



NEWSLETTER ⁶ NO.

PLATAFORMA DE INVESTIGACIÓN CLÍNICA EN ENFERMEDAD DE CHAGAS
CHAGAS DISEASE CLINICAL RESEARCH PLATFORM

The need for consensus and answers on the Chagas Disease's knowledge gap encouraged a joint effort initiative to address the clinical studies, development and access challenges. In October 2009, the centenary year of the discovery of Chagas disease, DNDi and its partners officially launched the Chagas Clinical Research Platform (CCRP) during the XXV Annual Meeting of Applied Research in Chagas Disease and XII Annual Meeting of Applied Research in Leishmaniasis at Uberaba, Brazil.

Seven years later, the Chagas Platform continues searching for mechanisms and synergies in order to provide new drugs and tools for the treatment and diagnosis of the *Trypanosoma cruzi* infection. Creating an open, innovative, collaborative and patients' needs-driven environment, the Platform continues to support R&D by promoting annual meetings, trainings, standardization of protocols, regulatory aspects and integration of ethical principles.

The Chagas Platform currently brings together more than 300 members from 23 endemic and non-endemic countries. Representing more than 90 institutions, these people come from different backgrounds including researchers, academics, government representatives, international and national organizations and patient associations.

Recent clinical studies on Chagas disease have shown the benefits of treatment in the early stages of the disease. The need of improvements on benznidazol regimes and on the development of biomarkers is also highlighted. However, despite recent knowledge advances about Chagas disease, significant changes on access issues are still urgent: a huge difference remains between the estimated number of people living with Chagas and those who are actually diagnosed and treated.

The new knowledges and expertise in addition to the growth of researchers and initiatives aimed at fighting Chagas are motivations to renew our confidence and emphasize the importance of collaborative alliances. The search for collective solutions is an essential part in the battle against Chagas disease – following this vision, the Chagas Platform was consolidated and continues to pursuit integration and exchange among its members.

CHAGAS IS TREATABLE



Attention must be given to the diagnosis and treatment, currently estimated to be **below 1%**



All patients should receive treatment regardless of the disease phase.

BENEFIT TRIAL RESULTS



Urgent need for early diagnosis and treatment.



Further studies and efforts on new compounds for Chagas.

Need to ensure access to treatment for patients under 18 years old, women of childbearing age and acute cases.



Source: World Health Organization. BENEFIT Trial: Morillo CA et al. Randomized trial of benznidazole for chronic Chagas' cardiomyopathy. N Engl J Med 2015 Sep 1.

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THE CHAGAS DISEASE OUTLOOK IN 2016

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Kissing bug found at the municipality of El Espinal, Veracruz, Mexico.

the interruption of transmission via blood transfusion, has significantly impacted the incidence of new cases, primarily in the Americas, and more recently in nonendemic countries. However, the process is still ongoing. Prevention of vector transmission has had an uneven impact due to the varying degree of efficiency of vector control programs in different countries. While some countries achieved nationwide certification of transmission interruption, others only did so in part of their national territory, whereas still others have not formally initiated programs. Similarly, in some areas where entomological surveillance was interrupted, the reestablishment of vectoral transmission has been demonstrated, indicating the need for long-term, sustainable strategies. In areas where the vector-oral route is most prevalent, especially the Amazon region, transmission occurs in a pattern of outbreaks, so safe food manufacturing processes, early diagnosis, and timely treatment are fundamental to interrupting transmission and preventing mortality in the acute phase. Only a few health systems, mainly in the Southern Cone, are focusing on control of congenital transmission, but other countries in the Americas and beyond are gaining awareness of this issue. This route of transmission is currently the primary driver of new cases in many areas.

While there has been progress in prevention measures to limit the occurrence of new infections (even though these are still not fully adequate), the need to provide care to affected people has gained increasing importance in the public health agenda during the last decade. Most of the infected, who number in the millions, are in the chronic or indeterminate phase of infection, but new cases continue to emerge due to gaps in prevention efforts. For this reason, it is necessary to utilize tools and strategies that are readily available and efficient, especially at the level of primary care, while simultaneously optimizing new tools and healthcare strategies through ongoing research. This compels us to pursue simultaneous policies, working to assure equitable access to health TODAY, while also carrying out research TODAY to improve access TOMORROW.

Chagas disease, or American trypanosomiasis, causes one of the greatest burdens of healthy life years lost to disability/morbidity among the neglected diseases in Latin America. Control strategies must combine two courses of action: prevention of transmission to limit the appearance of new cases, and timely diagnosis and treatment of affected individuals to halt the clinical progression of the disease and foster recovery. These actions must be implemented in a profound and integrated manner to maximize their impact. Chagas disease cannot be totally eradicated because of the documented existence of wild triatomine populations in perpetual contact with domestic transmission cycles, which will always contribute to the appearance of at least some new cases. However, it is possible to interrupt the transmission of *Trypanosoma cruzi* in a large geographic area and to eliminate Chagas disease as a public health problem through a radical reduction in the burden of the disease.

Along these lines, the development of primary preventive actions since the beginning of the 1960s, particularly

FINDECHAGAS: THE IV GENERAL ASSEMBLY AND THE NEW PRESIDENCY

MARCELA DOBARRO, DNDI LATIN AMERICA

107 years ago, on April 14th, the Brazilian researcher Dr. Carlos Chagas announced the discovery of Chagas disease to the world by publishing an article in a German magazine. For this reason, the date was chosen by the International Federation of People Affected by Chagas Disease (FINDECHAGAS) to represent the International Day of the Fight Against Chagas in 2009, when the federation was founded in Uberaba, Brazil.

The IV Findechagas Assembly was held from April 14 to 16 in 2016, in La Plata, Argentina, with the objective of aligning the goals and efforts of patient organizations from several endemic and non-endemic countries. The proposal was also working on issues related to the management and associativism to strengthen the role of associations and elected the new officers and members of the advisory board.

The keynote address was attended by the National Chagas Program of Argentina, the World Health Organization, the Healthy World Foundation, Doctors Without Borders, DNDi and the Global Chagas Coalition. The Federation began programming the Assembly with presentations and updates on the last year of work of the associations of Argentina, Spain, Brazil, Colombia, Mexico, Bolivia, Italy, Switzerland, USA and Australia.



The IV Findechagas General Assembly was held in April 2016 at La Plata, Argentina.

As a result of the vote in the Assembly and workshops of the three-day meeting, the presidency was assumed by FINDECHAGAS ASAPECHAVAE, an association of Valencia, Spain. For vice-president the association of Mexico, AMEPACH, was elected, the secretariat was assumed by ASOCHAGAS, Colombian association, and the treasury by ASAPECHAVAE, an association of Murcia, Spain. They were ratified by seven members of the advisory board and included five new and non-institutional staff members. Mexico was elected to host the 2018 Assembly, which will include programming of practical activities in the health plan to contribute in the fight for the end of Chagas disease in the world.

THINKING ABOUT THE PROBLEM OF CHAGAS IN FOUR (OR MORE) DIMENSIONS

MARIANA SANMARTINO, SCIENCE TEACHING GROUP (IFLYSIB, CONICETUNLP), COORDINATOR OF THE WORKING GROUP: WHAT DO WE MEAN WHEN WE TALK ABOUT CHAGAS? (CONICET-UNLP-CIIE, ARGENTINA)

Beyond the significant progress that has been achieved (and is still being achieved) in knowledge and control of Chagas disease, the situation more than 100 years after its "discovery" is troubling. There are numerous reasons and explanations for this. However, in a humble effort to find new answers in this area, the Working Group "What do we mean when we talk about Chagas?" (in Spanish: Grupo ¿De qué hablamos cuando hablamos de Chagas? CONICET-UNLP-CIIE, Argentina) proposes, as a first step, to think through this problem in all its complexity.

