LEISHMANIASIS

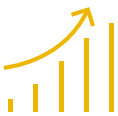
PARTNERING FOR A NEW GENERATION OF TREATMENTS

Caused by parasites transmitted by the bite of a sandfly, leishmaniasis has strong links to poverty, taking its heaviest toll on people affected by malnutrition, poor housing, and displacement. The disease comes in multiple forms. The most severe, visceral leishmaniasis (VL), also known as kala-azar, is deadly if not treated. Post-kala-azar dermal leishmaniasis (PKDL) and cutaneous leishmaniasis (CL) are non-lethal, but cause disfiguring skin lesions that can leave life-long scars and lead to severe social stigma.

LEISHMANIASIS STATISTICS

600 MILLION
people at risk of VL
across the globe

2,000 X
risk of developing active VL
for people living with HIV

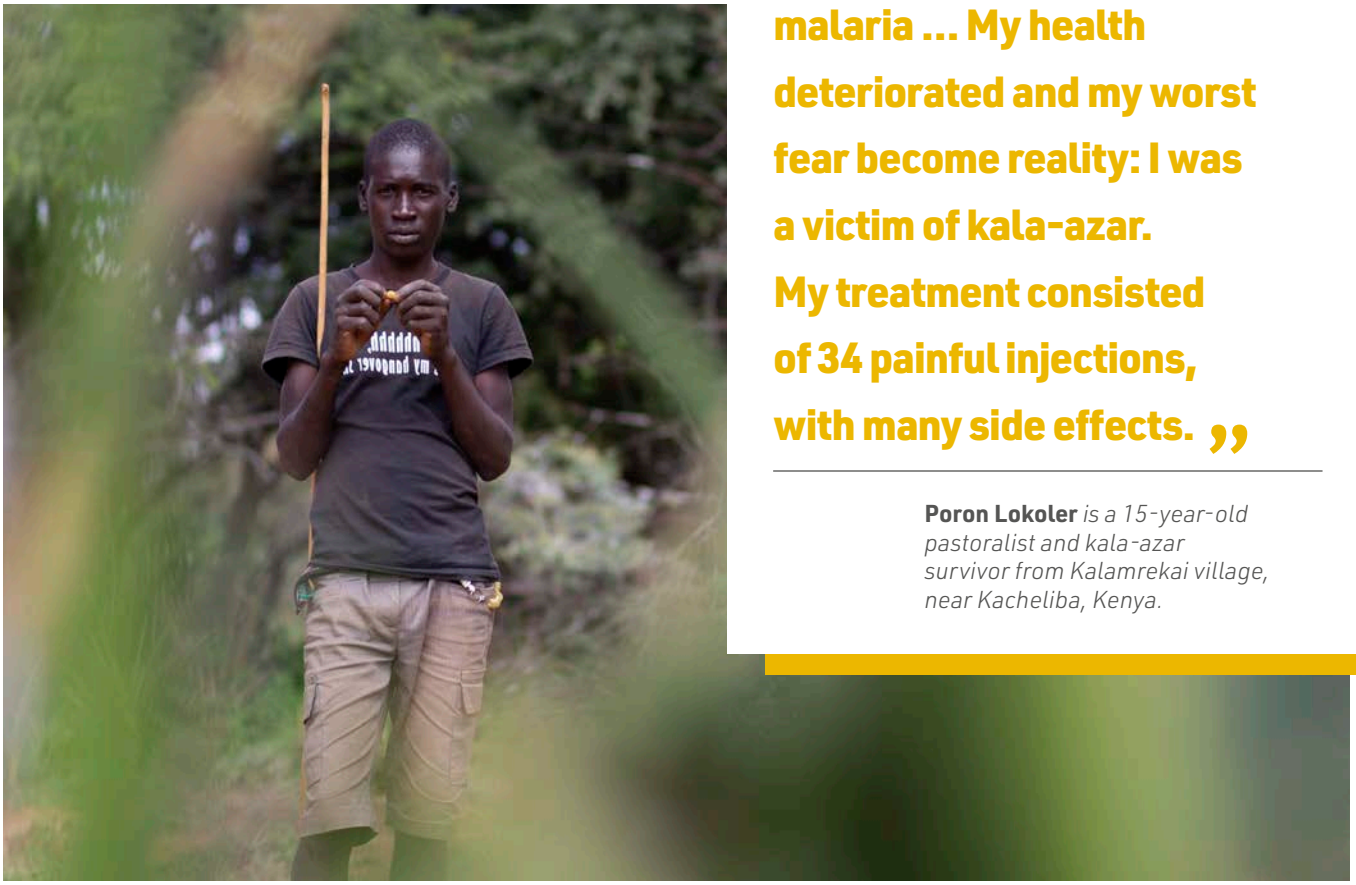


600,000 -1.2 MILLION
new cases of CL
each year

THE TREATMENT CHALLENGE

Better treatments for all forms of leishmaniasis are urgently needed. Existing drugs for VL can be lengthy, toxic, and costly, requiring hospitalization and daily injections, and treatment responses vary in different parts of the world. Current treatment for CL has many of the same serious shortcomings, relying on drugs known as antimonials developed over 70 years ago. Antimonials are not recommended for patients over 50 years of age due to cardiotoxicity, and cannot be given to pregnant women or people with liver or kidney problems.

DND*i* 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 oral drugs.



> **“Everyone thought it was malaria ... My health deteriorated and my worst fear become reality: I was a victim of kala-azar. My treatment consisted of 34 painful injections, with many side effects.”**
>
> **Poron Lokoler** *is a 15-year-old pastoralist and kala-azar survivor from Kalamrekai village, near Kacheliba, Kenya.*

Our long-term goal: All-new, oral treatments for leishmaniasis

With a strong consortium of R&D partners including the University of Dundee, Celgene (now part of Bristol-Myers Squibb), GSK, Pfizer, Takeda Pharmaceutical Company Limited, and TB Alliance, DND*i* is working to replace older, toxic, injectable leishmaniasis treatments with all-new, oral drugs that can both dramatically improve patients' lives and support efforts to control and eliminate the disease.

