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Risk factors for in-hospital mortality of visceral leishmaniasis patients in eastern Uganda

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Summary

OBJECTIVE To identify risk factors for in-hospital mortality in patients treated for visceral leishmaniasis (VL) in Uganda.

METHODS Retrospective analysis of VL patients' clinical data collected for project monitoring by Médecins Sans Frontières in Amudat, eastern Uganda.

RESULTS Between 2000 and 2005, of 3483 clinically suspect patients, 53% were confirmed with primary VL. Sixty-two per cent were children <16 years of age with a male/female ratio of 2.2. The overall case-fatality rate during pentavalent antimonial (n = 1641) or conventional amphotericin B treatment (n = 217) was 3.7%. There was no difference in the case-fatality rate between treatment groups (P > 0.20). The main risk factors for in-hospital death identified by a multivariate analysis were age <6 years and >15 years, concomitant tuberculosis or hepatopathy, and drug-related adverse events. The case-fatality rate among patients >45 years of age was strikingly high (29.0%).

CONCLUSION Subgroups of VL patients at higher risk of death during treatment with drugs currently available in Uganda were identified. Less toxic drugs should be evaluated and used in these patients.

keywords visceral leishmaniasis, pentavalent antimonials, amphotericin B, death rate, Uganda, retrospective analysis

Introduction

Visceral leishmaniasis (VL), a protozoal disease, is estimated to affect 500 000 persons every year worldwide (Desjeux 2004). In East Africa, VL is caused by a *Leishmania* species belonging to the *Leishmania donovani* complex (Jamjoom *et al.* 2004). The main endemic focus in Africa is Sudan, but the disease is also endemic in remote regions of Somalia, Ethiopia, Kenya and Uganda. VL is not part of the routine national data collection systems, which contributes to the lack of epidemiological and clinical data (Guerin *et al.* 2002).

Several drugs can be used for the treatment of VL, with different efficacy and safety profiles. Both parasite and host determinants can influence the rate of treatment failure (Croft *et al.* 2006). In East Africa, pentavalent antimonials (SbV) and amphotericin B (ampB) deoxycholate are used as first- and second-line treatments, respectively. In contrast to the situation in the Indian subcontinent (Olliaro *et al.* 2005), SbV drugs remain overall effective in East African countries. Branded (Pentostam™; Glaxo Smith Kline, UK) and generic (SAG; Albert David, India) sodium stibogluconate (SSG) and meglumine antimoniate (Glucantime™; Sanofi-aventis, France) are the three commercialized SbV drugs recommended by WHO (WHO 1996). Generic SSG is as safe and effective as Pentostam™ for the treatment of VL in Kenya, Ethiopia and Sudan (Veeken *et al.* 2000; Moore *et al.* 2001; Ritmeijer *et al.* 2001).

Adverse effects are frequent with SbV and death because of acute pancreatitis or cardiac disrhythmia may occur. The case-fatality rate in VL patients treated with SbV has been reported to be as high as 18.5% (Lyons *et al.* 2003). Death can be due to direct drug toxicity or VL itself in patients with advanced disease, as SbV drugs are rather slow-acting. Mortality is particularly high among HIV patients. A study undertaken in southern Sudan, analysing a cohort of 1207 adults treated with SSG, identified long duration of illness (>5 months), age >45 years, severe anaemia [haemoglobin (Hb) count <6 g/dl], severe malnutrition (Body Mass Index, BMI <14 kg/m^2) and vomiting as risk factors for death (Seaman *et al.* 1996). Another study conducted in the same setting analysed 3365 patients

treated with SSG (Collin *et al.* 2004). Age ≥45 years, malnutrition (BMI <13 kg/m^2), anaemia (Hb <8 g/dl) and duration of illness (≥5 months) were risk factors for death in adults, whereas age <2 years, malnutrition (weight-for-height <60%), anaemia (Hb <6 g/dl), and splenomegaly were identified as risk factors in children and adolescents. Diarrhoea, vomiting, and bleeding were also associated with a higher risk of death in Sudan and in Ethiopia (Lyons *et al.* 2003; Collin *et al.* 2004). Concomitant HIV infection was the strongest predictor of death [odds ratio (OR) = 4.5, 95% confidence interval (CI): 1.8–11.4] in the Ethiopian study (Lyons *et al.* 2003). High rates of severe adverse effects and death among HIV–VL co-infected patients treated with SbV have also been reported in Europe (Delgado *et al.* 1999).