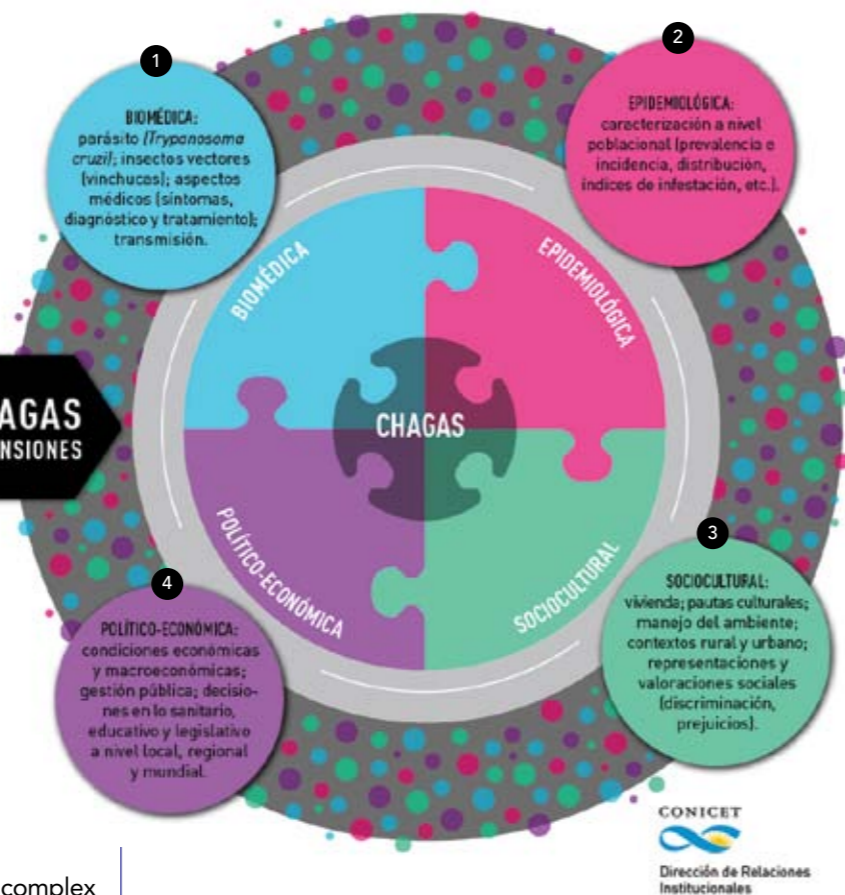
From our point of view, speaking about Chagas involves more than talking about a disease; while the impacts of *Trypanosoma cruzi* infection on the health of "affected" people are an important part of the problem, they are only one piece of the puzzle. Chagas is actually a complex socio-environmental health problem, in which various components converge and interact in different ways. Therefore, any attempt to address this issue requires consideration and awareness of its multidimensionality.

In our interpretation of the problem (one of many possible viewpoints), we employ the metaphor of a four-piece or four-dimensional jigsaw puzzle to understand symbolically that we may only achieve a complete idea of Chagas when we understand the importance of each of the aspects involved. However, in this multidimensional puzzle, the pieces

GRAPHICAL REPRESENTATION OF CHAGAS' FOUR DIMENSIONS:

- 1. Biomedical:** parasite (*Trypanosoma cruzi*); insect vectors (kissing bugs); medical aspects (symptoms, diagnosis and treatment); transmission.
- 2. Epidemiological:** profiling of the population level (prevalence and incidence, distribution, infestation rates, etc).
- 3. Sociocultural:** economic and macroeconomic conditions; public management; health, education and legislation decisions at the local, regional and global levels.
- 4. Political and Economic:** housing; cultural patterns; environmental management; rural and urban contexts; representations and social values (discrimination, prejudice).

EL CHAGAS EN 4 DIMENSIONES



are not discrete or self-contained, but are, in turn, complex subsystems with porous boundaries in dynamic, ongoing interaction. Consequently, while acknowledging the diverse aspects that make up its complexity, we address the problem of Chagas considering four interdependent dimensions:

- **Biomedical:** Involves the biology of the parasite and its insect vector, as well as medical issues related to the manifestation, diagnosis, treatment, and transmission routes of the disease.
- **Epidemiological:** Includes parameters which characterize the situation at a population level (such as prevalence, incidence, distribution, and infestation rates). It also comprises new geographical configurations of the problem, driven primarily by increasing migration.
- **Sociocultural:** Concerned with aspects related to cultural patterns of the different stakeholders involved, the particularities of rural and urban contexts, and representations, prejudices and societal attitudes (such as discrimination and stigmatization).
- **Political:** Includes issues related to planning and decision making in the areas of health, education and policy, at local, regional and global levels. It also encompasses public and private management of economic resources. Additionally, it includes decisions made by each of us, within our specific roles, when thinking about Chagas from a particular perspective.

In sum, given that we face an issue with multiple causes and implications, we must find a way to conceptualize, rethink, explain, and understand it in a holistic manner that transcends traditional approaches that are purely

technical or unidimensional. Understanding Chagas as a problem that transcends disciplinary, geographical, social and cultural borders also implies exploring various channels of communication to establish ongoing, respectful dialogue among different stakeholders, from both academic and political fields, and various sectors of civil society.

More information:
www.hablamosdechagas.com.ar
www.facebook.com/HablamosDeChagas/

FOR CONTROL AND UNIVERSAL ACCESS TO TREATMENT

INTERVIEW WITH SILVIA MORIANA
 – GLOBAL CHAGAS DISEASE COALITION

The Global Chagas Disease Coalition was founded in 2012 by a group of key actors calling for access, innovation, transmission control, public and policy awareness through greater cooperation among its members. In this interview, the coordinator Silvia Moriana presents the initiative, the current situation and challenges for Chagas disease.

1. WHAT ARE THE GOALS OF THE GLOBAL CHAGAS DISEASE COALITION?

The Global Chagas Disease Coalition's vision is "a world where Chagas disease is controlled and universal access to treatment is a reality." Currently, less than 1% of people infected with *T. cruzi* have access to diagnosis and treatment. Therefore, the Coalition works to promote access to diagnosis and treatment of patients with Chagas disease while accelerating efforts to stimulate innovation in new tools to fight the disease. We recently released a document called "Breaking the Silence: An Opportunity for Patients with Chagas Disease" (Rompiendo el silencio: una oportunidad para los pacientes de Chagas) where we describe the current access situation, outline challenges and steps needed to overcome current barriers in diagnosis and treatment, and share the experiences of programs or efforts that have managed to increase the number of people treated. Our goal for 2020 is to increase the proportion of people treated from the current level of less than 1% by achieving 100% diagnosis and treatment for newborns and those under 18, while expanding treatment of adults tenfold. But for this to happen, we need decisive action from political leaders and public health personnel, as well as activism from the people affected by the disease.

2. DOES THE MEDICAL COMMUNITY AGREE THAT CHAGAS DISEASE IS TREATABLE?

There is sufficient evidence that, with current anti-parasitic drugs, Chagas disease can be treated. These drugs are 100% effective in newborns, but the effectiveness decreases as time passes from the moment of infection, so treatment is recommended as early as possible. There has always been consensus regarding the treatment of acute cases and newborns. However, there was no consensus in the past regarding chronic cases. During the 1980s, the prevailing theory was that damage to cardiovascular or digestive tissues during the chronic phase was caused by an inflammatory autoimmune reaction rather than the parasite. According to this theory, it was not necessary to eliminate the parasite. Today, **there is more scientific evidence that the persistence of the parasite is crucial for the pathogenesis of chronic Chagas disease.** This creates a new paradigm, in which **the importance of eliminating the parasite** to prevent the development of complications is recognized.

PAHO and WHO recommendations are clear. Acute, recent chronic, pediatric, adolescent, and chronic cases with reactivation due to immunosuppression are definite indications for treatment. Treatment of chronic cases is also recommended subject to certain medical criteria. Treatment for cases with advanced Chagas cardiomyopathy with cardiac insufficiency or megaesophagus is not recommended.

The community of Chagas disease experts have no doubts regarding the treatment recommendations; however, their consensus has not yet achieved sufficient influence within the medical community. **An effort must be made to share this consensus** with family physicians, pediatricians, obstetricians, cardiologists, and others, many of whom still operate within the old paradigm.

3. WHAT ARE THE MEDICAL BENEFITS OF AVAILABLE THERAPIES?

The principal benefit of antiparasitic treatment, as its name suggests, is the elimination of *Trypanosoma cruzi* in the human body, thus preventing the progression of the disease, preventing lesions, and reducing mortality. In newborns, parasite eradication is 100% effective, eliminating future occurrence of lesions. In the chronic phase, efficacy decreases, but there are still benefits due to the reduction of parasitemia. In advanced chronic cases that have developed major lesions, nonetiological treatment should be offered. For women of childbearing age, treatment provides the added benefit of preventing congenital transmission. The risk of congenital transmission is 21 times higher in babies born to untreated mothers than those born to women who received treatment prior to pregnancy. (1)

4. WHAT SOLUTIONS ARE AVAILABLE FOR GOVERNMENTS AND PUBLIC HEALTH AUTHORITIES TO CONFRONT CHAGAS DISEASE?

Undoubtedly, authorities have several solutions within reach. Following are the most essential:

- **Include comprehensive care for Chagas disease** in the provision of health services, especially detection, diagnosis and treatment of the disease, and ensure cases that are detected in blood banks are properly referred for treatment. It may be useful to integrate screening for Chagas disease within existing programs such as family planning, vaccination, or screening for other communicable diseases.
- **Capacitate health personnel**, who are not always aware of the consensus in favor of treating Chagas disease and often lack the tools and expertise to confront the disease.
- Improve **health information systems** and make Chagas a reportable disease.
- Improve **control of congenital transmission** through universal detection of at-risk women of childbearing age, while sustaining efforts in vector control and systematic screening in blood banks and organ donation programs.
- **Assure provision of quality medicines** and supplies at accessible prices, which involves drug registration, forecast of demand, purchase of medicines and supplies based on needs, and improvement of the supply chain. Stimulate

research and development of new tools and medicines.

These solutions require decisive action by governments and funders. Consequently, the Global Coalition calls for:

- **A political commitment by national governments** to develop a global strategy to fight Chagas disease, with special emphasis on Latin America.
- **Implementation of programs to accelerate access to diagnosis and treatment.** Increased funding for Chagas disease programs.
- All those working with Chagas disease share in creating and working toward a **collective road map** for increasing access to diagnosis and treatment.

