MAJOR ARTICLE

Effectiveness of a 10-Day Melarsoprol Schedule for the Treatment of Late-Stage Human African Trypanosomiasis: Confirmation from a Multinational Study (IMPAMEL II)

Caecilia Schmid,[1] Michaleen Richer,[5,a] Constantin Miaka Mia Bilenge,[3] Théophile Josenando,[6] Francois Chappuis,[2] Claude R. Manthelot,[4] Auguste Nangouma,[7] Félix Doua,[8] Pedro N. Asumu,[9] Pere P. Simarro,[10,a] and Christian Burri,[1] for the IMPAMEL II Study[b]

[1]Swiss Tropical Institute, Basel, and [2]Médécins sans Frontières, Geneva, Switzerland; [3]Programme Nationale de Lutte contre la Trypanosomiase Humaine Africaine, Kinshasa, Democratic Republic of Congo; [4]Programme National de Lutte contre la Trypanosomiase, Brazzaville, Republic of Congo; [5]International Medical Corps, Nairobi, Kenya; [6]Instituto de Combate e de Controlo das Tripanossomíases, Luanda, Angola; [7]Programme National de Lutte contre la Trypanosomiase Humaine Africaine, Bangui, Central African Republic; [8]Projet de Recherche Clinique sur la Trypanosomiase, Daloa, Côte d'Ivoire; [9]Programa Nacional de Control de Tripanosomiasis, Bata, Equatorial Guinea; [10]Fundació Centro de Información y Documentación Internacionales en Barcelona, Barcelona, Spain

(See the editorial commentary by Moore, on pages 1793–5.)

Background. Treatment of late-stage human African trypanosomiasis (HAT) with melarsoprol can be improved by shortening the regimen. A previous trial demonstrated the safety and efficacy of a 10-day treatment schedule. We demonstrate the effectiveness of this schedule in a noncontrolled, multinational drug-utilization study.

Methods. A total of 2020 patients with late-stage HAT were treated with the 10-day melarsoprol schedule in 16 centers in 7 African countries. We assessed outcome on the basis of major adverse events and the cure rate after treatment and during 2 years of follow-up.

Results. The cure rate 24 h after treatment was 93.9%; 2 years later, it was 86.2%. However, 49.3% of patients were lost to follow-up. The overall fatality rate was 5.9%. Of treated patients, 8.7% had an encephalopathic syndrome that was fatal 45.5% of the time. The rate of severe bullous and maculopapular eruptions was 0.8% and 6.8%, respectively.

Conclusions. The 10-day treatment schedule was well implemented in the field and was effective. It reduces treatment duration, drug amount, and hospitalization costs per patient, and it increases treatment-center capacity. The shorter protocol has been recommended by the International Scientific Council for Trypanosomiasis Research and Control for the treatment of late-stage HAT caused by *Trypanosoma brucei gambiense.*

Human African trypanosomiasis (HAT; also called "sleeping sickness") ranks third among all parasitic diseases in sub-Saharan Africa, behind malaria and filariasis [1], in terms of disease burden as expressed in disability-adjusted life years [2]. Sixty million people in 36 African countries are at risk of becoming infected, and the number of cases is estimated at 350,000. At present, only a fraction of the population at risk is under surveillance; therefore, the 45,000 cases reported and treated per year may be a significant underestimation [3]. HAT is caused by the protozoan parasite *Trypanosoma brucei* subspecies and is transmitted by the bite of *Glossina* species tsetse flies [4].

Received 11 October 2004; accepted 14 December 2004; electronically published 2 May 2005.

[a] Present affiliations: World Health Organization (WHO), Nairobi, Kenya (M.R.); WHO Communicable Diseases Surveillance/Control, Prevention, and Eradication/Zoonoses, Foodborne Diseases, and Kinetoplastidae, Yaoundé, Cameroon (P.P.S.).

[b] Study group members are listed after the text.

Reprints or correspondence: Dr. Christian Burri, Swiss Tropical Institute, Socinstr. 57, 4002 Basel, Switzerland (christian.burri@unibas.ch).

The Journal of Infectious Diseases 2005; 191:1922–31

0022-1899/2005/19111-0020$15.00

Presented in part: 26th International Scientific Counsel for Trypanosomiasis Research and Control, Ouagadougou, Burkina Faso, October 2001 (Proceedings p. 248–252); 27th International Scientific Council for Trypanosomiasis Research and Control, Pretoria, South Africa, September 2003 (abstract 414); 52nd Annual Meeting of the American Society of Tropical Medicine and Hygiene, Philadelphia, December 2003 (abstract 463); 1st Congrès International de Brazzaville sur la Mouche Tsé-Tsé et les Trypanosomoses, Brazzaville, Republic of Congo, March 2004 (Méd Trop [Marseille] 2004; 64:125).

Financial support: Swiss Agency for Development and Cooperation (grant 7F-01977.02).

HAT occurs in 2 distinct forms: a chronic form caused by *Trypanosoma brucei gambiense* and an acute form caused by *Trypanosoma brucei rhodesiense; T. brucei gambiense* causes 99.5% of cases [1, 4]. During the early hemolymphatic disease stage, the trypanosomes multiply in blood and lymph glands; they then invade the central nervous system, which corresponds to the late or meningoencephalitic disease stage. Without treatment, the disease is invariably fatal.

Today, 2 drugs are available for the treatment of late-stage HAT—eflornithine and melarsoprol. Eflornithine is difficult to administer, requires good logistics, and is expensive to manufacture. Therefore, it is of very limited use in rural treatment centers. In addition, it is ineffective against the acute form of the disease (caused by *T. brucei rhodesiense*). For these reasons and the lack of alternatives, melarsoprol remains the drug of choice for the treatment of late-stage HAT, even though it is highly toxic and does not results in a 100% cure rate [5, 6]. A major problem with melarsoprol is its long treatment schedule, which was developed empirically; 55 years after its introduction onto the market, regimens still vary considerably [1]. Generally, 3–4 series of 3–4 injections of increasing doses are given, spaced with resting periods of 7–10 days. To optimize and standardize melarsoprol treatment, an abridged 10-day protocol has been elaborated on the basis of pharmacological investigations [7–9], animal experiments [10], and pilot testing of patients with HAT in the former Zaire [11]. The effectiveness of this regimen, in terms of safety and efficacy, in comparison with a standard treatment regimen was shown in a large-scale randomized clinical trial in Angola (the Improved Application of Melarsoprol [Impamel] I study) [12, 13]. To further assess the effectiveness of the 10-day regimen under natural conditions, we performed a multinational, multicenter drug-utilization study for the treatment of late-stage *T. brucei gambiense* HAT.

