# STRENGTHENING REGIONAL PARTNERSHIPS TO RESPOND TO THE NEEDS OF NEGLECTED PATIENTS





ver one billion people across the globe are affected by neglected diseases. Those most affected are the poorest populations, living in remote rural areas, urban slums, or conflict zones. Their needs are not prioritized by policy makers, pharmaceutical companies, or research and development (R&D) institutions, and as a result, there are major unmet treatment needs for many of the socalled neglected tropical diseases and also for neglected patient groups affected by diseases for which medicines are available but unaffordable or not adapted to the patient.

An assessment of the drug and vaccine landscape for neglected diseases in 2011\* found major gaps in R&D for neglected diseases. Out of the 850 new drugs and vaccines approved for all diseases at that time, only 4% (37) were for neglected diseases, though they represented 11% of the global burden of disease. Of the 336 brand-new drugs (new chemical entities) approved for all diseases, only four (1%) were for neglected diseases and of these, none were developed for any of the 17 neglected tropical diseases (NTDs) then listed by the World Health Organization (WHO).

\* Pedrigue B et al. (2013). The drug and vaccine landscape for neglected diseases (2000-11): A systematic assessment.

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Neglected tropical diseases (NTDs): Reported number of people requiring interventions against NTDs in 2016



#### List of NTDs according to WHO (2017):

Buruli ulcer, Chagas disease, dengue and chikungunya, dracunculiasis (guinea-worm disease), echinococcosis, foodborne trematodiases, human African trypanosomiasis (sleeping sickness), leishmaniasis, leprosy, lymphatic filariasis, mycetoma, chromoblastomycosis and other deep mycoses, onchocerciasis (river blindness), rabies, scabies and other ectoparasites, schistosomiasis, soil-transmitted helminthiases, snakebite envenoming, taeniasis/cysticercosis, trachoma, yaws (endemic treponematoses).



"These illnesses are one of the important reasons that the 1.4 billion people living under the poverty threshold cannot emerge from marginalization. They are the most common infections among the world's poorest, the main cause of chronic disability and poverty."

Dr Bernard Pécoul, DND/ Executive Director

"We need to create a sense of ownership and confidence in our African scientists to work together towards realizing our global health goals."

Dr Monique Wasunna, Director of DNDi Africa



RESPONDING TO THE NEEDS OF NEGLECTED PATIENTS

n October 1999, to address R&D gaps for neglected diseases, Médecins Sans Frontières brought together a group of international experts and created the Drugs for Neglected Diseases Working Group. This group recommended the creation of a new initiative, the Drugs for Neglected Diseases *initiative* (DND*i*), which was created in 2003 by seven founding member organizations. DND*i* is a collaborative, patient-needs driven, not-for-profit R&D organization that works to deliver new treatments for neglected diseases, particularly leishmaniasis, human African trypanosomiasis, Chagas disease, specific filarial infections, and mycetoma, and neglected patient populations, including those affected by paediatric HIV and hepatitis C.

# SINCE ITS INCEPTION, DND*i* HAS DELIVERED SEVEN 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,
- A paediatric dosage form of benznidazole for **Chagas disease**,
- A 'superbooster' therapy for children co-infected with **HIV and TB**.

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#### DND*i* AIMS TO DEVELOP 16-18 ADDITIONAL TREATMENTS BY 2023

DND*i* uses innovative and collaborative mechanisms to deliver treatments that are safe, effective, affordable, and well adapted for use in areas with limited healthcare resources.

