



# NEWSLETTER

CHAGAS DISEASE CLINICAL RESEARCH PLATFORM

The Chagas Disease Clinical Research Platform was created in 2009, the centennial anniversary of the discovery of the disease. Its main objective is to provide support with overcoming challenges in research and development (R&D) for Chagas disease through a flexible network focused on meeting health needs and facilitating diagnosis and treatment of *T. cruzi* infection.

In this manner, the Platform continues to pursue mechanisms and synergies to facilitate development of new drugs and tools for Chagas disease. By creating an open, innovative, collaborative and patient-oriented environment, the

Platform promotes annual meetings, training, standardization of protocols, regulatory aspects, and integration of ethical principles. The Platform provides a forum for technical discussions and exchange of information about Chagas disease, while supporting efficient use of resources by avoiding duplication of efforts.

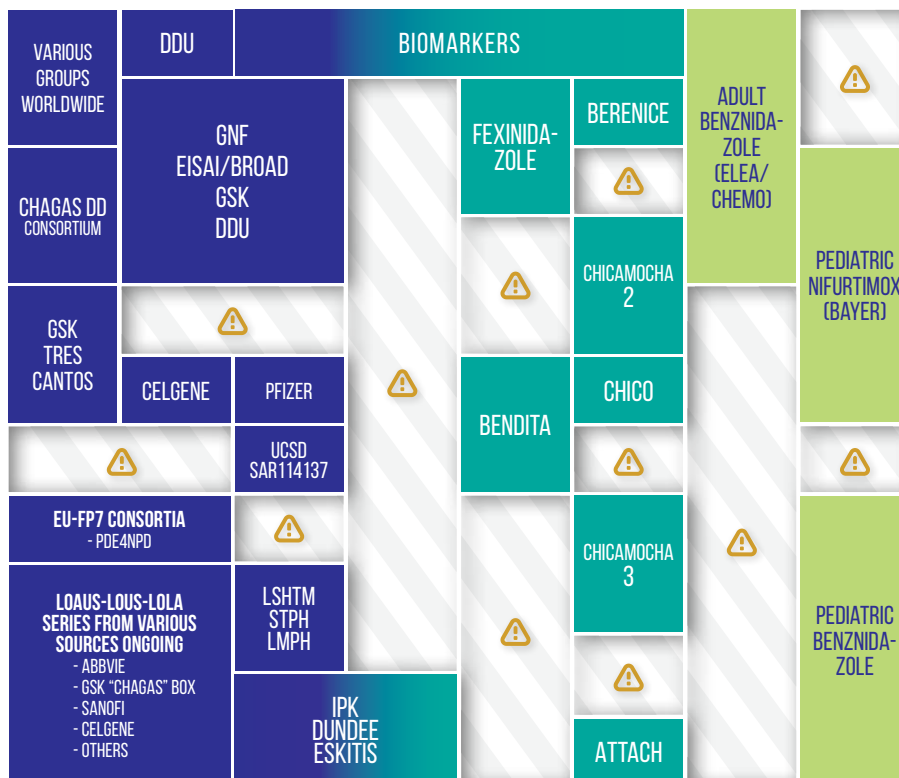
Currently, the network comprises more than 370 members from 23 endemic and nonendemic countries. Representing more than 90 institutions, these individuals come from diverse backgrounds including research, academia, government, international and national organizations, and

patient associations.

Recent advances in knowledge paired with an increasing number of research investigations and initiatives for Chagas disease provide renewed optimism and underline the importance of open collaboration and fluid exchange of information. Striving for cooperation among R&D initiatives, the Chagas Platform continues to facilitate clinical research, promote professional development, and strengthen institutional structures and capacities, while championing accessible, easy to administer treatments, as well as new tools for diagnosis and monitoring of the disease.

## CHAGAS R&D LANDSCAPE

### RESEARCH → TRANSLATIONAL → DEVELOPMENT



⚠ RESEARCH GAPS

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## PROGRESSES AND CHALLENGES IN THE 8 YEARS OF THE CHAGAS PLATFORM

ISABELA RIBEIRO AND SERGIO SOSA-ESTANI, DNDi



In 2005, DNDi launched an agenda for Chagas disease focused on developing a pediatric formulation of trypanocidal drugs and a research portfolio of treatment alternatives for chronic Chagas disease. This was the forerunner for what would become the Platform for Clinical Research in Chagas Disease, launched in 2009, which currently involves more than 300 stakeholders, including researchers from the public and private sectors, patient organizations, and health services personnel.

The Platform's has many significant accomplishments, such as the ones highlighted below:

- A profile for a target product for treatment of Chagas disease, defined in 2010 and revised periodically (most recently in March 2015);
- Led the process that helped achieve a consensus in the scientific community on a randomized clinical trial to evaluate response to new trypanocidal drugs within a maximum of two years, a design used by various groups to evaluate triazole compounds;
- Provided an environment for productive discussions on preclinical models;
- The Platform was a facilitator for the standardization and optimization of polymerase chain reaction (PCR) in the diagnosis and evaluation of the impact of Chagas treatment;
- Significant contributions were made to the investigation of biomarkers for treatment response, especially with the use of PCR, and in the evaluation of proteomics, multiplex assays, and recombinant antigens;
- Supported the initial speculation for later creation and evolution of the Chagas patient's associations, which gather people affected by the disease and healthcare workers;

- DNDi and the Platform provided support through technical consultancy during the registration process for pediatric formulations of benznidazole in Brazil, Argentina, and other Latin American countries, and currently supports ongoing efforts to expand registration of the drugs and promote access plans to optimize the use of the trypanocides Benznidazole and Nifurtimox.

