



# LEISHMANIASIS

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



Over

600 M

people at risk of VL worldwide

600,000  
-1 M

new cases of CL every year

About

50%



of people infected with VL and CL are children

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. Leishmaniasis treatment depends on several factors including the form of the disease, parasite species, and geographic location. For decades, treatments have required long hospital stays and painful injections of toxic antimonial drugs, such as sodium stibogluconate.

## The push for progress

With our partners, DNDi has delivered **four improved VL treatments**, including two in 2022 alone (see page 18). We have also 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 DNDi in 2003, has helped drive progress against the disease in Kenya, Ethiopia, Uganda, and Sudan. In 2014, we established **redeLEISH**, a network of CL experts working across 90 institutions in 28 countries to share know-how and to design and conduct vital clinical research.

**Our goal is now** to ensure access to safer, shorter treatments with existing drugs in the near term. Over the longer term, we aim to develop all-new treatments with new chemical entities 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.



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I am hopeful that this time I will be cured completely and won't have to go through this again. I want to be a doctor to help people from my community who cannot access healthcare.

Tekla, 10 years old, sits with her mother, Grace, on the grass patches outside the Kacheliba Sub-County Hospital in Kenya. Tekla is undergoing treatment for visceral leishmaniasis for the second time in five years.

## An improved standard of care for VL in Eastern Africa

Safer, simpler alternatives to the current standard treatment for VL in Eastern Africa are needed – particularly for **children, who represent up to 70% of the population at risk in the region**. DNDi partnered with the AfriKADIA consortium to launch a Phase III study in Ethiopia, Kenya, Sudan, and Uganda in 2018 to compare the combination of miltefosine and paromomycin (MF+PM) against the current standard treatment, sodium stibogluconate and paromomycin (SSG+PM).

Results published in *Clinical Infectious Diseases* in September 2022 showed that treatment with MF+PM was as effective as SSG+PM, but with fewer injections, a shorter treatment duration, and no risk of SSG-related toxicity. Treatment with MF+PM also reduced the risk of people subsequently developing post-kala-azar dermal leishmaniasis (PKDL) – a critical factor in reducing community transmission of VL. The evidence generated in the Phase III trial is under review and is expected to guide new recommendations for VL treatment in Eastern Africa.

## PKDL: Breaking the cycle of infection

PKDL is a complication of VL that appears as a rash or skin condition months or years after successful VL treatment. Although it is not deadly, it can be highly stigmatizing.

**Early and effective PKDL treatment is critical to achieving sustained reductions in VL transmission**, because PKDL can act as a reservoir for VL infection. DNDi completed two Phase II studies in 2021, one in Sudan, testing liposomal amphotericin B (LAmB)+MF and MF+PM, and one in India and Bangladesh, testing LAmB monotherapy and LAmB+MF. The positive results of these studies will be published soon, bringing **evidence for alternative shorter, safer treatments** to replace the current 60- to 90-day antimonial treatment in Sudan and 12-week miltefosine monotherapy treatment in South Asia.

## TWO NEW THERAPEUTIC OPTIONS DELIVERED IN 2022

### More effective treatment for people living with visceral leishmaniasis (VL) and HIV

People living with HIV are at least 100 times more likely to develop VL and often respond poorly to standard VL treatment – resulting in a higher risk of VL recurrence and a higher risk of death. In 2011, Médecins Sans Frontières (MSF) began administering a treatment combining liposomal amphotericin B (LAmB) with the oral drug miltefosine to people with VL and HIV under compassionate use in an effort to improve treatment outcomes.

Following promising early results, DNDi and partners conducted a **Phase III study to assess LAmB as monotherapy and LAmB in combination with miltefosine** in Ethiopia, which faces a high burden of VL/HIV coinfection. **The new combination treatment was shown to have an 88% efficacy rate compared to 55% for LAmB alone.** A similar study led by MSF in India also showed the combination treatment to be more effective.

In June 2022, based on the results of these two studies, the World Health Organization (WHO) released new

treatment guidelines for the treatment of VL in people also living with HIV, recommending the new treatment combination, which is now also included in Ethiopia's national treatment guidelines.

