NEW BENZNIDAZOLE REGIMES: HOPE FOR SHORTER, SAFER AND MORE EFFECTIVE TREATMENTS FOR CHAGAS DISEASE

The Chagas Disease Clinical Research Platform has been working since 2009 to overcome the research and development challenges related to this silent disease that kills up to 14,000 people every year around the world, mainly in Latin America.

The Chagas Platform members are scientists, scholars, policymakers, representatives of national and international non-governmental organizations, leaders of patient associations and healthcare professionals – more than 150 institutions in total. This diverse network brings together more than 500 professionals from 23 endemic and non-endemic countries.

The COVID-19 pandemic has been reinforcing the importance of collaborative research, sharing scientific information at a global level and strengthening local structures to develop accessible treatment for the populations that are most impacted by the novel coronavirus, as well as by historically neglected diseases. The Chagas Disease Clinical Research Platform operates based on these concepts of flexibility and cooperation, promoting meetings, training, integration of ethical principles and standardization. The network also provides a virtual forum for technical discussions and exchange of experience, seeking to optimize research resources and avoid duplication of efforts.

Even in front of one of the hardest moments in history for global health, the growing number of research projects related to Chagas disease renews our hope in collaborative work that widens therapeutic possibilities and overcomes longstanding barriers that separate people affected by illness from a safe, effective and affordable drug.
The Chagas Platform, Still in the Pandemic

Sergio Sosa-Estani, DND

We are writing this text after more than one year of experiencing one of the largest pandemics humanity has ever faced. More than 130 million people around the world have been infected so far with the novel coronavirus, and nearly 4 million have died. Even though there are still some unknowns, we have learned a lot about how to manage and mitigate the disease, and vaccines and other key tools have been developed at unprecedented speed.

Chagas disease and COVID-19 share an epidemiological overlap in Latin America, but also anywhere in the world where there is a person affected by Chagas disease. At the same time, this pandemic has become a new barrier, causing a decrease in Chagas disease care provided by health systems, with shifts in the investment priorities of public systems and funding agencies for intervention and research. We, the scientific community, have the ability and the obligation to leverage the lessons learned, to more intensively apply new forms of collaborative work to achieve more quickly, through research, the solutions needed to optimize access to diagnosis and treatment of the more than six million people affected.

There is consensus that simplifying the health care roadmap through research has become even more relevant in times of COVID-19. For example, quicker diagnosis with fewer visits to a healthcare center, and decentralization of diagnosis and treatment to the primary level of care, can not only alleviate pressure on the healthcare system (secondary and tertiary levels), but also reduce the exposure of people, patients and health care providers to COVID-19.

Finally, while research is looking for better solutions, the tools that are already validated must be applied more efficiently, employing coordinated models that optimize opportunity and coverage.

It is critical and necessary to integrate care for neglected diseases, such as Chagas disease, into the context of the COVID-19 pandemic, maintaining and increasing investment priorities that allow for research, validation and implementation of standard actions that ensure timely, high-quality prevention and care of affected people.

Managing Clinical Trials During the Pandemic: Experiences and Lessons Learned from Chagas Disease and Leishmaniasis

Marina Certo and Colin Forsyth, DND

The COVID-19 pandemic is having a profound impact on our society. While clinical trials for Sars-CoV-2 have picked up speed, other clinical studies are facing various challenges involving recruitment, follow-up and monitoring. In November 2020, the Chagas Platform and redLEISH brought researchers together for the workshop “Managing Clinical Trials During the Pandemic: Experiences and Next Steps Learned from Leishmaniasis and Chagas Disease,” aiming to share experiences and solutions to the challenges faced by studies that are already underway (in the case of Chagas, the BETTY, TESEO and MULTIBENZ trials), and to help studies that are being planned.

In 2020, researchers held systematic meetings to define risk management plans, assessing everything case by case, site by site. Considering the need for social distancing, the potential risk to the patient of contracting COVID-19 by going to the research site had to be assessed. Most studies had to halt recruiting and visits for a few months, gradually resuming activities at the end of 2020. There were cases of patients who were taking medication and who could not be assessed, and therefore had to discontinue from the trial. Other studies were able to continue following up with recruited patients during the months when travel to sites was restricted, with good results. As patients are assessed in person, the informed consent process should also be carried out in person.

Another challenge was the situation of multicenter studies, as each area loosened or tightened its lockdown measures according to the local epidemiological situation. This meant that some sites could reopen when others could not, and researchers needed to be flexible to adapt to the conditions. Another important point was the independence of screening sites, as travel between the sites was interrupted, impacting transportation.