All this scientific exchange and encouragement has brought to DNDi its strategic orientation, allowing the delivery of a pediatric formulation of benznidazole in 2011, screening of thousands of compounds, and the definition of steps for the optimization of new candidate compounds. A phase I trial was conducted to evaluate the safety of a drug combination, two phase II clinical trials were finalized, and there are two new trials currently under way. The current strategic plan includes two phase II clinical trials studying nine alternative arms that will furnish options for phase III trials, besides validating biomarkers of treatment response.

We will work in the Platform to seek coherence and efficiency in clinical and preclinical studies in Chagas disease, and to advance and fill knowledge gaps for the development of new tools. While all these studies are underway, access to current trypanocidal drugs using the prevailing regimens is being promoted.

We view the Platform as a dynamic organization that provides services together with strategic partners in the scientific and academic community and industry, acting as a facilitator with other stakeholders such as the Chagas Coalition, Ministries of Health, and PAHO-WHO, in programs for access that allow care for persons with Chagas diseases to become an increasing reality, with impact on a feasible path to the elimination of Chagas disease as a public health problem.

# THE CHAGAS PLATFORM 2016 PERFORMANCE SURVEY

MARINA CERTO, DND; LATIN AMERICA

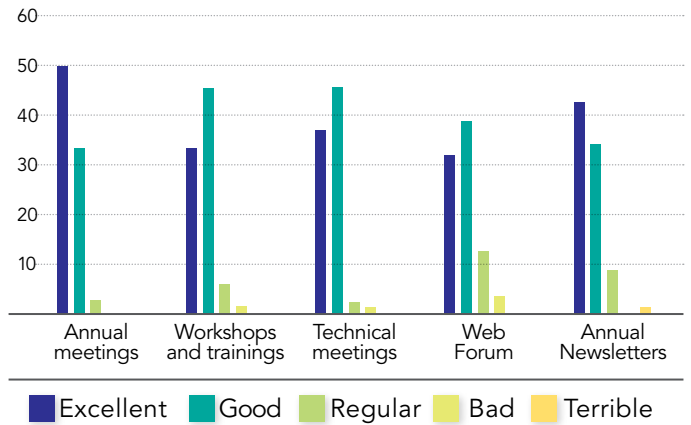
Since 2009, the Chagas Clinical Research Platform has been supporting the definition of a flexible and patient’s driven network.

By facilitating a structured strategy of R&D and access initiatives for Chagas disease, it aims a change of the diagnosis and treatment in Chagas disease paradigm while enhancing capacity building and cooperation in endemic and non-endemic countries.

The Chagas Platform has been constantly expanding and consolidating itself through a collaborative network of different stakeholders. The number of people involved in these activities has been growing constantly, totalizing 378 Web Forum members from 23 countries in April 2017. The 2016 Annual Meeting had more than 270 attendees, exceeding previous meetings by its larger number of participants and activities.

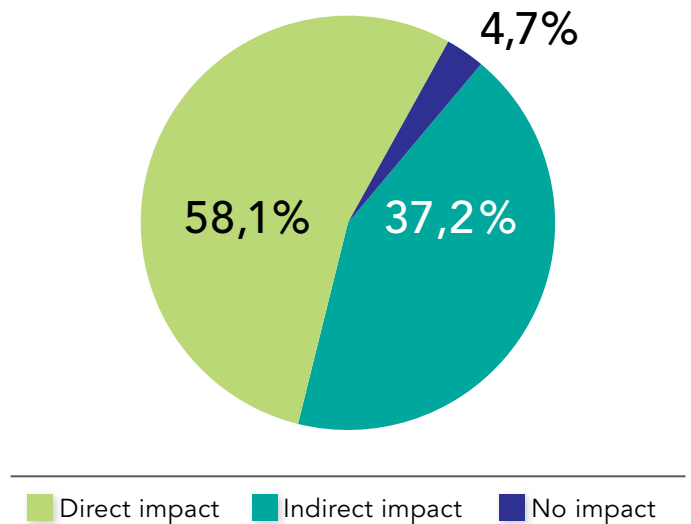
In 2016, the Chagas Platform Performance Survey was carried out with its the members, receiving very positive feedback from 86 answers. In this survey, it was possible to access the profiles of the Platform’s most active members. The results have shown that most of the members represent R&D institutions (38.1%), while National Health Programs (21.4%), educational institutions (19%) and NGOs (15.5%) are also numerous. Although most of the CCRP researchers are currently working on clinical projects (50%), many are also dedicating themselves to access issues (19.2%). Most of the active members are female (59%) and about 41% have completed a master’s degree, while 40% are doctors. The great majority of members work in South America (73%); 12% are in Europe and other 12% in North America.

