TOWARDS A NEW GENERATION OF TREATMENTS FOR LEISHMANIASIS

New partnerships and
new R&D strategies

DNDi
Drugs for Neglected Diseases *initiative*

Mohamed Yahya Hamad and his wife Radina Adam Hamad seek medical advice for their son, Dooka, Sudan.

Leishmaniasis is a neglected tropical disease (NTD) that threatens an estimated one billion people worldwide. It is a complex disease that presents in several forms – visceral, cutaneous, mucocutaneous, and post-kala-azar dermal leishmaniasis – and is caused by 20 different *Leishmania* parasite species.

Treating leishmaniasis is difficult, as it depends on several factors, including the form of the disease, other co-existing infections, the parasite species, and geographic location, as treatment responses differ by region.

Existing treatments for leishmaniasis are long, toxic, and/or expensive, and are not adapted to patients or their contexts. An estimated 700,000 to 1 million new cases of leishmaniasis occur annually, with 20,000 to 30,000 deaths.[1]

The development of next-generation treatments for all forms of leishmaniasis in all regions is therefore a priority for the Drugs for Neglected Diseases *initiative* (DND*i*).

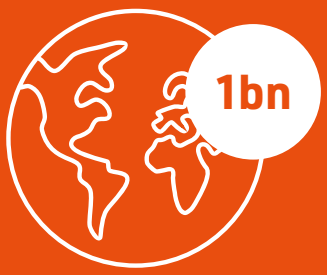
Existing treatments for leishmaniasis are long, toxic, and/or expensive, and are not adapted to patients or their contexts.

1 WHO (2018). Fact sheet: leishmaniasis. March 2018. Available at: http://www.who.int/news-room/fact-sheets/detail/leishmaniasis

FACTS ABOUT LEISHMANIASIS

700,000–1 million new cases every year

20,000–30,000 deaths annually



One billion people at risk across the globe

DND*i*'s research and development strategy for leishmaniasis is defined by patients' unmet needs and has a two-pronged approach: a short-term strategy based on the optimization of existing drugs to address immediate needs, and a long-term strategy to develop new chemical entities (NCEs) into effective, affordable, oral, short-course medicines to support the sustainable control or elimination of this neglected disease.

Though the past decade has seen improvements in the treatment, diagnosis, and prevention of leishmaniasis, particularly in South Asia, more research is needed to sustain these advances and to support efforts in other parts of the world.

The WHO roadmap for NTD elimination published in 2012,[2] supported by the London Declaration[3] the same year, targets the elimination of visceral leishmaniasis as a public health problem by the end of 2020 in South Asia (India, Bangladesh, and Nepal). Though the past decade has seen improvements in the treatment, diagnosis, and prevention of leishmaniasis, particularly in South Asia, more research is needed to sustain these advances and to support efforts in other parts of the world, particularly East Africa and Latin America, to achieve similar results.

To this end, and following its long-term strategy, DND*i* is currently progressing promising compounds through the development pipeline, establishing collaborations with the pharmaceutical industry, biotechnology companies, academia, and other product development partnerships (PDPs). Based on promising leads, it is hoped that the coming years will see the introduction of new field-adapted leishmaniasis treatments that respond to patients' needs.

In the meantime, DND*i* is working with researchers at partner organizations to answer scientific questions such as the role of post-kala-azar dermal leishmaniasis (PKDL) and asymptomatic cases as 'reservoirs' for sustaining transmission of the parasite that causes visceral leishmaniasis, which could jeopardize control and elimination efforts. DND*i* is also building and consolidating clinical research capacity in endemic countries by supporting regional disease research platforms.

2 WHO (2012). Accelerating work to overcome the global impact of neglected tropical diseases – A roadmap for implementation. Available at: http://unitingtocombatntds.org/wp-content/uploads/2017/11/who_ntd_roadmap.pdf

3 On 30 January 2012, pharmaceutical companies, donors, endemic countries and nongovernmental organizations came together to sign the London Declaration on Neglected Tropical Diseases. Together, they committed to control, eliminate or eradicate 10 diseases by 2020 and improve the lives of over a billion people. Available at: https://unitingtocombatntds.org/wp-content/uploads/2017/11/london_declaration_on_ntds.pdf

A global disease with many forms

Treatment responses vary by region

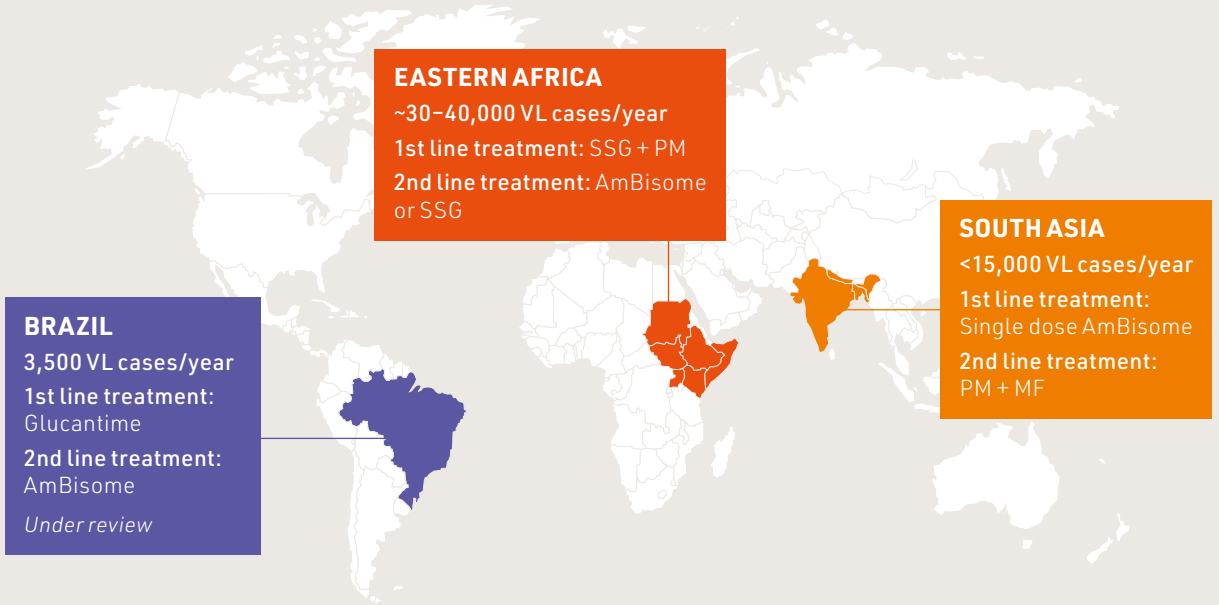
Caused by more than 20 species of the *Leishmania* parasite, leishmaniasis is a complex disease that presents in different forms. The disease is strongly associated with poverty and remains endemic in 98 countries across Latin America, Africa, and other regions, putting at risk a total of one billion people across the globe.[4]

