Combating kala azar: don't fail the patients

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 250-300,000 cases, with over 90 percent of those cases occurring in India, Bangladesh, Sudan, South Sudan, Ethiopia and Brazil. Like all neglected diseases, kala azar affects mainly the poorest and most invisible population, with little or no political power. Without treatment, almost all patients will die, however timely diagnosis and treatment will cure nearly all patients, even in resource-limited and remote circumstances.

There are many challenges in combating kala azar, as the strategies to fight the disease vary according to the context. Through its activities in the field, MSF has proved that it is possible to diagnose and treat kala azar patients with a high cure rate even in remote settings. It is now essential to increase patient access to proper diagnosis and treatment, scale up political and financial commitment to roll out and reinforce current control programmes, while at the same time investing in development of better tools to fight against the disease.

Reinforce control programmes at field level

- **East Africa:**

Most kala azar patients in East Africa face environments of war or conflict, extreme poverty and/or geographical remoteness which significantly hamper access to proper diagnosis and treatment.

Moreover, kala azar epidemics resulting in 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. Over the past two decades, protracted epidemics have taken place in South Sudan. In Jonglei and Upper Nile States, more than 10,000 patients were treated (5,000 by MSF) between the end of 2009 and October 2011.

Another big challenge is the co-infection of kala azar with HIV. Together, these diseases create a vicious circle: HIV patients are much more susceptible to developing kala azar; and kala azar is a stage 4 AIDS defining opportunistic infection and is more difficult to treat in HIV positive people.
In most of MSF's kala azar programmes, the percentage of co-infected patients is still low. However, due to its specific context, in Ethiopia, 20-40% of the kala azar patients are HIV-positive.

- What needs to be done?

Endemic countries should register VL drugs. Current kala azar treatment options include pentavalent antimonials, paromomycin, miltefosine, amphotericin B deoxycholate and liposomal amphotericin B (L-AmB). Treatment guidelines are continent-specific because of differing levels of efficacy. In East Africa, treatment with pentavalent antimonials is still very effective; however, it is lengthy, potentially toxic, and painful. The WHO Expert Committee recommends a combination regimen of 17 days pentavalent antimoninals and paromomycin to treat African kala azar in patients who are HIV negative. For HIV positive patients, higher dosage of L-AmB should be given, and ideally be combined with other drugs such as miltefosine.

However, not all anti-leishmanial drugs are registered in East African endemic countries, which limits the capacity to import them and to provide the necessary treatment options. For instance, in Ethiopia, paromomycin sulphate and SSG (a pentavalent antimonial) are still not registered.

Better diagnosis. The rapid diagnostic test, or RDT, (rK39 antigen-based dipsticks) can be used in many remote settings. The ease and convenience of this test has allowed decentralization of diagnostics and sometimes even treatment services to remote areas where laboratory services cannot be established. Overall, the test has improved access to care in endemic areas. However in East Africa, a positive rk39 RDT confirms the diagnosis, but suspected cases with a negative result still need further investigation using another serological test, the diagnostic agglutination test (DAT), or by microscopic examination of spleen, bone marrow or lymph node aspirates. These techniques are not only invasive to the patient, but also require technical expertise and laboratories that are seldom available in areas where kala azar thrives.

For this reason it is essential that a better diagnostic tool is developed for East Africa which allows for the decentralization of the treatment.

- **South Asia:**

In South Asia, kala azar has a relatively milder presentation than in East Africa and it is more sensitive to drugs other than antimonials. However, patients still die if they are not treated. In 2005, the governments of Bangladesh, India and Nepal, supported by the WHO, joined forces in an ambitious plan to eliminate the disease from the region by 2015. In February 2012, WHO updated this goal and in its new roadmap, is calling for elimination of kala azar in the Indian subcontinent by 2020. However, for elimination of kala azar from these countries to be feasible, substantial and sustained action, such as vector control activities and diagnosis and treatment for patients, needs to be scaled up.

The implementation of better treatment options to treat kala azar in South Asia will be a key element to move forward to this goal.

The treatment of Post Kala Azar Dermal Leihmaniasis (PDKL), a skin condition that occurs after or during kala azar infection and treatment, is another challenge in South Asia. Although PDKL is not dangerous for the patient, it can be highly infectious as parasites may be present in the raised areas of the skin, acting as a major reservoir for the parasite. For this reason, more effective and shorter treatment courses are needed in order to stop the spread of the disease.

- What needs to be done?

National kala azar elimination programmes in South Asia to implement the available better treatment regimens. In South Asia, especially in areas of India and Bangladesh, pentavalent antimonials, which have been the first-line treatment in most endemic countries for more than 70 years, are of limited effectiveness due the high rates of resistance.

In 2010, the leishmaniasis Expert Committee of the WHO published the Blue Book, which provided a preferential list of treatment recommendations for treating kala azar in India, Bangladesh and Nepal. These included liposomal amphotericin B and combination therapies as the first line choices. However, up until now, this recommendation has not yet been translated into treatment guidelines or national policy in India. The country still maintains miltefosine monotherapy as the first line drug in the treatment of kala azar, which although effective, is limited in its use due to teratogenicity, long treatment duration (therefore a risk of non-compliance or completion of full treatment) and the potential risk of developing drug-resistance.

Single doses of liposomal amphotericin B and combination therapies, based on already approved drugs, can play a key role in the future. MSF, together with DNDi, will implement a

pilot project in Bihar, India, to evaluate the safety and effectiveness of three new methods for the treatment of kala azar in field settings.

The endemic countries in South Asia need to implement the WHO recommended treatment options to treat as many patients as possible with better drugs.

Pay more attention to PKDL. There is a strong association between pentavalent antimonial treatment and the development of PKDL. As such, national protocols should restrict SSG based treatments. There also needs to be more research and development of a safe, feasible and cost-effective treatment for PKDL.

Increase commitment at international level

More funding is essential to work on the research and development needed to fight against kala azar. At field level, it is essential to improve and simplify diagnostic tools (mainly for East Africa) and it is also necessary to develop new drugs that are oral, safe, short course, cheap and effective in all endemic regions.

Increased international funding also needs to be allocated to control programmes in the field to ensure patient access to the tools available today. New and validated results need to be implemented in the public health system without delay.

Last January, several pharmaceutical companies, international donors and five Ministries of Health – Bangladesh, Brazil, Mozambique, Tanzania and Burkina – adopted the London Declaration on Neglected Tropical Diseases to highlight the increased commitment to controlling VL. However, this declaration should also be signed and supported by all Ministers of Health in endemic countries, in order to implement the required strategies to really scale up the access for patients to appropriate diagnosis and treatment.