## EVALUATION OF THE CHAGAS PLATFORM ACTIVITIES



To conclude, we emphasize that 43% of the survey answers stated that members had started a cooperative partnership that led to a specific project, thanks to Platform activities. In addition, 95.3% of the replies stated that the Platform influenced their work or in their organization’s performance, providing an indirect or direct impact on their activities. Thereby, eight years after its creation, the Chagas Platform remains as a main tool for knowledge-sharing, cooperation and regular debates about the latest scientific and political updates about Chagas disease, expanding community participating and strengthen capacities.

## CHAGAS PLATFORM IMPACT ON IT’S MEMBER’S WORK OR THEIR PERFORMANCE



# UPDATE ON CHAGAS DISEASE IN 2017

ROBERTO SALVATELLA AND LUIS GERARDO CASTELLANOS,  
OPAS/OMS

**Chagas disease or American trypanosomiasis, since its description in 1909 by the brilliant Brazilian scientist Carlos Chagas,** has undergone various epidemiological, political, social, economic, cultural, and technical and scientific phases in the Latin American societies plagued by this endemic, chronic, and silent disease.

As a “neglected disease”, it has never been a priority or highlight in the political and health policy decisions of the majority of the endemic countries. Chagas disease is a regional and rural disease, typical of rural and peripheral urban populations who carry little decision-making weight in the local or national scenario. As such, the disease has persisted and resisted the countries’ efforts at prevention, control, and treatment in the last 30 years.

Although several countries had already developed their own national programs for prevention and control, the most striking response to this parasitic disease in Latin America came in the early 1990s, when these countries decided to prioritize horizontal South-South technical cooperation to tackle the problem. Latin America then witnessed Sub-Regional Initiatives for the Prevention, Control, and Treatment of Chagas Disease in the Southern Cone (INCOSUR/Chagas), Central America and Mexico (IPCAM/Chagas), Andean Region (IPA/Chagas), and Amazonia (AMCHA/Chagas), all with PAHO as the Technical Secretariat.

The success of these Sub-Regional Initiatives has hinged fundamentally on the support, stimulus, and decisive participation of the Latin American technical and scientific community in Chagas disease.

## THE WORK BY THESE COUNTRIES REMAINS IN PROGRESS, HAVING ALREADY ACHIEVED THE FOLLOWING:

- Interrupt the domiciliary transmission of *Trypanosoma cruzi* by the principal triatomine species in part or all of the endemic areas in 17 countries;
- Eliminate imported vectors as a public health problem in several of these countries;
- Universal screening of blood donors for Chagas infection in public blood banks in the endemic countries;
- Gradually and progressively (although still incipiently) organize the hierarchical improvement of coverage and quality of care for Chagas patients.

Much remains to be done, and the scenario has changed, revealing new and challenging risk situations for transmission and the disease that require equally innovative tools, strategies, and methodologies to help the Latin American region make new strides against this disease, thereby protecting the health of the people of the Americas.

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# INTERVIEW WITH ASOCHAGAS - COLOMBIAN PATIENTS' ASSOCIATION



MARINA CERTO, DND; LATIN AMERICA

## 1. WHAT IS THE PURPOSE OF THE ASSOCIATION? CAN YOU PROVIDE SOME HISTORICAL BACKGROUND? HOW DID THE GROUP BEGIN ITS ACTIVITIES?

ASOCHAGAS aims to help Chagas patients not just individually, but collectively. Our main motivation is for government, which has the ultimate responsibility for the health of the Colombian people, to be aware of patients' reality regarding their surroundings, families, caregivers, and society at large; to assess the services provided to them; and to take the necessary steps to ensure good services.

The association was born from the need to continue the excellent leadership work done by Reynaldo Bohórquez, who died from the disease, and who before passing away suggested that others continue his struggle for Chagas patients. We embraced the organization's mission, announced our intention to the relevant institutions, and began collaborating with some of them.

## 2. HOW WOULD YOU DESCRIBE THE SITUATION OF PEOPLE WITH CHAGAS DISEASE IN COLOMBIA?

They suffer, because they lack access to treatment, follow-up, and control due to various factors, namely lack of awareness of their rights and duties and government inefficiency in providing quality services.

## 3. HOW DO YOU HELP MEMBERS ADAPT TO LIFE WITH THE DISEASE?

They feel useful when working for other patients, and insofar as possible we provide psychological follow-up and teach patients and their family members that patients can die with the disease, but not from the disease, as long as they follow a healthy lifestyle.

## 4. WHAT HAVE THE ASSOCIATION'S PRINCIPAL GAINS BEEN THUS FAR?

Having a seat on the board of FINDECHAGAS, and urging the Colombian government to take a more holistic view of patients.

## 5. WHAT IS YOUR VISION FOR THE FUTURE FOR CHAGAS PATIENTS? WHAT PROGRESS WOULD YOU LIKE TO SEE IN THE NEXT FEW YEARS?

Patients should be well treated by both the medical community and society, and have full knowledge of their disease and how to prevent it.



# THE GLOBAL CHAGAS DISEASE COALITION AT THE NEGLECTED TROPICAL DISEASES SUMMIT IN GENEVA, APRIL 2017

SILVIA MORIANA, GLOBAL CHAGAS COALITION

The Global Chagas Disease Coalition played an active role in the recent **Neglected Tropical Diseases Summit in Geneva** from April 20-22. The meeting was held a day after the WHO Global Partners Meeting on Neglected Tropical Diseases, featuring a progress report on control of neglected diseases in comparison to projected milestones. On April 20th and 21st, under the coordination of **Uniting to Combat NTDs**, the meeting celebrated the fifth anniversary since the London Declaration and reviewed the challenges facing ten neglected diseases, including Chagas.