Leishmaniasis breaks out in "foci", concentrated geographic areas, and is transmitted by the bite of a sand fly. An estimated 700,000 to 1 million new cases of the disease in its various forms occur annually, with an estimated number of 20,000 to 30,000 associated deaths.[5]

Treatment of leishmaniasis is difficult, as it depends on several factors, including the form of the disease, other co-existing infections, and the species of parasite. Treatment effectiveness also differs from region to region.

The disease is strongly associated with poverty and remains endemic in 98 countries.

TREATMENT RESPONSES VARY BY REGION, AND THEREFORE RECOMMENDED TREATMENT REGIMENS FOR VISCERAL LEISHMANIASIS ALSO DIFFER



4 *Op. cit.* 1
5 *Op. cit.* 1

VISCERAL LEISHMANIASIS: FATAL IF NOT TREATED

Visceral leishmaniasis (VL), also known as kala-azar, is deadly if not treated. Characteristically, the disease causes fever, weight loss, enlarged spleen and liver, and anaemia. Cases of VL are often mistaken for malaria.

Until recently, pentavalent antimonials, either sodium stibogluconate (SSG) or meglumine antimoniate (MA), were the mainstay of treatment, despite high cardiac, hepatic and renal toxicity. In the last decade, new drugs were developed, including liposomal amphotericin B (AmBisome), the oral drug miltefosine (MF), and the injectable paromomycin (PM), giving improved treatment options. However, even the more recent treatment options remain suboptimal, as they are too long, toxic and/or expensive.

VL

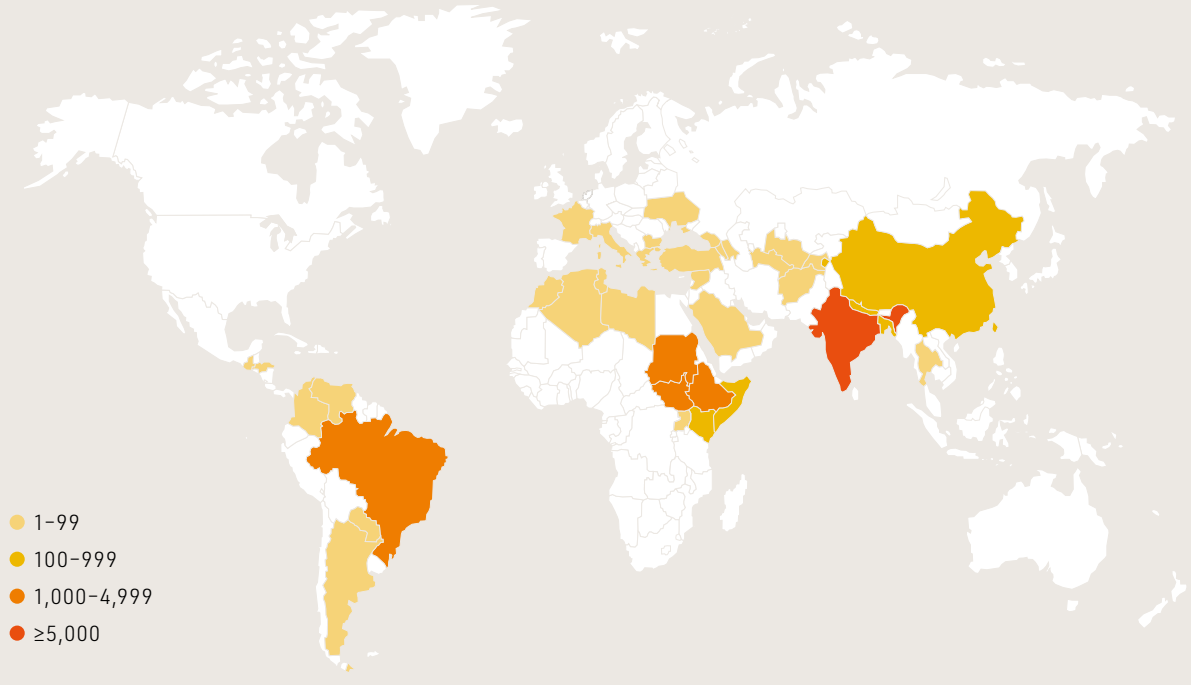
Over 600 million people at risk of VL infection

50,000-90,000 new cases worldwide each year[6]

Over 50% of patients in India, Sudan, and Brazil are children

More than 90% of new cases occur in seven countries[7]

