MSF and VL Control in East Africa: Operational Challenges

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VL endemic areas in East Africa
VL cases treated by MSF in East Africa, and outcomes, 1989-2006

<table>
<thead>
<tr>
<th></th>
<th>Admissions</th>
<th>Cure rate</th>
<th>Death rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern Sudan</td>
<td>33,467</td>
<td>92.2%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Southern Sudan</td>
<td>36,018</td>
<td>90.1%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>11,197</td>
<td>88.1%</td>
<td>10.1%</td>
</tr>
<tr>
<td>Uganda</td>
<td>2,437</td>
<td>96.3%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Somalia</td>
<td>1,671</td>
<td>93.2%</td>
<td>7.6%</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>84,790</strong></td>
<td><strong>90.9%</strong></td>
<td><strong>7.6%</strong></td>
</tr>
</tbody>
</table>
Hospital (Humera, north-west Ethiopia)

Field Hospital (Um-el-Kher, eastern Sudan)
Under the trees
_(southern Sudan)_
Characteristics of VL-endemic areas in East Africa

- Extremely remote and isolated areas
- Lack or absence of health infrastructure
- Lack of infrastructure
- Poor access during rainy season
- Active conflict or insecurity

Poor access to diagnosis & treatment facilities

Only an estimated 50% of VL patients can access treatment

Collin S. et al. 2006
Diagnosis of Visceral leishmaniasis

Clinical Case definition:
- Fever (>2 weeks) excluding malaria, with splenomegaly or lymphadenopathy, and wasting
  (Prior-probability in Sudan: ~50%)

Laboratory Confirmation Required:
- Microscopy (spleen or lymphnode aspirate)
- Direct Agglutination Test (DAT)
- Rapid serological strip test
lymph node aspirate

spleen aspirate
Direct Agglutination Test (DAT)

Simple field lab
Experienced technicians

Borderline concept:
High titer \((\geq 1:6400)\) : positive
Low titer \((\leq 1:400)\) : negative
Intermediate titer : \(\rightarrow\) aspirate
DiaMed-IT-Leish® rapid diagnostic test based on rK39 antigen

- Sudan: 90% sensitivity, 99% specificity
  Ritmeijer K. et al. 2006
- Uganda: 97% sensitivity, 99% specificity
  Chappuis F. et al. 2005
Primary VL Diagnostic Algorithm

Kala-azar suspect:
fever ≥ 2 wks + splenomegaly + wasting

rK39 RDT

Direct Agglutination Test (DAT)

Negative
< 1/400

Borderline
1/800 – 1/3200

Positive
≥ 1/6400

spleen or lymphnode aspiration

Non kala-azar
→ search other diagnosis + treat

kala-azar
→ treatment
Diagnostic Algorithm (future?)

Kala-azar suspect:
fever > 2 wks + splenomegaly + wasting

High Sensitive rK39 Rapid Screening Test

-

Seek alternative diagnosis

High Specific rK39 Rapid Diagnostic Test

+

Treat for Kala-azar

-

Aspirate

+

No alternative diagnosis found
SSG (sodium stibogluconate):
Still very effective in African VL,
Cheap generic drug:
($22 per patient vs. branded SSG (Pentostam): $200 per patient)

But:
• 30 days of daily painful injections
• SSG is toxic, especially in very sick patients, and those with HIV infection ➔ high mortality
Risk Factors for Death

“Severe Kala-azar”

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt;13</td>
<td>11.0</td>
</tr>
<tr>
<td>Hb &lt;8 g/dl</td>
<td>4.0</td>
</tr>
<tr>
<td>Age &lt;5 yrs</td>
<td>5.4</td>
</tr>
<tr>
<td>Age &gt;45 yrs</td>
<td>4.6</td>
</tr>
</tbody>
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Collin S. et al. 2004

Treatment of severe VL with AmBisome under field conditions
Essential management of complications:

- Intercurrent infections
- Malnutrition
Operational Strategies for VL control in East Africa

• No big gains to be expected from further medical improvements: difficult to further reduce mortality.

• Major gains to be expected from public health approach: increase access and coverage by further decentralisation of diagnostic and treatment services.

• Requires very simple diagnostic and treatment protocols in peripheral health units:

  Dipstick + SSG
Access to treatment:
Decentralised services
Primary Kala-azar Admissions, Lankien, South Sudan, 1999-2003
Short Course Combination Therapy – Neglected Research

- SSG + Paromomycin (17 days)
  - Good experience in epidemic circumstances
    - Melaku Y. et al. 2007
  - Currently studied in East Africa by DNDi

- SSG + AmBisome
- AmBisome + Miltefosine
- AmBisome + Paromomycin
- Miltefosine + Paromomycin
Bednet Distribution
Gedaref State, Eastern Sudan

• Epidemic situation 1997-1999; treatment capacity overwhelmed (>4,500 cases per year)
• 357,000 nets distributed (1999 – 2001)
• ITN, jersey polyester 300 mesh (sandfly-proof)
• 155 villages
• Community education campaigns

Ritmeijer K. et al. 2007
Operational Evaluation
Coverage, Utilisation

• 94% distribution coverage
• 2 years post-distribution 44% of nets were still present and reasonably intact
• main reason for use: mosquito nuisance
• bednet utilisation during dry hot season <10%, increasing during rainy season
• net utilisation  
  April:  1%  
  May:  10%  
  June:  55%
• bednets were put up between 9 and 11 p.m.
Epidemiological Evaluation