Amphotericin B deoxycholate is generally used to treat patients with SbV failures in East Africa. This drug frequently causes infusion-related adverse effects such as fever and chills. Severe adverse effects such as anaphylactic reactions, renal insufficiency or hypokalemia may occur. Whereas ampB deoxycholate was found to be effective and relatively safe in Indian rural hospitals (Thakur & Ahmed 2001), it did not perform better than SbV in Uganda (Mueller *et al.* 2008). Amphotericin B also exists in various lipid formulations, of which liposomal ampB (Ambisome™; Gilead Pharma, Foster City, CA, USA) has been the most extensively validated (Sundar *et al.* 2004; Bern *et al.* 2006). Liposomal ampB, which is better tolerated than ampB deoxycholate, is highly effective and safe in India and showed promising results in East Africa (Olliaro *et al.* 2005; Bern *et al.* 2006). Miltefosine and paromomycin, which have been recently evaluated and registered in India, are being studied in East Africa (Ritmeijer *et al.* 2006).

As several anti-leishmanial drugs are (or will be soon) available in East Africa, it is crucial to identify the subgroups of VL patients at increased risk of death with the currently used treatment. They might benefit from a different first-line therapy. We retrospectively analysed the clinical data on VL patients collected during a VL project conducted by Médecins Sans Frontières (MSF) in Amudat Hospital, eastern Uganda, to identify the risk factors for death during treatment.

Patients and methods

From January 2000 to December 2005, data were collected at Amudat Hospital, a 120-bed rural hospital located in Pokot County, Nakapiripirit District, Uganda. Pokot County is part of a larger VL endemic focus that also includes the Pokot North, West Pokot, East Pokot and Baringo districts in Kenya. The main objective of the MSF project in Pokot County was to support medical activities at Amudat Hospital, including the diagnosis and treatment of VL. All patients who were clinically suspect (fever for >14 days with splenomegaly or wasting) were further investigated for VL. The diagnosis algorithm is described elsewhere (Chappuis *et al.* 2005). In brief, diagnostic confirmation was obtained by serology or parasitology (spleen or lymph node aspirate). Serological methods were the direct agglutination test (DAT) from 2000 to 2004 or the rk39 antigen based DiaMed IT-Leish (DiaMed AG, Cressier sur Morat, Switzerland) dipstick test after its local validation in 2004 (Chappuis *et al.* 2005). Testing for HIV was not performed routinely because of the absence of voluntary counselling and testing facilities and the lack of available antiretroviral treatment in the district.

First-line treatment of primary VL was intramuscular meglumine antimoniate (Glucantime™) 20 mg SbV/kg/day for 30 days, without upper dose limit. Second-line treatment was intravenous ampB deoxycholate 1 mg/kg on alternate days for 30 days (15 doses). AmpB deoxycholate had to be introduced as first-line treatment during a 9-month shortage of Glucantime™ (August 2003–April 2004) (Mueller *et al.* 2008). Sodium stibogluconate (Pentostam™) was then used as the first-line treatment from May 2004 until December 2005.