#### FOUNDING PARTNERS:

Médecins Sans Frontières (MSF)/Doctors Without Borders; Indian Council of Medical Research, India; Kenya Medical Research Institute, Kenya; Ministry of Health, Malaysia; Oswaldo Cruz Foundation, Brazil; Institut Pasteur, France; World Health Organization (WHO) Special Programme for Research and Training in Tropical Diseases (TDR) (*permanent observer*)



## DNDi AFRICA REGIONAL OFFICE

BUILDING R&D PARTNERSHIPS TO MEET THE NEEDS OF NEGLECTED PATIENTS IN EASTERN AFRICA

The DND*i* Africa regional office was established in Nairobi, Kenya in 2003 to build and strengthen regional partnerships to carry out R&D activities for neglected patients in Eastern Africa. The office now works in five countries on multiple R&D projects, as well as capacity building initiatives within the Leishmaniasis East Africa Platform (LEAP).

The other DND*i* offices in Africa are based in the Democratic Republic of Congo and South Africa, providing support for clinical trials on sleeping sickness and antimicrobial resistance, respectively.

#### DND*i* AFRICA REGIONAL OFFICE – AT A GLANCE

- Over 30 staff
- Projects for four diseases: leishmaniasis, paediatric HIV, mycetoma, and neonatal sepsis
- 16 studies completed or ongoing
- Over 50 local partners and collaborators
- Three treatments delivered following clinical trials in the region: ASAQ and ASMQ for malaria, and SSG&PM for visceral leishmaniasis
- Oversight of 22 clinical trial sites
- Over 11,000 visceral leishmaniasis patients treated within and outside clinical studies since 2010
- Over 900 people trained on Good Clinical Practice, Good Clinical Laboratory Practice, and Good Financial Practice

# IN SEARCH OF NEW TREATMENTS FOR NEGLECTED PATIENTS

# LEISHMANIASIS

#### DNDi AIMS TO DELIVER:

A safe, effective, low-cost and short-course, oral treatment for VL

A new treatment for PKDL that is shorter and better tolerated than current options

A new treatment regimen for patients co-infected with HIV and VL

Over one billion people are at risk of leishmaniasis, a parasitic disease transmitted by the sandfly.

# LEISHMANIASIS IS A COMPLEX DISEASE, OCCURRING IN MULTIPLE FORMS:

- Visceral leishmaniasis (VL), also known as kala-azar, is fatal without treatment.
- **Post-kala azar dermal leishmaniasis (PKDL)** develops in some people after VL treatment and is characterized by lesions on the body.
- Cutaneous leishmaniasis (CL) usually presents as ulcers on exposed body parts (arms, legs, face).

**E** astern Africa has a high VL burden with an estimated 29,000–56,000 cases annually.<sup>\*</sup> Existing therapies have serious drawbacks in terms of safety, resistance, stability, ease of administration, and cost. For close to fifteen years, the DND*i* Africa regional office has supported the search for better treatments by conducting clinical trials in the region.

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"My dream is to be cured so that I don't have to come to hospital all the time. Then I can work and make sure my children remain in school. A new treatment will give me a better chance to do this."

Tsadik, a patient with HIV-VL Co-infection, Abdurafi, Ethiopia

### Visceral leishmaniasis ONE TREATMENT DELIVERED AND MORE IN THE PIPELINE

n 2010, following a landmark study, the DND*i* Africa regional office completed an important clinical trial together with its Leishmaniasis East Africa Platform (LEAP) partners to deliver the sodium stibogluconate and paromomycin (SSG&PM) combination therapy for Eastern Africa. This treatment has been adopted as the firstline treatment for VL in the region by WHO and endemic countries. Use of SSG&PM reduced the treatment from 30 to 17 days, thus decreasing the length of hospital stay though still requiring injections. Although this was a major step forward, DND*i* is now conducting research to reach its goal of an oral-only treatment for all patients suffering from VL.

In 2017, a clinical trial combining miltefosine (the first oral treatment registered for VL but currently not approved for use in Africa) and paromomycin began in Eastern Africa. The goal of this combination treatment is to further reduce the length of hospital stay and simplify drug administration (the current SSG&PM treatment requires two injections daily).

Together with its pharmaceutical partners, DND*i* has made major advances in its search for oral, field-adapted new chemical entities (NCEs) for VL. Following successes in the laboratory, selected NCEs have progressed to the clinical development phase and, if successful, will soon be taken through clinical trials in the region.

