# Epidemic Visceral Leishmaniasis in Sudan: A Randomized Trial of Aminosidine plus Sodium Stibogluconate versus Sodium Stibogluconate Alone

**J. Seaman, D. Pryce, H. E. Sondorp, A. Moody, A. D. M. Bryceson, and R. N. Davidson**

*Medecins Sans Frontieres–Holland, Amsterdam; Hospital for Tropical Diseases, London, and St. Mary's Hospital Medical School, Department of Infectious Diseases and Tropical Medicine, Lister Unit, Northwick Park Hospital, Harrow, United Kingdom*

**In a comparative trial of treatment in southern Sudan, visceral leishmaniasis was diagnosed by the following symptoms: fever for >1 month, splenomegaly, and antileishmanial direct agglutination test (DAT) titer of ≥1:25,600. Patients (200) were randomized to receive sodium stibogluconate ($Sb^v$) at 20 mg/kg/day for 30 days (groups S, $n$ = 99) or $Sb^v$ at 20 mg/kg/day plus aminosidine at 15 mg/kg/day for 17 days (group AS, $n$ = 101). Of 192 patients who had spleens or lymph nodes aspirated at entry, 134 (70%) were positive for parasites. During treatment, 7% in group S and 4% in group AS died. All 184 patients who completed treatment were clinically cured. At days 15–17, microscopy of aspirates showed that 57 (95%) of 60 in group AS were negative for parasites compared with 47 (81%) of 58 in group S ($P$ = .018). At day 30, 57 (93.4%) of 61 group S aspirates were negative.**

The western Upper Nile region of Sudan has suffered a major epidemic of visceral leishmaniasis (kala-azar, VL) since 1984. Although VL epidemics were reported in other parts of southern Sudan in the 1940s and 1950s, this area was not previously a focus for this disease [1]. By the end of 1991, ~40,000 people out of a population of roughly half a million had died of VL [2, 3]. The causes of the epidemic are uncertain and probably multifactorial. A civil war from 1961 to 1971 and from 1983 until the present has led to widespread malnutrition and migration of many combatants, civilians, and animals. The flooding of the Nile in the early 1960s devastated the acacia forest, which recently regained maturity to become a suitable habitat for the *Phlebotomus orientalis* sandfly, the vector of VL in southern Sudan [4, 5]. However, no patients in this area have been diagnosed as having human immunodeficiency virus (HIV)–related diseases, and two HIV seroprevalence studies found no HIV-positive sera [1, 3].

Doctors from Medecins Sans Frontieres–Holland (MSF) first realized that this epidemic was VL in 1988 [6]. MSF established treatment centers at Leer and Duar, two remote villages in the western Upper Nile, in 1989. At these centers as many as 2000 VL patients have been under treatment simultaneously, and a total of ~15,000 patients with VL had been treated by April 1993. The devastation caused by the epidemic may be gauged from surveys done in May–June 1991 near Duar, where 50% of the inhabitants were estimated to have died of VL; 9% of the survivors were direct agglutination test (DAT) positive (suggesting that they had recently recovered from or were incubating VL) and 36% were leishmanin skin test positive (immune) [7].

Of the two treatment centers, Duar, a small village, is more remote. It has the larger number of patients, being closer to most patients' homes, but is located in prime habitat for *P. orientalis*. The village is overcrowded, swamps are the major source of water, there are no latrines, food supplies are inadequate, and the center is unable to provide nutritional supplementation for all VL patients. During treatment for VL, death rates of ~13% have been documented [3], with most deaths occurring during the first 1–2 weeks of treatment and many being preceded by diarrhea.

Three closely related zymodemes of *Leishmania donovani* have been isolated from patients and vectors in the area [5], but no animal reservoir has been identified. Vector control is not feasible in this remote region in which vehicles are scarce and roads mined; therefore, treatment of patients is the only way to control the epidemic.