Demographic and medical data of all VL patients were entered in a Microsoft Excel spreadsheet. Only patients with confirmed VL and no history of previous anti-leishmanial treatment (primary VL) were retained for the analysis of risk factors for mortality. Statistical analysis was performed using the Stata 9™ software (Stata Corporation, College Station, TX, USA). First, a univariate analysis was performed exploring the association between the explanatory variables and the outcome (in-hospital mortality). Continuous variables were recoded into predefined categories to allow for comparison with previous studies (e.g. age, anaemia) or were categorized by centiles (e.g. spleen size, weight, height, weeks of illness). Crude odds ratio and its 95% CI were calculated. Variables showing non-normal distribution and discrete variables were analysed with the Kruskal–Wallis rank test. Categorization of nutritional status was based on percentage of the median weight-for-height (% W/H) for children under 137 cm (females) or 145 cm (males) (%W/H <70: severe malnutrition, %W/H 70 to 79: moderate malnutrition, %W/H 80 to 89: mild malnutrition, %W/H ≥90: no malnutrition), and on BMI for adults (BMI ≤16: severe malnutrition, BMI 16–17: moderate malnutrition, BMI 17–18: mild malnutrition, >18 kg: no malnutrition). For the analysis of risk factors for mortality, additional cut-offs were used in order to ensure comparability with previous studies (Seaman *et al.* 1996; Collin *et al.* 2004). Malnutrition assessed by the BMI and the weight/height ratio

were analysed separately as the two methods differ. Variables associated with the outcome in the univariate analysis at a level of significance of $P \leq 0.20$ were included in the multivariate analysis. The multivariate analysis was performed using a logistic regression model in a stepwise forward procedure. Results are presented with 95% confidence intervals where appropriate.

Results

Between 2000 and 2005, 3483 suspected VL patients were admitted to Amudat Hospital. Fifty-five per cent (1904) were then confirmed as VL patients. Among the non-VL cases, the most frequent diagnoses were hyperreactive malarial splenomegaly (HMS; previously known as tropical splenomegaly syndrome) and smear-proven malaria or brucellosis. Forty-six VL patients had a previous history of anti-leishmanial treatment and were excluded from analysis. Of the remaining 1858 patients, 68 died during hospitalization, resulting in a case-fatality rate of 3.7%. The diagnosis of VL was confirmed by DAT (titre >1:12 800) in 1176 patients (63%), by DiaMed IT-Leish in 499 patients (27%), by parasitological diagnosis of spleen aspirate in 178 patients (10%), and of lymph node aspirate in five patients.

Univariate analysis

The majority of the patients were children aged <16 years (62.8%), with a male:female sex ratio of 2.2. Mortality was lowest in the age category 6–15 years (Table 1), whereas age <6 years and >15 years were risk factors for higher mortality. In particular, age >45 years was a strong risk factor for death (OR = 33.05, 95% CI: 11.40–95.80). Other factors associated with mortality were female sex, residence 51–100 km from Amudat (compared with <15 km), and duration of illness >10 weeks (compared with <6 weeks). Only 20% patients were not malnourished (BMI >18 kg/m^2 or W/H ≥90%). Malnutrition, measured by either BMI or W/H was not a risk factor for death ($P > 0.20$ for all categories; Table 2). Severely enlarged spleen of more than 14 cm below the costal margin was a risk factor for death compared with spleen enlargement of less than 11 cm. Ninety-six per cent of patients presented with anaemia, which was not associated with increased mortality. Mild anaemia was negatively associated with mortality ($P = 0.004$).

Forty-five per cent of patients presented one or more concomitant infection(s) such as acute respiratory infections (32%), malaria (21%), ear, nose or throat infections

Table 1 Risk factors for in-hospital death among 1858 primary VL cases at Amudat hospital, Uganda: univariate analysis of demographic characteristics