### HIV-VL co-infection A CHALLENGE TO TREAT

IV-VL co-infection remains difficult to treat despite efforts to find improved therapies. Co-infected patients usually experience poor treatment outcomes, higher mortality, high risk of relapse (associated with low CD4 count), and risk of drug resistance.

In 2014, DND*i* conducted a clinical trial in two sites in Ethiopia (which currently has the highest global burden of HIV-VL co-infection) to identify a safe and effective treatment for co-infected patients. The 2016 results supported the implementation of an AmBisome and miltefosine combination as first-line treatment for HIV-VL co-infected patients, using the strategy of one or two treatment cycles as needed.



# PAEDIATRIC HIV

### Post-kala-azar dermal leishmaniasis

#### SHORTER, SAFER, AND EASIER TREATMENTS

A clinical trial to find a better treatment for severe cases of post-kala-azar dermal leishmaniasis (PKDL) in Africa began in Dooka, Sudan in 2018. The objective of this trial is to deliver an oral medication for PKDL that requires only a short hospitalization period and is safer to use and easy to administer. This clinical trial will assess the safety and efficacy of two treatment combinations. The first is a combination of paromomycin (an injectable treatment, currently used in combination with SSG to treat VL) combined with miltefosine (the first oral treatment registered for VL but currently not approved for use in Africa). The second treatment is a combination of liposomal amphotericin B (AmBisome, currently used as a second-line treatment for VL in Africa and administered intravenously) combined with miltefosine.

#### DND*i* AIMS TO:

Develop a child-friendly, taste-masked, first-line lopinavir-ritonavir-based fixeddose formulation in combination with two nucleoside reverse transcriptase inhibitors (3TC and ABC) – the so-called "4-in-1"

Introduce the recently US FDA-approved lopinavir-ritonavir pellets as an interim solution before the availability of better-adapted 4-in-1 products



"We need better formulations of these life-saving treatments [for babies and young children] but we also need improved testing for babies born to mothers with HIV. If, with improved testing, we could get babies on treatment early, we could save thousands of lives."

Dr Dalton Wamalwa, Associate Professor, Department of Paediatrics and Child Health, University of Nairobi and Coordinating Principal Investigator of the LIVING Study

H IV remains a major global public health challenge affecting an estimated 36.7 million people globally, including 2.1 million children under 15 years old. Sub-Saharan Africa has the largest burden of paediatric HIV in the world. Without treatment, one-third of infected children die in their first year of life, half by the age of two, and fourfifths by the age of five.<sup>\*</sup> This situation is further aggravated by insufficient treatment options for children living with HIV. The treatment currently recommended by WHO was not designed with children's needs in mind – the medicines come in the form of syrups that are bitter, hard to administer, and require refrigeration. Little investment has been made in developing child-appropriate formulations. DND*i* is working with the Indian generic company Cipla Ltd. to develop improved antiretroviral therapies for children. The first is a solid "2-in-1" fixed-dose combination of lopinavir/ritonavir taken with food. To increase access to this interim combination, DND*i* has been running the LIVING implementation study in Kenya, Uganda, and Tanzania. Interim results from this study have shown very high levels of adherence and clinical improvement as well as lower HIV viral loads in the children studied. The second is a child-friendly first-line "4-in-1" fixed-dose combination of abacavir/ lamivudine/lopinavir/ritonavir for infants and young children under three years of age that meets WHO recommendations. DND*i* will begin a study on the "4-in-1" in late 2018 in Uganda to provide clinical data on young infants and children living with HIV.

