LEISHMANIASIS

Visceral leishmaniasis patients waiting to see a healthcare worker at the Kala-Azar Medical Research Centre (KAMRC), Muzaffarpur, Bihar, India.

› **Leishmaniasis** affects the poorest of the poor and has strong links with malnutrition, low-quality housing, and lack of resources. Some 350 million people around the world are at risk of developing leishmaniasis in one of its many forms. There are more than 20 species of *Leishmania* parasite, transmitted to humans by approximately 30 species of phlebotomine sand flies found throughout the tropics and subtropics, as well as in temperate zones.

One of the two most common forms of disease, visceral leishmaniasis (VL) or kala-azar, is fatal without treatment. There are 200,000-400,000 new cases per year, albeit with a large reduction recently in South Asia. The WHO's roadmap for elimination - published in 2012 and supported by the London Declaration the same year - targets elimination of kala-azar as a public health problem by the end of 2020 in South Asia.

Surprisingly, the response of visceral leishmaniasis to treatment is not homogenous across continents, nor even within the same region, and different drugs and/or regimens are needed, particularly in eastern Africa. Intermediate results from an implementation trial which was underway in India, carried out by DND*i* and partners, led the government to change its treatment guidelines in 2014, abandoning miltefosine monotherapy in favour of single-dose AmBisome® as first-line and a combination of paromomycin/miltefosine as second-line treatment. These changes were subsequently also taken up by the governments of Bangladesh and Nepal. Similarly in Latin America, the interim results of an implementation trial carried out by DND*i* with partners in Brazil led to Ambisome® being included as second-line treatment after Glucantime®, with the final results now suggesting it would be more suitable as first-line treatment. In addition, Ambisome® alone or in combination with miltefosine is being evaluated in Ethiopia for treating VL patients who are co-infected with HIV.

Post kala-azar dermal leishmaniasis (PKDL) is a complication of VL. Treating PKDL patients, which may also remove a reservoir for reinfection and outbreaks, is likely to be key for sustained elimination of the disease. The safety and efficacy of Ambisome® alone or in combination with miltefosine will be assessed for treating PKDL patients in India and Bangladesh, whilst patients in Sudan will receive Ambisome® or paromomycin in combination with miltefosine.

Cutaneous leishmaniasis, although not life-threatening, is more common than the visceral form and is the cause of serious socio-economic problems in populations with already limited resources. Initial approaches will explore opportunities to better use the existing treatments in combination, together with the development of a topical formulation for small numbers of ulcerated, uncomplicated CL lesions. However, an oral treatment will be needed to treat multiple or large lesions, to be selected from compounds at early clinical stages or from the DND*i* discovery programme. PKDL and complicated forms of CL may be treatable with an immune modifier combined with chemotherapy.

Multiple approaches needed to address a complex family of diseases

DND*i* has recently identified new chemical entities from its drug discovery efforts and it is hoped that these, together with other leads expected to emerge from the NTD Drug Discovery Booster, launched in 2015, will lead to a generation of safe and effective oral treatments for VL and CL.

DND*i* is a member of the consortium for the Control and Elimination of Visceral Leishmaniasis, known as KalaCORE, which aims to tackle VL in South Asia and East Africa by supporting national efforts and coordinating with national VL control programmes.

Following the acceptance of a joint submission in 2015 by DND *i* and the Instituto de Salud Carlos III (ISCIII), a Madrid-based WHO collaborating Center for leishmaniasis for 19 years, the 6th World Congress on Leishmaniasis will take place in Toledo, Spain from 16 to 20 May 2017, with some 1500 attendees expected (see www.worldleish2017.org).

What are the current treatments and their limitations?

Existing drugs have serious drawbacks in terms of safety, resistance, stability, and cost. They have low tolerability, long treatment duration, and are difficult to administer. These drugs are used either as monotherapy or in combination for the various forms of leishmaniasis.

Pentavalent antimonials (sodium stibogluconate – SSG – and meglumine antimoniate): used for VL and CL for over 60 years. Acquired resistance in areas of high prevalence and high transmission has been reported. Serious cardiotoxicity leading to death is well documented. In monotherapy, they require a 30-day parenteral treatment for VL. For CL: intramuscular injections for 21 days; in the Old World, generally 1-2 intralesional applications per week for 3-7 weeks, sometimes alternating with cryotherapy (not used in the New World). Registered in South East Asia, Latin America, and some Mediterranean and African countries.