5. CHAGAS DISEASE IS MORE THAN JUST A PUBLIC HEALTH CONCERN...

Chagas is the deadliest parasitic disease in Latin America, causing the greatest burden of disability adjusted life years (DALYs) among tropical diseases, and the fourth greatest burden among all infectious diseases. (2) Disease control and access to treatment are not only desirable from a public health and health access standpoint. There is also an economic rationale due to the not insubstantial cost of the disease on a global level. Per capita, taking into account both medical costs and lost productivity, the disease costs \$4,660 annually, or \$27,684 throughout the life course of an affected person. (3)

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THE FDA PRIORITY REVIEW VOUCHER AND CHAGAS IN THE USA: WHAT CAN WE LEARN?

RACHEL M. COHEN, DNDI NORTH AMERICA

At the beginning of December last year, the Chagas community woke up to a nightmare: a company led by an infamous biotech entrepreneur in the US, known for hiking the price of a desperately-needed but decades-old drug to treat toxoplasmosis, announced its intention to register the Chagas drug benznidazole with the United States Food and Drug Administration (FDA).

On the face of it, this sounded like it could have been good news: registration of the only two drugs to treat the disease, benznidazole and nifurtimox, is an urgent priority. But when we dug a little deeper into the intentions of the company, known as KaloBios, we couldn't believe our eyes. In an investor presentation still available online, KaloBios announced that they intended to price benznidazole at levels "similar to hepatitis C drugs," which run up to \$100,000 per combination treatment course in the US.

What followed is now well-known. Our community was very vocal about concerns that benznidazole would be priced exorbitantly, making an already difficult situation of access to this drug worse, not better. Currently, Chagas treatments are only available through an investigational protocol from the US Centers for Disease Control and Prevention (CDC), and the process to access these drugs can be long and arduous. But at least they are not prohibitively priced.

These concerns were amplified when we learned of KaloBios' intention to apply for a lucrative FDA Priority Review Voucher and possibly other FDA designations to increase market exclusivity in the US. The controversial biotech entrepreneur was soon arrested on securities fraud charges (not related to KaloBios) and KaloBios declared bankruptcy, so for a time, it seemed the threat had subsided.

In April this year, the new leadership of KaloBios announced that it had changed its pricing policy and would charge at-cost plus a "reasonable and transparent profit margin" for any of its drugs, including benznidazole. This appears to be a positive step and a clear deviation from the path set by KaloBios under its previous leadership but so far, these are just words and clear actions will need to follow.

DNDI AND MUNDO SANO COLLABORATE TO SECURE AFFORDABLE AND SUSTAINABLE SUPPLY OF BENZNIDAZOLE

In November 2013, the Drugs for Neglected Diseases initiative (DNDi) and the Mundo Sano Foundation – both founding members of the Global Chagas Disease Coalition – joined forces to ensure the widespread use of affordable treatments for Chagas disease for both adults and children. Among key activities in this strategic collaboration was the development of an urgently needed second source of the pediatric dosage form of benznidazole. Mundo Sano, leading an Argentinian drug development consortium, partnered with ELEA to develop and register ABARAX (benznidazole 100 mg and 50 mg tablets) in 2012. DNDi had previously collaborated with the Brazilian public laboratory, LAFEPE, to develop what was at the time the only existing child-adapted formulation of benznidazole (12.5mg), registered in Brazil in 2011.

Since this time, the two organizations have been working closely to ensure a predictable, sustainable, and affordable supply of benznidazole for children and adults throughout Latin America and other places where Chagas disease is now present and where access to benznidazole (and nifurtimox) is a challenge, including in the United States.

In February 2016, DNDi and Mundo Sano signed another agreement focused on technical collaboration in support of a regulatory submission by Chemo Research to obtain U.S. Food and Drug Administration (FDA) approval of benznidazole for both children and adults, with the goal of

increasing access to treatment for Chagas patients in the U.S. This agreement also commits both organizations to developing a far-reaching global "access plan," including but not limited to the U.S., with specific commitments around availability and affordability of benznidazole.

Data from DNDi-sponsored clinical trials in adult and pediatric Chagas disease will contribute to the regulatory dossier. These data provide efficacy and safety data on patient populations for which limited information was available, including the very young. In the current context, DNDi exceptionally granted an exclusive license for a limited time-period: until FDA approval/refusal of benznidazole, but no longer than three years. Within the exclusivity period, Chemo Research will not hinder transfer of the data to third parties as long as their use is not for registration purposes.

Financing for this access plan will be sought from various sources. If Chemo/Mundo Sano obtain a U.S. FDA Priority Review Voucher (PRV), the DNDi/Mundo Sano agreement stipulates that at least 50% of any PRV-related financing would be dedicated to support not-for-profit programs to diagnose and treat Chagas disease. If certain amendments are made to the PRV program, or if Chemo/Mundo Sano do not obtain a PRV for any other reason, they remain committed to working with DNDi and other partners to develop and implement an ambitious access plan.

No doubt the pressure the Chagas community exerted on KaloBios played a role.

Now we need to take a step back and ask: What can we learn from this?

To begin with, we have not collectively put enough pressure on various players to register benznidazole (and nifurtimox) in the US, where an estimated 300,000 Chagas patients live. Although the overwhelming needs are obviously in Latin America, we must not overlook the needs of patients living in the US – who still face a number of hurdles to access this key drug. But registration must be accompanied by a commitment to access, to avoid the nightmare scenario that became a distinct possibility late last year.

Outside our community, millions of Americans who learned about the PRV through the KaloBios story discovered a program that is ripe for abuse. The PRV has made front page news in the US and hundreds of millions of dollars for companies, but in its almost nine years of existence, it has not led to increased access to novel treatments for neglected diseases. This incentive mechanism was initially proposed to both spur investments into research and development for innovative drugs, diagnostics, and vaccines, and to ensure patients in need would have access to these new health technologies. But so far, the neglected disease PRV has largely failed on both accounts:

of the three PRVs awarded for neglected diseases to date, two were for treatments that had already long-existed and were not at all new, and the only treatment that was genuinely new has been largely unaffordable and unavailable for patients in need.

We need a PRV that truly encourages innovation and importantly, requires companies that receive a PRV to develop and implement an access strategy. This strategy would ensure patients, governments and health care providers will have affordable and appropriate access to products for which a PRV has been awarded.

DNDi and MSF have joined forces with several other public health, global health, and R&D organizations to call on the US Congress to reform the PRV by adding a "novelty requirement" and mandating that sponsors publish and "access plan." Until these loopholes are closed, there is no guarantee that this incentive mechanism will deliver urgently needed and affordable biomedical innovations for Chagas and other neglected patients.

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CHAGAS DISEASE DRUG DISCOVERY: A NEW LANDSCAPE READY TO DELIVER?

ERIC CHATELAIN, DNDI GENEVA

The Chagas disease (CD) drug discovery landscape has changed dramatically during the last few years.

Indeed, there have been major advances since the clinical trials with azoles (posaconazole and E1224). Development and use of new technologies, tools or assays; a change in the processes to move compounds forward; and a number of major efforts/groups targeting this disease have emerged. [1] All of these should facilitate the delivery of compounds more suitable for the treatment of Chagas patients in the near future.

Key developments include:

- Commitment and involvement of various institutions in the area including pharmaceutical and biotech companies (GNF/Novartis, GSK, Anacor), translational research centers (DDU, Dundee) and PDPs (DNDi) to name but a few.
- Access to large collections or specific sets of compounds, and mechanisms providing access to characterized hit compounds - open resource from GSK for example. [2]
- New assays allowing the filtering of the best compounds; e.g. the functional CYP51 assay to triage those compounds having this mechanism of action – that of the azoles - as this target has been shown to be inadequate in clinical trials. [3]
- Development of new animal models – in particular those using BioLuminescent Imaging (BLI) technology and transgenic *T. cruzi* parasites - that are able to reproduce the conditions in clinical trials when comparing benznidazole and posaconazole, but might also shed some light on the specificities of *T. cruzi* dynamics in the body and the existence of potential reservoir sites. [4,5]
- Back-translation: generation of data in these new assays with compounds that have already been through clinical trials, allowing a better understanding of their properties against the disease.

In addition, there is an effort to move towards a more collaborative approach, not only between institutions working for a common goal – a new and safe drug to treat Chagas patients in the indeterminate stage of the disease - but also investigators from different disciplines sharing experience related to given compounds with different properties. This might provide much needed standardization and validation of the processes and assays in place and allow compounds to move forwards in proof-of-concept trials with more confidence. Compounds with

a different mechanism of action to that of benznidazole and nifurtimox –the currently used nitroheterocyclic drugs - are in the pipeline and show promise. Obviously, the drug discovery process is long and complex, but there is no doubt that it will deliver new drug candidates for Chagas disease within the next 2 years.

Nevertheless, challenges remain and further efforts are necessary to allow a better understanding of the compound efficacy drivers and PK /PD relationships. Moreover, more research into the earliest possible elucidation of the potential mechanism of action of compounds of interest should be undertaken, as this would allow for more appropriate testing of their potential, in particular when it comes to establishing a dosing regimen. At the end of the day, only the assessment of new drug candidates in proof-of-concept clinical trials will tell us if we are on the right path.

