**What is visceral leishmaniasis?**

Visceral leishmaniasis (VL), also known as kala azar, is a worldwide protozoal vector-borne disease, endemic in 76 countries. The annual incidence is estimated to be 500,000 cases, with over 90 percent of those cases occurring in India, Bangladesh, Sudan, Ethiopia, Nepal and Brazil—often affecting the poorest populations in those countries.

Visceral leishmaniasis is the second largest cause of parasitic death (after malaria). It is characterized by prolonged fever, severe weight loss, enlarged spleen, anemia and suppression of the immune system. Without treatment, almost all patients will ultimately die, but timely diagnosis and treatment can stave off death, even in resource-limited and remote circumstances.

VL epidemics associated with high mortality are frequent in contexts marked by conflict, population movements, malnutrition, and a lack of access to health care—all factors that can accelerate the development and spread of the disease. More than 10,000 patients were treated (4,000 by MSF) in the recent outbreak in South Sudan, which started at the end of 2009 and is still ongoing in 2011.

A major challenge is management of patients co-infected with kala azar and HIV. Both diseases influence each other in a vicious spiral: HIV/AIDS patients are much more susceptible to develop kala azar, and once infected, kala azar accelerates AIDS, is much more difficult to treat and usually relapses.

**Transmission and Diagnosis**

Different species of the Leishmania parasite cause the disease and are transmitted through bites of phlebotomine sand flies. Both animals and humans can act as reservoirs for the parasites. Post kala azar dermal leishmaniasis (PKDL) appears as a rash that occurs during VL or, more likely, after treatment. It can be highly infectious as parasites may be present in the raised areas of the skin, acting as a reservoir for anthroponotic VL (i.e., transmission by sand fly bite from a PKDL patient to another person who then might get VL).

Suspected patients who meet the clinical case definition for VL can be tested using the rk39 antigen-based rapid diagnostic test (RDT). RDTs only require a drop of blood and the result can be read after 20 minutes. In suspected cases with a negative RDT result, VL can be either ruled out (in areas where rk39 RDT have proved to be highly sensitive) or (in Africa) further investigated by another serological test, the diagnostic agglutination test (DAT), or by microscopic examination of spleen, bone marrow or lymph node aspirates. These techniques require technical expertise and laboratories that are seldom available in areas where VL thrives. ELISA and IFAT tests can also accurately diagnose VL, but their use is limited in the field because a well-equipped laboratory and skilled personnel are required.

**Treatment**

Current treatment options include pentavalent antimonials (generic sodium stibogluconate (SSG), Pentostam®, Glucantime®), paromomycin, miltefosine, amphotericin B deoxycholate and liposomal amphotericin B (currently registered as Ambisome®). Treatment guidelines are continent-specific because of different levels of efficacy according to regions. Combination therapies are recommended. Although the list of treatment options seems extensive, each has significant limitations.

Pentavalent antimonials are still used as first line therapy in some African countries, and are effective in most endemic areas. However, there is a 60% failure rate to this medication in Bihar State, India, and, in any setting, the regimen requires 30 days of painful daily intramuscular injections. This drug also has serious (cumulative) toxic side effects and is dangerous in HIV co-infected patients, with mortality being 5-10 times higher than in non HIV-infected (i, ii).

Several African countries are in the process of switching from 30 days SSG to the MSF and WHO recommended combination regimen of 17 days SSG/paromomycin (in those without HIV). Both drugs are administered by intramuscular injections.

Liposomal amphotericin B/AmBisome is to be used as first line therapy in severely ill patients, those co-infected with HIV, pregnant women and those over 45 years of age. It is also second line therapy for patients in East Africa, once SSG/PM fails. In Bihar State, India, given the high rate of treatment failures with antimonials, MSF used a short-course regimen of liposomal amphotericin B (20 mg/kg total dose). This treatment regimen showed over 98 percent initial cure rate and a very good safety profile (iii) and the cure rate at six months was 96 percent (iv) using single dose regimen of liposomal amphotericin B. Evaluation of the programmatic use of the single dose regimen is ongoing in other parts of India and South Asia.

