A Comparison of Miltefosine and Sodium Stibogluconate for Treatment of Visceral Leishmaniasis in an Ethiopian Population with High Prevalence of HIV Infection

Koert Ritmeijer,[1] Abren Dejenie,[1] Yibeltal Assefa,[2] Tadesse Beyene Hundie,[1] Jo Mesure,[1] Gerry Boots,[1] Margriet den Boer,[1] and Robert N. Davidson[1]

[1]Médecins Sans Frontières-Holland, Amsterdam, The Netherlands; and [2]Tigray Bureau of Health, Mekelle, Tigray, Ethiopia

Background. Antimonials are the mainstay of visceral leishmaniasis (VL) treatment in Africa. The increasing incidence of human immunodeficiency virus (HIV) coinfection requires alternative safe and effective drug regimens. Oral miltefosine has been proven to be safe and effective in the treatment of Indian VL but has not been studied in Africa or in persons with HIV and VL coinfection.

Methods. We compared the efficacy of miltefosine and sodium stibogluconate (SSG) in the treatment of VL in persons in Ethiopia. A total of 580 men with parasitologically and/or serologically confirmed VL were randomized to receive either oral miltefosine (100 mg per day for 28 days) or intramuscular SSG (20 mg/kg per day for 30 days).

Results. The initial cure rate was 88% in both treatment groups. Mortality during treatment was 2% in the miltefosine group, compared with 10% in the SSG group. Initial treatment failure was 8% in the miltefosine group, compared with 1% in the SSG group. Among the 375 patients (65%) who agreed to HIV testing, HIV seroprevalence was 29%. Among patients not infected with HIV, initial cure, mortality, and initial treatment failure rates were not significantly different (94% vs. 95%, 1% vs. 3%, and 5% vs. 1% for the miltefosine and SSG groups, respectively). Initial treatment failure with miltefosine occurred in 18% of HIV-coinfected patients, compared with treatment failure in 5% of non–HIV-infected patients. At 6 months after treatment, 174 (60%) of the 290 miltefosine recipients and 189 (65%) of the 290 SSG recipients experienced cure; 30 (10%) of 290 in the miltefosine group and 7 (2%) of 290 in the SSG group experienced relapse, and the mortality rate was 6% in the miltefosine group, compared with 12% in the SSG group. HIV-infected patients had higher rates of relapse (16 [25%] of 63 patients), compared with non–HIV-infected patients (5 [5%] of 131).

Conclusions. Treatment with miltefosine is equally effective as standard SSG treatment in non–HIV-infected men with VL. Among HIV-coinfected patients, miltefosine is safer but less effective than SSG.

Visceral leishmaniasis (VL; also called "kala-azar") caused by *Leishmania donovani* is endemic in the lowlands around Humera and Metema in northern Ethiopia, with an incidence of 1000–2000 cases annually; 20%–40% of the persons affected are HIV coinfected [1, 2]. The only antileishmanial drug available in Ethiopia is sodium stibogluconate (SSG, a pentavalent antimonial). Although this is not yet a problem in Africa, in India, primary resistance to antimonials is common [3, 4]. Although VL is treated similarly in patients with HIV infection and patients without HIV infection [5, 6], HIV coinfection results in lower VL cure rates, higher death and relapse rates, and greater toxicity from antimonials [1, 2, 7]. SSG re-treatment regimens are lengthy (30–60 days), are difficult to tolerate, and are not always successful. Miltefosine, a membrane-active alkyl phospholipid, was developed as an anticancer agent and was found to have antileishmania activity in animal VL models [8, 9]. In 1995, ASTA Medica/Zentaris and the World Health Organization–Special Programme for Research and Training in Tropical Diseases developed miltefosine for the treatment of VL. Several

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Reprints or correspondence: Dr. Koert Ritmeijer, Médecins sans Frontières/MSF-Holland, Plantage Middenlaan 14, 1018 DD Amsterdam, The Netherlands (koert.ritmeijer@amsterdam.msf.org).

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dose-finding studies were done [10–14]. Phase III clinical trials in India showed that miltefosine is very effective for treating VL in both adults and children, including those who experienced failure with antimonials. Miltefosine given orally for 28 days at 100 mg per day (~2.5 mg/kg per day) had a 95%–100% initial clinical and parasitological cure rate.

Miltefosine was registered for treatment of VL in India in 2002, in Germany in 2004, and in 5 Latin American countries in 2005, where it was also registered for treatment of cutaneous leishmaniasis. We wished to establish the utility of miltefosine in east African VL, where the parasite strain is different and patients have severe comorbidities [15]. Our strategy was first to evaluate miltefosine as monotherapy and to subsequently evaluate miltefosine-SSG combinations. The latter might achieve the ultimate goal of short course treatment, a high cure rate, low toxicity, low cost, and lower probability of inducing resistance to either drug.

