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Safety and effectiveness of meglumine antimoniate in the treatment of Ethiopian visceral leishmaniasis patients with and without HIV co-infection

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ABSTRACT

In sub-Saharan Africa, visceral leishmaniasis (VL) is treated with either Pentostam™ (sodium antimony gluconate) or generic sodium stibogluconate (SSG), except in Uganda where Glucantime® (meglumine antimoniate) has been in use for at least a decade. Between January 2008 and February 2009, 54 Ethiopian VL patients were treated with Glucantime. The medical charts of these patients were reviewed to assess the effectiveness and safety profile of Glucantime in a routine healthcare setting. None of the patients from south Ethiopia ($n = 24$) and 46.4% of the patients from north Ethiopia ($n = 30$) were HIV co-infected. At completion of treatment (Day 31), cure rates were 78.6% (95% CI 59.0–91.7%) in north Ethiopia and 100% (95% CI 85.8–100%) in south Ethiopia. Thirty-three non-serious and six serious adverse events (two pancreatitis, one renal failure and three deaths) were observed in 26 patients. One-third of the non-serious adverse events were due to biochemical pancreatitis. During treatment, a case–fatality rate of 10.0% in north Ethiopia and 0.0% in south Ethiopia was noted. These data show that Glucantime can be as effective as Pentostam or SSG in HIV-negative patients. The data also point to clinical pancreatitis as a safety concern, especially in patients with HIV co-infection.

1. Introduction

Visceral leishmaniasis (VL), also known as kala-azar, is a fatal parasitic disease that kills nearly 100% of untreated patients. Drugs currently available for treating this disease are either toxic or costly and require prolonged administration. Pentavalent antimonials (Sb^v), although antiquated, are still being used as first-line treatment in many countries,[1] except in Bihar, India, where widespread resistance has recently culminated in its abandonment.[2] Sb^v are available in different pharmaceutical formulations, including the commonly available proprietary brands of sodium antimony gluconate (SAG) (e.g. Pentostam™; GSK Pharma, Uxbridge, UK) and meglumine antimoniate (MA) (e.g. Glucantime®; Specia, Paris, France) as well as the generic sodium stibogluconate (SSG) (Albert David, Kolkata, India). Alternative treatments include conventional and liposomal formulations of amphotericin B (AmB), aminosidine (paromomycin) and miltefosine. In

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Bihar, these drugs have already replaced Sb^v.[3,4] However, both AmB and miltefosine, despite being effective, are associated with many adverse reactions and high cost.[5]

The supply of SAG and SSG in endemic areas of sub-Saharan African (SSA) countries such as Ethiopia has always been unreliable and to date remains in the custody of the WHO, non-governmental organisations such as Médecins Sans Frontières (MSF) and a few research centres. This illustrates how VL remains neglected even when very impressive campaigns on the control and elimination of neglected tropical diseases are presently being waged.

Based on the results of limited field studies, SSG and SAG have shown comparable clinical efficacy in Ethiopia,[6] Sudan[7] and Kenya.[8] On the other hand, MA has found limited clinical use in SSA, except in Uganda where several hundreds have been treated with Glucantime in the last decade.[9,10] In Ethiopia, Glucantime was first used in the early 1990s (March 1990 to August 1991) to treat 37 HIV-negative VL patients.[11]

Treatment of VL, at least in SSA, is expected to depend on antimonials until better and more cost-effective treatment options become available. Therefore, monitoring the effectiveness of antimonials is a necessary element of VL control in the region. In light of this, we performed a retrospective analysis of clinical data from 54 Ethiopian VL patients treated with Glucantime between January 2008 and February 2009. The patients came from two endemic localities with contrasting baseline HIV co-infection rates. It was hypothesised that treatment of Ethiopian VL patients with MA would be as effective and as safe as SSG or SAG treatment.

2. Patients and methods

2.1. Study design, patients, diagnosis and treatments

The medical records of 54 VL patients treated in Gondar University Hospital (GUH) (Gondar, Ethiopia) and Arba Minch Hospital (AMH) (Arba Minch, Ethiopia) during a 13-month period (January 2008 to February 2009) were reviewed and analysed. During this period, SSG and SAG were unavailable in the hospitals, the former owing to temporary closure of manufacturing facilities in India. Glucantime as 5 ml ampoules (Lot# 816) was supplied by Laboratoire Aventis (Paris, France), with each ampoule containing 1.5 g of MA equivalent to 405 mg of antimony. The drug was imported with permission of the Drug Administration & Control Authority of the Ethiopian Government.

