therapeutic course, a multicentre randomized controlled trial was initiated, under the sponsorship of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), to compare a 7-day regimen of intravenous eflornithine with the standard 14-day regimen.

Methods

Four treatment centres participated in the study: Nioki hospital, in the Democratic Republic of the Congo; Adjumani hospital, in north-west Uganda (18 patients were also enrolled in the nearby Omugo hospital); a specialized trypanosomiasis research centre, in Daloa, Côte d'Ivoire; and the central hospital of Brazzaville, in the Congo. The study protocol was approved in each country by the national health authorities, and verbal informed consent was obtained from each patient. Eligible patients included parasitologically confirmed "new cases" of Gambian sleeping sickness who had not received any prior treatment, and "relapsing cases", who had been diagnosed in the past, treated with another drug, and had subsequently relapsed. A lymph node aspirate for trypanosomes was carried out on all new cases if they had palpable cervical lymph nodes, and examinations of blood (wet or thick smears, haematocrit centrifugation technique, miniature anion-exchange centrifugation technique) were performed if trypanosomiasis was suspected but trypanosomes were not found in lymph nodes. All patients had a lumbar puncture, and the cerebrospinal fluid (CSF) was examined for trypanosomes and white cells; only those with a CSF white cell count (WCC) $>5/mm^3$ were eligible. Relapsing cases were identified during a follow-up lumbar puncture, when trypanosomes were found in the CSF and/or when a substantial increase in CSF WCC was documented. An additional eligibility criterion was if it was thought likely that the patient would complete the 2-year follow-up; enrolment in Nioki was restricted to patients living within the district, and in Uganda to Ugandan nationals (refugees were not eligible). For new cases only, pregnant women and patients moribund on admission to hospital were excluded.

Patients who agreed to participate in the study were randomized to receive either 7 or 14 days of IV eflornithine at 100 mg/kg given every 6 h. Randomization was carried out in each hospital and was stratified between new cases and relapsing cases. Blinding was not feasible. Information was collected about past history and past treatment of trypanosomiasis (for relapsing cases), current symptoms, findings of the clinical examination, and results of laboratory investigations. Haemoglobin levels and the leukocyte counts in peripheral blood were also determined before and on the last day of treatment. Adverse effects were treated symptomatically.

After completion of treatment, patients were asked to return for follow-up lumbar punctures after 1, 3, 6, 12, 18, and 24 months. If the results of one of these tests was doubtful, the next lumbar puncture was carried out sooner, usually after 1 or 2 months. A treatment failure was diagnosed if, during follow-up, trypanosomes were found in the CSF (or blood or lymph node) and/or if there was a significant increase in CSF WCC defined as follows: CSF WCC $\geqslant 50/mm^3$ and higher than the previous determination; or a CSF WCC of $20–49/mm^3$, higher than the previous determination, with the patient complaining of symptoms compatible with a relapse (persistent headaches or somnolence). These patients were then treated with melarsoprol. The term "relapsing cases" is used in this article to refer to patients who had relapsed prior to being enrolled in the trial, and "treatment failures" refers to patients found to relapse after having received eflornithine in the course of this trial.

It was planned that each centre would enrol 80 patients. Assuming that 5% of patients receiving the 14-day regimen would fail to respond, such a sample size would have corresponded to 80% power (α value = 0.05) of detecting a threefold higher rate of treatment failure in patients receiving the short course. Enrolment started in July 1993. Enrolment was slow in Côte d'Ivoire and Congo, and so additional patients were recruited from the Democratic Republic of the Congo and Uganda. Follow-up was hampered by the 1997 civil war in Brazzaville, the 1996–97 civil war in Zaire, and an ongoing guerrilla war in north-west Uganda. Enrolment continued until February 1996, and follow-up was completed in April 1998.

Univariate comparisons between groups were carried out using χ^2 tests with Yates's correction or by Fisher's exact tests if the frequencies were small. Continuous data were compared between groups using *t*-tests if the data were normally distributed and by the Wilcoxon test if the data were non-normal. Survival analyses were carried out using Kaplan–Meier plots and Cox's proportional hazards regression. The follow-up time was calculated from the date of randomization to either the date of treatment failure, the date last seen, or the date of death. Statistical significance was tested by the likelihood ratio test.

Results

Baseline characteristics

A total of 321 patients (age range, 3–77 years) were recruited into the study. The overall characteristics for both new and relapsing cases are shown in Table 1. Baseline patient characteristics were similar for the two treatment regimens. However, these characteristics varied between treatment centres (Table 2): patients recruited in the Democratic Republic of the Congo were older on average than those recruited at the other sites; those recruited in Uganda had a lower CSF WCC, were more likely to be lymph node aspirate positive, less likely to have stupor, and a higher proportion were new cases compared with those recruited at the other sites; fewer of the patients recruited in Uganda and the Democratic Republic of the Congo had trypanosomes in their CSF compared with those recruited at the other sites ($P < 0.01$ in each case). The majority of patients were new cases of Gambian trypanosomiasis, and most were recruited in the Democratic Republic of the Congo or Uganda. Relapsing cases had received melarsoprol (40 patients) or pentamidine (7) as their first treatment. A total of 46 of the relapsing patients had been treated with melarsoprol at some stage of their illness. The interval between the first treatment and the administration of eflornithine varied from 82 days to 9.6 years (median, 1.5 years).