MATERIALS AND METHODS

Study population. Kafta-Humera Woreda (Tigray, Ethiopia) is a remote, tropical region where extensive agriculture is performed manually by large numbers of migrant laborers. It is served by Humera Hospital (Humera, Ethiopia) and surrounding clinics, including Mycadra (Tigray, Ethiopia), which fall under the responsibility of the Tigray Bureau of Health (Mekelle, Tigray, Ethiopia). Médecins Sans Frontières-Holland has supported the care of patients with VL since 1997. More than 200 patients per month are treated during the peak season (December–February). More than 80% of patients with VL are male migrant workers infected with *L. donovani* while sleeping in the fields; 19% were previously reported to be coinfected with HIV [1].

Patients. Males aged ⩾15 years with parasitologically and/or serologically confirmed VL attending Humera Hospital and Mycadra Health Center were enrolled in the study. Because of the potential teratogenicity of miltefosine, females were excluded. Previous antileishmanial treatment was recorded at hospital admission. Patients were enrolled in the study after giving informed consent. Potentially eligible patients were only excluded if they had such severe comorbidity that they were considered to be likely to die during the month's treatment.

HIV status. HIV serostatus of the patient was determined after voluntary counseling and testing, which is routine at the hospital. HIV antibodies were detected by parallel testing with 2 rapid tests: HIV-Determine (Abbott Diagnostics) and HIV-Capillus (Trinity Biotech). In the instance of discordant test results, a third test (Unigold; Trinity Biotech) was performed. HIV-infected patients had access to a package of health care that includes medical follow-up in a dedicated clinic, prophylaxis against opportunistic infections, and antiretroviral treatment. Participation in the study and HIV testing were not linked to each other, and participation in either was voluntary.

Diagnosis. The World Health Organization case definition of VL was used for initial screening: a history of fever for >2 weeks (with malaria excluded) in combination with wasting, and either splenomegaly or lymphadenopathy [16, 17]. For patients whose illness met this case definition, VL was confirmed by a high titer leishmania direct agglutination test (DAT [Royal Tropical Institute]; titer⩾1:6400) [18]. In patients with an intermediary DAT titer (1:800–1:3200), splenic or lymph node aspiration was performed, and VL was confirmed by microscopic examination. Persons with suspected VL with a negative DAT titer (⩽1:400) were evaluated for alternative illnesses and were retested if signs and symptoms persisted. Severely ill patients were aspirated without delay, so that a diagnosis could be made as quickly as possible. Patients with previous antileishmanial treatment were only admitted if they had a positive aspirate result.

Treatment. Miltefosine (Impavido, Zentaris) was provided in foil-wrapped blister packs of 50-mg capsules. Miltefosine dosage was 100 mg per day for 28 days (all patients weighed >25 kg). Capsules were taken with a meal of high energy, high protein biscuits, directly observed by the Médecins Sans Frontières-Holland nurse.

SSG was provided in 30-mL vials, each containing 100 mg/mL of SSG (Albert David); the vials were provided by International Dispensary Association (Amsterdam, The Netherlands). SSG dosage was 20 mg/kg per day by intramuscular injection for 30 days. Patients who had previously received SSG and who had experienced relapse were randomized to receive either miltefosine (100 mg per day for 28 days) or SSG (20 mg/kg per day for 40–60 days) until 2 consecutive weekly aspirates had negative results.

Patients who did not respond clinically or parasitologically to miltefosine treatment or who showed severe symptoms possibly caused by miltefosine received treatment with SSG (20 mg/kg per day for 30 days). Patients who did not respond to SSG treatment or who developed intolerable SSG toxicity were treated exprotocol with amphotericin B deoxycholate. Patients who relapsed after the study were treated with SSG.

All VL patients received free treatment. Patients who did not participate in the study were treated with SSG, which is the standard of care in Ethiopia. Nurses were educated to overcome any preconceived preference for either drug and were supervised to ensure accuracy in the recording of data.

Test of cure. A test of cure (TOC) aspirate was done at day 27–30 to evaluate parasitological cure. In patients with a palpable spleen at the end of treatment, a splenic aspirate was performed; in other patients, a lymph node aspirate was performed. We have previously found lymph node aspirates to be comparable to splenic aspirates (data available on request). In

Table 1. Patient characteristics at baseline.