Clinical and laboratory data included in this report were part of the routine medical procedures in place at the dedicated VL treatment centres. Laboratory procedures, including the normal ranges of the two treatment centres, were standardised beforehand.

Diagnosis of VL was achieved by clinical and serological screening followed by parasitological confirmation. Serological screening was performed by direct agglutination test (supplied by the Royal Tropical Institute, Amsterdam, The Netherlands) and/or rK39 dipstick (DiaMed-IT-Leish; DiaMed AG, Cressier sur Morat, Switzerland). Parasitological diagnosis was performed by microscopic examination of tissue smears obtained from splenic or bone marrow aspirates. Giemsa-stained smears were examined under 1000× magnification and when amastigotes were present the parasite load was determined by counting the Leishman–Donovan bodies and assigning grades from 0 (0 parasites/1000 fields) to 6+ (>100 parasites/field) as per WHO guidelines.[12] Parasite grades were obtained at baseline, at the end of treatment (EOT) and when aspirates were made at 6-month follow-up (6MFU). The 6MFU assessment was not compulsory as most patients had come from distant localities. Parasitological assessment at 6MFU was carried out if signs and symptoms of VL were noted, otherwise patients were taken as cured. Baseline and weekly evaluations included physical examinations, complete blood counts and blood chemistry. Additional evaluations were CD4 counts for HIV-positive patients as well as other serological and microbiological tests. To classify nutritional status, weight-for-age values were used for children (4–14 years) and body mass index in adults (≥15 years).

Glucantime at 20 mg/kg body weight/day of antimony (i.e. 75 mg/kg body weight/day of active ingredient) was administered i.m. for 30 days with a maximum daily antimony dose of 850 mg. The i.m. injections were given to patients slowly while lying in bed. Liposomal amphotericin B 50 mg (AmBisome), manufactured by Gilead Sciences Ltd (Blackrock, Ireland), was given as a second-line treatment for patients withdrawn from Glucantime treatment owing to presumed/proven side effects or treatment failure. The main criteria for discontinuation of Glucantime were serious adverse events (SAE), specific indications for clinical pancreatitis (vomiting, abdominal pain/bleeding) and poor response to treatment. AmBisome at 3 mg/kg body weight/day was administered as an i.v. infusion once daily for 6 days (Days 1, 2, 3, 4, 5 and 10). Antiretroviral (ARV) treatment was organised by independent HIV/AIDS follow-up clinics and was not interrupted during VL treatment.

2.2. Outcome measures

Primary effectiveness outcome was measured by the presence or absence of parasites in tissue aspirates as well as by clinical response (remission of fever, improvements in haematological and biochemical values and regression of spleen size) at EOT. Secondary outcomes were measured by: (i) presence or absence of parasites or by clinical response at 6MFU; and (ii) safety indicators reported from EOT to 6MFU. Presence of parasites or receipt of second-line medication at any time was considered treatment failure. Two patients with missing data (owing to death unrelated to MA treatment) were excluded from the analysis of effectiveness.

A SAE was defined as any event that was fatal, life threatening, disabling or incapacitating, or as any event that resulted in (re)hospitalisation or prolongation of hospital stay or was associated with congenital abnormality, cancer or overdose (either accidental or intentional). A non-serious adverse event (NSAE) was defined as any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes.

2.3. Statistical analysis

Continuous data were summarised using mean ± SD if normally distributed; otherwise, median and interquartile range (IQR) were used. Parametric ANOVA and non-parametric Wilcoxon rank-sum tests were used to make comparisons for continuous data, whilst χ^2 or Fisher's exact tests were used for categorical data. The number and percentage of patients cured for both primary and secondary outcomes of effectiveness are presented together with their 95% CI for the overall data set and for each study centre. In comparing various data sets, a *P*-value of <0.05 (at $\alpha = 5\%$) was considered statistically significant. Data analysis was done using STATA version 9.2 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Baseline demographic and clinical/laboratory characteristics

Observed demographic characteristics and a high HIV co-infection rate in GUH (46.4%) differentiates the GUH patients from those of AMH, and GUH patients were also more malnourished ($P < 0.05$) (Table 1). Forty-nine of the 54 patients (25 from GUH and 24 from AMH) were primary VL cases; the rest ($n = 5$) were VL relapses from GUH. All but two patients from GUH and all patients from AMH volunteered for HIV testing.

