Hagares disease is transmitted predominantly through contact with the faeces of infected triatomine bugs, deposited on the skin during a blood meal. These insects typically hide in crevices of poorly-constructed homes in rural or suburban areas. Blood, organ transplant, and congenital transmission also occurs, and cases of oral transmission through ingestion of food infected by bugs have recently been documented.

The distribution and impact of the disease varies from country to country. In Bolivia, it is likely that the majority of the population is affected by Chagas disease: prevalence estimates vary between 40-70% of the adult population, and are difficult to assess more accurately without sero-epidemiological surveys, given the frequently asymptomatic nature of the chronic form of the disease. In Brazil, only 2% of the population is infected, although given that the population exceeds 200 million people, the actual numbers affected are huge.

Maximizing the impact of diagnosis and treatment

Until recently Chagas disease was confined to the Americas, principally Latin America, but over the years it has spread to North America and Europe due to population flows. Today, one of the most important areas of work in Chagas disease is access to medicines and diagnosis. The majority of patients with Chagas disease are asymptomatic and just a very small fraction of those affected are being detected and treated. The numbers are staggering, with estimates of less than 1% of Chagas disease patients receiving treatment with either benznidazole or nifurtimox. A number of factors are involved, but there is a clear need for concerted multi-disciplinary action to change the current situation. Despite growing evidence of drug efficacy and the different operational approaches employed, no medical or operational consensus has been reached in many endemic countries. It is necessary and imperative to ensure registration of existing drugs against Chagas disease in all endemic countries. In order to evaluate which deployment models have the greatest local impact, DNDi and partners will initiate a series of pilot projects in strategic countries which aim to assess the impact of scaling up diagnosis and treatment, with integration into local health systems. Different delivery models will be evaluated and defined with local stakeholders, from governments to academia and civil society, and are expected to be sustainable and replicable in similar contexts.

DNDi, as part of the Global Chagas Coalition and with other partners, advocates strongly for increased diagnosis and access to treatment across all age groups, but notably infants, young children and non-pregnant women of child-bearing age. Recent data indicate that treating the latter prevents transmission of Chagas disease during pregnancy, and is therefore an important disease control strategy.

There is also a need for international registries to support surveillance of diagnosis and treatment of chronic cases, pharmacovigilance, and long-term follow-up for a better understanding of Chagas epidemiology and distribution, as well as to identify major gaps in existing data.
The disease has two clinical phases, the **acute phase** (fatal for 2-8% of children), which is often asymptomatic or unrecognized, and the **chronic phase**, which can be divided into two stages:

- **The chronic, asymptomatic (or indeterminate)** stage, during which patients can transmit the parasite to others (mostly through blood, congenital transmission or occasionally organ transplant) and which may last decades after infection.
- **The chronic, symptomatic** stage, developing later in up to 30% of infected patients. Chagas disease causes abnormal dilation of the large intestine (megacolon), and is the leading cause of infectious heart disease (cardiomyopathy) in the world and the leading cause of death from a parasitic disease 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 has been limited due to lack of guidelines and policies supporting implementation. 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 the chronic form of the disease with target organ involvement.

### 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 in 2011. 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 solely manufactured by LAFEPE. Collaborative activities will continue to support country registration and adoption, and greater treatment availability to patients.

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 and duration of treatment in monotherapy and combination treatment with E1224 are being explored. Fexinidazole, also 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 (see p. 53), which was launched in 2009.

Ideally, a new treatment would be for both **acute and chronic** phases of the disease, useful against most parasite species in all regions, with a better **safety** profile than existing drugs, non-inferior **efficacy** to benznidazole, **easy-to-use** (oral, once-a-day for less than 30 days, requiring no hospitalization and little or no monitoring), **affordable, and adapted** to tropical climates.

By 2020, DNDi aims to deliver from its Chagas-specific portfolio:

- **An effective and safe new oral treatment regimen 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**