Amphotericin B deoxycholate: only an alternative treatment for VL in areas with high rates of unresponsiveness to antimonials where no other options are available. Need for hospitalization, constant renal monitoring of patients, 28-day duration of treatment, and infusion-related adverse events are notable drawbacks. Amphotericin B displays dose-limiting toxicity. Registered in South Asian countries and some countries in Africa and Latin America.

AmBisome®: a liposomal formulation of amphotericin B, which is comparatively much safer and highly efficacious. A single infusion of 10mg/kg has shown a 96.4% cure rate in Asia. However, high cost and the need for a cold chain limit widespread use. Registered for VL in India, USA, and Europe and used as a second-line drug for the treatment of VL in East Africa at higher doses than in India and for VL in Brazil. It is also used to treat PKDL cases in Sudan. A donation to WHO facilitates free distribution of AmBisome® to the three countries involved in the elimination strategy in South Asia for primary VL patients, and as a rescue treatment for African VL. It is not properly evaluated for cutaneous leishmaniasis (CL).

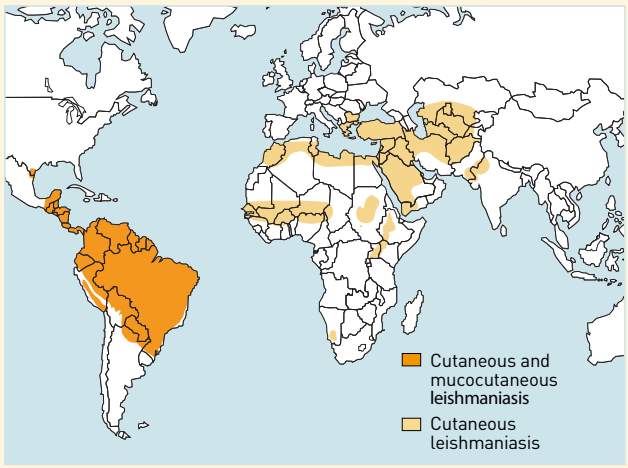
Miltefosine: an oral drug administered twice daily, registered for use in India for VL, and requires 28-day treatment. Major limitations include low compliance, risk of resistance, contraindication in pregnancy, and mandatory contraception for women of child-bearing age for the duration of therapy and three months beyond. A recent study in Asia indicated an emerging lack of efficacy of monotherapy in the region, probably associated with drug underexposure in children, and the same has been observed in Africa. For CL, currently approved for lesions caused by three *Leishmania* species. Miltefosine is not registered in many endemic countries and is consequently not available.

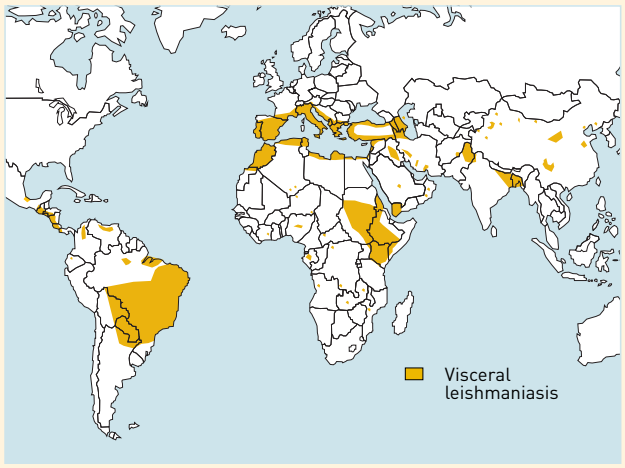
Paromomycin: a low-cost parenteral formulation that requires three weeks of painful intramuscular administration is also highly efficacious in Asia but is associated with some degree of renal and ototoxicity; limited efficacy as monotherapy in East Africa.

350
million people
at risk in
98
countries

0.7-1.2
million cases
of CL annually

0.2-0.4
million cases
of VL annually,
although with a marked reduction in the number of cases observed in the Indian subcontinent





DNDi
Drugs for Neglected Diseases *initiative*

WHAT IS DND*i* DOING TO ADDRESS UNMET TREATMENT NEEDS?