On admission, all patients had fever (>37.5 °C) and the majority had an enlarged spleen (98.1%) and anaemia (98.1%), with no significant difference in spleen size between the two treatment centres (mean size of 10.1 cm and 11.5 cm in GUH and AMH, respectively). Other signs and symptoms are given in Table 2. There was no difference in the frequency of these signs/symptoms of VL in HIV-positive and -negative patients ($P > 0.05$). In GUH, HIV co-infected patients had significantly higher ($P = 0.01$) parasite grade (median = 4.5; IQR 4–6) compared with HIV-negative patients at the same hospital (median = 2.5; IQR 1–3). HIV co-infected patients comprised five relapse cases and eight of the 25 primary VL cases from GUH. During VL diagnosis, nine of the 13 HIV co-infected patients were on highly active antiretroviral therapy (HAART) (Supplementary Tables 1 and 2).

3.2. End of treatment and 6-month follow-up treatment outcomes

The number of patients who successfully completed MA treatment (having received ≥24 daily doses) was 48 (24 each in GUH and AMH). The rest died during treatment (three patients) or received AmBisome as second-line treatment (three patients). HIV status could not be

Table 1
Demographic and baseline clinical characteristics of visceral leishmaniasis patients diagnosed and treated in Gondar University Hospital (GUH) (north Ethiopia) and Arba Minch Hospital (AMH) (south Ethiopia), January 2008 to February 2009

Characteristic	Treatment centre		*P*-value[a]
	GUH ($n = 30$)	AMH ($n = 24$)	
Age (years)			
Mean (SD)	26.5 (7.2)	14.3 (12.2)	0.01
Median (IQR)	25.0 (20.0–30.0)	10.5 (6.0–18.5)	<0.001
Sex [*n* (%)]			
Female	0	6 (25.0)	0.005
Male	30 (100)	18 (75.0)	
Body temperature (axillary) (°C)			
Mean (SD)	37.9 (2.0)	37.8 (1.2)	0.514
Median (IQR)	38 (36.8–38.8)	38 (36.9–38.7)	0.695
Nutritional status [*n* (%)]			
Severely underweight	14 (60.9)	4 (17.4)	<0.001
Underweight	9 (39.1)	11 (47.8)	
Normal	0	8 (34.8)	
Unknown	7	1	
HIV test [*n* (%)]			
Positive	13 (46.4)	0	<0.001
Negative	15 (53.6)	24 (100)	
Unknown	2	0	
Parasite grade			
5+/6+	6	9	
3+/4+	10	11	
1+/2+	6	3	0.017
Positive, but not graded	8	0	
Parasitology not done	0	1	
Mean (SD) grade	3.5 (1.7)	4.0 (1.3)	
Median (IQR) grade	3 (2–5)	4 (3–5)	

IQR: interquartile range.
[a] The *P*-value for comparing GUH and AMH is based on parametric ANOVA test for continuous data employing mean (and SD), non-parametric Wilcoxon rank-sum test for continuous data employing median (and IQR) and χ^2 or Fisher's test for categorical data.

Table 2
Frequency of abnormal baseline clinical (signs/symptoms) and laboratory features in visceral leishmaniasis patients diagnosed and treated in Gondar University Hospital (GUH) (north Ethiopia) and Arba Minch Hospital (AMH) (south Ethiopia), January 2008 to February 2009

Signs/symptoms and biological parameters	No. (%) of patients		*P*-value [a]
	GUH (n = 30)	AMH (n = 24)	
Fever (>37.5 °C)	30 (100.0)	24 (100.0)	1.000
Splenomegaly	30 (100)	23 (95.8)	0.444
Hepatomegaly	5 (16.7)	14 (58.3)	0.002
Lymphadenopathy	1 (3.3)	6 (25.0)	0.036
Weight loss	29 (96.7)	24 (100)	1.000
Cough	27 (90.0)	16 (66.7)	0.046
Diarrhoea	19 (63.3)	9 (37.5)	0.099
Bleeding	6 (20.0)	8 (33.3)	0.272
Fatigue	30 (100)	24 (100)	1.000
Anaemia			
Hb <12.0 g/dl	29 (96.7)	24 (100)	1.000
Hb <9.0 g/dl	22 (73.3)	20 (83.3)	0.515
Leukopenia (total WBC count <4000 cells/μl)	29 (96.7)	23 (95.8)	1.000
Thrombocytopenia (platelet count <150 000/μl)	30 (100)	18 (75.0)	0.005
Amylase >150 U/l	3 (60.0)[b]	2 (8.3)	1.000
Increased hepatic transaminases (ALT >41 U/l; AST >38 U/l)	12 (40.0)	5 (20.8)	0.153
Alkaline phosphatase >500 U/l	8 (26.7)	0	0.006
Increased BUN (>23 mg/dl)	2 (6.7)	4 (16.7)	0.389
Increased serum bilirubin (>1.0 mg/dl)	9 (30.0)	0	0.003
Increased serum creatinine (>1.1 mg/dl)	9 (30.0)	0	0.003