COVID-19 testing is recommended during recruitment, although this has posed complications due to the high cost, with no guarantee that the study would be refinanced; moreover, there are also the extra costs of maintaining medical staff and purchasing PPE. Funding will be a major challenge for many studies, which are at risk of being left with reduced resources and sample sizes. This is a concern for the researchers that need to be addressed to ensure patient follow-up.

In some situations, it was possible to organize remote monitoring even with remote initiation visit reports—however, not all sites have the infrastructure to work remotely, leaving no choice but to implement face-to-face visits, depending on the risk. Certain problems are perceived through face-to-face visits that could not be identified remotely, but in some cases it was possible to try a hybrid strategy with less frequent face-to-face visits.

Finally, the greatest risk of suspending research activities in neglected diseases is that often the trial means access to treatment, and the patient may need urgent health care. We still do not know the real impact of the pandemic on populations affected by neglected diseases, but during this period there are likely many access barriers to Chagas disease health care.

https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html?bda75f474a0f-4d2f99424b6f88e9dcf5
Fiocruz Leads Strategic Research to Implement Healthcare Access for Chagas Disease in Latin America

Andréa Silvestre de Sousa,1 Alberto Novaes Ramos Jr.,2 Debbie Vermeij1 and Fernanda de Sardinha Mendes1

In the midst of the greatest health challenge in the modern world – the COVID-19 pandemic, – April 14, 2021 may be remembered for the intense mobilization and visibility of Chagas disease (CD), with significant events and actions in many parts of the world. We highlight, in the Brazilian and Latin American scenario, the launch of two important projects, interconnected at their origin, and which are being developed as a result of a collective effort led by the Oswaldo Cruz Foundation (Fiocruz) with Brazilian public universities – the Integrachagas Brasil and CUIDA Chagas projects.

IntegraChagas Brasil is a strategic project ordered and financed by the Ministry of Health (MH) of Brazil, planned as a pilot for the Unitaid initiative. It aims to expand access for the detection and treatment of chronic CD in primary health care, based on implementation research methods, under the coordination of the Evandro Chagas National Institute of Infectology (IN/ Fiocruz) in partnership with the Federal University of Ceará (UFCE). The expected result is the generation of intervention models that can be replicated in other scenarios in the country.

The Brazilian cities of Espírito Santo and Porteirinha (Minas Gerais), São Desidério (Bahia), Itacuruçá (Pernambuco) and São Luís de Montes Belos (Goiás) were chosen for this pioneering action to integrate care and monitoring for people with chronic CD. It is expected that a potential diagnosis of Chagas disease will be identified in 6,000 people, including adults and children. Social mobilization actions are already being planned, including support for the formation of the Association of People with Chagas Disease of Goiás, the newest association in Brazil. The project will be a historic opportunity to strengthen CD control actions in Brazil and strengthen the Unified Public Health System (SUS).

The CUIDA Chagas project (which stands for Communities United for Innovation, Development and Attention for Chagas Disease) is an initiative financed by Unitaid and the MH of Brazil, with technical support from WHO and PAHO, in addition to active civil society participation via FINDECHAGAS Coordinating by Fiocruz in association with its support foundation (Fiotec), CUÍDA Chagas has the following partners: National Institute of Health Laboratories (INLASA) of Bolivia, National Institute of Health (INS) of Colombia, and National Service for the Eradication of Malaria (SENEPA) of Paraguay, in addition to the non-governmental organization Foundation for Innovative New Diagnostics (FINDI). DNDi and the Brazilian office of the Netherlands Hansen Relief (NHR) act as collaborating institutions.

The general objective of CUIDA Chagas is to contribute to the elimination of congenital transmission of CD, expanding and improving access to diagnosis, treatment and comprehensive care through innovative and sustainable approaches in Bolivia, Brazil, Colombia and Paraguay. The implementation protocol will take place in 32 territories in the four countries, through the comprehensive strategic action of “testing, treating and care”. An estimated 234,000 women of childbearing age, their babies, children and household contacts will be actively and systematically evaluated, in a manner that is integrated with local health systems. As a component of innovation, new diagnostic algorithms for chronic CD based on rapid tests will be validated and a new therapeutic scheme with short benznidazole treatment will be tested in a Phase III clinical trial.