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NEW PERSPECTIVES ON THE THERAPEUTIC USE OF BENZNIDAZOL

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DNDI LATIN AMERICA

The current treatment for Chagas disease has important limitations regarding safety and tolerability, and it is actually restricted to two drugs: nifurtimox and benznidazole (BZN). Current treatment schemes for adults with BZN imply high dosages, a long-term treatment (60 days) and a twice-daily administration.

This treatment scheme has not yet been systematically assessed. Dosages, treatment duration and dosing intervals derive from a few series of patients cases, followed for decades, with few comparisons with each other. However, data from recently finished studies suggest that there are possibilities for optimizing BZN treatment schemes.

A clinical phase 2 study sponsored by DNDi, with E1224 and BZN in adults with indeterminate chronic Chagas disease, conducted between 2011 and 2013 in Bolivia, showed parasitological response of all patients after a 2-week treatment with BZN, which was sustained 12 months after the treatment in 81% of cases. E1224 proved to be effective in removing parasite *Trypanosoma cruzi* at the end of treatment, without maintaining the elimination of the parasite. The BZN safety data show a proportion of patients (10-20%) who do not complete the treatment, most due to adverse drug reactions (ADRs)¹.

Regarding the regimen of administration, pharmacokinetic studies suggest an overexposure in most patients and possible efficacy at lower dosages^{2,3}. Regarding the duration, there are pre-clinical evaluations⁴, a pilot study with intermittent dosage regimens, and several publications about 10 to 30-month^{5,6,7} treatments with parasitological cure rates similar to standard treatment.

Therefore, there are two approaches to optimize the treatment of Chagas disease, using different BZN treatment dosages and durations in monotherapy, as well as combinations to improve treatment response and tolerability, and to potentially reduce the possibility of a resistance development.

Combination therapy is a well-known treatment modality in many diseases. The E1224 is a ravuconazole prodrug, a broad spectrum antifungal agent with a good safety profile. Experimental data suggest a positive interaction betweenazole compounds and BZN for treating Chagas disease.

The BENDITA (BENZnidazole New Doses Improved Treatment and Associations) is a randomized, double-blind, double-dummy proof of concept study for evaluation of new schemes BZN that reduces dosages of BZN in monotherapies and in combination with E1224.

The study will be conducted in three countries (Bolivia, Argentina and Spain), initially in 9 centers. A total of 270 subjects were included in the study, which will be followed until 12 months after the end of treatment.

The recruitment will begin during the second semester of 2016 and the study should be enclosed in 2018. The primary parameters of evaluation of the effectiveness will be the parasitological response determined by the serial



Couple from Morelos, Mexico, diagnosed with Chagas disease. While he was treated with Benznidazole and now has negative test results, she continues the treatment and still remains as an indefinite case.

PCR sustained until 12 months of treatment. The parasite load determined by PCR in several follow-up visits, the cumulative probability of treatment failure up to 12 months, and the reduction of conventional and unconventional serology titles were evaluated among the secondary efficacy parameters. The pharmacokinetic population assessments, as well as the pharmacokinetic-pharmacodynamics evaluation will be carried out. For safety, incidence and severity of adverse events will be evaluated.

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NEW CLINICAL TRIALS WITH DIFFERENT DOSES OF BENZNIDAZOLE

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The need to acquire new information about Chagas disease has galvanized the scientific community. In recent years, various investigations and clinical trials have generated scientific evidence at a faster rate than can be easily digested. Within this framework, various drugs, old and new, have been evaluated in the quest for an alternative to the decades-old nitroheterocyclic compounds such as benznidazole and nifurtimox. Unfortunately, none of the compounds tested so far has surpassed the efficacy of benznidazole. (1) Moreover, the current tools used to

measure trypanocidal activity have yielded surprising results that will be difficult for studies of new compounds to exceed. Therefore, it seems the therapeutic arsenal we will be able to offer our patients in the coming years will essentially be the same as that of the past 40 years.

Taking this into consideration, there is a need to better understand clinical indications for treatment as well as posology. Recent studies based on population pharmacokinetics suggest benznidazole is currently administered at an overdose level. (2,3) In a similar vein, animal experiments suggest that shorter treatment periods are comparable to the standard. (4) Although this supposition has never been tested via clinical practice, Viotti et al analyzed cure rates (seroconversion) of patients who had to suspend treatment prematurely due to side effects. (5) Eighty-one adult patients with Chagas disease were followed after receiving incomplete treatment with benznidazole for a median of 10 days. Twenty percent of these patients (16/81) met the criteria for cure.

Interestingly, despite scant available evidence, we can find contradictory data. Recent *in vitro* assays that measure the time required to eliminate parasites (time-to-kill assays) show that nitroheterocyclic compounds, such as benznidazole, are dose dependent. (6) On the other hand, analyzing information obtained in different animal models evaluating the efficacy of benznidazole, it may be seen that both the dose and exposure are directly related to the medication's efficacy.

Finally, a fact that has rarely been taken into account is the possibility of a "country effect". Most clinical trials evaluating the efficacy of benznidazole against Chagas disease have been conducted in Argentina and Brazil. The few examples from other geographical areas yield totally different results, from an 87% seroconversion in parts of Central America to only 5% or 0% in parts of Bolivia. (7) Therefore, there could be a broad spectrum of the disease that varies considerably in different regions of the Americas, which not only translates into a diverse clinical spectrum but also varying susceptibility to treatment with benznidazole. (8)

Consequently, since there is evidence of overdosage in current treatment regimens, while the exposure of the drug is clearly related to its efficacy, it seems reasonable to evaluate different therapeutic schemes taking into account these premises: decreasing the total dose of the drug (reduction of the daily dosage while maintaining the treatment period, or maintaining the daily dosage but reducing the number of days of treatment), maintaining exposure at the expense of reducing the daily dose.

Currently, there are at least two initiatives that will test these assumptions: the BENDITA study by DNDi and the BERENICE consortium project's study. Within the existing spirit of scientific cooperation in the Chagas Clinical Research Platform, both initiatives have agreed to share the protocols of their respective studies in order to avoid redundancy, and envision joining forces to multiply their

impact, while constantly seeking complementarity and ensure the systematization and standardization of the therapeutic response assessment and other components of these studies. In addition, DNDi and the consortium considered the possibility of working together for the implementation of the BERENICE study, with the activities of preparation at the realization sites as well as the establishment of quality control measures.

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CHAGAS VACCINE LANDSCAPE

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Chagas disease affects approximately 10 million people worldwide [1, 2] and is the leading cause of non-ischemic dilated cardiac disease in Latin

America [3]. Drug treatments with benznidazole or nifurtimox are highly efficacious during acute infection, but induce significant side effects, have limited efficacy beyond the acute phase, and cannot reverse existing cardiac disease or prevent cardiac death [4-7]. Lifelong management of Chronic Chagasic Cardiomyopathy is costly, thus new treatment options, such as vaccines, are urgently needed [8, 9].

Parasite persistence is a key driver of cardiac pathology [10] and strong antigen specific CD8+ cytotoxic and IFN γ responses correlate with more favorable clinical outcomes [11]. Both preventative and therapeutic vaccines have been proposed to control parasite burdens by inducing an appropriate immune response. While preventative vaccination could prevent acute infection and would be cost effective [8], the general consensus is that development of new anti-parasitic therapies to augment existing drug treatment is the higher priority. A therapeutic vaccine that boosts *Trypanosoma cruzi* specific immunity could be used alone or in combination with existing chemotherapy, and be both cost effective and cost saving [9].

The Chagas Vaccine Landscape and the successful advancement of suitable candidates through product development is quite complex, but key discoveries over the past 100 years of research have more clearly defined a path toward a licensed vaccine. Early studies showed that inoculation with avirulent parasites conferred significant protection in animal models, indicating that protective antigens could be separated from virulence factors [12, 13]. Subsequent vaccine efforts identified dozens of candidate antigens that reduce parasite burdens and increase survival in experimental animal models. These include trans-sialidases [14-16], surface proteins [17, 18], flagellar proteins [19, 20], and mucin-associated surface proteins [21]. Monovalent and multivalent vaccine constructs tested in mouse models have been delivered as plasmid DNA vaccines [14, 15, 22-26], viral vectors [27, 28], and recombinant proteins combined with TH1 biasing adjuvants [16, 29, 30] leading to increased survival, and reduced tissue parasite burdens and cardiac pathology. Studies in canine models show that vaccination concomitantly reduces cardiac conduction disturbances [22-24, 31-33]. Canine models provide evidence for the feasibility of using a vaccine to prevent or delay cardiac disease progression, which could be used in conjunction with current chemotherapies to bridge the efficacy and tolerability gap [9].