Hb: haemoglobin; WBC: white blood cell; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen.
[a] *P*-value using χ^2 or Fisher's exact test.
[b] In GUH, amylase was measured for five patients at baseline and for only one patient during follow-up.

determined in two patients. These patients did not receive ARV drugs. Data on treatment outcomes of these two patients were discarded when analysis was carried out with stratification by HIV status (Table 3).

The lower cure rate of 78.6% (95% CI 59.0–91.7%) in GUH compared with AMH (100%; 95% CI 85.8–100%) was attributable to the high rate (46.4%) of HIV co-infection (Table 3); the difference, which was marginally significant (P = 0.052), turned non-significant (P = 0.400) when analysed with adjustment for HIV co-infection. At EOT, seven of eight HIV co-infected patients (87.5%) had significantly reduced parasite load (data shown in Supplementary Tables 1 and 2). Detailed data on clinical prognosis and time series changes from baseline laboratory parameters are shown in Table 4 and Supplementary Figures 1 and 2, respectively.

Analysis of the initial cure rates by age group (data not shown) showed 100% initial cure (95% CI 80.5–100%) in children and 85.3% initial cure (95% CI 68.9–95%) in adults. This analysis includes HIV co-infected adults, whose initial cure rate was 58.3% (95% CI 27.7–84.8%) (Table 3). This difference between children and adults was not significant (P = 0.156).

3.3. Safety and treatment-emergent changes in laboratory measurements

A total of six SAEs (two pancreatitis, one renal failure and three deaths) were reported in four patients from GUH (three HIV-positive and one HIV-negative); five of these were treatment emergent, whilst one occurred during follow-up. Two of the six SAEs (i.e. two deaths) were unrelated to MA treatment, whereas the rest, including one death due to pancreatitis, were possibly related to MA treatment. One SAE due to pancreatitis was non-fatal (considered moderate) and resolved within 2 weeks. All the three deaths occurred during initial hospitalisation in GUH (10.0% case–fatality rate).

Overall, 33 NSAEs (32 treatment-emergent and one follow-up) were documented among 22 patients (21 treatment-emergent and one follow-up); six of these 33 events (18.2%) were among HIV-positive patients. Of

Table 3
Definitive cure rates in visceral leishmaniasis patients treated with meglumine antimoniate at end of treatment (EOT) and at 6-month follow-up (6MFU) in patients with and without HIV co-infection

Cure rate	GUH			AMH
	HIV-positive (n = 12)[a]	HIV-negative (n = 14)[a]	Total (n = 28)[a,b]	HIV-negative (n = 24)
At EOT [n (%)] [95% CI for efficacy]	7/12 (58.3%) [27.7–84.8%]	13/14 (92.9%) [66.1–99.8%]	22/28 (78.6%) [59.0–91.7%]	24/24 (100%) [85.8–100%]
At 6MFU [n (%)] [95% CI for efficacy]	1/3 (33.3%) [0.10–90.6%]	6/6 (100%) [54.1–100.0%]	8/10 (80.0%) [44.4–97.5%]	6/6 (100%) [54.1–100.0%]

GUH: Gondar University Hospital; AMH: Arba Minch Hospital.
[a] The combined number of HIV-positive and HIV-negative patients (n = 26) at EOT in GUH is less than the total (n = 28) as two patients refused HIV tests.
[b] Two patients from GUH who died during early stages of treatment, i.e. after two and six doses of MA, were excluded from analysis of cure rates.

