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Clinical Epidemiology, Diagnosis and Treatment of Visceral Leishmaniasis in the Pokot Endemic Area of Uganda and Kenya

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Abstract. Between 2000 and 2010, Médecins Sans Frontières diagnosed and treated 4,831 patients with visceral leishmaniasis (VL) in the Pokot region straddling the border between Uganda and Kenya. A retrospective analysis of routinely collected clinical data showed no marked seasonal or annual fluctuations. Males between 5 and 14 years of age were the most affected group. Marked splenomegaly and anemia were striking features. An rK39 antigen-based rapid diagnostic test was evaluated and found sufficiently accurate to replace the direct agglutination test and spleen aspiration as the first-line diagnostic procedure. The case-fatality rate with sodium stibogluconate as first-line treatment was low. The VL relapses were rare and often diagnosed more than 6 months post-treatment. Post-kala-azar dermal leishmaniasis was rare but likely to be underdiagnosed. The epidemiological and clinical features of VL in the Pokot area differed markedly from VL in Sudan, the main endemic focus in Africa.

INTRODUCTION

Visceral leishmaniasis (VL) is a disease caused by protozoa of the *Leishmania donovani* complex (*L. donovani* and *L. infantum*). The parasite infects cells of the reticuloendothelial system and causes progressive splenomegaly, and sometimes hepatomegaly, lymphadenopathies, wasting, and anemia.[1] The disease is transmitted by female sandflies of the genera *Phlebotomus* in the Old World and *Lutzomyia* in the New World. It is mainly found in South Asia (India, Bangladesh, and Nepal) and East Africa, where the most affected countries are Sudan, South Sudan, Ethiopia, Kenya, Somalia, and Uganda. In East Africa, *Phlebotomus orientalis* and *Phlebotomus martini* are the main vectors of VL[2]; these two species of sandfly are found in very different habitats. *Phlebotomus orientalis* is a dry season species, associated with the *Acacia seyal-Balanites aegyptica* woodlands and black cotton soil found in Sudan and north-west Ethiopia, whereas *P. martini* appears to favor more humid habitats, for example termite mounds.[3] The clinical picture of VL varies according to the setting, reflecting differences in parasite strains,[4] vectors, and hosts. It is important to understand the clinical epidemiology of VL to guide appropriate clinical diagnosis and management.

The first outbreak of VL to be reported in Kenya was among soldiers in the north-east of the country in 1942.[5] Another outbreak was later described in 1950 in the Kitui reserve in central Kenya,[6] and was followed by further outbreaks in the Baringo District.[7] In the neighboring North Pokot District, an epidemiological survey undertaken in 1986 found a prevalence of 3.9% (76 of 1,937) of positive *Leishmania* skin tests among the surveyed population (N = 2,139).[8] In Uganda, cases of VL were sporadically reported in the north-east of the country between 1946 and 1957, resulting in an entomological and clinical study in Amudat between May 1967 and January 1968.[9] This study identified *P. martini* as the probable vector. Cases were reported only in the east of Nakapiripirit District (Pokot County), which neighbors the North Pokot District of Kenya.

Médecins Sans Frontières (MSF) began working in Amudat Hospital in Uganda in 1997. It soon became apparent that VL was endemic, so treatment was made available in 1998 and a specific VL program deployed in 2000. As the majority of VL patients were living on the Kenyan side of the border, a further VL treatment center was opened in Kacheliba in Kenya in 2006, whereas clinical management of VL in Amudat was handed over to the Ministry of Health, supported by the Drugs for Neglected Diseases Initiative (DNDi). The introduction of rK39 rapid diagnostic tests (RDTs) in 2006 enabled diagnosis to be decentralized to peripheral health centers. As clinical and epidemiological characteristics of VL vary according to geographical setting and have yet to be described in this focus, we present here the features of VL as observed in a large cohort of VL patients diagnosed and treated by MSF and based on our experience gained over the past 11 years. The specific aims were to describe the epidemiology, clinical characteristics, and treatment outcomes.