	Total (n = 1858)		Deaths (n = 68)	CFR			
	n	%	n	%	P-value	OR	95% CI of OR
Age							
0–5 years	335	18.3	14	4.2	0.001	3.52	1.54, 8.05
6–15 years	818	44.6	10	1.2		1	
16–45 years	650	35.4	31	4.8	<0.001	4.05	1.96, 8.35
Over 45 years	31	1.7	9	29.0	<0.001	33.05	11.40, 95.80
Sex							
Male	1283	69.0	39	3.0		1	
Female	575	31.0	29	5.0	0.033	1.69	1.04, 2.77
Country of origin							
Uganda	565	30.5	15	2.6		1	
Kenya	1290	69.5	53	4.1	0.125	1.57	0.88, 2.81
Distance from Amudat							
0–15 km	345	19.4	7	2.0		1	
16–50 km	782	44.0	28	3.6	0.167	1.79	0.77, 4.15
51–100 km	492	27.7	26	5.3	0.017	2.69	1.15, 6.30
>100 km	157	8.8	3	1.9	>0.20	0.94	0.24, 3.69
Duration of illness							
0–5 weeks	579	31.4	14	2.4		1	
6–10 weeks	650	35.2	19	2.9	>0.20	1.21	0.60, 2.45
>10 weeks	617	33.4	33	5.3	0.009	2.28	1.20, 4.31

P-value based on chi-square tests.
CFR, case-fatality rate.
Missing values: 24 for variable age, 0 for sex, 3 for origin, 82 for distance, and 12 for duration of illness.

Table 2 Risk factors for in-hospital death among 1858 primary VL cases at Amudat hospital, Uganda: univariate analysis of clinical characteristics

	Total (n = 1858)		Deaths (n = 68)	CFR			
	n	%	n	%	P-value	OR	95% CI of OR
Nutritional status							
BMI (n = 775)							
>18.0	155	20.0	9	5.8		1	
17.1–18.0	150	19.3	10	6.7	>0.20	1.16	0.46, 2.94
16.1–17.0	171	22.1	11	6.4	>0.20	1.11	0.45, 2.77
15.1–16.0	150	19.3	5	3.3	>0.20	0.56	0.18, 1.72
14.1–15.0	82	10.6	4	4.9	>0.20	0.83	0.25, 2.80
13.1–14.0	44	5.7	3	6.8	>0.20	1.19	0.31, 4.60
≤13.0	23	3.0	0	0.0	>0.20	0.00	–
W/H (n = 1024)							
≥90	210	20.5	5	2.4		1	
80–89	490	47.8	10	2.0	>0.20	0.85	0.29, 2.53
70–79	268	26.2	8	3.0	>0.20	1.26	0.41, 3.92
<70	56	5.5	2	3.6	>0.20	1.52	0.29, 8.07
Spleen size on admission							
<11 cm	587	31.9	14	2.4		1	
11–14 cm	599	32.5	17	2.8	>0.20	1.20	0.58, 2.45
>14 cm	654	35.5	33	5.0	0.014	2.17	1.15, 4.11
Anaemia on admission							
None (Hb >11 g/dl)	67	3.6	6	9.0		1	
Mild (Hb 7.3–10.7 g/dl)	1116	60.5	30	2.7	0.004	0.28	0.11, 0.70
Moderate (Hb 5.3–6.7 g/dl)	606	32.9	26	4.3	0.089	0.46	0.18, 1.15
Severe (Hb <5.3 g/dl)	54	2.9	5	9.3	>0.20	1.04	0.30, 3.62
Concomitant diagnosis							
ARI	595	32.0	22	3.7	>0.20	1.02	0.60, 1.70
Malaria	387	20.8	14	3.6	>0.20	0.98	0.54, 1.79
ENT infections	69	3.7	3	4.3	>0.20	1.21	0.37, 3.94
Diarrhoea	65	3.5	6	9.2	0.015	2.84	1.18, 6.84
Pregnancy	10	0.5	2	20.0	0.006	6.75	1.40, 32.53
Hepatopathy	8	0.4	3	37.5	<0.001	16.48	3.81, 71.18
Tuberculosis	7	0.4	3	42.9	<0.001	20.61	4.46, 95.20
Adverse events	119	6.6	15	22.1	<0.001	3.97	2.17, 7.29

P-value based on chi-square tests.
ARI, acute respiratory infections; ENT, ear, nose and throat.
Missing values: spleen size (n = 18), anaemia (n = 15).