Characteristic	Patients randomized to receive miltefosine (n = 290)	Patients randomized to receive sodium stibogluconate (n = 290)	P
Age, mean years ± SD (median)	29.1 ± 9.9 (26)	29.5 ± 9.6 (27)	.62
Mean body mass index[a] ± SD (median)	17.3 ± 2.1 (17.2)	17.4 ± 1.8 (17.4)	.72
Hemoglobin level, mean g/dL ± SD (median)	9.2 ± 2.3 (9)	9.2 ± 2.3 (9.1)	.72
Spleen size, mean cm ± SD (median)	9.3 ± 5.6 (8.5)	9.5 ± 5.7 (9)	.65
Duration of illness, mean no. of months ± SD (median)	2.6 ± 2.1 (2)	2.6 ± 2.1 (2)	.80
No. (%) of migrant workers	203/289 (70.2)	212/289 (73.4)	.46
No. (%) unable to walk unaided	32/290 (11.0)	28/290 (9.7)	.68
HIV serostatus			
HIV infected, no. (%)[b]	63/194 (32.5)	44/181 (24.3)	.10
Non–HIV infected, no. (%)[b]	131/194 (67.5)	137/181 (75.7)	.10
Unknown, no. (%)	96/290 (33.1)	109/290 (37.6)	.30

[a] Calculated as body weight (kg) divided by height (m^2).
[b] The numbers of HIV-infected and non–HIV-infected patients reflect only those who were tested.

case of a positive TOC aspirate result, patients were treated with SSG until 2 consecutive TOC aspirates had negative results. In patients without palpable spleen or lymph nodes, cure could only be established clinically.

Outcome parameters. The main outcome of analysis was the final cure rate at the 6-month follow-up visit. Secondary outcomes were as follows: (1) initial cure (defined as initial parasitological clearance as demonstrated by TOC aspirate in combination with clinical improvement, or clinical cure alone [clearance of fever, in combination with spleen regression, increased hemoglobin, or weight gain] for a patient for whom a TOC aspirate could not be performed); (2) initial treatment failure (defined as parasitological and/or clinical failure after initial treatment); (3) adverse effects (especially vomiting and diarrhea); (4) intercurrent events (e.g., death, default [defined as starting but failing to complete treatment because of reasons other than death or decision by the clinician], bleeding, diarrhea, vomiting, or pneumonia); and (5) relapse (defined as clinical symptoms of infection with parasitological confirmation within the 6-months follow-up).

Follow-up. Patients were asked to return after 6 months or sooner if any symptoms of VL recurred. If relapse was suspected (according to clinical case definition) an aspirate was performed to confirm VL. If no relapse occurred by 6 months after discharge, the patient was considered to be finally cured. Any further laboratory investigations to assess final cure were not possible. We attempted to actively trace those who had not returned by 6 months.

Randomization. After the diagnosis of VL was made, and if the patient satisfied the inclusion criteria, informed oral and written consent was sought; once given, the patient was randomized to receive miltefosine or SSG according to a computer-generated number list. The allocation ratio was 1:1. The study was unblinded; miltefosine is oral medication and SSG is injection medication.

Statistical analysis. Data were analyzed on an intent-to-treat basis with Epi Info software, 2002 revision 2 (Centers for Disease Control and Prevention). Groups were compared by Yates' corrected χ^2 test and Fisher's exact test for categorical variables and either by t test or the Mann-Whitney U test for numerical variables, as appropriate. A multivariate logistic regression was done to analyze for independence of risk factors for death.

Formal and ethics approval. This study was approved by the Tigray regional and Ethiopian national health authorities and their ethical review boards, as well as by the Médecins Sans Frontières-Holland international ethics review board. The study was performed in accordance with the World Medical Association's Declaration of Helsinki concerning medical research in humans [19].

RESULTS

Patients. A total of 580 adult male VL patients were enrolled in the study. Randomization produced groups with no significant differences in the main baseline characteristics (e.g., age, body mass index, hemoglobin level, spleen size, duration of illness, and level of weakness) (table 1).

