



“ I am very grateful to the health workers for the care and treatment offered to my son. My only worry now is how to control the continuous pain associated with the daily treatment injections. ”

Lwalatta Loteroi, father to Lorus Tuliemuk, a three-year-old receiving treatment at the Kacheliba District Hospital in West Pokot County, Kenya.



LEISHMANIASIS

TOWARDS A NEW GENERATION OF TREATMENTS

Leishmaniasis comes in multiple forms:

- **the most deadly, visceral leishmaniasis (VL)**, is also known as kala-azar, or ‘black fever’. VL causes fever, weight loss, spleen and liver enlargement, and, if not treated, death.
- **post-kala-azar dermal leishmaniasis (PKDL)** is a complication of VL and appears as a rash or skin condition months or years after someone has successfully completed treatment for VL. PKDL is not life-threatening but can be a disfiguring and stigmatizing disease.
- **cutaneous leishmaniasis (CL)** is the most common form and is characterized by skin lesions that can be severely disfiguring and stigmatizing, particularly for women. In its mucocutaneous form, it can lead to the destruction of the mucosal membranes of the nose, mouth, and throat.



1 BILLION
people at risk across the globe



20,000-30,000
deaths annually

New drugs for leishmaniasis – the long-term goal

DNDi's long-term goal for leishmaniasis is to radically transform patient therapy: from today's poorly-adapted, complex and toxic treatments, to patient-friendly, simple oral therapies that are short-course, affordable, safe, and effective in both children and adults in all regions.

Together with partners at the Drug Discovery Unit and Wellcome Trust Centre for Anti-Infectives Research at the University of Dundee, at pharmaceutical companies GlaxoSmithKline, Pfizer, Takeda, and Celgene, and at the product development partnership TB Alliance, DNDi has built an unprecedented portfolio of lead series, and pre-clinical and clinical candidates for leishmaniasis from different chemical classes with different mechanisms of action against *Leishmania* parasites.

In a novel consortium with these partners, DNDi will work to advance this unique portfolio, with the goal of progressing drug candidates through Phase I clinical development, and for several clinical candidates to be selected for a Phase II clinical trial testing the safety and efficacy of a combination of two entirely new chemical entities.

VISCERAL LEISHMANIASIS

THE MOST FATAL FORM

Sustaining elimination in South Asia

Bangladesh, India, and Nepal, all once highly endemic for VL, are poised to eliminate the disease as a public health problem by 2020. But sustaining VL elimination in South Asia will require answering outstanding research questions. DNDi is actively exploring the role played by PKDL in the transmission of leishmaniasis (see p. 14), and identifying indicators to predict disease evolution from VL to PKDL and the likelihood of treatment failure or relapse.

Searching for better therapies in East Africa

There is a pressing need for a safer treatment to replace the toxic drug currently used in East Africa. Based on the

good results DNDi had with combination therapies in South Asia, a Phase III study was launched in 2018 in Ethiopia, Kenya, Sudan, and Uganda. The goal is to compare the combination regimen of miltefosine and paromomycin with the current standard VL treatment, sodium stibogluconate and paromomycin.

50,000 TO 90,000
new cases a year

50%
of all cases in the most affected countries
are children

THE TREATMENT CHALLENGE

Treating leishmaniasis depends on the form of the disease, the species of infecting parasite, and the country, as treatment responses differ from region to region. Co-existing infections such as HIV make treatment more difficult.

Current treatments for leishmaniasis require patients to take poorly tolerated, sometimes toxic, and costly drugs, often over a long period of time with painful injections.

DNDi aims to make treatments safer, shorter, and more affordable and effective for all forms of leishmaniasis. In the short term, better treatment regimens are being developed using existing drugs. In the long term, the goal is to develop an entirely new generation of all-oral drugs.

