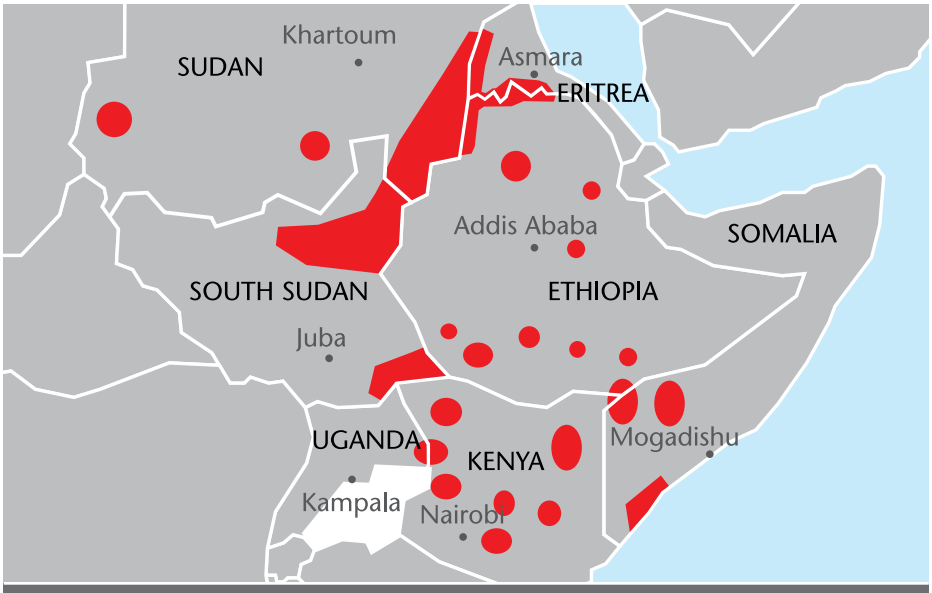
THE DOUBLE BURDEN:
HIV/visceral leishmaniasis co-infection in East Africa

Visceral leishmaniasis patient, Leer Hospital, Unity State, South Sudan.

Visceral leishmaniasis (VL), also known as kala azar, is a neglected tropical disease caused by different species of the *Leishmania* parasite (*L. donovani* in Africa) and is transmitted through bites of phlebotomine sandflies. Large parts of Sudan and South Sudan are endemic for visceral leishmaniasis, as well as areas of Kenya, Ethiopia and Somalia. Visceral leishmaniasis is deadly if left untreated.



Visceral leishmaniasis endemic areas in East Africa[1]

VL interacts with HIV/AIDS, and numerous patients are co-infected as they suffer from both diseases. The East of Africa is particularly hard hit. North-western Ethiopia has the highest burden of VL/HIV co-infection: 25–41% of VL patients are co-infected with HIV.[2] VL is an AIDS-defining condition and is an indication for starting antiretroviral therapy irrespective of the patient's CD4 count.[3]

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MEDECINS SANS FRONTIERES

Importance of testing for VL: In endemic areas, all HIV positive people should be investigated for VL. When the clinical case definition (see box) for primary, or first episode, VL is met, a rapid diagnostic test should be performed. VL rapid tests have suboptimal (77%) sensitivity in HIV positive patients in East Africa.[4] Therefore, a negative rapid test result in a suspected patient needs to be followed by either the Direct Agglutination Test or tissue aspiration microscopy.

The clinical picture of visceral leishmaniasis

The clinical case definition of primary VL is fever for more than two weeks with malaria excluded / treated, accompanied by splenomegaly or lymphadenopathy, and wasting.

DOUBLE THE BURDEN

The interaction of VL with HIV/AIDS adds considerable complexity to the treatment of both diseases.

Risks are increased: HIV and *Leishmania donovani* both attack the cellular immune system and reinforce each other in a detrimental manner. HIV-positive patients are much more susceptible to develop VL after being bitten by a sand fly. They may also reactivate latent VL as an opportunistic infection, as their immune response begins to weaken because of HIV. Because of the much higher parasite burden in their body, VL/HIV co-infected patients are also important reservoirs for disease transmission.

Response to HIV treatment is impaired: VL accelerates progression to AIDS. Co-infected patients respond less well to antiretroviral therapy.[4]

Response to VL treatment is impaired: At the same time, in HIV-positive patients, treatment of VL is less effective, has higher drug toxicity and higher mortality. Because all anti-leishmanial drugs lack efficacy in people co-infected with HIV/VL in Africa, better high-dose combination treatment regimens are needed.