GEOGRAPHICAL DISTRIBUTION OF NEW VISCERAL LEISHMANIASIS CASES IN 2016[8]



6 WHO (2017), Unveiling the neglect of leishmaniasis. Available at: http://www.who.int/leishmaniasis/Unveiling_the_neglect_of_leishmaniasis_infographic.pdf?ua=1

7 Burza S, Croft SL, Boelaert M (2018). Leishmaniasis. Seminar. *Lancet*. 2018;392:951–70. Available at: https://www.thelancet.com/action/showPdf?pii=S0140-6736%2818%2931204-2

8 WHO (2018). *Weekly Epidemiological Record*, No. 40, 5 Oct. 2018. Available at: http://apps.who.int/iris/bitstream/handle/10665/275333/WER9340.pdf?ua=1

POST-KALA-AZAR DERMAL LEISHMANIASIS: THE DISEASE THAT STRIKES BACK

Post-kala-azar dermal leishmaniasis (PKDL) is a non-lethal complication of VL that has been clinically and epidemiologically neglected, partly because many affected people do not seek treatment due to the difficulty in recognizing and diagnosing the disease. PKDL can develop months or years after VL treatment has concluded and can be severely disfiguring, as the symptoms are characterized by a skin rash that is usually on the face and may last for months or years.

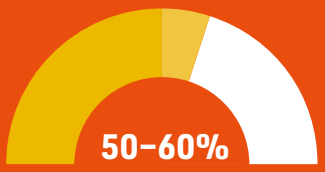
PKDL is most common in Eastern Africa (mainly Sudan) and Asia, though it differs epidemiologically and clinically in each region. Unlike VL, PKDL is not life-threatening. However, untreated PKDL may act as a "reservoir" for ongoing infection by transmitting parasites to sand flies that bite affected individuals, thus potentially jeopardizing elimination efforts, notably in the South Asia region. As a result, diagnosing and treating PKDL may be important not only for individual patient management but also to prevent VL outbreaks.

PKDL patients are treated with the same anti-leishmanial drugs as VL patients, but treatment duration is longer. In Sudan, for example, current practice is treatment with pentavalent antimonials (SSG) for 40 to 60 days or even longer, administered parenterally once a day in a hospital setting.

PKDL

5–10%

In Asia, 5–10% of people who have had VL develop PKDL



50–60%

In Africa, PKDL occurs in 50-60% of VL cases[9]

When Ruby Devi, 20, moved with her husband from India's poorest state, Bihar, to Delhi, she thought that her ordeal with VL, known in India as kala-azar, was over. Previously, she had fallen ill with the disease, suffering from fever and weight loss, but received life-saving treatment and got cured. Two years later, living in the capital, she became pregnant and began to notice skin rashes and spots on her face that wouldn't go away. When they spread to cover her entire body, she went to see a doctor who diagnosed her with PKDL, a skin condition that can develop a few months or even years after someone has successfully completed treatment for kala-azar. For Ruby, leishmaniasis struck back.

Photo: Kishore Pandit/DNDi

9 WHO (2012). Post-kala-azar dermal leishmaniasis: a manual for case management and control. Report of a WHO consultative meeting, Kolkata, India, 2–3 July 2012. Available at: http://apps.who.int/iris/bitstream/handle/10665/78608/9789241505215_eng.pdf?sequence=1

Photo: Kishore Pandit/DNDi

> "I felt ashamed of myself and didn't feel like going anywhere. People around laughed at me with sarcasm and sometimes hatred. I felt humiliated because of these scars on my face."
>
> Ruby Devi, PKDL patient diagnosed when seven-month pregnant, New Delhi, India

HIV/VL: DOUBLE NEGLECT

VL has emerged as an important opportunistic infection associated with HIV, and the interaction of the two diseases is a major threat to VL control. People living with HIV are more susceptible to active VL, whether they are prior asymptomatic carriers of *Leishmania* infection who become symptomatic or due to new VL infections. VL infection can accelerate the onset of AIDS. There are also concerns that HIV/VL co-infected patients have particularly high levels of the *Leishmania* parasite and therefore may also play an important role in the ongoing transmission of VL.

HIV/VL patients require special care, as they tend to respond poorly to standard VL treatment and face an increased risk of death. Current VL treatment for people living with HIV is most often liposomal amphotericin B (AmBisome), given at a higher-than-usual dose.

HIV/VL

x100–2,320

The risk of developing active VL is 100 to 2,320 times greater in people living with HIV[10]

35 countries have reported cases of HIV/VL co-infection

15–30%

15-30% of VL cases in Ethiopia occur in people living with HIV[11]

10 WHO (no date). Leishmaniasis and HIV coinfection. Available at: http://www.who.int/leishmaniasis/burden/hiv_coinfection/burden_hiv_coinfection/en/

11 *Id.*

CUTANEOUS LEISHMANIASIS: HIGHLY STIGMATIZING BUT NON-LETHAL, AND NEGLECTED AS A RESULT

Cutaneous leishmaniasis (CL) is the most common form of leishmaniasis, but because it is not fatal, it receives little attention from R&D and public health efforts. The disease is characterized by skin lesions, which in the most complicated forms become chronic, debilitating, and disfiguring, causing severe social stigma and economic loss.

Mucocutaneous leishmaniasis (MCL) is considered to be a subset of CL and can occur several months or even years after skin ulcers heal. Lesions can lead to partial or total destruction of the mucosal membranes of the nose, mouth, and throat cavities and surrounding tissues, resulting in social stigma. MCL never heals on its own and must therefore be treated.