MATERIALS AND METHODS

The Ugandan and Kenyan Pokot territory derives its name from the Pokot tribe living in this border region. Situated on a semi-arid plateau at an altitude of 1,200 to 1,800 m, it is bordered by Mounts Moroto, Kadam, and Elgon to the west and the western wall of the Eastern Rift Valley to the east. Heavy rains fall between March and June, and sparse rains in October and November. Villages typically consist of a cluster of compounds—*manyattas*—surrounded by a thick fence made of acacia branches. Several households live in a *manyatta*. Households usually keep livestock, (cows, goats, sheep, and camels) in corrals close to their houses. During the day and sometimes for longer periods Pokot boys and youths herd the livestock away from the compounds to graze them.

Analyses were performed on data collected for the routine monitoring of the project. As experimental investigation was absent, this analysis was exempted from review by the Ethical Review Board of MSF. Data on VL patients were collected at both MSF treatment facilities (Uganda's Amudat Hospital

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and Kenya's Kacheliba Health Center, Kenya) on standardized patient files that changed only slightly over the years. In addition to diagnosed VL patients, data were also collected at Amudat Hospital on all patients with suspected VL, whereas in Kacheliba data collection was restricted to confirmed cases of VL.

At Amudat Hospital, symptoms were recorded at the time of admission as open questions, whereas at Kacheliba Health Center symptoms were systematically checked and recorded during consultation. Nutritional status was addressed differently according to the age group. In children ≤ 5 years of age, severe malnutrition was defined as a z-score for weight-for-length/height below –3 or the presence of oedema, and moderate malnutrition as a z-score for weight-for-length/height between –3 and –2. For children between 6 and 19 years of age severe malnutrition was defined as a z-score for body mass index (BMI)-for-age below –3 and moderate malnutrition as a z-score for BMI-for-age between –3 and –2. For adults, severe malnutrition was defined as a BMI of < 16 kg/m2 and moderate malnutrition as a BMI between 16 and 17 kg/m2.

Diagnosis of VL was based either on demonstration of the parasite in spleen tissue obtained by spleen aspiration,[10] on a positive direct agglutination test (DAT), or on a RDT detecting antibodies against rK39 antigen.

Treatment of primary VL relied mostly on antimonials, meglumine antimoniate, or sodium stibogluconate (SSG), at an intramuscular dose of 20 mg/kg for a period of 30 days. Amphotericin B deoxycholate (1 mg/kg administered on alternate days for 15 days) was temporarily used as first-line treatment in Amudat during a stock-out of antimonials, with no difference in outcome compared with antimonials.[11] In a retrospective analysis of patients treated between 2000 and 2006, patients with a high risk of death during treatment with antimonials were identified,[12] leading to recommend amphotericin B deoxycholate and later AmBisome as the first-line treatment of vulnerable patients (human immunodeficiency virus [HIV] co-infected patients, pregnant women, patients > 45 years of age, and patients in very poor general health).

A VL suspect case was defined as a patient presenting with a history of fever lasting at least 2 weeks and splenomegaly (defined as a palpable spleen below the costal margin on the medioclavicular line) and/or wasting (or a recent history of weight loss). A primary VL case was defined as a suspect case without any history of previous VL treatment and either 1) positive parasitology (demonstrated parasites in a lymph node, spleen, or bone marrow aspirate), 2) positive direct DAT (titer > 1:12800), or 3) a positive rk39-based rapid test (DiaMed IT-Leish, DiaMed GmbH, Cressier, Switzerland). Relapse VL cases were defined as patients with a history of treated VL and parasites found in a lymph node, spleen, or bone marrow aspirate. Post-kala-azar dermal leishmaniasis (PKDL) cases were defined as patients previously treated for VL, presenting with a macular and/or nodular rash.

In Uganda, village names were entered manually in the Excel (Microsoft Corp., Redmond, WA) sheet for each patient, resulting in different spellings for the same locations. In the database used in Kenya, the list of possible villages was predefined, based on administrative divisions, which reduced the risk of errors. The GPS (Global Positioning System) coordinates of the villages of residence of VL cases seen at Amudat Hospital and Kacheliba Health Center were collected in 2007, and were combined with the number of VL cases seen between 2000 and 2010 using the Quantum GIS software version 1.7.0. High-resolution data on elevation were derived from data collected by the shuttle radar topography mission across Africa at 90 m × 90 m spatial resolution (http://srtm.usgs.gov).