Protective Effect

- simulation model comparing actual and predicted VL incidence per village and per month
- 1,060 cases prevented between June 1999 and January 2001
- calculated protective effect: 27%
- protective effect increased with time, with greatest effect 17-20 months post-intervention: 59% (C.I. 25-78%)

- Potentially strong reduction in VL incidence following a community distribution of ITNs.
- Effectiveness of ITNs depends on behavioural factors, which differ between communities
HIV/VL co-infection
Diagnostic and Treatment Challenges

- HIV co-infection rates in VL patients in East Africa:
  - **Humera / Northern Ethiopia**:
    - 1998-1999: 19%
    - 1999-2000: 23%
    - 2003-2004: 29%
    - 2006: 34%
  - **Um-el-Kher / Eastern Sudan**
    - 2005: 9%
  - **Upper Nile / Southern Sudan**
    - 2002: 0.4% (rural)
    - 2005: 5% (urban)
HIV / VL co-infection in Ethiopia

- VL is main OI in HIV
- >30% of VL patients are HIV co-infected
- >30% of HIV patients have a history of VL
Field evaluation of serological tests for diagnosis of visceral leishmaniasis in a population with high HIV prevalence

Good performance of rK39 and DAT in non-HIV-infected VL in East Africa

Parasitology: splenic aspirate
rK39: DiaMed-IT-Leish®
DAT: quantitative titre assessment

HIV testing:
HIV positive: **34.4%**
(95% CI: 26.2 – 43.3%)

Cross-sectional diagnostic accuracy study in Humera, Ethiopia (2006-2007)
(n=699 clinical suspects)
Preliminary study results

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>rK39 DiaMed-IT-Leish</th>
<th>DAT (titre ≥1:6400)</th>
<th>rK39 + DAT Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-Negative</td>
<td>86.9%</td>
<td>86.9%</td>
<td>98.8%</td>
</tr>
<tr>
<td>HIV-Positive</td>
<td>77.3%</td>
<td>75.0%</td>
<td>90.9%</td>
</tr>
</tbody>
</table>

- rK39 specificity in clinical suspects: 92%
- rK39 specificity in endemic controls: 99%
- rK39 can be implemented at every level of care
- DAT requires established basic laboratory

Recommended diagnostic algorithm:
Antimonial (SSG) treatment outcome and HIV status

(SSG vs. Pentostam study, Humera, 1999)

<table>
<thead>
<tr>
<th></th>
<th>HIV neg</th>
<th>HIV pos</th>
</tr>
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<tbody>
<tr>
<td># Treated</td>
<td>112</td>
<td>27</td>
</tr>
<tr>
<td>Death rate during treatment</td>
<td>3.6%</td>
<td>33.3%</td>
</tr>
<tr>
<td>Final Cure Rate (6m follow-up)</td>
<td>92.1%</td>
<td>43.5%</td>
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</tbody>
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Ritmeijer K. et al. 2001
Study design:
randomised open study
n = 580 adult men with VL

HIV status:
HIV positive: 28.5%

Ritmeijer K. et al. 2006

Miltefosine vs. Sodium Stibogluconate for Treatment of Visceral Leishmaniasis in an Ethiopian Population with High HIV prevalence

Miltefosine
100 mg/day x 28 days oral

sodium stibogluconate (SSG)
20 mg/kg/day x 30 days IM
Miltefosine vs. SSG for treatment of VL in a population with high HIV prevalence

- 6-fold higher odds of mortality associated with SSG treatment, as compared with miltefosine in those with positive or unknown HIV status ($P=0.0003$).
- Indication that much of the mortality in HIV co-infected is caused by SSG itself.
- Miltefosine is less effective (higher initial parasitological failure and relapse rates), but safer (lower mortality) than SSG in treating VL in a population with high HIV prevalence.
- Miltefosine is safe and effective in HIV-negative VL patients.
- The safer profile of Miltefosine makes it a preferential drug over SSG in HIV co-infected patients, as it may prolong survival.
Treatment of VL in HIV co-infected: HAART

- Patients relapse 3-6 months; successive relapses become less typical and less acute, but more frequent
- Patients get less responsive to treatment with each relapse, and eventually become unresponsive to all drugs
  → Can HAART protect against relapse?

- VL itself causes low CD4 counts
- Baseline CD4 lower in HIV co-infected VL patients than in HIV-negative patients
- Increment of CD4 count at completion of treatment much lower in HIV-positive patients
  → Can HAART improve CD4 count?

- Prospective study of 356 HIV/VL co-infected patients,
- Includes almost 600 episodes of VL
CD4 trends on HAART; patients with relapse vs. patients without relapse on HAART

VL episodes during follow-up for patients on HAART
- No VL or a single VL episode (primary or relapse)
- Multiple VL relapses

Note: vertical bars indicate 95% confidence interval
Relapse probability curve – lowest CD4 and previous VL episodes

Probability of VL relapse within 12 months of HAART initiation

VL history prior to HAART initiation
- None or primary VL
- One relapse
- Two or more relapses
Impact of HAART on relapse

HAART has only partial protective effect against relapse

Hazard ratio 0.46 (95% CI: 0.26-0.82)

Yet 28% of first VL relapses occurred despite CD4 >200
Conclusion: Main Research Priorities

Diagnostics:
• Simple “point of care” field diagnostic antigen test (for primary VL, relapse VL, test-of-cure)
• Improved rK39 dipstick tests: combination of highly sensitive screening test and highly specific diagnostic test

Treatment:
• Evaluation of short-course combination therapies

HIV/VL co-infection:
• Evaluation of combination drugs in HIV/VL co-infected (AmBisome, Miltefosine)
• Efficacy and tolerability of secondary prophylaxis / maintenance therapy in preventing relapse