Pentavalent antimonials, either SSG or MA, are the most often recommended and frequently used treatment worldwide and have been the drugs of choice for more than six decades despite their toxicity. Unsurprisingly, treatment compliance is very low due to adverse events and poor tolerance. These drugs are contraindicated in pregnant and breastfeeding women, patients with cardiac, renal or hepatic problems, and patients with suppressed immune systems. The effectiveness of antimonials varies from 50-90% depending on the region and the infecting parasite species, disease severity, and the immunological status of the patient.

CL

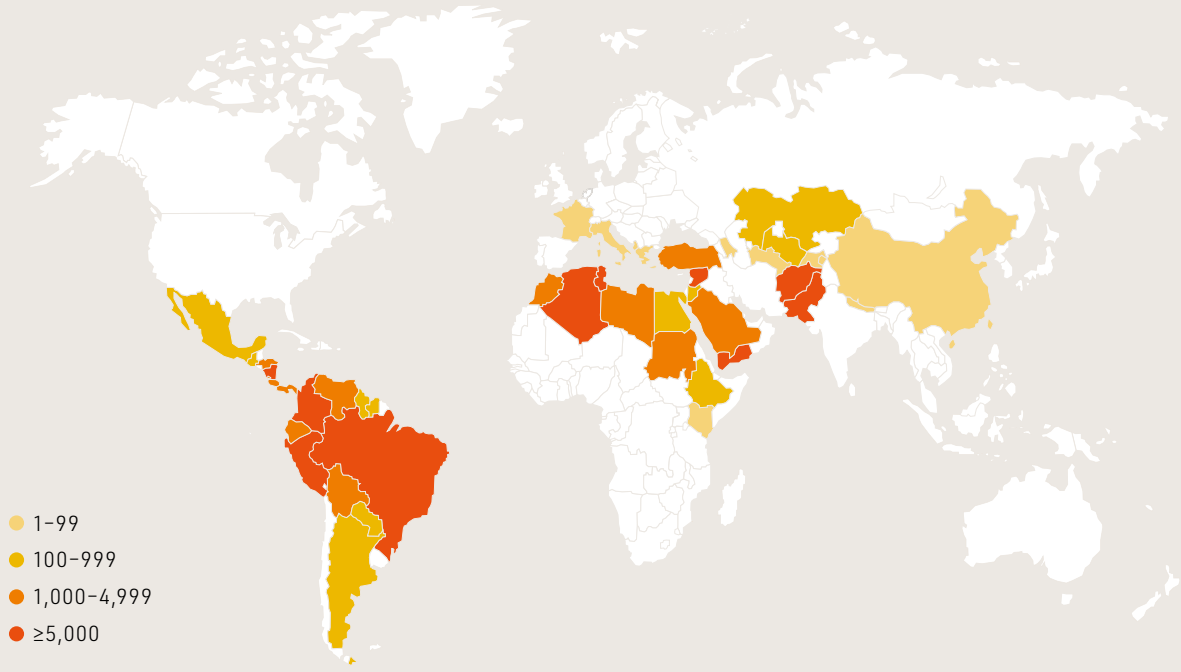
600,000–1m

CL affects from 600,000 to 1 million people annually[12]

Afghanistan
Algeria
Brazil
Colombia
Iran
Syria

Up to 70% of the world's cases occur in just six countries

GEOGRAPHICAL DISTRIBUTION OF NEW CUTANEOUS LEISHMANIASIS CASES IN 2016[13]



12 *Op. cit.* 1
13 *Op. cit.* 8

How to achieve and sustain elimination of VL in South Asia

Outstanding research questions still need answering

Three countries in South Asia (Bangladesh, India, and Nepal) that were once highly endemic for VL are poised to eliminate the disease as a public health problem by 2020. Efforts have resulted in a sharp decrease in the number of new cases. In 2012, 1,902 cases were reported in Bangladesh, and five years later there were just 255. In India, the reported number of cases dropped from 20,572 to 6,249, and in Nepal, 231 cases occurred in 2017, down from 575 in 2012.

Two factors contributed to this dramatic shift:

- **Increased commitment from countries:** In 2005, Bangladesh, India and Nepal launched a regional VL elimination initiative supported by the World Health Organization (WHO). The aim of this partnership was to reduce cases to less than one case per 10,000 people every year at the district or sub-district level. The strategy focused on early diagnosis and treatment of the most vulnerable populations, together with stronger disease and vector surveillance and control.

- **Improved treatment options:** The new treatment options developed over the past 10-15 years, and the results from an effectiveness study conducted by DND*i* and partners, were instrumental in providing the evidence that led Indian national control programmes to recommend the use of a shorter, safer and more effective treatment option for VL patients (first- and second-line treatment options of single-dose liposomal amphotericin B (LAB) and a combination of MF-PM, among other interventions).

However, to prepare for and sustain VL elimination in South Asia, funding is still needed for research to answer important outstanding research questions, including: better understanding the precise role in *Leishmania* transmission played by PKDL and asymptomatic infections; how best to respond when a new case is identified in an area where leishmaniasis was under control; and identifying predictive markers that can anticipate evolution to active VL and PKDL, and the likelihood of treatment failures or relapses. Any new evidence in these areas would also help to further define the needs for safer oral formulations for new treatments in South Asia.

Photo: Kishore Pandit/DND*i*

“Our kala-azar ward used to be full of patients because of the long 28-day treatment. Since single-dose AmBisome has been included in the national treatment protocol, the face of the disease has changed dramatically. Now patients come, take treatment, and go home the same day. With this, the number of patients has drastically come down.”

Nutan Kumari, nurse in-charge at the kala-azar ward, Sadar Hospital, Hajipur, Bihar State, India.

DND*i*'s strategy

The search for short-course, safe, effective, affordable, and context-appropriate oral treatments

Long-term strategy: **Develop new, context-appropriate oral combination treatments with new chemical entities** by collaborating with the pharmaceutical biotechnology industries, academia, and other PDPs.