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#### DNDi AIMS TO DELIVER:

#### A new safe, effective, and affordable treatment for patients with limited fungal mycetoma (eumycetoma)

M ycetoma, whose overall global burden is unknown, is a chronic infection mainly of the foot that can spread to other parts of the body and cause severe deformity. Infection probably comes from the soil or animal dung, and it is thought that most patients are infected by walking barefoot, sustaining minor cuts from the thorns of the acacia tree. The disease is endemic in tropical and subtropical areas of what is often referred to as the 'mycetoma belt', which includes Chad, Ethiopia, India, Mauritania, Mexico, Senegal, Somalia, Sudan, Venezuela, and Yemen.

#### MYCETOMA OCCURS IN TWO FORMS:

- Actinomycetoma a bacterial infection with a 90% cure rate using antibiotics
- **Eumycetoma** a fungal infection with only 25-35% cure rate with antifungals and surgery

Treatment of eumycetoma has proven to be difficult and typically includes antimicrobial agents and surgery (amputation is needed in the absence of other treatment options). Faced with the need to fill the R&D gap for mycetoma and provide new treatment tools to patients, DND*i* included the disease in its dynamic portfolio in 2015. In 2017, together with the Mycetoma Research Centre in Sudan and Japanese pharmaceutical company Eisai, DND*i* launched the first-ever clinical trial for a promising antifungal treatment, fosravuconazole (formerly known as E1224) for mycetoma.<sup>\*</sup>

10 \* Clinical trial for a better treatment for mycetoma starts in Sudan, Press release, June 2017. https://www.dndi. org/2017/media-centre/press-releases/clinical-trial-for-mycetoma-treatment-starts-in-sudan/

#### MYCETOMA IS ADDED TO WHO LIST OF NEGLECTED TROPICAL DISEASES

Policy and advocacy efforts by DND*i* played a major role in the inclusion of mycetoma on WHO's official list of neglected tropical diseases. DND*i* organized numerous advocacy meetings, coupled with awareness-raising through local and international media and content collection, to showcase the terrible impact of this woefully neglected disease and support the petition for its inclusion.

Including mycetoma on WHO's official list gives this disease the political prominence that is so desperately needed for increased funding and new global programmes to better define the epidemiology, risk factors, treatment strategies, and early diagnosis.

"An effective, safe, affordable, and shorter-term curative treatment which is appropriate for rural settings is desperately needed for neglected patients suffering from mycetoma."

Dr Ahmed Fahal, Professor of Surgery at the University of Khartoum and Director of the Mycetoma Research Centre, Sudan.



The Global Antibiotic Research & Development Partnership (GARDP) was established in May 2016 as a joint initiative by WHO and DND*i*. Its mission is to develop new and improved antibiotic treatments addressing antimicrobial resistance (AMR), while ensuring their sustainable access.

# NEONATAL SEPSIS

AMR is a rapidly growing global health challenge, with estimates of up to 700,000 deaths per year.<sup>\*</sup> Despite significant breakthroughs made in reducing child mortality, neonatal deaths represent 44% of all deaths in children under five. Of particular concern is the estimated 214,000 neonatal deaths in 2015 attributed to drug-resistant infections.<sup>\*\*</sup>

A major challenge is the lack of evidence on how to treat sepsis in newborns. Through an observational study taking place in 11 countries, including Kenya and Uganda, GARDP aims to provide an evidence base as part of its broader programme to develop and deliver new antibiotic treatments for newborns with drug-resistant bacterial infections. This also includes conducting a clinical trial in Kenya to confirm the correct dose and evaluate safety for a drug licensed over 40 years ago that has not been widely used in newborns with sepsis.

<sup>\*</sup> O'Neill, J. (2016). Tackling drug-resistance globally: Final report and recommendations. Available at: https://amr-review.org/sites/default/ files/160525\_Final%20paper\_with%20cover.pdf

<sup>\*\*</sup> Laxminarayan, R. *et al.* (2016). Antimicrobials: access and sustainable effectiveness 1; Access to effective antimicrobials: a worldwide challenge. *Lancet.* 387:168-75

### **DND***i* **DATA CENTRE** SUPPORTING CLINICAL TRIALS WITH HIGH-QUALITY DATA MANAGEMENT & ANALYSIS

The management of data is critical to ensuring high-quality clinical trials, from study design and implementation through to reporting.

