



Securing access to current treatments while researching better options

The WHO estimates that about 7 to 8 million people are infected with this potentially life-threatening disease. It predominantly affects people in Latin America, but is now spreading to other continents due to population flows. Today, only an estimated 1% of those affected are treated. *Trypanosoma cruzi* parasites are mainly transmitted by contact with the faeces of infected blood-sucking triatomé 'kissing' bugs, but infection can also occur through eating food contaminated by infected insects, blood transfusions, organ transplants, and from an infected mother to her baby during pregnancy or childbirth. Newborns are included among the many who are not diagnosed with the infection and so do not receive treatment.

Benznidazole is one of two drugs currently used to treat Chagas disease, and LAFEPE and DNDi have successfully developed a formulation suitable for children up to the age of two. Although it is currently the best available treatment option, benznidazole does have frequent side effects in adults, and so DNDi is also working with partners to develop new improved treatments and regimens, with decisions taken in 2013 to pursue studies on fexinidazole and alternative dosing of benznidazole. Drug development is a challenging process, all the more so for diseases such as Chagas where reliable animal models are lacking. Two potential new compounds from the same drug class, posaconazole and E1224, had shown promise *in vitro* and *in vivo*, but produced disappointing results when tested as monotherapies in clinical trials. It is vitally important that the correct tools and decision-making processes are in place to maximize the available opportunities and keep development costs to a minimum. The data from the E1224 trial (which also tested benznidazole), the first ever Phase II clinical trial to take place in Bolivia, provided clear efficacy and safety information for both compounds and will be valuable in guiding further drug development.

Recently, progress has been made towards improving the availability of current treatments for Chagas disease patients. In December 2012, the Mundo Sano Foundation

and DNDi launched a collaboration agreement to work together on the Mundo Sano-led drug consortium's (notably ELEA) vital second source of benznidazole for children affected by Chagas disease. The agreement focuses on drug production, patient access, and on securing affordability and accessibility to patients. In addition, the Global Chagas Disease Coalition brings together DNDi and major partners – including the Sabin Vaccine Institute and Texas Children's Hospital Center for Vaccine Development and National School of Tropical Medicine at Baylor College of Medicine (USA), the Mundo Sano Foundation (Argentina), CEADES (Bolivia), and ISGlobal (Spain) – with the support of Doctors Without Borders (MSF), the International Federation of People Affected by Chagas Disease (FINDECHAGAS), and the Health Institute of the Carlos Slim Foundation.



The aim of the Coalition is to address patients' needs by boosting access to existing health tools and treatments, supporting integrated vector-control prevention measures, and expanding global efforts to stimulate innovation for new and improved tools to treat and control Chagas disease.⁽¹⁾ Such action is urgently needed by the 99% of Chagas patients who are not accessing treatment today, despite increasing evidence of the impact of treatment even in the adult chronic stage of the disease.

Ideal Target Product Profile for Chagas Disease

A new treatment for both acute and chronic phases:

- Useful against most parasite species in all regions
- Better **safety** profile than existing drugs
- Non-inferior **efficacy** to benznidazole
- **Easy-to-use** treatment: oral, once-a-day for less than 30 days, requiring no hospitalization and little or no monitoring
- **Affordable**
- **Adapted to tropical climates** (minimum three-year shelf-life)

(1) Declaration of the Global Chagas Disease Coalition. PLOS Blogs. October 21, 2013.

→ FACT SHEET

WHAT IS THE IMPACT OF CHAGAS DISEASE?

Chagas disease is endemic to 21 countries in Latin America, where 100 million people are at risk. It is estimated that 8 million people are infected, leading to approximately 12,000 deaths every year in the region⁽¹⁾ and substantial economic burden.⁽²⁾ There are approximately 55,000 new cases each year.⁽³⁾ Increased migration and population movements have changed the epidemiology and geographic distribution of Chagas disease, which is now found outside Latin America, including in the United States, Europe, Australia, and Japan.

HOW IS CHAGAS DISEASE TRANSMITTED?

Chagas disease is related to infection by the kinetoplastid protozoan parasite *Trypanosoma cruzi*, most commonly transmitted by a triatomine vector known as the 'kissing bug'. Other routes of transmission include blood transfusion, organ transplantation, as well as congenital and, less often, oral routes through ingestion of contaminated food or beverages, especially in Amazonia.

