Strategies to enhance access to diagnosis and treatment for Chagas disease patients in Latin America.

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Title: Strategies to enhance access to diagnosis and treatment for Chagas disease patients in Latin America.

Structured abstract (maximum 200 words): Chagas disease, caused by infection with the parasite *Trypanosoma cruzi*, represents a huge public health problem in the Americas, where millions of people are affected. Despite the availability of two drugs against the infection (benznidazole and nifurtimox), multiple factors impede their effective usage: 1) gaps in patient and healthcare provider awareness; 2) lack of access to diagnosis; 3) drug toxicity and absence of treatment algorithms to address their adverse effects; 4) failures in drug supply and distribution; and 5) inconsistent drug efficacy against the symptomatic chronic stage. Here we review new approaches and technologies to enhance diagnosis and treatment algorithms as a means to reduce the disease burden. We also provide an updated picture of recently published and ongoing anti-*T. cruzi* drug clinical trials. Although there has been progress improving the research and development (R&D) landscape for this traditionally forgotten disease, it is unclear whether any new licensed treatments will emerge soon. Therefore, in parallel with R&D approaches we summarize the needs to continue awareness and advocacy efforts by patient associations, local and national governments and international agencies, and why health system strengthening is essential to ensure vector control commitments, as well as patient access to diagnosis and treatment.

Keywords: Chagas disease, comprehensive care, clinical trials, diagnosis, drug treatment, patients associations, pharmacovigilance, vector control.

1

1. Introduction.

Chagas disease, or American trypansosomiasis, is caused by the protozoan parasite *Trypanosoma cruzi* (*T. cruzi*) and remains one of the most deadly and intractable neglected tropical diseases (NTDs) in the Western Hemisphere [1]. Updated information from the Global Burden of Disease Study (GBD) 2016 indicates that 7,100 people die from Chagas disease annually, roughly the same number of Chagas disease-related deaths that occurred a decade previously [2]. However, these numbers may represent highly conservative estimates with further findings that as many as 200,000 people living with *T. cruzi* infection may die over the next five years [3]. The GBD 2016 also finds that 7.2 million now live with Chagas disease, while 180,000 new *T. cruzi* infections occur annually [4].

Beyond its horrific disease burden and contribution to infectious disease mortality, there is a profoundly disturbing social impact dimension to Chagas disease related to its importance as a health disparity. Today, tens of thousands of people face a death sentence from their *T. cruzi* infection due to Chagasic cardiomyopathy, which could be prevented by timely access to diagnosis and anti-parasitic treatment with one of two nitroheterocyclic drugs – benznidazole (BNZ) and nifurtimox (NFX). Fueling a growing outrage from the global health community is the finding that approximately 90% of people infected with *T. cruzi* infection now live in Latin America's three wealthiest economies: Argentina, Brazil, and Mexico. In the United States of America (USA), the richest country of the continent and main destiny of those looking for a better future, there are at least 200,000 immigrants from Latin America living with Chagas disease with limited or no access to treatment [5,6]. Furthermore, in Europe there are around 120,000 immigrants from Latin America living with Chagas diseases with a disparity of situations regarding access to care and treatment [7,8].

The overwhelming majority of Chagas disease sufferers are unable to gain access to diagnosis and treatment, not only because they are poor, but also because governmental leaders are either uninformed or uninterested. For example, it is noteworthy that the registration of BNZ for the treatment of pediatric Chagas disease in the USA has not been approved until very recently [9]. Documenting such assertions is not easy and seeking solutions to diagnosis and treatment access are not straightforward endeavors. In Mexico, for example, there are almost one million people living with Chagas disease, although even that number may represent a profound underestimate [10]. Yet, only 3,013 *T. cruzi* infection cases were registered nationally between the years 2007 and 2011, less than 1%

2

of the actual number of people affected with the disease [11]. A similar situation has been documented for the USA [12] and also likely holds true across the Americas. We are facing a situation where less than 1% of Chagas disease patients have access to timely and appropriate diagnosis and treatment [13,14].

Limiting access to essential medicines also has important implications for new research and development (R&D) related to therapeutic interventions. An exciting development on this front is a new orally bioavailable nitroheteorcyclic drug, fexinidazole, which is also effective against human African trypanosomiasis [15]. Additional drugs are also under development, as well as there are Chagas disease vaccine (immunotherapeutic) candidates at pre-clinical stage [16]. In this respect, the Texas Children's Hospital Center for Vaccine Development, a Product Development Partnership, is exploring an approach that links therapeutic vaccination to pharmacotherapy [17]. However, any R&D successes must still face a formidable gauntlet of truncated and mostly failed global access mechanisms. Similar forces are a barrier for access to new and innovative diagnostics [18].

Here we report on some of the major hurdles that currently block access to the diagnosis and treatment of Chagas disease. The problems include both scientific and socioeconomic obstacles. This paper aims to elucidate the challenges they pose and offer solutions.

2. The need of more practical and useful diagnostics.

The poor access rate to Chagas disease therapeutic treatments has its roots in the clinical nature of the disease itself and its silent progression from the mostly asymptomatic acute stage into the symptomatic chronic one [1]. Unfortunately, biomarkers of disease progression and standardized tools to determine early response-to-treatment are yet unavailable, which greatly complicates the prognosis and follow-up of patients [19].

Treatment administration, as in any other disease, needs to be preceded by an adequate diagnosis. In the case of Chagas disease, when a clinical diagnosis is achieved, tissue disruptions might already be too advanced for a chemotherapeutic intervention. Therefore, parasite detection must be sought before the onset of overt symptomatology. In the acute infection stage, for instance upon congenital transmission of the parasite, parasitemia can be detected by direct microscopic observation [1]. However, this stage is short lasting and generally goes unnoticed as there are often no symptoms at all.

3

Approximately 30% of these infected individuals will progress to evidence of either Chagasic cardiac or gastrointestinal disease. Those without clinical evidence of disease are said to be at the indeterminate stage, whereas those with cardiac or gastrointestinal involvement are at the determinate stage. The development of life-threatening heart and/or digestive tract disruptions, which can be massive and are called mega-syndromes, occurs in the long lasting chronic stage that follows [1].

In both indeterminate and determinate Chagasic patients parasitemia is typically low and intermittent and the diagnosis of the infection is made by means of indirect serological tests, like enzyme-linked immunosorbent assays (ELISAs). This is possible because high levels of parasite-specific immunoglobulins are produced upon *T. cruzi* infection (Figure 1). Anti-*T. cruzi* type G immunoglobulins (IgGs) levels remain above detection thresholds for many years, which is advantageous for the serological diagnosis of the infection (Figure 1). However, it turns out to be an inconvenience for a serology-based assessment of drug responses as it can take several years for them to revert after the administration of treatment [20].

Some studies indicate that treatment interventions while patients are in the indeterminate or early determinate stages are critically important in order to prevent advanced disease progression. In contrast, from the multi-centered BENEFIT trial to evaluate benznidazole efficacy it was found that patients with significant cardiac involvement progressed to advanced disease or even died despite receiving specific antiparasitic chemotherapy [3,21]. Currently a Kushnir grading system is in place to differentiate people with early-stage (grades I-II) versus late stage (Kushnir III-IV) determinant cardiac disease [1]. Treatment of patients with Kushnir grades III-IV was not encouraged previously [1], a finding that appears to hold up in light of the recent BENEFIT findings.

These findings highlight the importance of identifying both indeterminate patients with Chagas disease and possibly those with Kushnir grades I-II since they might be successfully treated with antiparasitic therapy if they were captured during population-wide screening campaigns [3]. In this way, it would be possible to identify and treat chronically infected people before they develop the symptomatology. Women at child-bearing age and newborns should receive special attention because the treatment of mothers-to-be has been shown to largely reduce the transmission rate [22–25], and the efficacy and tolerability of current drugs by infected newborns is ~100% [1]. Moreover, health economics studies evaluating Chagas disease surveillance in endemic and non-

4

endemic settings indicate that widespread screening would be highly cost-effective [26–29]. In the two disease scenarios studied, congenital (acute infection transmitted by chronically infected mothers) and indeterminate (chronic asymptomatic stage), mass screening would save health costs even at *T. cruzi* prevalence rates as low as 0.9% or 0.05% respectively (estimated in the non-endemic setting) [26,28].

Due to the very limited resources available for Chagas disease management, and echoing the answers provided by Latin American experts enquired by Picado et al. [18], efforts should focus on making widely available point-of-care (PoC) tests to diagnose congenital transmission and indeterminate chronic patients [18]. However, if we want to enable generalized Chagas disease diagnosis, there is an urgent need of more practical diagnostic reagents and kits. Availability of easy-to-use tools for the early assessment of treatment response would also be highly valuable to promote and support the administration of drugs against the infection. In this regards, there are some biomarkers under research [19], but the evaluation of anti-*T. cruzi* drug responses yet relies on the molecular amplification of the parasite DNA from periphery blood obtained at distinct times post-treatment. Unfortunately, its associated high costs and technical requirements restrict its use to the context of well-funded clinical trials [30].

2.1. Current Chagas disease diagnostics are impractical in many regions.

Regarding acute stage diagnostics, classical parasitological methods (micromethod, hemoculture and xenodiagnoses) are microscopy-based and rely on finding motile trypomastigotes in blood, thus they provide both low sensitivity and specificity. Due to their poor performance, current algorithm to diagnose congenital transmission involves two micromethods (at birth and at 1-2 months of age), and a further confirmatory serological test once mother-derived IgGs have waned at infant´s 8-12 months of age [31]. This has two major drawbacks: a very high loss-to-treatment risk during pediatric follow up, and the reduction of drug efficacies the longer the treatment is delayed [31]. Molecular amplification of *T. cruzi* DNA, either by conventional polymerase chain reaction (PCR) or by quantitative PCR (qPCR), has been shown to be more sensitive and specific than classical parasitological techniques [20]. Several laboratories have worked on the standardization of the techniques so that their outcomes can be comparable and implemented in clinic-based laboratories [20]. But molecular biology laboratories are expensive to mount and maintain, plus they require highly trained personnel to run them. Therefore, despite its very good performance, molecular detection

5

is not generally used beyond regional or national reference laboratories in endemic regions.

In relation to the current chronic stage diagnostics, conventional serological tests (like ELISAs, indirect immune-fluorescence or indirect hemagglutination assays) use serum or plasma samples that entail venous extraction and blood segregation by centrifugation, and they require a cold chain to preserve the test reagents and the samples. Moreover, due to the parasite´s antigenic diversity, the advice from the World Health Organization (WHO) is to run two tests based on distinct antigenic sets and if their outcomes are not concurrent, to employ a third technique [14]. This algorithm is costly, and it requires equipment and resources that are usually not available in many laboratories of endemic regions. Furthermore, the turnaround of results to the patient can take several weeks, which involves a high risk of losing contact with the patient for treatment.

2.2. What solutions could be implemented?

Fortunately, recent technological advancements are procuring solutions to overcome the limitations mentioned above. We will outline them separately considering first those for the diagnosis of acute stage and then those for the diagnosis of chronic Chagas disease.

In recent years, isothermal amplification methods that do not require expensive equipment (such as thermocyclers or gel visualization systems) and are easier to perform than PCR assays have been developed for the molecular detection of several NTDs [20]. At present, a prototype of Loop isothermal AMPlification for *T. cruzi*-DNA (LAMP, Eiken Co., Japan) has been tested with clinical samples and shown to have a comparable performance to qPCR with blood-EDTA samples [32]. Another LAMP test developed in house by Rivero et al. [33] has also been shown to provide a comparable performance to current congenital transmission algorithm. LAMP is based on a microbiological DNA polymerase that works at a constant temperature of 65 ºC for 45 minutes with a set of 4 to 6 complex primer sequences to provide a highly sensitive and specific amplification [34]. LAMP readout is qualitative and the results can be naked eye visualized in a short time given a probe (e.g. calcein) is added to the reaction mix. If a digital fluorimeter is used (e.g. Genie III) the reading can even be semi-quantitative [32]. Notably, in EIKEN´s *T. cruzi*-LAMP prototype, reagents are provided dried out in the lids of the reaction tubes which allow a ready-to-use format and a much desirable room temperature storage [32]. More recently, a Recombinase Polymerase Assay (RPA), which even requires a lower

6

amplification temperature and shorter amplification time (40 ºC for 30 min) than LAMP, has been tested with samples from naturally *T. cruzi*-infected dogs [35]. This RPA has been coupled to a lateral flow strip for results reading and it was shown to provide excellent agreement with qPCR results [35]. There are RPAs for the detection of other NTDs [36,37], so it could also be very useful for Chagas disease molecular diagnosis.

For the serological detection of *T. cruzi*-specific IgGs, rapid diagnostic tests (RDTs) have been commercially developed during the last two decades [38,39]. RDTs have clear advantages over conventional serology, as they can be stored at room temperature, use a very small volume (5-25 µl) of finger pricked whole blood, have an easy-to-run and read cassette format, and provide a fast turnaround of results (less than 45 minutes) [39]. Several studies now support their implementation as they have been extensively validated against conventional tests [40–42]. For instance, a RDT is currently used for primary screening of chronic Chagas disease in Bolivia [38]. Nonetheless, following the WHO guidelines of two-tests concordance, confirmation of that RDT primary result must yet be made with a conventional serological test [14]. Such recommendations reduce the advantages of RDTs.

With the aim to fully exploit RDTs advantages and to determine whether they can substitute conventional tests, combinatory use of two RDTs has been proposed [40]. So far, in a proof-of-concept study performed in the city of Sucre (Bolivia), perfect agreement between the two RDTs used was observed, and their sensitivity and specificity in comparison with three conventional tests was 100% and 99.3%, respectively [40]. However, despite a promising performance in Bolivia [40,42], RDTs have not worked so well when they have been used in other geographical regions [43]. This might be related to the high prevalence of the disease in Bolivia, which may allow an easier detection, or to the fact that the parasite strains used to produce the RDTs antigens are those circulating in Bolivia. In any case, until more results from different epidemiological areas are available, preliminary geographical testing of the RDTs performance has been proposed before using them in a particular region [43]. In view of the advantages they bring versus conventional tests, RDTs implementation for Chagas disease surveillance should be evaluated at larger scales.

3. Treatment of Chagas disease, and issues related to it.

3.1. Drug regimens.

Evidence about the benefits of Chagas disease treatment, together with a growing

7

understanding of the pathogenesis of the disease, led to the paradigm that all *T. cruzi*-seropositive patients should receive treatment with anti-*T. cruzi* drugs [44]. The recently published results of the SaMi-Trop cohort study further reaffirm this statement as they demonstrate a beneficial effect of BNZ in reducing the cardiac clinical progression of chronic Chagas disease patients [45]. Therefore, anti-trypanosomatid should be provided to all *T. cruzi*-infected people who do not present with advanced cardiac complications (Kushnir grades III-IV), as by then clinical manifestations might not be improved [46]. Nonetheless, access to treatment confronts important limitations. BNZ and NFX, the only drugs available for *T. cruzi* infection, exhibit reduced efficacy during the chronic stage of the disease, and require a long period of administration which causes frequent unwanted drug-related adverse reactions (ADRs) [47–49]. Furthermore, variable drug susceptibility has been already described among distinct *T. cruzi* strains [50]. In this context, there is an urgent need for more efficacious and safer drugs or drugs´ regimens, in particular for the treatment of the chronic stage of the infection.

One alternative is the reduction of the BNZ dose and/or schedule in order to improve safety and adherence to treatment; an approach that is supported by clinical and experimental data. In a pilot study Álvarez et al. [51] assessed a new scheme of BNZ administration in a small cohort of chronic Chagas disease patients treated with intermittent doses of BNZ at 5 mg/kg/day every 5 days for a total of 60 days. The study showed a satisfactory safety profile, with low rates of treatment suspension and treatment failure [51]. Furthermore, an experimental study using a mouse model of chronic *T. cruzi* infection demonstrated the effectiveness of an intermittent scheme of BNZ administered every 5 days for 40 days [52]. These findings support the intermittent administration of BNZ as a new dosage schedule, but further research to confirm its efficacy by long-term assessment of larger cohorts is needed. Another therapeutic option under investigation is the co-administration of an immunotherapeutic (vaccine) treatment and BNZ. In this regards, enhancement of a *T. cruzi*-specific immune response has been shown to contribute to support the efficacy of reduced BNZ dosages in a mouse model of acute *T. cruzi* infection [17].