In 2004, DND*i* established a fully-fledged Data Centre to carry out data management activities and statistical analyses for clinical trials to meet ICH<sup>\*</sup> Good Clinical Practice standards. In addition to training researchers and data managers for DND*i*'s own clinical trials, the Data Centre expanded its footprint in 2012 by offering data management services to external studies carried out by DND*i* partners and collaborators, including the World Health Organization, Médecins Sans Frontières, and the Kenya Medical Research Institute.

In 2016, the Data Centre began a collaboration with the Infectious Diseases Data Observatory to share information about leishmaniasis crucial to answering scientific and operational questions, so that researchers and clinicians can improve patient treatment and help ensure co-ordinated and effective responses to neglected and emerging infections.

In 2017, the Data Centre trained more than 50 people, including personnel for DND*i* paediatric HIV, visceral leishmaniasis (VL), and mycetoma clinical studies, as well as personnel for partners' studies, including an MSF study on multi-drug-resistant tuberculosis in Uzbekistan, Belarus, and South Africa, and a WHO trial on Buruli ulcer in Ghana and Benin. The Data Centre also provided training to the Kenya Ministry of Health on the DHIS2 platform for managing data for VL surveillance.

# STRENGTHENING REGIONAL RESEARCH CAPACITY

ncreasing endemic countries' ability to respond to their own research needs by strengthening existing clinical research capacities is part of DND*i*'s mission. It is especially important in regions where DND*i* conducts clinical trials in some of the most remote locations with little clinical infrastructure, a lack of trained personnel, and the risk of political instability. Considerable effort is required to carry out high-quality clinical research under such conditions.

The DND*i* Africa regional office has consistently integrated sustainable capacity strengthening into its projects to ensure R&D activities are compliant with international clinical trial standards. Disease-specific research platforms created by DND*i* and its partners are central vehicles for strengthening capacity by training, encouraging knowledge sharing, and amplifying the scientific research led by regional scientists, as well as by managing clinical trial sites through platform members.

#### "I am proud to be part of a team that gained new knowledge through training and participation in a clinical trial for the first time."

Martin Kundu Sunguti, Lab Head Kacheliba, West Pokot, Kenya on participating in a DND*i* clinical trial.



#### LEISHMANIASIS EAST AFRICA PLATFORM (LEAP)

The LEAP Platform has been instrumental in knowledge and skill development in the region. This clinical research network brings together experts drawn from leishmaniasis-endemic East African countries to facilitate clinical testing and improved access to better treatments for leishmaniasis in the region. Launched by DNDi in 2003. LEAP has over 60 members from four member countries: Ethiopia, Kenya, Sudan, and Uganda. In its new phase, known as LEAP 2.0, LEAP hopes to bring onboard other endemic countries such as South Sudan. Somalia. and Eritrea. The LEAP platform 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 Eastern Africa. The platform is also a base for ongoing cross-learning between countries, and standardization of

procedures and practices within the East African region, where possible. Over the years, LEAP has trained clinical trial site teams, upgraded site infrastructure, and fortified treatment access initiatives across the region.

"I was just a young man when the Leishmaniasis East African Platform was launched. LEAP has developed me as a researcher over the years. Through this exposure, I have acquired a desire to mentor other researchers in the field of endemic diseases."

Dr Ahmed Musa, Director, Institute of Endemic Diseases, Khartoum, Sudan



### INTEGRATING ADVOCACY TO ENHANCE POLICY DEVELOPMENT AND ADOPTION

**D** ND*i* is involved in advocacy activities with the aim of improving access to treatments and encouraging R&D for neglected diseases (see text box p. 11). These include working with health ministries, communities, the media, and other stakeholders to create awareness around new and effective treatments. These efforts have been further augmented by governments, who are now showing a growing willingness of the need to strengthen R&D and evidence-based decision making for public health. However, a great deal of effort is still needed so that evidence from regional R&D has an impact on local and international policy.