Recent pre-clinical studies using adjuvants and delivery systems that have already undergone safety testing in humans have moved candidate vaccines even further along the path to licensure. Examples include a therapeutic vaccine, consisting of recombinant Tc24 protein and CpG encapsulated in FDA approved poly(lactic-co-glycolic acid) (PLGA) nanoparticles, that reduced cardiac parasite

burdens in acutely infected mice [30], and a prophylactic vaccine, consisting of a glycosylated mutant trans-sialidase protein combined with the immune complex ISCOMATRIX, which induced robust antigen specific CD8+ IFN γ + immune response and reduced parasite burdens in both acutely and chronically infected mice [16]. With identification of several protective antigens, safe adjuvants and delivery systems, and evidence that therapeutic vaccination significantly reduces parasite burdens and cardiac pathology, a licensed therapeutic human vaccine is swiftly becoming a reality.

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UPDATE ON BIOMARKERS FOR CHAGAS DISEASE

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The lack of early biomarkers of therapeutic efficacy is one of the most important limitations for chronic Chagas disease. It has an impact both on clinical treatment of affected patients with antiparasitic drugs, and on clinical trials in which new drugs or drug combinations are evaluated.

Chronic Chagas disease poses challenges for this type of research: clinical symptoms are not useful indicators, due to the slow and progressive development of the disease. In addition, many organic lesions, once manifested, cannot be reversed by antiparasitic therapy. With the current tools available, the fact that T. cruzi affects all types of tissues makes it impossible to know if treatment has effectively eradicated the parasite.

Therefore, the discovery and confirmation of biomarkers indicating the persistence or eradication of the parasite would represent one of the most important advances in Chagas disease. A recent study systematically reviewed potential biomarkers that have been evaluated in studies of patients with chronic Chagas disease and outlines ideal and acceptable criteria for future biomarkers. (1)

Of all the potential biomarkers proposed over the years, few have been evaluated properly. Two types of recombinant proteins were identified that may be useful as biomarkers and continue to be investigated. (2,3) Markers dependent on changes caused by host-parasite interaction have been investigated. Highlights include the murine receptor of the M2 antigen, although it has only been evaluated only in patients under 18, and other biomarkers such as ApoA1, fibronectin, F1 + 2 and ETP, about which encouraging results have recently been published. (4-6) The detection of the parasite's nucleic acid through PCR, which currently offers the best sensitivity and specificity in the diagnosis of infection, has been extensively evaluated internationally and is used in clinical trials of new medications. It allows accurate detection of treatment failure, but cannot confirm eradication of the parasite with certainty.

Due to the characteristics of T. cruzi infection, it will be difficult to find a biomarker that is useful on its own to assess the therapeutic efficacy of antiparasitic drugs. The vision for the future is a group of biomarkers, each

detecting a distinct facet of the parasite or the host-parasite interaction. There is a need not only for clinical trials which jointly evaluate multiple potential biomarkers, but for discovery of new molecules that lead to new possibilities.

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PROSPECTS FOR THE BIOMARKERS DEVELOPMENT:

- Two sets of recombinant proteins
- Markers that rely on changes in the host-parasite interaction
- Muscarinic receptor of the M2 antigen
- Nucleic acid detection of parasites by PCR

THE BENEFIT TRIAL: A WAKE-UP CALL TO ACCELERATE THE DIAGNOSIS, TREATMENT AND RESEARCH FOR CHAGAS DISEASE

GLOBAL CHAGAS DISEASE COALITION



A family of Cochabamba, Bolivia, who discovered that they were all infected with Chagas after the father died of a heart attack.

WITHOUT A MORE EFFICIENT TREATMENT, MORE THAN 200,000 PEOPLE LIVING WITH CHAGAS DISEASE WILL DIE FROM HEART DISEASE IN THE NEXT FIVE YEARS

The international, multicenter, double-blind and placebo-controlled “Benznidazole Evaluation for Interrupting Trypanosomiasis” (BENEFIT) trial initiated more than 10 years ago in order to determine whether the estimated 1.2 million people now living

with chronic Chagas heart disease could benefit from treatment with benznidazole. Although the answer may seem to be “no”, according to an article published in Plos NTDs by the Global Chagas Disease Coalition, what the study ultimately indicates is the clear need to initiate

treatment at earlier stages of the disease.

The study did not show incremental benefits in cardiac outcome, underlining the need to revisit the current strategies for anti-parasitic chemotherapy in patients with chagasic heart disease. Furthermore, 17-18% of patients in both the treated and placebo arms died over a period of five years, meaning that roughly 200,000 people will die from Chagas cardiomyopathy in the next five years. This number is comparable to that of women in the US who will die from breast cancer in the same period. However, in contrast with breast cancer, there is little advocacy and support for research and development in Chagas disease.

Despite the negative results, the BENEFIT trial highlights research issues that need to be urgently addressed, such as the best dosing schedule for benznidazole, the development of reliable surrogate markers that can predict clinical outcomes, and the role of co-infections and non-communicable diseases when treating patients chronically infected with *Trypanosoma cruzi*. It also presents new opportunities to evaluate new formulations and drugs that are currently in the pipeline.

“The newest information coming from the BENEFIT trial highlights the urgency to develop improved therapeutics for millions of people now living with Chagas disease” said Professor Peter Hotez, senior author of the article and Dean of the National School of Tropical Medicine at Baylor College of Medicine. “We urgently need to redouble our efforts to identify and treat young people who are still in the early stages of their illness, but ultimately we need to find better treatments and new cures”, emphasize the authors in the article.

SOME NUMBERS ON CHAGAS DISEASE:

- 5.7-9.4 million people live with Chagas Disease
- Less than 1% has access to diagnosis and treatment
- More than 50% of infected persons live in Latin America’s wealthiest countries (Argentina, Brazil and Mexico)
- Hundreds of thousands of infected people live in USA and Europe, where parasite transmission can occur through blood and organ transfusions and from mother to child

More information: chagascoalition.org

TRAENA: BENZNIDAZOLE TREATMENT IN ADULT PATIENTS WITH LOW RISK CHRONIC CHAGAS DISEASE - A PHASE 3 RANDOMIZED CLINICAL TRIAL

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INTRODUCTION.

The current situation of chronic Chagas disease treatment is gradually changing over the past 20 years. In the 90’s, two randomized clinical trials (RCT) in children and an observational study in adults showed a parasiticide effect per dosage of benznidazole (BZN). With this framework, TRAENA, the first RCT conducted in adult patients with chronic Chagas disease started in 1999, in order to assess whether the BZN (@ Radanil Lab. Roche) at a dosage of 5 mg/kg/d for 60 days was able to inhibit the clinical progression of adult patients with low-risk chronic Chagas disease, and if new serological and parasitological methods could be predictors of that potential clinical effect.

MATERIAL AND METHODS.

TRAENA is a controlled RCT, double blind vs BZN Placebo (PL). The selected population corresponded to urban patients with chronic Chagas disease, residents in the City of Buenos Aires and Greater Buenos Aires, most of them having born in an endemic area of Argentina, Bolivia and Paraguay. To participate in the study, patients had to be reactive IFI and ELISA, and the population was characterized by a natural distribution of the different stages of chronic Chagas disease. The clinical, serological and parasitological posttreatment monitoring was performed every 4 months until 2 years, every 6 months until 4 years and then annually until the end of the study. Patients were randomized by a restrictive system of random numbers in blocks of variable size, stratified by clinical stage. The sample size was determined with an N=750 with an 80% of power to detect a 50% of reduction in the incidence of clinical events in BZN arm, assuming

an incidence of 20% in the PL arm and maintaining a level of 5%. Primary and secondary clinical endpoints were considered, the secondary serological ones were analyzed by conventional ELISA (cELISA) and ELISA F29, a T. cruzi recombinant antigen, and parasitological ones by quantitative real-time PCR (qPCR). Longitudinal mixed models were estimated to adjust cELISA profiles, ELISA F29 and IFI, according to treatment group, looking for a significant effect between groups BZN and PL on the average speed in shares decreasing. The qPCR was measured in parasitic/ml equivalents and the asymmetric distribution of the data was analyzed by the Mann-Whitney test.

PRIMARY CLINICAL ENDPOINTS WERE.

total mortality, cardiovascular mortality, development of heart failure (HF), severe arrhythmias with hemodynamic compromise, or permanent pacemaker insertion or Cardioverter Defibrillator.

SECONDARY CLINICAL ENDPOINTS WERE.

secondary electrocardiographic events characterized by the presence of new changes in the ECG other than those ones in the initial phase; Left ventricle increase on echocardiography, new developed HF and CVA; And also combined events (when two or more echocardiographic and electrocardiographic changes were occurring simultaneously). The progression in the clinical stage was another way of measuring secondary events and all changes described previously were considered, except mortality, which would allow defining clinical outcomes.

ITTM and PP were performed, PP in patients with total continuity until the 2009-2012 period.

Throughout the study, TRAENA had an international supervision, and three IA and the FA were evaluated by an external MC. TRAENA concluded in December 2012.

RESULTS.

Patients were included between March 1999 and November 2003. Randomization distributed 763 patients, 382 and 381 in BZN and PL respectively. By ITTM, 711 subjects were analyzed, distributed in 353 and 358 subjects in BZN and PL respectively, and by PP a total of 552 patients, corresponding to 272 and 280 in BZN and PL respectively. The distribution according to clinical stage was 74.7% in indeterminate stage, 22.1% in stage 1, and 3.1% in stage 2 and 3 of chronic Chagas disease. The absolute total loss of patients was 4.8%, 19 and 18 in NBZ and PL respectively. There were no differences in baseline variables such as age, sex, origin, clinical stage, etc.