With financial support from the Global Health Innovative Technology Fund, Wellcome, and others, together with partners we have built an unprecedented portfolio of lead series and pre-clinical and clinical drug candidates for leishmaniasis.

In 2019, the consortium made significant progress advancing compounds in Phase I development in preparation for the first Phase II studies in patients. There are currently two new chemical entities in pre-clinical development and three undergoing Phase I safety studies in healthy volunteers. Complementing consortium R&D efforts, DND*i* initiated a collaboration and licence agreement with Novartis in early 2020 to jointly develop the first-in-class compound LXE408 as a potential new oral treatment for VL.

Better VL treatments in Eastern Africa

Patients need alternatives to the current double-injection standard treatment used for VL in East Africa – particularly children, who represent a high proportion of the population at risk. Following positive outcomes using the combination of oral miltefosine and paromomycin (MF+PM) in South Asia, DND*i* is now testing MF+PM in a Phase III study across seven sites in Ethiopia, Kenya, Sudan, and Uganda. Study enrolment was completed in May 2020, with 439 patients enrolled – more than 70% of whom were children. Study results are expected in mid-2021.

> ***“Our strategic investment to support DNDi's comprehensive programme for leishmaniasis builds on Wellcome's commitment to driving innovation that can transform the lives of people affected by devastating neglected diseases.”***
>
> ***Steve Caddick***
> *Director of Innovation, Wellcome*

HIV/VL co-infection: Building evidence for better treatment recommendations

People living with HIV have a 2,000 times greater risk of developing active VL. HIV also increases the severity of VL, increasing relapse rates and heightening the risk of death.

In search of a treatment solution, humanitarian organization MSF began using a compassionate regimen in Ethiopia in 2011, combining liposomal amphotericin B (LAmB), an injectable, with the oral drug miltefosine. Results were promising.

