LEISHMANIASIS

Delivering safer, simpler treatments to save lives and reduce social stigma

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. Visceral leishmaniasis (VL) – also known as kala-azar – causes fever, weight loss, spleen and liver enlargement, and, if not treated, death. Cutaneous leishmaniasis (CL) leaves lifelong scars, mostly on the face, causing social stigma, particularly for women and children. Current treatments differ from region to region, but all either require hospital stays or complex infusions, or consist of drugs with serious side effects.

The push for progress

With our partners, DND*i* has developed improved VL treatments that are now part of national treatment guidelines in East Africa as well as South Asia, where elimination efforts have contributed to a sharp decline in cases. Additionally, we have replenished the R&D pipeline with an unprecedented portfolio of all-new potential drugs that could revolutionize treatment and accelerate progress towards global elimination goals. The Leishmaniasis East Africa Platform (LEAP), founded by DND*i* in 2003, has helped drive progress against the disease in Ethiopia, Kenya, Uganda, and Sudan. In 2014, we established redeLEISH, a network of CL experts working across 90 institutions in 20 countries to share know-how and to design and conduct vital clinical research.

Our goal is now to deliver safer, shorter treatments with existing drugs while developing new, all-oral combination treatments with new chemical entities (NCEs) that are safe, effective, and easier to manage at the primary healthcare level, with the aim of bringing prompt diagnosis and treatment closer to patients.

FACTS

600 M

people at risk of VL across the globe

600,000-1 M

new cases of CL each year

At least

100x

greater risk of developing active VL for people living with HIV

DNDi
Drugs for Neglected Diseases *initiative*

Photo credit: Sydelle Willow Smith-EDCTP

Worke Tafete, 18 years old, is from a village near Metemma, in northwestern Ethiopia. She and her two brothers were diagnosed with VL when she was 10 years old. Worke's 30-day treatment required hospitalization, which made her unable to attend school or help on her family's farm. Seven years later, she was diagnosed with post-kala-azar dermal leishmaniasis.

> “If my treatment was not so long and difficult, I wouldn't have had to miss school.

Advancing all-new, all-oral drugs to make treatment more accessible and more effective

In 2021, our teams made important progress in the development of NCEs that have the potential to dramatically improve the safety and efficacy of leishmaniasis treatment. Working with partners across the globe, particularly in leishmaniasis-endemic areas, we have advanced multiple candidates from the early stages of drug discovery to translational research, including Phase I and proof-of-concept studies.

With support from Wellcome, DND*i* is collaborating with Novartis on the joint development of LXE-408. Promising results from a Phase I study completed in 2021 suggest good tolerability and support progression to Phase II trials in India beginning in 2022. Phase I studies of DNDI-0690 were also completed in 2021, and a new tablet formulation better suited to use in the field is under development – with a view to launching proof-of-concept studies in 2023. Phase I studies continued for DNDI-6148 and GSK245/DDD1305143 (conducted by GSK).

This brings the total number of NCEs for leishmaniasis advancing in clinical trials to five – all with novel modes of action. With support from Japan's Global Health Innovative Technology (GHIT) Fund, DND*i*'s collaboration with Eisai Co., Ltd. on pre-clinical studies and optimization of a sixth NCE, DNDI-6174, also progressed in 2021.

Moving towards an improved standard of care for the treatment of VL in East Africa

Safer, simpler alternatives to the current standard treatment used for VL in East Africa are urgently needed – particularly for children, who represent up to 70% of the population at risk in the region. While a significant improvement over previous options, the current treatment requires two painful daily injections, as well as hospitalization for the entirety of the 17-day treatment period.

In 2021, our teams and partners completed a Phase III trial of the miltefosine and paramomycin (MF+PM) combination treatment across seven study sites in Ethiopia, Kenya, Sudan, and Uganda, collecting valuable data on treatment outcomes in both adults and children. Initial results from this study, conducted in partnership with the AfriKADIA consortium, appear very promising, indicating similar efficacy to the current treatment with one less painful injection each day and overall treatment duration reduced by three days. Notably, 70% of the 439 participants in the East Africa trial were children. Final results are expected to be published in 2022.

New hope for people living with both VL and HIV

People living with HIV are at least 100 times more likely to develop VL, and it is often more difficult to treat people living with both diseases as they do not respond well to standard treatments – facing more frequent and more severe side effects from treatment and higher risks of disease recurrence and death. Until now, the standard treatment for VL/HIV co-infection consisted of injections of liposomal amphotericin B (LAmB), with long periods of hospitalization and a relatively poor rate of recovery.