Short-term strategy: **Improve treatments with existing drugs** through combination therapies; overcome the barriers to affordability; and reduce treatment duration, the burden on health systems and patients, and the risk of drug resistance.

RESEARCH			TRANSLATION			DEVELOPMENT		IMPLEMENTATION
Screen	Hit to lead	Lead Opt.	Pre Clinical	Phase I	Phase IIa/PoC	Phase IIb/III	Registration	Access
Screening	Leish H2L – Booster H2L – Daiichi-Sankyo LH2L	DNDI-5421 DNDI-5610 – Amino pyrazoles – CGH VL Series 1 – Leish L205 Series	DNDI-6148 – DNDI-0690 – DNDI-5561 – GSK 3186899 DDD 853661 – GSK 3494245 DDD 1305143 – CpG-D35 (CL)		New CL Combination	New Treatments for HIV/VL – New Treatments for PKDL – MF/PM Combo for Africa	New VL Treatments Latin America	SSG&PM Africa – New VL Treatments Asia

DND*i*'s objectives for leishmaniasis are to develop next-generation treatments for VL, CL, PKDL and HIV/VL, and to build successful regional research platforms and consortia to facilitate clinical studies and increase endemic country research capacity. To this end, DND*i* employs a two-pronged strategy (see table above).

DND*i* has now developed a strong R&D portfolio for leishmaniasis, with a total of 21 projects ongoing for various forms of leishmaniasis across the different stages of drug development, of which 19 projects are for VL.

For short-term treatment solutions, the final cycle of studies to assess combination treatments using existing drugs is underway for VL, CL, HIV/VL, and PKDL.

In terms of new drug development, there is a robust portfolio of drug candidates from different chemical classes and mechanisms of action in the early phases of development. Four new compounds are ready to enter first-in-human studies, and a novel therapeutic approach with the pre-clinical development of an immunomodulator for CL is ongoing.

SHORT-TERM STRATEGY: IMPROVING TREATMENTS WITH EXISTING DRUGS

DND*i*'s short-term strategy for leishmaniasis in the past decade has focused on improving treatments using existing drugs as monotherapy or in combination to improve their efficacy and safety, and to reduce long regimens to short-course or even single-dose regimens. As a result, new VL regimens have been developed and adopted in World Health Organization (WHO) and national treatment guidelines (see right).

By 2020 to 2021, it is expected that all the following studies assessing new regimens using existing drugs will be completed – and, it is hoped, translated into national policy changes for improved treatment regimens.

2010 | DND*i* delivers sodium stibogluconate & paromomycin (SSG&PM) combination therapy to treat VL in **Africa**

2014 | DND*i* delivers single-dose liposomal amphotericin B (LAB) and miltefosine–paromomycin (MF-PM) to treat VL in **Asia**

VL

A Phase III clinical trial testing a new combination therapy of MF-PM is underway in both paediatric and adult patients in Ethiopia, Kenya, Sudan, and Uganda.

This study is also assessing diagnostic tools and is being conducted within the context of the new 10-partner AfriKADIA Consortium (www.afrikadia.org) with funding from the European & Developing Countries Clinical Trials Partnership (EDCTP) – part of the EDCTP2 programme supported by the European Union under Horizon 2020, its Framework Programme for Research and Innovation.

PKDL

Two Phase II trials are testing AmBisome monotherapy, and a combination of AmBisome and MF in India and Bangladesh, and AmBisome in combination with MF, and a combination of MF-PM in Sudan.

Two studies in Bangladesh and Sudan aim to establish: the infectivity of macular and nodular forms of PKDL to sand flies; the infectivity according to the duration of PKDL infection; and quantification of the parasite burden capable of infecting sand flies. This will help to determine whether PKDL patients contribute to maintaining inter-epidemic transmission of VL. If confirmed, early treatment of PKDL patients would become a critical element of any public health and VL elimination strategy.

HIV/VL

The development of better treatment for HIV/VL is in progress, with promising results from a Phase III trial testing a combination therapy of AmBisome and MF.

Results of a Phase III study were presented to Ethiopian authorities and WHO in Addis Ababa, Ethiopia in June and December 2017 to promote the AmBisome and MF combination as a more effective first-line treatment for HIV/VL co-infected patients, using the strategy of one or two treatment cycles. A paper to be published in late 2018 will start discussions with other stakeholders to support new recommendations for treating VL in people living with HIV.

In India, DND*i* is providing support for a Phase III study sponsored by MSF and started at the Rajendra Memorial Research Institute in Bihar in 2017 to evaluate AmBisome monotherapy and AmBisome in combination with MF for HIV/VL co-infection. Recruitment of 150 patients has been completed, and results will inform the national road map of kala-azar elimination in India.

CL

A Phase II clinical trial using a combination of therapeutic approaches (thermotherapy and oral treatment) is currently being conducted in Peru and Colombia.

A combination of one single application of thermotherapy at 50°C for 30 seconds with a three-week course of oral MF for uncomplicated CL cases is being tested, to demonstrate whether this combination may improve treatment effectiveness, and reduce treatment duration and the rate of adverse events of current CL treatments.

In 2011, a Phase IV study sponsored by the Brazilian Ministry of Health (FINEP) tested the efficacy and safety of Amphotericin B deoxycholate, AmBisome, and a combination of AmBisome and Glucantime, in comparison to Glucantime monotherapy, the first-line VL treatment. Brazilian national guidelines for VL were revised in 2013 based on the interim safety data from this trial, with AmBisome replacing Amphotericin B deoxycholate as the second-line treatment, though Glucantime remained the first-line treatment. FINEP is now reviewing its policy with regard to the adoption of AmBisome as first-line treatment for VL in Brazil.

