

## Kala Azar (Visceral Leishmaniasis)



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## MSF FACT SHEET

### KALA AZAR Visceral Leishmaniasis

#### WHAT IS VISCERAL LEISHMANIASIS?

Visceral leishmaniasis (VL), also known as kala azar, is a worldwide protozoal vector-borne disease, endemic in 47 countries with approximately 200 million people at risk of infection. The annual incidence is estimated to be 500,000 cases, with 90% occurring in India, Bangladesh, Nepal, Sudan, and Brazil (60% in the Indian subcontinent alone). The disease often affects the poorest populations. VL is the second leading cause of parasitic death, characterized by fever, weight loss, hepatosplenomegaly, anemia and depression of the immune system. Without treatment, nearly all patients will die. Death can be avoided by timely treatment, even in basic field circumstances.

Epidemics associated with high mortality are frequent where conditions such as complex emergencies, mass migration, high rates of HIV and poor nutritional status accelerate the development and spread of the disease, and where many patients do not have access to treatment. The recent (end 2009) VL outbreak in South Sudan involved ~1,000 patients, and is considered the start of a much larger re-emerging epidemic in the region.

A major challenge is co-infection of VL and HIV. Both diseases influence each other in a vicious spiral: HIV patients are much more susceptible to develop kala azar, and once infected, kala azar accelerates the onset of full-blown AIDS.

#### TRANSMISSION AND DIAGNOSIS

Different species of the Leishmania parasite causing the disease are transmitted by the phlebotomine sandfly. Both animals and humans can act as the parasite's reservoir. Post kala azar dermal leishmaniasis (PKDL) appears as a rash that occurs after or during VL infection and 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 (ie, transmission by sandfly bite from PKDL patient to new patient) between epidemic cycles.

Initial screening relies on history of prolonged fever and clinical splenomegaly. Clinical suspect patients can be investigated for VL using rK39 antigen-based rapid diagnostic test (RDT). RDTs only require a drop of the patient's blood. In suspect cases with negative RDT result, VL can be either ruled out (in areas where rK39 RDT have proved to be highly sensitive) or further searched by another serological test (e.g. DAT) or by microscopic examination of spleen, bone marrow or lymph node aspirates.

These techniques require technical expertise and laboratories that are often not available in areas where most patients are located. ELISA and IFAT tests have been developed for the diagnosis of VL, however their use is limited in the field since a well-equipped laboratory and skilled personnel are required.



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#### TREATMENT

Current treatment options include pentavalent antimonials (Pentostam®, generic SSG, Glucantime®), amphotericin B deoxycholate, liposomal amphotericin B (AmBisome®), paromomycin and miltefosine. Combination therapies will be available in the near future. Although the list of treatment options seems extensive, each has significant limitations.

**Pentavalent antimonials**, given as daily intramuscular injection for 30 days, are used as first-line therapy in most countries. It is still effective in most endemic areas. However, 60% failure rate to this drug is seen in Bihar State, India. It can cause serious toxic side effects, and is poorly tolerated in HIV co-infected patients, with mortality 10 times higher than in non HIV-infected.

**Miltefosine** is contraindicated during pregnancy, and should ideally be taken in combination to avoid the development of drug resistance. The treatment in monotherapy is 28 days, so adherence to non-directly observed treatment is another barrier and can also contribute to drug resistance. Miltefosine is well tolerated but less effective in HIV co-infected patients.

**Paromomycin** is administered intramuscularly for 21 days, which may trigger lack of adherence. This is the cheapest available drug. While its efficacy is high in India, it is less effective in East Africa where higher dosage or use in combination will be required.

**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.

**Liposomal amphotericin B** is used as second-line therapy for patients in East Africa, once SSG fails. In India, given the high levels of resistance to antimonials, it is the best first-line therapy option on a regimen of 20 mg/kg b.w. divided over 5 infusions with excellent tolerability, safety and efficacy. More recent data show that 10 mg/kg b.w. as a single shot in India is equally efficacious and safe. In East Africa, a higher dose of 30 mg/kg is needed for effective cure. It can be used in pregnant women. However, its current cost remains an important barrier to treatment.

The treatment landscape is evolving, and treatment regimens are being simplified. Studies showing efficacy and safety of liposomal amphotericin B at a reduced dose (single shot 10 mg/kg b.w.) in the Indian subcontinent are promising. Results of combination treatment studies are also anticipated, with the intent 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 95,000 kala azar patients in Sudan, Ethiopia, Kenya, Somalia, Uganda, Nepal and India. MSF has validated and introduced a rapid diagnostic test (rK39 antigen-based dipstick), which 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.

Bihar State, one of the poorest states in India and the world, is where MSF has been treating patients with liposomal amphotericin B since 2007. To date more than 4,000 patients have been treated, with promising results in terms of both efficacy and safety. The results of this project have shown that treatment infused at 20 mg/kg (total dose) in 5 injections given over a period of 10 days (in contrast with the longer treatment regimen needed with conventional amphotericin-B) is successful in both hospital and primary health care settings.

In Ethiopia, where more than 30% 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 and poor tolerability to antimonials, and the poor effectiveness of liposomal amphotericin B (even in high doses) in these patients. VL cannot be permanently cured in HIV-infected patients, and will inevitably result in repeated relapse, even if patients are on antiretroviral therapy (ART). In HIV co-infected patients, full-course combinations with well-tolerated drugs (liposomal amphotericin B, miltefosine) are recommended.

## CHALLENGES

VL is still a very much neglected and under-resourced disease. Recognition of VL as a main opportunistic infection in HIV co-infected patients in endemic areas will be an important step in getting more attention for the disease.



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## MSF CALLS FOR:

- **Lowering price of existing drugs:** A key barrier to patients receiving treatment is the cost of the current treatments.
- **Registration of drugs:** Not all treatment options are registered in all endemic countries, making entry and use of these drugs in those countries difficult.
- **New 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.
- **Better use of existing drugs:** Results of drug combination studies are anticipated shortly, providing alternative effective and safe treatment for patients.
- **Increased access to diagnosis and treatment of patients in remote areas:** National control programs and other key health providers need to develop innovative ways of reaching populations from flood-prone rural areas through to areas of conflict.
- **Improved surveillance systems:** Epidemics are a reality with this disease, and with improved active screening, diagnosis and reporting, patients have a better chance of survival.
- **Investment in R&D:** New drugs are needed 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 who are infected with HIV.
- **Improved funding of national control programs:** Some degree of integration of VL diagnosis and treatment within public health facilities is already possible with existing tools and could be bolstered by improved funding and political will.