POST-KALA-AZAR DERMAL LEISHMANIASIS

THE DISEASE THAT STRIKES BACK

Understanding infectivity

The results of a DNDi study in Bangladesh confirmed that PKDL acts as a reservoir for leishmaniasis infection. This shows it is important to diagnose and treat PKDL quickly because the sandflies that bite people with PKDL can go on to transmit the parasite that causes VL. In Sudan, preparation for a similar infectivity study is underway.

Improving treatments

People with PKDL are treated with the same anti-leishmanial drugs as people with VL, but treatment duration is longer. In South Asia, DNDi's Phase II study seeks to assess whether shorter options are possible, with either liposomal amphotericin B as monotherapy or with a combination of liposomal amphotericin B plus miltefosine. The study

completed patient enrolment in three clinical sites in India and Bangladesh, with results expected in 2020.

In East Africa, a clinical trial to evaluate a potentially better treatment for severe or chronic cases of PKDL began in Dooka, Sudan and had recruited 39 patients by the end of the year. In Sudan the two treatments under assessment are a combination of liposomal amphotericin B with miltefosine and a combination of paromomycin with miltefosine.

5-10%

of people treated for VL develop PKDL in South Asia

50-60%

of people treated for VL develop PKDL in East Africa

HIV/VL CO-INFECTION

A DEADLY COMBINATION

Better treatment recommendations on the horizon

HIV infection increases the severity of visceral leishmaniasis, increasing relapse rates and heightening the risk of death. In search of a treatment solution, humanitarian organization Médecins Sans Frontières (Doctors Without Borders, or MSF) began using a compassionate regimen in Ethiopia in 2011, combining liposomal amphotericin B, with the oral drug miltefosine. Results were promising.

To provide the necessary scientific evidence, DNDi ran a Phase III study, starting in 2014, testing this combination against the current WHO treatment recommendations, liposomal amphotericin B monotherapy. Results published in 2018 showed that the combination was more effective than standard therapies for treating VL in people living with HIV. Success

rates improved to 88% when a second course of VL treatment was given to patients whose first round of treatment hadn't fully cleared the parasite from their bodies.

These results from Ethiopia should be strengthened by the top-line results expected in 2019 of a Phase III study sponsored by MSF in India, and in which DNDi is a technical partner. The complementary results will support discussions with national and international stakeholders for a new and improved treatment recommendation for VL in people co-infected with HIV.

2,000 TIMES

The risk of developing active VL is up to 2,000 times greater in people living with HIV

“ When patients come to our ward, they are sick and have no physical strength, but when they go home smiling, healthy, and happy with gratitude towards us, it is so satisfying. That is the most rewarding part of my job, I feel that I made a difference in someone's life. ”

Vineeta Xalko, a nurse in the HIV/VL ward run by Médecins Sans Frontières at Rajendra Memorial Research Institute, Patna, India. DNDi is a technical partner in the MSF-led study with RMRI to find the best treatment for HIV/VL infections.

CUTANEOUS LEISHMANIASIS

NON-FATAL BUT HIGHLY STIGMATIZING

Searching for shorter, safer treatments

DNDi is running a Phase II clinical trial in Peru and Colombia to assess a combination of thermotherapy plus oral miltefosine for CL. This combination could improve treatment effectiveness and reduce treatment duration and the rate of adverse events compared to current recommended treatments. The strength of the interim results supports the preparation of a Phase III study, which is being planned in five clinical sites in four countries in Latin America. MSF is running a similar trial in Pakistan – the results from both trials could therefore help improve

treatment both in the Americas and the Middle East and South Asia, where treatment responses usually vary.

DNDi is also offering technical support to a study in Brazil being run by the Ministry of Health for shorter and safer treatments for mucocutaneous leishmaniasis.

600,000-1.2 MILLION
new cases a year

“There is a huge lack of information on the disease that leads to the use of several things to get cured, such as burned oil from cars. The scars are very ugly, so there is lots of stigma and discrimination faced by patients.”

Ana Marilus Reyes Morales, whose two children have cutaneous leishmaniasis, Ancas, Peru. It takes them 12 hours to get to the hospital to receive treatment.