Diagnosis of VL was confirmed by DAT titer in 449 patients (77%), and by positive results of aspirate microscopic examination in 131 (23%). There was no significant difference in mean DAT titer between HIV-infected and non–HIV-infected patients (P = .49). In patients whose illness was diagnosed parasitologically, the parasite density was significantly higher in HIV-infected patients, compared with non–HIV-infected patients (P = .0003). Thirty-four patients (5.9%) experienced re-

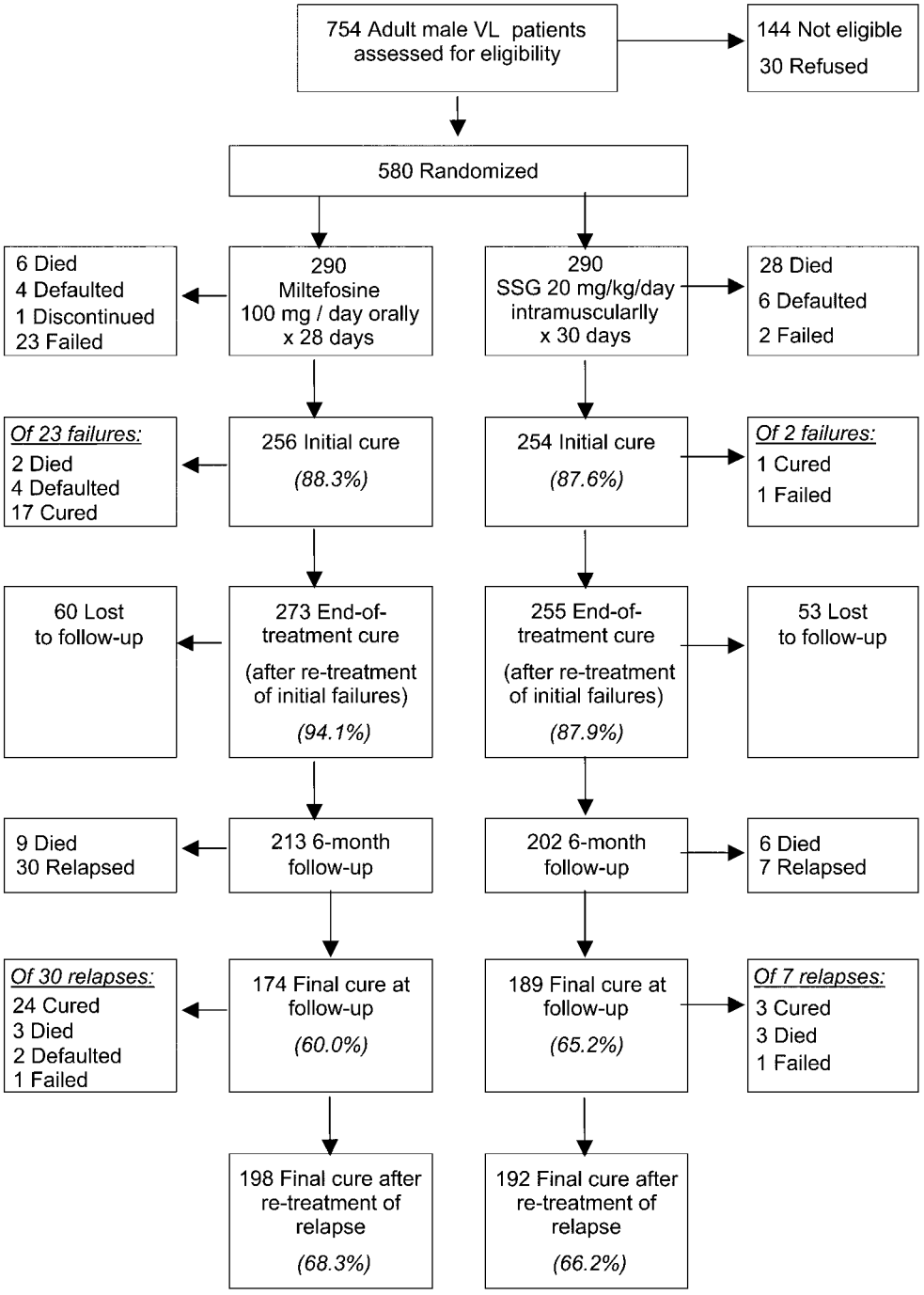

Figure 1. Flow diagram of patient outcomes during the study. SSG, sodium stibogluconate.

lapse after previous SSG treatment for VL (17 were randomized to each treatment arm). The progress of patients through the study and the main outcomes are shown in figure 1.

Initial response to treatment. After evaluation of clinical response, a TOC aspirate was performed in 434 patients (81.1%; there were 329 spleen aspirates and 105 lymph node aspirates performed). In the other 146 patients, no TOC aspirates could be performed because of absence of palpable spleen or lymph nodes. As shown in tables 2 and 3, there was no difference in initial cure rate between the miltefosine group (88.3%; 95% CI, 84.0%–91.7%) and the SSG group (87.6%; 83.2%–91.2%) ($P = .90$). However, initial treatment failure with survival was more frequent in the miltefosine group (7.9% in the miltefosine group vs. 0.7% in the SSG group; OR, 12.4; $P < .0001$), whereas mortality was lower in the miltefosine group (2.1% in the miltefosine group vs. 9.7% in the SSG group; OR, 0.20; $P = .0002$).