We view the NTD Summit as a crucial moment for reflecting on current challenges for controlling Chagas disease, calling attention to the urgent

need to increase access to diagnosis and treatment and reinforce the presence of Chagas disease on the global health agenda. During the summit, the Coalition coordinated the specific sessions on Chagas disease that focused on: 1) current challenges and future prospects for improving access to diagnosis and treatment; 2) operational models that have demonstrated the possibility of integrating care for Chagas disease within the healthcare system; and 3) research and development priorities to support greater access. We drew on contributions from different perspectives, ranging from public health officials to patients in affected countries, and including representatives from the WHO, academia, industry, and nonprofits, among others.

The NTD Summit also provided an opportunity for stakeholders working on Chagas disease to join forces with other communities of neglected diseases with a long history of collaboration toward common goals. The challenges for the various diseases are often similar, and it is necessary to collaborate and issue a common call on the importance of continued investment to further improve progress. In addition, integrated strategies can foster progress in controlling these neglected diseases. At the end of the summit, our contribution was reflected in the manifesto by all the NTD communities which will be delivered to the new WHO administration.



Chagas Coalition on the NTD Summit

# DRUG DISCOVERY IN ENDEMIC AREAS: UPDATES FROM DNDi'S LEAD OPTIMIZATION LATIN AMERICA (LOLA) CONSORTIUM

JADEL MÜLLER KRATZ, DNDi LATIN AMERICA



Team of the São Paulo University in São Carlos, led by Prof. Adriano Andricopulo

The pathway from the identification of an active compound against *Trypanosoma cruzi* to its clinical development for Chagas disease is long and full of hurdles. Accumulation of knowledge about the disease and parasite, together with the implementation of new technologies and in vitro/in vivo models, is undoubtedly assisting the researchers working within this pipeline. But there is still a major need for novel collaborative approaches, in which multidisciplinary investigators work together in the discovery and development of new chemical entities (NCEs).

In this view, DNDi launched in 2013 its drug discovery activities for Chagas disease in Latin America. The creation of the Lead Optimization Latin America (LOLA) consortium is aligned with one of the three pillars of DNDi's mission: continuous capacity strengthening in endemic areas. In this case, the consortium is building a medicinal chemistry research

network. A full lead optimization team (10-12 scientists) is now in place within the two official LOLA partners in Brazil – the group of organic synthesis at UNICAMP, Campinas/SP, led by Dr. Luiz Carlos Dias, and the group of medicinal and computational chemistry at the University of São Paulo (USP), São Carlos/SP (photo), led by Dr. Adriano Andricopulo and Dr. Glaucius Oliva. The teams benefit from the support of international DNDi partners in academia and industry (e.g. AbbVie, University of Antwerp, Swiss Tropical and Public Health Institute, London School of Hygiene and Tropical Medicine) and the consultancy from medicinal chemists with large expertise on NCE development. The consortium is

currently funded in large part via a BNDES grant in partnership with Fiocruz (with complementary DNDi core support and in-kind contributions from partners). Present hit-to-lead activities include, but are not limited to, the optimization of three chemical series and the in-house validation of an in vitro screening cascade implemented at USP/IFSC.

Despite progress, many challenges still lay ahead until formal preclinical candidates emerge. The commitment and involvement of additional Latin American partners is being pursued to promote the inclusion of in vivo proof-of-concept studies and supplementary DMPK activities into the consortium. In fact, the interaction with multiple discovery groups is highly desirable, regardless of the level of engagement (e.g. formal collaboration agreements, consultancy, fee-for-service contracts). It allows the exchange of expertise and resources, and avoids redundancy of efforts in the quest for novel and affordable medicines for Chagas disease.

# BIOMARKERS OF CHAGAS DISEASE: TOWARDS A BETTER STRATEGY TO A NTD

MARIA JESUS PINAZO, SENIOR SPECIALIST, INTERNATIONAL HEALTH SERVICE, HOSPITAL CLINIC OF BARCELONA. INVESTIGATOR. TECHNICAL COORDINATOR OF THE COMPREHENSIVE CARE PLATFORM FOR PATIENTS WITH CHAGAS DISEASE IN BOLIVIA. ISGLOBAL. BARCELONA, SPAIN

## It is always disappointing for a clinician to face a person with *T. cruzi* infection who is eligible to start antiparasitic treatment

(even if it is not always well tolerated), and who poses the following question: "I want to start treatment for my Chagas disease, and I trust that it will be effective, but when will we know if it worked?" On the other hand, the lack of prognosis and progression markers for chronic Chagas disease is also a limitation for testing new and better tolerated drugs to treat this neglected disease.

To inform patients about treatment outcomes and have a tool to assess antiparasitic drugs' efficacy early after treatment, several research groups have been working over the past few decades on the development of prognosis and progression biomarkers. Among the most promising, are nucleic acid amplification techniques, which have developed exponentially during recent years. Up to now, the main use of PCR has been to assess therapeutic failure, but due to the increasing sensitivity of RT-qPCR methods, nucleic acid amplification techniques are today considered the primary option for congenital Chagas diagnosis, and a valuable tool for the management of patients with immunosuppressive conditions. The use of RNA ligands (aptamers) is also included in this group.