In the first years of the project, data were recorded in an Excel spreadsheet. Since 2006, a specific Access-based program was developed to simplify data entry. After data cleaning, the two treatment center databases were merged and analyzed using the Stata 11 software (StataCorp LP, College Station, TX). All the results were stratified by treatment center. Data were pooled if the results were comparable between centers; otherwise, results are presented by treatment center. Tests of hypotheses were based on χ^2 for categorical variables and t test for continuous variables, using a level of significance of 0.05. Some patients were present with more than one record in the database, if they had received more than one course of treatment. For the description of primary VL cases, 9 cases from Amudat and 12 cases from Kacheliba were excluded because the diagnosis of VL was not confirmed (incomplete laboratory results or diagnosis based on clinical features only).

RESULTS

Patient characteristics. At Amudat Hospital, there were 4,428 admissions for VL investigation between 2000 and

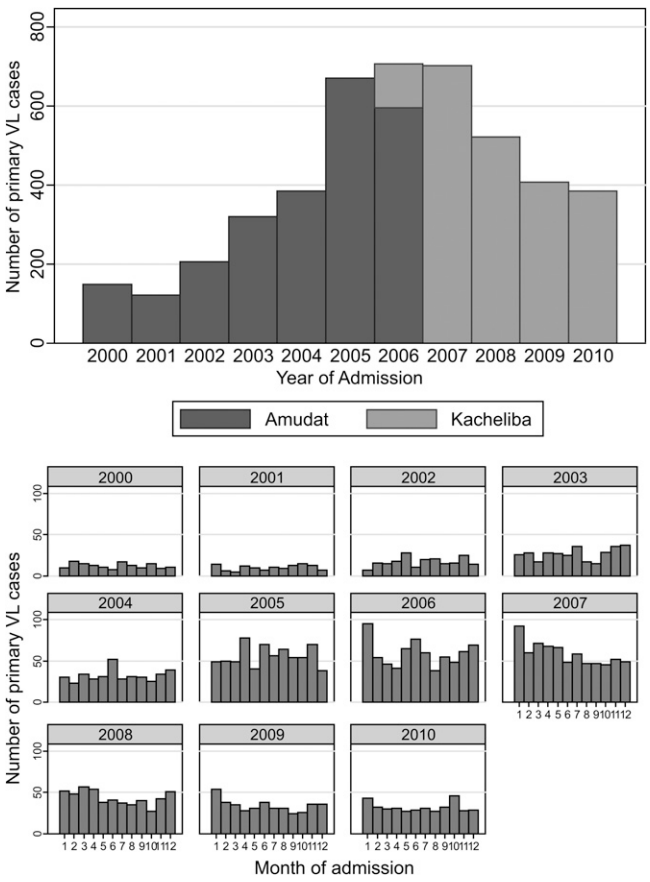

FIGURE 1. (Top) Admissions for primary visceral leishmaniasis to Amudat and Kacheliba Treatment Centers, Pokot area, Uganda and Kenya. (Bottom) Monthly admissions, by year, from January 2000 to December 2010.

2006, including 2,461 primary VL, 56 relapses, 4 PKDL, and 1,907 cases ultimately viewed as non-VL cases. In Kacheliba, 2,301 cases of leishmaniasis were diagnosed between 2006 and 2010, including 2,144 primary VL, 81 relapses, and 75 PKDL. Figure 1 presents the monthly admissions for primary VL, by year, 2000 to 2010. The number of primary VL cases treated by MSF peaked in the years 2005 to 2007. The catchment area, after increasing during the first few years, shifted over to the Kenyan side of the border after 2006, and remained very similar thereafter (data not shown). The number of monthly admissions by year (Figure 1) showed no marked or consistent seasonal fluctuations.

At Amudat Hospital, 68% out of the 2,452 primary VL cases were coming from Kenya and 25% from Uganda, although the country of residence was not given for the remaining 7%. In Kacheliba, almost all of the 2,130 cases (97%) were from Kenya. We were able to collect GPS coordinates for 149 villages (123 in Kenya and 26 in Uganda), representing the stated location of residence for 92% of the total number of cases. Figure 2 shows the number of cases treated by village of residence.