The pentavalent antimonials sodium stibogluconate ($Sb^v$) and meglumine antimoniate were introduced as treatment for VL in the early and late 1940s, respectively [8], but increasing $Sb^v$ resistance has been reported from many areas [8–10]. The standard treatment regimen in use in the western Upper Nile has been intramuscular (im) sodium stibogluconate (Pentostam; Wellcome Foundation, Crewe, UK) at 20 mg/kg/day for 30 days. Similar regimens of $Sb^v$, by im or intravenous administration, are recommended by the World Health Organization [9] and others [8, 10]. This regimen cured 90% of patients in northern Sudan [10, 11] and cleared

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Aminosidine was donated by Farmitalia Carlo Erba, Milan, Italy. Informed consent was obtained from the patients or their parents or guardians. Ethical approval was obtained from Medecins Sans Frontieres–Holland and was conducted in accordance with the Declaration of Helsinki as adopted by the World Health Organization.

Reprints or correspondence: Dr. Robert N. Davidson, St. Mary's Medical School, Dept. of Infectious Diseases and Tropical Medicine, Lister Unit, Northwick Park Hospital, Harrow, Middlesex HA1 3UJ, United Kingdom.

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splenic aspirates of parasites in 90% of patients in southern Sudan [3] but is expensive, prolonged, and possibly toxic.

A meeting of VL experts was held in 1991 [3] to address these problems. A shortened course of treatment was suggested: A constraint was that treatment could practicably be administered only once daily. Aminosidine (Gabbromycin; Farmitalia Carlo Erba, Milan, Italy) is an aminoglycoside antibiotic that has been in sporadic use since 1971. It is identical to paromomycin and monomycin. It has good activity against all *Leishmania* species against which it has been tested in animals and in vitro [12, 13] and is synergistic with $Sb^v$ in vitro [14]. The combination of aminosidine plus $Sb^v$ had shown promise as a shorter course (mean, 14 days) of treatment for VL in Kenya [15]; in that study, aminosidine alone was less efficacious than the combination, and so the combination of aminosidine plus $Sb^v$ was selected for this study.

It was felt important to compare the combination of aminosidine plus $Sb^v$ to standard treatment under field conditions before recommending its large-scale adoption. A definitive cure of VL is defined by most authorities as resolution of the signs and symptoms of VL with no relapse during 6 months of follow-up [16]. Patients could not be followed up after treatment, so parasitologic response and clinical parameters were be used as measures of drug efficacy.

## Subjects and Methods

All patients seen during December–February 1992 with suspected VL who had not previously been treated were assessed for eligibility to enter the study. The eligibility criteria were fever for >1 month, palpable splenomegaly, and a positive leishmania DAT titer of ≥1:25,600.

*Setting.* The treatment center at Duar was the study site. It was staffed by 2 MSF doctors and 2 MSF nurses, supported by local volunteer nurses. There were no permanent buildings; clinical examinations, laboratory tests, procedures, and treatment were done in the shade of trees, in tents, or in temporary mud huts. Supplies were brought in by light aircraft, as the war has disrupted road and river links. The study was done during the cool dry months of December–February, when malaria prevalence was thought to be lowest. During previous years, patients with VL had been noted to be relatively more healthy during this season. The leishmania transmission season is thought to be March–May.

*Randomization.* At presentation, each patient was allocated a sequential number, had a capillary blood sample taken, and had a leishmania DAT test. Every third (and on 1 admitting day, every second) number with a DAT titer ≥1:25,600 was allocated alternately to one of the two treatment groups. Each patient was examined by a physician (J.S.). Patients with a typical history and with a palpable spleen were entered into the study. Once randomized, no patient was permitted to move from one treatment group to the other; ~700 patients with VL who did not enter the trial started conventional treatment.