#### CHANGING NATIONAL TREATMENT GUIDELINES

DND*i*'s aim is to quickly see proven treatments registered in countries and included in treatment guidelines, both at a global level through WHO and at a national level through health ministries, to ensure rapid access for patients. The DND*i* Africa regional office has supported the uptake of new treatments through:

- Supporting health ministries to develop and launch new guidelines for clinicians after registering new treatments.
- Training health workers to diagnose and administer new treatments, in partnership with health ministries.

#### TO REACH ITS OBJECTIVES BY 2023, DNDi's OVERALL RESOURCES NEEDED IS EUR 730 M

#### HOW DNDi's GLOBAL RESOURCES ARE ALLOCATED



Status: Sept. 2018

### JOIN US IN THE FIGHT FOR NEGLECTED PATIENTS

Despite encouraging progress, there is still so much to do to ensure that neglected patients get the effective and affordable treatment they so desperately need.

**S** ince its founding, DND*i* seeks diversified funding sources, from governments, public institutions, companies, foundations, NGOs, individuals, and alternative mechanisms that share a commitment to DND*i*'s vision and mission. This diversification is crucial to guarantee independence and avoid dependence on any one donor. Every effort is made to ensure that no single donor contributes over 25% of all donations.

#### THANK YOU TO DNDi's DONORS\*

UK aid, UK: Bill & Melinda Gates Foundation, USA: Federal Ministry of Education and Research (BMBF) through KfW, Germany; Médecins Sans Frontières International; Dutch Ministry of Foreign Affairs (DGIS), The Netherlands; Swiss Agency for Development and Cooperation (SDC), Switzerland; US Agency For International Development (USAID), USA; French Development Agency (AFD), France; Unitaid; European and Developing Countries Clinical Trials Partnership (EDCTP2 Programme) supported by the European Union; Global Health Innovative Technology Fund (GHIT Fund), Japan; Wellcome Trust, UK; Ministry of Health, Malaysia; International Development Research Centre (IDRC). Canada: Associação Bem-Te-Vi Diversidade. Brazil: Banco Nacional de Desenvolvimento Econômico e Social (BNDES), Brazil: Medicor Foundation, Liechtenstein: Stavros Niarchos Foundation, USA, Switzerland; Republic and Canton of Geneva, International Solidarity Office, Switzerland



The Drugs for Neglected Diseases *initiative* (DND*i*) is a patient-needs driven, not-for-profit research and development (R&D) organization that develops safe, effective, and affordable treatments for the millions of people across the world affected by neglected diseases, notably human African trypanosomiasis (sleeping sickness), leishmaniasis, Chagas disease, filariasis, paediatric HIV, mycetoma, and hepatitis C.

The DND*i* Africa regional office was established in 2003 in Nairobi, Kenya to build and strengthen regional partnerships against neglected diseases in Africa, specifically leishmaniasis, paediatric HIV, and mycetoma. Since then, the office has supported the delivery of three treatments: two fixed-dose antimalarials (ASAQ and ASMQ) and sodium stibogluconate and paromomycin (SSG&PM) combination therapy for visceral leishmaniasis. DND*i* Africa is also the secretariat of the Leishmaniasis East Africa Platform, a clinical research network that brings together experts from leishmaniasis endemic Eastern African countries to facilitate clinical testing and improved access to better treatments.

DND*i* also has offices in Kinshasa, Democratic Republic of Congo, and in Cape Town, South Africa.

DNDi is committed to conducting its clinical trials using the highest standards possible. In 2015, the DNDi Africa regional office embarked on an ambitious Quality Management System (QMS) process to further improve internal management and operational processes to enhance performance, communication, and planning. In 2017, the office was ISO 9001:2008-certified, and in 2018, the office began pursuing ISO 9001:2015 certification to align with the new ISO structure and expectations.



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