Table 4
End-of-treatment (EOT) (Day 31) changes in biological parameters shown as mean difference from baseline (MDB)

Parameter	GUH				AMH			
	N	Baseline mean (SD)	MDB at EOT (95% CI)	*P*-value	*N*	Baseline mean (SD)	MDB at EOT (95% CI)	*P*-value
Weight (kg)	23	46.5 (8.4)	1.65 (0.41 to 2.89)	0.011	24	30.2 (15.4)	1.38 (0.73 to 2.04)	0.001
Temperature (°C)	23	37.9 (2.0)	−1.56 (−2.29 to −0.83)	<0.001	24	37.8 (1.2)	−1.38 (−1.80 to −0.96)	<0.001
Spleen size (cm)	23	10.1 (3.8)	−5.57 (−6.61 to −4.52)	<0.001	24	11.5 (4.1)	−5.89 (−6.70 to −5.09)	<0.001
Liver size (cm)	14	4.1 (2.1)	−0.91 (−1.45 to −0.38)	0.012	14	3.9 (2.0)	−0.62 (−1.03 to 1.32)	0.797
Haemoglobin (g/dl)	21	7.6 (2.1)	1.49 (0.17 to 2.80)	0.029	24	6.9 (1.8)	2.04 (1.33 to 2.75)	<0.001
WBC count ($\times 10^3/\mu l$)	21	1.5 (1.0)	2.46 (1.20 to 3.72)	0.001	24	2.1 (0.7)	2.68 (1.84 to 3.51)	<0.001
Platelets ($\times 10^3/\mu l$)	21	63.8 (32.1)	161.10 (93.13 to 229.06)	<0.001	24	121.9 (69.7)	164.2 (121.23 to 201.17)	<0.001
Amylase (U/l)	4	216.8 (152.0)	NM	–	24	80.4 (39.9)	69.67 (38.96 to 100.38)	<0.001
Alkaline phosphatase (U/l)	8	533.5 (595.0)	260.25 (−110.05 to 630.55)	0.141	24	224.9 (86.7)	151.69 (50.89 to 252.48)	0.010
AST (U/l)	9	113.8 (149.1)	−23.56 (−231.39 to 184.28)	0.800	24	59.3 (94.5)	−16.85 (−72.87 to 39.17)	0.473
ALT (U/l)	9	52.5 (58.9)	−3.67 (−58.96 to 51.63)	0.882	24	36.2 (34.8)	−0.08 (−17.37 to 17.21)	0.874
Bilirubin (mg/dl)	4	1.2 (1.4)	−0.15 (−0.64 to 0.34)	0.406	22	0.7 (0.2)	−0.22 (−0.31 to −0.12)	<0.001
BUN (mg/dl)	9	14.8 (6.6)	−2.17 (−6.51 to 2.17)	0.282	24	20.5 (4.4)	1.56 (−1.39 to 4.51)	0.113
Creatinine (mg/dl)	9	1.1 (0.5)	0.05 (−0.11 to 0.21)	0.492	24	0.8 (0.4)	−0.04 (−0.14 to 0.07)	0.324

GUH: Gondar University Hospital; AMH: Arba Minch Hospital; WBC: white blood cell; NM: not measured at EOT; AST: aspartate aminotransferase; ALT: alanine aminotransferase; BUN: blood urea nitrogen.

the 33 NSAEs, 14 were in children and 19 were in adults (data not shown); the median number of NSAEs per patient was 1 (0–3) and 0 (0–3), respectively. This difference between children and adults was not significant ($P = 0.079$). Biochemical pancreatitis (increased blood amylase) comprised one-third ($n = 11$) of the 33 NSAEs, with the rest being due to increased blood levels of aspartate aminotransferase (four events), alanine aminotransferase (three events) or alkaline phosphatase (three events), raised creatinine (two events) and 10 other NSAEs due to hypertension, hypoglycaemia, raised bilirubin, raised blood urea nitrogen, herpes zoster, otitis media, bronchitis, malaria, giardiasis and post-kala-azar dermal leishmaniasis.

4. Discussion

The effectiveness of VL treatment with antimonials or other antileishmanial agents depends on several factors, including disease stage (advanced or early), drug toxicity, level of hospital care and biological risk factors relating to individual patients (e.g. age, pregnancy, malnutrition, immunosuppression, etc.). In the first set of HIV-negative Ethiopian VL patients treated with MA in southern Ethiopia, a cure rate of >94% was noted.[13] The 54 patients whose medical records were reviewed and included in this report are the second set of VL patients treated with MA in Ethiopia. In this retrospective study, it was found that MA is at least as good as SAG and SSG, with cure rates of 92.9% and 100% in HIV-negative patients from GUH and AMH, respectively (Table 3). Field studies in northwest Ethiopia by MSF–Holland found SSG cure rates of 87.6% (EOT) and 66.2% (6MFU) in a setting of high HIV co-infection.[14] In European HIV co-infected patients, parasitological cure rates of 78% (per-protocol analysis) and 37% (intention-to-treat analysis) were reported.[15] Data from African and European VL patients reiterate the challenges of achieving cure in patients with underlying immune suppression.