In both treatment centers, young males were the most affected group (Table 1). Male patients were slightly older than female patients ($P < 0.001$). Pregnant women represented 0.7% of all patients ($N = 34$). Patients reported earlier at Kacheliba than at Amudat (Table 2; $P < 0.001$). Although details of symptoms were not consistently recorded in Amudat, the most frequently reported symptoms in Kacheliba (in addition to fever, which was part of the case definition) were weight loss (87.8%), loss of appetite (86.8%), spleen enlargement (77.1%), nose bleeding (21.9%), vomiting (16.5%), headache (14.6%), abdominal pain (13.0%), abdominal swelling (11.4%), and diarrhea (8.5%). On clinical examination, mean spleen size was 12.3 cm below the costal margin in Amudat (SD 4.2 cm) and 11.4 cm in Kacheliba (SD 4.4 cm; *t* test $P < 0.001$). In Kacheliba, an enlarged liver was reported in 13.5% out of 2,130 cases, although lymph nodes were enlarged in only 1.3% of cases. Other signs such as pallor, oedema, and jaundice were reported in respectively 45.8%, 8%, and 2.3% of cases. More than half of the patients were malnourished on admission, with 24.7% severely malnourished and another 27.6% moderately malnourished.

Testing for HIV was systematically proposed in Kacheliba after the introduction of AmBisome treatment of HIV-VL co-infected patients. Out of 740 patients tested for HIV, 2.3% ($N = 17$) were found to be positive. In Amudat, blood