LONG-TERM STRATEGY: DEVELOPMENT OF NEW FIELD-ADAPTED ORAL COMBINATION TREATMENTS WITH NEW CHEMICAL ENTITIES

Although new treatments issuing from DND*i*'s short-term strategy have brought improvements over pentavalent antimonial monotherapy, new treatments should ideally be safer, more effective, more affordable and shorter-course oral combination therapies that are easier to use in difficult and remote settings. To address this need, DND*i* defined the characteristics of an optimal treatment in its target product profile (TPP) and developed a long-term strategy based on the discovery and the development of entirely new chemical entities (NCEs).

The underlying objective of DND*i*'s long-term strategy is to contribute to the sustainable elimination of VL in South Asia (see p. 9), and disease control in Eastern Africa and Latin America, and the control of CL. The strategy supports the WHO VL elimination framework that identifies partnership-building, and clinical and operational research as three of the five key strategies for achieving VL elimination goals, and WHO's objective of detection and treatment of CL patients.

> **"Our main demand is for new treatments, for research and innovation in medicines."**
>
> Moacir Zini, father of two and a CL patient for the past 27 years, Ipiranga do Norte, in the state of Mato Grosso, Brazil. He has gone through countless treatments and suffered greatly from drug toxicity, including a heart attack, loss of one kidney, and high blood pressure. He continues to relapse.

Photo: Mariana Abdalla/DND*i*

UNPRECEDENTED PORTFOLIO OF PROMISING NEW COMPOUNDS

DND*i*'s recent efforts to develop modern treatments for leishmaniasis through its discovery pipeline are bearing fruit.

DND*i* and its partners (GlaxoSmithKline (GSK), the Drug Discovery Unit (DDU) and Wellcome Centre for Anti-Infectives Research at the University of Dundee, Novartis, Pfizer, Takeda and Celgene) have built an unprecedented portfolio of ten new chemical classes (four lead series, four pre-clinical candidates, and two clinical candidates) with different mechanisms of action against *Leishmania* parasites.

This pipeline provides a strong basis for advancing towards one or more new oral therapies for both visceral and cutaneous leishmaniasis, and it provides back-up options to overcome attrition in development.

In 2017, one new compound from the aminopyrazole class, DNDI-5561, developed with Takeda, was nominated for pre-clinical development. In addition, GSK, the University of Dundee DDU, and DND*i* entered into an agreement for the pre-clinical development of two compounds developed by the DDU-GSK collaboration, one an inhibitor of CRK12, DDD53651/GSK3186899 and one from the proteasome inhibitor class DDD01305143/GSK3494245.

This collaboration builds upon the successful previous bilateral relationships between the three organisations and will enable prioritisation and focus on the most promising series in the pipeline, sharing of expertise and experience, and pooling of resources to maximise productivity and avoid duplication of effort.

Two other compounds from the oxaborole and nitroimidazole classes, respectively – DNDI-6148 (developed by DND*i*, based on a "hit" molecule from Anacor, now Pfizer) and DNDI-0690 (developed by DND*i* after its discovery in a collaboration with the University of Auckland) – have completed pre-clinical development, with preparations underway for Phase I clinical studies in 2018 and the potential for drug candidates for both visceral and cutaneous leishmaniasis.

More specifically for CL, one of DND*i*'s long-term strategies is based on a novel therapeutic approach. The objective is to test the hypothesis that chemotherapy alone does not kill 100% of reinvading parasites and that by stimulating the innate immune system with a new drug, the host's immune system will eliminate remaining parasites in patients with numerous or large lesions.

This is a different approach from current CL treatment recommendations for CL that could provide a major step forward over existing monotherapies or combination therapies targeting only the parasite. CpG-D35 is the immunomodulator that is expected to reach Phase I by early 2020.


Photo: Paul Kamau/DND*i*

Collaborative approaches to sustain a strong drug development pipeline

Open access and drug discovery

DND*i*'s model is based on partnerships and collaborations in all phases of drug research and development. In the very earliest stages of drug discovery, from molecule screening through to lead selection and optimization, this collaborative work takes place through key partnerships and drug discovery consortia. DND*i* is working with drug development consortia on hit-to-lead and lead optimization for VL with partners in Australia, Brazil, Canada, China, Europe, India, Japan, Korea, and the US.

Since 2015, DND*i* has also been exploring open innovation approaches to drug discovery, through which a variety of partners collaborate without the restraints of intellectual property.

These open innovation approaches range from working with university chemistry teaching labs to joining a virtual Open Pharma community that supports the lead optimization of compounds that could one day become new drugs.

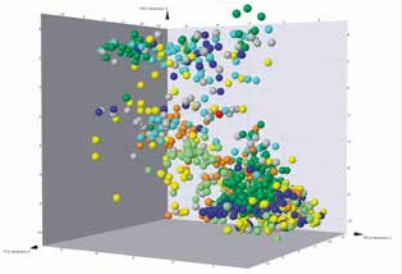
DND*i*'s model is based on partnerships and collaborations in all phases of drug research and development.

THE NTD DRUG DISCOVERY BOOSTER: ACCELERATING DRUG DISCOVERY AND CUTTING COSTS

The "Neglected Tropical Diseases Drug Discovery Booster" consortium was launched in 2015 to accelerate, expand, and cut the costs of early-stage discovery of new drugs for leishmaniasis and Chagas disease. This experiment initially brought DND*i* together with six pharmaceutical companies (Astellas Pharma Inc, Eisai Co Ltd, Shionogi & Co Ltd, Takeda Pharmaceutical Company Limited, AstraZeneca plc., and Celgene Global Health). In 2017, two new members – AbbVie and Merck – signed on to the Drug Discovery Booster to bring the total to eight companies.