Adverse events

Table 3 shows the adverse events that occurred during the course of treatment. A total of 6 patients died: 3/274 (1.1%) among new cases compared with 3/47 (6.4%) among relapsing cases ($P = 0.04$). One of the six patients who died, who was a relapsing case, was on the 7-day regimen, whereas the other five were on the 14-day regimen ($P = 0.2$). Significantly more deaths occurred among patients who had convulsions than among those who had not (4/17 (23.5%) vs 2/303 (0.7%), $P < 0.0001$). Convulsions

Table 1. **The baseline characteristics of patients treated with a 7-day or a 14-day regimen of eflornithine according to past history of trypanosomiasis**

	New cases[a]		Relapsing cases[a]	
	7-day	**14-day**	**7-day**	**14-day**
Total number recruited	132	142	26	21
No. recruited at each site				
Côte d'Ivoire	11	15	4	3
Congo	7	9	9	7
Democratic Republic of the Congo	60	61	10	9
Uganda	54	57	3	2
Median age (years)[b]	30; *11, 77*[c]	27; *9, 74*	25; *3, 52*	24; *11, 58*
No. of females	68 (52)[d]	73 (51)	13 (50)	14 (67)
No. with positive lymph node aspirate	70 (53)	78 (55)	1 (4)	0 (0)
CSF white cell count/mm^3				
⩽ 20	22 (17)	30 (21)	2 (7)	0
21–99	35 (26)	38 (27)	9 (35)	7 (33)
⩾ 100	75 (57)	74 (52)	15 (58)	14 (67)
No. with trypanosomes in CSF	74 (56)	81 (57)	18 (69)	18 (86)
No. with stupor[e]	17 (13)	13 (9)	8 (31)	4 (19)

[a] $P > 0.3$ for each 7-day versus 14-day comparison.

[b] Age not available from one new case on the 7-day regimen.

[c] Figures in italics are the range.

[d] Figures in parentheses are percentages.

[e] Status not available from one relapsing case on the 14-day course.

Table 2. **The baseline characteristics of patients recruited at the four study sites**

	Côte d'Ivoire	Congo	Democratic Republic of the Congo	Uganda
No. recruited	33	32	140	116
Median age (years)	29; *7, 64*[a]	26; *3, 56*	33; *14, 77*	24[b]; *12, 70*
No. of females	16 (49)[c]	16 (50)	78 (56)	51 (44)
No. of relapsing cases	7 (21)	16 (50)	19 (14)	5 (4)
No. with positive lymph node aspirates	8 (24)	8 (25)	46 (33)	87 (75)
Geometric mean CSF WCC/mm^3	208; *34, 1222*	121; *8, 1040*	96; *5, 1430*	69; *6, 1516*
CSF WCC /mm^3				
⩽ 20	0	5 (16)	21 (15)	28 (24)
21–99	7 (21)	6 (19)	37 (26)	39 (34)
⩾ 100	26 (79)	21 (66)	82 (59)	49 (42)
Trypanosomes in CSF	28 (85)	26 (81)	75 (54)	62 (54)
Stupor	10 (30)	17[d] (55)	14 (10)	1 (1)

[a] Figures in italics are the range.

[b] Age not available for one patient.

[c] Figures in parentheses are percentages.

[d] Data not available for one patient.

were more common among relapsing cases than among new cases (6/47 (12.8%) vs 11/273 (4.0%), $P = 0.03$), and among patients with a CSF WCC = 100/mm^3 compared with those with a CSF WCC < 100/mm^3 (14/177 (7.9%) vs 3/143 (2.1%), $P = 0.04$). Diarrhoea and secondary infections were significantly more common on the 14-day than on the 7-day regimen. The majority of the secondary infections were reported from Uganda (4/57 (7.0%) on the 14-day regimen vs 22/59 (37.3%) on the 7-day regimen; $P = 0.0001$). A total of 12 patients developed upper respiratory tract infections, 8 had catheter-related infections, 2 had pneumonia, 6 developed miscellaneous infections of mild severity, and 1died of sepsis of unknown source. The three episodes of bleeding reported were trivial. No differences were found between the two treatment regimens in the proportion of patients who developed anaemia or leukopenia during treatment (data not shown).

Treatment failures

Table 4 shows the number of treatment failures and the proportion of patients successfully followed up. Overall, 84% of patients were followed-up for more than 1 year and 65% for 2 years. Follow-up varied considerably among centres but was similar on the 7-day and 14-day regimens at each centre. A total of 42 treatment failures were documented, 22 on the basis of trypanosomes seen in the CSF and 20 because of a significant increase in the CSF WCC. A total of 17 of the treatment failures were diagnosed in the first year of follow-up, 20 in the second year, and 5 after = 24 months.

Among new cases, the overall hazard ratio (HR) of treatment failure on the 7-day versus the 14-day regimen was 2.1 (95% CI: 1.1, 4.1, $P = 0.02$). The 2-year probability of cure was 70% (standard error, 5.6) on the 7-day regimen compared with 81% (standard error, 7.6) on the 14-day regimen. Overall, there were more treatment failures in Uganda than in Côte d'Ivoire, Congo, and the Democratic Republic of the Congo combined (HR = 4.1, 95% CI: 2.1, 7.9; $P < 0.0001$). Furthermore, the hazard ratio of treatment failure on the 7-day versus the 14-day

Table 3. **Distribution of patients who suffered adverse events during the 7-day or 14-day course of eflornithine**

	No. of patients		*P*-value
	7-day (*n* = 158)	14-day (*n* = 163)	
Death	1 (0.6)[a]	5 (3)	0.22
Convulsions	7 (4)	10 (6)	0.7
Alteration of consciousness	3 (2)	6 (4)	0.5
Diarrhoea	13 (8)	26 (16)	0.05
Vomiting	7 (4)	13 (8)	0.3
Abdominal pains	13 (8)	23 (14)	0.13
Hearing loss	0 (0)	2 (1)	0.5
Infection	5 (3)	24 (15)	0.001
Bleeding	1 (0.6)	2 (1)	1.0

[a] Figures in parentheses are percentages.