Table 2. Baseline characteristics of patients with and without HIV coinfection, by HIV serostatus.

	Positive		Negative		Unknown		All patients	
Characteristic	Mean ± SD	Median (range)	Mean ± SD	Median (range)	Mean ± SD	Median (range)	Mean ± SD	Median (range)
Age, years	33.4 ± 9.5	32 (18–67)	26.3 ± 9.0	27 (16–60)	31.2 ± 9.7	29 (16–65)	29.3 ± 9.8	27 (16–67)
Body mass index[a]	17.2 ± 2.0	17.2 (11.2–22.2)	17.4 ± 1.8	17.5 (13.3–22.6)	17.3 ± 1.9	17.3 (11.9–22.2)	17.4 ± 1.9	17.3 (11.2–22.6)
Spleen size, cm	9.4 ± 5.7	9 (0–22)	10.0 ± 5.8	10 (0–30)	8.8 ± 5.3	8 (0–25)	9.4 ± 5.6	9 (0–30)
DAT titer, well[b]	8.3 ± 1.4	8 (6–11)	8.3 ± 1.3	8 (4–11)	8.4 ± 1.4	8 (6–11)	8.4 ± 1.3	8 (4–11)
Parasite density[c]	3.7 ± 1.8	4 (0–6)	2.3 ± 1.5	2 (0–6)	2.6 ± 1.8	2 (0–6)	2.7 ± 1.8	2 (0–6)

NOTE. DAT, direct agglutination test.

[a] Calculated as body weight (kg) divided by height (m^2).

[b] DAT titer is expressed as the highest dilution at which agglutination is still visible: well 4, 1:800 dilution; well 6, 1:3200; well 7, 1:6400; well 8, 1:12800; well 11, 1:102400.

[c] The parasite density score uses a log scale ranging from 0 (no parasites per 1000 oil-immersion fields) to +6 (>100 parasites per oil-immersion field).

All patients who experienced initial treatment failure (23 patients in the miltefosine group and 2 in the SSG group) were immediately re-treated with 30 days of SSG treatment. This strategy increased the end-of-treatment cure rates to 94.1% in the miltefosine group (95% CI, 90.8%–96.5%), compared with 87.9% in the SSG group (95% CI, 83.6%–91.4%) ($P = .014$); mortality remained significantly lower in the miltefosine group (2.8% vs. 9.7% in the SSG group; OR, 0.27; $P = .001$).

HIV coinfection and initial treatment outcomes. The percentage of patients who underwent voluntary counseling and testing for HIV infection was 64.7% (375 of 590), with no difference between treatment groups ($P = .30$). Of the 375 patients who were tested, 107 (28.5%; 95% CI, 24.0%–33.4%) were HIV-infected, with no significant difference between both treatment groups (table 1). HIV coinfection was more prevalent among migrant workers than among residents (33.7% vs. 17.2%; OR, 2.44; $P = .0017$) and was more prevalent among patients with relapse of VL than it was among patients with primary VL (89.5% vs. 25.3%; OR, 25.1; $P < .0001$). Twenty-one (75%) of the 28 people who died in the SSG group had an unknown HIV status, as they died before HIV testing. Six (5.6%) of 107 HIV-infected patients received a diagnosis of tuberculosis, and 13 (4.9%) of 268 non–HIV-infected patients and 22 (10.7%) of 205 patients with unknown HIV status also received a diagnosis of tuberculosis.

HIV coinfection was a major determinant of events during treatment and outcomes (tables 2 and 3) Among non–HIV-infected patients, there was no significant difference in initial cure rate, mortality, or initial treatment failure between the miltefosine and SSG groups. Initial miltefosine treatment failure was mainly experienced by HIV-coinfected patients (17.5% vs. 4.6% in non–HIV-infected patients; OR, 4.41; $P = .044$). Similarly, HIV seroprevalence was significantly higher among patients who experienced initial failure than in patients who experienced cure (63.2% vs. 26.0%; OR, 4.89; $P = .0001$).

Tolerability of miltefosine and SSG. Thirty-four deaths occurred during treatment. Death occurred a median of 13 days into treatment (range, 2–30 days), with no significant difference in time to death between treatment groups. After multivariate logistic regression, the independent risk factors for death were determined to be receiving SSG rather than miltefosine (OR, 6.53; 95% CI, 2.53–16.89), being HIV-infected or having an unknown HIV status (OR, 3.54; 95% CI, 1.25–10.06), and vomiting (OR, 2.97; 95% CI, 1.28–6.87). Other risk factors for death (age, body mass index, hemoglobin level, diarrhea, and inability to walk unaided) were interdependent.