(4%) and diarrhoea (3%) during hospitalization. Tuberculosis, liver disease (defined by clinical jaundice and/or by a positive hepatitis B surface antigen) and diarrhoea were associated with fatal outcome. Pregnancy was also strongly associated with death; 861 (46%) patients were treated with Pentostam™, 666 (36%) with Glucantime™, 217 (12%) with ampB deoxycholate, and 109 (6%) with Glucantime™ completed by Pentostam™. Five patients died in the hospital before treatment was started. There was no difference in case-fatality rates between the different treatments used (3.7% for Pentostam, 2.8% for Glucantime, 1.8% for a combination of both, and 4.6% for ampB; $P > 0.20$). Adverse events, reported in 7% of the cases (n = 134), were associated with higher mortality.

Multivariate analysis

All 13 variables associated with death in the univariate analysis were included in the multivariate logistic regression model. After adjusting for the other variables in the model, home location 51–100 km from Amudat, duration of illness >10 weeks and diarrhoea were not found to be significantly associated with increased mortality, and were therefore excluded from the model. The association

between pregnancy and death also lost its statistical significance, but the variable 'pregnancy' was kept in the final model because of its clinical meaningfulness. Spleen size <11 cm and 11–14 cm were merged into a single category because of similar odd ratios for death. We found a significant interaction between spleen size and sex (likelihood-ratio test for interaction: $P = 0.003$) and therefore stratified the results. There were no other significant interactions detected in the model. Because of missing values, the final model was based on 1801 observations, representing 97% of the total data.

After adjustment for the other variables in the model, age <6 years and >15 years remained strongly associated with death compared with age 6–15 years (OR = 3.90, 95% CI: 1.48–10.27 and OR = 4.01, 95% CI: 1.78–9.03, respectively) (Table 3). In particular, age >45 years was a very strong risk factor for death (OR = 38.21, 95% CI: 11.84–123.21). Female sex was a risk factor in patients with spleen size ≤14 cm (OR = 3.21, 95% CI: 1.42–7.28), whereas the association was not found in patients with spleen size >14 cm. Spleen size >14 cm was identified as a risk factor in males (OR = 4.22, 95% CI: 1.95–9.13), but not in females (OR = 0.64, 95% CI: 0.22–1.84). Concomitant tuberculosis (OR = 10.52, 95% CI: 1.61–68.68) and hepatopathy (OR = 14.87, 95% CI: 2.87–76.92) remained strongly associated with increased mortality. The association between pregnancy and death lost its significance but a trend towards increased mortality remained (OR = 5.19, 95% CI: 0.89–30.18). Mild anaemia was a protective factor compared with the absence of anaemia (OR = 0.21, 95% CI: 0.07–0.68), whereas moderate to severe anaemia was not associated with death (OR = 0.40, 95% CI: 0.12–1.30).

Adverse events

Adverse events were strongly associated with mortality (OR = 4.84, 95% CI: 2.41–9.70). After stratification of data by the type of drug, adverse events recorded in patients treated with Glucantime™ (OR = 5.28, 95% CI:

Table 3 Multivariate analysis of risk factors for in-hospital death among 1801 primary VL cases at Amudat hospital, Uganda