Table 4. **Distribution of treatment failures and period of follow-up, by site and treatment regimen**

	Côte d'Ivoire		Congo		Democratic Republic of the Congo		Uganda		Overall	
	7-day (*n* = 15)	14-day (*n* = 18)	7-day (*n* = 16)	14-day (*n* = 16)	7-day (*n* = 70)	14-day (*n* = 70)	7-day (*n* = 57)	14-day (*n* = 59)	7-day (*n* = 158)	14-day (*n* = 163)
No. treatment failures										
<12 months	2	0	0	0	4	0	3	8	9	8
12–23 months	0	0	0	0	5	2	10	3	15	5
⩾24 months	0	0	0	0	2	0	2	1	4	1
No. who died during treatment	1	2	0	0	0	1	0	2	1	5
No. deaths reported during follow-up										
<12 months	0	0	0	0	2	4	0	0	2	4
12–23 months	0	0	0	0	0	2	1	0	1	2
⩾24 months	0	1	0	0	0	0	0	0	0	1
No. followed up successfully										
⩾12 months	12 (100)[a]	16 (100)	12 (75)	7 (44)	64 (100)	63 (97)	38 (70)	34 (69)	126 (86)	120 (82)
⩾24 months	9 (75)	14 (87.5)	5 (31)	4 (25)	55 (93)	55 (90)	15 (35)	18 (39)	84 (65)	91 (65)

[a] Figures in parentheses are percentages.

regimen was smaller in Uganda than in Côte d'Ivoire, Congo, and the Democratic Republic of the Congo combined ($P = 0.054$).

Among the new cases seen in Côte d'Ivoire, Congo, and the Democratic Republic of the Congo combined, the hazard ratio of treatment failure on the 7-day versus the 14-day regimen was 6.72 (95% CI: 1.5, 31.0) (Table 5). The 2-year probability of cure was 86.5% on the 7-day regimen compared with 97% on the 14-day regimen. Fig. 1 shows the Kaplan–Meier curves for the two regimens, which were significantly different ($P = 0.008$, log-rank test). In new cases from Uganda, the hazard ratio of treatment failure on the 7-day to 14-day regimen was 1.45 (95% CI: 0.7, 3.1) (Table 5). The 2-year probability of cure was 62% on the 7-day regimen compared with 73% on the 14-day regimen. Fig. 2 shows the Kaplan–Meier curves for the two regimens among Ugandan new cases. The overall difference between the two regimens was not statistically significant ($P = 0.34$, log-rank test).

Table 5 also shows the data for relapsing cases according to the above geographical stratification. There were only five relapsing cases enrolled in Uganda. Among relapsing cases in all four countries combined, the two-year probability of cure was 94% on the 7-day regimen compared with 100% on the 14-day regimen ($P = 0.4$, log-rank test).

Risk factors for treatment failure

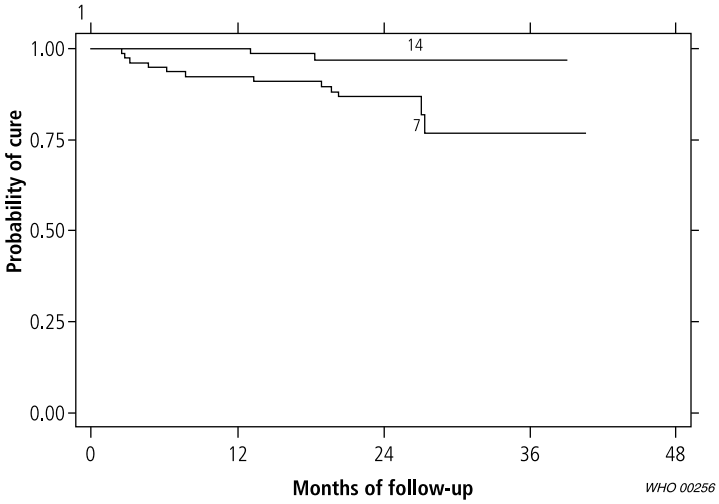
In the univariate analysis, the risk of treatment failure decreased with age, was higher in Uganda, among new cases, those whose lymph node aspirate was positive, and those who were not stuporous on admission to hospital ($P < 0.05$ in each instance) (Table 6). Risk of treatment failure also increased with CSF WCC or with trypanosomes in the CSF, although neither of these associations reached statistical significance. Gender had no influence on the risk of treatment failure. Having trypanosomes in the lymph node aspirate and trypanosomes in the CSF was inversely correlated: 68 of 149 (45.6%) patients with a positive lymph node aspirate had CSF trypanosomes compared with 123/172 (64.4%) with a negative lymph node aspirate ($P < 0.001$); however, patients who had a positive lymph node aspirate were more likely to fail treatment irrespective of whether or not they had trypanosomes in the CSF (adjusted HR: 6.5; 95% CI: 3.0–14.1). Overall, 70 subjects had a CSF WCC $\geqslant 100/mm^3$ and were lymph node aspirate positive, of whom 22 failed treatment; 64 had a CSF WCC $<100/mm^3$ and were lymph node negative, of whom only one failed eflornithine (HR: 22.7; 95% CI: 3.2, 191.6, $P < 0.001$).

Table 7 shows the independent predictors of treatment failure. In a Cox's regression model that did not include a term for the treatment centre effect, the strongest predictor of treatment failure was having a positive lymph node aspirate. Not being stuporous on admission, having trypanosomes in the CSF, and having a CSF WCC $\geqslant 100/mm^3$ were also associated with a higher risk of treatment failure, whereas age was associated with a lower risk of treatment failure. Adding a treatment regimen to this model did not alter any of the hazard ratios (as would be expected from a randomized trial of this size). Past history of

trypanosomiasis did not contribute significantly to the model and was omitted: the apparent association between past history and treatment failure observed in univariate analysis was confounded primarily by new cases being 8.2 times (95% CI: 2.1, 32.2; $P < 0.0001$) more likely to be lymph node aspirate positive than relapsing cases. Age also acted as a confounder but with the opposite and lesser effect: new cases were significantly older than relapsing cases (difference in medians = 6.5 years; $P = 0.01$). Interactions between combinations of variables were tested and not found to be significant.