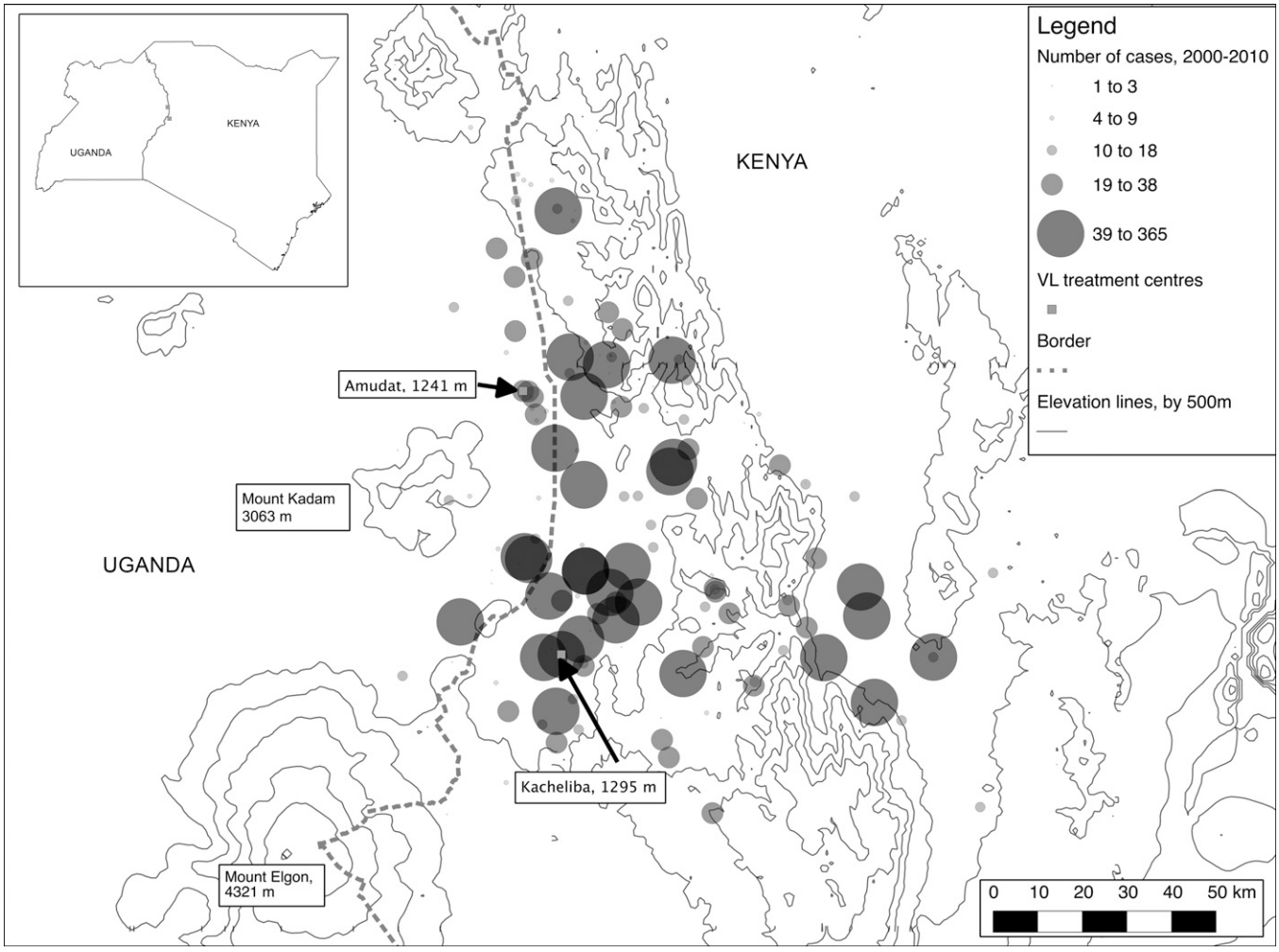

FIGURE 2. Map of number of primary visceral leishmaniasis cases treated between 2000 and 2010 in Amudat and Kacheliba Treatment Centers, per village of residence. (a total of 4,216 cases with Global Positioning System [GPS] locations out of 4,582 cases; 137 cases from Baringo District are outside the map area).

TABLE 1

Distribution of primary visceral leishmaniasis cases, by age group and gender, Amudat and Kacheliba Treatment Centers, Pokot area, Uganda and Kenya

	Female		Male		Not known	Total	
Age group (in years)	n	(%)	n	(%)	n	n	(%)
< 1	6	(0.4)	1	(0.0)	0	7	(0.1)
1–4	303	(21.3)	375	(11.9)	2	680	(14.8)
5–14	601	(42.3)	1413	(44.9)	2	2,016	(44.0)
15–44	446	(31.4)	1239	(39.4)	7	1,692	(36.9)
45–99	50	(3.5)	110	(3.5)	1	161	(3.5)
Not known	15	(1.0)	10	(0.3)	1	26	(0.6)
Total (%)	1,421 (31.0)		3,148 (68.7)		13 (0.3)	4,582	(100.0)

from 206 VL patients anonymously screened for HIV in 2003 found 1.4% prevalence. Patients were systematically screened for malaria using a blood smear examination. Over the years, the prevalence of positive malaria slides varied between 3.8% and 21.4% in Kacheliba, and between 5.3% and 34.4% in Amudat, with no clear trend identified over time. The mean hemoglobin level was 7.9 g/dL (SD 1.8 g/dL).

Laboratory diagnosis. The procedure for confirming VL diagnosis evolved over the years. Initially, diagnosis was based on spleen aspirates, which were performed on over 400 patients with no major bleeding complication. Spleen puncture was rapidly omitted for patients with negative DAT (≤ 1:100) or high DAT titers (≥ 1:51,200), but continued to be performed along with DAT in all other patients up to August 2001. The DAT titers were then compared with results of a microscopic reading of spleen aspirates, defining the DAT threshold titers later used in the program: < 1:1,600 (negative), 1:3,200–1:12,800 (borderline) and ≥ 1:25,600 (positive). The resulting diagnostic algorithm used from September 2001 to February 2005, resulted in a dramatic decrease in the number of spleen punctures performed, from 35.1% to 11.7% of suspected VL cases (Table 3).

Following the completion of a diagnostic evaluation study,[13] the rK39 DiaMed IT LEISH was fully deployed as first-line diagnostic test in March 2005 (Table 3). The DAT was still required for patients with a negative rk39 test because of the relatively low sensitivity reported elsewhere in East Africa.[14,15] This new algorithm (Figure 3) led to a further reduction in the number of spleen aspirates performed (0.2%), and a sharp decrease in the number of DAT (17.1%) (Table 3).