Regarding other biomarkers related to the parasite itself, several proteins and glycoproteins isolated from the parasite (i.e., the F29 protein), as well as recombinant proteins and groups of proteins purified from different forms of the parasite (KMP11, PFR2, Tgp63, HSP70) have proven to

be good prognosis markers, and fulfill criteria established by a TPP designed to evaluate potential biomarkers of response to treatment. Among them, parasite-derived glycoproteins and synthetic neoglycoconjugates are especially interesting molecules, and are currently being used in the development of a glycan-based preventive and therapeutic vaccine.

The groups of biomarkers related to the host response to the parasite are also of high interest. Biochemical biomarkers such as apolipoprotein, fibronectin fragments and hypercoagulability markers have been tested early after specific treatments in patients in different stages of CD. Cytokines and surface markers are also promising molecules that can be used to characterize host cellular responses, but their role in diagnosis and prognosis of *T. cruzi* infection and as biomarkers of response to treatment should be further studied.

The development and future use of biomarkers will allow for dramatic improvement of therapeutic options for people who suffer from this neglected disease.

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# DEVELOPMENT OF A PEDIATRIC FORMULATION OF NIFURTIMOX - CLINICAL TRIAL

JAIME ALTCHER, RICARDO GUTIÉRREZ CHILDREN'S HOSPITAL

**The efficacy and safety of drug therapy for Chagas disease in children is supported by a growing body of evidence.** Few trials have been conducted in the pediatric population, however. In recent years, a study developed at the Ricardo Gutiérrez Children's Hospital in Buenos Aires laid the foundations for the development of a pediatric formulation. Nifurtimox, which was widely used in Argentina, was only available in one pharmaceutical form: 120 mg tablets designed for treating adults. Because of this limitation, the tablets had to be divided. This made administration tricky and it was hard to establish an appropriate dose regimen for the drug, especially in the case of small children.

At the same time, there has been a dearth of published pharmacokinetic data in children up to now. This information is of vital importance for proper definition of the doses and duration of treatment in children, these having previously been deduced empirically from the data in adults. The knowledge gap that exists regarding the pharmacokinetic properties of nifurtimox in the pediatric population led to planning and implementation of a study to provide the information needed to adjust pediatric doses and treatment regimens based on knowledge generated specifically in trials involving children.

The pharmaceutical company Bayer started to develop a 30 mg dispersible pediatric formulation and planned the necessary trials to validate previous knowledge on nifurtimox with a view to getting it registered with the FDA. The first trial assessed the equivalence between the available 120 mg formulation and a new

30 mg dispersible pediatric formulation in 24 adult volunteers with Chagas disease (NCT01927224). The pharmacokinetic properties of the 30 mg tablet administered directly and after dissolution in 2 ml water were also studied in 12 subjects. An open-label, randomized, single-dose cross-over design was used. This trial found adequate pharmacokinetic equivalence between the two formulations. The adverse events recorded were mild and of a gastrointestinal nature.

Nifurtimox is sparingly soluble and highly permeable, and its absorption might be affected by ingestion with food, although this has not been properly assessed. A Phase I trial was conducted which compared the pharmacokinetic properties of the drug when administered on an empty stomach and after eating in 36 adult subjects with Chagas disease (NCT02606864). The pharmacokinetic parameters showed an increase in nifurtimox absorption in the presence of food. This trial confirmed the usual advice: when treatment is indicated in children, nifurtimox should be taken with food.

At the same time, a Phase 3 trial was envisioned which required significant capacity building for recruitment of patients for a multicenter clinical trial complying with the highest standards of quality of care, clinical practice and research (NCT02625974). To this end, the PedChagas multicenter network for studying pediatric Chagas disease was established with support from Bayer. This consisted of experts in pediatric medicine, pharmacology and clinical research with an interest in Chagas disease. Fifteen centers joined in Argentina, three in Bolivia, and three in Colombia. At present, the trial has an adequate recruitment rate among children between 0 and 18 years old in all the centers involved, and the adverse event rate is no higher than that reported previously. The trial is expected to provide short-term efficacy and safety data that will enable the product to be registered. As an innovation, the efficacy of treatment for 30 vs. 60 days will be compared. The development of a new pediatric formulation will improve the availability of and access to treatment for infected pediatric patients.

## BENDITA STUDY UPDATE

FABIANA BARREIRA AND BETHANIA BLUM, DND; LATIN AMERICA

The **BENDITA study (BENZnidazole New Doses Improved Treatment and Associations)** is a phase II trial whose objective is to identify an improved treatment for adult patients with indeterminate chronic Chagas disease. Optimization of the safety profile of benznidazole (BZN) will involve evaluating regimens with shorter duration (300 mg for two to four weeks) and a lower dose (150 mg for four weeks).

To improve efficacy, BZN was paired with E1224, a broad-spectrum antifungal agent. The hope is that this combination will also enhance treatment tolerance and reduce the development of resistance. The combination will be evaluated with two different regimens of BZN (150 mg for four weeks versus 300 mg in intermittent weekly doses).