CLINICAL EVENTS.

A total of one hundred and sixteen events (15.2%) occurred

in TRAENA, 58 per arm. From the 38 primary events, 26 (3.4%) were all-cause mortality, 14 and 12 in BZN and PL respectively. From these 26, only 13 were attributable to Chagas disease, corresponding to 7 (2.0%) and 6 (1.7%) to BZN and PL respectively. Other primary events: 12 were pacemaker/cardioverter defibrillator, arrhythmia with hemodynamic decompensation and heart failure, with 3 and 9 events in BZN and PL respectively. Secondary endpoints were 78 (10.2%). From those, 41 (10.7%) and 37 (9.7%) were NBZ and PL respectively. They were characterized by the development of new and permanent electrocardiographic changes, 17 combined events, 10 and 7 in BZN and PL respectively, and 4 CVAs, all in the BZN arm. Kaplan Meyer curves of survival comparing primary events: [P= 0.317. HR (Mantel-Haenszel): 0.957. 95% IC: 0.497-1.840], secondary [P= 0.618. HR: 0.864. 95% IC: 0.501-1.490] or progression in the clinical stage [P= 0.808. HR: 0.950. 95% IC: 0.631-1.431], regarding BZN and PL. ITTM and PP showed no differences between the two arms.*

SEROLOGICAL EVENTS.

In the BZN group, 29.1% (96/330) of patients were seronegative for cELISA of which 15.4% (51/330) were also for ELISA F29. BZN total negativization in ELISA F29 was 39.9% (126/337).

PL group: 12.2% (42/344) became negative for cELISA, of which 4.4% (15/344) were seronegative for both ELISAs, and 10.7% (36/337) were seronegative for ELISA F29. IFI was associated to negativization in both ELISAs with a significant decrease of shares during the follow-up. (The values showed high statistical significance).

PARASITOLOGICAL EVENTS.

In the BZN group, the parasite load, at time 0, 60 days post-treatment (pt) and 12-14 months pt, had a median of 6.59 (IC95% 5.11-10.5) eq. parasi/ml, 4.10 (IC95% 0.10 -7.15) and 0.00 ** (IC95% 0.00 -0.00) respectively, with a P= 0.032 between T0 and 60 days pt and P<0.0001 between 12-14 months vs T0 pt, being the measurements stable at posterior times in relation to the last one, until the end of TRAENA. In the PL group, the variability of qPCRs along the follow-up is significant, with some occasional non-detectable qPCR values, very different from the BZN arm profile.

SECURITY IN TRAENA.

BZN produced the exclusion of 22% of patients. The causes were reiteration of the dermatopathy when restarting the treatment, toxic hepatitis, leukopenia, and, less frequently, arthralgia. Only one patient required hospitalization for a serious adverse event.

CONCLUSION.

In TRAENA, in general a low risk clinical population, the BZN used in the scheme had no clinical impact on morbidity and mortality. The primary and secondary events were few (and often lower than estimated in the study design),

distributed evenly in both arms and, in general, delayed throughout the follow-up.

A clear parasiticide effect, in relation to BZN, was observed by both ELISAs, which became negative through 5 years of follow-up, being more relevant the one detected by ELISAF29. IFI attended the seronegativization by ELISAs by a significant decrease in shares. Patients with seronegativization by the action of NBZ, like those from PL group, who did it spontaneously, presented basal shares significantly lower than those who remained positive throughout the follow-up. The franc parasiticide effect by serology and qPCR was not associated with differences in clinical events. The statistical sampling conducted in the study design in 1998, based on studies published in that decade on etiological treatment in adult patients with Chagas disease, and the BZN regime used were proved insufficient to demonstrate the initially estimated clinical impact in TRAENA, a randomized clinical trial, during its follow-up period between 1999-2012.

* Only statistical data is shown by ITTM.

** 0.00 qPCR values equals to undetectable parasitic equivalent.

Abbreviations: IA: Interim Analysis. FA: Final Analysis. MC: Monitoring Committee. CVA: Cerebrovascular Accident. IFI: Indirect Immunofluorescence. ITTM: Intention-To-Treat Analysis. PP: Analysis by Protocol.

ACUTE PHASE

Characterized by fever, malaise, facial edema, generalized lymphadenopathy and hepatosplenomegaly.

It may disappear spontaneously in a few weeks, but causes the death of 5% of children with Chagas disease.

CHRONIC PHASE

"Indeterminate" stage: asymptomatic, can last for a decade.

"Symptomatic" phase: affects 10% to 30% of infected patients and often jeopardizes the heart and the gastrointestinal tract.

CHAGAS DISEASE IN THE USA

SHEBA MEYMANDI, CENTER OF EXCELLENCE FOR CHAGAS DISEASE AT OLIVE VIEW-UCLA MEDICAL CENTER

Chagas disease (CD) is a slowly progressing disease endemic to Latin America, caused by the protozoa *Trypanosoma cruzi*. It is a chronic disease with a predilection for cardiac involvement. Roughly a third of patients diagnosed with CD will progress to developing cardiac manifestations, ranging from conduction abnormalities to cardiomyopathy to sudden death. CD is one of the leading causes of congestive heart failure (CHF) worldwide and is believed to affect 13-15 million people, primarily in Latin America. However, little is known about the prevalence of CD in the United States. Increasing evidence suggests CD may be more prevalent in the US than previously believed. Studies of blood donors have detected a much higher than expected prevalence of CD. (1,2) A screening survey of blood donors in Los Angeles County revealed a prevalence of 0.46% in Latin American immigrants. (1)

The Latin American immigrant population in the US has skyrocketed over the last 25 years, from 5.8 million in 1980, to 8.4 million in 1990, to over 21 million according to the 2010 US Census. There are over 5 million Latin American immigrants residing in California alone, with over 70% of these residents from Central America and Mexico. Los Angeles County has approximately 2 million Latin American immigrants. This population represents an underserved population that is frequently overlooked in clinical trials.

The Center of Excellence for CD at Olive View-UCLA Medical Center has actively evaluated CD prevalence in many different conditions in a population composed largely of Latin American immigrants. Our findings are as follows:

The Center of Excellence for CD at Olive View-UCLA Medical Center has actively evaluated CD prevalence in many different conditions in a population composed largely of Latin American immigrants. Our findings are as follows:

- We have screened more than 5000 immigrants in the Los Angeles County area over the past 7 years. The prevalence of CD in this population is 1.2%.
- Amongst approximately 400 asymptomatic Latin American immigrants with unexplained conduction abnormalities on electrocardiogram, we have found a 5.5% prevalence of CD. This population represents patients with early myocardial involvement of the disease prior to the development of clinical manifestations.
- We have also screened approximately 400 Latin American immigrants with nonischemic cardiomyopathy and have

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found a CD prevalence of 19% in that population. In further analyses those with Chagas cardiomyopathy (CCM) had 4-fold higher mortality than those with non-Chagas cardiomyopathy despite a similar ejection fraction and ventricular size.

Our findings, and the recently published results of the Benefit Trial, stress the importance of recognizing early stage Chagas disease. Early treatment can cure or at least delay the progression of CD. The goal ultimately is to prevent the complications of CD, including the late stages of cardiomyopathy and overt CHF. It is imperative to screen and diagnose patients as early as possible. We feel that the best place to provide early diagnosis, screening and treatment is the primary care setting. With the help and support of DNDi and MSF we are embarking on implementing and expanding CD screening in primary care clinics. This will be done in a gradual roll-out throughout Los Angeles County. We are in the process of developing a simple model of care for CD that can be implemented throughout the US.

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CHAGAS DISEASE IN ITALY

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The first description of a case of Chagas disease (CD) in Italy was in 1997 by Crovato and Rebora. (1) **Prophetically**, these authors mentioned CD as a potential plague for Europe, taking into account increasing international travel and migration, in conjunction with the disease's features. For more than ten years, no news on CD was recorded in Italy until Guerri-Guttemberg and colleagues published the first estimations of the number of CD cases (around 3000) based on official data on migrants. (2) 2009 marked the 100th anniversary of the discovery of CD. In September of that year, under the auspices of the World Health Organization (WHO) and during the Sixth European Congress on Tropical Medicine and International Health, a number of experts in the field from different European countries met to discuss CD control

in nonendemic countries. The meeting was considered a milestone in the process of control of CD in nonendemic areas. The Nonendemic Countries Initiative (NECi) created by the WHO began to draw a roadmap to combat CD on a global scale. (3) Two months later the same experts met in Geneva for an informal WHO meeting which contributed to the collection of important data on epidemiology, control measures, recommendations and laws in different European countries concerning CD. (4)

Italy ranks second only to Spain in terms of the size of its population of Latin American immigrants. Currently, around 300,000 Latin Americans have legal residence in Italy, whereas an estimated 150,000 are in the country without documentation. The largest contingents are from Peru and Ecuador. Additionally, there are around 14,000 Bolivians. The distribution of Latin American communities in Italy is uneven and does not follow a predictable pattern. This is one of the major obstacles to establishing a common control strategy for CD. In recent years, thanks to the work of a network of Institutions focused on CD, among which the Centre for Tropical Diseases (CTD) took a leading role, some successes have been registered and the "epidemiological silence" has been broken. (5) Organ and blood donors undergo serological evaluation for CD if epidemiologically at risk. Congenital transmission of the disease in Italy is not widely monitored; only Tuscany Region and Bergamo Province have implemented an official program for screening pregnant women and infants; the CTD also follows an institutional congenital CD protocol and is promoting its extension throughout the Veneto Region.