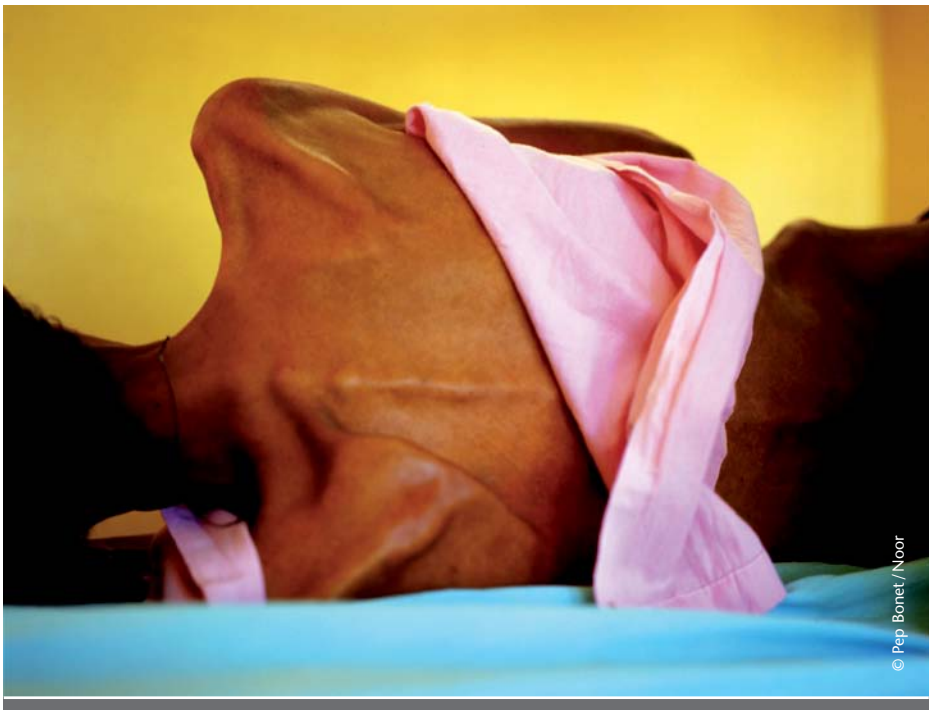
Pentavalent antimonials (sodium stibogluconate – SSG) have an unacceptable high mortality (due to toxicity) during treatment in HIV co-infected visceral leishmaniasis patients (16-33%[5,6]) and should not be used.

Liposomal amphotericin B (L-AmB, currently registered as AmBisome) in high doses (30 mg/kg over six doses) is safe, but unfortunately not very effective in co-infected patients in East Africa. MSF recently demonstrated that high dose L-AmB in Ethiopian HIV co-infected primary VL patients led to an 'initial' cure (when a patient is cured at the end of the treatment course) in only 74% of cases. In HIV co-infected relapse patients, the initial cure rate was only 38%.[7]

Initial results of a more recent MSF study suggest that combining L-AmB with miltefosine in HIV-positive VL patients enhances its effectiveness, with significantly lower treatment failure rates when compared with L-AmB monotherapy, especially in relapse patients.[8] Further study on this combination therapy is planned.

Outcomes are poorer: In HIV-positive patients, unlike in people who are HIV-negative, VL cannot be fully cured, even after extensive anti-leishmanial treatment.[9] In Africa (as opposed to southern Europe, where VL is caused by another species of *Leishmania* parasite), antiretroviral treatment only partially improves the immune status of co-infected patients, and only partially delays relapses of VL.[10,11]

Co-infection is therefore an almost untreatable mix that results in repeated relapses, increased drug unresponsiveness, and eventually death, even if treatment for both infections can be accessed.



Kahsay Abera Hospital in Humera, north-west Ethiopia, where the first ART in Ethiopia was provided.

Getting it right first time

HIV-positive people that still have demonstrable *Leishmania* parasites at the end of VL treatment will relapse much sooner than those who have achieved "parasitological cure". As successive relapses become more and more difficult to treat, it is of utmost importance to obtain treatment success at first VL episode in HIV positive patients. This means treating with a safe (i.e. not SSG) and effective combination regimen (i.e. high dose L-AmB/miltefosine) until a demonstrated parasitological cure is obtained, and adding antiretroviral therapy as soon as possible.

Research on secondary prophylaxis to prevent further relapse in HIV/VL patients with a high risk of relapse will start soon.

WHAT NEEDS TO HAPPEN

Prevention of VL in people living with HIV in VL-endemic areas should be promoted and diagnosis and treatment of VL in HIV-positive patients should be scaled up.

Better prevention: Impregnated bed nets provide some personal protection against VL. Access needs to improve, especially for those most exposed. Innovation in impregnated clothing is needed.

In HIV-positive patients who are infected by *L. donovani* but who have not developed VL, early use of antiretroviral therapy (ART) may be the best way of preventing reactivation of latent VL as an opportunistic infection. This calls for the rapid implementation of the WHO guidelines in favour of early initiation of ART (CD4<350/mm3) in countries where VL is endemic.

Better access to diagnosis and treatment: Early diagnosis and treatment of VL patients saves lives and reduces disease transmission. In endemic areas, all HIV positive people should be investigated for VL.

Access to L-AmB is a major challenge, partly because of logistical issues – the drug needs to be transported by cold chain and stored at below 25C – and partly because the price is too high for national control programmes. AmBisome, the L-AmB produced by Gilead, is currently available at WHO-negotiated prices of US$ 18 per vial (Table 1). As more than 25 vials are usually necessary to treat co-infected patients in Africa, the cost of AmBisome per treatment course often exceeds $450.