	Total (n = 1801)		Deaths (n = 59)	CFR	Adjusted		
	n	%	n	%	OR	95% CI of OR	P-value
Age							
0–5 years	327	18.2	12	3.7	3.90	1.48, 10.27	0.006
6–15 years	807	44.8	8	1.0	1		
16– years	637	35.4	30	4.7	4.01	1.78, 9.03	0.001
over 45 years	30	1.7	9	30.0	38.21	11.84, 123.21	<0.001
Sex							
Spleen size ≤14 cm							
Males	797	68.4	13	1.6	1		
Females	368	31.6	16	4.3	3.21	1.42, 7.28	0.005
Spleen size >14 cm							
Males	459	72.2	23	5.0	1		
Females	177	27.8	7	3.9	0.49	0.18, 1.33	0.160
Spleen size on admission							
Males							
≤14 cm	797	63.5	13	1.6	1		
>14 cm	459	36.5	23	5.0	4.22	1.95, 9.13	<0.001
Females							
≤14 cm	368	67.5	16	4.3	1		
>14 cm	177	32.5	7	3.9	0.64	0.22, 1.84	>0.20
Anaemia							
None (Hb >11 g/dl)	60	3.3	4	6.7	1		
Mild (Hb 7.3–10.7 g/dl)	1097	60.9	28	2.5	0.21	0.07, 0.68	0.009
Moderate to severe (Hb 0–6.7 g/dl)	644	35.8	27	4.2	0.40	0.12, 1.30	0.127
Concomitant diagnosis							
Hepatopathy	8	0.4	3	37.5	14.87	2.87, 76.92	0.001
TB	7	0.4	3	42.9	10.52	1.61, 68.68	0.014
Pregnancy	9	0.5	2	22.2	5.19	0.89, 30.18	0.067
Adverse events	132	7.3	14	10.6	4.84	2.41, 9.70	<0.001

1.79–15.53) or Pentostam™ (OR = 5.09, 95% CI: 2.29–11.29) were associated with death, but no association was found in patients treated with ampB deoxycholate. The adverse events recorded for the patients who died while on Glucantime™ (n = 5) were: epigastric pain (n = 1), acute pancreatitis (n = 1), disrhythmia (n = 1), cardiac failure (n = 1), and sudden death (n = 1), whereas those recorded for the patients who died while on Pentostam™ (n = 10) were vomiting (n = 6), anorexia (n = 2) and respiratory failure (n = 2).

Discussion

The overall mortality rate among 1858 primary VL patients admitted between 2000 and 2005 at Amudat Hospital, eastern Uganda was 3.7%. Several risk factors for in-hospital death were identified: age <6 and >15 years (in particular >45 years), female sex in patients with spleen sizes <14 cm, spleen size >14 cm in males, concomitant tuberculosis or liver disease, and occurrence of adverse events during treatment. We do not have an explanation for the observed interaction between sex and spleen size, which may be related to another, unmeasured variable.

Young children (<5–6 years) and adults >45 years are at greater risk of death when treated with SbV in Ethiopia and Sudan (Seaman *et al.* 1996; Lyons *et al.* 2003; Collin *et al.* 2004). We found a strikingly high (29%) case-fatality rate among >45-year-old patients in Uganda, which is consistent with previous findings in Ethiopia (36%) and Sudan (26–28%) (Seaman *et al.* 1996; Lyons *et al.* 2003; Collin *et al.* 2004). The reason for the high mortality in this age group is not known but an increased prevalence of co-morbidities, a weakened immune system and/or a greater susceptibility to severe adverse events with SbV may be causal factors.

Chronic liver disease or tuberculosis was associated with rising mortality. This is likely to be caused by a direct synergistic impact of these conditions on the general condition of the patients, delayed diagnosis due to similar clinical presentation (e.g. VL and miliary tuberculosis), increased toxicity of anti-leishmanial drugs, or a combination of these factors. Tuberculosis may be an indicator of concomitant HIV infection, which is strongly associated with fatal outcome in patients treated with SbV in East Africa (Ritmeijer *et al.* 2001, 2006; Lyons *et al.* 2003). Both SbV and ampB deoxycholate are more toxic and less efficient in HIV–VL co-infected patients. HIV testing was not done routinely at Amudat Hospital. The lack of this potential essential prognostic determinant is unlikely to have had a significant impact on our analysis. Indeed, low (1.4%) HIV seroprevalence was found among 206 consecutive VL patients during an unlinked anonymous testing conducted at Amudat hospital in 2002 and 2003 (F. Chappuis, personal communication).