Fiocruz reiterates its responsibility and historic commitment in taking the lead in this research. These projects open a fertile space for comprehensive care of Chagas disease patients in the chronic phase of Chagas disease without evidence of pathology. The study will take place in six different sites in Argentina. All approvals have been obtained and recruitment is planned to begin in June, 2021. Total study duration is estimated at 21 months.

Ongoing studies will address other questions such as whether the antiparasitic effect observed in BENDITA will prevent congenital transmission. Important evidence will be provided by multiple trials which are currently ongoing or being planned, including TESEO, which is taking place in Bolivia, BETTY (described in the 2020 edition of the newsletter), and as part of the CUIDA Chagas Project (described in this edition) led by the Oswaldo Cruz Foundation in consortium with FINDI, the Ministries of Health of Brazil, Bolivia and Colombia and with collaboration from DNDi. Future research will also be needed to assess whether some of the other clinical benefits of the current standard treatment, such as the decreased heart failure and mortality observed in treated patients in several longitudinal studies, or the serological cure of acute infections, can also be attained with alternative treatment regimens.

Results of the BENDITA study were published in April, 2021 in Lancet Infectious Diseases. The DNDi-sponsored Phase II, double-blind, double dummy, proof-of-concept study, which took place at multiple sites within the Bolivian Chagas Platform for Comprehensive Care of Chagas Disease supported by Fundación Ciencia y Estudios Aplicados para el Desarrollo en Salud y Medio Ambiente (CEADES) and Institut de Salut Global de Barcelona (ISGlobal), evaluated shorter and intermittent treatments of benznidazole (BZN), both as monotherapy and in combination with fosravuconazole (E1224) in 210 participants with the chronic indeterminate form of Chagas disease. Participants were randomized to seven groups: BZN 300 mg daily for two, four or eight weeks; BZN 150 mg daily for four weeks, as monotherapy and in combination with fosravuconazole; BZN 300 mg weekly plus fosravuconazole for eight weeks; or placebo. The primary endpoint was sustained parasitological clearance at six months follow-up and incidence/severity of adverse events, including severe adverse events and those causing treatment discontinuation. Total follow-up extended to 12 months.

In all treatment arms, efficacy as measured by sustained parasitological clearance exceeded or was high at six months (83-89%) in the intention-to-treat population, with little drop-off at 12 months (78-89%). Overall, there were 15 adverse events leading to permanent treatment discontinuation, but no such events, nor any serious or severe adverse events, in the group receiving two weeks of benznidazole, 300 mg daily. This result is particularly encouraging, since reducing treatment from the current 60 days to two weeks, with a concomitant reduction in side effects, could greatly facilitate adherence for patients and simplify clinical management for healthcare personnel.

Since mid-2020, DNDi in conjunction with partners Mundo Sano Foundation and ELEA-Phoenix has been leading the development of a new study to confirm the promising results of the two-week, 300 mg daily arm of BENDITA. Nueva Esquema (Nuevo Esquema para Tratamiento con Benznidazol, New Scheme for Treatment with Benznidazole), a Phase III, open-label, prospectively controlled, non-inferiority study, aims to confirm the efficacy and safety of a two-week, 300 mg daily treatment of benznidazole, compared to the current standard (an eight-week treatment) based on historic controls, in adult patients in the chronic phase of Chagas disease without evidence of pathology. The study will take place in six different sites in Argentina. All approvals have been obtained and recruitment is planned to begin in June, 2021. Total study duration is estimated at 21 months.

Results from the BENDITA Trial and Next Steps for Evaluation of New Treatments

Tayná Marques, Colin Forsyth and Fabiana Barreira, DNDi
Parasite Dormancy in Chagas disease: Myth or Reality?

Fanny Escudé (OND), John Kelly (London School of Hygiene and Tropical Medicine), and Eric Chatelain (OND)

Dormancy or disease latency is a ubiquitous phenomenon mediated by a wide range of mechanisms that can contribute to the establishment of long-term pathogen infections or cancers. The terms “persistent”, “dormant” and “metabolically quiescent” are used interchangeably to describe pathogens/cells that exist in a state spanning a range of traits, from lack of any measurable cellular activity to various forms of growth arrest. The “persistent” phenotype does not involve the acquisition of selected mutations, may arise stochastically or in response to environmental changes (e.g. nutrient starvation, host immune response), is reversible and is often associated with treatment failure, antibiotic tolerance being the best studied example.