3.2. Drug availability.

Drug access is still a huge problem in some endemic areas [13]. BNZ, generally the first line therapy for Chagas disease, is part of the WHO List of Essential Medicines [53]. It was produced during more than 40 years by Roche (Basilea, Switzerland), which

transferred its production rights to Laboratório Farmacêutico de Pernambuco (LAFEPE), a Brazilian public enterprise, at the end of the twentieth century. Sadly, BNZ production and distribution by LAFEPE failed to meet expectations in terms of meeting supply and demand requirements and in 2011 an important shortage of the drug occurred. It lasted 1.5 years and left thousands of patients without treatment worldwide [13,53]. This fact led to the development of a Private-Public Partnership in Argentina involving Maprimed (for the synthesis of the drug) and ELEA (for its development and production), to promote equitable availability of BNZ [55]. Since 2012, this Argentinian Partnership has worked to guarantee the availability of the drug, distributing BNZ to the countries in the region [55]. NFX, which is mostly used as the second line treatment option, is produced and donated by the pharmaceutical company Bayer, and distributed through the Pan-American Health Organization (PAHO) Strategic Fund [56]. Recently, a NFX produced by Gador has also been registered in Argentina. Definitely, a regular, safe and accessible production of these two antiparasitic drugs is necessary to guarantee the treatment to diagnosed patients, and the access to drugs has to be ensured in adequate quantity, quality, location and timing.

3.3. Pharmacovigilance.

A major limitation of current Chagas disease treatments is the onset of Adverse Drug Reactions (ADRs), which may lead to poor medication adherence, and cause thereby therapeutic failure or ineffective treatment [46-48]. ADRs are defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" [57]. The most commonly observed ADRs related to BNZ are headache, dermatological manifestations and gastrointestinal symptoms [47,48]. Concerning NFX, digestive symptoms are the most frequent [46]. Nevertheless, with an adequate clinical management most of the patients are able to finish treatment in the advent of ADRs [47]. Close medical follow-up, adequate monitoring of ADRs and implementation of robust pharmacovigilance systems are essential factors to avoid patient abandonment and achieve therapeutic success.

Although pharmacovigilance is crucial, it is still a neglected area. Latin-American countries are making important efforts to report ADRs, but these activities are recent and need reinforcement [58,59]. Results of an unpublished study conducted by Cortes-Serra

9

et al. in Bolivia during 2016 indicate that 35.4% of the total patients treated for Chagas disease in fourteen healthcare centers of the department of Cochabamba suffered ADRs related to it. From all ADRs classified as moderate or severe (25% of the total ADRs registered), only about half of them (51.43%) were reported to the Bolivian Pharmacovigilance system [60]. This data illustrates the urgency of implementing policies to promote training in pharmacovigilance to all healthcare professionals, as well as strictly recommend the follow-up on drug monitoring and ADR reporting. Altogether, these features are fundamental to achieve strong and consolidated ADR reporting systems, which will improve patient safety, drug efficacy and adherence to treatment.

4. Patients´ comprehensive care: reference and counter-reference circuits.

With less than 1% people treated [13,14], and an economic burden of $7.19 billion per year and $188.80 billion per lifetime [61], Chagas disease remains neglected despite the efforts performed by several institutions focused on development and research [13]. Migratory flows have changed the epidemiology of the disease that is now emerging in some non-endemic countries [7]. During the last decades, collaboration and knowledge transfer between institutions from endemic (CEADES, Bolivia) and non-endemic countries (ISGlobal, Spain) has been strategic to build attention models for the Chagas disease patient. Such models could be scaled-up by national health systems in endemic and non-endemic countries in order to expand Chagas disease healthcare to people living in areas with limited access to health (e.g. rural areas in endemic countries) or to vulnerable populations (e.g. migrants in endemic and non-endemic countries).

4.1. The Platform for integral care of Chagas disease patients.

The work made by this Platform in recent years have produced a quantitative and qualitative improvement in the healthcare provided to Chagas disease patients in Bolivia, but this improvement certainly needs to be strengthened. The experience gained with the Platform in the country has shown that the implementation of specialized centers to manage people at risk of having Chagas disease is highly effective, both based on the percentage (and number) of people diagnosed with the infection, and amongst them, those who received and completed treatment [62]. This vertical strategy has been essential to design the attention model for patients with Chagas, making the medical assistance to these people look like a normalized and necessary action [62]. Nevertheless, the sustainability of such model ultimately depends on continuously securing external funds,

10

which greatly complicates its expansion to larger geographical levels, like national coverage by the national health system (Figure 2).

4.2. Vertical-to-horizontal healthcare model transition.

In order to have a higher impact in terms of diagnosis and treatment coverage, as well as to ensure the sustainability for the model of care of Chagas disease patients already installed, it is mandatory to search for a comprehensive horizontal strategy together with local higher level entities of the public health system. In fact, based on WHO recommendations, the strategy to include the Chagas disease attention roadmap as part of the regular activities of all healthcare levels seems to be the most appropriate approach [63].

Simplifying the vertical Chagas disease model of healthcare to more realistic protocols established together with the national health institutions has allowed the improvement of healthcare access for people at risk of having the disease living in remote areas of an endemic country [62]. Researchers at ISGlobal (authors of this review) have yet unpublished data which demonstrate that the health coverage, in terms of patients diagnosed and treated in the selected area in which the project has expanded its activity, was five times higher in the three years following the horizontal comprehensive care model than the number of people covered in the five previous years with the vertical strategy (Pinazo et al, unpublished).

So far, the outcome of the vertical-to-horizontal healthcare model transition highlight that it could be worthy to replicate and/or adapt it to other regions or countries. The first step would be to coordinate with local health authorities at different levels in order to design an appropriate strategy. For the implementation of a healthcare model, the identification of interested health workers is a key issue. Even if it is simplified, a strategy to offer a comprehensive care for people at risk of suffering from Chagas disease should include: (a) specific training of health workers on the disease management; and (b) a strategy to increase the demand of the civil society, based on promotional and educational community activities. In this regard, the establishment of referral and counter-referral circuits tailored to each epidemiological and logistic situation is highly relevant, even in nearby areas.

4.3. Requirements for the expansion of the Chagas disease healthcare model.

11

Referral and counter-referral circuits, in terms of patients and samples for diagnosis or any other test, should include different healthcare levels to cover different levels of complexity in terms of care. The specialized centers in which the model of care has been rehearsed in Bolivia are key towards organizing these circuits, as well as to act as reference centers for complicated cases and to accompany the doubts and the continuing education of health professionals from primary care centers. This is particularly important in health systems where there is often a fast renewal of healthcare personnel. Another crucial point to make sustainable a comprehensive horizontal strategy against Chagas disease is to promote an inter-sectorial collaboration with vector control authorities (promoters of house refurbishment, disinfestation programs,...) and the educational system itself. Vector control interventions are fundamental to halt vector-dependent transmission and enable an enhanced drug control of the cases. Whereas educational activities to widen the population knowledge and perception of the disease, its impact, and treatment possibilities are crucial, because producing changes in beliefs, attitudes, and behaviors on both medical staff and patients still stands as one of the major challenges that must be faced when dealing with Chagas disease. All these measures have a role to play in order to consolidate the successful management of the disease.

On the other hand, lessons learned from the primary healthcare network have shown that it is mandatory to ensure the supervision of the circuits and surveillance the quality of the process, tasks that should be carried out by the national health system responsible personnel in duty. Political engagement at this point is mandatory to contribute to a better control of the disease as a Public Health problem. In this context, it is important to respect the capability of local health institutions, agreeing with them timelines and a progressive increase of the number of people diagnosed and treated, in order to answer adequately to people's demands. It must be noted that external factors like the poor availability of drugs for Chagas disease treatment have a sourly negative impact on any planning.

5. Patients treatment in relationship with vector control.

Access to diagnosis and treatment of Chagas disease in areas with active vector transmission requires a multidisciplinary approach. It involves the participation of players from several areas of expertise and different government sectors, from vector control authorities to health service providers, including primary healthcare [64].

12

Following the advice from the PAHO, intergovernmental regional initiatives were created at the end of the twentieth century and beginning of the twenty first century to establish supranational levels of action to bolster and monitor the implementation of activities to prevent, control, diagnose and treat Chagas disease in Latin America. These initiatives were started by Southern Cone countries in 1991, and then followed by Andean countries and Central American countries in 1997 and Amazonian countries in 2004 [65,66]. Despite these efforts, it is evident that in the region there was, and still is, a breach between the programs for vector control and the areas that are responsible for providing universal health care (including diagnosis and etiological treatment) [67].

It is important to consider that although policies related to the primary prevention of Chagas disease are defined at the national level, primary healthcare attention for the patient is the responsibility of the provincial/departmental or municipal/local entities [68]. Often times, these final effectors of national policies have little or no relation/communication with the national entity and are sometimes even unaware of the policies themselves. For example, suggestion of treatment of the infection by *T. cruzi* for postpartum women and their newborns, and the mandatory treatment for women of childbearing age and children under the age of one with Chagas disease that are in the national or supranational norms [31], make no specific mention of which protocols need to be applied with respect to vector surveillance in the houses of those patients living in endemic areas with active vector transmission. However, recent public health interventions have shown that activities related to access to diagnosis or treatment of the disease are usually implemented and promoted by those responsible for vector control programs [69]. Thus, without consideration of the need of appropriate structures and circuits (i.e. access to an adequate laboratory for diagnosis or presence of anti-trypanosomal drugs), which are not usually present in rural areas, one of the main actions needed is to establish and/or strengthen the link between vector control programs and the health system providers [69]. Thereafter, following a stepwise approach, another action to accomplish would be to provide technical recommendations to establish criteria for categorizing the risk of vector transmission status in an endemic area. With that information available, it could be possible to explicitly detail under which conditions Chagas disease diagnosis and treatment has to be made mandatory in the area for the entire population, or segments of it (i.e. women at childbearing age, newborns). Finally, a most desired third action would definitely be to integrate the procedures for disease diagnosis and treatment within the health system as a transversal program.

13

Nowadays there are already a few experiences that have been able to coordinate vector control actions together with diagnosis and treatment in a successful manner [70, 71]. These could serve as proof-of-concept strategies for integral interventions to build on, improve and replicate. As an example, the experience of Fundación Mundo Sano, with direct and uninterrupted action in the field since 2002, is worth mentioning. Its integral program includes vector control and sanitary improvement of rural houses in the Department of General Taboada (Santiago del Estero, Argentina). In 2015, after 13 years of vector surveillance and control, Mundo Sano was able to install two doctors' offices dedicated to the diagnosis and treatment of Chagas disease together with local institutions, one in Añatuya City and another one in Colonia Dora. Since then, they have been struggling with the problems of having a mono-disease health service in a community that did not demand treatment. Despite the difficulties, after almost three years of implementation, the amount of people diagnosed and treated begun to increase. The work from these two Chagas disease specific offices was integrated to the local hospital of Añatuya in 2018, thus reaching a higher amount of *T. cruzi*-infected individuals derived from obstetrics, gynecology and cardiology services in addition to those attending the offices from spontaneous demand. In the same line, the Platform for the Integral Care of Chagas disease Patients was settled in Bolivia in 2009. Initially in the province of Cochabamba in the center of the country, the Platform now works also in municipalities of the provinces of Chuquisaca and Tarija [62]. Each experience, proposal or pilot study must be evaluated objectively in order to improve and multiply its impact, avoiding a future with a new inequality: one were those affected by the disease will have access to health depending on whether they live in an endemic or non-endemic area.

6. The role of patients' associations.

Similarly to what happens with other NTDs programs to promote scaling up of healthcare interventions, strategies towards the control of Chagas disease often confront with structural weaknesses of the health systems in which they aim to be integrated [72–74]. Therefore, more effective strategies to strengthen those health systems are required to ensure a sustainable integration of the required health innovations within them. Importantly, these strategies need to incorporate the patients´ perspective in order to overcome key access barriers [13,14,75]. Barriers that nowadays still hinder the access to diagnosis and treatment, barriers impeding a better health care.

In recent years, several associations of Chagas disease patients have emerged and joined in a Federation of Associations whose purposes are: (i) to increase the visibility of the disease at all levels as well as of its overwhelming impact in the patients´ health status; and (ii) to promote a more active role of the people affected by the disease in the decision-making processes. But these associations face many difficulties (dispersion of objectives, multiplicity of voices with different requirements, little real mobilization in many countries, and lack of resources) to achieve their objective of having an effective role in the health policies makings of their countries.

The WHO global strategy on integral health services centered on people could be a way through which these associations can play an important practical role [76]. In fact one of the goals of such program is to empower individuals, families and communities by including in it some well-known activities led by patients such as community education, groups of patients for mutual support, expert patients to engage and help others, etc. [76]. In addition, this WHO program goes beyond a single disease and has the virtue of encompassing other actors with decisive roles in health systems performance, like governmental policy-makers, municipalities, donors, and providers.

Overall, the strategy is thus envisaged to allow the community and patients to actively participate in the decision-making process, together with other involved actors, in issues regarding their health. By doing so, they also play a role on the way the health system is organized, for instance ensuring that community and primary healthcare are prioritized. Therefore, patients associations should look after the implementation and compliance with this WHO strategy as it underlies the activities they are already taking on.

7. The R&D Agenda: clinical trials for new drugs or new strategies of treatment with current drugs.

7.1. Results from recently completed trials.

Upon the questioned efficacy of currently available therapies (BNZ and NFX) against the chronic symptomatic stage of the disease, clinical testing of new drugs and/or of new regimens of BNZ and NFX is being pursued. Nonetheless, some major obstacles are in the way to getting more adequate treatments, including the poor understanding of the infection pathophysiology leading to the disease clinical progression, and the lack of biomarkers to determine prognosis and cure (see review by Pinazo et al., [19]). Particularly the latter hinders the follow-up of treated patients both in the daily clinic and

15

in clinical trials. At present, an absence of molecular amplification of *T. cruzi* DNA from periphery blood is used as surrogate of "treatment success". But this approach is far from optimal, especially at the chronic stage of the disease when the parasitemia is low and intermittent. A negative result obtained at a determined time point does not exclude the possibility that a positive one will be obtained in the next visit. A false-negative PCR, i.e., a negative PCR result ("treatment success" event) in the patient follow up is then less informative than a positive determination, as this one will indeed define a case of treatment failure.

Despite this limitation, several clinical trials have been completed in the last years, and there are several more currently ongoing. This advance represents a major shift in the research landscape of this historically forgotten NTD. The vast majority of the performed trials have been Phase 2 randomized, multi-centric, double-blinded, efficacy and safety studies to evaluate oral dosage schemes for the treatment of adult patients at indeterminate (asymptomatic) chronic stage (see Table 1). Amongst them, CHAGASAZOL [77], STOP CHAGAS [78] and E1224 [30] have evaluated for the first time two triazole anti-fungal drugs (posaconazole (POS), and the ravuconazole precursor E1224) for their anti-*T. cruzi* properties. In addition, the BENEFIT trial that evaluated the use of BNZ for chronic stage treatment must also be highlighted as it has been the largest Phase 3 Chagas disease trial performed so far [46].

CHAGASAZOL and E1224 trials entailed a direct comparison of POS and E1224 monotherapy at a high and a low dose to a BNZ standard dosage group (5 mg/kg/day orally divided in two daily doses for 60 days) [30,77]. In addition to monotherapy branches, STOP CHAGAS trial also included a study group that received POS and BNZ as combined therapy [78]. In the latter, treatment success was defined as a negative PCR value at the day 180 follow-up visit [78], whereas parasitological cure in CHAGASAZOL was determined by a negative PCR result at 12 months follow-up [77]. The most stringent success criteria was that of E1224 trial, which involved serial negative PCR results (3 negative PCR results from 3 samples collected over 7 days) at 65 days after end of treatment and a further negative PCR outcome at 12 months follow-up [30].

Although both POS and E1224 drugs showed good safety and efficacy profiles at end of treatment in the three studies, the suppressive effect on parasite clearance after 12 months was much reduced in comparison to BNZ, which showed early and sustained efficacy until 12 months of follow-up (Table 1). Thus, neither POS nor E1224 were as good as BNZ and could not substitute it as monotherapies.

16

In the BENEFIT trial, the treatment response was evaluated in a sub-group of 1,896 subjects who had PCR results at baseline (60.5% of them were positive) by PCR conversion at the end of treatment, and at two and five years post-treatment [46]. Being a large multi-national study, the PCR conversion rates varied geographically with Bolivia and Argentina showing the best results, though it must be noticed that such conversion did not correlate with clinical outcome [46]. BENEFIT was devised to study whether BNZ administration to patients at the chronic stage of the disease would widely have a clinical benefit for them [21,46]. Sadly, its conclusions, far from reassuring the role of BNZ turned out to be a setback, as they suggested not-to treat patients with advanced cardiac disease [46]. As it has been criticized elsewhere, this devastating conclusion drains from the fact that many subjects with advanced cardiac involvement were enrolled in the study [3,21]. Despite its negative outcome due to a rather questionable study protocol design [21], the BENEFIT trial involved ample cooperation between multiple study sites opening the door to the performance of multi-national Phase 3 Chagas disease trials in South America [46].