PATIENTS, MATERIALS, AND METHODS

Centers and patients. The study was implemented in 16 HAT treatment centers suggested by the respective national HAT programs or by nongovernment organization (NGOs), where applicable, in 7 sub-Saharan African countries where *T. brucei gambiense* is endemic. The minimal conditions for the center selection were reasonable accessibility, the availability of retrospective data on HAT treatment, and the exclusive use of the new treatment schedule for 12 consecutive months.

Study design and implementation. A very simple study design, without randomization and sample-size calculation, was chosen to monitor the effectiveness of the 10-day treatment schedule for melarsoprol under true field conditions (drug utilization; Impamel II). The enrollment period for each center was 12 months, to balance for seasonal variation. The study was approved by the ethics committee of the 2 cantons of Basel (Ethikkommission beider Basel) and the relevant ethics committees and authorities in the respective countries. In the selected centers, the abridged schedule was introduced as the standard treatment; therefore, no consent was obtained from the patients.

The patient inclusion criterion was confirmed late-stage gambiense HAT. At present, the methodology and criteria for diagnosis and staging of the disease are still not standardized among African countries; patients were included according to the staging criteria of the respective national HAT control programs. Generally, diagnosis of late stage was made by microscopic examination of the cerebrospinal fluid (CSF) for the presence of trypanosomes and/or an increased white blood cell (WBC) count. Different cutoff criteria for the WBC in CSF were used: >5 cells/mm^3 in Central African Republic, Democratic Republic of Congo, Republic of Congo, and Sudan; $\geqslant$10 cells/mm^3 in Equatorial Guinea; and $\geqslant$20 cells/mm^3 in Angola and Côte d'Ivoire.

Treatment. Patients were treated with 2.2 mg/kg/day of melarsoprol for 10 days, as a 3.6% solution in propylene glycol (Arsobal; Aventis), by slow intravenous (iv) injection. Before melarsoprol treatment, all patients received supplementary medication: antimalarials, mebendazole, multivitamins, and paracetamol (acetaminophen). During melarsoprol treatment, different prophylactic corticosteroid treatments were administered: prednisolone at a dose of 1 mg/kg on days 1–7, 0.75 mg/kg on day 8, 0.5 mg/kg on day 9, and 0.25 mg/kg on day 10 in Democratic Republic of Congo, Equatorial Guinea, and Sudan; 1 mg/kg on days 1–9, 0.75 mg/kg on day 10, 0.5 mg/kg on day 11, and 0.25 mg/kg on day 12 in Angola; 1 mg/kg on days 1–9, 0.75 mg/kg on day 10, and 0.5 mg/kg on day 11 in Central African Republic; 0.75 mg/kg on days 1–10 in Republic of Congo; and 1 mL of bethamethasone in Côte d'Ivoire. No prednisolone was administered, but, on days 1–10, promethazine (antihistamine) was given to the patients in 1 center in Democratic Republic of Congo (Centre Neuro-Psycho Pathologique/Cliniques Universitaires de Kinshasa).

When an encephalopathic syndrome developed, treatment with melarsoprol was suspended, and the patient was treated according to national guidelines—for example, with adrenaline (epinephrine), corticosteroids (usually hydrocortisone), and/or diazepam. If possible, the melarsoprol treatment was resumed after 1–3 days or was considered to have been completed if $\geqslant$8 doses had already been given. For each patient, a case-report form was filled out that contained information on demographic, diagnostic, and clinical characteristics before and after treatment and an assessment of adverse events on a graded scale from 0 to 2 (no, moderate, or severe reactions).

Outcome measures. Efficacy of the treatment was demonstrated, by the absence of trypanosomes, by microscopic examination of the blood and/or lymph and CSF and/or a reduction in WBC count. Patients were scheduled for clinical examination, including lumbar puncture (LP), 24 h after treatment and every 6 months for 2 years after treatment, to monitor

for treatment failures and relapses. Treatment failures were defined as patients in whom trypanosomes could still be found in any body fluid 24 h after treatment; relapses were defined as patients presenting during follow-up with (1) trypanosomes in any compartment and/or (2) an increase in CSF WBC count to >50 cells/mm^3 that was double that seen at the previous examination or a WBC count of 6–49 cells/mm^3 that was accompanied by clear symptoms attributed to relapse (somnolence, long-lasting headache, and recurrent fever). The primary efficacy outcome was parasitological cure 24 h after treatment (treatment failures), and the secondary efficacy outcome was relapse within the follow-up period.

The safety of treatment was determined by the frequency of adverse events. The primary safety outcomes were death in temporal relation to treatment and the frequency of encephalopathic syndromes. The rate of other severe adverse reactions was defined as a secondary outcome.

Data management and statistical analysis. All data were double entered and verified by use of EpiData 2.1 [14] software, and analysis was done by use of the statistical software package STATA (version 7.0; Stata). The findings were compared with historical data from the participating centers, literature, and the randomized clinical trial recently conducted in Angola [12, 13]. For calculation of the efficacy, the total number of all treated patients was used as the denominator, to allow comparison with previously reported rates.

RESULTS

Study population and baseline characteristics. A total of 2800 patients were enrolled between June 1999 and June 2002; 780 patients were not eligible for the analysis for several reasons (figure 1). The final cohort consisted of 2020 patients who had been correctly diagnosed and were treated with the 10-day melarsoprol schedule in 10 HAT treatment centers in 5 countries.

The demographic, diagnostic, and clinical characteristics of the patients are shown in table 1. Distributions by age, sex, and nutritional status at the time of admission were similar among patients at different centers. The diagnostic findings varied from center to center, probably because of different methodologies and cutoff criteria. The majority of patients had lymphadenopathies, headaches, pruritus, general weaknesses, and sleeping disorders; a large variation in clinical manifestations among the centers was evident.

Treatment compliance. The average rate of adherence to the treatment regimen was 67.1% (1355/2020; figure 2); 78.1% (1578/2020) finished the treatment with an interruption of <2 days. Overall, 88.8% (1793/2020) of patients received 10 doses. Nonadherence resulted from treatment interruption due to severe adverse reactions; however, in most cases, treatment was resumed after 2–4 days (median, 2 days; mean, 4 days; SD, 4 days; range, 1–24 days). Most of the interruptions occurred between days 8 and 10 of treatment.