There are an estimated 10-12,000 cases in Italy (2013), of whom only a negligible proportion (roughly 5%) have been identified and treated. Access to diagnosis and care is the biggest challenge Italy faces. Only a few centres regularly offer CD diagnosis through serology. Aside from congenital CD programs and temporary surveys (notably those promoted by MSF in 2010-2013 in Bergamo, Milan and Rome), screening initiatives are ongoing only in Florence (Careggi Hospital, Unit of Infectious and Tropical Diseases) and in Negrar, where a mobile team led by CTD members promotes screening in communities of Latin American immigrants (Project Garantizando Derechos or Guaranteeing Rights). In conclusion, the major challenges concerning CD in Italy are the following:

- Increase case detection
- Increase availability of free/low-cost diagnostic tools
- Make benznidazole easily available nationwide
- Establish a stronger network of reference centres
- Extend programs to prevent congenital transmission
- Establish an effective surveillance system (pharmacovigilance, acute/congenital cases)

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ACCESS

ACHIEVEMENTS AND NEXT STEPS IN THE FIGHT AGAINST CHAGAS DISEASE IN COLOMBIA

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Looking back on the past five years, there have been many achievements, including greater leadership by the national program, development and adjustment of guidelines for clinical care, consensus on congenital Chagas disease, and an increase in the purchase and distribution of medication. In 2014, ten cities received certification of the interruption of domestic vector transmission from the Intergovernmental Commission of the Andean Initiative. Chagas disease has been included in the healthcare priorities of the Ministry of Health, a pilot project was developed for treatment of Chagas disease in four cities at the primary care level, and ELISA tests are being validated for confirmatory use in public laboratories. The Ministry of Health has expressed its commitment to the fight against Chagas disease and wants Colombia to take a leading role, much as it did with the elimination of onchocerciasis.

However, important challenges remain, especially regarding the lack of access to diagnosis and treatment. In all, only 53,700 individuals have been screened outside of blood banks. Also, while 2,000 new cases are annually diagnosed by blood banks, less than 1,000 have received etiological treatment. Laboratory confirmation can take up to nine months since it is currently handled only in the capital.

ACCESS

In Colombia, Chagas disease has only been treated in advanced phases with cardiac involvement, by cardiologists in specialized centers. Health professionals are dubious about the benefits of early detection in young people and etiological treatment as a mechanism to avoid future complications. Also, fear regarding the side effects of treatment with the available medications is widespread.



The Benznidazol is still not registered and available throughout all Latin American countries.

DNDi has been working with the national Chagas program to identify treatment barriers and find solutions. The most difficult challenges are assuring sufficient numbers of personnel trained in managing the disease, simplifying diagnosis and treatment so they can be available to patients at the primary care level, and assuring adequate levels of medications and supplies in order to offer quality care. Although the program guarantees enough medication to meet current needs, it is not registered in the country, which could pose a future problem for supplies, especially in light of the commitment to treat all minors under 18 who are detected through screening, in addition to all who are diagnosed when donating blood or receiving prenatal care.

It is exciting to see what has been achieved in a short time with the backing of the national program and the support of DNDi, but there is still a long road to follow before all those affected can access treatment.

THE SECOND BRAZILIAN CONSENSUS ON CHAGAS DISEASE, 2016

ALBERTO NOVAES, DEPARTMENT OF COMMUNITY HEALTH, SCHOOL OF MEDICINE, FEDERAL UNIVERSITY OF CEARÁ, FORTALEZA, BRAZIL

The Second Brazilian Consensus on Chagas Disease is the fruit of extensive work by Brazilian investigators who have dedicated themselves to the study of the disease and served as experts at both a national and international level. Under the leadership of the Brazilian Society of Tropical Medicine (BSTM), this process was supported by the country's Ministry of Health, through the Secretary of Health Surveillance. The aim was to systematize evidence to strengthen efforts on multiple fronts, including epidemiology, administration, communication, education, research, and provision of care to the people affected by Chagas disease and their families. This includes the development of parasitological, clinical, epidemiological, and social science research, as well as operational studies.

The challenges are amplified by the fact that in 2015, more than 80% of people affected worldwide lack access to diagnosis and treatment, underscoring the disease's substantial social component. The unfortunate context of individual, systemic, and sociopolitical marginalization impacting people with Chagas disease further complicates the mission. Various efforts have been made to embed care and treatment of people with Chagas disease within national health systems, as a key component of primary health care and part of a broader, integrated approach to neglected diseases. However, the scope of these actions has thus far been limited to simply guaranteeing access.

Brazil and the other Latin American countries play a key role in driving this process. The results of the coordinated multinational initiatives to fight the disease launched in 1991 underscore this. In addition, the active participation of non-endemic countries provides new possibilities of reflection and action. A recent and fundamental development was the establishment of the International Association of People Affected by Chagas disease (FindeChagas), with the participation of various representatives from Brazil and other countries. The empowerment brought about by active participation has expanded opportunities for engaging in dialogue and participating in evidence-based decision making at an administrative and policy level. Translating the main elements outlined in the Consensus is of key importance to these movements.

In 2005, in a historic undertaking, BSTM and its members, in partnership with the Ministry of Health, published the first edition of the Brazilian Consensus on Chagas Disease, a document that became a significant milestone for the country, and even beyond its borders. Health administrators and professionals, researchers, academics, graduate and postgraduate students, and society in general began employing it as a reference tool.

Since then, based on accumulated knowledge and experience, and considering major gaps and the clear need to review the original document to reflect the most current scientific evidence available at a national and international level, work was undertaken to prepare the **Second Brazilian Consensus on Chagas Disease**, published in 2016. It is hoped that dissemination of the contents of this document contributes to the improvement of clinical practice, prevention, development of new research, and public policy planning directed at all aspects of surveillance and control of Chagas disease in order to reduce its incidence, morbidity and mortality.

FOLLOWING THE SDG PATH

LEIRE PAJÍN IRAOLA, BARCELONA INSTITUTE FOR GLOBAL HEALTH - ISGLOBAL

It is a fact that diseases spread without regard for national borders. Bacteria, viruses and parasites have all played a key role in our evolution. Today their extent and impact is even greater, which is fundamentally driven by demographic change. Another important phenomenon is the instantaneous and global character of communications, which transcends barriers of time and space since information and knowledge of outbreaks travel faster than the actual pathogens. Truly, today we can no longer say that a disease is limited to a specific group of people within a particular locale. Public health responses need to be orchestrated on a global scale. For many years, Chagas disease was associated with impoverished populations living in rural areas of Latin America. Today, population movements have enabled the disease to cross national and international barriers, and the currently Chagas disease can be found in urban areas of Latin America, Japan, Spain or Europe, even though these are not endemic areas. The transitory nature of the disease is what originally encouraged ISGlobal to work with CEADES through the Chagas platforms, thus making a modest contribution to the diagnosis and treatment of patients. In a sense, we have constructed two-way, multinational channels of research, diagnosis and treatment of patients, which has helped us develop a broad, holistic perspective.

Although we have undoubtedly made progress in research thanks to the work of the scientists involved (among whom those of the Chagas coalition and the members of the NHEPACHA network have distinguished themselves), and in awareness and sensibility thanks to patient associations, the Global Chagas Disease Coalition and its members, PAHO, and other organizations, there is still a long way to go. Chagas disease remains silent and silenced. Silent because its symptoms do not manifest and present with the same immediacy and visibility of other diseases, and silenced because, unfortunately, it is not included in core policies or agendas in global health. In fact, of the more than six million people infected with Chagas, it is currently estimated that less than 1% have access to diagnosis and treatment.

The main obstacle is that the impact and the scope of the problem are still unknown. We need to become more precisely aware of the current reality, which requires a concerted effort of research and dissemination of data. Moreover, since it is a silent and silenced disease, Chagas disease has not taken the stage as an urgent public health issue, although it is estimated that, in the case of Latin America, it causes the highest burden of mortality of all parasitic diseases. In a region where public health challenges

(access, coverage, epidemics, etc.) are substantial, Chagas disease is not considered a pressing concern, especially when all the attention is focused on other issues such as the outbreak of zika.

