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. 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; these two species of sandfly are found in very different habitats. Phlebotomus orientalis is a dry season species, associated with the Accia 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. The clinical picture of VL varies according to the setting, reflecting differences in parasite strains, 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. Another outbreak was later described in 1950 in the Kitui reserve in central Kenya, and was followed by further outbreaks in the Baringo District. 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). 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. 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...
and Kenya’s Kacheliba Health Center, Kenya) on standar-
dized 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 alter-
native days for 15 days) was temporarily used as first-line treat-
ment in Amudat during a stock-out of antimonials, with no 
difference in outcome compared with antimonials.11 In a ret-
rospective analysis of patients treated between 2000 and 2006, 
patients with a high risk of death during treatment with anti-
monials were identified, 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 treat-
ment center. Data were pooled if the results were comparable 
between centers; otherwise, results are presented by treat-
ment center. Tests of hypotheses were based on χ² for cate-
gorical 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](http://example.com/figure1.png)
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
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, which were performed on over 400 patients to 30 mg/kg (5 mg/kg/day IV) of amphotericin B deoxycholate or AmBisome treatment. There was an increase over time in PKDL cases 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).

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

| Age group (in years) | Female | | Male | | Not known | | Total |
|---------------------|--------|--------|------|--------|--------|--------|
|                     | n      | (%)    | n    | (%)    | n      | n      | Total | (%)    |
| < 1                 | 6      | (0.4)  | 1    | (0.0)  | 0      | 7      | 13    | (0.3)  |
| 1–4                 | 303    | (21.3) | 375  | (11.9) | 2      | 680    | 1,421 | (31.0) |
| 5–14                | 601    | (42.2) | 1,413| (44.9) | 2      | 2,016  | 3,418 | (68.7) |
| 15–44               | 446    | (31.4) | 1,239| (39.4) | 7      | 1,692  | 4,582 | (100.0)|
| 45–99               | 50     | (3.5)  | 110  | (3.5)  | 1      | 161    | 453   | (1.0)  |
| Not known           | 15     | (1.0)  | 10   | (0.3)  | 1      | 26     | 26    | (0.6)  |
| Total (%)           | 1,421  | (31.0) | 3,148| (68.7) | 13     | 4,582  | 4,582 | (100.0)|

**Table 1**

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

<table>
<thead>
<tr>
<th>Duration of illness (in months)</th>
<th>Kacheliba (N = 2,130)</th>
<th>Amudat (N = 2,452)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>(%)</td>
</tr>
<tr>
<td>0–1 month</td>
<td>1,216</td>
<td>(57.1)</td>
</tr>
<tr>
<td>2 months</td>
<td>527</td>
<td>(24.7)</td>
</tr>
<tr>
<td>3–5 months</td>
<td>326</td>
<td>(15.3)</td>
</tr>
<tr>
<td>≥ 6 months</td>
<td>59</td>
<td>(2.8)</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>(0.1)</td>
</tr>
<tr>
<td><em>P</em> value &lt; 0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2**

**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.
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. 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). However, a longer period before seeking treatment may partly explain this difference. 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.

![Diagnostic algorithm of visceral leishmaniasis used by Médecins Sans Frontières since March 2005 at Amudat and Kacheliba Treatment Centers, Pokot area, Uganda and Kenya.](image)

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**Table 3**

<table>
<thead>
<tr>
<th>Diagnostic tests to diagnose primary visceral leishmaniasis (VL), by diagnostic algorithm, Amudat Treatment Center, Uganda</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DAT validation</strong> (up to September 2001)</td>
</tr>
<tr>
<td>Number of tests</td>
</tr>
<tr>
<td>n (%)</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>rK39 RDT*</td>
</tr>
<tr>
<td>DAT*</td>
</tr>
<tr>
<td>Spleen aspirates</td>
</tr>
<tr>
<td>Total suspected cases</td>
</tr>
</tbody>
</table>

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

Received March 21, 2013. Accepted for publication October 6, 2013. Published online November 11, 2013.

Acknowledgments: We thank not only the staff of Amudat Hospital and Kacheliba Health Centre for their dedicated work, but also the Pokot communities for their warm welcome to the MSF team over the years.

Financial support: This work was supported by Médecins Sans Frontières. SJB is supported by a Wellcome Trust Senior Fellowship in Basic Biomedical Science (098045).

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