7.2. Ongoing clinical trials of anti-T. cruzi drugs.

There are now some active and/or ongoing clinical trials. Some test alternative BNZ dosing regimens to reduce exposure, improve tolerability and maintain efficacy as described elsewhere [51], based also on the description of BNZ pharmacokinetics (PK) in Chagas disease adult patients [79]. In others the evaluation of NFX has gained prominence under the promotion of Bayer, NFX producer. The use of fexinidazole, a nitroimidazole drug like BNZ that is being trialed for human African trypanosomiasis and leishmaniasis (respectively caused by *T. cruzi* closely related Kinetoplastid parasites *T. brucei gambiense* and *T. brucei rhodensiense,* and by *Leishmania spp.*), and of the antiarrhythmic drug amiodarone are also being clinically assessed for the first time against *T. cruzi* based on their anti-parasitic capacities [80,81]. These ongoing trials range from smaller Phase 1 to larger Phase 2 and 3 efficacy studies. There are: (1) a Phase 1 safety, tolerability and bioavailability assessment of new NFX tablets and another Phase 1 study to determine NFX PK in relation to dietary habits; (2) a Phase 2 study to evaluate different BNZ regimens (MULTIBENZ); (3) another Phase 2 study to evaluate reduced and intermittent BNZ regimens, either given alone or in combination with E1224 (BENDITA); (4) two more Phase 2 studies evaluating fexinidazole to respectively determine dosing regimens and the minimal efficacious and safety dose; (5) a Phase 2-3

17

trial to compare safety and efficacy of NFX and BNZ (EQUITY); (6) a Phase 3 study to assess amiodarone, a commonly used antiarrhythmic with selective anti-*T. cruzi* properties, administered over 6 months to individuals with mild-to-moderate Chagas cardiomyopathy (ATTACH); (7) a Phase 3 study of a pediatric formulation of NFX (CHICO); and (8) a very recently added Phase 3 study to evaluate a short dose of BNZ in child-bearing age women (BETTY) (Table 2).

All Phase 2 or above trials in Table 2 but CHICO involve the evaluation of drugs in chronically infected adult patients, and the measurement of treatment success will rely on molecular detection of the parasite DNA. In contrast, in CHICO, designed to assess NFX performance in Chagas disease infant population, the way to measure cure is seroconversion a year after treatment because this is much easier to timely occur in children than in adults and its readout is less ambiguous than the PCR output. All these studies are currently in the recruiting stage, except FEXI NCT02498782 and CHICO which are active but not recruiting, and BETTY that is not yet recruiting (https://clinicaltrials.gov). Regarding the latter, benefits of treating *T. cruzi*-infected women before pregnancy have been described by several smaller studies [22–25]. Hopefully BETTY´s outcome will serve to enforce treatment administration to all child-bearing age women as soon as possible.

Expert Commentary: 500-1000 words (included in overall word count).

A huge drawback in the management of Chagas disease has traditionally been the lack of awareness of the disease and its impact by both health professionals and the patients themselves, as well as by governmental institutions with the power to dictate health policies. However, Chagas disease awareness is gradually increasing, so that efforts to combat this neglected tropical disease now need to shift in order to address its often insidious onset and silent clinical progression. These features currently complicate the access to timely diagnosis and treatment, which is also ballasted by the very limited resources available for research and development of improved treatment and disease prevention methodologies.

After so many years of neglecting Chagas disease, new efforts at R&D have the potential for high returns on investment. However, the R&D needs for Chagas disease are pervasive and span requirements for both basic and applied research, as well as new drugs, diagnostics and vaccines. With the ultimate goal of controlling the disease in endemic and non-endemic regions, the consequences of widening our understanding on

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Chagas disease and the pathogen that causes it will have an impact on the lives of millions of people. For instance, research on parasite-host interactions is needed to fully comprehend the pathogenic processes that lead to the life-threatening symptomatology characteristic of chronic *T. cruzi* infections. Furthermore, considering that in the absence of treatment ~30% of those chronically infected will develop cardiac and/or digestive tract disruptions, studies on both parasite and host genomics (and other omics) are required to determine the key factors leading to the development of pathogenesis. Deeper understanding of the parasite biology and of its interactions with the host is fundamental for the discovery of safer drugs or vaccines. Another challenge is the dearth of public policies and advocacy that so far has mostly failed to attract requisite funding.

Currently the most urgent needs include an expansion in clinical studies to test an enlarged portfolio of new drugs, together with improved biomarkers to monitor disease progress. There is also urgency for inexpensive and accessible point-of-care diagnostics, especially for mass screenings as well as for the early assessment of treatment responses. Their availability will widen access to treatment because they would introduce a more accurate picture of the disease epidemiology, as well as the ability to acknowledge cure upon treatment.

Five-year view

We expect that increasing awareness on the prevalence and health impact of Chagas disease among patients, health practitioners and political health authorities may eventually translate to enhanced population-based diagnostic screening and treatment interventions. The tools needed to facilitate this activity are being tested currently in the field and incorporate more practical and point-of-care diagnostics, new drugs regimens, and the standardization of daily clinical care routines. In addition, efforts to obtain biomarkers of disease prognosis and early assessment of treatment are also being achieved and will probably yield results soon.

Upon failure of azoles, the majority of presently ongoing Chagas disease clinical trials either evaluate alternative regimens of current drugs or other chemical entities (e.g., fexinidazole, amiodarone) with the aim to identify dosages with lower toxicity and at least equal efficacies compared to present chemotherapy with either benznidazole or nifurtimox. There is optimism that a new treatment is scheduled for Chagas disease in the next few years. Further complementing the new antiparasitic drugs is a new therapeutic biologic, a vaccine, now advancing to the clinic. However, access to these new drugs and

19

innovations will require enhanced policies and advocacy activities. In parallel, it will be essential to shape and disseminate pharmacovigilance protocols so that drugs performance can be closely monitored, and patient and healthcare provider confidence on these therapies promoted and maintained.

The functional deployment of counter-reference circuits fully integrated in the national health services will also be required to scale up the attention to Chagas disease patients. In this regards, improved coordination between vector control authorities and sanitary authorities will need strengthening in those regions with active vector transmission of the infection. Widespread access to diagnosis and treatment will not yield the desired outcome unless chances to get re-infected are minimized or eliminated. This approach also requires maintaining blood screening and programs to stop congenital transmission. An improved maternal diagnosis and treatment would in itself reduce congenital transmission.

Chagas disease management and control is still a huge challenge. Success relies on continued involvement with key actors, including patients associations, health authorities at regional and national levels, governmental and non-governmental institutions, basic and clinical researchers, and of course financial partners.

Key issues

- Chagas disease is a neglected disease caused by the parasite *Trypanosoma cruzi.* It affects millions of people in the Americas where it has a devastating health and socioeconomic impact. The disease affects most those with lower resources, binding them to poverty and leaving them aside. It was traditionally considered a stigma, hidden by society and ignored by governments. Thankfully to medical researchers, patients' associations and several other actors who have raised awareness and promoted education on the disease and its management, there has been a dramatic shift towards improved diagnosis, treatment and control in recent decades.

- There are highly sensitive and specific diagnostics for both the acute and the chronic stages of the infection. However, they are not widely implemented in many areas distant from reference laboratories due to logistical issues and the lack of equipped facilities and trained personnel. Therefore, more practical methodologies and algorithms should be used to provide point-of-care diagnostics prior to gaining access to treatment.

20

- Two drugs are currently available to treat the infection: benznidazole and nifurtimox. Both are highly efficacious in newborns, but access to treatment generally occurs at the chronic stage when symptomatology arises. Due to the frequent adverse side effects associated to their long administration regimens, pharmacovigilance programs to report drugs toxicities and a better management of these in primary care establishments must be implemented to ensure tighter adherence to medication.

- Stronger involvement of public health institutions and authorities is fundamental to progress in the disease control and its adequate management. The establishment of counter-reference circuits integrated in national health services working plans will be fundamental to catalyze and scale up the attention and care of Chagas disease patients in endemic and non-endemic settings.

- Although great progresses in the control of vector-related transmission has been made in some regions, there are many where vector transmission is still active. Therefore, increased cooperation between vector control programs and medical (diagnostic and treatment) programs must be put on place to maximize their impact in public health.

- The role of patients' associations must remain active and exert pressure on other stakeholders in order to keep up Chagas disease visibility. Patient organizations are at the frontline to demand attention from the responsible authorities, ensure adequate medical care, and highlight the potential returns on investment from R&D.

- In line with the shift on the disease awareness, the clinical research landscape has recently changed for the better. At present there are several clinical trials ongoing and their results are expected to generate improvements in diagnosis and treatment algorithms and policies in the near future. They may also lead to the advancement and licensure of new drugs, diagnostics, and vaccines.

21

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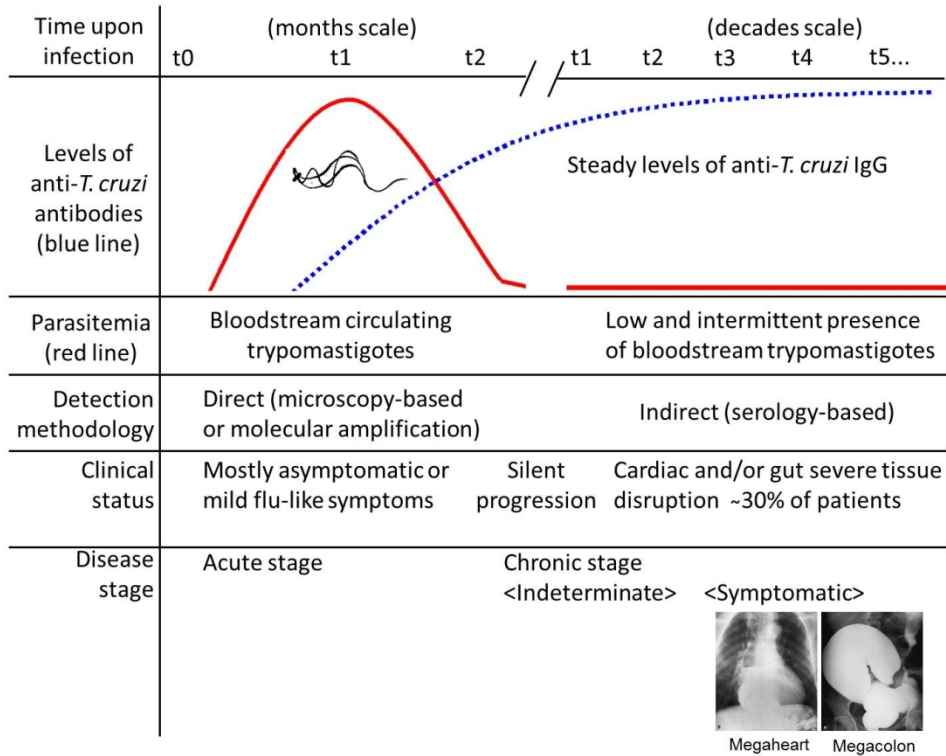
Timescale scheme of Chagas disease diagnosis and clinical status progression.

253x193mm (150 x 150 DPI)

1 **Title:** Strategies to enhance access to diagnosis and treatment for Chagas disease
2 patients in Latin America.

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4 **Structured abstract (maximum 200 words):**

5 Introduction: Chagas disease, caused by infection with the parasite *Trypanosoma cruzi*,
6 represents a huge public health problem in the Americas, where millions of people are
7 affected. Despite the availability of two drugs against the infection (benznidazole and
8 nifurtimox), multiple factors impede their effective usage: 1) gaps in patient and
9 healthcare provider awareness; 2) lack of access to diagnosis; 3) drug toxicity and
10 absence of algorithms to address adverse effects; 4) failures in drug supply and
11 distribution; and 5) inconsistent drug efficacy against the symptomatic chronic stage.
12 Areas covered: we review new approaches and technologies to enhance access to
13 diagnosis and treatment as a means to reduce the disease burden. We also provide an
14 updated picture of recently published and ongoing anti-*T. cruzi* drug clinical trials.
15 Despite progress improving the research and development landscape, it is unclear
16 whether new treatments will emerge soon. Search methodologies included multiple
17 queries to public databases and the use of own-built libraries.
18 Expert opinion: besides R&D, there is a major need for continue awareness and
19 advocacy efforts by patient associations, local and national governments and
20 international agencies. Overall health system strengthening is essential to ensure vector
21 control commitments, and patients access to diagnosis and treatment.

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35 ~~summarize the needs to continue awareness and advocacy efforts by patient~~
36 ~~associations, local and national governments and international agencies, and why health~~
37 ~~system strengthening is essential to ensure vector control commitments, as well as~~
38 ~~patient access to diagnosis and treatment.~~

39

40 **Keywords:** Chagas disease, comprehensive care, clinical trials, diagnosis, drug
41 treatment, patients associations, pharmacovigilance, vector control.

42

43 <u>**Article highlights:**</u>
44 • Chagas disease is a neglected disease caused by the parasite *Trypanosoma cruzi* (*T.*
45 *cruzi*). It affects millions of people in the Americas where it has a devastating health
46 and socioeconomic impact. The disease affects most those with lower resources,
47 binding them to poverty and leaving them aside. It was traditionally considered a
48 stigma, hidden by society and ignored by governments. Thankfully to medical
49 researchers, patients' associations and several other actors who have raised
50 awareness and promoted education on the disease and its management, there has
51 been a dramatic shift towards improved diagnosis, treatment and control in recent
52 decades.
53 • There are highly sensitive and specific diagnostics for both the acute and the chronic
54 stages of the infection. However, they are not widely implemented in many areas
55 distant from reference laboratories due to logistical issues and the lack of equipped
56 facilities and trained personnel. Therefore, more practical methodologies and
57 algorithms should be used to provide point-of-care diagnostics prior to gaining
58 access to treatment.
59 • Two drugs are currently available to treat the infection: benznidazole and
60 nifurtimox. Both are highly efficacious in newborns, but access to treatment
61 generally occurs at the chronic stage when symptomatology arises. Due to the
62 frequent adverse side effects associated to their long administration regimens,
63 pharmacovigilance programs to report drugs toxicities and a better management of
64 these in primary care establishments must be implemented to ensure tighter
65 adherence to medication.
66 • Stronger involvement of public health institutions and authorities is fundamental to
67 progress in the disease control and its adequate management. The establishment of
68 counter-reference circuits integrated in national health services working plans will

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69   be fundamental to catalyze and scale up the attention and care of Chagas disease

70   patients in endemic and non-endemic settings.

71 • Although great progresses in the control of vector-related transmission has been

72   made in some regions, there are many where vector transmission is still active.

73   Therefore, increased cooperation between vector control programs and medical

74   (diagnostic and treatment) programs must be put on place to maximize their impact

75   in public health.

76 • The role of patients' associations must remain active and exert pressure on other

77   stakeholders in order to keep up Chagas disease visibility. Patients´ organizations

78   are at the frontline to demand attention from the responsible authorities, ensure

79   adequate medical care, and highlight the potential returns on investment from R&D.

80   In line with the shift on the disease awareness, the clinical research landscape has recently

81   changed for the better. At present there are several clinical trials ongoing and their results

82   are expected to generate improvements in diagnosis and treatment algorithms and

83   policies in the near future. They may also lead to the advancement and licensure of new

84   drugs, diagnostics, and vaccines.

85

86 **Body of the article.**

87 **Expert Commentary:** 500-1000 words (included in overall word count).

88   A huge drawback in the management of Chagas disease has traditionally been

89   the lack of awareness of the disease and its impact by both health professionals and the

90   patients themselves, as well as by governmental institutions with the power to dictate

91   health policies. However, Chagas disease awareness is gradually increasing, so that

92   efforts to combat this neglected tropical disease now need to shift in order to address its

93   often insidious onset and silent clinical progression. These features currently complicate

94   the access to timely diagnosis and treatment, which is also ballasted by the very limited

95   resources available for research and development of improved treatment and disease

96   prevention methodologies.

97   After so many years of neglecting Chagas disease, new efforts at R&D have the

98   potential for high returns on investment. However, the R&D needs for Chagas disease

99   are pervasive and span requirements for both basic and applied research, as well as new

100 drugs, diagnostics and vaccines. With the ultimate goal of controlling the disease in

101 endemic and non-endemic regions, the consequences of widening our understanding on

102 Chagas disease and the pathogen that causes it will have an impact on the lives of

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103 millions of people. For instance, research on parasite-host interactions is needed to fully
104 comprehend the pathogenic processes that lead to the life-threatening symptomatology
105 characteristic of chronic *T. cruzi* infections. Furthermore, considering that in the
106 absence of treatment ~30% of those chronically infected will develop cardiac and/or
107 digestive tract disruptions, studies on both parasite and host genomics (and other omics)
108 are required to determine the key factors leading to the development of pathogenesis.
109 Deeper understanding of the parasite biology and of its interactions with the host is
110 fundamental for the discovery of safer drugs or vaccines. Another challenge is the
111 dearth of public policies and advocacy that so far has mostly failed to attract requisite
112 funding.