To provide the necessary scientific evidence, DND*i* and partners ran a Phase III study starting in 2014 to test this combination as well as LAmB alone, the treatment currently recommended by WHO. Results published in 2019 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.

DND*i* and the Rajendra Memorial Research Institute in India acted as technical partners in a second Phase III study sponsored by MSF to evaluate the combination in Bihar, and the last patient follow-up visit was completed in May 2019.

Results of the study in Ethiopia have been presented to national authorities, and guidelines are now under review at the national level to consider adopting the new combination treatment. At the international level, a WHO Guideline Development Group is expected to evaluate HIV/VL treatment recommendations in 2020.

> ***"Patients co-infected with HIV/VL are at high risk of treatment failure for VL – with fatal outcomes. The results of our Phase III trial with DNDi strongly support a recommendation of this combination regimen as the first-line strategy for safe and effective treatment of patients with HIV/VL in eastern Africa. "***
>
> ***Dr Rezika Mohammed***
> *Assistant Professor of Internal Medicine, Leishmaniasis Research and Treatment Centre, University of Gondar, Ethiopia*

> ***"Because PKDL is not fatal it has largely been ignored by public health efforts, but our research with DNDi shows that early treatment of PKDL patients will be a critical element of any leishmaniasis public health and elimination strategy. "***
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> ***Dr Dinesh Mondal***
> *Senior Scientist, International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)*

Post-kala-azar dermal leishmaniasis: The disease that strikes back

Patients can develop PKDL – skin lesions in the form of hypopigmented lesions (macules) and nodules – after successfully completing treatment for VL. Between 50% and 60% of people treated for VL in Sudan and between 5% and 10% of people treated for VL in South Asia develop PKDL.

PKDL lesions contain the same parasite that causes VL, and as a result may play a role in sustaining transmission of the disease from person to person. The results of an innovative 'infectivity' study conducted by DND*i* and the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) published in 2019 confirm that nodular and macular PKDL can be infectious to sandflies. To confirm the role of PKDL in infectivity in Eastern Africa, DND*i* is now preparing to carry out a similar study with our partners at University of Gedaref in Sudan.

> **“My son had to have injections at the health centre every day for 20 days.”**
>
> **Sirane and her son, Daniel**, *live in the rural area of Teolandia, Bahia, Brazil. Both were diagnosed and treated for CL.*

CUTANEOUS LEISHMANIASIS IN FOCUS

Combining existing tools for shorter, safer, more effective treatment

DND*i* is working to find safer, more effective CL treatments to replace current options that have been used for nearly 70 years despite their severe side effects. Using a combination of existing therapeutic approaches may improve efficacy and reduce both treatment duration and the rate of adverse events.

Preliminary results of DND*i*'s Phase II study completed in April 2019 show the combination of thermotherapy (applying heat to a patient's lesion) with a shorter course of oral miltefosine to be significantly better than thermotherapy alone for the treatment of uncomplicated CL in the Americas.

With financial support from Brazil's Ministry of Health and National Council for Scientific and Technological Development (CNPq), planning is now underway for a Phase III study of the combination at sites in Brazil, Peru, Bolivia, and Panama with DND*i*'s Brazilian research partner, the Oswaldo Cruz Foundation (Fiocruz).

> ***“We hope our research partnership with DNDi can confirm earlier positive results of a new treatment combination that could help improve the lives of people with cutaneous leishmaniasis in Latin America.”***
>
> ***Marcia Hueb***
> *Researcher and principal investigator of the Phase III CL study, Mato Grosso Federal University, Brazil*

Stimulating the immune system's response to fight infection

Together with partners GeneDesign and with financial support from Global Health Innovative Technology Fund, DND*i* is preparing to conduct the first clinical studies for a novel 'immune modulator' – CpG-D35 – for the treatment of complicated CL.

Leishmania parasites are able to persist in human cells by evading or exploiting immune mechanisms. CpG-D35 is being developed as a therapeutic 'booster' to promote the immune system's response to the parasitic infection that causes CL and improve the efficacy of existing drugs.