*Data.* Height, weight, age (nurses' estimate if unknown), sex, district of residence, and clinical findings were recorded. Hemoglobin concentration was determined by color densitometry, and leishmania DAT was done by using a standard field kit [17]. On admission, spleens or lymph nodes were aspirated, and smears were stained with Giemsa. In group A, aspiration was repeated at the end of treatment (day 17). In group S, aspiration was repeated in the middle (days 15–17) and at the end of treatment (day 30).

Lymph nodes were aspirated if they were palpable and the patient was in advanced pregnancy or if the patient (e.g., a distressed child) was considered unable to lie quietly during spleen puncture. All aspirates done at the end of treatment were evaluated in the field, and patients whose aspirates were still positive were continued on treatment ex protocol. All aspirate samples were subsequently read by expert microscopists at the Hospital for Tropical Diseases, London, who were unaware of the patient's status, and verified by one of us (A.M.). Body mass index (BMI) was calculated as weight ÷ height$^2$ (kg/m$^2$) for subjects who were >16 years old and who neither had signs of pregnancy nor were <1 month postpartum.

Walking status was used as an indicator of severity of illness in adults and children aged >5 years and was categorized as unassisted, supported, or carried. Spleen and liver were measured (centimeters) during quiet respiration. The spleen was measured along its axis at right angles to the left costal margin, and the liver was measured at the midclavicular line below the right costal margin. The measurements of weight, spleen, and liver were repeated at day 17 for group AS and days 15–17 and 30 for group S.

The occurrence of diarrhea (defined by a history of passage of watery stools), vomiting, bleeding, and pneumonia (defined by clinical features) and use of drugs for these conditions were recorded daily. Clinical cure was defined as disappearance of fever and a decrease in spleen size.

*Treatment.* Group S received conventional treatment, 20 mg/kg $Sb^v$ im daily for 30 days (minimum dose, 200 mg/day; maximum, 850 mg/day). Group AS received 20 mg/kg $Sb^v$ plus 15 mg/kg aminosidine im daily, both for 17 days. Each drug was injected into separate sites, and there was no minimum or maximum dose for aminosidine. Injections were given daily by a local volunteer nurse. Alternate Sundays were rest days for the nurses and no treatment was given. All patients also received antimalarial prophylaxis (adult dose, 300 mg of chloroquine base/week), tinidazole for presumed giardiasis (adult dose, 2 g/week), and daily iron and vitamin tablets.

*Statistical methods.* Groups were compared by Yates' corrected $\chi^2$ test for categoric variables and either the $t$ test or the Mann-Whitney $U$ test for numerical variables, as appropriate.

## Results

*Entry characteristics.* A total of 200 patients entered the study (104 males, 96 females). Patients came from seven districts. Ages ranged from 4 months to 65 years (mean ± SD, 16.8 ± 13 years); 97 patients were <14 years old (43 in group S, 54 in group AS), and 31 were <5 years old (11 in group S, 20 in group AS). Severe malnutrition, as defined by

BMI <16 kg/m$^2$ [18], was present in 62.5% of patients who were >16 years old, had no signs of pregnancy, and were not <1 month after delivery.

Of those >5 years old, 30% were unable to walk unsupported; 99 patients were randomized to group S and 101 to group AS. There were no significant differences between groups S and AS in age, sex, district of residence, walking status, number of pregnant or postpartum women, spleen or liver size, or type of aspiration done.

Weight was higher in group S than in group AS (mean, 37.0 vs. 31.3 kg; $P = .014$); 90 patients weighed >42.5 kg (49 in group S, 41 in group AS), and these patients therefore received <20 mg of $Sb^v$/kg/day. Six patients in group S and 3 in group AS weighed >57 kg and thus received <15 mg of $Sb^v$/kg/day. BMI (calculated where appropriate) was higher in group S (mean, 16.2 vs. 15.1 kg/m$^2$; $P = .002$), and fewer in group S (49%) than in group AS (76%) were severely malnourished [18], with a BMI of <16 kg/m$^2$ ($P = .016$). More patients in group S could walk unassisted (73% vs. 68%), but this difference was not statistically significant ($P = .79$). Mean hemoglobin concentration on entry was significantly higher in group S than in group AS (8.65 vs. 7.89 g/dL; $P < .01$).