Treatment outcomes. The overall case-fatality rate in VL patients was 1.0% in Kacheliba as compared with 3.0% in Amudat ($P < 0.001$; Table 4). Case fatality rates were different for patients treated with antimonials, i.e., 1.0% in Kacheliba versus 2.6% in Amudat (χ^2 $P < 0.001$), although it was not significantly different in the other treatment groups. In October 2008, AmBisome was introduced in Kacheliba, for use in the case of 1) treatment failure (non-response or relapse), 2) intolerance to antimonials (e.g., intractable vomiting), and 3) contraindication(s) for antimonials. Initially, the total dose was 20 mg/kg, as previously recommended by the World Health Organization (WHO).[16] However, a high proportion of patients treated with this regimen relapsed (6 of 46; 13.0%), which concurred with observations made by other MSF programs in East Africa.[17,18] This led to an increase in total dose to 30 mg/kg (5 mg/kg/day IV × 6 doses) from November 2009, resulting in a lower proportion of relapses (2/51 = 3.9%; $P = 0.075$).

TABLE 2

Duration of symptoms in primary visceral leishmaniasis patients, by treatment center, Pokot area, Uganda and Kenya

	Kacheliba ($N = 2,130$)		Amudat ($N = 2,452$)	
	n	(%)	n	(%)
Duration of illness (in months)				
0–1 month	1,216	(57.1)	830	(33.8)
2 months	527	(24.7)	771	(31.4)
3–5 months	326	(15.3)	732	(29.8)
≥ 6 months	59	(2.8)	66	(2.7)
Missing	2	(0.1)	53	(2.2)
P value < 0.001				

Relapses. The ratio of relapses versus primary VL cases was 2.4% in Amudat ($N = 58$), compared with 3.8% in Kacheliba ($N = 81$). Active follow-up was not implemented, resulting in low 6-month follow-up rates: 16.7% in Kacheliba and < 3% in Amudat, where it was not a priority of the program. The median period between initial treatment and relapse was 186 days (range 11–543). In Kacheliba, relapse patients had been previously treated with antimonials (60.5%), amphotericin B deoxycholate (18.5%), AmBisome (12.3%), or unknown (8.6%), whereas in Amudat they had received antimonials (55.2%), amphotericin B deoxycholate (19%), or an unknown drug (25%). Out of 32 relapse patients tested for HIV in Kacheliba, four were positive (12.5%).

PKDL. In Amudat a single patient was diagnosed with PKDL and admitted four times because of recurrences, sometimes accompanied by VL or post-kala-azar ocular leishmaniasis (uveitis). In all, between 2000 and 2002 he received five courses of treatment during four admissions. He died during the last course of treatment probably caused by antimonial-induced pancreatitis. In Kacheliba, 75 PKDL cases were treated, with a PKDL to primary VL ratio of 3.5%. Previous treatment consisted of antimonials (66 of 75, 88%) or was unknown (9 of 75, 12%). No PKDL was reported after amphotericin B deoxycholate or AmBisome treatment. There was an increase over time in PKDL cases in Kacheliba treatment center.

DISCUSSION

A total of 4,605 primary VL, 137 relapses, and 79 PKDL patients were treated by MSF in Amudat (Uganda) and Kacheliba (Kenya) between 2000 and 2010. The VL in the Pokot area is a disease that mainly affects young males, although both genders and all age categories are affected. This probably reflects differences in exposure to sandflies.

TABLE 3
Diagnostic tests to diagnose primary visceral leishmaniasis (VL), by diagnostic algorithm, Amudat Treatment Center, Uganda

	DAT validation (up to September 2001)			DAT-based algorithm (up to March 2005)			rK39-based algorithm (from March 2005 onwards)		
	Number of tests	Primary VL diagnosed		Number of tests	Primary VL diagnosed		Number of tests	Primary VL diagnosed	
		n	(%)		n	(%)		n	(%)
rK39 RDT*	0	0	(0.0)	0	0	(0.0)	1,729	1,113	(95.1)
DAT*	530	147	(66.2)	1,892	956	(89.9)	303	53	(4.5)
Spleen aspirates	187	71	(32.0)	224	100	(9.4)	4	3	(0.3)
Total suspected cases	532	222†	(100.0)	1,919	1,063†	(100.0)	1,772	1,170†	(100.0)

*DAT = direct agglutination test; RDT = rapid diagnostic test.
†Five primary VL cases diagnosed by lymph node puncture and seven on clinical grounds.

