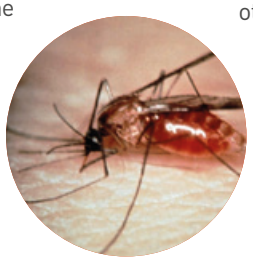
LEISHMANIASIS

A Global Disease with Regional Challenges

Leishmaniasis is a complex disease caused by more than 20 species of the *Leishmania* parasite, with over a million new cases occurring every year.[1] It breaks out in foci across tropical and temperate regions around the world, in areas where the sandfly, responsible for its transmission, lives. In anthroponotic leishmaniasis (transmission between humans by the sandfly) humans are the only reservoir, whereas animals such as dogs or rodents, also act as an important reservoir in zoonotic leishmaniasis (transmission from animals to humans by the sandfly).

Cutaneous leishmaniasis (CL) is the most common manifestation of the disease, with between 700,000 and 1.2 million new cases every year.[2] Although it is generally not fatal, the unsightly skin lesions it causes lead to ostracism by the local community, and economic loss.



Visceral leishmaniasis, or kala-azar, is deadly if not treated, and accounts for 200,000 to 400,000 new cases and 20,000 to 40,000 deaths each year. Characteristically, the disease causes fever, weight loss, enlarged spleen and liver, and anaemia. In addition, following treatment for visceral leishmaniasis (VL), a non-itching or painful skin rash may develop from six months to two years or more after the apparent cure. This post-kala-azar dermal leishmaniasis (PKDL) occurs mainly in East Africa and on the Indian subcontinent, and is thought to be a reservoir for transmission. An additional phenomenon is constituted by asymptomatic carriers, who do not seem to develop the disease, despite having been in contact with the parasite. Current treatments for VL are not optimal as nearly all still require injections or intravenous infusions. Adequate monitoring and control are key if the WHO goal of eliminating anthroponotic VL from the Indian subcontinent by 2020[3] is to be achieved, particularly as the role of PKDL and asymptomatic VL patients as disease reservoirs is poorly understood.

People living with HIV are prone to VL infection, whether they are prior asymptomatic carriers of VL who become symptomatic or due to new VL infections. In these cases, VL infection can accelerate the onset of AIDS. There are also concerns that HIV/VL co-infection may increase the transmission of leishmaniasis.

Some key endorsers of the London Declaration have undertaken to sustain, expand, and extend certain drug access programmes to ensure the necessary supply of drugs and other interventions to help control VL and other neglected diseases.

While the last decade has seen improvements in the treatment, diagnosis, and prevention of leishmaniasis notably in South Asia, supported by the development of liposomal amphotericin B, paromomycin, and miltefosine, response to treatment differs among regions (e.g. East Africa, Latin America,

Ideal Target Product Profile for VL

A new treatment for adults and children:

- Efficacious against **all species of parasite** in all regions
- Active against **resistant strains**
- At least **95% efficacy**
- **Short course** (1/day for 10 days oral; or 3 shots over 10 days)
- **Easy to use**: oral or intra-muscular, requiring no monitoring
- **No contraindications**
- No interactions. **Compatible for combination therapy**
- **Safe** in pregnant and breastfeeding women
- **For immunocompetent and immunosuppressed patients**
- **Affordable**
- **Adapted to tropical climates** (minimum three-year shelf-life)

(1) WHO Fact sheet No 375, January 2014. (2) Alvar J, Vélez ID, Bern C, Herrero M, Desjeux P, et al. (2012) Leishmaniasis Worldwide and Global Estimates of Its Incidence. PLoS ONE 7(5): e35671. doi:10.1371/journal.pone.0035671. (3) Sustaining the drive to overcome the global impact of neglected tropical diseases: second WHO report on neglected diseases (2013). World Health Organization.

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South Asia). DND*i*'s strategy seeks to develop new treatments that appropriately address the patient needs, specific to each affected region.