Table 7 also shows the hazard ratios after adjusting for treatment centre and the risk factors considered above. In the univariate analysis, patients in Uganda had been 4.5 times more likely to fail therapy than patients from the three other countries, but they were also younger, more likely to be lymph node aspirate positive, less likely to be stuporous (all of which increased their risk of treatment failure), had lower CSF WCC, and were less likely to have CSF trypanosomes (which reduced their risk of treatment failure). In this multivariate model, being treated in Uganda rather than in the three other countries was independently associated with a 2.9-fold higher risk of treatment failure, after adjusting for the other risk factors. Although the association between a positive lymph node aspirate and treatment failure was to some extent confounded by the treatment centre, it remained highly significant. Not being stuporous and having a CSF WCC $\geqslant 100/mm^3$ were also significantly associated with treatment failure, whereas a nonsignificant trend was observed for CSF trypanosomes. Age remained associated with a lower risk of treatment failure. Again, no statistically significant interaction was found in this second model.

Fig. 1. **Kaplan–Meier plot showing the probability of cure in the 7-day and 14-day treatment groups among 163 new cases of Gambian sleeping sickness in Côte d'Ivoire, Congo, and the Democratic Republic of Congo**



Deaths during follow-up

A total of 7 deaths were reported during follow-up in patients who had received the 14-day course compared with three among those on the 7-day regimen ($P = 0.34$). Eight of the reported deaths occurred in the Democratic Republic of the Congo, where follow-up after 2 years exceeded 90%. Overall, the mortality hazard ratio for the 14-day relative to the 7-day regimen was 2.26 (95% CI: 0.57, 9.0) ($P = 0.22$, likelihood ratio test). Patients who died were significantly older than those who survived (median age 43 years and 28 years, respectively, $P = 0.009$), but baseline CSF WCC, stupor, trypanosomes in lymph node aspirate, and a past history of

Table 5. **Distribution of treatment failures and the 2-year probability of cure for the 7-day and the 14-day regimen of eflornithine according to past history of trypanosomiasis**

Case history	Regimen	No. of months of follow-up	No. of treatment failures	Two-year probability of cure	Hazard ratio	*P*-value
New cases						
Côte d'Ivoire	7-day	1798	12	86.5; *4.0*[a]	6.72 (1.5,31.0)[b]	0.003
Congo	14-day	1962	2	97.1; *2.0*	1.0	
Democratic Republic of the Congo						
Uganda	7-day	929	15	61.6; *8.7*	1.45 (0.7, 3.1)	0.3
	14-day	1086	12	73.4; *7.0*	1.0	
Relapsing cases						
Côte d'Ivoire	7-day	529	1	93.8; *6.1*	–	0.3
Congo	14-day	374	0	100		
Democratic Republic of the Congo						
Uganda	7-day	75	0	100	–	–
	14-day	2	0	100		

[a] Figures in italics are standard errors.

[b] Figures in parentheses are 95% confidence intervals

Fig.2. **Kaplan-Meier plot showing the probability of cure in the 7-day and 14-day treatment groups among 112 new cases of Gambian sleeping sickness in Uganda**

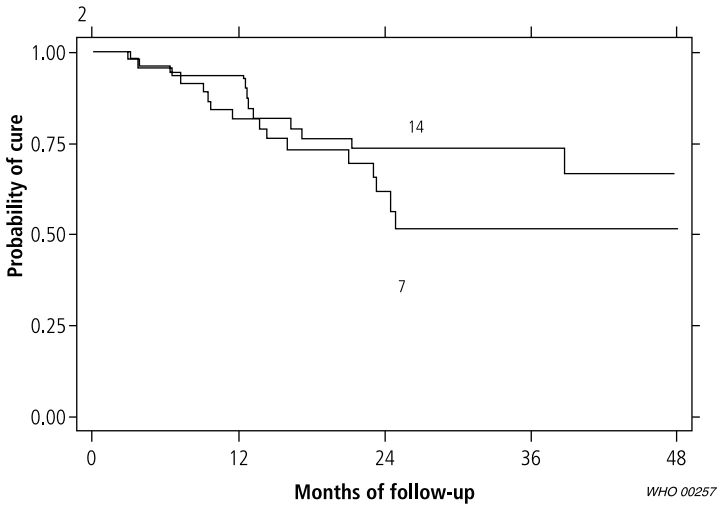


Table 6. **Factors associated with treatment failure in the univariate analysis**

Variable	Proportion of treatment failures	Hazard ratio	*P*-value
Study centre			
Côte d'Ivoire	2/33; *6*[a]	0.17 (0.04, 0.74)[b]	0.0001
Congo	0/32; *0*	0.00	
Democratic Republic of the Congo	13/140; *9*	0.27 (0.13, 0.52)	
Uganda	27/116; *23*	1.0	
Age (years)[c]			
<20	15/80; *19*	3.1 (1.1, 8.6)	0.07
20–39	22/162; *14*	2.0 (0.76, 5.5)	
⩾40	5/78; *6*	1.0	
Past history			
Relapses	1/49; *2*	0.14 (0.018, 1.05)	0.006
New cases	41/272; *15*	1.0	
Lymph node aspirate			
Positive	33/149; *22*	4.9 (2.3, 10.3)	0.0001
Negative	9/172; *5*	1.0	
CSF WCC/mm^3			
⩽ 20	4/54; *7*	1.0	0.08
21–99	8/89; *9*	1.12 (0.33, 3.8)	
⩾100	30/178; *17*	2.3 (0.78, 6.6)	
Trypanosomes in CSF			
Yes	30/191; *16*	1.8 (0.9, 3.5)	0.08
No	12/130; *9*	1.0	
Stupor			
Yes	1/42; *2*	0.16 (0.021, 1.2)	0.013
No	41/278; *15*	1.0	
Treatment regimen			
7-day	28/158; *18*	2.0 (1.1, 3.9)	0.02
14-day	14/ 163; *9*	1.0	

[a] Figures in italics are percentages.

