Fact Sheet
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 250,000 to 300,000 cases, with over 90% of those cases occurring in India, Bangladesh, Sudan, South Sudan, Ethiopia and Brazil, where it often affects the poorest populations in those countries.

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VL is the second largest cause of parasitic death (after malaria). It is characterized by prolonged fever, weight loss, enlarged spleen, anaemia and suppression of the immune system. Without treatment, almost all patients will ultimately die, but timely diagnosis and treatment will cure nearly all patients, 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. In the current outbreak in South Sudan, more than 10,000 patients (5,000 by MSF) were treated between the end of 2009 and October 2011.

A major challenge is management of patients co-infected with VL and HIV. Both diseases influence each other in a vicious spiral: HIV/AIDS patients are much more susceptible to develop VL, and once infected, VL 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. In East Africa and South Asia, humans are the main reservoir of the parasites. In these regions, post kala azar dermal leishmaniasis (PKDL), a rash that sometimes appears following VL treatment, further contributes to disease transmission.

Patients who are clinically suspected to have VL can be tested using the rK39 antigen-based rapid diagnostic test (RDT). In the Indian subcontinent, even if used alone, this test has sufficient sensitivity and specificity to exclude or confirm VL. In East Africa, a positive rk39 RDT confirms the diagnosis, but suspected cases with a negative result still need further investigation 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.

Treatment

Current treatment options include pentavalent antimonials (i.e. sodium stibogluconate (SSG) and meglumine antimoniate), paromomycin, miltefosine, amphotericin B deoxycholate and liposomal amphotericin B (L-AmB) (currently registered as AmBisome). Treatment guidelines are continent-specific because of different levels of efficacy according to regions. Although the list of treatment options seems extensive, each has significant limitations. Combination treatments with existing drugs have also been developed to optimize the efficacy and safety of treatment and reduce costs and hospitalization time.

Pentavalent antimonials (SSG), when used alone, require 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 five to ten times higher than in non HIV-infected. Paromomycin (PM) is a cheap anti-leishmanial drug but needs to be administered in combination with another drug in order to optimize its use. African countries are in the process of switching from 30 days SSG to the WHO-recommended combination regimen of 17 days SSG&PM (in those without HIV), developed by DNDi and the Leishmaniasis East African Platform (LEAP) partners, including MSF. Both drugs are administered by intramuscular injections.

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 and requires strict adherence.

L-AmB 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]. Its current cost remains an important barrier to treatment. Nevertheless, there are many reasons to believe that L-AmB could soon become the mainstay of first-line treatment for all patients, either used alone or in combination with an oral drug.

In India and Bangladesh, MSF has used short-course regimens of L-AmB (15-20 mg/kg total dose) with an initial cure rate over 98% and a very good safety profile. In 2010, a WHO Expert Committee recommended L-AmB in a *single dose* or in short-course regimen as first-line therapy in South Asia. MSF is now working together with DNDi and other partners in a clinical study evaluating effectiveness and feasibility in the field of single dose L-AmB (10 mg/kg) and combination regimens (L-AmB with miltefosine and miltefosine with paromomycin). The results of this study will help countries in South Asia to update their treatment recommendations. The current VL elimination plan launched in 2005 by India, Nepal and Bangladesh still relies on miltefosine only. L-AmB in Africa is less effective and requires higher doses compared to

the Indian subcontinent. However, it should be used in treatment failures, severely ill patients, those co-infected with HIV, pregnant women and those over 45 years of age.

Amphotericin-B deoxycholate is a cumbersome treatment that needs to be given in slow intravenous (IV) infusions daily or every other day for 15 doses. Careful hydration and potassium intake of patients are needed to avoid renal toxicity and hypokalemia. With the advent of L-Amb, its use should be discouraged.

MSF and visceral leishmaniasis

Since 1988, MSF has treated more than 100,000 VL 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 for the decentralization of diagnostic and some treatment services to remote areas, where laboratories cannot be established, and thus has improved access to care in endemic areas.

In East Africa, Georgia and Asia, MSF's findings and operational research have actively influenced national and international treatment policy changes. For African VL, a WHO Expert Committee has now recommended the combination therapy of SSG&PM, which was studied and implemented by MSF in South Sudan since 2002 and recently thoroughly evaluated in DNDi-sponsored studies.

In Ethiopia, where 20% to 40% of the VL patients are HIV infected, VL 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. VL in HIV infected patients needs to be better managed in order to reduce the very high relapse and mortality rates seen in many centres. Based on initial promising data, MSF is now working to validate a standard package of management that includes an optimized primary treatment (L-AmB combined with miltefosine), prompt ART initiation and secondary prophylaxis (monthly pentamidine injections).

MSF is calling for:

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- **National VL elimination programmes in South Asia to implement the available better treatment regimens:** single dose or short course L-AmB or short course combination regimens.
- **Endemic countries to register VL drugs:** not all treatment options are registered in all endemic countries, limiting access to these drugs in those countries.
- **Reduced price for liposomal amphotericin B** to accelerate its roll-out wherever it is needed.
- **Donors and endemic countries** to increase funding for VL control programs.

MSF is calling for increased funding of more needs-driven R&D:

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- **Improved and simplified diagnostic tools:** For primary diagnosis of VL in East Africa, a more sensitive test than the current rK39 RDTs is needed. Overall a single, practical rapid diagnostic test that can be used for primary diagnosis, test of cure and detection of relapse worldwide is also required.
- **New drugs** that are oral, safe (including during pregnancy), short course, cheap and effective in all endemic regions are needed. Improved treatments for patients co-infected with HIV and the development of an oral drug for PKDL are both required

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