In an effort to address the unmet health needs of developing countries, in 2013 the WHO called for 'demonstration projects' (see page 51) to provide evidence on innovative mechanisms to fund and coordinate research and development for diseases disproportionately affecting developing countries, as recommended by the Consultative Expert Working Group (CEWG). The 'Visceral Leishmaniasis (VL) Global R&D Access Initiative' proposed by DND*i* and partners, was one of four proposals selected in early 2014 to move forward. The proposal seeks to develop safe and effective oral treatments for VL patients, and potentially for asymptomatic carriers and PKDL patients, as well as diagnostics for the detection of asymptomatic carriers. In addition, the development of a shared open-access database to identify determinants of treatment effectiveness was proposed.[4]

Ideal Target Product Profile for CL

A new topical or oral treatment:

- Efficacious against all species of *Leishmania*
- At least 95% efficacy
- Easy to use: short course (14-28 days), requiring no monitoring
- No interactions. Compatible for combination therapy
- Leaving minimal scarring
- Safe in pregnant and breastfeeding women
- Affordable
- Adapted to tropical climates (minimum three-year shelf-life)

(4) *The Visceral Leishmaniasis (VL) Global R&D & Access Initiative (2013) Drugs for Neglected Diseases initiative. http://www.who.int/phi/implementation/VL_global_R_D_access_initiative.pdf*

FACT SHEET

WHAT IS THE IMPACT OF LEISHMANIASIS?

A total of 98 countries and 3 territories on 5 continents reported endemic leishmaniasis transmission. Among parasitic diseases, morbidity and mortality caused by leishmaniasis are surpassed only by malaria and lymphatic filariasis. It is estimated that 350 million people are at risk of the disease, most of them children. The annual incidence is estimated at approximately 0.7 to 1.3 million CL cases and 0.2 to 0.4 million VL cases, with a case-fatality rate of 10% for visceral leishmaniasis per year (i.e. 20,000 to 40,000 deaths per year).[1] However, mortality data are extremely sparse and generally represent hospital-based deaths only, so actual figures are expected to be higher. Co-infection with other infectious diseases is an increasing concern: HIV-VL co-infection has been reported in 35 countries worldwide.

HOW IS LEISHMANIASIS TRANSMITTED?

More than 20 species of the kinetoplastid protozoan parasite *Leishmania* can be transmitted to humans via some 30 species of phlebotomine sandflies.

CL is most frequently caused by *Leishmania* major, *L. tropica*, *L. infantum*, and *L. aethiopica* in the Old World (Africa, Europe, Asia), and *L. braziliensis*, *L. mexicana*, and related species in the New World (notably the Americas). Mucocutaneous leishmaniasis (MCL) can develop as a complication of CL. Depending on the species of *Leishmania*, the life cycle can be anthroponotic (transmitted from human to animal) or zoonotic (transmission from animal to human). In the latter case, animals act as a reservoir for the disease.

VL is usually caused by *L. donovani* and *L. infantum*.

PKDL occurs during, or more often after, recovery from VL. It is caused by *L. donovani* and is believed to be a parasite reservoir for human VL.

WHAT ARE THE SYMPTOMS?

VL is characterized by progressive fever, weight loss, enlarged spleen and liver, and anaemia. Untreated symptomatic VL is fatal in almost all cases.

CL is a small erythema that develops after a variable period of time at the site where an infected sandfly has bitten the host. The erythema develops into a papule, then a nodule that progressively ulcerates to become the lesion characteristic of the disease. Depending on the species, CL usually heals spontaneously within one to two years, but results in lifelong scars, which, depending on the size and location, may cause substantial trauma in affected individuals, particularly children.

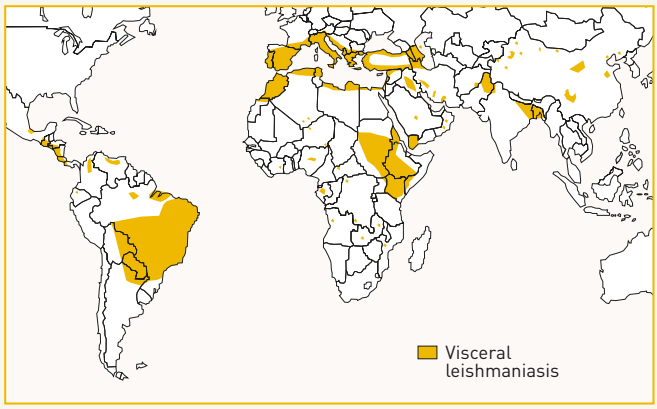
Mucocutaneous leishmaniasis (MCL) is characterized by partial or total destruction of mucous membranes of the nose, mouth, and throat.