Efficacy. The parasitological cure rate 24 h after treatment was 93.9% (1897/2020; range among centers, 85.7%–100%) (table 2). A total of 119 (5.9%) patients died during treatment, and trypanosomes were detected in 4 (0.2%) patients who were treated for relapse. Two years after treatment, the observed cure rate was 86.2% (1742/2020), with considerable intercenter variation (range, 70.9%–100%). Follow-up participation was highly variable (15%–100%; data not shown). Many of the patients who were cured at discharge did not attend any of the clinical follow-up examinations (936/1897 [49.3%]) and were considered to have remained cured. Some 50.7% (961/1897) attended at least 1 of 4 prescribed follow-up examinations with LP; 144 of these (7.1%) were diagnosed as having relapses. During follow-up, 18 (0.9%) patients died, 7 (0.3%) after relapsing. In 53 (36.8%) of the patients who relapsed, trypanosomes were found in blood (7 [4.9%]) or CSF (46 [31.9%]). All other relapses were diagnosed by an elevated CSF WBC count of >50 cells/mm^3 (61 [42.4%]) or by a CSF WBC count that had at least doubled since discharge from the hospital that was accompanied by clear symptoms of disease (30 [20.8%]). Relapses were not further analyzed, because of the large variation of the follow-up coverage among the different centers.

Safety. The safety results are presented in table 3 by severity and country. These results reflect the expected large variation observed in the treatment of HAT.

During treatment, 119 patients died, an average after 9 days of treatment (range, 1–29 days). The major causes were encephalopathic syndromes, which contributed to 67.2% (80) of the fatalities. Other causes were advanced HAT (15 [12.6%]), concomitant diseases (10 [8.4%]), unknown etiology (9 [7.6%]), and bullous skin reactions (5 [4.2%]).

A total of 176 (8.7%) patients had an encephalopathic syndrome; they generally received iv steroids at different doses. The onset of the encephalopathic syndrome was reported after an average of 9 days of treatment (median, 9 days; mean, 9.2 days; range, 1–28 days). In patients who survived, treatment was resumed after a suspension of 3 days (median, 3 days; mean, 3.2 days; range, 1–12 days). No significant seasonal variation was observed in any of the centers (data not shown). Headache preceded the onset of the encephalopathic syndrome in 34.1% (60/176) and fever in 54.0% (95/176) of patients. In 22.7% (40/176) of patients with an encephalopathic syndrome, malaria parasites were detected during the syndrome, which probably caused the fever in 20 (11.4%) of them. The effect of the prophylactic use of prednisolone could only be evaluated for 2 southern Sudanese centers that provided reliable information for each patient. In those centers, 163 (26.8%) of 607 patients received prednisolone. Patients who did not receive prednis-

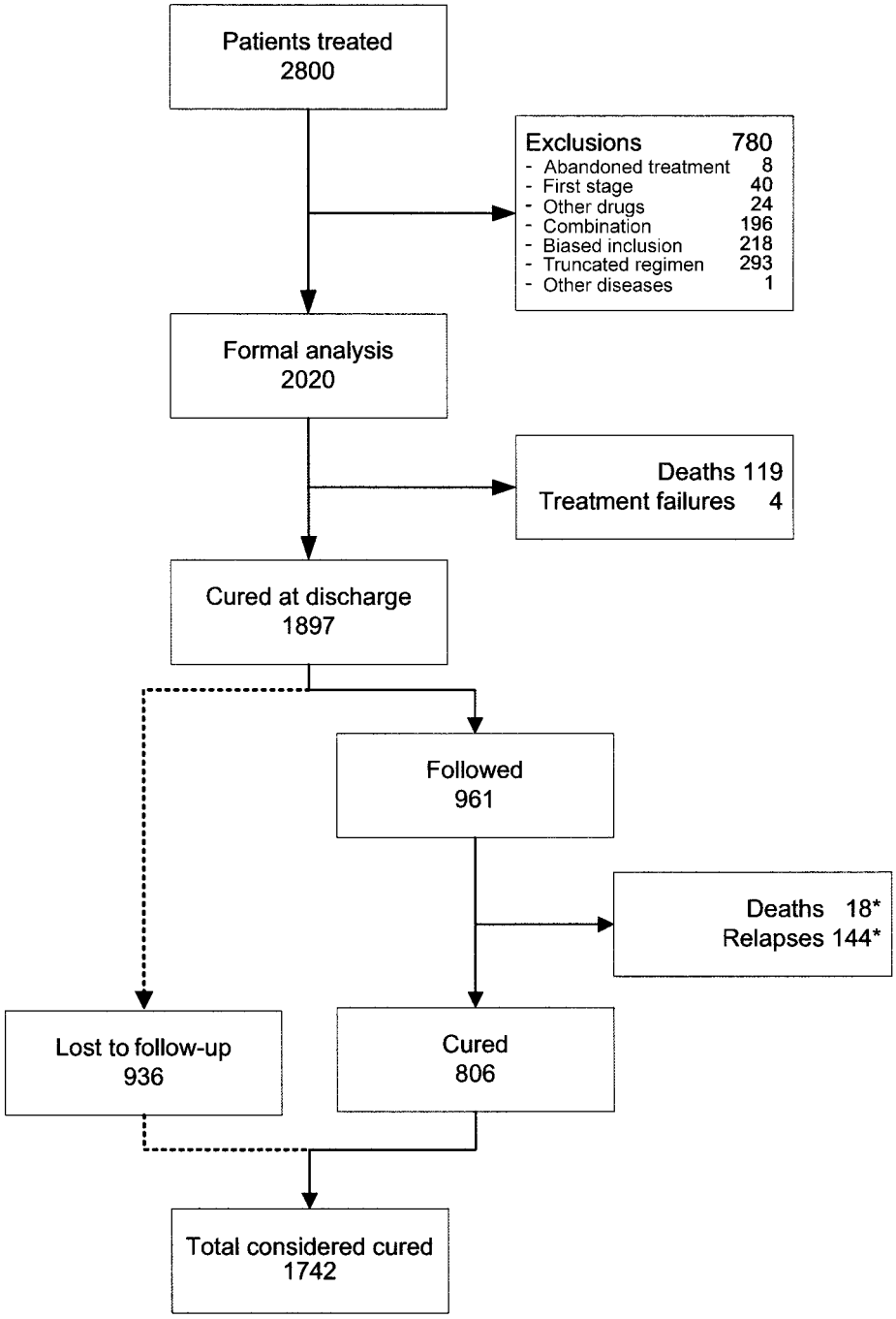

Figure 1. Study profile of IMPAMEL II. *Seven of the patients who relapsed died during the follow-up period; their data are included in the deaths during follow-up. TB, tuberculosis.

olone were at a slightly (statistically nonsignificant) higher risk of developing an encephalopathic syndrome (relative risk [RR], 1.3 [95% confidence interval {CI}, 0.8–2.2]; $P = .286$) or of dying (RR, 1.4 [95% CI, 0.5–3.9]; $P = .598$).