Mean spleen size on entry was similar in the two groups: 7.3 cm in group S and 6.9 cm in group AS ($P = .532$). The mean liver size was also similar: 1.2 cm in group S and 1.0 cm in group AS ($P = .510$). Spleens (90%) or lymph nodes (10%) were aspirated on entry in 192 patients (96%); there was no significant difference between group S and AS in type of aspirate ($P = .15$). Parasites were found in aspirates of 134 patients (70%), 67 in each group; the characteristics of these 134 patients are shown in table 1.

Compared with patients with positive aspirates, the 58 patients with negative aspirates were older (mean age, 22 vs. 15 years; $P < .001$) and had smaller spleens, (mean, 5.3 vs. 8.1 cm; $P < .001$), smaller livers (mean, 0.5 vs. 1.4 cm; $P < .001$), and higher hemoglobin concentrations (9.1 vs. 7.9 g/dL; $P < .01$). The mean BMI was similar (15.9 vs. 15.8 kg/m$^2$; $P = .6$).

*Response to treatment.* All 184 VL patients who completed treatment with either regimen were clinically cured. Their fevers were gone and their spleen size had decreased. By the end of treatment (day 17), the mean spleen size in group AS had decreased to 2.4 cm and the mean liver size to 0.42 cm. These changes were highly significant ($P < .001$). In group S the mean spleen size decreased to 3.3 cm at days 15–17 and 1.6 cm at day 30 ($P < .001$); the mean liver size decreased to 0.54 cm at days 15–17 ($P = .002$) and 0.27 cm at day 30 ($P < .001$). There were no significant differences between groups S and AS in the changes in these parameters.

For the 134 parasitologically confirmed patients, the equivalent data are shown in tables 1 and 2. Aspirates were available for examination at the end of treatment from 121 of these patients, 61 in group S and 60 in group AS. At day 17, which was also the end of their treatment, 57 (95%) of 60 patients in group AS had negative smears. At days 15–17, a comparable point in time although in the middle of the treatment, an aspirate was assessed in 58 patients (89%) in group S; 47 (81%) of these were negative ($P = .039$, $\chi^2$ comparing proportions in groups S and AS). At day 30, which was the end of their treatment, 57 (93.4%) of 61 patients in group S had negative smears. Thus, at the end of both treatments (day 17 for group AS, day 30 for group S), the proportions of patients who had negative smears were almost identical.

**Table 1.** Features of 134 patients with parasitologically confirmed visceral leishmaniasis at presentation (week 0) and after 2 and 4 weeks of treatment.

| | Group S ($n = 67$) | Group AS ($n = 67$) | $P$ |
|---|---|---|---|
| Age in years | 15.2 ± 11.3 | 13.8 ± 11.1 | NS |
| (range) | (0.3–45.0) | (1–42) | |
| Male/female | 39/28 | 29/38 | NS |
| No. pregnant | 3 | 3 | NA |
| No. postpartum | 0 | 2 | NA |
| Weight range (kg) | 5–62 | 7.0–60.5 | |
| Week 0 | 34.8 ± 16.0 | 32.7 ± 15.6 | NS |
| Week 2 | 34.0 ± 15.3 | 31.5 ± 15.2 | NS |
| Week 4 | 33.6 ± 15.2 | — | NA |
| BMI (kg/m$^2$) | 16.2 ± 1.6 | 15.4 ± 1.2 | .04 |
| Spleen size (cm) | | | |
| Week 0 | 8.0 ± 3.8 | 8.1 ± 5.0 | NS |
| Week 2 | 3.2 ± 3.4 | 2.7 ± 3.5 | NS |
| Week 4 | 1.6 ± 2.2 | — | NA |
| Liver size (cm) | | | |
| Week 0 | 1.35 ± 1.9 | 1.38 ± 1.9 | NS |
| Week 2 | 0.7 ± 1.5 | 0.4 ± 1.0 | NS |
| Week 4 | 0.3 ± 0.7 | — | NA |
| Hemoglobin (g/dL) | 8.2 ± 1.8 | 7.6 ± 1.9 | .002 |
| Walking status* (%) | | | |
| No. carried | 9 (16) | 7 (14) | NS |
| No. supported | 10 (18) | 9 (18) | NS |
| No. unassisted | 36 (65) | 33 (67) | NS |
| No. died (%) | 5 (7.8) | 3 (4.5) | NS |
| No. defaulted (%) | 2 (3) | 2 (3) | NS |

