

CHAGAS DISEASE



Health workers at the Mizque health care centre, Cochabamba, Bolivia.

› **Chagas disease** is endemic in 21 Latin American countries and in the USA, and is of increasing concern in Europe due to migrant populations. The asymptomatic nature of chronic disease means that it is difficult to know exactly how many people are infected, but current estimates are of 5.7 million people in Latin America alone, indicating that more than 6 million people are likely to be affected worldwide. It is the leading cause of infectious cardiomyopathy in the Western hemisphere. Chagas disease mostly affects those living in poverty, and to date less than 1% of people infected with *Trypanosoma cruzi* have access to diagnosis and treatment, despite the fact that more than one-half of Chagas disease sufferers live in Latin America's wealthiest countries – Argentina, Brazil, and Mexico. The only drugs developed which successfully kill *T. cruzi* parasites are nifurtimox and benznidazole, both more than 40 years old, and although effective, they are used as long treatment regimens and cause frequent side effects. Benznidazole is currently produced in Brazil and Argentina.

The benznidazole/fosravuconazole (E1224) trial carried out by DNDi and partners confirmed the long-term efficacy of benznidazole, although with the already observed side effects, and further trials are planned to evaluate shorter treatment courses and lower doses of benznidazole with and without fosravuconazole, aiming to maintain or increase efficacy and improve safety. In addition, the recently completed Merck-sponsored STOP Chagas trial in adults with asymptomatic chronic disease confirmed the efficacy of benznidazole and the lack of sustained effect by the azole class of compounds as treatment for Chagas. However, the BENEFIT (Benznidazole Evaluation for Interrupting Trypanosomiasis) trial showed benznidazole treatment was not effective in preventing progression of disease in patients with known Chagas cardiac involvement. These

results highlighted the importance of early diagnosis and treatment of Chagas patients. Fexinidazole is also being evaluated in adults with chronic indeterminate disease and early stage drug discovery efforts are aiming to identify entirely new chemical entities for development.

In response to the lack of access to treatments, DNDi proposed a project to assess the feasibility of scaling up treatment and access to benznidazole, in five countries in the Americas. Previous work undertaken has shown an important paradigm shift over the past two years, from discussing vector control to focusing on the urgent need to scale up access to diagnosis and treatment in Latin America. Throughout 2015, DNDi has worked closely with the Colombian Chagas National Control Programme, providing technical support to create the enabling environment needed to scale up access to diagnosis and treatment for Chagas in Colombia. As a result of meetings and discussions between the Ministry of Health, the National Control Programme, and the Red Chagas Colombia

programme, a comprehensive roadmap for Chagas has been developed which defines operational interventions – such as implementation of pilot projects in four different regions in the country, registration of benznidazole, and support for validation of a new national diagnostic protocol for Chagas disease – which are due to start in 2016. A project in Mexico will focus on short- and medium-term approaches to further assess the disease burden, raise awareness, and ultimately improve patient access by working with the Ministry of Health and other stakeholders. Furthermore, there is the aim to identify and address barriers to access diagnosis and treatment in the USA, as there are large numbers affected by Chagas disease in areas with large populations from endemic countries – such as in California, Florida, and Texas – who are excluded from the healthcare system.

Improving treatments and access to medicines

CHAGAS DISEASE

The disease has two clinical phases, the **acute phase** (fatal for 2-8% of children), which is often asymptomatic or poorly symptomatic and 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), 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 in the chronic indeterminate 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 (chronic symptomatic stage).

Endemic in

21 countries

IN LATIN AMERICA

70 million
people at risk

5.7 million

people infected,
leading to approximately
7,000 deaths every year

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 by LAFEPE (2011), and was included on the WHO Essential Medicines List for children in 2013. An agreement signed in 2013 with the Mundo Sano Foundation ensures a second source of the paediatric dosage form to be produced by ELEA. 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 nitroimidazoles and the new triazole antifungals, for activity against *T. cruzi* in adult chronic patients. A proof-of-concept trial showed fosravuconazole (E1224) monotherapy did not show sustained efficacy, as measured by sustained parasite clearance one year after end of treatment. In contrast, the current regimen of benznidazole was very efficacious over the period of 12 months of follow-up. Alternative benznidazole regimens, including reduced dosing and duration of treatment in monotherapy, and combination treatment with fosravuconazole, are now being explored.

Fexinidazole, a non-genotoxic nitroimidazole currently in development for HAT and VL, is also being evaluated for treatment of adult indeterminate Chagas disease. 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. 60), which was launched in 2009.

Ideally, a new treatment would target both acute and chronic phases of the disease, with activity against most parasite species in all endemic regions, with a better safety profile than existing drugs and non-inferior efficacy to benznidazole, being 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, safe, new oral treatment regimen for chronic indeterminate Chagas disease, ideally also effective against the acute form of the disease
- Biomarkers to gain understanding of disease progression and support evaluation of treatment response to support drug development