[b] Figures in parentheses are 95% confidence intervals.

[c] Median age, 23 years (range: 14–60 years) among treatment failures compared with 29 years (range: 3–77 years) among non-treatment failures. The hazard rate for age was 0.962 (95% CI: 0.93–0.99; $P = 0.004$), i.e. the risk of treatment failure decreases by 0.962 for each year that the patient gets older.

trypanosomiasis were not associated with death during follow-up ($P > 0.1$ in each case).

Discussion

The study was conducted under difficult field conditions, with civil wars breaking out in three of the four participating countries. In Africa, war and civil strife, which can hamper disease control programmes over prolonged periods, have become a sad but typical feature of the current epidemiology of sleeping sickness (*1, 2*). Despite these difficulties, we achieved satisfactory follow-up rates of 84% after 1 year and 65% after 2 years.

Eflornithine was generally well tolerated. The mortality rate among new cases was 1.1%, lower than the 2–10% reported with melarsoprol for similar patients (*3, 4*). Convulsions were the only severe adverse effect, and these were associated with mortality. The precise causes of death were difficult to delineate, and it is unclear whether convulsions were related causally to death or merely a marker for a more advanced disease that was itself associated with a higher risk of death. Convulsions may reflect a direct neurotoxicity of eflornithine; they were more common in patients with a high CSF WCC, and CSF inflammation leads to better penetration (*7*) of a drug causing convulsions in animals when given intraventricularly (*8*). Eflornithine might also induce immune-mediated encephalopathy, similar to that seen with melarsoprol, but less frequent because eflornithine is trypanostatic rather than trypanocidal, resulting in a slower release of parasite antigens. There was a somewhat higher death rate during treatment among patients on the 14-day course than in those on the 7-day course, but the difference was far from being statistically significant. Deaths after treatment, also more common in the 14-day group, were associated with older age and not with variables found to be associated with failure of eflornithine therapy, suggesting further that this difference in late mortality occurred by chance. The gastrointestinal effects of eflornithine, more common on the 14-day regimen, are well known and without serious consequences. The apparently high incidence of infections in Uganda was probably the result of more systematic reporting of rather trivial events, rather than due to a true increase in the incidence of secondary infections.

An unexpected finding was the high treatment failure rate among new cases in north-western Uganda, much higher than in all other countries where eflornithine has been used so far. A Cox's regression analysis showed that even though Ugandan patients differed from those in the three other countries with respect to factors independently associated with eflornithine failure (such as having a positive lymph node aspirate, and being younger), they had a higher risk of failure even after adjusting for all these confounding factors. This cannot be attributed to protocol violations, since 97% of Ugandan patients

Table 7. **Independent risk factors for treatment failure, by Cox's regression**

Variable	Hazard ratio excluding centre effect	*P*-value	Hazard ratio including centre effect	*P*-value
Age (in years)	0.971 (0.94, 1.0)[a]	0.02	0.977 (0.95, 1.0)	0.01
Lymph node aspirate positive	6.0 (2.8, 13.1)	<0.0001	4.1 (1.8, 9.4)	0.0002
CSF white cell count /mm^3				
⩽20	1.0		1.0	
21–99	1.1 (0.3, 3.9)	0.051	1.1 (0.3, 3.9)	0.007
⩾100	2.7 (0.9, 3.9)		3.5 (1.1, 10.9)	
CSF trypanosomes present	2.1 (1.0, 4.6)	0.046	1.9 (0.9, 4.1)	0.09
Patient stuporous	0.14 (0.018, 1.0)	0.006	0.18 (0.023, 1.4)	0.03
Treatment centre				
Uganda			2.9 (1.4, 5.9)	0.003
All others			1.0	

[a] Figures in parentheses are 95% confidence intervals.

received all planned doses of eflornithine. The ongoing civil war could have biased the estimate of the probability of treatment failure, if patients experiencing symptoms compatible with a relapse were more likely to make the dangerous journey for the follow-up lumbar puncture than patients feeling well; but losses to follow-up were similar for the two regimens, and the factors associated with treatment failure did not differ significantly between those lost to follow-up and those successfully followed (data not shown). Coinfection with human immunodeficiency virus (HIV) decreases the likelihood of cure with eflornithine (*3, 5*), but its prevalence is unlikely to be high enough in the remote study villages to have a measurable impact on cure rates. Some events that we considered "treatment failures" could have rather been reinfections, and the annual incidence of trypanosomiasis was higher in north-western Uganda than in the other centres, resulting in a higher risk for reinfection; however, epidemiological data support the view that the vast majority of such "second episodes" of trypanosomiasis occurring within 2 years of treatment are relapses rather than reinfections (*9*).