NOTE. Group S received sodium stibogluconate at 20 mg/kg/day intramuscularly for 30 days; group AS received same daily dose of sodium stibogluconate plus aminosidine at 15 mg/kg/day for 17 days. Data are mean ± SD unless otherwise indicated. Postpartum, <1 month after delivery; BMI, body mass index (weight/height$^2$); NS, not significant; NA, not applicable.

* Applies only to patients >5 years old.

*Toxicity and intercurrent events.* By the end of treatment, 11 (5.5%) of the 200 patients had died. In group S, 2 patients died on days 2 and 13 and 1 each on days 4, 7, and 18. In group AS there were 4 deaths, 2 on day 2 and 1 each on days 13 and 14. Five patients (3 in group S, 2 in group AS) defaulted during treatment. For various reasons, 5 (5%) of group S and 4 (4%) of group AS missed 1 day of treatment in the first week; in the 2nd week, 1 day was missed by 5 and 6 patients, respectively (1 in each group missed 2 days and 1 in group AS missed 3 days). In the third and fourth weeks, 2

**Table 2.** Intercurrent events during each week (1/2/3+4) of treatment for 134 patients with parasitologically confirmed visceral leishmaniasis.

| | Group S ($n$ = 67) | Group AS ($n$ = 67) | $P$ |
|---|---|---|---|
| Diarrhea | | | |
| % of patients | 31/57/33 | 21/33/NA | NS/.009/NA |
| Days/week | 0.7/1.8/0.9 | 0.5/1.1/NA | NS/.013/NA |
| No. of loose stools* | 4.5/7.4/4.6 | 2.7/5.6/NA | NS/.009/NA |
| Vomiting | | | |
| % of patients | 48/37/21 | 43/36/NA | NS/1.0/NA |
| Days/week | 1.1/1.1/0.1 | 0.7/0.9/NA | NS/NS/NA |
| % treated for vomiting | 48/31/11 | 42/33/NA | NS/NS/NA |
| % of patients with | | | |
| Pneumonia | 41/3/4 | 17/6/NA | .005/NS/NA |
| Nasal/oral bleeding | 8/7/2 | 6/2/NA | NS/NS/NA |

NOTE. Group S received sodium stibogluconate at 20 mg/kg/day intramuscularly for 30 days; group AS received same daily dose of sodium stibogluconate plus aminosidine at 15 mg/kg/day for 17 days. Numbers are means for group or percentages where indicated. Statistical comparisons are between groups S and AS at same point in time. NS, not significant ($P >$ .05); NA, not applicable.

* Per patient per week.

patients in group S missed 1 day, and 1 missed 2 days. No statistically significant difference was found between groups AS and S in mortality or missed treatment days.

Diarrhea was more common in week 2 than in week 1 and, during week 2, patients in group AS had a mean of 0.5 fewer days of diarrhea ($P$ = .03) and a mean of 1.8 fewer loose stools per patient per week ($P$ = .03). Vomiting and nasal or oral bleeding were similarly frequent in both groups. During the first week of treatment, fewer patients in group AS were treated for pneumonia (22%) than in group S (32%), but this difference was not significant ($P$ = .21).