Life-threatening side effects of antimonials, albeit rare, are mainly pancreatic and cardiac toxicity.[10,16,17] Other side effects of antimonials include hepatic and renal toxicity, arthralgia and injection-site pain.[16,18] In a recent Brazilian study, a high frequency of pancreatitis (six episodes), hepatic failure/hepatitis (five episodes) and renal failure (eight episodes) leading to five deaths was reported.[19] Electrocardiographic abnormalities in patients treated with antimonials are not uncommon and were reported in 12% of patients in one Italian study.[20] Among HIV-positive and -negative Ethiopian patients with normal renal function, a 30-day treatment with Sb^v was rarely associated with clinically significant bradycardia and, when it occurred, it often was transient, resolving following temporary cessation of treatment.[21]

Clinical pancreatitis is a frequent adverse event in patients treated with MA, especially in HIV co-infected VL patients,[15,17], but is rare among immunocompetent children.[22] In a Spanish trial comparing the efficacy of AmB and MA in HIV co-infected VL patients, eight of 19 patients were withdrawn from MA owing to SAEs, including four patients with clinical pancreatitis.[15] Two of the patients in the current study with HIV co-infection had

life-threatening or fatal clinical pancreatitis; however, in the HIV-negative patients, Glucantime, as well as being effective, was well tolerated. These data indicate that clinical pancreatitis should indeed be a major criterion for withdrawing patients from antimony-based treatments. The 10.0% case–fatality rate observed in GUH indeed exceeds those reported in Ugandan patients,[10] although it was much lower than previously reported in patients at GUH.[23–25] The immune system of VL patients is suppressed during the active stage of the disease and can be expected to lead to a high risk of death. In a study conducted in southern Ethiopia, we reported a mortality rate of 2.5–5.6% during SAG and MA treatment, which was mainly associated with nosocomial infections.[13]

Considering the high frequency of SAEs and NSAEs among HIV co-infected VL patients, the pros and cons of co-administering ARVs needs to be critically evaluated in terms of prognosis, drug–drug interactions and safety. To date, little is known about the interactions between antimonials and ARVs. This paucity of pharmacokinetic data has led to the absence of a treatment guideline for VL patients with HIV co-infection and remains to be one of the top research priorities. A recent in vitro study showed that SSG could stimulate HIV-1 virus replication.[26] Furthermore, the effectiveness of currently available ARVs in reconstituting the immune system of HIV co-infected VL patients has been questioned[27] owing to the fact that relapses of VL could not be prevented with HAART.[28] These observations suggest that VL patients with HIV co-infection may require novel combinations of ARV drugs. HIV protease inhibitors were shown to have a dose-dependent antileishmanial activity[29] and to reduce intracellular growth of *Leishmania* in monocyte-derived macrophages co-infected with HIV-1.[30] Such observations warrant further research in clinical settings.

In summary, these data, albeit limited in scope, show that MA-containing drugs such as Glucantime are effective in treating HIV-negative Ethiopian VL patients and as such are as good and as safe as SAG and SSG. Thus, inclusion of Glucantime in the national drug list of Ethiopia is recommended. Furthermore, the data also indicate that antimonials are not the drugs of choice in patients with HIV/AIDS and advanced disease. If use of antimonials cannot be avoided, it will be a good clinical practice to monitor safety, especially in patients on HAART.

Authors' contributions: MB, AH, ZH, WH, TW, HT, RO and SY were involved in the conception and design of the study; RO together with WH, TW and AH analysed the data; TW, ZH, WH, HT and SY supervised the treatment of patients; AH and RO prepared the draft manuscript. All authors critically revised the content of the manuscript and read and approved the final version. AH, WH and TW are guarantors of the paper.

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Conflicts of interest: None declared.

Ethical approval: All patients included in this report were those who sought routine medical care. In compliance with national guidelines, permission to compile patient data was obtained from Gondar University and Arba Minch Hospitals (Ethiopia).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.trstmh.2010.07.007.

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