Chagas disease (CD), caused by the kinetoplastid Trypanosoma cruzi (T. cruzi), affects over six million people, mainly in Latin America. Two old nitroheterocyclic drugs, with unsatisfactory safety profiles and debatable efficacy, are the only available treatments. Molecular and phenotypic characterization of T. cruzi parasite populations using advanced technologies such as single cell RNA sequencing, tissue imaging and high-confidence assays and to underpin new drug discovery paradigms. Indeed, to date, the question remains: Are dormant T. cruzi persisters part of a growth rate spectrum – from fast- to slow-replicating parasites that includes transient dormancy – or do they represent a specific phenotype that is part of the parasite life-cycle (as for Plasmodium falciparum or Toxoplasma gondii)?

Given the scarcity of resources for CD drug development, the statement “Share knowledge rather than dormancy” therefore remains more important than ever for the Chagas research community.

The GI tract is an important site of parasite persistence during chronic Trypanosoma cruzi infections in mice. The images show parasite-infected smooth muscle myocytes from the colon. Intracellular amastigotes are green; DAPI staining (blue) identifies host cell nuclei. In the right hand image, there has been a robust immune response characterized by major recruitment of T cells to the site of infection (stained red; anti-CD3). The parasite “nest” in the left hand image is apparently in a non-proliferative form that is part of the parasite life-cycle (as for Plasmodium falciparum or Toxoplasma gondii).

Is the New Roadmap for Neglected Diseases Realistic and Feasible?

Javier Sancho, Chagas Coalition

On January 28th, the World Health Organization (WHO) launched the new Roadmap for Neglected Diseases, titled Ending the Neglect to Attain the Sustainable Development Goals.

Why is this important?

The Roadmap is an effort to agree on and reach impact targets and goals to prevent, control and eliminate neglected tropical diseases (NTDs) from 2021 to 2030. It has been approved by all WHO countries and is aligned with the Sustainable Development Goals. It provides a general framework for each country to develop its own national plan and adapt those objectives to its context.

The Roadmap is built on three pillars to support the response of health policies to NTDs: A. Accelerating the action of health policies aiming to provide impact indicators. B. Intensifying transversal approaches. C. Changing the operating model and culture to help countries own the agenda and feel empowered.

What are the most significant goals for 2030?

- A 90% decrease in the number of people needing NTD treatment
- 100 countries eliminate at least one NTD
- 2 eradicated NTDs (dracunculiasis and yaws)
- A 75% decrease in NTD-related disability-adjusted life years (DALYs)

What are the general objectives for Chagas?

Chagas is in the group of diseases for which the goal is elimination as a public health problem by 2030 (the accuracy of this term is important, as it is different from being eradicated or eliminated altogether). Critical actions have been established to improve the response of health systems and health workers. In specific terms:

- By 2030, 15 countries have stopped transmission (from vector, mother to child, transfusion, and transplant)
- 75% of the eligible population has coverage for antiparasitic treatment.

Is this realistic?

It is important to consider that this Roadmap was designed in 2018 and 2019, before the onset of the COVID-19 pandemic. We are not sure if all Chagas disease programs or subprograms are completely familiar with the roadmap. In any case, neither the programs nor the health systems around the world are in the same state now as they were then. Another critical issue is that, for the Roadmap to be viable, each country needs a plan to review and raise the necessary resources.

What should countries do?

Countries should review the roadmap and study how to adapt it to their own national plans with necessary adjustments. The Roadmap establishes several review periods; the first will be in 2023. The active participation of the countries where Chagas is endemic will be key. It is advisable for countries to jointly discuss the Roadmap with organizations that work with the disease and with groups of people affected by it. It is always best to have a plan with the highest level of international consensus.
Prediction of Parasitological Cure in Trypanosoma cruzi-infected Children using a Novel Multiplex Serological Assay (Multi-Cruzi)

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Jaime Altcheh, Hospital de Niños Dr. R. Gutiérrez
Eric Chatelain, DNDi

Chagas disease (CD), which affects over six million people, was discovered to be caused by Trypanosoma cruzi parasites more than 100 years ago by Carlos Chagas. Thanks to the introduction of serodiagnostic screening tests in the 1940s, widespread T. cruzi infections throughout Latin America could finally be demonstrated. Despite all these important discoveries and ongoing multinational initiatives, patients still lack access to adequate drug treatments. Moreover, proper counselling of patients following drug treatment remains a challenge. Indeed, the current consensus for parasitological cure is to monitor conversion from positive to negative serology. However, seroreversion by standard tests can take many years to decades in adults, making evaluation of treatment efficacy difficult within standard clinical trial settings. A test to assess parasitological cure in a timely manner is therefore of highest priority.