Uganda is the only country where both *T.b. gambiense* and *T.b. rhodesiense* are found, but the former type is thought to be endemic only in the north-west of the country and the latter in the south-east. A hitherto undetected overlap in the distribution of the two subspecies could have led to frequent treatment failures since *T.b. rhodesiense* is intrinsically resistant to eflornithine because of its high turnover of ornithine decarboxylase, the drug target (*10*). However, a recent investigation in north-western Uganda confirmed that only *T.b. gambiense* is endemic there; furthermore, out of four local isolates of *T.b. gambiense* tested for drug susceptibility, two exhibited a significantly reduced in vitro sensitivity to eflornithine (R. Brun, R. Kaminsky, J. Enyaru, personal communication, 1999). This did not result from drug pressure, since eflornithine had never been used in north-west Uganda prior to the current trial. Since this region is at the watershed between *T.b. gambiense* and *T.b. rhodesiense* distribution, local strains of trypanosomes might have characteristics that are intermediate between those of the two subspecies, resulting in a poorer response to an ornithine decarboxylase inhibitor such as eflornithine.

In the Congo basin and in Côte d'Ivoire, treatment failures were less frequent than in Uganda, but among new cases the 7-day course was significantly inferior to the standard 14-day regimen. The 86.5% probability of cure with the short course precludes further consideration of this regimen for new cases, even in Central and West Africa. Notwithstanding cost issues, a strategy of using 7 days of eflornithine as first-line treatment and giving melarsoprol only to those who fail eflornithine would not save many lives compared with using more toxic melarsoprol as the first-line drug, since under routine conditions a substantial fraction of the relapses might not come for follow-up and die in their villages without the benefit of a second treatment. Why no such difference was seen between the two treatment regimens in Uganda is puzzling. Based on the above-mentioned findings, we hypothesize that there might be two subpopulations of trypanosomes circulating in north-western Uganda, with many strains resistant to eflornithine at such a high level that even doubling treatment duration would not have lowered the risk of failure.

For relapsing cases, there was no difference in efficacy between the 7-day and the standard 14-day course. Overall, a small number of relapsing cases were enrolled in the trial, and we had low power to detect differences in efficacy between treatment regimens or between treatment centres. However,

the current observations are in line with those from an open trial conducted in Zaire where only 3 (6.5%) treatment failures were documented among 47 relapsing cases treated with a 7-day course of eflornithine (*11*). Relapsing cases respond better to eflornithine than new cases, perhaps because of better CSF penetration of the drug in patients with an impaired blood–brain barrier (*7*) but probably more so because they rarely have positive lymph node aspirates, a strong predictor of failure with eflornithine treatment. Despite limited global experience with this short course therapy, we recommend that relapsing cases of Gambian trypanosomiasis (those who need this drug the most) should be treated with 7 days of intravenous eflornithine, so that this life-saving treatment becomes available to a larger number of patients throughout Africa.

Unexpectedly, having a positive lymph node aspirate was strongly correlated with treatment failure. This association was seen consistently in each country — except in Congo, where no treatment failure was documented. It was seen in patients with a CSF WCC $<100/mm^3$ but also in those with a CSF WCC $\geqslant 100/mm^3$, and in patients with or without trypanosomes in the CSF. No information is available on the penetration of eflornithine in lymph nodes, which might act as a sanctuary allowing survival of a few trypanosomes during treatment, ultimately leading to a relapse. However, eflornithine penetrates well into the CSF (*7*), and it is difficult to conceive that a drug could cross the blood–brain or blood–CSF barrier without penetrating well into lymph nodes. More plausibly, the presence of trypanosomes in the lymph nodes might be a marker for a high trypanosomal load in blood and spleen, potentially one of the true determinants of the risk of eflornithine failure. Blood examinations were not, however, routinely carried out if trypanosomes had already been found in lymph node aspirates or in the CSF. Another possible explanation is that, in animal models, a good immune response is necessary for eflornithine to be curative (*12*). This is supported by the observation that the small number of trypanosomiasis patients known to be coinfected with HIV and treated with eflornithine have responded poorly (*3, 5*). Thus, it could be hypothesized that patients who still have trypanosome-infected cervical lymphadenopathy when late-stage sleeping sickness is diagnosed have a relatively deficient immune response to trypanosomes compared with patients who have cleared their lymphadenopathy, which in turn leads to treatment failure when they are treated with eflornithine. Among patients treated with melarsoprol, a drug which kills trypanosomes rapidly and for which the contribution of the immune response may be less relevant, conflicting results have been obtained: a positive lymph node aspirate was not associated with a higher risk of treatment failure in Zaire (*13*) but was associated with failure in a recent study from another part of north-western Uganda (*14*).

A CSF WCC $\geqslant 100/mm^3$ was a strong predictor of treatment failure with eflornithine, whereas the presence of CSF trypanosomes was a weaker predictor of failure after adjustment for other risk factors. An association between CSF WCC and failure of eflornithine treatment was seen in an earlier open trial (*5*). In patients treated with melarsoprol, the presence of CSF trypanosomes is a risk factor for treatment failure but not CSF WCC, which is merely confounded by CSF trypanosomes (*13*). For late-stage trypanosomiasis to be cured, trypanosomes in the central nervous system need to be killed, and therefore it is not surprising that the presence of CSF trypanosomes, a simple measure of the target parasites, tended to be associated with a higher risk of failure. It is unexpected, however, that treatment failure was more strongly related to CSF WCC than to CSF trypanosomes; we hypothesize that a CSF WCC $\geqslant 100/mm^3$ is correlated with a high trypanosomal load, whereas the simple measure of whether or not any trypanosome has been seen in the CSF fails to reflect quantitative variations in parasite load between patients.