The study began in November 2016 in three sites located at the Platforms for Comprehensive Care for Patients with Chagas Disease in Cochabamba, Tarija, and Sucre, Bolivia. In Argentina, as soon as regulatory approval is issued, two new sites will join the study.

Despite some difficulties in mobilizing patients during vacation months and holiday seasons, the sites have achieved the expected recruitment. An estimated total of 210 study subjects will be enrolled by mid-2017. In the first semester, interim analyses will be conducted to monitor safety and efficacy.

All patients will be followed for twelve months. However, primary safety and efficacy criteria will be evaluated at six months. Efficacy will be determined by continuous negativity measured by serial PCR, and safety will be evaluated by incidence and severity of adverse events.

The study will also evaluate population pharmacokinetics, as well as the PK/PD ratio and response by other biomarkers. These secondary data are valuable for advancing the development of new therapies for the disease. An expected outcome at the conclusion of the study is identification of specific regimens for further evaluation in a multicenter, multinational phase III study.

## PROGRESS WITH CLINICAL TRIALS FOR CHAGAS DISEASE IN COLOMBIA

JUAN CARLOS VILLAR, UNIVERSIDAD AUTÓNOMA DE BUCARAMANGA

We take pleasure in reporting on the progress of new trials in Colombia sponsored by Colciencias.

**CHICAMOCHA 3 - Equivalence of Usual Interventions for Trypanosomiasis (EQUITY).** This trial seeks to evaluate trypanocidal effect and safety in seropositive adults without clinical evidence of cardiomyopathy, comparing treatment with benznidazole versus nifurtimox (2 treatment regimens each, at the conventional dose for 60 days or half the dose for double the time) versus no treatment/placebo. The primary outcome is the detection of *Trypanosoma cruzi* by PCR (3 tests repeated on different weeks) at 12 months post-initiation of treatment. As of March 6, 2017, the study had recruited 204 participants in two Colombian centers. The current strategy is to expand the study to include participants from other centers outside of Colombia and complete a total sample of at least 500 participants. (*ClinicalTrials.gov Identifier: NCT02369978, Organization in charge: Universidad Autónoma de Bucaramanga*).

**A Trial Testing Amiodarone for Chagas disease (ATTACH).** This trial with seropositive individuals with clinical signs (evidence of structural damage and alterations in cardiac rhythm or electrical conduction) aims to evaluate the clinical and trypanocidal effect of treatment with amiodarone for at least 6 months and up to 24 months, versus placebo/no treatment. The primary clinical outcome is the detection, during follow-up, of a composite of cardiovascular events, and the parasitological outcome is the presence of *Trypanosoma cruzi* by PCR (similar to CHICAMOCHA 3). Recruitment began in the first quarter of 2017. The strategy is to expand the study to include participants from other centers in Colombia and elsewhere to comprise a total sample of at least 500 participants. (*Organization in Charge, Fundación Cardioinfantil – Instituto de Cardiología, Bogotá*).

It is hoped that the next meeting of the Chagas Platform will attract involvement from more researchers interested in helping to solve these important research questions.

# BERENICE UPDATE

ISRAEL MOLINA, INSTITUTO CATALÁN DE LA SALUD

The consortium for the Berenice project financed by the European Commission is entering the final stage with the implementation of a clinical trial, the MULTIBENZ study. Following four years of multidisciplinary work, the time has come to put the lessons learned into practice.

The Berenice project was created with the aim of obtaining a more effective, safer and cheaper alternative to the current treatment for Chagas disease. With this objective in mind, a group of biologists, chemists, pharmacists, biotechnologists, and clinicians set to work to turn this idea into something tangible that could benefit patients. The paths of science are always full of challenges to tackle, and this project has not been free of setbacks. These four years, which may seem like a long time, have involved a race against time to meet deadlines and budgets. Finally, as the result of highly fruitful collaborative efforts, we have obtained sufficient scientific evidence to launch the MULTIBENZ clinical trial. Data obtained from in vitro and in vivo preclinical studies indicate current doses of benznidazole can be optimized by proposing regimens with smaller amounts of the drug. At the same time, we have obtained initial data indicating the toxicity may stem from a genetic substrate that predisposes patients to adverse reactions. These suppositions are being evaluated in an international multicenter clinical trial that includes patients from Brazil, Colombia, Argentina, and Spain.

Meanwhile, our study incorporates new candidate biomarkers of cure to offer an alternative to the current evaluation methods. If our hypotheses are confirmed, it could mean the beginning of a restructuring of the current treatment regimens as well as increasingly individualized therapy.

Meanwhile, new trypanocidal drugs have been evaluated, with highly promising results. Due mainly to budget constraints, these drugs have not reached the clinical development phase, but the preliminary knowledge obtained certainly poses a new challenge and opportunity for the consortium to build on its current momentum and launch a new clinical trial.



Our clinical trial is also intended to complement other trials currently under way, such as the CHICAMOCHA study, led by the University of Bucaramanga, and the BENDITA study, promoted by DNDi and other stakeholders. The combined results of these studies will allow a much more global vision of the disease, including its geographic specificities.

We hope to share the clinical trial's initial results very soon.