Through a multilateral, simultaneous search process across participating companies, DND*i* can access compounds generated over many decades of research. State-of-the-art technology is used to pinpoint compounds that have promising characteristics that merit further testing. The innovation lies not only in the multilateral approach, but also in the iterative nature of the search, meaning companies will continually examine their libraries for better matches as the search is refined.

In its three years of operation, the Booster has already saved tens of thousands of dollars in compound synthesis costs and has sped up the drug discovery process by an estimated two or three times. To date, the Booster has already been applied to 17 series and resulted in four series moving into *in vivo* infection models for further assessment.



The chemical universe around a DND*i* lead molecule (the red dot) is explored through sharing of molecules from the chemical databases of each NTD Booster partner (each colour represents a partner).

THE OPEN SYNTHESIS NETWORK: HARNESSING THE CAPACITIES OF CHEMISTRY TEACHING LABS

Launched in 2016, the Open Synthesis Network (OSN) is a collaborative project that aims to engage master's and undergraduate students in research for neglected diseases. OSN today includes 18 participating institutions in Brazil, Germany, India, Switzerland, the UK, and the US.

The OSN process works by DND*i* sharing data on existing compounds from one of its active research projects with all OSN participants, along with a list of new, 'wanted' chemical compounds. Students can then explore the existing data, understand the design rationale for the new compounds through open discussion with DND*i* experts, and carry out the synthesis for one or more of these 'wanted' compounds as part of their lab training. Students can also opt to use the data to make their own designs for new compounds. DND*i* will then test all new compounds for anti-parasitic activity, sharing the results openly with all OSN participants. Any successful compounds that come from the OSN project will be evaluated further as part of DND*i*'s discovery pipeline.

Any successful compounds that come from the OSN project will be evaluated further as part of DND*i*'s discovery pipeline.

Students are currently working on compounds that kill *Leishmania donovani* and *Leishmania infantum*, the parasites that cause VL.

Adam Abdalla with his 6-year old son Mohammed Adam, affected with both malaria and visceral leishmaniasis, in their village in Dooka, North Western Sudan.

Photo: Abraham Ali/Imageworks/DND*i*

Six-year-old Mohamed was a playful child until he became feverish and weak. Not knowing what was wrong, his parents fed him bananas and chicken because they hoped this food would make him better. However, his condition worsened, so his parents took him to a hospital in their village in Dooka, North Western Sudan. Health workers at the hospital referred Mohamed to the Prof. El Hassan Centre for Tropical Diseases – a leishmaniasis treatment centre built with DND*i*'s support. At the Centre, Mohamed was diagnosed with both malaria and kala-azar (visceral leishmaniasis). He stayed in the hospital for 26 days, first receiving malaria treatment and then SSG&PM, a treatment developed by DND*i* to treat kala-azar.

Consolidating capacity for clinical research in endemic countries

Working through regional disease platforms and networks

Photo: Paul Kamau/DNDi

Conducting clinical trials for neglected diseases often means that research must be done in some of the most remote areas where there is little infrastructure of any kind, yet alone health infrastructure, and where there may also be political instability. Carrying out clinical research that meets international standards of quality in such conditions is possible, and necessary, but it requires adequate infrastructure, trained staff, specialized ethics committees, and well-functioning regulatory authorities.

Since its inception in 2003, DND*i* has worked to integrate capacity strengthening in all projects in a sustainable manner. As an integral part of its model, R&D regional research platforms form part of a broader, positive trend of research networks that incorporate North-South and more importantly, South-South collaborations.

Their objectives are to:

- Bring together key regional actors in health fields (e.g., representatives of health ministries, national control programmes, regulatory authorities, academia, civil society groups, and pharmaceutical companies, as well as clinicians and health professionals) to share experiences, knowledge, and problem-solving techniques;
- reinforce and build on existing clinical capacities in endemic regions, and address infrastructure needs where necessary;
- provide on-site training in clinical research in sometimes remote settings;
- be operational in the conduct of clinical trials.

These platforms also have an advocacy role to play at community, national, and international levels. As representatives of countries most affected by neglected diseases, they have the legitimacy to showcase the plight of what patients endure and how best to meet their urgent needs.

redeLEISH

The redeLEISH Network brings together leishmaniasis experts in Latin America to increase collaboration and maximize existing resources and expertise in areas where serious gaps exist.

The network enables the exchange of technical and scientific knowledge among participants.

The network promotes the sharing of information on treatment, diagnosis, and development of clinical trial design for cutaneous leishmaniasis. It also enables the exchange of technical and scientific knowledge among participants, and it contributes to the implementation of strategic policies and research priorities. Through the mapping of possible research centres and the implementation of training in Good Clinical Practice, redeLEISH also strengthens institutional capacity for clinical research. redeLEISH comprises more than 139 representatives from over 62 institutions in eight Latin American countries (Bolivia, Brazil, Colombia, Guatemala, Mexico, Panama, Peru, Venezuela).

A web forum facilitates the exchange of information and technical discussions to support the implementation of clinical trials in the region.

It was created in 2015 as a virtual tool to integrate its members and to promote dialogue among them, as well as to update the progress and implementation of clinical trials, provide documents and publication sharing and generate discussions on the challenges in the development of and access to treatments for CL.

redeLEISH
Network of Investigators and Collaborators in Leishmaniasis

LEISHMANIASIS EAST AFRICA PLATFORM

Launched by DND*i* in 2003, the Leishmaniasis East Africa Platform (LEAP) aims to strengthen clinical research capacity, which is lacking in part due to the remoteness and geographic spread of the patients, most of whom live in the most impoverished regions of Africa.

The platform also is a base for ongoing educational cooperation between the countries in the East African region and standardization of research procedures and practices within the region, to the extent possible.