In contrast with previous studies in Ethiopia and Sudan, we did not find severe anaemia or malnutrition to be associated with increased mortality (Seaman *et al.* 1996; Lyons *et al.* 2003; Collin *et al.* 2004). The odds ratio for death in patients with different degrees of anaemia was compared with patients with no anaemia. The absence of apparent anaemia cannot always be considered as a sign of well-being, as it can be due to moderate or severe dehydration (haemoconcentration). This may explain why mild anaemia was associated with a better outcome in our study.

Adverse effects during treatment with Pentostam™ or Glucantime™, but not with ampB deoxycholate, were associated with higher mortality. Pentavalent antimonials have a high potential of toxicity in VL patients. They should be promptly interrupted in presence of ominous adverse effects consistent with acute clinical pancreatitis (e.g. epigastric pain not responding to antacids) or disrhythmias (e.g. palpitations), which usually cannot be investigated in rural areas of East Africa. It should be emphasized that some life-threatening adverse effects caused by ampB deoxycholate, such as hypokalemia and acute renal failure, are likely to have been overlooked as they are difficult to diagnose clinically, and as blood potassium and creatinine were not monitored during treatment. This statement is supported by the similar case-fatality rates found in patients treated with ampB deoxycholate or SbV at Amudat Hospital, Uganda, as was previously reported (Mueller *et al.* 2008).

We found a trend towards a higher case-fatality rate among pregnant women. Two of the nine patients died, one treated with SbV and one treated with ampB deoxycholate. The low number of patients precludes any conclusion but a recent report from Sudan highlights the toxicity of SbV on the foetus, as 13 of 39 pregnant VL patients treated with SbV suffered abortions (compared with none in patients treated with Ambisome) (Mueller *et al.* 2006). Women of childbearing age should undergo a pregnancy test to avoid the administration of SbV in this population.

Distance to the health centre was not associated with a higher mortality in the multivariate analysis. Nevertheless, it is striking that 70% of the patients were from Kenya, sometimes traveling large distances. This fact motivated MSF in 2006 to transfer the VL management and treatment centre to Kacheliba hospital, which is located on the Kenyan part of the Pokot VL focus.

The main limitations of this study are related to data quality and change in diagnostic algorithm over time. Spleen size measurement was not sufficiently standardized, which may have resulted in variable techniques of measuring among the different physicians. Haemoglobin

estimates were only semi-quantitative and subject to interpretation (Lovibond method). The diagnostic algorithm changed twice during the data collection. Although both the DAT and the rK39 dipsticks were locally validated against the previous test in use (spleen aspiration and DAT, respectively), we cannot exclude a slight shift in the population of confirmed VL cases over time. Final outcome of VL treatment is traditionally assessed at 6 months after treatment. Active follow-up, however, was not possible in our setting because of logistic constraints. Our study refers only to in-hospital mortality, and this should be taken into account when comparing these results with other reports.

Our study provides further evidence that there is an urgent need for new VL drugs in East Africa. Miltefosine was effective in HIV-negative Ethiopian VL patients and markedly safer than sodium stibogluconate in HIV co-infected patients (Ritmeijer *et al.* 2006). Despite its teratogenicity, miltefosine should be further evaluated in East Africa, preferably in combination with another anti-leishmanial drug. Indeed, most VL experts agree that drug combinations are the way to go (Bryceson 2001). Paromomycin combined with sodium stibogluconate is currently being re-evaluated in several East African countries. Moreover, the Drugs for Neglected Diseases initiative will sponsor studies on Ambisome-based combinations in this region. While new treatments are likely to replace SbV mono-therapy in the future, the treatment approach for patients at high risk of death with SbV must change now. Ambisome is very effective and safe for the treatment of VL, and is being used as first-line treatment in developed countries (Bern *et al.* 2006). A recent agreement between the WHO and Gilead Pharma led to a drastic price reduction (20 US$ per 50 mg vial) for non-profit groups treating VL patients in developing countries. Despite the fact that Ambisome remains more expensive than SbV, it should be used in VL patients over 45 years of age, with severe co-morbidities (e.g. HIV infection, tuberculosis, liver disease), during pregnancy, or in patients presenting ominous adverse effects during SbV treatment.

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