MSF together with DNDi will soon start a clinical study evaluating field effectiveness and feasibility of single dose liposomal amphotericin B (10 mg/kg) in India and Bangladesh and the combination regimen of liposomal amphotericin B with miltefosine (a third arm to this study will look at miltefosine and paromomycin combination) in India.

Liposomal amphotericin B in Africa is less effective and requires higher doses compared to the Indian subcontinent. Its current cost remains an important barrier to treatment. The drug is administered intravenously and must be stored and transported in a manner...
that ensures the vial is not exposed to temperatures over 25˚ Celsius (77˚ Fahrenheit). Miltefosine, an oral drug, is contra-indicated during pregnancy, and should ideally be taken in combination in order to avoid the development of drug resistance. The treatment in monotherapy lasts 28 days. Poor adherence to non-directly observed treatment increases the risk of development of drug resistance.

Amphotericin-B deoxycholate is a cumbersome treatment that needs to be given in slow IV infusions daily or every other day for 14 doses. Careful hydration and potassium intake are needed to avoid renal toxicity and hypokalemia.

Results of combination treatment field studies of paromomycin, miltefosine and liposomal amphotericin B are anticipated. The rationale behind all combination treatment is to (1) reduce the risk of the parasite developing resistance to the drugs, (2) optimize the efficacy and safety of treatment, and (3) reduce costs and hospitalization time.

MSF and Visceral Leishmaniasis

Since 1988, MSF has treated more than 100,000 kala-azar patients, mainly in Sudan, South Sudan, Ethiopia, Kenya, Somalia, Uganda, India and Bangladesh.

MSF and others have validated and introduced a rapid diagnostic test (rK39 antigen-based dipsticks) that can be used in remote settings. The ease and convenience of this test has allowed decentralization of diagnostic and sometimes treatment services to remote areas, where laboratories cannot be established, and thus has improved access to care in endemic areas such as Sudan and India.

Both in East Africa and Asia, MSF’s findings and operational research have actively influenced national and international treatment policy changes. For African kala azar, the WHO recommends now the combination therapy of SSG and paromomycin, which was studied and implemented by MSF in South Sudan since 2002 and recently thoroughly evaluated in DNDi-sponsored studies.

In Ethiopia, where more than 30 percent of the kala azar patients are HIV infected, kala-azar and HIV care are closely integrated. A major challenge in the management of HIV/VL co-infected patients is the high toxicity of antimonials and the poor effectiveness of liposomal amphotericin B (even in high doses) in these patients. Kala-azar cannot be permanently cured in HIV infected patients and will inevitably result in repeated relapse, even if patients are on anti-retroviral treatment (ART).


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MSF is calling for:

- **Implementation of the latest treatment protocols:** National VL programs to translate international WHO guidelines into practice.

- **Endemic countries to register VL drugs:** not all treatment options are registered in all endemic countries, limiting access to these drugs in those countries.

- **Inclusion of drugs for VL in the WHO Pre-Qualification scheme** to support use of quality assured drugs.

- **Reduced price for liposomal amphotericin B** to accelerate its roll-out wherever it is needed.

- **Increased investment in R&D for improved and simplified diagnostic tools:** A practical and rapid diagnostic test that can be used for the diagnosis of VL relapse and as test of cure is deeply needed. For primary diagnosis of VL in East Africa, a more sensitive test than the current rK39 RDTs is also needed.

- **Increased investment in R&D for new drugs** that are less toxic, given orally, with shorter administration and safe for women at child-bearing age and during pregnancy. Improved treatments are also required for patients co-infected with HIV.

- **Increased programmatic funding for VL:** Donors and endemic countries to include kala azar in (inter)national integrated NTD programs and funding.

- **Improved treatment of PKDL** in Asia and Africa.