Over the years, LEAP has trained clinical trial site teams (120 people were trained in 2017), upgraded site infrastructure, and fortified treatment access initiatives across the region.

LEAP comprises more than 62 members from over 20 institutions coming from four member countries: Ethiopia, Kenya, Sudan, and Uganda. In its new phase, known as LEAP 2.0, LEAP hopes to extend membership to other endemic countries such as South Sudan, Somalia, and Eritrea.

LEAP
LEISHMANIASIS
EAST AFRICA PLATFORM

Photo: Abraham Ali/Imageworks/DND*i*

“LEAP has developed me as a researcher over the years. I acquired leadership skills and because of this the University of Khartoum selected me to direct the Institute of Endemic Diseases due to my six-year tenure as a Chairperson of LEAP. I was also exposed to the scientific community when I received a scholarship through DND*i* to study at the London School of Hygiene & Tropical Medicine. Through this exposure I have acquired a desire to mentor others as researchers in the field of endemic diseases.”

Prof. Ahmed Musa, Director, Institute of Endemic Diseases, University of Khartoum, Sudan

DNDi
Drugs for Neglected Diseases *initiative*

15 Chemin Louis-Dunant
1202 Geneva, Switzerland
Tel: +41 22 906 9230
Fax: +41 22 906 9231
Email: dndi@dndi.org

www.dndi.org

facebook.com/dndi.org
linkedin.com/company/dndi
twitter.com/dndi
youtube.com/dndiconnect
instagram.com/drugsforneglecteddiseases
Subscribe to DND*i*'s newsletter:
www.dndi.org/newsletter

DND*i* AFRICA
Tetezi Towers, 3rd Floor, George Padmore Road, Kilimani,
P. O. Box 21936-00505, Nairobi, Kenya | Tel: +254 20 3995 000

DND*i* DRC
Avenue Milambo, no.4, Quartier Socimat, Commune
de la Gombe, Kinshasa, Democratic Republic of the Congo
Tel: +243 81 011 81 31

DND*i* INDIA
PHD House, 3rd Floor, 4/2 Siri Institutional Area,
New Delhi 110016, India | Tel: +91 11 4550 1795

DND*i* JAPAN
3F Parkwest Bldg, 6-12-1 Nishi-Shinjuku, Shinjuku-ku,
Tokyo 160-0023, Japan | Tel: +81 (0)3 4550 1199

DND*i* LATIN AMERICA
Rua São Jose, 70 – Sala 601 20010-020 Centro,
Rio de Janeiro, Brazil | Tel: +55 21 2529 0400

DND*i* SOUTH-EAST ASIA
L10-7, Menara Sentral Vista, 150, Jln Sultan Abdul
Samad, Brickfields 50470, Kuala Lumpur, Malaysia
Tel: +60 3 2716 4159

DND*i* NORTH AMERICA
40 Rector Street, 16th Floor, New York, NY 10006, USA
Tel: +1 646 215 7076

DND*i* SOUTH AFRICA
South African Medical Research Council, Francie van Zijl
Drive, Parow Valley, Cape Town, 7501, South Africa

A not-for-profit research and development organization, DND*i* works to deliver new treatments for neglected diseases, notably leishmaniasis, human African trypanosomiasis, Chagas disease, specific filarial infections, and mycetoma, and for neglected patients, particularly those living with paediatric HIV and hepatitis C.

Since its inception in 2003, DND*i* has delivered eight treatments: two fixed-dose antimalarials (ASAQ and ASMQ), nifurtimox-eflornithine combination therapy (NECT) for late-stage sleeping sickness, sodium stibogluconate and paromomycin (SSG&PM) combination therapy for visceral leishmaniasis in Africa, a set of combination therapies for visceral leishmaniasis in Asia, paediatric dosage forms of benznidazole for Chagas disease, a 'super-booster' therapy for children co-infected with HIV and TB , and the first all-oral drug for sleeping sickness (fexinidazole).

Cover image: Divya lives in India's poorest state Bihar, the ground zero in the country for visceral leishmaniasis. In 2012 she fell sick with the disease. She appeared to be cured after a first treatment, but after a few months the disease came back. After a second treatment, she was finally cured. Without treatment, the disease is fatal. Photo: Kishore Pandit/DND*i*.

Thank you to our leishmaniasis programme donors:

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra
Swiss Agency for Development and Cooperation SDC

MEDECINS SANS FRONTIERES

UKaid from the British people

BILL & MELINDA GATES foundation

Federal Ministry of Education and Research through KFW

GHIT Fund
Global Health Innovative Technology Fund

Ministry of Foreign Affairs of the Netherlands

EDCTP

AFD

BEM-TE-VI DIVERSIDADE

MINISTÉRIO DA SAÚDE BRASIL

Liberté • Égalité • Fraternité
RÉPUBLIQUE FRANÇAISE
MINISTÈRE DE L'EUROPE ET DES AFFAIRES ÉTRANGÈRES

medicor foundation Liechtenstein

Australian Government

NIH National Institute of Allergy and Infectious Diseases

STARR International Foundation

Fondation de bienfaisance du groupe Pictet

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

BNDES

Organização Pan-Americana da Saúde

Organização Mundial da Saúde Américas

PANAFTOSA Centro Pan-Americano de Febre Aftosa Saúde Pública Veterinária

Rockefeller Foundation
Innovation for the Next 100 Years

FIOCRUZ Fundação Oswaldo Cruz

Regione Toscana

Fundación BBVA

PCLB
The Peter and Carmen Lucia Buck Foundation

ruta n
MEDELLÍN

aecid
Agencia Española de Cooperación Internacional para el Desarrollo

& private individuals and foundations