

Kala Azar (Visceral Leishmaniasis)



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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 and putting 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, (and 60% in the Indian subcontinent alone). The disease often affects the poorest populations. This is the second largest cause of parasitic death, characterized by fever, weight loss, hepatosplenomegaly, anemia and a 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) 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 kala azar 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 parasites 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.

Initially 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. the 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. ELISA and IFAT tests have been developed for the diagnosis of VL, however their use is limited in the field as 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, is used as first line therapy in most countries. It is still effective in most endemic areas. However, there is a 60% failure rate to this medication in Bihar State, India. It can cause serious toxic side effects, and is poorly tolerated in elderly, moribund, pregnant and HIV co-infected patients, with mortality being significantly higher than in non HIV-infected.

Miltefosine 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 is 28 days so adherence to non-directly observed treatment is another barrier and can also contribute to drug resistance.

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 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 days for 14 doses. Careful hydration and potassium intake are needed to avoid renal toxicity and hypokalemia.

Ambisome® 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 an excellent tolerability, safety and efficacy. 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 Ambisome® 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 rapid diagnostic test (rK39 antigen-based dipsticks), that can be used in remote settings. The ease and convenience of this test has allowed decentralisation 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 Ambisome® since 2007. To date more than 4,000 patients have been treated, with very promising results in terms of both efficacy and safety. The results of this project have shown that treatment infused at 20mg/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 very successful in both hospital and primary health care settings.

In Ethiopia, where more than 30 % 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 and poor tolerability to antimonials, and the poor effectiveness of AmBisome (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).

CHALLENGES

Visceral leishmaniasis is still a very much neglected and under-resourced disease. Recognition of kala azar 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 IS CALLING 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.
- **Investment in R&D:** 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 who are infected with HIV.
- **Improved funding of national control programs:** some degree of integration of kala-azar diagnosis and treatment within public health facilities is already possible with existing tools and could be bolstered by improved funding and political will.