113 Currently the most urgent needs include an expansion in clinical studies to test
114 an enlarged portfolio of new drugs, together with improved biomarkers to monitor
115 disease progress. There is also urgency for inexpensive and accessible point-of-care
116 diagnostics, especially for mass screenings as well as for the early assessment of
117 treatment responses. Their availability will widen access to treatment because they
118 would introduce a more accurate picture of the disease epidemiology, as well as the
119 ability to acknowledge cure upon treatment.

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121 **Five-year view**

122 We expect that increasing awareness on the prevalence and health impact of
123 Chagas disease among patients, health practitioners and political health authorities may
124 eventually translate to enhanced population-based diagnostic screening and treatment
125 interventions. The tools needed to facilitate this activity are being tested currently in the
126 field and incorporate more practical and point-of-care diagnostics, new drugs regimens,
127 and the standardization of daily clinical care routines. In addition, efforts to obtain
128 biomarkers of disease prognosis and early assessment of treatment are also being
129 achieved and will probably yield results soon.

130 Upon failure of azoles, the majority of presently ongoing Chagas disease clinical
131 trials either evaluate alternative regimens of current drugs or other chemical entities
132 (e.g., fexinidazole, amiodarone) with the aim to identify dosages with lower toxicity and
133 at least equal efficacies compared to present chemotherapy with either benznidazole or
134 nifurtimox. There is optimism that a new treatment is scheduled for Chagas disease in
135 the next few years. Further complementing the new antiparasitic drugs is a new
136 therapeutic biologic, a vaccine, now advancing to the clinic. However, access to these

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137 new drugs and innovations will require enhanced policies and advocacy activities. In
138 parallel, it will be essential to shape and disseminate pharmacovigilance protocols so
139 that drugs performance can be closely monitored, and patient and healthcare provider
140 confidence on these therapies promoted and maintained.

141   The functional deployment of counter-reference circuits fully integrated in the
142 national health services will also be required to scale up the attention to Chagas disease
143 patients. In this regards, improved coordination between vector control authorities and
144 sanitary authorities will need strengthening in those regions with active vector
145 transmission of the infection. Widespread access to diagnosis and treatment will not
146 yield the desired outcome unless chances to get re-infected are minimized or eliminated.
147 This approach also requires maintaining blood screening and programs to stop
148 congenital transmission. An improved maternal diagnosis and treatment would in itself
149 reduce congenital transmission.

150   Chagas disease management and control is still a huge challenge. Success relies
151 on continued involvement with key actors, including patients associations, health
152 authorities at regional and national levels, governmental and non-governmental
153 institutions, basic and clinical researchers, and of course financial partners.

154

155 **Key issues**

156 • Chagas disease is a neglected disease caused by the parasite *Trypanosoma cruzi*. It
157   affects millions of people in the Americas where it has a devastating health and
158   socioeconomic impact. The disease affects most those with lower resources, binding
159   them to poverty and leaving them aside. It was traditionally considered a stigma,
160   hidden by society and ignored by governments. Thankfully to medical researchers,
161   patients' associations and several other actors who have raised awareness and
162   promoted education on the disease and its management, there has been a dramatic
163   shift towards improved diagnosis, treatment and control in recent decades.

164 • There are highly sensitive and specific diagnostics for both the acute and the chronic
165   stages of the infection. However, they are not widely implemented in many areas
166   distant from reference laboratories due to logistical issues and the lack of equipped
167   facilities and trained personnel. Therefore, more practical methodologies and
168   algorithms should be used to provide point-of-care diagnostics prior to gaining
169   access to treatment.

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170 • Two drugs are currently available to treat the infection: benznidazole and
171   nifurtimox. Both are highly efficacious in newborns, but access to treatment
172   generally occurs at the chronic stage when symptomatology arises. Due to the
173   frequent adverse side effects associated to their long administration regimens,
174   pharmacovigilance programs to report drugs toxicities and a better management of
175   these in primary care establishments must be implemented to ensure tighter
176   adherence to medication.

177 • Stronger involvement of public health institutions and authorities is fundamental to
178   progress in the disease control and its adequate management. The establishment of
179   counter-reference circuits integrated in national health services working plans will
180   be fundamental to catalyze and scale up the attention and care of Chagas disease
181   patients in endemic and non-endemic settings.

182 • Although great progresses in the control of vector-related transmission has been
183   made in some regions, there are many where vector transmission is still active.
184   Therefore, increased cooperation between vector control programs and medical
185   (diagnostic and treatment) programs must be put on place to maximize their impact
186   in public health.

187 • The role of patients' associations must remain active and exert pressure on other
188   stakeholders in order to keep up Chagas disease visibility. Patient organizations are
189   at the frontline to demand attention from the responsible authorities, ensure adequate
190   medical care, and highlight the potential returns on investment from R&D.

191 • In line with the shift on the disease awareness, the clinical research landscape has
192   recently changed for the better. At present there are several clinical trials ongoing
193   and their results are expected to generate improvements in diagnosis and treatment
194   algorithms and policies in the near future. They may also lead to the advancement
195   and licensure of new drugs, diagnostics, and vaccines.

196

1. Introduction.

198   Chagas disease, or American trypansosomiasis, is caused by the protozoan
199 parasite *Trypanosoma cruzi* (*T. cruzi*) and remains one of the most deadly and
200 intractable neglected tropical diseases (NTDs) in the Western Hemisphere [1]. Updated
201 information from the Global Burden of Disease Study (GBD) 2016 indicates that 7,100
202 people die from Chagas disease annually, roughly the same number of Chagas disease-

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related deaths that occurred a decade previously [2]. However, these numbers may represent highly conservative estimates with further findings that as many as 200,000 people living with *T. cruzi* infection may die over the next five years [3]. The GBD 2016 also finds that 7.2 million now live with Chagas disease, while 180,000 new *T. cruzi* infections occur annually [4].

Beyond its horrific disease burden and contribution to infectious disease mortality, there is a profoundly disturbing social impact dimension to Chagas disease related to its importance as a health disparity. Today, tens of thousands of people face a death sentence from their *T. cruzi* infection due to Chagasic cardiomyopathy, which could be prevented by timely access to diagnosis and anti-parasitic treatment with one of two nitroheterocyclic drugs – benznidazole (BNZ) and nifurtimox (NFX). Fueling a growing outrage from the global health community is the finding that approximately 90% of people infected with *T. cruzi* infection now live in Latin America's three wealthiest economies: Argentina, Brazil, and Mexico. In the United States of America (USA), the richest country of the continent and main destiny of those looking for a better future, there are at least 200,000 immigrants from Latin America living with Chagas disease with limited or no access to treatment [5,6]. Furthermore, in Europe there are around 120,000 immigrants from Latin America living with Chagas diseases with a disparity of situations regarding access to care and treatment [7,8].

The overwhelming majority of Chagas disease sufferers are unable to gain access to diagnosis and treatment, not only because they are poor, but also because governmental leaders are either uninformed or uninterested. For example, it is noteworthy that the registration of BNZ for the treatment of pediatric Chagas disease in the USA has not been approved until very recently [9]. Documenting such assertions is not easy and seeking solutions to diagnosis and treatment access are not straightforward endeavors. In Mexico, for example, there are almost one million people living with Chagas disease, although even that number may represent a profound underestimate [10]. Yet, only 3,013 *T. cruzi* infection cases were registered nationally between the years 2007 and 2011, less than 1% of the actual number of people affected with the disease [11]. A similar situation has been documented for the USA [12] and also likely holds true across the Americas. We are facing a situation where less than 1% of Chagas disease patients have access to timely and appropriate diagnosis and treatment [13,14].

Limiting access to essential medicines also has important implications for new research and development (R&D) related to therapeutic interventions. An exciting

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development on this front is a new orally bioavailable nitroheteorcyclic drug, fexinidazole, which is also effective against human African trypanosomiasis [15]. Additional drugs are also under development, as well as there are Chagas disease vaccine (immunotherapeutic) candidates at pre-clinical stage [16]. In this respect, the Texas Children's Hospital Center for Vaccine Development, a Product Development Partnership, is exploring an approach that links therapeutic vaccination to pharmacotherapy [17]. However, any R&D successes must still face a formidable gauntlet of truncated and mostly failed global access mechanisms. Similar forces are a barrier for access to new and innovative diagnostics [18].

Here we report on some of the major hurdles that currently block access to the diagnosis and treatment of Chagas disease. The problems include both scientific and socioeconomic obstacles. This paper aims to elucidate the challenges they pose and offer solutions.

2. The need of more practical and useful diagnostics.

The poor access rate to Chagas disease therapeutic treatments has its roots in the clinical nature of the disease itself and its silent progression from the mostly asymptomatic acute stage into the symptomatic chronic one [1]. Unfortunately, biomarkers of disease progression and standardized tools to determine early response-to-treatment are yet unavailable, which greatly complicates the prognosis and follow-up of patients [19].

Treatment administration, as in any other disease, needs to be preceded by an adequate diagnosis. In the case of Chagas disease, when a clinical diagnosis is achieved, tissue disruptions might already be too advanced for a chemotherapeutic intervention. Therefore, parasite detection must be sought before the onset of overt symptomatology. In the acute infection stage, for instance upon congenital transmission of the parasite, parasitemia can be detected by direct microscopic observation [1]. However, this stage is short lasting and generally goes unnoticed as there are often no symptoms at all. Approximately 30% of these infected individuals will progress to evidence of either Chagasic cardiac or gastrointestinal disease. Those without clinical evidence of disease are said to be at the indeterminate stage, whereas those with cardiac or gastrointestinal involvement are at the determinate stage. The development of life-threatening heart and/or digestive tract disruptions, which can be massive and are called mega-syndromes, occurs in the long lasting chronic stage that follows [1].

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271   In both indeterminate and determinate Chagasic patients, parasitemia is typically

272   low and intermittent and the diagnosis of the infection is made by means of indirect

273   serological tests, like enzyme-linked immunosorbent assays (ELISAs). This is possible

274   because high levels of parasite-specific immunoglobulins are produced upon *T. cruzi*

275   infection (Figure 1). Anti-*T. cruzi* type G immunoglobulins (IgGs) levels remain above

276   detection thresholds for many years, which is advantageous for the serological diagnosis

277   of the infection (Figure 1). However, it turns out to be an inconvenience for a serology-

278   based assessment of drug responses as it can take several years for them to revert after

279   the administration of treatment [20]. Another issue to take into account in the diagnosis

280   of the infection is the wide genetic variability of the parasite, which encompasses seven

281   different genotypes grouped in Discrete Typing Units (DTUs) [21]. A role of the

282   parasite and host genetics interplay has been suggested in relation to the sensibility to

283   treatment of the distinct isolates, the pathological signatures of the infection, and also in

284   the anti-*T. cruzi* immune response [21].

285   Some studies indicate that treatment interventions while patients are in the

286   indeterminate or early determinate stages are critically important in order to prevent

287   advanced disease progression. In contrast, from the multi-centered BENEFIT trial to

288   evaluate benznidazole BNZ efficacy it was found that patients with significant cardiac

289   involvement progressed to advanced disease or even died despite receiving specific

290   antiparasitic chemotherapy [3,21]. Currently a Kushnir grading system is in place to

291   differentiate people with early-stage (grades I-II) versus late stage (Kushnir III-IV)

292   determinant cardiac disease [1]. Treatment of patients with Kushnir grades III-IV was

293   not encouraged previously [1], a finding that appears to hold up in light of the recent

294   BENEFIT findings. Currently several classifications (for instance AHCC, or Kuschnir´s

295   modified) are in place to differentiate people with early-stage (grades A-B or 0-I

296   respectively) versus late stage (grades C-D or II-III respectively) cardiac disease.

297   Treatment of patients with grades C-D or II-III was not encouraged previously [1], a

298   finding that appears to hold up in light of the recent BENEFIT findings.

299   These findings highlight the importance of identifying both indeterminate

300   patients with Chagas disease, and possibly those with AHCC grades A-B or modified

301   Kuschnir grades 0-I too, since they might be successfully treated with antiparasitic

302   therapy if they were captured during population-wide screening campaigns [3]. In this

303   way, it would be possible to identify and treat chronically infected people before they

304   develop the symptomatology. Women at child-bearing age and newborns should receive

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305 special attention because the treatment of mothers-to-be has been shown to largely

306 reduce the transmission rate [23–26], and the efficacy and tolerability of current drugs

307 by infected newborns is ~100% [1]. Moreover, health economics studies evaluating

308 Chagas disease surveillance in endemic and non-endemic settings indicate that

309 widespread screening would be highly cost-effective [27–30]. In the two disease

310 scenarios studied, congenital (acute infection transmitted by chronically infected

311 mothers) and indeterminate (chronic asymptomatic stage), mass screening would save

312 health costs even at *T. cruzi* prevalence rates as low as 0.9% or 0.05% respectively (in

313 fact estimated in the a non-endemic setting) [2627,2829].

314   Due to the very limited resources available for Chagas disease management, and

315 echoing the answers provided by Latin American experts enquired by Picado et al. [18],

316 efforts should focus on making widely available point-of-care (PoC) tests to diagnose

317 congenital transmission and indeterminate chronic patients [18]. However, if we want to

318 enable generalized Chagas disease diagnosis, there is an urgent need of more practical

319 diagnostic reagents and kits. Availability of easy-to-use tools for the early assessment of

320 treatment response would also be highly valuable to promote and support the

321 administration of drugs against the infection. In this regards, there are some biomarkers

322 under research [19], but the evaluation of anti-*T. cruzi* drug responses yet relies on the

323 molecular amplification of the parasite DNA from periphery blood obtained at distinct

324 times post-treatment. Unfortunately, its associated high costs and technical requirements

325 restrict its use to the context of well-funded clinical trials [31].

326

327 **2.1. Current Chagas disease diagnostics are impractical in many regions.**

328   Regarding acute stage diagnostics, classical parasitological methods

329 (micromethod, hemoculture and xenodiagnoses) are microscopy-based and rely on

330 finding motile trypomastigotes in blood, thus they provide both low sensitivity and

331 specificity. Due to their poor performance, current algorithm to diagnose congenital

332 transmission involves two micromethods (at birth and at 1-2 months of age), and a

333 further confirmatory serological test once mother-derived IgGs have waned at infant´s

334 8-12 months of age [32]. This has two major drawbacks: a very high loss-to-treatment

335 risk during pediatric follow up, and the reduction of drug efficacies the longer the

336 treatment is delayed [32]. Molecular amplification of *T. cruzi* DNA, either by

337 conventional polymerase chain reaction (PCR) or by quantitative PCR (qPCR), has

338 been shown to be more sensitive and specific than classical parasitological techniques

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339   [20]. Several laboratories have worked on the standardization of the techniques so that

340   their outcomes can be comparable and implemented in clinic-based laboratories [20].

341   But molecular biology laboratories are expensive to mount and maintain, plus they

342   require highly trained personnel to run them. Therefore, despite its very good

343   performance, molecular detection is not generally used beyond regional or national

344   reference laboratories in endemic regions.

345   In relation to the current chronic stage diagnostics, conventional serological tests

346   (like ELISAs, indirect immune-fluorescence or indirect hemagglutination assays) use

347   serum or plasma samples that entail venous extraction and blood segregation by

348   centrifugation, and they require a cold chain to preserve the test reagents and the

349   samples. Moreover, due to the parasite´s antigenic diversity, the advice from the World

350   Health Organization (WHO) is to run two tests based on distinct antigenic sets and if

351   their outcomes are not concurrent, to employ a third technique [14]. This algorithm is

352   costly, and it requires equipment and resources that are usually not available in many

353   laboratories of endemic regions. Furthermore, the turnaround of results to the patient

354   can take several weeks, which involves a high risk of losing contact with the patient for

355   treatment.

356

357   ***2.2. What solutions could be implemented?***

358   Fortunately, recent technological advancements are procuring solutions to

359   overcome the limitations mentioned above. We will outline them separately considering

360   first those for the diagnosis of acute stage and then those for the diagnosis of chronic

361   Chagas disease.

362   In recent years, isothermal amplification methods that do not require expensive

363   equipment (such as thermocyclers or gel visualization systems) and are easier to

364   perform than PCR assays have been developed for the molecular detection of several

365   NTDs [20]. At present, a prototype of Loop isothermal AMPlification for *T. cruzi*-DNA

366   (LAMP, Eiken Co., Japan) has been tested with clinical samples and shown to have a

367   comparable performance to qPCR with blood-EDTA samples [33]. Another LAMP test

368   developed in house by Rivero et al. [34] has also been shown to provide a comparable

369   performance to current congenital transmission algorithm. LAMP is based on a

370   microbiological DNA polymerase that works at a constant temperature of 65 ºC for 45

371   minutes with a set of 4 to 6 complex primer sequences to provide a highly sensitive and

372   specific amplification [35]. LAMP readout is qualitative and the results can be naked

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373   eye visualized in a short time given a probe (e.g. calcein) is added to the reaction mix. If

374   a digital fluorimeter is used (e.g. Genie III) the reading can even be semi-quantitative

375   [33]. Notably, in ~~EIKEN~~Eiken´s *T. cruzi*-LAMP prototype, reagents are provided dried

376   out in the lids of the reaction tubes which allow a ready-to-use format and a much

377   desirable room temperature storage [33]. More recently, a Recombinase Polymerase

378   Assay (RPA), which even requires a lower amplification temperature and shorter

379   amplification time (40 ºC for 30 min) than LAMP, has been tested with samples from

380   naturally *T. cruzi*-infected dogs [36]. This RPA has been coupled to a lateral flow strip

381   for results reading and it was shown to provide excellent agreement with qPCR results

382   [36]. There are RPAs for the detection of other NTDs [~~36,~~37,38], so it could also be

383   very useful for Chagas disease molecular diagnosis.