Studies conducted by DND*i* and partners in Ethiopia and by MSF and partners in India showed greater efficacy of combined treatment with miltefosine and LAmB (88% in Ethiopia, 96% India) than treatment with LAmB alone (55% in Ethiopia, 88% in India). Following the results of the studies, WHO's Guideline Development Group evaluated VL/HIV treatment recommendations for South Asia and East Africa. Revised WHO guidelines recommending the new combination regimen for both regions were released in June 2022, offering new hope for people living with both VL and HIV. India, Ethiopia, and other countries with high burdens of VL/HIV co-infection are expected to adapt their own treatment guidelines to include the new WHO-recommended treatment.

Post-kala-azar dermal leishmaniasis: Breaking the cycle of infection

Post-kala-azar dermal leishmaniasis (PKDL) – a complication of VL that appears as a rash or skin condition months or years after successful VL treatment – is not deadly but can be highly stigmatizing. Because PKDL can act as a reservoir for VL infection, early and effective PKDL treatment is critical to achieving sustained reductions in VL transmission. Our Phase II study in Sudan testing both LAmB in combination with miltefosine, and paromomycin in combination with miltefosine, completed enrolment and follow-up of all 110 participants in May 2021. A similar Phase II study conducted by DND*i* in India and Bangladesh to assess the safety and efficacy of LAmB monotherapy and a combination of LAmB and miltefosine for patients with PKDL completed two-year follow-up of study participants in April 2021. Final results for both studies are expected to be published in 2022. While preliminary results from these trials suggest improvements over previous standards of care, more needs to be done to meet the treatment needs of people living with PKDL and stop the cycle of VL transmission. CpG-D35, an immunomodulator used as an adjunct to drug therapy to fight parasitic infection that is being developed primarily for CL, could also play an important role in preventing the development of PKDL.

Boosting access to treatment in Eastern Africa

DND*i* kicked off the LeishAccess Project in 2021, with the aim of catalysing the use of new diagnosis and treatment options for all forms of leishmaniasis in five Eastern African countries: Ethiopia, Kenya, Sudan, South Sudan, and Uganda. The three-year project will work to increase national and regional support for new testing and treatment recommendations, and work to fill knowledge gaps through operational research on access to diagnosis and treatment in vulnerable communities.

Photo credit: Vinicius Berger-DNDi

Jonas de Jesus is a 38-year-old farm worker from Corte de Pedra, a rural area in Bahia, northeastern Brazil. He was diagnosed with cutaneous leishmaniasis (CL) 10 years ago but continues to fight the disease, having had to discontinue previous treatments that were long and painful. His wife, **Tatiele Maria de Jesus**, was successfully treated for CL after becoming ill when she was pregnant. But after she gave birth, Jonas sadly waited weeks to hold their baby boy for fear that he might transmit his infection to the newborn. The fear remained even after his doctor told him there was no such risk.

CUTANEOUS LEISHMANIASIS

Shorter, safer, more effective treatment to replace toxic antimonials

Current treatments for CL are costly, and often require weeks of painful injections of toxic drugs called antimonials. Despite their severe side effects, these drugs have been used to treat the disease for nearly 70 years.

Using a combination of existing therapeutic approaches that excludes antimonials may improve outcomes for patients and reduce both side effects and treatment duration. DNDi's Phase II study in 2019 showed that a combination of thermotherapy (applying heat to a patient's lesion) with a shorter course of oral miltefosine is significantly better than thermotherapy alone for the treatment of uncomplicated CL in the Americas. With these promising results, we initiated a Phase III study at four study sites in Brazil, Panama, and Peru in 2021 and obtained approval to initiate the study at a fifth trial site in Bolivia in 2022.

CpG-D35: Stimulating the immune system's response to fight infection

Leishmania parasites are able to persist in human cells by evading or exploiting immune mechanisms. Together with partners GeneDesign, an Ajinomoto company, and with financial support from Japan's Global Health Innovative Technology (GHIT) Fund, our teams are developing CpG-D35 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.

Following completion of pre-clinical toxicology studies in late 2020, clinical and pharmaceutical development of CpG-D35 continued in 2021, and we progressed to first-in-human clinical trials with a single ascending dose study completed in 2021. A multiple ascending dose study is planned for 2022.