The frequency of skin reactions was high (28.3% [571/2020]) but varied between the centers. However, the majority of recorded skin reactions were moderate pruritus; this was consistently not considered to be a significant problem by the treating staff and could be controlled with steroids or promethazine. Patients in south Sudan who received prednisolone as prophylactic treatment were at a lower risk of developing a moderate skin reaction (RR, 0.6 [95% CI, 0.4–0.8]; $P = .0004$).

Other adverse reactions that were often reported included fever and headache. However, these are common symptoms

Table 1. Pretreatment characteristics of the patients.

Characteristic	Total (n = 2020)	Angola (n = 337)	Côte d'Ivoire (n = 27)	Democratic Republic of Congo (n = 532)	Equatorial Guinea (n = 13)	Sudan (n = 1111)
Age, median (range), years	27 (1–80)	25 (1–74)	15 (2–51)	30 (1–80)	30 (11–64)	26 (1–70)
Male sex	988 (49)	177 (53)	13 (48)	261 (49)	9 (69)	528 (48)
Nutritional status						
BMI, mean ± SD, kg/m^2	18.5 ± 3.1	18.2 ± 3.4	17 ± 2.7	18.8 ± 3.6	19 ± 2.9	18.4 ± 2.8
Severe malnutrition[a]	551 (27)	115 (34)	7 (26)	153 (29)	5 (38)	271 (24)
Previous treatment for HAT[b]	151 (7)	17 (5)	8 (30)	17 (3)	0 (0)	109 (10)
Received Arsobal	45 (30)	1 (6)	1 (13)	12 (71)	0 (0)	31 (28)
Diagnostic findings						
Lymphadenopathy	1178 (58)	192 (57)	9 (33)	288 (54)	13 (100)	676 (61)
Trypanosomes in any compartment	1755 (87)	278 (82)	27 (100)	508 (95)	12 (92)	930 (84)
Trypanosomes in CSF	816 (40)	227 (67)	25 (93)	229 (43)	6 (46)	329 (30)
Trypanosomes in blood/lymph	1043 (52)	176 (52)	15 (56)	260 (49)	11 (85)	581 (52)
White blood cell count in CSF						
5–19 cells/μL	536 (26)	2 (1)	0 (0)	151 (28)	0 (0)	383 (34)
20–100 cells/μL	604 (30)	100 (29)	4 (15)	131 (25)	6 (46)	363 (33)
>100 cells/μL	880 (44)	235 (70)	23 (85)	250 (47)	7 (54)	365 (33)
Median (mean ± SD)	70 (180 ± 240)	170 (230 ± 210)	278 (320 ± 210)	82 (240 ± 3100)	118 (200 ± 210)	37 (130 ± 200)
Clinical manifestations						
Drowsiness	318 (16)	108 (32)	3 (11)	128 (24)	1 (8)	78 (7)
Headache	1616 (80)	308 (91)	19 (70)	342 (61)	11 (85)	954 (86)
Fever (>37.5°C)	326 (16)	41 (12)	13 (48)	25 (5)	ND	247 (22)
Pruritus	1017 (50)	106 (31)	15 (56)	168 (32)	11 (84)	717 (65)
Weakness	692 (34)	131 (39)	7 (26)	244 (86)	7 (54)	303 (27)
Walking difficulties	419 (21)	113 (34)	5 (19)	89 (17)	5 (38)	207 (19)
Abnormal movements	201 (10)	39 (12)	8 (30)	71 (13)	0 (0)	83 (7)
Speech impairment	266 (13)	77 (23)	6 (22)	79 (15)	2 (15)	102 (9)
Sleeping disorder	1466 (73)	202 (60)	25 (93)	504 (95)	12 (92)	723 (65)
Strange behavior	520 (26)	54 (16)	18 (67)	81 (15)	2 (15)	365 (33)

NOTE. Data are no. (%) of patients, unless otherwise indicated. BMI, body mass index; CSF, cerebrospinal fluid; HAT, human African trypanosomiasis; ND, no determination or not done.

[a] BMI < 16.5; adjusted for age and sex in children.

[b] Within 2 years before admission in IMPAMEL II.