Table 4 shows the incidence of intercurrent events. Vomiting was more common in the miltefosine group (159 [54.8%] of 290, vs. 93 [32.1%] of 290 in the SSG group; OR, 2.57; $P < .0001$) and of slightly longer duration (mean duration, 3.3 vs. 2.6 days; $P = .02$). However, vomiting was less severe in miltefosine patients: only 14 (4.8%) of 290 miltefosine patients had treatment interrupted for vomiting, compared with 27 (9.7%) of the 290SSG patients (OR, 0.47; $P = .037$). The odds of vomiting in HIV-infected patients, compared with non–HIV-infected patients, were 2.85 ($P < .0001$), and the duration of vomiting was longer (mean duration, 3.5 vs. 2.5 days; $P = .013$). The incidence and duration of diarrhea were similar in both treatment groups, but diarrhea was more common among HIV-infected patients (OR, 2.14; $P = .015$). There was no difference in the incidence of bleeding or pneumonia between the miltefosine and SSG groups, or between HIV-infected and non–HIV-infected patients. One patient discontinued miltefosine therapy (on day 21) because of an itchy rash; this patient was lost to follow-up.

Clinical response, as indicated by spleen regression and hemoglobin level increase, was similar in both treatment groups, but weight gain was significantly lower in the miltefosine group (table 4).

Final cure at 6 months. Six months after hospital discharge, 415 patients (79% of treatment survivors) were traced. For 15 patients (2.8%), death since hospital discharge had been recorded. All patients who experienced relapse returned for treatment within 6 months after hospital discharge. There was

Table 3. Events during treatment and outcomes of patients with and without HIV coinfection randomized to receive miltefosine or sodium stibogluconate (SSG).

	HIV infected		Non–HIV infected		HIV status unknown		All patients	
Value	Miltefosine (n = 63)	SSG (n = 44)	Miltefosine (n = 131)	SSG (n = 137)	Miltefosine (n = 96)	SSG (n = 109)	Miltefosine (n = 290)	SSG (n = 290)
Intercurrent event								
Vomiting	41 (65.1)	20 (45.5)	59 (45.0)	26 (19.0)	59 (61.5)	47 (43.1)	159 (54.8)	93 (32.1)
Duration, days	4.1	2.3	2.7	2.2	3.2	2.9	3.25	2.58
Drugs withheld, n/N (%)	3/41 (7.3)	7/20 (35.0)	3/59 (5.1)	3/26 (11.5)	8/59 (13.6)	17/47 (36.2)	14/159 (8.8)	27/93 (29.0)
Diarrhea	34 (54.0)	32 (72.7)	57 (43.5)	58 (42.3)	58 (60.4)	63 (57.8)	149 (51.4)	153 (52.8)
Duration, days	4.0	4.5	3.4	3.0	3.6	4.3	3.62	3.84
Pneumonia	21 (33.3)	14 (31.8)	31 (23.7)	41 (29.9)	27 (28.1)	40 (36.7)	79 (27.2)	95 (32.8)
Bleeding	10 (15.9)	9 (20.5)	36 (27.5)	30 (21.9)	18 (18.8)	25 (22.9)	64 (22.1)	64 (22.1)
Initial treatment outcome								
Death	1 (1.6)	3 (6.8)	1 (0.8)	4 (2.9)	4 (4.2)	21 (19.3)	6 (2.1)	28 (9.7)
Initial cure	49 (77.8)	40 (90.1)	123 (93.8)	130 (94.9)	84 (87.5)	84 (77.1)	256 (88.3)	254 (87.6)
Initial failure	11 (17.5)	1 (2.3)	6 (4.5)	1 (0.7)	6 (6.3)	0 (0.0)	23 (7.9)	2 (0.7)
Discontinuation	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Default	2 (3.2)	0 (0.0)	0 (0.0)	2 (1.5)	2 (2.1)	4 (3.7)	4 (1.4)	6 (2.1)
End-of-treatment outcome								
Death	3 (4.8)	3 (6.8)	1 (0.8)	4 (2.9)	4 (4.2)	21 (19.3)	8 (2.8)	28 (9.7)
Cure	56 (88.9)	40 (90.1)	128 (97.7)	131 (95.6)	89 (92.7)	84 (77.1)	273 (94.1)	255 (87.9)
Failure	1 (1.6)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Default	3 (4.8)	0 (0.0)	2 (1.5)	2 (1.5)	3 (3.1)	4 (3.7)	8 (2.8)	6 (2.1)
Final outcome								
Final cure	29 (46.0)	25 (56.8)	99 (75.6)	106 (77.4)	46 (47.9)	58 (53.2)	174 (60.0)	189 (65.2)
Relapse	16 (25.4)	5 (11.4)	6 (4.6)	0 (0.0)	8 (8.3)	2 (1.8)	30 (10.3)	7 (2.4)
Death	7 (11.1)	5 (11.4)	1 (0.8)	6 (4.4)	8 (9.4)	23 (21.1)	17 (5.9)	34 (11.7)
Lost to follow-up	11 (17.5)	9 (20.5)	25 (19.1)	25 (18.2)	33 (34.4)	26 (23.9)	69 (23.8)	60 (20.7)