Stuporous patients had a lower risk of treatment failure than those with a normal level of consciousness on admission to hospital. We can only speculate that such patients might have more severely impaired blood–brain and blood–CSF barriers than others, so that they could end up with higher eflornithine levels in the CSF and in the brain. The risk of treatment failure decreased with age, which is consistent with previous studies (*5*, *15*), and is probably a consequence of age-dependent variations in eflornithine pharmacokinetics. Compared with older patients given the same daily dosage of 200 mg/kg every 12 h, children under the age of 12 years had, at the end of a 2-week treatment, mean CSF and serum eflornithine levels that were, respectively, only 36% and 56% of those of adults (*7*). Thus, it seems that children and teenagers treated with eflornithine should be given a higher dosage per kg of weight than is administered to adults. Pending the availability of pharmacokinetic studies performed in this age group, we empirically recommend that patients under 20 years of age be given at least 500 $mg.kg^{-1}.day^{-1}$ of eflornithine.

In summary, for relapsing cases of *T.b. gambiense* sleeping sickness, a 7-day course of intravenous eflornithine is satisfactory and will result in substantial savings compared with the standard 14-day regimen. Such a short-course therapy could be used by national control programmes and hospitals in endemic areas, provided that its efficacy is monitored closely. The current drug cost of a 7-day regimen is US$ 254, which is prohibitive for endemic countries, and external assistance to meet these costs represents the only hope of survival for patients in such countries. For new cases, such a short course leads to an unacceptable rate of treatment failure; in Uganda both the 7-day and the 14-day treatment regimens are unsatisfactory. A 14-day course of eflornithine, although very effective in West and Central Africa, is not economically viable, and melarsoprol will remain the only therapeutic option for new cases over at least the next 10 years. Molecular studies and animal experiments have shown that

eflornithine and melarsoprol act synergistically against trypanosomes since the former drug decreases the production of trypanothione, the target of the latter (*16, 17*). The time has now come for human trials of such combination therapy, which might result in regimens that are cheaper than eflornithine monotherapy, and less toxic than melarsoprol monotherapy. ■

Acknowledgements

This study was funded by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. Eflornithine was kindly provided by Dr G. Roscigno, Aventis (formerly Hoechst Marion Roussel). We are indebted to the many nurses without whose hard work, in difficult conditions, these data could not have been accumulated. Dr Rudy Manthelot provided some of the late follow-up data from Brazzaville. Dr Michèle John, Dr Damien Bates, and Médecins Sans Frontières provided important help in Uganda. Professor Brian Greenwood and Dr Hilton Whittle kindly reviewed the manuscript. Shabbar Jaffar is supported by the United Kingdom Medical Research Council.

Résumé

Traitement de courte durée par l'éflornithine dans la maladie du sommeil due à *Trypanosoma brucei gambiense* : essai contrôlé randomisé multicentrique

L'éflornithine est le seul traitement efficace chez les patients atteints de maladie du sommeil due à *T. b. gambiense* qui rechutent après un traitement par le mélarsoprol. Pour les nouveaux cas, l'éflornithine est aussi efficace que le mélarsoprol tout en étant beaucoup moins toxique. Toutefois, la posologie actuelle, qui prévoit l'administration d'éflornithine par voie intraveineuse pendant 14 jours, est trop coûteuse pour les pays d'endémie et ce médicament reste peu utilisé. En raccourcissant la durée du traitement, il serait possible de le rendre plus accessible.

Nous décrivons ici les résultats d'un essai contrôlé randomisé visant à déterminer si un traitement de 7 jours par l'éflornithine intraveineuse (100 mg/kg toutes les 6 heures) est aussi efficace que la posologie standard de 14 jours contre les stades tardifs de la maladie du sommeil due à *T. b. gambiense*. Au total, 321 malades ont été choisis par tirage au sort pour recevoir l'un ou l'autre traitement dans quatre centres participants au Congo, en Côte d'Ivoire, en Ouganda et en République démocratique du Congo, et ont été suivis pendant deux ans. Parmi ces cas, 274 étaient des nouveaux cas de trypanosomiase et 47 étaient des malades ayant rechuté après avoir reçu un traitement autre que l'éflornithine.

Six malades sont décédés pendant le traitement : 3 sur 274 (1,1 %) parmi les nouveaux cas et 3 sur 47 (6,4 %) chez les malades ayant rechuté (p = 0,04). L'un d'eux était soumis au traitement de 7 jours et les cinq autres au traitement de 14 jours (p = 0,2). On a observé une différence marquée de la réponse à l'éflornithine entre l'Ouganda et les autres pays. Parmi les nouveaux cas vus en Ouganda, la probabilité de guérison à 2 ans était de 73 % pour le traitement de 14 jours contre 62 % pour le traitement de 7 jours (rapport de risque (RR) pour l'échec du traitement, 7 jours contre 14 jours = 1,45 ; intervalle de confiance (IC) à 95 % : 0,7-3,1 ; p = 0,3). Parmi l'ensemble des nouveaux cas vus en Côte d'Ivoire, au Congo et en République démocratique du Congo, la probabilité de guérison à 2 ans était de 97 % pour le traitement de 14 jours contre 86,5 % pour le traitement de 7 jours (RR pour l'échec du traitement, 7 jours contre 14 jours = 6,72 ; IC 95 % : 1,5-31,0 ; p = 0,003). Parmi les cas de rechute vus dans les quatre pays, la probabilité de guérison à 2 ans était de 94 % pour le traitement de 7 jours et de 100 % pour le traitement de 14 jours.

Les modèles de risques proportionnels de Cox ont indiqué que plusieurs facteurs étaient associés à un risque plus élevé d'échec du traitement : ponction de suc ganglionnaire positive (RR = 4,1 ; IC 95 % : 1,8-9,4), leucorachie $\geqslant$ 100/mm^3 (RR = 3,5 ; IC 95 % : 1,1-10,9), malade traité en Ouganda (RR = 2,9 ; IC 95 % : 1,4-5,9) et présence de trypanosomes dans le liquide céphalo-rachidien (RR = 1,9 ; IC 95 % : 0,9-4,1). Un état stuporeux à l'admission était associé à un risque plus faible d'échec du traitement (RR = 0,18 ; IC 95 % : 0,02-1,4), de même que l'âge (RR = 0,977 ; IC 95 % : 0,95-1,0, pour chaque année supplémentaire).