VISCERAL LEISHMANIASIS

Improved treatment options for VL patients in some areas have already been delivered. DND*i*'s short-term approach has been to develop new treatments by combining existing drugs and/or shortening treatment duration in order to increase tolerability, reduce burden on health systems, and offer greater affordability, whilst also preventing or delaying emergence of resistance, and the geographical extension of existing drugs in other countries and regions. In 2010, DND*i* and LEAP partners delivered the SSG&PM combination therapy for East Africa , now recommended as first-line treatment for VL in the region. In India, a Phase III trial demonstrated the efficacy of combination therapies of already-registered drugs (see p. 35). In 2014, based on the evidence generated by this trial and one conducted by Sundar *et al.*, the government of India recommended use of single-dose AmBisome® as a first option and paromomycin/miltefosine combination as the second option for treatment instead of using miltefosine as monotherapy, with the same policy change also taken up in Bangladesh and Nepal. DND*i* later collaborated with the National Control Programmes of India and Bangladesh, MSF, the Bihar State Health Society, and the Indian Council for Medical Research to assess the effectiveness and safety of these new treatments at the primary healthcare level and facilitate their introduction. In Latin America , DND*i* is participating in a study sponsored by the Brazilian Innovation Agency (FINEP) to evaluate the safety and efficacy of Glucantime®, AmBisome®, and amphotericin B as monotherapies, and of AmBisome®/Glucantime® combination to treat VL patients. The national control programme has extended the use of AmBisome® as second-line treatment based on the interim safety data from this trial.

Leishmania and HIV co-infection is a growing problem, difficult to manage clinically due to poor response to treatment with frequent relapses of disease, and is eventually fatal. DND*i* is working with partners towards better treatment for HIV/VL co-infected patients in Africa and Asia .

In the medium term , DND*i* is assessing the combination of fexinidazole and miltefosine for the treatment of VL patients in eastern Africa. This could be the first oral-only combination therapy for VL.

The role of Post-Kala Azar Dermal Leishmaniasis (PKDL, a common complication of VL) in infectivity is poorly understood and treatment options remain limited, requiring long and often repeated courses of treatment including with antimonials. It is a particular problem in Sudan and Bangladesh, and needs to be addressed if VL is to be controlled. DND*i* is working with partners to facilitate additional research in epidemiology, diagnosis, pathogenesis, and treatment.

DND*i*'s long-term strategy for VL is to bring new oral drug candidates into clinical development through its lead optimization programme with the ultimate goal of improving the safety profile and efficacy of the existing tools with a second oral-only combination treatment.

In addition, DND *i* supports the Leishmaniasis East Africa Platform (LEAP) (see p. 58).

A new VL treatment for adults and children based on a new chemical entity would ideally beefficacious against all species of *Leishmania* in all regions as well as against resistant strains, have at least 95% efficacy, be short course(once a day for 10 days oral; or 3 shots over 10 days),easy to use, compatible for combination therapy, safein pregnant and breastfeeding women and for immunocompetent/immunosuppressed patients,affordable, and adapted to tropical climates. The TPP for the combination treatment will be reviewed in 2016.

By 2020, DND*i* aims to deliver from its VL-specific portfolio:

- **A safe, effective, low-cost, and short-course combination treatment**
- **A new treatment for PKDL that is shorter course and better tolerated than current options**
- **Treatment options for HIV/VL co-infected patients**
- **A new first-line treatment regimen for VL in Latin America**

CUTANEOUS LEISHMANIASIS

For CL, DND*i*'s objective is to develop short, safe, efficacious, affordable, and field-adapted treatments, at least for lesions caused by *L. tropica* and *L. braziliensis*. As a medium-term strategy, DND*i* is developing a topical treatment based on amphotericin B. In addition, we aim to improve treatment strategies using currently available treatment modalities and will be evaluating a single application of heat therapy combined with a short course of oral miltefosine. In the medium to long term, DND*i* aims to develop an oral drug and an immune-modulator for use in combination with chemotherapy. This novel approach aims to initially eliminate parasites with chemotherapy, followed by enhancement of the patient's immune response with an immune-stimulating agent.

A new topical or oral treatment for CL would ideally be efficacious against all species, show at least 95% efficacy , be easy to use, short course (14-28 days), compatible for combination therapy, produce minimal scarring , be safe in pregnant and breastfeeding women, affordable, and adapted to tropical climates .

By 2020, DND*i* aims to deliver from its CL-specific portfolio: A safe, effective, and shorter-course treatment for CL