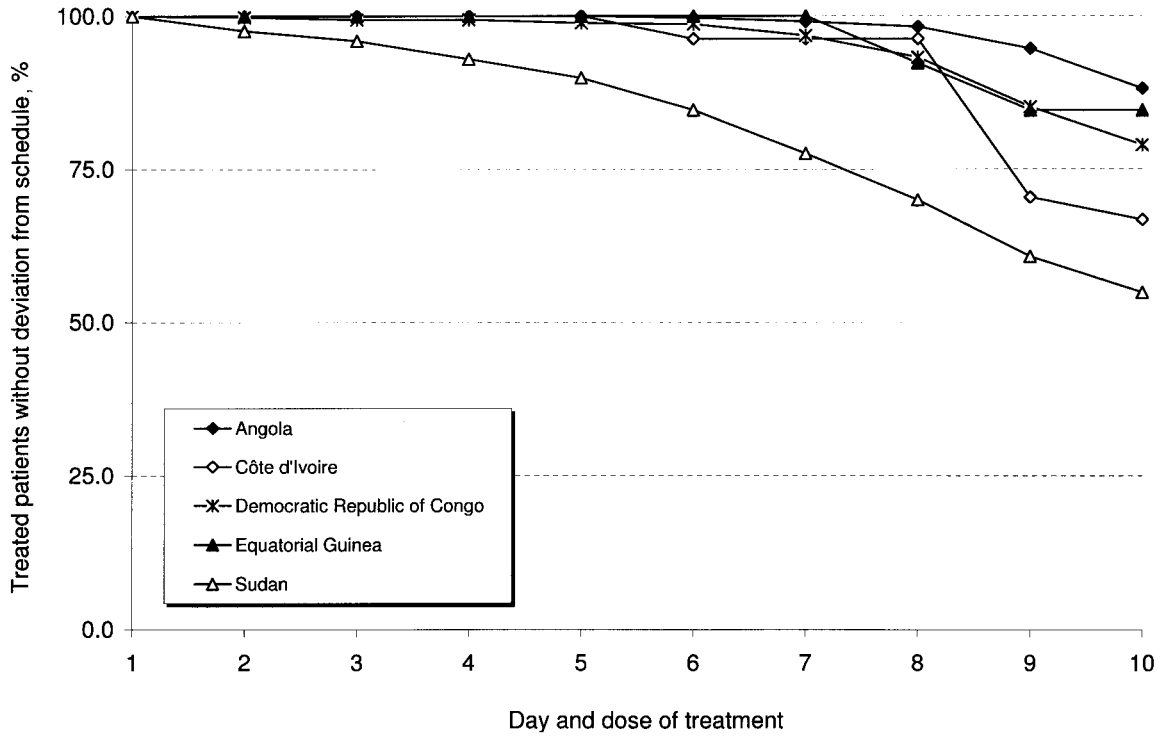

Figure 2. Compliance with treatment schedule, by country

and signs of the disease and are not easily discriminated from adverse events caused by treatment. Less frequently reported reactions included polyneuropathies, diarrhea, jaundice, and hypotension.

DISCUSSION

The present work (IMPAMEL II) was a noncontrolled, multinational, multicenter drug-utilization study to evaluate, under true field conditions, the abridged treatment schedule of melarsoprol during late-stage *T. brucei gambiense* HAT. Because of the very basic equipment available in treatment centers, the often low level of staff qualifications, and the lack of experience in the conduct of clinical trials in most centers, it was not possible to conduct a randomized study. Cluster randomization was also considered to be impossible, because of the inherent differences in the outcome of HAT treatment in different centers and countries and the limited number of centers available. The 12-month enrollment period was chosen to reveal a potential seasonal variation of the outcome [15]; centers that enrolled patients for <12 months were excluded from the for-

Table 2. Short- and long-term efficacy of 10-day melarsoprol treatment (24 h after treatment and during follow-up), compared with IMPAMEL I results, center history, and literature.

Efficacy measurement	IMPAMEL II, 10-day treatment (n = 2020)	Center history, standard treatment (n = 2215)	IMPAMEL I		Literature, standard treatment, %[a]
			10-day treatment (n = 250)	Standard treatment (n = 250)	
Fatalities during treatment	119 (5.9)	117 (5.3)	6 (2.4)	6 (2.4)	9.4
Treatment failures at discharge	4 (0.2)	18 (0.8)	0 (0)	0 (0)	<1
Cured at time of discharge	1897 (93.9)	2080 (93.9)	244 (97.6)	239 (95.6)	90
Fatalities during follow-up	18 (0.9)[b]	ND	6 (2.8)	8 (3.6)	ND
Relapses during follow-up	144 (7.7)[b]	54 (2.6)	12 (5.5)	11 (4.9)	<30
Lost during follow-up[c]	936 (49.3)	ND	26 (10.7)	15 (6.3)	ND
Cured 2 years after treatment[c]	1742 (86.2)	2026 (91.5)	226 (90.4)	230 (92)	70–90

NOTE. Data are no. (%). ND, no data available.

[a] The total no. of subjects was highly variable; often, only percentages were published.

[b] Seven of the patients with relapse later died and are included in both categories.

[c] We assumed that all patients lost to follow-up were cured. We used as a denominator the total no. of all patients treated.

Table 3. Adverse events during melarsoprol treatment, by severity and country.

Adverse event	Total (n = 2020)	Angola (n = 337)	Côte d'Ivoire (n = 27)	Democratic Republic of Congo (n = 532)	Equatorial Guinea (n = 13)	Sudan (n = 1111)
Fatalities[a]	119 (5.9)	24 (7.1)	2 (7.4)	45 (8.5)	1 (7.7)	47 (4.2)
ES						
Total	176 (8.7)	18 (5.3)	0 (0)	49 (9.2)	1 (7.7)	108 (9.7)
Grade 3 (fatal)	80 (4.0)	13 (3.9)	0 (0)	33 (6.2)	1 (7.7)	33 (3)
Case fatality rate, %	45	72	0	67	100	31
Grade 2 (coma or convulsions)	72 (3.6)	5 (1.5)	0 (0)	13 (2.4)	0 (0)	54 (4.9)
Grade 1 (psychosis)	24 (1.2)	0 (0)	0 (0)	3 (0.6)	0 (0)	21 (1.9)
Bullous eruptions						
Any	30 (1.5)	7 (2.1)	0 (0)	12 (2.3)	1 (7.7)	10 (0.9)
Severe	17 (0.8)	3 (0.9)	0 (0)	8 (1.5)	0 (0)	6 (0.5)
Maculopapular eruptions						
Any	228 (11.3)	31 (9.2)	9 (33.3)	58 (10.9)	1 (7.7)	129 (11.6)
Severe	138 (6.8)	25 (7.4)	7 (26.0)	45 (8.5)	0 (0)	61 (5.5)
Pruritus						
Any	478 (23.7)	41 (12.2)	4 (14.8)	44 (8.3)	2 (15.4)	387 (34.8)
Severe	66 (3.2)	1 (0.3)	0 (0)	26 (4.9)	0 (0)	39 (3.5)
Motor polyneuropathy						
Any	128 (6.3)	13 (3.9)	0 (0)	9 (1.7)	0 (0)	106 (9.5)
Severe	37 (1.4)	6 (1.8)	0 (0)	8 (1.5)	0 (0)	23 (2.1)
Sensitivity polyneuropathy						
Any	64 (3.2)	1 (0.3)	0 (0)	4 (0.7)	0 (0)	59 (5.3)
Severe	24 (1.2)	0 (0)	0 (0)	3 (0.6)	0 (0)	21 (1.9)
Fever						
Any (37.5°C–39°C)	653 (32.3)	39 (11.6)	24 (88.9)	109 (20.5)	2 (15.4)	479 (43.1)
Severe (>39°C)	233 (11.5)	17 (5.0)	11 (40.7)	53 (10.0)	1 (7.7)	151 (13.6)
Headache						
Any	599 (29.6)	43 (12.8)	4 (14.8)	21 (4)	4 (30.8)	527 (47.6)
Severe	146 (7.2)	16 (4.8)	0 (0)	11 (2.1)	2 (15.4)	117 (10.5)
Diarrhea						
Any	173 (8.6)	5 (1.5)	0 (0)	11 (2.1)	3 (23.1)	154 (13.9)
Severe	45 (2.2)	1 (0.3)	0 (0)	3 (0.6)	1 (7.7)	40 (3.6)
Hypotension						
Any	60 (3.0)	5 (0.5)	0 (0)	23 (4.3)	0 (0)	32 (2.9)
Severe	16 (0.8)	0 (0)	0 (0)	13 (2.4)	0 (0)	3 (0.3)
Jaundice						
Any	9 (0.5)	1 (0.3)	0 (0)	2 (0.4)	0 (0)	6 (0.5)
Severe	5 (0.2)	0 (0)	0 (0)	2 (0.4)	0 (0)	3 (0.2)