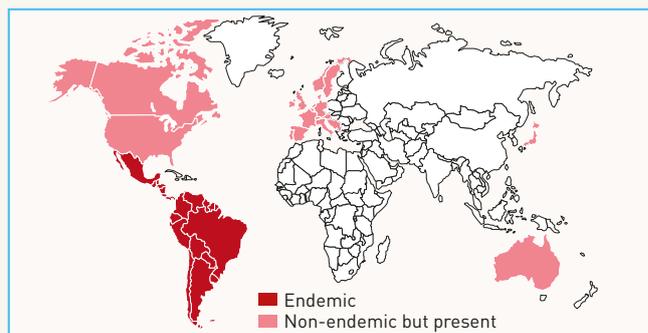
WHAT ARE THE SYMPTOMS?

The disease has two clinical phases:

→ **The acute phase** (fatal for 2-8% of children),⁽⁴⁾ often asymptomatic or unrecognized due to non-specific symptoms, such as fever, malaise, and enlarged lymph nodes, spleen, and liver. In less than half the cases, first visible signs can be a skin lesion or a purplish swelling of one eyelid (known as Romaña's sign). These symptoms spontaneously resolve in 4-6 weeks.

→ **The chronic phase**, which can be divided into two stages:

- The chronic and asymptomatic 'indeterminate' stage, during which patients can transmit the parasite to others, especially through vertical transmission or transfusion, while showing no signs of the disease, and which may last decades after infection.
- The chronic, symptomatic stage, developing later in up to 30% of infected patients, causes cardiopathies, digestive tract pathologies, and nervous system irregularities.⁽⁵⁾ Chagas disease is the leading cause of infectious heart disease (cardiomyopathy) in Latin America.



WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

Current treatments, **benznidazole and nifurtimox**, are effective against the acute phase of infection, and while there is increasing evidence of their efficacy against the chronic phase of the disease, broad use of these drugs is limited due to safety and tolerability issues. Drawbacks

include long treatment periods (60-90 days), dose-dependent toxicity, and a high drop-out rate of patients due to side-effects. There is currently no approved treatment for chronic disease with target organ involvement. In 2011, DNDi and partners produced a paediatric dosage form of benznidazole to fill the treatment gap for this population.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

DNDi's **short-term** goal was to make better use of existing treatments, for example through the development of a paediatric dosage form of benznidazole – a goal which was achieved. The treatment is registered in Brazil (2011), and was included on the WHO Essential Medicines List for children in 2013. An agreement signed in 2013 with the Mundo Sano Foundation will ensure a second source of the treatment previously manufactured solely by LAFEPE. Collaborative activities will continue to support greater treatment availability and adoption by countries.

As a **medium-term** strategy, DNDi has been assessing known families of compounds such as the new azole antifungal drug, E1224, for activity against *T. cruzi* in adult chronic patients. Results from a proof-of-concept trial showed E1224 monotherapy to have some short-term effect on parasite clearance but with insufficient long-term efficacy, and the current regimen of benznidazole to be efficacious in the long term, but with side effects. Alternative benznidazole regimens, including reduced dosing in monotherapy and combination treatment are being explored. Fexinidazole, currently in development for HAT and VL, is also being evaluated. Additionally, DNDi continues to search for potential biomarkers of treatment response to enhance clinical trial capabilities for evaluation of new compounds.

As part of its **long-term** strategy, DNDi continues to identify and engage partners from private and public sectors in order to identify, characterize, and advance the development of promising compounds as well as to pursue discovery efforts for innovative therapies.

In addition, DNDi supports clinical research capabilities and access through the **Chagas Clinical Research Platform**, which was launched in 2009.

By 2018, DNDi aims to deliver from its Chagas-specific portfolio:

- An effective and safe oral therapy for the treatment of chronic indeterminate Chagas disease, ideally also effective against the acute form of the disease
- Biomarkers to gain understanding of disease progression and ease the development of tools for evaluation of treatment response to support drug development

(1) http://new.paho.org/hq/index.php?option=com_content&task=view&id=5856&Itemid=4196 (2) *Lancet Infect Dis.* 2013 Apr;13(4):342-8. doi: 10.1016/S1473-3099(13)70002-1. Epub 2013 Feb 8. (3) *Estimacion cuantitativa de la enfermedad de Chagas en las Americas.* Montevideo, Uruguay: Organizacion Panamericana de la Salud, 2006. (4) Parada H, Carrasco HA, Anez N, Fuenmayor C, Inglessis I. Cardiac involvement is a constant finding in acute Chagas' disease: a clinical, parasitological and histopathological study. *Int J Cardiol.* 1997. 60: 49-54. (5) http://www.msfaaccess.org/sites/default/files/MSF_assets/NegDis/Docs/NEGDIS_report_Chagas_UpdateOnProgress_ENG_2006.pdf