Evaluating new treatment regimens for visceral leishmaniasis in people living with HIV in India and Ethiopia

DND*i* and Médecins Sans Frontières (MSF) sponsored two clinical trials to evaluate new treatment regimens for visceral leishmaniasis (VL) in people living with HIV. The studies took place in Northwest Ethiopia, led by DND*i*, and in Bihar, India, led by MSF, in areas with high dual burdens of VL/HIV co-infection. Participating patients were treated with liposomal amphotericin B alone or a combination of liposomal amphotericin B with miltefosine.

1 WHY WERE THESE TRIALS CONDUCTED?

One third of all people living with HIV live in areas endemic for VL, and their risk of developing VL is between 100 and 2300 times higher than that of people who are HIV-negative. HIV increases the severity of VL, making treatments less effective and raising relapse rates as well as mortality rates. Access to care for people living with HIV who are co-infected with VL is hampered by stigma, financial barriers, and a lack of appropriate, coordinated services.

At the time of these studies, the WHO-recommended treatment regimen for VL in people living with HIV was infusion of amphotericin B lipid formulations 3-5 mg/kg daily or intermittently, up to a total dose of 40 mg/kg. Data on treatment results for VL/HIV co-infected patients was limited, due to a lack of randomized trials. Most of the available data came from observational studies with short follow-up periods that miss later relapses, and often with high rates of patients lost to follow-up.

It was important to conduct studies in two different regions because there is considerable geographical variation in the host-parasite relationship, meaning that treatment results from one region and/or species of *Leishmania* parasite may not be the same in another.

2 WHAT WAS EVALUATED AND HOW?

> Bihar, India

The Indian study was a parallel-arm, open-label, randomized, noncomparative Phase III trial conducted in a specialist VL research hospital in Patna, the state capital of Bihar. Adult patients with confirmed co-infection were included in the study, regardless of previous episodes of VL, unless they had severe underlying disease, hypersensitivity to the study drugs, a baseline serum creatinine of more than 1.2 mg/dL, or were pregnant or breastfeeding. Women of child-bearing potential who were not using or unwilling to use an assured method of contraception were excluded because miltefosine is potentially teratogenic – i.e., could potentially cause birth defects.

Participating patients were hospitalized for 29 days while they received treatment with one of the following:

- **Liposomal amphotericin B**: total dose 40 mg/kg by slow intravenous infusion of 5 mg/kg on days 1–4, 8, 10, 17, and 24, or
- **Liposomal amphotericin B**: total dose 30 mg/kg by slow intravenous infusion of 5 mg/kg on days 1, 3, 5, 7, 9, and 11 at the same time as **miltefosine** administered as one 50-mg capsule orally twice a day for 14 days.

The primary endpoint was relapse-free survival at 6 months after the start of treatment. A parasitological test of cure was conducted on day 29, and patients were followed up for over a year. All adverse events were recorded up to one month after the last dose of study medication (day 58). This study was registered in Clinical Trial Registry India with study ID number CTRI/2015/05/005807.

> Northwest Ethiopia

The Ethiopian study was an open-label, randomized, noncomparative Phase III trial with a sequential design that allowed recruitment to be stopped if the observed efficacy was too low or sufficiently high. It was conducted at the Leishmaniasis Research and Treatment Centre at the University of Gondar and the Abdurafi Health Centre, MSF Hospital. Patients with confirmed co-infection were included, regardless of whether they had had previous episodes of VL. 20 patients received liposomal amphotericin B only, and 39 received the combination of liposomal amphotericin B with miltefosine.

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- **Liposomal amphotericin B**: total dose 40 mg/kg by slow intravenous infusion of 5 mg/kg on days 1–5, 10, 17, and 24, or
- **Liposomal amphotericin B**: total dose 30 mg/kg by slow intravenous infusion of 5 mg/kg on days 1, 3, 5, 7, 9, and 11 at the same time as **miltefosine** administered as one 50-mg capsule orally twice a day for 28 days.

The primary endpoint was parasitological clearance at day 29 after the start of treatment. Patients who had clinically improved but still had detectable parasites at day 29 were given extended treatment using the same regimen they had received during the study. A new test of cure was done at completion of the second cycle (day 58) to determine if patients had achieved parasitological cure. Patients were followed up for one year. All adverse events were recorded up to one month after the last dose of study medication. The study was registered at ClinicalTrials.gov with study ID number NCT02011958.

3 WHAT WERE THE RESULTS?

In Bihar, India, of the 75 patients who were treated only with liposomal amphotericin B, 93% had no detectable parasites 29 days after starting treatment and 85% were relapse-free after six months. Of the 75 treated with the combination of liposomal amphotericin B with miltefosine, 99% had no detectable parasites at day 29 and 96% were relapse-free after six months.

In Northwest Ethiopia, of the 20 patients who received only liposomal amphotericin B, 50% had no detectable parasites 29 days after starting treatment. Of the 39 patients who received the combination of liposomal amphotericin B with miltefosine, 67% had no detectable parasites on day 29. Subsequently, after a second cycle of treatment for those who had not achieved cure, not much improvement was observed in the efficacy rate for patients treated only with liposomal amphotericin B (55%), whereas patients treated with the combination therapy (liposomal amphotericin B with miltefosine) reached a satisfactory efficacy of 88% with no detectable parasites.

In both trials, the treatment regimens appear to be safe and well tolerated. Adverse events and adverse drug reactions were mostly mild and expected, according to what is already known about these drugs. During the safety monitoring period, 14 severe adverse events were reported in Bihar and 10 in Ethiopia, including 4 deaths in each trial. One of the deaths (in Ethiopia) was considered related to the rescue treatment, which was a combination of sodium stibogluconate and paromomycin, given due to treatment failure.

4 WHAT DO THE RESULTS OF THESE STUDIES MEAN FOR THE FUTURE TREATMENT OF VL/HIV CO-INFECTION?

The results of these two studies have made an important contribution to the available evidence on how best to treat VL in people living with HIV. The Ethiopian government is changing their national treatment guidelines for VL/HIV co-infection to make the liposomal amphotericin B and miltefosine combination the country's new first-line treatment regimen. The Indian government is also planning to update their treatment guidelines. The World Health Organization has reviewed all available evidence, including the results of these two trials, and has issued new treatment guidance for VL/HIV co-infection as of June 2022, with the liposomal amphotericin B and miltefosine combination as the recommended treatment for VL in people living with HIV.

IF YOU WOULD LIKE TO LEARN MORE, YOU CAN READ THE PUBLISHED STUDIES:

- Diro E et al. A randomized trial of AmBisome® monotherapy and AmBisome® and miltefosine combination to treat visceral leishmaniasis in HIV co-infected patients in Ethiopia. *PLOS Neglected Tropical Diseases* 2019, 13(1): e0006988. Available at: https://doi.org/10.1371/journal.pntd.0006988

- Burza S et al. AmBisome monotherapy and combination AmBisome – miltefosine therapy for the treatment of visceral leishmaniasis in patients co-infected with HIV in India: a randomised open label, parallel arm, phase 3 trial. *Clinical Infectious Diseases* 2022. Available at: https://doi.org/10.1093/cid/ciac127

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