NOTE. Data are no. (%) of patients, unless otherwise indicated. The results are comparable to those obtained in the controlled clinical trial [12]. ES, encephalopathic syndrome.

[a] All fatalities during treatment, including those due to fatal ES.

mal analysis, and data for a longer period were truncated after the first 12 months. Other patients excluded from the formal analysis were those who received any treatment other than 10-day melarsoprol or who were preselected on the basis of the self-defined criteria of a treatment center—for example, adults only or patients admitted in good health.

The study population corresponded to the average population of African countries [16], except for the patients treated in Côte d'Ivoire (n = 27), who were much younger (median age, 15 years) than the overall study population (median age, 27 years). The clinical conditions and the diagnostic characteristics of the patients at the time of admission were highly variable among centers, which reflects the different levels of surveillance activities in each country, the diverse qualifications of staff and their perception of illnesses and adverse reactions (nurses vs. medical doctors; national control programs vs. NGOs), and differences in laboratory equipment among the centers. However, there was no difference in the outcome of treatment among the cohorts that were diagnosed according to the different cutoff criteria in use (data not shown).

The average short-term (93.9%) and long-term (86.2%) efficacies, with "all patients treated" as the denominator and considering patients who not seen during the follow-up to be cured, were comparable to published data [5, 12, 17–22] and the

Table 4. Severe adverse events during treatment with melarsoprol in the IMPAMEL II study, compared with standard treatment (IMPAMEL I), center history, and literature.

Adverse event	IMPAMEL II, 10-day treatment (n = 2020)	Center history, standard treatment (n = 2215)	IMPAMEL I		Literature, standard treatment, mean % (range)[a]
			10-day treatment (n = 250)	Standard treatment (n = 250)	
Fatalities	119 (5.9)	117 (5.3)	6 (2.4)	6 (2.4)	9.4 (2.7–34)
ES[b]	152 (7.5)	184 (8.3)	14 (5.6)	14 (5.6)	4.7 (1.5–23.5)
Grade 3	80 (4.0)	87 (3.9)	6 (2.4)	6 (2.4)	4.1 (3.3–34)
Case fatality rate, %	52.6	47.3	42.9	42.9	43.8 (33–100)
Skin reactions	166 (8.2)	35 (1.6)	23 (9.2)	13 (5.2)	<3
Bullous eruptions	17 (0.8)	4 (0.2)	3 (1.2)	1 (0.4)	< 1
Maculopapular eruptions	138 (6.8)	20 (0.9)	12 (4.8)	6 (2.4)	ND
Pruritus	66 (3.3)	11 (0.5)	8 (3.2)	6 (2.4)	5
Polyneuropathies[c]	54 (2.7)	24 (1.1)	2 (0.8)	1 (0.4)	<10
Febrile reaction	233 (11.5)	72 (3.2)	15 (6.0)	12 (4.8)	12
Headache	146 (7.2)	43 (1.9)	ND	ND	ND
Diarrhea	45 (2.2)	19 (0.9)	6 (2.4)	4 (1.6)	<25
Hypotension	16 (0.8)	19 (0.9)	ND	ND	<1
Jaundice	5 (0.2)	3 (0.1)	ND	ND	<3

NOTE. Data are no. (%) of patients, unless otherwise indicated. ES, encephalopathic syndrome; ND, not determined or no data available.

[a] The total no. of subjects was highly variable; often, only percentages were published.

[b] Grades 2 (convulsion or coma) and 3 (fatal).

[c] Motor or sensitivity polyneuropathies.

centers' histories (table 2). This approach is somewhat unsatisfactory, because it leads to an overestimation of effectiveness. The assessment of long-term efficacy is complicated by generally low follow-up rates; thus, no consistent information on follow-up coverage is given in the literature. Our approach yielded the best comparison to recently published studies [12, 17–23] and to the centers' histories. The proportion of patients in our study who attended a follow-up examination was highly variable among centers (0%–100%). On average, one-half of all patients attended at least 1 follow-up examination, mostly within the first year after treatment; therefore, the failure rates in the present study are difficult to estimate and to compare to reported rates. The overall rate of treatment failures and relapses in our study was 7.1% (144/2020), a value that compares well with those in the literature (5%–8% [24]). However, because alarmingly high rates—up to 30%—have been documented in some areas (Uganda [23], Angola [25], and Sudan [26]), failure rates by disease focus should be reported more carefully. In our study, most of the relapses (136/144) were reported in southern Sudanese centers, which may be explained (at least partially) by the enhanced follow-up activities conducted by the executing organizations, which resulted in a 12.2% (136/1111) failure rate in this area. However, this is still much lower than reported rates from this area (centers' histories, 15%–25%; literature, 16%–24% [22]).

The safety and tolerability of the 10-day melarsoprol treatment schedule were similar to those of standard treatment schedules [12, 27–31], with the exception of skin reactions, fevers, and headaches (table 4). The variability of the adverse events among the different study centers was expectedly high, and comparable results were found in a separate analysis of data from the patients who had been excluded from the formal analysis. Mild symptoms and signs such as fever (32.3%), headache (29.6%), and pruritus (23.7%), which are also common symptoms and signs of HAT, were more frequently reported during the study. This may be an observation bias prompted by solicitation of information that usually is not recorded. That more treatment interruptions caused by moderate adverse events were reported in centers operated by NGOs supports this reflection.