384   For the serological detection of *T. cruzi*-specific IgGs, rapid diagnostic tests

385   (RDTs) have been commercially developed during the last two decades [~~38~~39,~~39~~40].

386   RDTs have clear advantages over conventional serology, as they can be stored at room

387   temperature, use a very small volume (5-25 μl) of finger pricked whole blood, have an

388   easy-to-run and read cassette format, and provide a fast turnaround of results (less than

389   45 minutes) [40]. Several studies now support their implementation as they have been

390   extensively validated against conventional tests [41–43]. For instance, a RDT is

391   currently used for primary screening of chronic Chagas disease in Bolivia [~~39~~41].

392   Nonetheless, following the WHO guidelines of two-tests concordance, confirmation of

393   that RDT primary result must yet be made with a conventional serological test [14].

394   Such recommendations reduce the advantages of RDTs.

395   With the aim to fully exploit RDTs advantages and to determine whether they

396   can substitute conventional tests, combinatory use of two RDTs has been proposed [41].

397   So far, in a proof-of-concept study performed in the city of Sucre (Bolivia), perfect

398   agreement between the two RDTs used was observed, and their sensitivity and

399   specificity in comparison with three conventional tests was 100% and 99.3%,

400   respectively [~~40~~41]. However, despite a promising performance in Bolivia [~~40~~41,~~42~~43],

401   RDTs have not worked so well when they have been used in other geographical regions

402   [44]. This might be related to the high prevalence of the disease in Bolivia, which may

403   allow an easier detection, or to the fact that the parasite strains used to produce the

404   RDTs antigens are those circulating in Bolivia. In any case, until more results from

405   different epidemiological areas are available, preliminary geographical testing of the

406   RDTs performance has been proposed before using them in a particular region [44]. In

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407 view of the advantages they bring versus conventional tests, RDTs implementation for

408 Chagas disease surveillance should be evaluated at larger scales.

409

410 **3. Treatment of Chagas disease, and issues related to it.**

411 ***3.1. Drug regimens.***

412 Evidence about the benefits of Chagas disease treatment, together with a

413 growing understanding of the pathogenesis of the disease, led to the paradigm that all *T.*

414 *cruzi*-seropositive patients should receive treatment with anti-*T. cruzi* drugs [45]. The

415 recently published results of the SaMi-Trop cohort study further reaffirm this statement

416 as they demonstrate a beneficial effect of BNZ in reducing the cardiac clinical

417 progression of chronic Chagas disease patients [46]. Therefore, anti-trypanosomatid

418 treatment should be provided to all *T. cruzi*-infected people who do not present with

419 advanced cardiac complications (Kuschnir grades III-IV), as by then clinical

420 manifestations might not be improved [47]. Nonetheless, access to treatment confronts

421 important limitations. BNZ and NFX, the only drugs available for *T. cruzi* infection,

422 exhibit reduced efficacy during the chronic stage of the disease, and require a long

423 period of administration which causes frequent unwanted drug-related adverse reactions

424 (ADRs) [48–50]. Furthermore, variable drug susceptibility has been already described

425 among distinct *T. cruzi* strains [51]. In this context, there is an urgent need for more

426 efficacious and safer drugs or drugs´ regimens, in particular for the treatment of the

427 chronic stage of the infection.

428 One alternative is the reduction of the BNZ dose and/or schedule in order to

429 improve safety and adherence to treatment; an approach that is supported by clinical and

430 experimental data. In a pilot study Álvarez et al. [52] assessed a new scheme of BNZ

431 administration in a small cohort of chronic Chagas disease patients treated with

432 intermittent doses of BNZ at 5 mg/kg/day every 5 days for a total of 60 days. The study

433 showed a satisfactory safety profile, with low rates of treatment suspension and

434 treatment failure [52]. Furthermore, an experimental study using a mouse model of

435 chronic *T. cruzi* infection demonstrated the effectiveness of an intermittent scheme of

436 BNZ administered every 5 days for 40 days [53]. These findings support the

437 intermittent administration of BNZ as a new dosage schedule, but further research to

438 confirm its efficacy by long-term assessment of larger cohorts is needed. Another

439 therapeutic option under investigation is the co-administration of an immunotherapeutic

440 (vaccine) treatment and BNZ. In this regards, enhancement of a *T. cruzi*-specific

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441 immune response has been shown to contribute to support the efficacy of reduced BNZ

442 dosages in a mouse model of acute *T. cruzi* infection [17].

443

3.2. Drug availability.

445 Drug access is still a huge problem in some endemic areas [13]. BNZ, generally

446 the first line therapy for Chagas disease, is part of the WHO List of Essential Medicines

447 [54]. It was produced during more than 40 years by Roche (Basilea, Switzerland),

448 which transferred its production rights to Laboratório Farmacêutico de Pernambuco

449 (LAFEPE), a Brazilian public enterprise, at the end of the twentieth century. Sadly,

450 BNZ production and distribution by LAFEPE failed to meet expectations in terms of

451 meeting supply and demand requirements and in 2011 an important shortage of the drug

452 occurred. It lasted 1.5 years and left thousands of patients without treatment worldwide

453 [13,5355]. This fact led to the development of a Private-Public Partnership in Argentina

454 involving Maprimed (for the synthesis of the drug) and ELEA (for its development and

455 production), to promote equitable availability of BNZ [56]. Since 2012, this Argentinian

456 Partnership has worked to guarantee the availability of the drug, distributing BNZ to the

457 countries in the region [56]. NFX, which is mostly used as the second line treatment

458 option, is produced and donated by the pharmaceutical company Bayer, and distributed

459 through the Pan-American Health Organization (PAHO) Strategic Fund [57]. Recently,

460 a NFX produced by Gador has also been registered in Argentina. Definitely, a regular,

461 safe and accessible production of these two anti-parasitic drugs is necessary to

462 guarantee the treatment to diagnosed patients, and the access to drugs has to be ensured

463 in adequate quantity, quality, location and timing.

464

3.3. Pharmacovigilance.

466 A major limitation of current Chagas disease treatments is the onset of Adverse

467 Drug Reactions (ADRs), which may lead to poor medication adherence, and cause

468 thereby therapeutic failure or ineffective treatment [4648-4850]. ADRs are defined as

469 "an appreciably harmful or unpleasant reaction, resulting from an intervention related to

470 the use of a medicinal product, which predicts hazard from future administration and

471 warrants prevention or specific treatment, or alteration of the dosage regimen, or

472 withdrawal of the product" [58]. The most commonly observed ADRs related to BNZ

473 are headache, dermatological manifestations and gastrointestinal symptoms

474 [4749,4850]. Concerning NFX, digestive symptoms are the most frequent [4648].

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475 Nevertheless, with an adequate clinical management most of the patients are able to
476 finish treatment in the advent of ADRs [4749]. Close medical follow-up, adequate
477 monitoring of ADRs and implementation of robust pharmacovigilance systems are
478 essential factors to avoid patient abandonment and achieve therapeutic success.

479 Although pharmacovigilance is crucial, it is still a neglected area. Latin-
480 American countries are making important efforts to report ADRs, but these activities are
481 recent and need reinforcement [5859,5960]. Results of an unpublished study conducted
482 by Cortes-Serra et al. in Bolivia during 2016 indicate that 35.4% of the total patients
483 treated for Chagas disease in fourteen healthcare centers of the department of
484 Cochabamba suffered ADRs related to it. From all ADRs classified as moderate or
485 severe (25% of the total ADRs registered), only about half of them (51.43%) were
486 reported to the Bolivian Pharmacovigilance system [61]. This data illustrates the
487 urgency of implementing policies to promote training in pharmacovigilance to all
488 healthcare professionals, as well as strictly recommend the follow-up on drug
489 monitoring and ADR reporting. Altogether, these features are fundamental to achieve
490 strong and consolidated ADR reporting systems, which will improve patient safety,
491 drug efficacy and adherence to treatment.

492

493 **4. Patients´ comprehensive care: reference and counter-reference circuits.**

494 With less than 1% people treated [13,14], and an economic burden of $7.19
495 billion per year and $188.80 billion per lifetime [62], Chagas disease remains neglected
496 despite the efforts performed by several institutions focused on development and
497 research [13]. Migratory flows have changed the epidemiology of the disease that is
498 now emerging in some non-endemic countries [7]. During the last decades,
499 collaboration and knowledge transfer between institutions from endemic (CEADES,
500 Bolivia) and non-endemic countries (ISGlobal, Spain) has been strategic to build
501 attention models for the Chagas disease patient. Such models could be scaled-up by
502 national health systems in endemic and non-endemic countries in order to expand
503 Chagas disease healthcare to people living in areas with limited access to health (e.g.
504 rural areas in endemic countries) or to vulnerable populations (e.g. migrants in endemic
505 and non-endemic countries).

506

507 *4.1. The Platform for integral care of Chagas disease patients.*

15

508   The work made by this Platform in recent years have produced a quantitative
509   and qualitative improvement in the healthcare provided to Chagas disease patients in
510   Bolivia, but this improvement certainly needs to be strengthened. The experience gained
511   with the Platform in the country has shown that the implementation of specialized
512   centers to manage people at risk of having Chagas disease is highly effective, both
513   based on the percentage (and number) of people diagnosed with the infection, and
514   amongst them, those who received and completed treatment [63]. This vertical strategy
515   has been essential to design the attention model for patients with Chagas, making the
516   medical assistance to these people look like a normalized and necessary action [63].
517   Nevertheless, the sustainability of such model ultimately depends on continuously
518   securing external funds, which greatly complicates its expansion to larger geographical
519   levels, like national coverage by the national health system (Figure 2).

520

4.2. Vertical-to-horizontal healthcare model transition.

522   In order to have a higher impact in terms of diagnosis and treatment coverage, as
523   well as to ensure the sustainability for the model of care of Chagas disease patients
524   already installed, it is mandatory to search for a comprehensive horizontal strategy
525   together with local higher level entities of the public health system. In fact, based on
526   WHO recommendations, the strategy to include the Chagas disease attention roadmap
527   as part of the regular activities of all healthcare levels seems to be the most appropriate
528   approach [64].

529   Simplifying the vertical Chagas disease model of healthcare to more realistic
530   protocols established together with the national health institutions has allowed the
531   improvement of healthcare access for people at risk of having the disease living in
532   remote areas of an endemic country [63]. Researchers at ISGlobal (authors of this
533   review) have yet unpublished data which demonstrate that the health coverage, in terms
534   of patients diagnosed and treated in the selected area in which the project has expanded
535   its activity, was five times higher in the three years following the horizontal
536   comprehensive care model than the number of people covered in the five previous years
537   with the vertical strategy (Pinazo et al., unpublished).

538   So far, the outcome of the vertical-to-horizontal healthcare model transition
539   highlight that it could be worthy to replicate and/or adapt it to other regions or
540   countries. The first step would be to coordinate with local health authorities at different
541   levels in order to design an appropriate strategy. For the implementation of a healthcare

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542 model, the identification of interested health workers is a key issue. Even if it is

543 simplified, a strategy to offer a comprehensive care for people at risk of suffering from

544 Chagas disease should include: (a) specific training of health workers on the disease

545 management; and (b) a strategy to increase the demand of the civil society, based on

546 promotional and educational community activities. In this regard, the establishment of

547 referral and counter-referral circuits tailored to each epidemiological and logistic

548 situation is highly relevant, even in nearby areas.

549

550 *4.3. Requirements for the expansion of the Chagas disease healthcare model.*

551 Referral and counter-referral circuits, in terms of patients and samples for

552 diagnosis or any other test, should include different healthcare levels to cover different

553 levels of complexity in terms of care. The specialized centers in which the model of care

554 has been rehearsed in Bolivia are key towards organizing these circuits, as well as to act

555 as reference centers for complicated cases and to accompany the doubts and the

556 continuing education of health professionals from primary care centers. This is

557 particularly important in health systems where there is often a fast renewal of healthcare

558 personnel. Another crucial point to make sustainable a comprehensive horizontal

559 strategy against Chagas disease is to promote an inter-sectorial collaboration with vector

560 control authorities (promoters of house refurbishment, disinfestation programs,...) and

561 the educational system itself. Vector control interventions are fundamental to halt

562 vector-dependent transmission and enable an enhanced drug control of the cases.

563 Whereas educational activities to widen the population knowledge and perception of the

564 disease, its impact, and treatment possibilities are crucial, because producing changes in

565 beliefs, attitudes, and behaviors on both medical staff and patients still stands as one of

566 the major challenges that must be faced when dealing with Chagas disease. All these

567 measures have a role to play in order to consolidate the successful management of the

568 disease.

569 On the other hand, lessons learned from the primary healthcare network have

570 shown that it is mandatory to ensure the supervision of the circuits and surveillance the

571 quality of the process, tasks that should be carried out by the national health system

572 responsible personnel in duty. Political engagement at this point is mandatory to

573 contribute to a better control of the disease as a Public Health problem. In this context,

574 it is important to respect the capability of local health institutions, agreeing with them

575 timelines and a progressive increase of the number of people diagnosed and treated, in

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576 order to answer adequately to people's demands. It must be noted that external factors

577 like the poor availability of drugs for Chagas disease treatment have a sourly negative

578 impact on any planning.

579

580 **5. Patients treatment in relationship with vector control.**

581 Access to diagnosis and treatment of Chagas disease in areas with active vector

582 transmission requires a multidisciplinary approach. It involves the participation of

583 players from several areas of expertise and different government sectors, from vector

584 control authorities to health service providers, including primary healthcare [65].

585 Following the advice from the PAHO, intergovernmental regional initiatives

586 were created at the end of the twentieth century and beginning of the twenty first

587 century to establish supranational levels of action to bolster and monitor the

588 implementation of activities to prevent, control, diagnose and treat Chagas disease in

589 Latin America. These initiatives were started by Southern Cone countries in 1991, and

590 then followed by Andean countries and Central American countries in 1997 and

591 Amazonian countries in 2004 [6566,6667]. Despite these efforts, it is evident that in the

592 region there was, and still is, a breach between the programs for vector control and the

593 areas that are responsible for providing universal health care (including diagnosis and

594 etiological treatment) [68].

595 It is important to consider that although policies related to the primary

596 prevention of Chagas disease are defined at the national level, primary healthcare

597 attention for the patient is the responsibility of the provincial/departmental or

598 municipal/local entities [69]. Often times, these final effectors of national policies have

599 little or no relation/communication with the national entity and are sometimes even

600 unaware of the policies themselves. For example, suggestion of treatment of the

601 infection by *T. cruzi* for postpartum women and their newborns, and the mandatory

602 treatment for women of childbearing age and children under the age of one with Chagas

603 disease that are in the national or supranational norms [32], make no specific mention of

604 which protocols need to be applied with respect to vector surveillance in the houses of

605 those patients living in endemic areas with active vector transmission. However, recent

606 public health interventions have shown that activities related to access to diagnosis or

607 treatment of the disease are usually implemented and promoted by those responsible for

608 vector control programs [70]. Thus, without consideration of the need of appropriate

609 structures and circuits (i.e. access to an adequate laboratory for diagnosis or presence of

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610 anti-trypanosomal drugs), which are not usually present in rural areas, one of the main

611 actions needed is to establish and/or strengthen the link between vector control

612 programs and the health system providers [70]. Thereafter, following a stepwise

613 approach, another action to accomplish would be to provide technical recommendations

614 to establish criteria for categorizing the risk of vector transmission status in an endemic

615 area. With that information available, it could be possible to explicitly detail under

616 which conditions Chagas disease diagnosis and treatment has to be made mandatory in

617 the area for the entire population, or segments of it (i.e. women at childbearing age,

618 newborns). Finally, a most desired third action would definitely be to integrate the

619 procedures for disease diagnosis and treatment within the health system as a transversal

620 program.