By the end of week 2, both groups showed a similar decrease in weight (mean, 0.79 kg in group S, 1.28 kg in group AS); this difference was statistically significant compared with weight at entry within a group ($P <$ .002), but there was no significant difference between the groups. By the end of their treatment at day 30, group S had lost a mean of 1.21 kg.

## Discussion

The criteria used in selecting patients for the study were two clinical parameters and a positive serologic test. These entry criteria excluded VL patients with fever of <1 month's duration, those without splenomegaly, and those with a DAT titer <1:25,600. The study patients had advanced disease and were weak, anemic, and malnourished. Although randomization produced two groups well matched for most characteristics, the group randomized to receive combination treatment had some indicators of more advanced disease.

The value of the leishmania DAT test in Sudan has been validated. In a serologic study at Leer hospital, 95% of 76 patients diagnosed clinically as having VL had a DAT titer of >1:3200 or a titer of >1:100 using the immunofluorescent antibody test; the concordance between the two serologic tests at these titers was 95%. In a survey of two villages near Duar, 9% of healthy villagers had DAT titers of >1:3200 [7]. DAT titers of ≥1:25,600 were previously shown to have a positive predictive value of >90% for the presence of parasites on a sample of 476 patients in this area [3]. In a series of 132 Sudanese patients with suspected VL, a DAT titer of >1:3200 was equated with a parasitologic diagnosis. The sensitivity of a positive DAT test was 94% and the specificity was 72%; the predictive value of a negative test was 92% [17].

The clinical criteria for entry to the study are likely to be less accurate than the DAT. Both splenomegaly and fever are characteristic of VL. All 45 adults and 42 children with parasitologically confirmed VL (studied in Khartoum but originating from the western Upper Nile) had fever, and 93% and 98%, respectively, had splenomegaly [11]. The specificity in this population of fever of >1 month's duration and palpable splenomegaly is not known. Both malaria and schistosomiasis may cause splenomegaly, and both are endemic in the western Upper Nile region, although their prevalence is uncertain. In a survey conducted near Duar in May 1989, the splenomegaly rate was 11.6% and the malaria seroprevalence was 88% among villagers who were seronegative for *L. donovani* [1].

Because the combination of clinical and serologic parameters was likely to be highly specific for VL and because facilities and time for careful examination of aspirates were severely constrained, we chose not to use the presence of visible parasites on Giemsa-stained aspirates as an entry requirement. Independent examination of the pre- and posttreatment aspirates permitted objective assessment of a subgroup after the study was concluded. A recent report from the Sudan [19] found that examination of Giemsa-stained aspirates of spleens and lymph nodes detected 96% and 58%, respectively, of VL. Thus, 177 (92%) of the 192 patients who underwent aspiration could have been anticipated to be positive parasitologically, whereas 134 (70%) were in fact positive. The fact that some pretreatment aspirates were negative may be due to the fact that the material obtained was scantier than what can be obtained under hospital conditions and that fixative and stains were not optimal.

Taken together, our data suggest that most, if not all, of the 58 patients in the study whose pretreatment aspirates were negative for parasites did indeed have VL. These patients responded well to antileishmanial treatment, as indicated by a reduction in spleen size [16]. It is possible that parasite-negative patients may have had milder VL or have been in the phase of spontaneous recovery that can occur in VL. Residual splenic and hepatic enlargement may persist for many months after effective treatment for VL, and coex-

isting malaria and schistosomiasis may cause visceromegaly to persist long-term.

In this region, the civil war, a lack of infrastructure, severe poverty, and a widely dispersed population mean that there could be no assured follow-up of our patients after treatment, and we do not know the relapse rate. Both regimens produced clinical cure, defined for the purpose of the study as a resolution of fever and a reduction in spleen size, in all patients who completed treatment.