The frequency of treatment-related death was 5.9% (119/2020), and the most severe reactions were encephalopathic syndromes (8.7% [176/2020]). These rates are comparable to published data [32, 33], although they are at the upper end of the range. In accordance with the findings of previous reports [12, 27–31], encephalopathic syndromes occurred between days 1 and 28 after the initial injection of melarsoprol, with most of them occurring between days 9 and 11 (mean, 9.2 days; SD, 4 days), which supports the view that the event is independent of the treatment schedule and the dose applied. Also, the resumption of melarsoprol after interruption and patients' improvement did not result in a recurring reaction. The effect of prednisolone prophylaxis could only be evaluated for 2 treatment centers in Sudan, because other centers used dosage regimens that were slightly aberrant from the study protocol, had interruptions in drug stocks, or provided information for many patients that was not detailed enough. In the analyzed population, there was no statistically significant prophylactic effect of prednisolone on the development of an encephalopathic syn-

drome or a difference in the case-fatality rate in this cohort, as was suggested by Pepin et al. [30]. However, with prednisolone treatment, we observed clear protection against the development of moderate drug-related skin reactions [33].

The present results corroborate those of a randomized, controlled clinical trial previously conducted in Angola [12] (IMPAMEL I) that demonstrated that a 10-day regimen was not inferior to the lengthy standard treatment schedule. The overall frequency of adverse events was high, but, again, there was no increase, compared with that of standard treatment schedules, except for skin reactions. At the time of discharge from the hospital, symptoms and signs—such as pruritus, fever, headache, tremor, weakness, and unusual behavior—had substantially improved (data not shown). Also, the long-term efficacy of our approach appeared to be equivalent to that of standard treatment schedules [13] when follow-up activities were purposely not assisted. The 10-day schedule has several advantages over the very lengthy standard schedules: it is favorable in socioeconomic (less drug is used and shorter hospitalizations are required), technical (10 consecutive days and no dosage adjustment), pharmacologic (the dosage used is the basis of all combinations of melarsoprol in the compassionate treatment of refractory cases), and psychological (patient and physician compliance) terms.

Clearly, the tolerability and safety of melarsoprol are inferior to those of eflornithine [34]. However, the administration of eflornithine as slow infusions every 6 h over the course of 14 days is difficult and requires qualified staff and very good logistics. Therefore, eflornithine remains restricted to centers that receive substantial and consistent support from NGOs, and the vast majority of patients are still treated with melarsoprol.

Also, melarsoprol is still is the only treatment for *T. brucei rhodesiense,* because of the inconsistent efficacy of eflornithine against this form of the parasite. However, the use of the 10-day melarsoprol schedule against *T. brucei rhodesiense* is strongly discouraged. The clinical nature of this form is very different, and high parasitemia levels are observed. Confirmation of the clinical evaluation of the 10-day schedule for rhodesiense HAT has yet to be performed.

On the basis of the results of IMPAMEL I and II and the experiences in each country, in September 2003 [35], the 10-day melarsoprol schedule was discussed, at the request of the World Health Organization, by the International Scientific Council for Trypanosomiasis Research and Control and was recommended as the standard schedule for the treatment of late-stage *T. brucei gambiense* HAT with melarsoprol. Its use was continued after the study in several countries (Central African Republic, Côte d'Ivoire, Democratic Republic of Congo, Equatorial Guinea, and Republic of Congo), and it is currently being implemented by the national HAT programs.

IMPAMEL II STUDY

In addition to the authors, the IMPAMEL II study was conducted by investigators in the following countries. Angola: Dr. Gedeão Vatunga, Dr. Francisco Manuel, Inacio Zua Antonio, and Dr. Andre Jose Ribeiro; Central African Republic: Dr. Sylvestre Mbadingai and Dr. André Sandoka; Côte d'Ivoire: Dr. Norbert Dje N'goran; Democratic Republic of Congo: Dr. Pascal Lutumba, Jean Kwete, Mandefu, Landu Rando Malu, Dr. Leon Kazumba, and Bonga Nsangu; Equatorial Guinea: Dr. Mario Sarsa, Dr. Jose Ramon Franco, and Eustaquio Nguema Ndong; Republic of Congo: Ngondongo Philippe, Dr. Sonja van Osch, Dr. Genevieve Kabonga, Dr. Unni Karunakara, and Dr. Diakite Drissa; and Sudan: Dr. Cedric Yashimoto, Dr. Mario Enrile, Dr. Anne Pittet, and Dr. Luca Flamingui.

Acknowledgments

We are indebted to our patients and their families; to the members of the data and safety monitoring board, Pierre Cattand, Lars Rombo, Dr. Blaise Genton, and Dr. Steve Bennett; to Dr. Jean Jannin (World Health Organization), for logistical support and drug supply; to the medical advisors, Drs. Johannes Blum and Jorge Seixas; to the statistical consultants, Dr. Penelope Vounatsou and Thomas Smith; to the project assistant, Doris Magdalinski; to the data entry clerks, Cedric Wasser, Kirsten Gillingwater, Katrin Bettge, and Verena Schäfer; to the scientific advisors, Dr. Anne Moore, Reto Brun, and Philippe Buscher; and to Dan Anderegg, for manuscript revision. Logistic and technical support was provided by the World Health Organization, International Medical Corps, Médécins sans Frontières, the Fundació Centro de Información y Documentación Internacionales en Barcelona, and the Ministries of Health of the participating countries.