PKDL is characterized by a macular, maculopapular, and nodular rash; starting from the face, it spreads to other parts of the body. PKDL is subject to geographical variations and can spontaneously heal, but can also develop into severe or persistent forms, requiring long courses of treatment.

CURRENT TREATMENTS AND THEIR LIMITATIONS

Existing drugs for VL have serious drawbacks in terms of safety, resistance, stability, and cost.[2] They have low tolerability, long treatment duration, and are difficult to administer.

→ **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. Serious cardiotoxicity leading to death well documented. Require a 30-day parenteral treatment for VL. Registered in South East Asia, Latin America, and some Mediterranean and African countries.



→ **Amphotericin B deoxycholate**: first-line treatment for VL in areas with high rates of unresponsiveness to antimonials and second-line treatment elsewhere. Need for hospitalization, constant renal monitoring of patients, prolonged duration of treatment, and infusion-related adverse events are notable drawbacks. Amphotericin B displays dose-limiting toxicity. It is registered in South Asia and some countries in Africa and Latin America.

→ **AmBisome®**: a liposomal formulation of amphotericin B, it is much safer and highly efficacious. A single infusion of 10mg/kg has shown a 96.4% cure rate in Asia.[3] However, high cost and the need for a cold chain limit its widespread use.[4] Registered for VL in India, USA, and Europe and used as a second-line drug for the treatment of PKDL in East Africa at higher doses than in India and for VL in Brazil.

→ **Miltefosine**: oral drug registered for use in India for VL, but expensive[5] and requires 28-day treatment. Major limitations include low compliance, with risk of resistance, and contraindication in pregnancy and mandatory contraception for women of child-bearing age for the duration of therapy and 3 months beyond. A recent study in Asia indicated an emerging lack of efficacy in monotherapy in the region.[6]

→ **Paromomycin (PM)**: a low-cost parenteral formulation that requires 3 weeks of painful intramuscular administration and is associated with some degree of renal and ototoxicity with limited efficacy as monotherapy in East Africa.

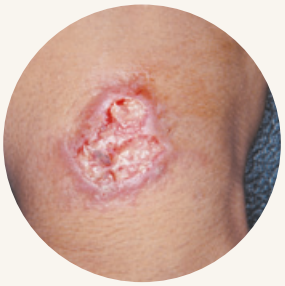
In 2010, DND*i* and LEAP partners **delivered the SSG&PM combination therapy for East Africa** (see page 28) that is recommended as first-line treatment for VL in the region by the WHO Expert Committee on the Control of Leishmaniases. SSG&PM has been included in the national guidelines of Sudan, South Sudan, Ethiopia, and in Kenya and it is in the process of being adopted in some of these countries. PM is registered in Uganda (2011) and Kenya (2013), and is in the process of being registered in Sudan and Ethiopia.

In India, a Phase III trial demonstrated the efficacy of combination therapies of already registered drugs: liposomal

(1) Leishmaniasis Worldwide and Global Estimates of Its Incidence. Alvar J. et al., (2012) PLoS ONE 7(5): e35671. doi:10.1371/journal.pone.0035671 *(2) Structures, Targets and Recent Approaches in Anti-Leishmanial Drug Discovery and Development. Seifert K., Open Med Chem J. 2011; 5:31–39. doi: 10.2174/1874104501105010031* *(3) Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India : an open-label, non-inferiority, randomised controlled trial, Sundar S. et al., The Lancet 2011, Feb 5;377(9764):477-86. doi: 10.1016/S0140-6736(10)62050-8. Epub 2011 Jan 20.* *(4) Through the WHO, significant cost reduction of both AmBisome® and miltefosine is available for the public sector of key endemic countries as of 2007.* *(5) Ibid.* *(6) Increasing Failure of Miltefosine in the Treatment of Kala-azar in Nepal and the Potential Role of Parasite Drug Resistance, Reinfection, or Noncompliance, Rijal S. et al., Clin Infect Dis. 2013 Jun;56(11):1530-8. doi: 10.1093/cid/cit102. Epub 2013 Feb 20.*

amphotericin, miltefosine, and paromomycin. AmBisome® monotherapy and combination therapies are recommended by the WHO Expert Committee on the Control of Leishmaniases. DND*i* is collaborating 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 Health Care level and facilitate their introduction for the treatment of VL in South Asia.