NOTE. Data are no. (%) of patients, unless otherwise indicated. Initial treatment outcome refers to outcome after the initial course of treatment, end-of-treatment outcome refers to the outcome after the re-treatment of patients who initially experienced treatment failure, and final outcome refers to the outcome at the 6-month follow-up visit.

no difference in follow-up rates between the 2 treatment groups ($P = .80$). Final outcomes are presented in figure 1 and in tables 2 and 3. The final cure rate in the miltefosine group was 60.0% (95% CI, 54.1%–65.7%), which was not significantly different from the rate in the SSG treatment group (cure rate, 65.2%; 95% CI, 59.4%–70.6%) ($P = .23$). The final cure among non–HIV-infected patients 6 months after treatment was not different between the miltefosine group (cure rate, 75.6%; 95% CI, 67.3%–82.7%) and the SSG group (cure rate, 77.4%; 69.4%–84.1%) ($P = .84$). Relapse was more common in the miltefosine group (10.3% vs. 2.4% in the SSG group; OR, 5.05; $P < .0001$). This was not wholly caused by HIV coinfection; among non–HIV-infected patients, those in the miltefosine group also had a higher relapse rate (4.6% vs. 0.0% in the SSG group; $P = .01$). Overall mortality at 6 months was significantly lower in the miltefosine group (5.9% vs. 11.7% in the SSG group; OR, 0.49; $P = .019$). When patients lost to follow-up are excluded, the final cure rates among non–HIV-infected patients were 93.4% (95% CI, 86.9%–97.3%) in the miltefosine group and 94.6% (95% CI, 88.7%–98.0%) in the SSG group.

Of the 30 patients who experienced relapse in the miltefosine group, 24 experienced cure after re-treatment with a full course of SSG; in the SSG group, 3 of the 7 patients who experienced relapse experienced cure after re-treatment. After treatment of patients with relapse, the final cure rate in the miltefosine treatment group was 68.3% (198 of 290 patients), compared with 66.2% (192 of 290 patients) in the SSG treatment group (OR, 1.10; $P = .66$). The final death rate after re-treatment of patients with relapse was significantly lower in the miltefosine group (20 [6.9%] of 290 vs. 37 [12.8%] of 290 in the SSG group; OR, 0.51; $P = .026$).

No significant difference was observed in final outcomes between migrant workers and residents, but follow-up rates were lower among migrant workers than among residents (74.2% vs. 85.3%; $P = .006$). Final outcomes among patients who had received previous treatment for VL were significantly worse, with

Table 4. Intercurrent events and response to treatment.

Event	Miltefosine treatment group	Sodium stibogluconate treatment group	*P*
Vomiting, n/N (%)	159/290 (54.8)	93/290 (32.1)	<.0001
Duration, mean days ± SD	3.25 ± 2.6	2.58 ± 1.8	.02
Drugs withheld, n/N (%)	14/159 (8.8)	27/93 (29.0)	.0001
Diarrhea, n/N (%)	149/290 (51.4)	153/290 (52.8)	.80
Duration, mean days ± SD	3.62 ± 3.1	3.84 ± 3.0	.53
Bleeding, n/N (%)	64/290 (22.1)	64/290 (22.1)	1.00
Pneumonia, n/N (%)	79/290 (27.2)	95/290 (32.8)	.17
Spleen regression, mean cm ± SD	2.9 ± 3.1	2.9 ± 3.7	.99
Hemoglobin increase, mean g/dL ± SD	0.7 ± 2.2	0.7 ± 2.3	.66
Weight gain, mean kg ± SD	0.13 ± 2.8	1.64 ± 3.1	<.0001

higher relapse rates and death rates. Of previously untreated patients, 355 (65.0%) of 546 achieved final cure, 41 (7.5%) of 546 died, and 27 (4.9%) of 546 experienced relapse. Among previously treated patients enrolled in the study, these outcomes were 8 (24%) of 34, 10 (29%) of 34, and 10 (29%) of 34, respectively.