# CHAGAS DISEASE IN THE UNITED STATES: NEW DIRECTIONS, NEW THREATS

COLIN FORSYTH, DNDI AND CENTER OF EXCELLENCE FOR CHAGAS DISEASE

**In 2016, our understanding of the epidemiology of Chagas disease (CD) in the United States deepened.** A study using immigration data and the WHO's 2010 CD prevalence rates<sup>1</sup> estimated 326-347,000 cases in the Latin American-born population.<sup>2</sup> There is also an undetermined number of cases in the U.S.-born population due to congenital and autochthonous transmission. The Center of Excellence for Chagas Disease (CECD) is one of the only facilities dedicated to treating CD in the U.S. For 10 years, the CECD has conducted free screening in the Latin American community of Los Angeles, finding a CD prevalence of 1.24%,

which implies >30,000 cases in Los Angeles alone.<sup>3</sup>

Unfortunately, routine screening for CD does not take place outside of blood banks, and <1% of estimated cases have received diagnosis and treatment.<sup>4</sup> Multiple factors impede treatment of CD in the U.S., as elsewhere. Our research indicates transportation, patient-provider language differences, and lack of awareness among providers are key barriers to expanding CD treatment access. Antitrypanosomal medications can only be acquired through the Centers for Disease Control, adding bureaucratic complexity to the treatment process, and the U.S. lacks a stable supply of benznidazole.

CD is only one of a host of challenges the CECD's Latin American-born patients confront; 63.4% earn income below the federal poverty line and 72.3% depend on subsidized healthcare. Their situation is worsening under the new administration, which is proposing major cuts to funding for public health and insurance while engaging in aggressive deportation tactics that discourage undocumented patients from seeking medical care. CD patients frequently express anxiety and fear about their health, and suffer intense stigmatization as immigrants who bear a disease. Few programs or resources exist to help CD patients cope with the emotional and social burden of the disease.

Despite these challenges, access can be expanded significantly by moving screening and treatment into the primary care level and by simplifying the process for acquiring medications. This, in tandem with incorporation of CD treatment into medical school curricula and expansion of social marketing efforts to inform the public about CD, can help finally bring the disease out of the shadows of neglect.

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Chagas care on health fair



# AN UPDATE ON THE STATUS OF CHAGAS DISEASE IN THE UNITED STATES

MELISSA NOLAN GARCIA, BAYLOR COLLEGE OF MEDICINE

**Our understanding of Chagas disease in the United States (U.S.) has dramatically shifted over the past five years** due to a resurgence of interest among public health, research, and clinical communities. Chagas disease patients in the U.S. represent a wide breadth of socioeconomic status, transmission sources, and clinical manifestations. The U.S. is home to both imported and locally acquired cases that present with a range of clinical disease. Several seroepidemiologic studies have confirmed the national presence of Latin American acquired Chagas dilated cardiomyopathy cases<sup>1, 2, 3</sup>; yet, sadly, most of these cases were only identified due to the presence of a dedicated seroepidemiologic investigation. While these studies have established the veritable burden of Chagas-related heart failure in Latin American-born patients, misdiagnosis is still rampant and compounded by an incredibly low U.S. physician awareness rate<sup>4, 5</sup>. Furthermore, an alarming inequality exists with less than 1% of known cases receiving treatment due to a plethora of barriers<sup>6</sup>.

Misdiagnosis and subsequent mistreatment is further complicated by a significant gap in knowledge as to the epidemiologic profiles of Chagas disease cases, specifically U.S.-acquired cases. Triatomine vectors inhabit 27 continental states with active sylvatic mammal transmission cycles documented in 16 continental states<sup>7</sup>. While sylvatic transmission has been well documented and widely accepted by the scientific community, the exact implications for human transmission in the U.S. are still largely debated. Autochthonous human case reports date back to the 1950s, yet the southern United States is still regarded as a non-endemic region for human transmission. Our investigations in Texas have identified the largest geographic clustering of locally acquired human cases<sup>8, 9</sup>, and these studies are just the tip of the colloquial iceberg. Thanks in large part to the national implementation of blood donor screening, we are identifying contemporary cases in geographic regions and patient populations never previously described<sup>10, 11, 12</sup>. Military personnel, hunters, rural residents, and outdoor enthusiasts are being identified as high-risk populations for acquiring new infections due

to their increased vector exposures. Similar to what we are seeing in Latin America, Chagas disease in the U.S. is not restricted to the rural poor. Our patient profiles include upper socioeconomic status residents, and our ongoing investigations are proving that triatomine vector habitats are abundant in major urban areas.

As the unfolding tragedy of Chagas disease in the U.S. continues to be laid out over the next several years, we are going to start seeing new autochthonous cases from regions never known to be endemic for human transmission. If all goes well, the public health response will be prepared to react and in doing so, shift the paradigm of how this neglected tropical disease is clinically managed in the U.S.

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# COMPREHENSIVE CARE FOR CHAGAS DISEASE

ANDREA SILVESTRE, OSWALDO CRUZ FOUNDATION

**Comprehensive care has emerged as a recurrent theme in recent forums for the discussion of Chagas disease.** Comprehensive care is the set of all actions that promote health, ranging from preventive measures (expanding diagnosis and identifying risks) to patient care itself, all integrated with recovery or rehabilitation. It should take place at all levels, but especially in primary health care.