There is no clear seasonal pattern. The incidence appeared to fluctuate slowly over the years, but we did not see marked epidemic surges as described in Sudan.[19] In recent years, the annual number of new VL cases diagnosed in Kacheliba has stabilized at around 400 cases, suggesting that passive case-finding of VL patients is not sufficient to control the disease, despite the implementation of decentralized diagnosis in several sites. This could either be because most of the transmission occurred either before or at the beginning of the symptomatic phase, or that many cases remained untreated, maintaining a constant parasite reservoir.

The clinical picture of VL in the Pokot area differed from Sudan. Lymph node enlargement was not as pronounced. The average spleen size was larger than in Sudanese patients (12 cm versus 5–7 cm).[20,21] However, a longer period before seeking treatment may partly explain this difference.[22] Interestingly, spleen size was also large among clinically suspected VL cases finally not diagnosed with VL (data not shown). Other diseases resulting in massive splenomegaly such as hyperactive malarial splenomegaly could be prominent in this region. The introduction of rK39 RDT as the first-line diagnostic test allowed to simplify the diagnostic algorithm

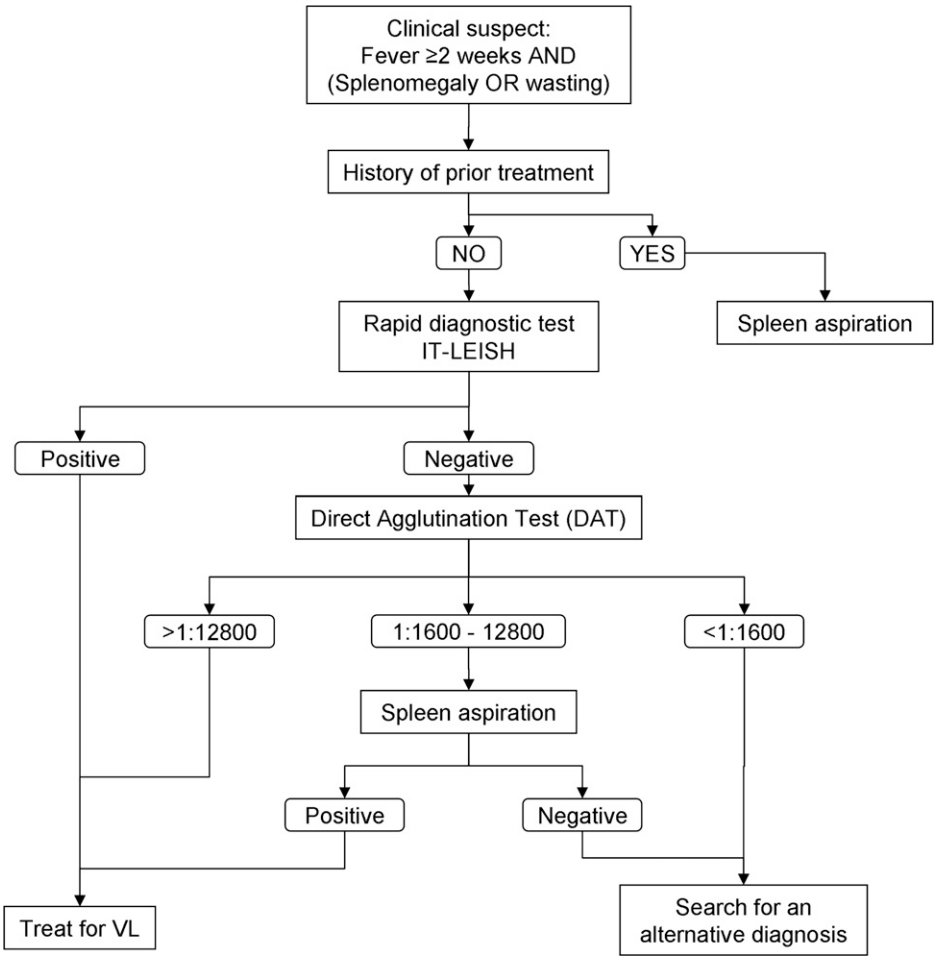

FIGURE 3. Diagnostic algorithm of visceral leishmaniasis used by Médecins Sans Frontières since March 2005 at Amudat and Kacheliba Treatment Centers, Pokot area, Uganda and Kenya.