DISCUSSION

In this, the largest randomized, controlled trial of VL treatment ever conducted, we have shown that miltefosine is an acceptable alternative to SSG as treatment for Ethiopian men with VL. Except for the fact that all were adult males, the patients in this study were clinically similar in severity to the ~70,000 patients with VL treated by Médecins Sans Frontières-Holland in the East African region since 1989, and they were clinically very different from the patients with VL who have received miltefosine in India [10–14]. For example, the mortality rates in the Indian miltefosine trials have been <0.2%. Many of our eligible patients were severely ill with massively enlarged spleens, anemia, malnutrition, inability to walk unaided, and HIV coinfection. Death, diarrhea, bleeding, vomiting, and pneumonia often complicated their clinical course. We determined that miltefosine is equivalent to SSG for treatment of VL in non–HIV-infected patients, and it is probably safer but less effective for treatment in HIV-coinfected patients. Patients were treated with a standard miltefosine regimen, as has been recommended for non–HIV-infected persons in India; optimal miltefosine dose regimens for African patients with VL and HIV coinfection still have to be established.

A valid comparison of miltefosine and SSG treatment in HIV-coinfected patients was made difficult by the fact that 21 (75%) of the 28 patients in the SSG group who died had an unknown HIV status. HIV testing was done after the patient was well enough to volunteer for counseling and testing. We consider it likely that many HIV-coinfected patients receiving treatment with SSG died before they could be tested for HIV.

The lack of effectiveness of miltefosine in the treatment of HIV-VL–coinfected patients (defined as experiencing initial treatment failure and/or relapse) was outweighed, in our view, by a far lower mortality rate, compared with the mortality rate in the SSG treatment group. Because VL is currently often incurable in HIV-coinfected patients and many coinfected persons will ultimately experience relapse [1], the safety profile of miltefosine makes it a preferred drug for the treatment of HIV-coinfected patients.

The final cure rate at 6 months is probably better than indicated in the intent-to-treat analysis, in which patients lost to follow-up are counted as having experienced treatment failure; many of the patients lost to follow-up might, in fact, have been cured. Considering only patients who could be traced, the final cure rate among non–HIV-infected patients is ~94% in both the miltefosine and the SSG treatment groups.

Our study confirms the good tolerability of miltefosine found in the Indian studies [10–14], with only gastrointestinal symptoms being common; these were not prolonged and only of mild-to-moderate severity.

It has been repeatedly shown that antimonials are poorly tolerated among patients coinfected with HIV and VL in Europe [20, 21]. The 6-fold higher odds ($P = .0003$) of mortality associated with SSG treatment, compared with miltefosine treatment, among patients who were either HIV positive or whose HIV status was unknown strongly indicates that much of the mortality among HIV-infected patients was caused by the SSG treatment itself. The poor final outcomes in patients who were enrolled in the study as having experienced relapse after previous treatment may be attributed to the high HIV coinfection rate (90%).

In contrast to European experience [22], we found a high sensitivity of the serological DAT test in HIV-coinfected patients. This might reflect the fact that, in Ethiopia, patients are unlikely to survive with very advanced HIV disease, or that coinfection with *L. donovani,* being more virulent than *Leishmania infantum* coinfection, occurs at an earlier stage of HIV infection.

Although it is convenient because it is an oral drug, widespread use of miltefosine for treatment of VL gives cause for concern. Animal studies have shown reproductive toxicity; thus, miltefosine is contraindicated during pregnancy, and women of childbearing age must use effective contraception during and for 3 months after treatment. Pioneers in the use of miltefosine in India have recently expressed concern that unsupervised use of miltefosine in India might lead to high relapse rates [23]. It is known that HIV-coinfected patients frequently experience relapse, and when they do, they may be unresponsive to antileishmanial drugs. In Europe, such patients are highly susceptible to infection transmitted by sandflies, particularly if their $CD4^+$ cell count is low [24]. The long serum half-life of miltefosine (7 days) may favor emergence of resistant mutations. HIV-coinfected patients who have experienced relapse may become an important reservoir of drug-resistant *L. donovani,* either by being parasitaemic or by having post–kala-azar dermal leishmaniasis. This is of public health concern in Africa, where transmission of *L. donovani* is anthroponotic, and resistance could spread quickly [25]. Therefore, combination therapies should be considered to delay the emergence of resistance to miltefosine. Further research is required into drug combinations that might enhance the effectiveness of miltefosine treatment, thus establishing safe and effective drug regimens for patients with VL in areas with high HIV coinfection rates.

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