Comprehensive care needs to take individuals' social context into account in order to meet their demands and needs. Successful care or treatment cannot occur when a patient does not understand the physician's prescription or the medicines are not available. For many years, medicine has focused on the biological model of disease and concerned itself solely with cure through medication. Especially in light of the adverse social context affecting our work with Chagas disease, such a model is flawed, since the medicines are usually inaccessible or not fully explained to patients, who have many other needs that go unmet.

In order to promote comprehensive care for Chagas disease, we need to embrace individuals who have the disease and assist them in dealing with a whole range of difficulties in terms of access, understanding the disease and its treatment (medicines and other modalities), fear prompted by the diagnosis, anxieties concerning the limitations arising from the disease, and comorbidities. We should encourage positive lifestyle changes and, whenever possible, keep these individuals employed while promoting their social reinsertion. This can only happen through multidisciplinary efforts in which the patient rather than the illness is the protagonist, and through interdisciplinary collaboration involving the patient, nurses, physicians, nutritionists, pharmacists, social workers, psychologists, and physical therapists or exercise professionals, who join forces to promote health, quality of life, and rehabilitation through personalized treatment plans. Drugs to treat diseases can be generalized, but comprehensive care only becomes a reality when it is individualized, since we are all unique in our needs.



# ACCESS TO DRUGS FOR CHAGAS DISEASE: THE IMPORTANCE OF ESTIMATING DEMAND

GABRIELA COSTA CHAVES, OSWALDO CRUZ FOUNDATION

**In order to guarantee access to drugs for neglected diseases like Chagas, a chain of initiatives is needed whose links may be weak.**

On the health system side, the mere procurement and availability of the drug may be insufficient if the treatment is not part of a broader context of diagnosis and care.

On the supply side, neglected diseases have been marked by the limited existence of adequate technologies for the affected populations' needs. Even when such technologies exist, there are important challenges for timely supply, since many drugs have only one or a handful of manufacturers, thus presenting challenges for production planning to assure a constant supply in a scenario of uncertain and irregular demand.

Estimating demand is not an easy task. It involves pharmaceutical programming, a key stage in the so-called Pharmaceutical Care Cycle that aims to estimate the amount of the drug needed to meet the demand by a health service or population during a specific period of time. Various factors are

taken into consideration (epidemiological profile, historical consumption, adjusted consumption). Programming aims to ensure timely supply and avoid both shortages and waste.

In 2010, PAHO, DNDi, and MSF/Doctors without Borders joined forces to develop a tool to estimate the demand for Chagas drugs. Revised and updated at least twice, it was applied in a group of Latin American countries in 2012 and produced important lessons. These included the importance of collective facilitation of joint procurement processes, the value of strengthening information systems to generate reliable data, and the gap between the demand for treatments and treatment needs based on prevalence of the disease in the countries.

When a drug has a limited number of producers, estimating demand can also help production planning. Collective effort by governmental and nongovernmental stakeholders to generate reliable information on demand is a key part of comprehensive solutions to expand access to diagnosis and treatment of neglected diseases.

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## PROCESSES INVOLVED IN THE DEVELOPMENT OF DEMAND FORECASTING AND THEIR RESPECTIVE CALCULATION

### POPULATION

- **Data Entry:** total population
- **Classification of endemic and non-endemic areas**
- **Estimated prevalence by age group**
- **Obtained results:** estimation of infected population

### DIAGNOSIS

- **Data Entry:** estimation of infected population
- **Diagnostic capability**
- **Obtained results:** possible diagnostics

### TREATMENTS

- **Data Entry:** total population
- **Classification of endemic and non-endemic areas**
- **Estimated prevalence by age group**

### TABLETS

- **Data Entry:** possible treatments
- **Demand for tablets according to the selected product**

Costa Chaves G, Abi-Saab Arrieche M, Rode J, Mechali D, Ouverney Reis P, Vieira Alves R, et al. *Estimación de la demanda de medicamentos antichagásicos: una contribución para el acceso en América Latina*. *Rev Panam Salud Publica*. 2017;41:e45

# THE WAYS OF THE WIND - EDUARDO GALEANO

IN MEMORIAN OF RODOLFO VIOTTI, WHO DIED WHILE WRITING AN ARTICLE FOR THE NEWSLETTER

May we be worthy of your hopeless hope.

May we have the courage to be alone and the bravery to risk being together, because a tooth outside of the mouth serves no purpose, neither a finger separate from the hand.

May we be disobedient, each time we receive orders that humiliate our conscience or violate our common sense.

May we be worthy of being called crazy, as the Mothers of the Plaza de Mayo have been called crazy, for committing the insanity of refusing to forget in times of obligatory amnesia.

May we be so stubborn as to continue believing, against all evidence, that the human condition is worth the pain, because we have been poorly made, but we are not finalized.

May we be able to continue walking the ways of the wind, despite the falls and the betrayals and the defeats, because history continues, beyond ourselves, and when she says goodbye, she is saying: until later.

May we keep alive the certainty that it is possible to be compatriot and contemporary of all those who live fueled by the will of justice and the will of beauty, may they be born where they were born and live when they may live, because the maps of the soul and of time have no frontiers.



Published by the Drugs for Neglected Diseases initiative (DNDi) and supported by the National Economic and Social Development Bank (BNDES - Brazil) and the Oswaldo Cruz Foundation (FIOCRUZ)

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