References

1. World Health Organization (WHO). Control and surveillance of African trypanosomiasis. WHO technical report series. Vol 881. Geneva: WHO, **1998**.
2. World Health Organization (WHO.) World health report 2004: changing history. Geneva, WHO: **2004**.
3. World Health Organization. African trypanosomiasis or sleeping sickness—fact-sheet. Wkly Epidemiol Rec **2004**; 79:297–300.
4. Burri C, Brun R. Human African trypanosomiasis. In: Cook G, Zumla A, eds. Manson's tropical diseases. 21st ed. London: WB Saunders, **2002**: 1303–23.
5. Legros D, Fournier C, Etchegorry MG, Maiso F, Szumilin E. Therapeutic failure of melarsoprol among patients treated for late-stage of *T. b. gambiense* human African trypanosomiasis in Uganda [in French]. Bull Soc Pathol Exot **1999**; 92:171–2.
6. Stanghellini A. African human trypanosomiasis: therapeutic strategies [in French]. Bull Soc Pathol Exot **2000**; 93:31–3.
7. Burri C, Baltz T, Giroud C, Doua F, Welker HA, Brun R. Pharmacokinetic properties of the trypanocidal drug melarsoprol. Chemotherapy **1993**; 39:225–34.
8. Burri C. Pharmacological aspects of the trypanocidal drug melarsoprol [Ph.D. thesis]. Basel, Switzerland: Swiss Tropical Institute, University of Basel, **1994**.
9. Burri C, Brun R. An in vitro bioassay for quantification of melarsoprol in serum and cerebrospinal fluid. Trop Med Parasitol **1992**; 43:223–5.
10. Burri C, Onyango JD, Auma JE, Burudi EM, Brun R. Pharmacokinetics of melarsoprol in uninfected vervet monkeys. Acta Trop **1994**; 58:35–49.
11. Burri C, Blum J, Brun R. Alternative application of melarsoprol for

treatment of *T. b. gambiense* sleeping sickness: preliminary results. Ann Soc Belg Med Trop **1995**; 75:65–71.
12. Burri C, Nkunku S, Merolle A, Smith T, Blum J, Brun R. Efficacy of new, concise schedule for melarsoprol in treatment of sleeping sickness caused by *Trypanosoma brucei gambiense:* a randomised trial. Lancet **2000**; 355:1419–25.
13. Schmid C, Nkunku S, Merolle A, Vounatsou P, Burri C. Efficacy of 10-day melarsoprol schedule 2 years after treatment for late-stage gambiense sleeping sickness. Lancet **2004**; 364:789–90.
14. Lauritsen J, Bruus M. EpiData (version 2.1): a comprehensive tool for validated entry and documentation of data. Odense, Denmark: EpiData Association, 2000–2005. Available at: http://www.epidata.dk. Accessed 21 April 2005.
15. Ancelle T, Barret B, Flachet L, Moren A. 2 epidemics of arsenical encephalopathy in the treatment of trypanosomiasis, Uganda, 1992–1993 [in French]. Bull Soc Pathol Exot **1994**; 87:341–6.
16. United Nations Development Programme. Human development report 2003, millennium development goals: a compact among nations to end human poverty. Available at: http://hdr.undp.org/reports/global/2003/pdf/hdr03_HDI.pdf. Accessed 21 April 2005.
17. Pepin J, Mpia B, Iloasebe M. *Trypanosoma brucei gambiense* African trypanosomiasis: differences between men and women in severity of disease and response to treatment. Trans R Soc Trop Med Hyg **2002**; 96:421–6.
18. Atouguia JLM, Kennedy PGE. Neurological aspects of human African trypanosomiasis. In: Davis LE, Kennedy PGE, ed. Infectious diseases of the nervous system. 1st ed. Oxford: Reed Educational and Professional Publishing, **2000**.
19. Richet P, Lotte M, Foucher G. Résultat des traitements de la trypanosomiase humaine a *Trypanosoma gambiense* par le Mel B ou l'Arsobal. Med Trop (Mars) **1959**; 19:253–65.
20. Dutertre J, Labusquiere R. La thérapeutique de la trypanosomiase. Med Trop (Mars) **1966**; 26:342–56.
21. Bertrand E, Rive J, Serie F, Kone I. Encéphalopathie arsenicale et traitement de la trypanosomiase. Med Trop (Mars) **1973**; 33:385–90.
22. Brun R, Schumacher R, Schmid C, Kunz C, Burri C. The phenomenon of treatment failures in human African trypanosomiasis. Trop Med Int Health **2001**; 6:906–14.
23. Legros D, Evans S, Maiso F, Enyaru JC, Mbulamberi D. Risk factors for treatment failure after melarsoprol for *Trypanosoma brucei gambiense* trypanosomiasis in Uganda. Trans R Soc Trop Med Hyg **1999**; 93:439–42.
24. Pepin J, Milord F, Khonde A, Niyonsenga T, Loko L, Mpia B. Gambiense trypanosomiasis: frequency of, and risk factors for, failure of melarsoprol therapy. Trans R Soc Trop Med Hyg **1994**; 88:447–52.
25. Stanghellini A, Josenando T. The situation of sleeping sickness in Angola: a calamity. Trop Med Int Health **2001**; 6:330–4.
26. Brun R, Baeriswyl S, Kunz C. In vitro drug sensitivity of *Trypanosoma gambiense* isolates. Acta Trop **1989**; 46:369–76.
27. Blum J, Nkunku S, Burri C. Clinical description of encephalopathic syndromes and risk factors for their occurrence and outcome during melarsoprol treatment of human African trypanosomiasis. Trop Med Int Health **2001**; 6:390–400.
28. Doua F, Yapo FB. Human trypanosomiasis in the Ivory Coast—therapy and problems. Acta Trop **1993**; 54:163–8.
29. Nkanga NG, Mutombo L, Kazadi K, Kazyumba GL. Neuropathies arsenicales apres traitement de la trypanosomiase humaine au melarsoprol. Med Afr Noire **1988**; 35:73–6.
30. Pepin J, Milord F, Guern C, Mpia B, Ethier L, Mansinsa D. Trial of prednisolone for prevention of melarsoprol-induced encephalopathy in gambiense sleeping sickness. Lancet **1989**; 1:1246–50.
31. Pepin J, Milord F, Khonde AN, et al. Risk factors for encephalopathy and mortality during melarsoprol treatment of *Trypanosoma brucei gambiense* sleeping sickness. Trans R Soc Trop Med Hyg **1995**; 89:92–7.
32. Kuzoe FA. Current situation of African trypanosomiasis. Acta Trop **1993**; 54:153–62.
33. Pepin J, Milord F. The treatment of human African trypanosomiasis. Adv Parasitol **1994**; 33:1–47.
34. Burri C, Brun R. Eflornithine for treatment of human African trypanosomiasis. Parasitol Res **2003**; 90(Supp 1):S49–52.
35. Anonymous. Recommendations of the 27th International Scientific Council for Trypanosomiasis Research and Control (ISCTRC) at Pretoria. Pretoria, South Africa: ISCTRC, **2003**.