### Safer, shorter treatment for people with VL in the Americas

Until recently, first-line treatment recommendations for VL in Latin America included the use of toxic antimonials that require lengthy hospitalization. To evaluate the efficacy and safety of other available treatment options compared to the standard treatment, the University of Brasília, together with DNDi, conducted a **multicentre, randomized, open-label, controlled trial at five sites in Brazil, sponsored by the Ministry of Health.** The study showed that with lower toxicity and acceptable efficacy, LAmB was **a more suitable first-line treatment for VL than the antimonial-based treatment.** In June 2022, based on final results from the trial, the Pan American Health Organization (PAHO) published new guidelines recommending LAmB as first-line treatment for VL in the Americas. The new recommendation must now be adopted in national guidelines.

## Progress towards all-new, all-oral drugs

In 2022, our teams and partners made significant advances in the development of entirely new chemical entities that have the potential to dramatically improve leishmaniasis treatment.

DNDi is collaborating with Novartis on the joint development of **LXE-408**, a first-in-class compound. After results from a Novartis Phase I study completed in 2021 showed good tolerability and exposure, the compound is **progressing to Phase II trials** sponsored by DNDi, with the first participant recruited in India in late 2022 and recruitment planned to start in Ethiopia in Q3 2023.

DNDi and partners completed a thorough evaluation of **DNDI-6899** (formerly GSK899/DDD853651) in 2022 and we are now prioritizing its development given the compound's unique mode of action as demonstrated through additional data generated by the University of Dundee. **Preparations for a Phase I multiple ascending dose study** of DNDI-6899 are expected to resume in 2023, following consultation with the UK Medicines and Healthcare Products Regulatory Agency.

In early 2022, DNDi completed a **Phase I single ascending dose study of DNDI-6148** and also completed a **Phase I evaluation** of the safety and pharmacokinetic properties of **DNDI-0690**. Based on data collected in the two studies, DNDI-6148 and DNDI-0690 have been deprioritized in favour of DNDI-6899.

DNDi's collaboration with Eisai Co., Ltd. on **DNDI-6174** the insertion also progressed in 2022, with the company manufacturing three batches of drug product for pre-clinical studies, drug product development, and future clinical trials. **Pre-clinical toxicology studies of the compound were also completed.**





“ If I could create the ideal treatment for my patients with cutaneous leishmaniasis, it would be a treatment that they can take at home.

Dr Juliana Quintero is a general physician and researcher working at PECET, the Programme for Study and Control of Neglected Diseases, in Medellín, Colombia. DNDi partners with PECET to advance R&D for new patient-friendly cutaneous leishmaniasis treatments that are affordable, safe, and effective for both children and adults.

Photo credit: Sydelle Willow Smith-DNDi

## CUTANEOUS LEISHMANIASIS

### Shorter, safer, more effective treatments to replace toxic antimonials

For nearly 70 years, treatments for cutaneous leishmaniasis (CL) have been costly and have often required weeks of painful injections of toxic drugs called antimonials. In 2019, DNDi conducted a Phase II study showing that a **combination of thermotherapy** – where heat is applied to a person’s lesions – **and a short course of miltefosine** was significantly better than thermotherapy alone in treating uncomplicated CL in the Americas.

Based on results from our Phase II study, we initiated a **Phase III study at four sites in Brazil, Panama, and Peru in 2021, and at a fifth site in Bolivia in 2022**. Enrolment continued throughout 2022 and will be completed in 2023.

### Stimulating the immune system’s response to fight infection

*Leishmania* parasites can persist in human cells by evading or exploiting immune mechanisms. Together with our partner Ajinomoto Bio-Pharma Services (GeneDesign, Inc.), our teams are developing **CpG-D35 (DNDI-2319) as a therapeutic ‘booster’ to promote the immune system’s insertion response against the parasitic infection** that causes CL and improve the efficacy of existing drugs.

DNDi completed a Phase I single ascending dose study in 2021. Results analysed in 2022 showed CpG-D35 to be safe and well tolerated after a single subcutaneous dose and supported **advancement to a multiple ascending dose study**. The study design, protocol, and other key documents were submitted to ethics authorities in late 2022 for review and approval, with the study due to start in Medellín, Colombia in 2023. DNDi is also exploring CpG-D35 for the important role it could play in preventing PKDL following VL infection.