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 guidelines for VL were revised in 2013 based on the safety interim data for AmBisome® in this trial.



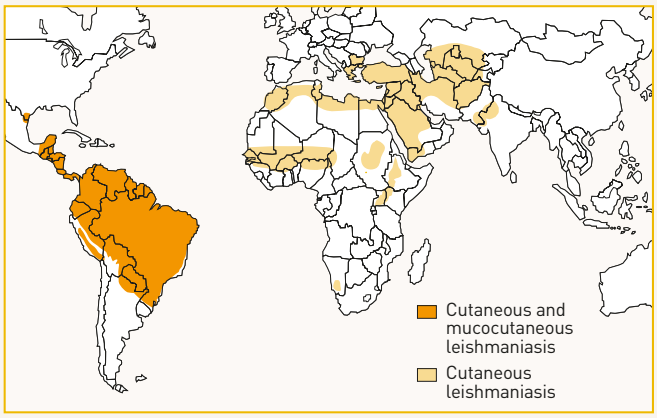
Existing treatments for CL are not satisfactory. Many treatment regimens are associated with significant failure rates and considerable toxicity. Relapses are common and there are increasing reports of drug resistance emergence.

→ **Pentavalent antimonials**: given as first-line drugs through a series of intramuscular, intravenous, or intralesional injections. Serious side effects, require long treatment, not affordable for most patients, variable efficacy and difficult to administer in poor rural areas.

→ Alternative treatments: **Liposomal amphotericin-B**, not fully tested on CL. Even if efficacious, cannot be deployed widely because of cost and delivery requirements.

Miltefosine, potentially teratogenic and has side effects that make it unsuitable to treat CL. Registered in Colombia. Other treatments, such as thermotherapy and cryotherapy are used in certain clinics, but are expensive.

→ A promising approach is to combine **chemotherapy with immune-modulation**: initial elimination of parasites with chemotherapy, followed by modification of the patient's immune response by an immune-enhancing agent (either a **therapeutic vaccine** or an appropriate adjuvant) could lead to quick recovery and control of persisting parasites. Therapeutic vaccines have yielded some positive results for CL. Several chemical immunomodulators have been tested for cancer and other diseases, and could be useful for CL therapy.



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

DND*i*'s **short-term** approach for **VL** was 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. Another objective was to assess efficacy and safety of existing drugs in other countries and regions to extend registration and availability to patients.

Leishmania and HIV co-infection is a growing problem. It is a very difficult to manage clinical entity, due to poor response to treatment with frequent relapses of disease, and is eventually fatal. DND*i* is working with MSF towards better treatment for HIV/VL co-infected patients in Africa using existing drugs at different dose/regimen and in combination, and collaborates with ITM-Antwerp in a secondary prophylaxis study.

In the **medium term**, DND*i* is assessing fexinidazole, also under evaluation for the treatment of HAT and soon Chagas disease, for the treatment of primary VL patients.

DND*i*'s **long-term** strategy for VL is to bring new candidates into clinical development through its lead optimization programme with the ultimate goal of developing an oral combination treatment.

For **CL**, DND*i*'s objective is to develop short, safe, efficacious, affordable, and field-adapted treatments for CL caused by *L. tropica* and *L. braziliensis* – because of the severity of the disease and its public health importance. As a **short-term** strategy, DND*i* is developing a topical treatment based on amphotericin B. In the **longer term**, DND*i* aims to develop a novel field-adapted modality of treatment for CL caused by *L. tropica* and *L. braziliensis* that would combine anti-parasite and immune-modifying agents, with a strong emphasis on safety, efficacy, cost, size of scar, and reduced need for follow-up and interaction with health systems.

In addition, DND*i* supports the **Leishmaniasis East Africa Platform** (LEAP) that aims to geographically extend all currently available **VL** drugs in East Africa and to develop new therapies suitable for the region, as well as to build and sustain capacity in the region for conducting clinical trials.

By 2018, DND*i* aims to deliver from its VL-specific portfolio:
→ An oral, safe, effective, low-cost and short-course treatment
→ A new treatment for PKDL that is shorter course and better tolerated than current options
→ Treatment options for HIV/VL co-infected patients

By 2018, DND*i* aims to deliver from its CL-specific portfolio:
→ A safe, effective, and shorter-course treatment for CL

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