Using a novel multiplex immunoassay Multi-Cruzi, DNDi, Infynty Biomarkers (France), and the Parasitology service of the Hospital de Niños Ricardo Gutierrez (Buenos Aires, Argentina) have now shown that the Multi-Cruzi ELISA assay can give insight of parasitological cure in T. cruzi-infected children (Lancet Infectious Diseases: https://doi.org/10.1016/S1473-3099(20)30729-5). In this study, T. cruzi-infected infants and children were examined. The advantage of studying the serology of this population is that children become seronegative faster than adults. Therefore, we were able to observe the kinetics of antibody decline and the potential treatment effect on serology. We show that the Multi-Cruzi ELISA, thanks to its multiparametric nature (15 different parameters), can provide accurate serological information (the following figures that illustrate a discrete but measurable change in the serological signature; such changes are not detectable by conventional immunoassays). In combination with a mathematical algorithm, the Multi-Cruzi assay can predict parasitological cure in T. cruzi-infected children substantially earlier than a conventional ELISA assay. The test emphasizes the concept of “serological signatures” and could represent a paradigm shift in forecasting serological outcomes after treatment in T. cruzi-infected individuals.

Based on these results we now aim to transpose the predictive model by applying and fine-tuning it for adults, which could pave the way for this original strategy for monitoring clearance of parasite post-treatment. We are seeking well characterized clinical samples of retrospective follow-up studies. As part of our biomarker identification/validation/research program at DNDi, we are therefore now reaching out to the Chagas Platform and the entire clinical and diagnostic Chagas community to access and test Chagas patients’ samples using the Multi-Cruzi assay and developed interpretation algorithm. The Multi-Cruzi assay will be operational in the laboratory of Dr Jaime Altcheh as of Q2-2021. Should the assay confirm a significant time gain over the established reference method, it can be positioned in the protocols of ongoing/future drug evaluation clinical trials.

In parallel, we are currently exploring the use of the Multi-Cruzi assay in experimentally-infected laboratory animals and further investigating whether parasite elimination as assessed by Bio-luminescence and PCR is associated with a decrease in serological signature. Positive results could then bridge pre-clinical and clinical settings testing of new drugs for CD and improve translational value of the experimental Chagas disease model.
Algorithm to Evaluate the Response after Treatment with Antiparasitic Drugs for Chronic Chagas

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As part of the XXXI Annual Meeting of the Argentinean Society of Protozoology, DNDi’s Chagas Clinical Research Platform led a workshop with the aim of developing a tool to facilitate the decision-making process for assessing the response to antiparasitic treatment in people with chronic Chagas disease receiving care through healthcare services. This text summarizes the main themes addressed, the evidence used, and the conclusions of the workshop.

The World Health Organization recommends etiological treatment with trypanocidal drugs (benznidazole and nifurtimox) for people with chronic Chagas disease. The indication of trypanocidal aims to ensure the person’s well-being and the maintenance of the same clinical state as at the beginning of treatment. The probability of demonstrating a “cure” (the disappearance of anti-T. cruzi antibodies) is higher when the younger the person’s age at the beginning of treatment and the longer the time elapsed between treatment and follow-up. The probability of demonstrating a “failure” (detection of circulating parasite DNA) increases with the frequency of polytherapy (at least two antiparasitic drugs) and the number of years (3 consecutive years) since treatment.

Based on the categories considered and taking into account personal experience as well as the available evidence, the participants worked in groups with the task of sketching, freely, a flowchart indicating the steps to follow during the follow-up of people with chronic Chagas after treatment.

We can highlight the following conclusions from the workshop:

- There was a suggestion to differentiate between endemic and non-endemic areas, especially for inconclusive cases when lab work needs to be redone.
- The age range of 1-19 was considered very broad, whereas the categories of <2, 2-12, and >12 would be more aligned to a response pattern, since, for example, children in the third group would have a similar response to that of treated adults.
- Qualitative PCR results (detectable or positive, and not detectable or negative) were deemed sufficient for clinical practice.
- Participants discussed the feasibility of using the results from two serological tests alongside a molecular test to build a tentative clinical algorithm, which could then be used to develop a decision tree (inference statistics). This is currently being developed.