TABLE 4

Treatment of primary visceral leishmaniasis cases and case-fatality ratios by treatment, Amudat and Kacheliba Treatment Centers, Pokot area, Uganda and Kenya

	Amudat				Kacheliba				Total	
	Cases		Deaths	CFR	Cases		Deaths	CFR	Cases	
Treatment	n	(Col %)	n	(Row %)	n	(Col %)	n	(Row %)	n	(Col %)
Antimonials	2,230	(90.9)	59	(2.6)	2,034	(95.4)	21	(1.0)	4,265	(93.1)
Liposomal Amphotericin B	0	(0.0)	NA	NA	54	(2.5)	1	(1.8)	54	(1.2)
Amphotericin B Deoxycholate	217	(8.8)	10	(4.6)	41	(1.9)	0	(0.0)	258	(5.6)
Miltefosine	0	(0.0)	NA	NA	1	(0.0)	0	(0.0)	1	(0.0)
Not treated	5	(0.2)	5	(100.0)	0	(0.0)	NA	NA	5	(0.1)
Total	2,452	(100.0)	74	(3.0)	2,130	(100.0)	22	(1.0)	4,582	(100.0)

and decrease the use of more demanding (DAT) or invasive (spleen aspirate) procedures. However, the limited sensitivity of rK39 RDT in East Africa remains a severe constraint.[14]

Relocating the MSF treatment facility from Amudat to Kacheliba closer to the center of the endemic area led to earlier patient presentation. The proportion of Ugandans seen in Kacheliba was lower compared with Amudat, because Ugandans still accessed treatment in Amudat Hospital after 2006. The introduction of rK39-based rapid tests in peripheral sites made diagnosis more accessible, but led to neither earlier presentations nor better treatment outcomes (data not shown). The limited quality and scope of services in peripheral health centers and the good reputation of VL treatment centers were important factors in attracting patients. For example, half of the VL cases originating from one of the decentralized diagnostic sites (Sigor Subdistrict Hospital) had traveled a long distance to Kacheliba treatment center for testing.

We observed a lower case-fatality rate for primary VL cases in Kacheliba compared with Amudat, but it is not possible to differentiate the impact of earlier presentation, the different treatment regimen (e.g., liposomal amphotericin B for vulnerable groups), and other unmeasured differences in case management. The optimal dosage of AmBisome for VL treatment in East Africa is not known. Despite the methodological limitations (retrospective review of sequential cohorts) and the limited proportion (29.6%) of patients followed at 6 months post-treatment, our data suggest that a total dose of 30 mg/kg of AmBisome is more effective than 20 mg/kg.

The median period to diagnosis of relapse was 6 months after initial treatment (after a median period of symptoms of 1 month). A 6-month follow-up period may therefore not be appropriate to define final cure for the Pokot setting. The proportion of PKDL cases was very low compared with Sudanese patients, 50% of whom develop PKDL.[22] Population-based data are not available, which may severely underestimate the true incidence of PKDL. We observed an increasing number of PKDL cases identified over time, which probably reflects the improved post-treatment follow-up. Sodium stibogluconate-paromomycin (SSG-PM) combination treatment was introduced as the first-line treatment in Kacheliba in December 2011. This may further reduce the incidence of PKDL, as suggested by data from the randomized trial conducted in East Africa comparing SSG with SSG-PM.[23]

The simplification of diagnostic algorithm and optimization of treatment regimen were crucial first steps to improve access to quality VL care in the Pokot area. However, the impact and sustainability of these achievements will be minimal and short-lived without increased commitment of Kenyan public health authorities at both the national and local level. Pokot people live in a remote area and have little political voice. Even the basics of VL control, i.e., availability of diagnosis and treatment, were not secured in the last decades because of lack of a national VL control program and dedicated resources. Fortunately, there has been some positive development over the last years. A national VL control program was recently released by the Ministry of Health and the revision of VL national guidelines was completed in 2012. The rK39 RDT for diagnosis and the combination SSG/PM were included in the revised guidelines. To ensure that VL diagnosis and treatment are routinely accessible to the marginalized population of the remote Pokot area, however, the Kenyan government will need to show its commitment to the national VL control program and provide it with sufficient funding.

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