621   Nowadays there are already a few experiences that have been able to coordinate

622 vector control actions together with diagnosis and treatment in a successful manner [71,

623 72]. These could serve as proof-of-concept strategies for integral interventions to build

624 on, improve and replicate. As an example, the experience of Fundación Mundo Sano,

625 with direct and uninterrupted action in the field since 2002, is worth mentioning. Its

626 integral program includes vector control and sanitary improvement of rural houses in

627 the Department of General Taboada (Santiago del Estero, Argentina). In 2015, after 13

628 years of vector surveillance and control, Mundo Sano was able to install two doctors'

629 offices dedicated to the diagnosis and treatment of Chagas disease together with local

630 institutions, one in Añatuya City and another one in Colonia Dora. Since then, they have

631 been struggling with the problems of having a mono-disease health service in a

632 community that did not demand treatment. Despite the difficulties, after almost three

633 years of implementation, the amount of people diagnosed and treated begun to increase.

634 The work from these two Chagas disease specific offices was integrated to the local

635 hospital of Añatuya in 2018, thus reaching a higher amount of *T. cruzi*-infected

636 individuals derived from obstetrics, gynecology and cardiology services in addition to

637 those attending the offices from spontaneous demand. In the same line, the Platform for

638 the Integral Care of Chagas disease Patients was settled in Bolivia in 2009. Initially in

639 the province of Cochabamba in the center of the country, the Platform now works also

640 in municipalities of the provinces of Chuquisaca and Tarija [63]. Each experience,

641 proposal or pilot study must be evaluated objectively in order to improve and multiply

642 its impact, avoiding a future with a new inequality: one were those affected by the

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643   disease will have access to health depending on whether they live in an endemic or non-

644   endemic area.

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6. The role of patients' associations.

647   Similarly to what happens with other NTDs programs to promote scaling up of

648   healthcare interventions, strategies towards the control of Chagas disease often confront

649   with structural weaknesses of the health systems in which they aim to be integrated [73–

650   75]. Therefore, more effective strategies to strengthen those health systems are required

651   to ensure a sustainable integration of the required health innovations within them.

652   Importantly, these strategies need to incorporate the patients´ perspective in order to

653   overcome key access barriers [13,14,75]. Barriers that nowadays still hinder the access

654   to diagnosis and treatment, barriers impeding a better health care.

655   In recent years, several associations of Chagas disease patients have emerged

656   and joined in a Federation of Associations whose purposes are: (i) to increase the

657   visibility of the disease at all levels as well as of its overwhelming impact in the

658   patients´ health status; and (ii) to promote a more active role of the people affected by

659   the disease in the decision-making processes. But these associations face many

660   difficulties (dispersion of objectives, multiplicity of voices with different requirements,

661   little real mobilization in many countries, and lack of resources) to achieve their

662   objective of having an effective role in the health policies makings of their countries.

663   The WHO global strategy on integral health services centered on people could

664   be a way through which these associations can play an important practical role [77]. In

665   fact one of the goals of such program is to empower individuals, families and

666   communities by including in it some well-known activities led by patients such as

667   community education, groups of patients for mutual support, expert patients to engage

668   and help others, etc. [77]. In addition, this WHO program goes beyond a single disease

669   and has the virtue of encompassing other actors with decisive roles in health systems

670   performance, like governmental policy-makers, municipalities, donors, and providers.

671   Overall, the strategy is thus envisaged to allow the community and patients to

672   actively participate in the decision-making process, together with other involved actors,

673   in issues regarding their health. By doing so, they also play a role on the way the health

674   system is organized, for instance ensuring that community and primary healthcare are

675   prioritized. Therefore, patients associations should look after the implementation and

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676 compliance with this WHO strategy as it underlies the activities they are already taking

677 on.

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7. The R&D Agenda: clinical trials for new drugs or new strategies of treatment

679

680 **with current drugs.**

681 *7.1. Results from recently completed trials.*

682   Upon the questioned efficacy of currently available therapies (BNZ and NFX)

683 against the chronic symptomatic stage of the disease, clinical testing of new drugs

684 and/or of new regimens of BNZ and NFX is being pursued. Nonetheless, some major

685 obstacles are in the way to getting more adequate treatments, including the poor

686 understanding of the infection pathophysiology leading to the disease clinical

687 progression, and the lack of biomarkers to determine prognosis and cure (see review by

688 Pinazo et al., [19]). Particularly the latter hinders the follow-up of treated patients both

689 in the daily clinic and in clinical trials. At present, an absence of molecular

690 amplification of *T. cruzi* DNA from periphery blood is used as surrogate of "treatment

691 success". But this approach is far from optimal, especially at the chronic stage of the

692 disease when the parasitemia is low and intermittent. A negative result obtained at a

693 determined time point does not exclude the possibility that a positive one will be

694 obtained in the next visit. A false-negative PCR, i.e., a negative PCR result ("treatment

695 success" event) in the patient follow up is then less informative than a positive

696 determination, as this one will indeed define a case of treatment failure.

697   Despite this limitation, several clinical trials have been completed in the last

698 years, and there are several more currently ongoing. This advance represents a major

699 shift in the research landscape of this historically forgotten NTD. The vast majority of

700 the performed trials have been Phase 2 randomized, multi-centric, double-blinded,

701 efficacy and safety studies to evaluate oral dosage schemes for the treatment of adult

702 patients at indeterminate (asymptomatic) chronic stage (see Table 1). Amongst them,

703 CHAGASAZOL [78], STOP CHAGAS [79] and E1224 [31] have evaluated for the first

704 time two triazole anti-fungal drugs (posaconazole (POS), and the ravuconazole

705 precursor E1224) for their anti-*T. cruzi* properties. In addition, the BENEFIT trial that

706 evaluated the use of BNZ for chronic stage treatment must also be highlighted as it has

707 been the largest Phase 3 Chagas disease trial performed so far [47].

708   CHAGASAZOL and E1224 trials entailed a direct comparison of POS and

709 E1224 monotherapy at a high and a low dose to a BNZ standard dosage group (5

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710 mg/kg/day orally divided in two daily doses for 60 days) [3031,7778]. In addition to

711 monotherapy branches, STOP CHAGAS trial also included a study group that received

712 POS and BNZ as combined therapy [79]. In the latter, treatment success was defined as

713 a negative PCR value at the day 180 follow-up visit [79], whereas parasitological cure

714 in CHAGASAZOL was determined by a negative PCR result at 12 months follow-up

715 [78]. The most stringent success criteria was that of E1224 trial, which involved serial

716 negative PCR results (3 negative PCR results from 3 samples collected over 7 days) at

717 65 days after end of treatment and a further negative PCR outcome at 12 months follow-

718 up [31].

719   Although both POS and E1224 drugs showed good safety and efficacy profiles

720 at end of treatment in the three studies, the suppressive effect on parasite clearance after

721 12 months was much reduced in comparison to BNZ, which showed early and sustained

722 efficacy until 12 months of follow-up (Table 1). Thus, neither POS nor E1224 were as

723 good as BNZ and could not substitute it as monotherapies.

724   In the BENEFIT trial, the treatment response was evaluated in a sub-group of

725 1,896 subjects who had PCR results at baseline (60.5% of them were positive) by PCR

726 conversion at the end of treatment, and at two and five years post-treatment [47]. Being

727 a large multi-national study, the PCR conversion rates varied geographically with

728 Bolivia and Argentina showing the best results, though it must be noticed that such

729 conversion did not correlate with clinical outcome [47]. BENEFIT was devised to study

730 whether BNZ administration to patients at the chronic stage of the disease would widely

731 have a clinical benefit for them [2122,4647]. Sadly, its conclusions, far from reassuring

732 the role of BNZ turned out to be a setback, as they suggested not-to treat patients with

733 advanced cardiac disease [47]. As it has been criticized elsewhere, this devastating

734 conclusion drains from the fact that many subjects with advanced cardiac involvement

735 were enrolled in the study [3,2122]. Despite its negative outcome due to a rather

736 questionable study protocol design [22], the BENEFIT trial involved ample cooperation

737 between multiple study sites opening the door to the performance of multi-national

738 Phase 3 Chagas disease trials in South America [47].

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740 **_7.2. Ongoing clinical trials of anti-T. cruzi drugs._**

741   There are now some active and/or ongoing clinical trials. Some test alternative

742 BNZ dosing regimens to reduce exposure, improve tolerability and maintain efficacy as

743 described elsewhere [52], based also on the description of BNZ pharmacokinetics (PK)

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744 in Chagas disease adult patients [80]. In others the evaluation of NFX has gained

745 prominence under the promotion of Bayer, NFX producer. The use of fexinidazole, a

746 nitroimidazole drug like BNZ that is being trialed for human African trypanosomiasis

747 and leishmaniasis (respectively caused by *T. cruzi* closely related Kinetoplastid

748 parasites *T. brucei gambiense* and *T. brucei rhodensiense,* and by *Leishmania* spp.), and

749 of the antiarrhythmic drug amiodarone are also being clinically assessed for the first

750 time against *T. cruzi* based on their anti-parasitic capacities [8081,8182]. These ongoing

751 trials range from smaller Phase 1 to larger Phase 2 and 3 efficacy studies. There are: (1)

752 a Phase 1 safety, tolerability and bioavailability assessment of new NFX tablets and

753 another Phase 1 study to determine NFX PK in relation to dietary habits; (2) a Phase 2

754 study to evaluate different BNZ regimens (MULTIBENZ); (3) another Phase 2 study to

755 evaluate reduced and intermittent BNZ regimens, either given alone or in combination

756 with E1224 (BENDITA); (4) two more Phase 2 studies evaluating fexinidazole to

757 respectively determine dosing regimens and the minimal efficacious and safety dose; (5)

758 a Phase 2-3 trial to compare safety and efficacy of NFX and BNZ (EQUITY); (6) a

759 Phase 3 study to assess amiodarone, a commonly used antiarrhythmic with selective

760 anti-*T. cruzi* properties, administered over 6 months to individuals with mild-to-

761 moderate Chagas cardiomyopathy (ATTACH); (7) a Phase 3 study of a pediatric

762 formulation of NFX (CHICO); and (8) a very recently added Phase 3 study to evaluate a

763 short dose of BNZ in child-bearing age women (BETTY) (Table 2).

764 All Phase 2 or above trials in Table 2 but CHICO involve the evaluation of

765 drugs in chronically infected adult patients, and the measurement of treatment success

766 will rely on molecular detection of the parasite DNA. In contrast, in CHICO, designed

767 to assess NFX performance in Chagas disease infant population, the way to measure

768 cure is seroconversion a year after treatment because this is much easier to timely occur

769 in children than in adults and its readout is less ambiguous than the PCR output. All

770 these studies are currently in the recruiting stage, except FEXI NCT02498782 and

771 CHICO which are active but not recruiting, and BETTY that is not yet recruiting

772 (https://clinicaltrials.gov). Regarding the latter, benefits of treating *T. cruzi*-infected

773 women before pregnancy have been described by several smaller studies [23–26].

774 Hopefully BETTY´s outcome will serve to enforce treatment administration to all child-

775 bearing age women as soon as possible.

776

777 **Conclusion.**

778   Increasing the awareness on the prevalence and health impact of Chagas disease
779 among patients, health practitioners and political health authorities may eventually
780 translate to enhanced population-based diagnostic screening and treatment
781 interventions. The tools needed to facilitate this activity are being tested currently in the
782 field and incorporate more practical and point-of-care diagnostics, new drugs regimens,
783 and the standardization of daily clinical care routines. In addition, efforts to obtain
784 biomarkers of disease prognosis and early assessment of treatment are also being
785 pursued and will probably yield results soon.

786   Upon failure of azoles, the majority of presently ongoing Chagas disease clinical
787 trials either evaluate alternative regimens of current drugs or other chemical entities
788 distinct from azoles (e.g., fexinidazole, amiodarone) with the aim to identify dosages
789 with lower toxicity and at least equal efficacies compared to present chemotherapy with
790 either benznidazole or nifurtimox. There is certain optimism on that a new treatment for
791 Chagas disease can be scheduled in the next few years. Further complementing the new
792 anti-parasitic drugs is a new therapeutic biologic, a vaccine, now advancing to the
793 clinic. However, access to these new drugs and innovations will require enhanced
794 policies and advocacy activities. In parallel, it will be essential to shape and disseminate
795 pharmacovigilance protocols so that the drugs performance can be closely monitored,
796 and patients´ and healthcare providers´ confidence on these therapies is promoted and
797 maintained.

798   The functional deployment of counter-reference circuits fully integrated in the
799 national health services will be required to scale up the attention to Chagas disease
800 patients. In this regards, improved coordination between vector control authorities and
801 sanitary authorities needs strengthening in those regions with active vector transmission
802 of the infection. Widespread access to diagnosis and treatment will not yield the desired
803 outcome unless chances to get re-infected are minimized or eliminated. This approach
804 also requires maintaining blood screening and programs to stop congenital transmission.
805 An improved maternal diagnosis and treatment protocol would in itself reduce
806 congenital transmission.

807   Despite recently achieved advancements, Chagas disease management and
808 control is still a huge challenge. Therefore, to succeed in this matter it will be
809 paramount the continued involvement of key actors, including patients associations,
810 health authorities at regional and national levels, governmental and non-governmental
811 institutions, basic and clinical researchers, and of course financial partners.

24

Expert Opinion.

A huge drawback in the management of Chagas disease has traditionally been the lack of awareness of the disease and its impact by both health professionals and the patients themselves, as well as by governmental institutions with the power to dictate health policies. However, Chagas disease awareness is gradually increasing, so that efforts to combat this neglected tropical disease now need to shift in order to address its often insidious onset and silent clinical progression. These features currently complicate the access to timely diagnosis and treatment, which is also ballasted by the very limited resources available for research and development of improved treatment and disease prevention methodologies.

After so many years of neglecting Chagas disease, new efforts at R&D have the potential for high returns on investment. However, the R&D needs for Chagas disease are pervasive and span requirements for both basic and applied research, as well as new drugs, diagnostics and vaccines. With the ultimate goal of controlling the disease in endemic and non-endemic regions, the consequences of widening our understanding on Chagas disease and the pathogen that causes it will have an impact on the lives of millions of people. For instance, research on parasite-host interactions is needed to fully comprehend the pathogenic processes that lead to the life-threatening symptomatology characteristic of chronic *T. cruzi* infections. Furthermore, considering that in the absence of treatment ~30% of those chronically infected will develop cardiac and/or digestive tract disruptions, studies on both parasite and host genomics (and other omics) are required to determine the key factors leading to the development of pathogenesis. Deeper understanding of the parasite biology and of its interactions with the host is fundamental for the discovery of safer drugs or vaccines. Another challenge is the dearth of public policies and advocacy that so far has mostly failed to attract requisite funding.

Currently the most urgent needs include an expansion in clinical studies to test an enlarged portfolio of new drugs, together with improved biomarkers to monitor disease progress. There is also urgency for inexpensive and accessible point-of-care diagnostics, especially for mass screenings as well as for the early assessment of treatment responses. Their availability will widen access to treatment because they would introduce a more accurate picture of the disease epidemiology, as well as the ability to acknowledge cure upon treatment.

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Specialized centres:
Vertical strategy

- Protocolized attention: high complexity
- 2nd level healthcare centres
- Limited human resources
- Urban and rural areas
- Prototype (Project)
- Highly effective
- Activities included: prevention, diagnosis, treatment, IEC, training and RESEARCH
- External funds are needed

VS

Chagas national network:
Horizontal strategy

- Simplified protocolized attention
- **All healthcare levels integrated**
    →including primary healthcare
- Human resources of National Health System
- Urban and **rural areas**
- Model accepted by the National Health System
- Activities included: prevention, diagnosis, treatment, IEC, and training
- Depends on national funds

Comparison of the respective characteristics and requirements (in boxes) of the vertical and horizontal strategies to implement Chagas disease healthcare.

228x118mm (148 x 150 DPI)

1 **Title:** Strategies to enhance access to diagnosis and treatment for Chagas disease

2 patients in Latin America.

3

4 **Structured abstract (maximum 200 words):**

5 Introduction: Chagas disease, caused by infection with the parasite *Trypanosoma cruzi*,

6 represents a huge public health problem in the Americas, where millions of people are

7 affected. Despite the availability of two drugs against the infection (benznidazole and

8 nifurtimox), multiple factors impede their effective usage: 1) gaps in patient and

9 healthcare provider awareness; 2) lack of access to diagnosis; 3) drug toxicity and

10 absence of treatment algorithms to address adverse effects; 4) failures in drug supply

11 and distribution; and 5) inconsistent drug efficacy against the symptomatic chronic

12 stage.

13 Areas covered: we review new approaches and technologies to enhance access to

14 diagnosis and treatment as a means to reduce the disease burden. We also provide an

15 updated picture of recently published and ongoing anti-*T. cruzi* drug clinical trials.