Le traitement de 7 jours par l'éflornithine est efficace contre les rechutes de trypanosomiase à *T. b. gambiense*. Cependant, pour les nouveaux cas, le traitement de 7 jours est moins efficace que la posologie standard de 14 jours et ne peut être recommandé. En Ouganda, le traitement par l'éflornithine, quelle que soit sa durée, n'est pas satisfaisant pour les nouveaux cas. Des recherches supplémentaires sont nécessaires pour comprendre la raison pour laquelle on observe un plus grand risque d'échec en Ouganda et chez les malades ayant une ponction ganglionnaire positive. Le risque plus élevé d'échec du traitement chez les malades jeunes est probablement la conséquence de différences de pharmacocinétique de l'éflornithine liées à l'âge. Les enfants et adolescents traités par l'éflornithine devront recevoir des doses plus élevées que les adultes, et nous recommandons de façon empirique des doses quotidiennes d'au moins 500 mg/kg.

Resumen

Tratamiento breve con eflornitina contra la enfermedad del sueño por *Trypanosoma brucei gambiense*: ensayo multicéntrico aleatorizado controlado

La eflornitina es la única terapia eficaz para los pacientes con enfermedad del sueño gambiense que recaen tras haber recibido melarsoprol. En los casos nuevos, la eflornitina es igual de eficaz y mucho menos tóxica que este último. Sin embargo, el régimen actual de 14 días de eflornitina intravenosa es demasiado costoso para los países endémicos, lo que explica que el fármaco siga siendo poco utilizado. El acortamiento de la duración del tratamiento haría que el medicamento fuese más asequible.

Describimos aquí los resultados de un ensayo aleatorizado controlado destinado a determinar si la administración intravenosa de eflornitina (100 mg/kg cada 6 horas) durante 7 días era tan eficaz como el régimen estándar de 14 días en el tratamiento de la fase avanzada de la enfermedad del sueño por *Trypanosoma brucei gambiense*. Un total de 321 pacientes fueron asignados aleatoriamente en 4 centros participantes del Congo, Côte d'Ivoire, la República Democrática del Congo y Uganda a una de esas dos pautas de tratamiento, y sometidos luego a seguimiento durante 2 años. En total se contabilizaron 274 casos nuevos de tripanosomiasis, mientras que 47 casos correspondían a recidivas de pacientes que habían recibido anteriormente un tratamiento diferente de la eflornitina.

Seis pacientes murieron durante el tratamiento: 3/274 (1,1%) entre los casos nuevos, frente a 3/47 (6,4%) entre las recaídas ($P = 0,04$). Uno de los pacientes fallecidos seguía el régimen de 7 días, mientras que los otros 5 habían comenzado la pauta de 14 días ($P = 0,2$). La respuesta a la eflornitina fue en Uganda notablemente distinta de la observada en otros países. Entre los casos nuevos correspondientes a ese país, la probabilidad de curación a los 2 años fue del 73% con el régimen de 14 días, frente al 62% con el régimen de 7 días (cociente de riesgo instantáneo (CR) para el fracaso terapéutico, 7 días frente a 14 días: 1,45, intervalo de confianza del 95% (IC95%): 0,7–3,1, $P = 0,3$). Entre los casos nuevos del conjunto del Congo, Côte d'Ivoire y la República Democrática del Congo, la probabilidad de curación a los 2 años fue del 97% con el régimen de 14 días, frente a 86,5% con el régimen de 7 días (CR para el fracaso terapéutico, 7 días frente a 14 días: 6,72, IC95%: 1,5–31,0, $P = 0,003$). Entre las recaídas detectadas en los 4 países, la probabilidad de curación a los 2 años fue del 94% con 7 días y del 100% con 14 días de tratamiento.

Los modelos de riesgo instantáneo proporcional de Cox mostraron la asociación de varios factores a un riesgo mayor de fracaso terapéutico: un aspirado de ganglios linfáticos positivo (CR 4,1, IC95%: 1,8–9,4), un recuento de leucocitos en líquido cefalorraquídeo (LCR) $\geqslant$ 100/mm^3 (CR 3,5, IC95%: 1,1–10,9), el hecho de haber recibido tratamiento en Uganda (CR 2,9; IC95%: 1,4–5,9), y la presencia de tripanosomas en el LCR (CR 1,9; IC95%: 0,9–4,1). La existencia de estupor en el momento del ingreso se asoció a un menor riesgo de fracaso terapéutico (CR 0,18; IC95%: 0,02–1,4), al igual que el aumento de la edad (CR 0,977; IC95%: 0,95–1,0, por cada año adicional).

El régimen de 7 días de eflornitina es un tratamiento eficaz de las recidivas de la tripanosomiasis gambiense. Sin embargo, ante los casos nuevos, una pauta de 7 días es inferior al régimen estándar de 14 días y no debe recomendarse. En Uganda, los dos regímenes fueron insatisfactorios en los casos nuevos. Es necesario emprender investigaciones adicionales para averiguar por qué el riesgo de fracaso terapéutico es mayor en Uganda y en los pacientes con un aspirado de ganglios linfáticos positivo. El mayor riesgo de fracaso observado en los pacientes más jóvenes refleja probablemente los cambios asociados a la edad de la farmacocinética de la eflornitina. A los niños y los adolescentes tratados con eflornitina se les debería administrar una dosis mayor que a los adultos; sobre la base de observaciones empíricas, recomendamos que se les administren al menos 500 mg $\star$ kg^{-1} $\star$ día^{-1}.

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