Serology | PCR | Interpretation | Conduct
--- | --- | --- | ---
POS | POS | THERAPEUTIC FAILURE | New treatment*
POS | NEG | Probable (success/failure) | Annual follow-up
NEG | POS | Repeat serology | According to follow-up results
DISC | NEG | Probable success | Annual follow-up
NEG | NEG | THERAPEUTIC SUCCESS | Annual follow-up (3 consecutive years)

Serology POS = Reactive
NEG = Non-Reactive
PCR POS = Detectable DNA
NEG = No detectable DNA

* Antiparasitic drug selected according to evaluation of adherence.

The story of an insect, a family, and a neglected disease

Daisy Hernández

The first time his heart bothered him, Carlos was fifteen. He didn’t know it was his heart. He only knew that he needed to cry, and he wanted to be alone, which was strange for him. He had a big family. He loved being around his parents, brothers, and sisters. They lived in a one-room house in a rural area of Central America, a house made of paja, or straw, that gave them shade from the burning sun. His father farmed the fields, and his mother, Mamá Tila, tended the chickens and cleaned and prepared meals and raised the children. The civil war had been underway for five years by then—the death squads and the murders of four Americans including three nuns were known—but that day when Carlos went to be alone by the river, he was not crying about the war.

And then he started to fall.

He was nineteen and one day, while out on a walk, he fell face-down. His heart pounded inside his rib cage. What was happening to him? Where he lived in Central America, doctors were a luxury. He got to his feet and moved on.

1 U.S. journalist. Has written a book about Chagas disease a book that was published June 1, 2021. The Kissing Bug: A True Story of an Insect, a Family and a Nation’s Neglect of a Deadly Disease (Tin House) chronicles the story of how Chagas affected the author’s family and what she learned about the disease’s impact on families in the United States. You can learn more about her work at www.daisyhernandez.com. What follows is an excerpt from the book about one patient’s story.
Listening to Carlos, I remembered the familiar exhortation: “Listen to your heart.” But no one points out that the heart speaks its own language, possesses its own syntax and vocabulary. Listen to your heart, but who teaches you that the heart cries in alarm by exhausting you, by taxing your lungs, by fatiguing you when you’re only a teenage boy?

... The word Carlos used the most with me was dañado, or damaged. He had heard it from a number of doctors over the course of three decades.

He told me in Spanish, “That’s where they detected that my heart was damaged.” He was twenty years old and had collapsed in the hospital while visiting his mother. About a year later, the doctor explained that Carlos’s heart failure had reached a point where he needed a pacemaker. His first. Two pacemakers and more than twenty years later, he needed the máquina, the LVAD. “The heart was very damaged,” he told me. “The pacemaker wasn’t helping anymore.”

For most of his life, Carlos did not know that he had the kissing bug disease. In 2011, at the age of forty-two, he was on his second pacemaker when he migrated to New Jersey and became a father. A year later, after splitting with his son’s mother, he moved to Boston where his brother Elias had found work in a soda factory. There Carlos planned to start his life over after the breakup, but at night when he tried to sleep, he felt like he was underwater, his chest turning into a river and the water rising. He woke up screaming, “I’m drowning! I’m drowning!”

Carlos started to sleep in a chair to avoid the drowning sensation and to avoid waking Elias, who worked a night shift and came home at three in the morning. But a man can sleep sitting up for only so many nights. Carlos finally consented to making a trip to the emergency room at the local hospital. The doctors told him el daño had gone too far. Carlos didn’t need another pacemaker—he needed a new heart.

One doctor in Boston grew suspicious about Carlos’s heart. He must have thought: Why would an otherwise healthy man in his forties have end-stage heart failure? The doctor happened to know about the kissing bug disease and showed Carlos photos of the triatomine insect, asking if he had ever seen one, maybe when he was a child. Carlos nodded. Of course. He had seen them everywhere back home. “There were a lot of chinches,” he told me in his living room by the window, using the nickname for the bug from his country.

Carlos would wake as a child with welts on his arms and legs, the evidence of where kissing bugs had feasted on his body during the night. If he had been treated as a child with one of the two drugs available for the kissing bug disease, he probably would not have needed a heart transplant decades later. In Boston, he said, the doctor told him he had the disease almost thirty years after he first experienced irregular heartbeats as a boy.

Again I remembered the words of the Argentinian physician Jaime Altcheh: “Every adult with Chagas is a child who was not treated.”

In need of a heart transplant and unable to work, Carlos moved to Maryland with Elias. They had two brothers there working in construction. Elias could get a job easily, they thought. The brothers would split the expenses of a one-bedroom apartment and wait for Carlos’s new heart. They were sure it would come.