16 Although there has been progress improving the research and development (R&D)

17 landscape, it is unclear whether any new treatments will emerge soon. Literature search

18 methodologies included multiple queries to public databases and the use of own-built

19 libraries.

20 Expert opinion: besides R&D, there is a major need for continue awareness and

21 advocacy efforts by patient associations, local and national governments and

22 international agencies. Overall, health system strengthening is essential to ensure vector

23 control commitments, as well as patient access to diagnosis and treatment.

24

25 **Keywords:** Chagas disease, comprehensive care, clinical trials, diagnosis, drug

26 treatment, patients associations, pharmacovigilance, vector control.

27

28 **Article highlights:**

29 • Chagas disease is a neglected disease caused by the parasite *Trypanosoma cruzi* (*T.*

30 *cruzi*). It affects millions of people in the Americas where it has a devastating health

31 and socioeconomic impact. The disease affects most those with lower resources,

32 binding them to poverty and leaving them aside. It was traditionally considered a

33 stigma, hidden by society and ignored by governments. Thankfully to medical

34 researchers, patients' associations and several other actors who have raised

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awareness and promoted education on the disease and its management, there has been a dramatic shift towards improved diagnosis, treatment and control in recent decades.

- There are highly sensitive and specific diagnostics for both the acute and the chronic stages of the infection. However, they are not widely implemented in many areas distant from reference laboratories due to logistical issues and the lack of equipped facilities and trained personnel. Therefore, more practical methodologies and algorithms should be used to provide point-of-care diagnostics prior to gaining access to treatment.

- Two drugs are currently available to treat the infection: benznidazole and nifurtimox. Both are highly efficacious in newborns, but access to treatment generally occurs at the chronic stage when symptomatology arises. Due to the frequent adverse side effects associated to their long administration regimens, pharmacovigilance programs to report drugs toxicities and a better management of these in primary care establishments must be implemented to ensure tighter adherence to medication.

- Stronger involvement of public health institutions and authorities is fundamental to progress in the disease control and its adequate management. The establishment of counter-reference circuits integrated in national health services working plans will be fundamental to catalyze and scale up the attention and care of Chagas disease patients in endemic and non-endemic settings.

- Although great progresses in the control of vector-related transmission has been made in some regions, there are many where vector transmission is still active. Therefore, increased cooperation between vector control programs and medical (diagnostic and treatment) programs must be put on place to maximize their impact in public health.

- The role of patients' associations must remain active and exert pressure on other stakeholders in order to keep up Chagas disease visibility. Patients´ organizations are at the frontline to demand attention from the responsible authorities, ensure adequate medical care, and highlight the potential returns on investment from R&D. In line with the shift on the disease awareness, the clinical research landscape has recently changed for the better. At present there are several clinical trials ongoing and their results are expected to generate improvements in diagnosis and treatment

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algorithms and policies in the near future. They may also lead to the advancement
and licensure of new drugs, diagnostics, and vaccines.

Body of the article.

-

1. Introduction.

Chagas disease, or American trypansosomiasis, is caused by the protozoan
parasite *Trypanosoma cruzi* (*T. cruzi*) and remains one of the most deadly and
intractable neglected tropical diseases (NTDs) in the Western Hemisphere [1]. Updated
information from the Global Burden of Disease Study (GBD) 2016 indicates that 7,100
people die from Chagas disease annually, roughly the same number of Chagas disease-
related deaths that occurred a decade previously [2]. However, these numbers may
represent highly conservative estimates with further findings that as many as 200,000
people living with *T. cruzi* infection may die over the next five years [3]. The GBD
2016 also finds that 7.2 million now live with Chagas disease, while 180,000 new *T.
cruzi* infections occur annually [4].

Beyond its horrific disease burden and contribution to infectious disease
mortality, there is a profoundly disturbing social impact dimension to Chagas disease
related to its importance as a health disparity. Today, tens of thousands of people face a
death sentence from their *T. cruzi* infection due to Chagasic cardiomyopathy, which
could be prevented by timely access to diagnosis and anti-parasitic treatment with one
of two nitroheterocyclic drugs – benznidazole (BNZ) and nifurtimox (NFX). Fueling a
growing outrage from the global health community is the finding that approximately
90% of people infected with *T. cruzi* infection now live in Latin America's three
wealthiest economies: Argentina, Brazil, and Mexico. In the United States of America
(USA), the richest country of the continent and main destiny of those looking for a
better future, there are at least 200,000 immigrants from Latin America living with
Chagas disease with limited or no access to treatment [5,6]. Furthermore, in Europe
there are around 120,000 immigrants from Latin America living with Chagas diseases
with a disparity of situations regarding access to care and treatment [7,8].

101   The overwhelming majority of Chagas disease sufferers are unable to gain
102 access to diagnosis and treatment, not only because they are poor, but also because
103 governmental leaders are either uninformed or uninterested. For example, it is
104 noteworthy that the registration of BNZ for the treatment of pediatric Chagas disease in
105 the USA has not been approved until very recently [9]. Documenting such assertions is
106 not easy and seeking solutions to diagnosis and treatment access are not straightforward
107 endeavors. In Mexico, for example, there are almost one million people living with
108 Chagas disease, although even that number may represent a profound underestimate
109 [10]. Yet, only 3,013 *T. cruzi* infection cases were registered nationally between the
110 years 2007 and 2011, less than 1% of the actual number of people affected with the
111 disease [11]. A similar situation has been documented for the USA [12] and also likely
112 holds true across the Americas. We are facing a situation where less than 1% of Chagas
113 disease patients have access to timely and appropriate diagnosis and treatment [13,14].

114   Limiting access to essential medicines also has important implications for new
115 research and development (R&D) related to therapeutic interventions. An exciting
116 development on this front is a new orally bioavailable nitroheteorcyclic drug,
117 fexinidazole, which is also effective against human African trypanosomiasis [15].
118 Additional drugs are also under development, as well as there are Chagas disease
119 vaccine (immunotherapeutic) candidates at pre-clinical stage [16]. In this respect, the
120 Texas Children's Hospital Center for Vaccine Development, a Product Development
121 Partnership, is exploring an approach that links therapeutic vaccination to
122 pharmacotherapy [17]. However, any R&D successes must still face a formidable
123 gauntlet of truncated and mostly failed global access mechanisms. Similar forces are a
124 barrier for access to new and innovative diagnostics [18].

125   Here we report on some of the major hurdles that currently block access to the
126 diagnosis and treatment of Chagas disease. The problems include both scientific and
127 socioeconomic obstacles. This paper aims to elucidate the challenges they pose and
128 offer solutions.

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130 **2. The need of more practical and useful diagnostics.**

131   The poor access rate to Chagas disease therapeutic treatments has its roots in the
132 clinical nature of the disease itself and its silent progression from the mostly
133 asymptomatic acute stage into the symptomatic chronic one [1]. Unfortunately,
134 biomarkers of disease progression and standardized tools to determine early response-

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135　　to-treatment are yet unavailable, which greatly complicates the prognosis and follow-up

136　　of patients [19].

137　　　　Treatment administration, as in any other disease, needs to be preceded by an

138　　adequate diagnosis. In the case of Chagas disease, when a clinical diagnosis is achieved,

139　　tissue disruptions might already be too advanced for a chemotherapeutic intervention.

140　　Therefore, parasite detection must be sought before the onset of overt symptomatology.

141　　In the acute infection stage, for instance upon congenital transmission of the parasite,

142　　parasitemia can be detected by direct microscopic observation [1]. However, this stage

143　　is short lasting and generally goes unnoticed as there are often no symptoms at all.

144　　Approximately 30% of these infected individuals will progress to evidence either

145　　Chagasic cardiac or gastrointestinal disease. Those without clinical evidence of disease

146　　are said to be at the indeterminate stage, whereas those with cardiac or gastrointestinal

147　　involvement are at the determinate stage. The development of life-threatening heart

148　　and/or digestive tract disruptions, which can be massive and are called mega-

149　　syndromes, occurs in the long lasting chronic stage [1].

150　　　　In both indeterminate and determinate Chagasic patients, parasitemia is typically

151　　low and intermittent and the diagnosis of the infection is made by means of indirect

152　　serological tests, like enzyme-linked immunosorbent assays (ELISAs). This is possible

153　　because high levels of parasite-specific immunoglobulins are produced upon *T. cruzi*

154　　infection (Figure 1). Anti-*T. cruzi* type G immunoglobulins (IgGs) levels remain above

155　　detection thresholds for many years, which is advantageous for the serological diagnosis

156　　of the infection (Figure 1). However, it turns out to be an inconvenience for a serology-

157　　based assessment of drug responses as it can take several years for them to revert after

158　　the administration of treatment [20]. Another issue to take into account in the diagnosis

159　　of the infection is the wide genetic variability of the parasite, which encompasses seven

160　　different genotypes grouped in Discrete Typing Units (DTUs) [21]. A role of the

161　　parasite and host genetics interplay has been suggested in relation to the sensibility to

162　　treatment of the distinct isolates, the pathological signatures of the infection, and also in

163　　the anti-*T. cruzi* immune response [21].

164　　　　Some studies indicate that treatment interventions while patients are in the

165　　indeterminate or early determinate stages are critically important in order to prevent

166　　advanced disease progression. In contrast, from the multi-centered BENEFIT trial to

167　　evaluate BNZ efficacy it was found that patients with significant cardiac involvement

168　　progressed to advanced disease or even died despite receiving specific anti-parasitic

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169   chemotherapy [3,21]. Currently several classifications (for instance AHCC, or
170   Kuschnir´s modified) are in place to differentiate people with early-stage (grades A-B or
171   0-I respectively) versus late stage (grades C-D or II-III respectively) cardiac disease.
172   Treatment of patients with grades C-D or II-III was not encouraged previously [1], a
173   finding that appears to hold up in light of the recent BENEFIT findings. These findings
174   highlight the importance of identifying both indeterminate patients with Chagas disease,
175   and possibly those with AHCC grades A-B or modified Kuschnir grades 0-I too, since
176   they might be successfully treated with antiparasitic therapy if they were captured
177   during population-wide screening campaigns [3]. In this way, it would be possible to
178   identify and treat chronically infected people before they develop the symptomatology.
179   Women at child-bearing age and newborns should receive special attention because the
180   treatment of mothers-to-be has been shown to largely reduce the transmission rate [23–
181   26], and the efficacy and tolerability of current drugs by infected newborns is ~100%
182   [1]. Moreover, health economics studies evaluating Chagas disease surveillance in
183   endemic and non-endemic settings indicate that widespread screening would be highly
184   cost-effective [27–30]. In the two disease scenarios studied, congenital (acute infection
185   transmitted by chronically infected mothers) and indeterminate (chronic asymptomatic
186   stage), mass screening would save health costs even at *T. cruzi* prevalence rates as low
187   as 0.9% or 0.05% respectively (in fact estimated in a non-endemic setting) [27,29].

188   Due to the very limited resources available for Chagas disease management, and
189   echoing the answers provided by Latin American experts enquired by Picado et al. [18],
190   efforts should focus on making widely available point-of-care (PoC) tests to diagnose
191   congenital transmission and indeterminate chronic patients [18]. However, if we want to
192   enable generalized Chagas disease diagnosis, there is an urgent need of more practical
193   diagnostic reagents and kits. Availability of easy-to-use tools for the early assessment of
194   treatment response would also be highly valuable to promote and support the
195   administration of drugs against the infection. In this regards, there are some biomarkers
196   under research [19], but the evaluation of anti-*T. cruzi* drug responses yet relies on the
197   molecular amplification of the parasite DNA from periphery blood obtained at distinct
198   times post-treatment. Unfortunately, its associated high costs and technical requirements
199   restrict its use to the context of well-funded clinical trials [31].

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201   ### 2.1. Current Chagas disease diagnostics are impractical in many regions.

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202   Regarding acute stage diagnostics, classical parasitological methods

203   (micromethod, hemoculture and xenodiagnoses) are microscopy-based and rely on

204   finding motile trypomastigotes in blood, thus they provide both low sensitivity and

205   specificity. Due to their poor performance, current algorithm to diagnose congenital

206   transmission involves two micromethods (at birth and at 1-2 months of age), and a

207   further confirmatory serological test once mother-derived IgGs have waned at infant´s

208   8-12 months of age [32]. This has two major drawbacks: a very high loss-to-treatment

209   risk during pediatric follow up, and the reduction of drug efficacies the longer the

210   treatment is delayed [32]. Molecular amplification of *T. cruzi* DNA, either by

211   conventional polymerase chain reaction (PCR) or by quantitative PCR (qPCR), has

212   been shown to be more sensitive and specific than classical parasitological techniques

213   [20]. Several laboratories have worked on the standardization of the techniques so that

214   their outcomes can be comparable and implemented in clinic-based laboratories [20].

215   But molecular biology laboratories are expensive to mount and maintain, plus they

216   require highly trained personnel to run them. Therefore, despite its very good

217   performance, molecular detection is not generally used beyond regional or national

218   reference laboratories in endemic regions.

219   In relation to the current chronic stage diagnostics, conventional serological tests

220   (like ELISAs, indirect immune-fluorescence or indirect hemagglutination assays) use

221   serum or plasma samples that entail venous extraction and blood segregation by

222   centrifugation, and they require a cold chain to preserve the test reagents and the

223   samples. Moreover, due to the parasite´s antigenic diversity, the advice from the World

224   Health Organization (WHO) is to run two tests based on distinct antigenic sets and if

225   their outcomes are not concurrent, to employ a third technique [14]. This algorithm is

226   costly, and it requires equipment and resources that are usually not available in many

227   laboratories of endemic regions. Furthermore, the turnaround of results to the patient

228   can take several weeks, which involves a high risk of losing contact with the patient for

229   treatment.

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2.2. What solutions could be implemented?

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232   Fortunately, recent technological advancements are procuring solutions to

233   overcome the limitations mentioned above. We will outline them separately considering

234   first those for the diagnosis of acute stage and then those for the diagnosis of chronic

235   Chagas disease.

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236   In recent years, isothermal amplification methods that do not require expensive

237 equipment (such as thermocyclers or gel visualization systems) and are easier to

238 perform than PCR assays have been developed for the molecular detection of several

239 NTDs [20]. At present, a prototype of Loop isothermal AMPlification for *T. cruzi*-DNA

240 (LAMP, Eiken Co., Japan) has been tested with clinical samples and shown to have a

241 comparable performance to qPCR with blood-EDTA samples [33]. Another LAMP test

242 developed in house by Rivero et al. [34] has also been shown to provide a comparable

243 performance to current congenital transmission algorithm. LAMP is based on a

244 microbiological DNA polymerase that works at a constant temperature of 65 ºC for 45

245 minutes with a set of 4 to 6 complex primer sequences to provide a highly sensitive and

246 specific amplification [35]. LAMP readout is qualitative and the results can be naked

247 eye visualized in a short time given a probe (e.g. calcein) is added to the reaction mix. If

248 a digital fluorimeter is used (e.g. Genie III) the reading can even be semi-quantitative

249 [33]. Notably, in Eiken´s *T. cruzi*-LAMP prototype, reagents are provided dried out in

250 the lids of the reaction tubes which allow a ready-to-use format and a much desirable

251 room temperature storage [33]. More recently, a Recombinase Polymerase Assay

252 (RPA), which even requires a lower amplification temperature and shorter amplification

253 time (40 ºC for 30 min) than LAMP, has been tested with samples from naturally *T.*

254 *cruzi*-infected dogs [36]. This RPA has been coupled to a lateral flow strip for results

255 reading and it was shown to provide excellent agreement with qPCR results [36]. There

256 are RPAs for the detection of other NTDs [37,38], so it could also be very useful for

257 Chagas disease molecular diagnosis.

258   For the serological detection of *T. cruzi*-specific IgGs, rapid diagnostic tests

259 (RDTs) have been commercially developed during the last two decades [39,40]. RDTs

260 have clear advantages over conventional serology, as they can be stored at room

261 temperature, use a very small volume (5-25 µl) of finger pricked whole blood, have an

262 easy-to-run and read cassette format, and provide a fast turnaround of results (less than

263 45 minutes) [40]. Several studies now support their implementation as they have been

264 extensively validated against conventional tests [41–43]. For instance, a RDT is

265 currently used for primary screening of chronic Chagas disease in Bolivia [41].

266 Nonetheless, following the WHO guidelines of two-tests concordance, confirmation of

267 that RDT primary result must yet be made with a conventional serological test [14].

268 Such recommendations reduce the advantages of RDTs.

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269   With the aim to fully exploit RDTs advantages and to determine whether they

270   can substitute conventional tests, combinatory use of two RDTs has been proposed [41].

271   So far, in a proof-of-concept study performed in the city of Sucre (Bolivia), perfect

272   agreement between the two RDTs used was observed, and their sensitivity and

273   specificity in comparison with three conventional tests was 100% and 99.3%,

274   respectively [41]. However, despite a promising performance in Bolivia [41,43], RDTs

275   have not worked so well when they have been used in other geographical regions [44].