In addition, not all the drugs required to treat VL in HIV-infected patients are available in endemic countries. The majority are not registered in East African endemic countries (Table 2). This limits the capacity to import drugs for VL and therefore provide the needed treatment options to patients co-infected by HIV.


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TABLE 1: DRUGS FOR HIV/VL CO-INFECTION IN AFRICA – PRICE INFORMATION

Drug	Commercial name and manufacturer	Price information
Liposomal Amphotericin B (L-AmB)	AmBisome, Gilead, USA	WHO-negotiated price: US$ 18 per 50mg vial
Miltefosine (MF)	Impavido, Paladin, Canada, Single source	WHO-negotiated prices (for orders of large quantities): For adults: €45.28–54.92 for 56 (50mg) capsules For children: €34.36–39.3 for 56 (10mg) capsules

Source: Technical Report series (TRS) 949, WHO, Geneva, 2010

TABLE 2: DRUGS FOR HIV/VL CO-INFECTION – REGISTRATION STATUS IN EASTERN AFRICAN COUNTRIES

Drug	South Sudan	Ethiopia	Kenya	Sudan
Liposomal Amphotericin B (L-AmB), AmBisome	Drugs are on the Essential Medicines List but no registration procedure is in place	Yes (final documentation pending)	No	No
Miltefosine (MF), Impavido		No	No	No

RECOMMENDATIONS

A patient with visceral leishmaniasis at Kahsay Abera Hospital in Humera, north-west Ethiopia.

- **Donors and national HIV programmes in VL-endemic countries should include interventions that scale up prevention, diagnosis and treatment of VL.** Access to early ART for those most vulnerable to VL, including rural migrant labourers and resettled and internally migrated populations should also be improved.
- **Optimal treatment of co-infected patients should be assured:** SSG should be avoided, and high-dose L-AmB-based combination treatments given until parasitological 'cure' has been achieved, with ART added as soon as possible. VL should be included as an indication for initiation of ART, irrespective of CD4 count in ART guidelines in endemic settings.
- **Access to treatments should be secured:** Gilead, the manufacturer of AmBisome should reduce the price further; the feasibility of development and quality assessment of alternative generic sources of L-AmB should be explored; manufacturers of VL drugs should undertake registration in endemic countries, and endemic countries authorities facilitate registration.
- **Enhanced research** into prevention, diagnosis, treatment and secondary prophylaxis of this neglected opportunistic infection should be pursued.

REFERENCES

1. Source: Leishmaniasis control in Eastern Africa: past and present efforts and future needs. November 2010 – Malaria Consortium / COMDIS.

2. Diro E, Hailu A, Lynen L, et al. VL-HIV co-infection in East-Africa: current challenges and perspectives. Abstract at 7th European Congress on Tropical Medicine and International Health, Barcelona, Oct 2011.

3. Control of the leishmaniases WHO Technical Report series 949, 2010.

4. Ter Horst R, Tefera T, Assefa G, et al. Field Evaluation of Rk39 And DAT Serological Tests for the Diagnosis of Visceral Leishmaniasis in a Population with High HIV Prevalence in Ethiopia. Am J Trop Med Hyg, 2009, 80(6): 929-34.

5. Ritmeijer K, Veeken H, Melaku et al. Ethiopian visceral leishmaniasis: generic and proprietary sodium stibogluconate are equivalent; HIV co-infected patients have a poor outcome. Trans R Soc Trop Med, 2001, 95;668-72.

6. Ritmeijer K, Dejenie A, Assefa Y, et al. A comparison of Miltefosine and Sodium Stibogluconate for treatment of Visceral Leishmaniasis in an Ethiopian population with high HIV-prevalence. Clin Infec Dis, 2006, 43 (3): 357-64.

7. Ritmeijer K, ter Horst R, Chane S, et al. Limited effectiveness of high-dose liposomal amphotericin B (AmBisome®) for treatment of visceral leishmaniasis in an Ethiopian population with high HIV prevalence. Clin Infect Dis, 2011, Dec; 53(12): e152-8.

8. Ter Horst R, Ritmeijer, K. Management of Visceral leishmaniasis-HIV co-infection: experience from the field. ICASA 2011.

9. Alvar J, Aparicio P, Aseffa A, et al. The relationship between leishmaniasis and AIDS: the second 10 years. Clin Microbiol Rev 2008; 21(2): 334–359.

10. Ter Horst R, Collin S.M., Ritmijer K, et al. Concordant HIV infection and visceral leishmaniasis in Ethiopia: the influence of antiretroviral treatment and other factors on outcome. Clin Infect Dis, 2008, 46(11): 1702-9.

11. Cota G.F., de Sousa M.R., Rabello A. Predictors of visceral leishmaniasis relapse in HIV-infected patients: a systematic review. PLoS Negl Trop Dis, 2011, 5(6): e1153. Doi: 10.1371/journal.pntd. 0001153.

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A visceral leishmaniasis patient's daily consultation in an MSF health centre in Pibor, Jonglei State, South Sudan.