Parasitologic responses were evaluatable in a subgroup of 121 patients who had a second aspiration done at the end of treatment. In those aspirates that remained positive at the end of either course of treatment, parasites were extremely scanty. Most authorities believe that posttreatment clearance of scanty residual parasites is often accomplished by the host immune system, so these patients may indeed have been cured. Conversely, if immunity does not return, relapse is possible even if the posttreatment aspirates have been negative. Seventeen days of aminosidine at 15 mg/kg/day plus $Sb^v$ at 20 mg/kg/day cleared parasites from patients as effectively as $Sb^v$ alone for 30 days. There was no excess in mortality, defaulting, or missed treatment days among patients on the combination regimen. The combined treatment cleared 14% more aspirates of parasites by days 15–17, an important finding that suggests an additive or synergistic effect of the two drugs.

There are three published reports of aminosidine treatment for VL. In the comparative, nonrandomized, study by Chunge et al. in Nairobi [15], aminosidine at 15 mg/kg/day alone initially cured 16 of 19 VL patients after a mean of 17 days, with one relapse in 6 months. The combination of $Sb^v$ at 20 mg/kg/day plus aminosidine at 15 mg/kg/day produced initial clinical and parasitologic cure in all 23 patients after a mean of 14 days, with three relapses during 6 months of follow-up. Seven patients with Mediterranean VL treated in London were definitively cured (i.e., were initially clinically and parasitologically cured and did not relapse during 6 months of follow-up) or improved with aminosidine [20]. Aminosidine at 12 mg/kg/day plus $Sb^v$ at 20 mg/kg/day for 20 days definitively cured 18 of 24 patients with Indian VL (there were 2 deaths), and 4 patients showed parasitologic improvement at day 21 [21].

The main advantage of the combination regimen may lie in the shorter course of treatment. Seventeen days of $Sb^v$ alone did not appear to be adequate, although other studies have suggested that a shorter course of $Sb^v$ alone would be adequate if 12- or 8-h administration were possible [8]. At retail prices, aminosidine is less expensive than $Sb^v$, so the combined treatment for 17 days is cheaper than $Sb^v$ alone for 30 days. Although multiple daily injections are impractical in field conditions such as exist in the western Upper Nile, the simultaneous injection of aminosidine and $Sb^v$ at two sites was not difficult.

The study by Chunge et al. [15] and our own results (table 2) suggest that patients receiving aminosidine may have less pneumonia, and this could reflect its antibiotic spectrum. It is interesting that im aminosidine appeared to have a beneficial effect on the frequency and duration of diarrhea. The etiology of the diarrhea in our patients was not known, but aminosidine is effective when taken orally against intestinal protozoa including *Giardia lamblia* and *Entamoeba histolytica* [22].

As well as efficacy, toxicity is a major consideration in selecting a drug regimen for the field. In this study we could not make objective assessments of the oto- and nephrotoxicity that can occur with aminosidine [20] or of the adverse effects of $Sb^v$ [8, 16]. The overall mortality of 5.5% compares favorably to other studies in which $Sb^v$ was used alone [10, 11, 16]. The toxicity of both $Sb^v$ and aminoglycosides is cumulative but the 6 deaths that occurred on or before day 7 were unlikely to have been caused by drug toxicity.

Teratogenicity has not been reported with either drug, although data are scanty. Pregnant women were not excluded from the study because it was felt that the risks of VL to the mother outweighed those of either drug to the fetus. In addition, women of the Nuer tribe believe themselves to be pregnant at all times when not breast-feeding, with menstruation representing the premature end of pregnancy; therefore, only advanced pregnancy could be determined with confidence.

In the desperate conditions of the VL epidemic that exist in this region of the Sudan, aminosidine at 15 mg/kg/day plus $Sb^v$ at 20 mg/kg/day for a total of 17 days produced initial clinical and parasitologic cure rates as good as those of $Sb^v$ at 20 mg/kg/day for 30 days. Further studies should be done in other situations, particularly where monitoring of aminosidine levels, blood chemistry, and follow-up of patients for relapse are possible.

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