

## High Mortality among Older Patients Treated with Pentavalent Antimonials for Visceral Leishmaniasis in East Africa and Rationale for Switch to Liposomal Amphotericin B<sup>∇</sup>

Visceral leishmaniasis (kala azar), a fatal disease if left untreated, is one of the most neglected tropical diseases. Poor and remote areas of South Asia and East Africa are the most affected.

Pentavalent antimonial (SbV) drugs have been the mainstay of visceral leishmaniasis (VL) therapy in East Africa for the past 70 years. These drugs are administered parenterally for 30 days. Their potential for toxicity is high among VL patients, and drug-induced renal failure, acute pancreatitis, or cardiotoxicity can result in death.

A growing body of clinical evidence shows that patients  $\geq 45$  years of age with leishmaniasis are at higher risk of death or severe adverse reactions during SbV treatment (1–6). Two separate studies conducted by Médecins Sans Frontières (MSF) in South Sudan showed that VL patients  $\geq 45$  years old treated with the SbV drug sodium stibogluconate (SSG) had 4.6 (odds ratio [OR]; 95% confidence interval [CI], 2.7 to 7.7) (1) and 6.8 (relative risk [RR]; 95% CI, 4.4 to 10.4) (6) times higher risks of dying than younger patients (Table 1).

More recent data analysis of MSF's VL programs in Uganda and Ethiopia showed similar findings. In Uganda, where patients were primarily treated with either SSG or another SbV drug, meglumine antimoniate, an age of  $\geq 45$  years was the strongest independent risk factor for mortality, with an adjusted OR of 38.2 (95% CI, 11.8 to 123.2) (4). In Ethiopia, patients  $\geq 45$  years old treated with SSG had a 6.6 (OR; 95% CI, 3.2 to 13.9) times higher risk of death than patients 5 to 29 years old (2).

These risk ratios translated into case fatality rates (CFRs) of 12% (2) to 30%, with three of the four studies demonstrating CFRs of 26 to 30% (Table 1) (1, 4, 6).

This brief meta-analysis of MSF VL data shows that SbV treatment of patients  $\geq 45$  years old results in unacceptably high mortality in East Africa. This may be caused by SbV toxicity, increased disease severity, or a combination of both. It is therefore urgent to evaluate potentially safer and more rapidly active treatments in this age group, such as liposomal amphotericin B (LAmB), miltefosine, or combination therapies (e.g., SbV with paromomycin for 17 days), and adapt national guidelines accordingly.

LAmB (total dose, 30 mg/kg of body weight) is now used by MSF in East Africa as compassionate treatment for patients  $\geq 45$  years old and for other groups of patients at increased risk of complications or death due to SbV (e.g., HIV-tuberculosis coinfecting, severely sick, or pregnant patients). Of 87 patients  $\geq 45$  years old treated with LAmB by MSF in Sudan, Kenya, and Ethiopia since 2002, 7 patients have died, giving a CFR of 8% (unpublished data).

Despite recent drug price decreases, the cost of LAmB remains higher than the cost of SbV drugs, hindering its wider use. However, the incremental cost for increasing LAmB use would be expected to be relatively modest, since patients  $\geq 45$  years old represent a relatively small fraction (1.7 to 6.4%) of VL patients (Table 1). With a relatively small investment in LAmB, mortality among VL patients  $\geq 45$  years old in East Africa could be reduced with little delay.

TABLE 1. Summary of Médecins Sans Frontières studies examining an age of  $\geq 45$  years as a possible risk factor for death among VL patients treated with SbV in East Africa

Study	Country	No. of VL patients analyzed (no. $\geq 45$ years old)	Risk of death in patients $\geq 45$ years old (95% CI)	CFR among patients $\geq 45$ years old (%)
Collin et al. (1)	South Sudan	3,200 (110)	OR, 4.6 (2.7–7.7) <sup>a</sup>	28.2
Seaman et al. (6)	South Sudan	2,791 (179)	RR, 6.8 (4.4–10.4) <sup>b</sup>	26.3
Mueller et al. (4)	Uganda	1,801 (30)	OR, 38.2 (11.8–123.2) <sup>c</sup>	30.0
Herrero et al. (2)	Ethiopia	2,177 (106)	OR, 6.6 (3.2–13.9) <sup>d</sup>	12.3

<sup>a</sup> Adjusted only for sex; comparator age group, 16 to 24 years of age.

<sup>b</sup> Multivariable analysis; comparator age group, 5 to 14 years of age.

<sup>c</sup> Multivariable analysis; comparator age group, 6 to 15 years of age.

<sup>d</sup> Multivariable analysis; comparator age group, 5 to 29 years of age.

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