Despite this, I believe new windows of opportunity are opening. The UN's Sustainable Development Goals (SDGs) make the right to health and healthy living a priority objective for the next 30 years, with particular emphasis on neglected diseases, which still torment millions of people. We must take advantage of this opportunity, as well as the attention brought by other emerging diseases (such as zika), to place Chagas on the political agenda of countries in the region that are leading the struggle, while also emphasizing the positive effects that controlling diseases like Chagas can yield. In short, if the main global challenge we face today is to ensure universal access to healthcare, we must push to ensure that care is of high quality and fully integrated in national Chagas plans. By maintaining awareness of the need to reform regulations to allow further progress in treatment, as well as ensuring adequate professional training and development, we can start to erase barriers to access. While the SDGs are not always an easy path, we, along with patients struggling with Chagas, cannot afford to forsake the journey.



Kissing bugs often live and reproduce inside rural or semi-rural houses, mainly in the cracks of walls and ceilings.

OPERATIONAL AND IMPLEMENTATIONAL (OR/IR) RESEARCH FOR CHAGAS DISEASE CONTROL

FABIO ZICKER, OSWALDO CRUZ FOUNDATION - FIOCRUZ

Operational and Implementational Research (OR/IR) is a multidisciplinary field that seeks to understand factors or conditions associated with successful implementation of new policies, strategies, interventions and practices in public health. This helps to identify local solutions to local problems that lead to changes in policies and practices. Studies are conducted in “real world” settings where context plays a fundamental role. Different research methods, both quantitative and qualitative, are used to study access and implementation issues related to stakeholders, program strategies, intervention tools, healthcare workers, target populations, and administrative systems that may influence the scale-up of effective public health policies and programs. (1)

Guidelines are available providing step-by-step instructions on how to define OR/IR questions, design study protocols, collect appropriate information, analyze data, disseminate results, and promote the application of research findings to improve disease control. (2, 3) Common outcomes measured include acceptability, adoption, convenience, feasibility, and implementation cost, coverage, and sustainability, as well as indirect indicators of effective application. (4)

In light of efforts to expand diagnosis and treatment in areas with a heavy burden of Chagas disease, the following OR/IR agenda is proposed for discussion.

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HEALTH SYSTEMS

- What are barriers to decentralization of diagnosis and treatment to primary health care facilities?
- What skill set and knowledge are required for case management in healthcare centers?
- How can strategies for identifying patients, enrolling them in treatment, and assuring follow-up be progressively expanded?
- What is needed to maintain effective referral systems for clinical treatment?

DIAGNOSIS

- How can we establish active surveillance to identify patients in the early stage of infection?
- Is it feasible to employ parasite detection tests (such as PCR) in this field?
- How can quality control of diagnostic tools be assured at the primary care level?
- How can the effectiveness of blood screening be evaluated in specific settings?

TREATMENT

- How can we scale up parasitological treatment for young patients in the indeterminate phase?
- Is it feasible to introduce tests of cure for routine assessment of treatment success?
- What is the optimal follow-up schedule for treatment in public health institutions?
- What is the cost-benefit relationship of implementing a central registry for Chagas disease treatment?

TRANSMISSION

- How can we scale up effective screening and treatment of women of childbearing age?
- How feasible is it to test newborns for possible follow-up and treatment?
- What are the pros and cons of including Chagas disease treatment within programs of care for mothers and infants?
- How can health education practices to prevent oral transmission be implemented?



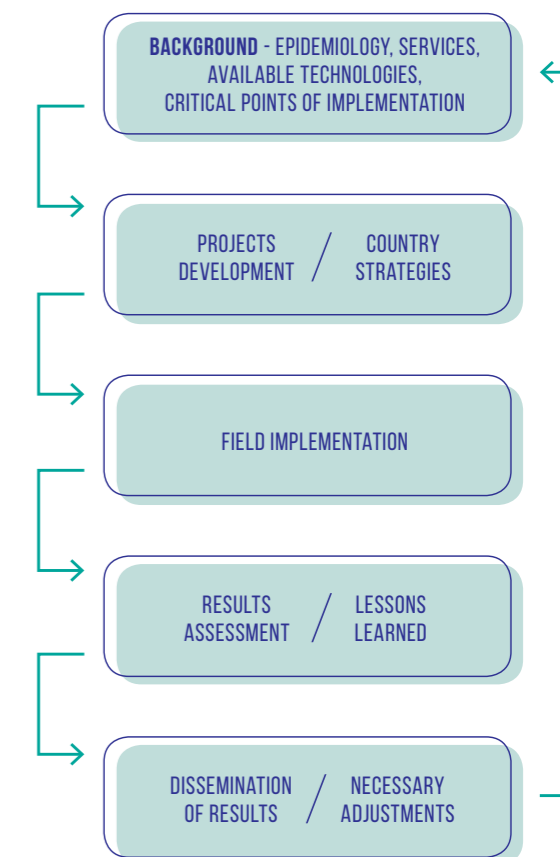
The Colombian Ministry of Health and Social Protection, international organizations, patients’ associations and local health leaders attended the seminar held in Colombia as part of the DNDi access implementation project.

FROM SCIENTIFIC EVIDENCE TO ACCESS

ANDREA MARCHIOL, DNDI LATIN AMERICA

We all know the founding principles of DNDi, whose merits have gained international recognition during the organization’s brief history. Nonetheless, we must not forget the circumstances that gave rise to this initiative. These include difficulties experienced by operations at ground level, working closely with those affected, due to the distressing reality of not being able to offer the most appropriate treatments to alleviate suffering and resolve the most common health problems affecting remote corners of the planet.

Thus DNDi, assuming this ambitious and challenging role, has been constructed in response to these needs. Moreover, in 2015 it assumes another role, which some may deem a departure from its purest principles: the assurance of ACCESS to treatment. Yet ACCESS in its broadest sense guarantees (whereas its absence problematizes) provision of timely, adequate treatment to those in need. In this manner DNDi, faithful to its founding principles and true to its original purpose, tackles the challenges associated with ACCESS to address the roots of difficulties in providing treatment, while seeking sustainable, shared, participatory, innovative, rigorous solutions framed in national health policies.



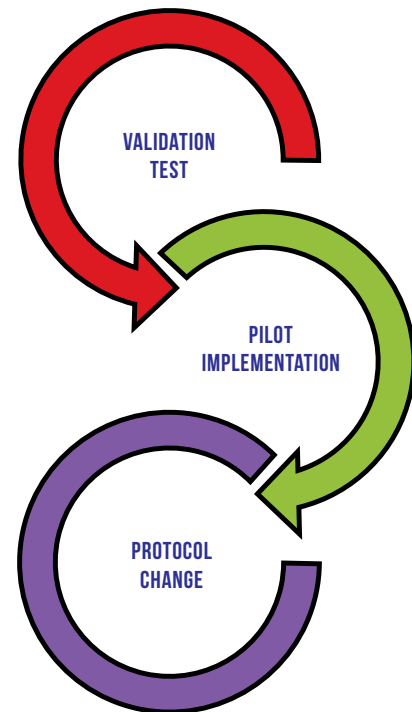
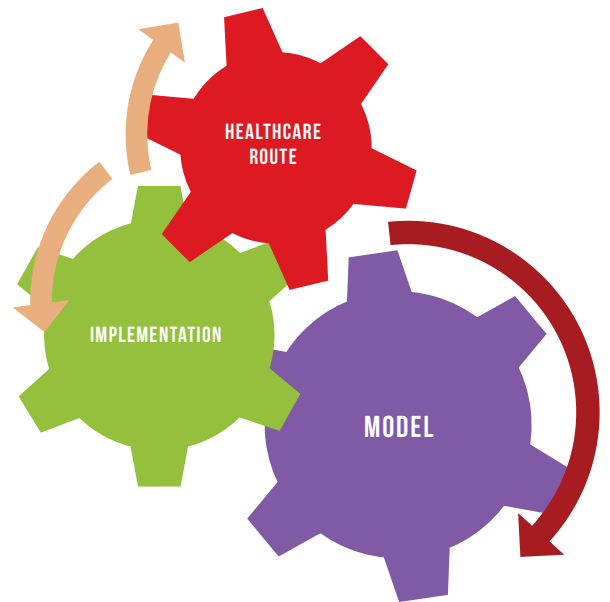
ACCESS

Consequently, since 2015, DNDi Latin America is collaborating with national programs in the region, looking to develop a novel approach that breaks down barriers to diagnosis and treatment of Chagas disease. Colombia has been our main focus, and we have thus far achieved initial successes that can serve as a guide enabling the country, the region, and DNDI to progress toward their own objectives. Colombia's program is the result of a joint model, collectively constructed, that combines recognition of the problem, political will to provide solutions, commitment to sustainable action, involvement of local entities in the process, and international technical collaboration that stimulates, promotes and supports the process under national leadership.

// *These (circumstances) include difficulties experienced by operations at ground level, working closely with those affected, due to the distressing reality of not being able to offer the most appropriate treatments to alleviate suffering and resolve the most common health problems affecting remote corners of the planet."*

Today, progress has been achieved through pilot projects in the most endemic municipalities in Colombia through identifying obstacles while also implementing concrete measures promoting a model which more directly impacts beneficiaries and breaks down barriers to diagnosis and treatment. This process has been based on feasibility and reinvention, and is committed, in the near future, to replication at the national level and transformation into health policies.

In this manner DNDi advances from **scientific evidence to support of implementation.**



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