276   This might be related to the high prevalence of the disease in Bolivia, which may allow

277   an easier detection, or to the fact that the parasite strains used to produce the RDTs

278   antigens are those circulating in Bolivia. In any case, until more results from different

279   epidemiological areas are available, preliminary geographical testing of the RDTs

280   performance has been proposed before using them in a particular region [44]. In view of

281   the advantages they bring versus conventional tests, RDTs implementation for Chagas

282   disease surveillance should be evaluated at larger scales.

283

284   **3. Treatment of Chagas disease, and issues related to it.**

285   *3.1. Drug regimens.*

286   Evidence about the benefits of Chagas disease treatment, together with a

287   growing understanding of the pathogenesis of the disease, led to the paradigm that all *T.*

288   *cruzi*-seropositive patients should receive treatment with anti-*T. cruzi* drugs [45]. The

289   recently published results of the SaMi-Trop cohort study further reaffirm this statement

290   as they demonstrate a beneficial effect of BNZ in reducing the cardiac clinical

291   progression of chronic Chagas disease patients [46]. Therefore, anti-trypanosomatid

292   treatment should be provided to all *T. cruzi*-infected people who do not present with

293   advanced cardiac complications (Kuschnir grades III-IV), as by then clinical

294   manifestations might not be improved [47]. Nonetheless, access to treatment confronts

295   important limitations. BNZ and NFX, the only drugs available for *T. cruzi* infection,

296   exhibit reduced efficacy during the chronic stage of the disease, and require a long

297   period of administration which causes frequent unwanted drug-related adverse reactions

298   (ADRs) [48–50]. Furthermore, variable drug susceptibility has been already described

299   among distinct *T. cruzi* strains [51]. In this context, there is an urgent need for more

300   efficacious and safer drugs or drugs´ regimens, in particular for the treatment of the

301   chronic stage of the infection.

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302   One alternative is the reduction of the BNZ dose and/or schedule in order to
303 improve safety and adherence to treatment; an approach that is supported by clinical and
304 experimental data. In a pilot study Álvarez et al. [52] assessed a new scheme of BNZ
305 administration in a small cohort of chronic Chagas disease patients treated with
306 intermittent doses of BNZ at 5 mg/kg/day every 5 days for a total of 60 days. The study
307 showed a satisfactory safety profile, with low rates of treatment suspension and
308 treatment failure [52]. Furthermore, an experimental study using a mouse model of
309 chronic *T. cruzi* infection demonstrated the effectiveness of an intermittent scheme of
310 BNZ administered every 5 days for 40 days [53]. These findings support the
311 intermittent administration of BNZ as a new dosage schedule, but further research to
312 confirm its efficacy by long-term assessment of larger cohorts is needed. Another
313 therapeutic option under investigation is the co-administration of an immunotherapeutic
314 (vaccine) treatment and BNZ. In this regards, enhancement of a *T. cruzi*-specific
315 immune response has been shown to contribute to support the efficacy of reduced BNZ
316 dosages in a mouse model of acute *T. cruzi* infection [17].

317

3.2. Drug availability.

319   Drug access is still a huge problem in some endemic areas [13]. BNZ, generally
320 the first line therapy for Chagas disease, is part of the WHO List of Essential Medicines
321 [54]. It was produced during more than 40 years by Roche (Basilea, Switzerland),
322 which transferred its production rights to Laboratório Farmacêutico de Pernambuco
323 (LAFEPE), a Brazilian public enterprise, at the end of the twentieth century. Sadly,
324 BNZ production and distribution by LAFEPE failed to meet expectations in terms of
325 meeting supply and demand requirements and in 2011 an important shortage of the drug
326 occurred. It lasted 1.5 years and left thousands of patients without treatment worldwide
327 [13,55]. This fact led to the development of a Private-Public Partnership in Argentina
328 involving Maprimed (for the synthesis of the drug) and ELEA (for its development and
329 production), to promote equitable availability of BNZ [56]. Since 2012, this Argentinian
330 Partnership has worked to guarantee the availability of the drug, distributing BNZ to the
331 countries in the region [56]. NFX, which is mostly used as the second line treatment
332 option, is produced and donated by the pharmaceutical company Bayer, and distributed
333 through the Pan-American Health Organization (PAHO) Strategic Fund [57]. Recently,
334 a NFX produced by Gador has also been registered in Argentina. Definitely, a regular,
335 safe and accessible production of these two anti-parasitic drugs is necessary to

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336 guarantee the treatment to diagnosed patients, and the access to drugs has to be ensured
337 in adequate quantity, quality, location and timing.

338

3.3. Pharmacovigilance.

340 A major limitation of current Chagas disease treatments is the onset of Adverse
341 Drug Reactions (ADRs), which may lead to poor medication adherence, and cause
342 thereby therapeutic failure or ineffective treatment [48-50]. ADRs are defined as "an
343 appreciably harmful or unpleasant reaction, resulting from an intervention related to the
344 use of a medicinal product, which predicts hazard from future administration and
345 warrants prevention or specific treatment, or alteration of the dosage regimen, or
346 withdrawal of the product" [58]. The most commonly observed ADRs related to BNZ
347 are headache, dermatological manifestations and gastrointestinal symptoms [49,50].
348 Concerning NFX, digestive symptoms are the most frequent [48]. Nevertheless, with an
349 adequate clinical management most of the patients are able to finish treatment in the
350 advent of ADRs [49]. Close medical follow-up, adequate monitoring of ADRs and
351 implementation of robust pharmacovigilance systems are essential factors to avoid
352 patient abandonment and achieve therapeutic success.

353 Although pharmacovigilance is crucial, it is still a neglected area. Latin-
354 American countries are making important efforts to report ADRs, but these activities are
355 recent and need reinforcement [59,60]. Results of an unpublished study conducted by
356 Cortes-Serra et al. in Bolivia during 2016 indicate that 35.4% of the total patients
357 treated for Chagas disease in fourteen healthcare centers of the department of
358 Cochabamba suffered ADRs related to it. From all ADRs classified as moderate or
359 severe (25% of the total ADRs registered), only about half of them (51.43%) were
360 reported to the Bolivian Pharmacovigilance system [61]. This data illustrates the
361 urgency of implementing policies to promote training in pharmacovigilance to all
362 healthcare professionals, as well as strictly recommend the follow-up on drug
363 monitoring and ADR reporting. Altogether, these features are fundamental to achieve
364 strong and consolidated ADR reporting systems, which will improve patient safety,
365 drug efficacy and adherence to treatment.

366

4. Patients´ comprehensive care: reference and counter-reference circuits.

368 With less than 1% people treated [13,14], and an economic burden of $7.19
369 billion per year and $188.8 billion per lifetime [62], Chagas disease remains neglected

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370 despite the efforts performed by several institutions focused on development and
371 research [13]. Migratory flows have changed the epidemiology of the disease that is
372 now emerging in some non-endemic countries [7]. During the last decades,
373 collaboration and knowledge transfer between institutions from endemic (CEADES,
374 Bolivia) and non-endemic countries (ISGlobal, Spain) has been strategic to build
375 attention models for the Chagas disease patient. Such models could be scaled-up by
376 national health systems in endemic and non-endemic countries in order to expand
377 Chagas disease healthcare to people living in areas with limited access to health (e.g.
378 rural areas in endemic countries) or to vulnerable populations (e.g. migrants in endemic
379 and non-endemic countries).

380

381 ### *4.1. The Platform for integral care of Chagas disease patients.*

382 The work made by this Platform in recent years have produced a quantitative
383 and qualitative improvement in the healthcare provided to Chagas disease patients in
384 Bolivia, but this improvement certainly needs to be strengthened. The experience gained
385 with the Platform in the country has shown that the implementation of specialized
386 centers to manage people at risk of having Chagas disease is highly effective, both
387 based on the percentage (and number) of people diagnosed with the infection, and
388 amongst them, those who received and completed treatment [63]. This vertical strategy
389 has been essential to design the attention model for patients with Chagas, making the
390 medical assistance to these people look like a normalized and necessary action [63].
391 Nevertheless, the sustainability of such model ultimately depends on continuously
392 securing external funds, which greatly complicates its expansion to larger geographical
393 levels, like national coverage by the national health system (Figure 2).

394

395 ### *4.2. Vertical-to-horizontal healthcare model transition.*

396 In order to have a higher impact in terms of diagnosis and treatment coverage, as
397 well as to ensure the sustainability for the model of care of Chagas disease patients
398 already installed, it is mandatory to search for a comprehensive horizontal strategy
399 together with local higher level entities of the public health system. In fact, based on
400 WHO recommendations, the strategy to include the Chagas disease attention roadmap
401 as part of the regular activities of all healthcare levels seems to be the most appropriate
402 approach [64].

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403   Simplifying the vertical Chagas disease model of healthcare to more realistic

404 protocols established together with the national health institutions has allowed the

405 improvement of healthcare access for people at risk of having the disease living in

406 remote areas of an endemic country [63]. Researchers at ISGlobal (authors of this

407 review) have yet unpublished data which demonstrate that the health coverage, in terms

408 of patients diagnosed and treated in the selected area in which the project has expanded

409 its activity, was five times higher in the three years following the horizontal

410 comprehensive care model than the number of people covered in the five previous years

411 with the vertical strategy (Pinazo et al., unpublished).

412   So far, the outcome of the vertical-to-horizontal healthcare model transition

413 highlight that it could be worthy to replicate and/or adapt it to other regions or

414 countries. The first step would be to coordinate with local health authorities at different

415 levels in order to design an appropriate strategy. For the implementation of a healthcare

416 model, the identification of interested health workers is a key issue. Even if it is

417 simplified, a strategy to offer a comprehensive care for people at risk of suffering from

418 Chagas disease should include: (a) specific training of health workers on the disease

419 management; and (b) a strategy to increase the demand of the civil society, based on

420 promotional and educational community activities. In this regard, the establishment of

421 referral and counter-referral circuits tailored to each epidemiological and logistic

422 situation is highly relevant, even in nearby areas.

423

4.3. Requirements for the expansion of the Chagas disease healthcare model.

425   Referral and counter-referral circuits, in terms of patients and samples for

426 diagnosis or any other test, should include different healthcare levels to cover different

427 levels of complexity in terms of care. The specialized centers in which the model of care

428 has been rehearsed in Bolivia are key towards organizing these circuits, as well as to act

429 as reference centers for complicated cases and to accompany the doubts and the

430 continuing education of health professionals from primary care centers. This is

431 particularly important in health systems where there is often a fast renewal of healthcare

432 personnel. Another crucial point to make sustainable a comprehensive horizontal

433 strategy against Chagas disease is to promote an inter-sectorial collaboration with vector

434 control authorities (promoters of house refurbishment, disinfestation programs,...) and

435 the educational system itself. Vector control interventions are fundamental to halt

436 vector-dependent transmission and enable an enhanced drug control of the cases.

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437 Whereas educational activities to widen the population knowledge and perception of the
438 disease, its impact, and treatment possibilities are crucial, because producing changes in
439 beliefs, attitudes, and behaviors on both medical staff and patients still stands as one of
440 the major challenges that must be faced when dealing with Chagas disease. All these
441 measures have a role to play in order to consolidate the successful management of the
442 disease.

443 On the other hand, lessons learned from the primary healthcare network have
444 shown that it is mandatory to ensure the supervision of the circuits and surveillance the
445 quality of the process, tasks that should be carried out by the national health system
446 responsible personnel in duty. Political engagement at this point is mandatory to
447 contribute to a better control of the disease as a Public Health problem. In this context,
448 it is important to respect the capability of local health institutions, agreeing with them
449 timelines and a progressive increase of the number of people diagnosed and treated, in
450 order to answer adequately to people's demands. It must be noted that external factors
451 like the poor availability of drugs for Chagas disease treatment have a sourly negative
452 impact on any planning.

453

5. Patients treatment in relationship with vector control.
454
455 Access to diagnosis and treatment of Chagas disease in areas with active vector
456 transmission requires a multidisciplinary approach. It involves the participation of
457 players from several areas of expertise and different government sectors, from vector
458 control authorities to health service providers, including primary healthcare [65].

459 Following the advice from the PAHO, intergovernmental regional initiatives
460 were created at the end of the twentieth century and beginning of the twenty first
461 century to establish supranational levels of action to bolster and monitor the
462 implementation of activities to prevent, control, diagnose and treat Chagas disease in
463 Latin America. These initiatives were started by Southern Cone countries in 1991, and
464 then followed by Andean countries and Central American countries in 1997 and
465 Amazonian countries in 2004 [66,67]. Despite these efforts, it is evident that in the
466 region there was, and still is, a breach between the programs for vector control and the
467 areas that are responsible for providing universal health care (including diagnosis and
468 etiological treatment) [68].

469 It is important to consider that although policies related to the primary
470 prevention of Chagas disease are defined at the national level, primary healthcare

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471   attention for the patient is the responsibility of the provincial/departmental or
472   municipal/local entities [69]. Often times, these final effectors of national policies have
473   little or no relation/communication with the national entity and are sometimes even
474   unaware of the policies themselves. For example, suggestion of treatment of the
475   infection by *T. cruzi* for postpartum women and their newborns, and the mandatory
476   treatment for women of childbearing age and children under the age of one with Chagas
477   disease that are in the national or supranational norms [32], make no specific mention of
478   which protocols need to be applied with respect to vector surveillance in the houses of
479   those patients living in endemic areas with active vector transmission. However, recent
480   public health interventions have shown that activities related to access to diagnosis or
481   treatment of the disease are usually implemented and promoted by those responsible for
482   vector control programs [70]. Thus, without consideration of the need of appropriate
483   structures and circuits (i.e. access to an adequate laboratory for diagnosis or presence of
484   anti-trypanosomal drugs), which are not usually present in rural areas, one of the main
485   actions needed is to establish and/or strengthen the link between vector control
486   programs and the health system providers [70]. Thereafter, following a stepwise
487   approach, another action to accomplish would be to provide technical recommendations
488   to establish criteria for categorizing the risk of vector transmission status in an endemic
489   area. With that information available, it could be possible to explicitly detail under
490   which conditions Chagas disease diagnosis and treatment has to be made mandatory in
491   the area for the entire population, or segments of it (i.e. women at childbearing age,
492   newborns). Finally, a most desired third action would definitely be to integrate the
493   procedures for disease diagnosis and treatment within the health system as a transversal
494   program.

495   Nowadays there are already a few experiences that have been able to coordinate
496   vector control actions together with diagnosis and treatment in a successful manner [71,
497   72]. These could serve as proof-of-concept strategies for integral interventions to build
498   on, improve and replicate. As an example, the experience of Fundación Mundo Sano,
499   with direct and uninterrupted action in the field since 2002, is worth mentioning. Its
500   integral program includes vector control and sanitary improvement of rural houses in
501   the Department of General Taboada (Santiago del Estero, Argentina). In 2015, after 13
502   years of vector surveillance and control, Mundo Sano was able to install two doctors'
503   offices dedicated to the diagnosis and treatment of Chagas disease together with local
504   institutions, one in Añatuya City and another one in Colonia Dora. Since then, they have

15

505 been struggling with the problems of having a mono-disease health service in a

506 community that did not demand treatment. Despite the difficulties, after almost three

507 years of implementation, the amount of people diagnosed and treated begun to increase.

508 The work from these two Chagas disease specific offices was integrated to the local

509 hospital of Añatuya in 2018, thus reaching a higher amount of *T. cruzi*-infected

510 individuals derived from obstetrics, gynecology and cardiology services in addition to

511 those attending the offices from spontaneous demand. In the same line, the Platform for

512 the Integral Care of Chagas disease Patients was settled in Bolivia in 2009. Initially in

513 the province of Cochabamba in the center of the country, the Platform now works also

514 in municipalities of the provinces of Chuquisaca and Tarija [63]. Each experience,

515 proposal or pilot study must be evaluated objectively in order to improve and multiply

516 its impact, avoiding a future with a new inequality: one were those affected by the

517 disease will have access to health depending on whether they live in an endemic or non-

518 endemic area.

519

520 **6. The role of patients' associations.**

521   Similarly to what happens with other NTDs programs to promote scaling up of

522 healthcare interventions, strategies towards the control of Chagas disease often confront

523 with structural weaknesses of the health systems in which they aim to be integrated [73–

524 75]. Therefore, more effective strategies to strengthen those health systems are required

525 to ensure a sustainable integration of the required health innovations within them.

526 Importantly, these strategies need to incorporate the patients´ perspective in order to

527 overcome key access barriers [13,14,75]. Barriers that nowadays still hinder the access

528 to diagnosis and treatment, barriers impeding a better health care.

529   In recent years, several associations of Chagas disease patients have emerged

530 and joined in a Federation of Associations whose purposes are: (i) to increase the

531 visibility of the disease at all levels as well as of its overwhelming impact in the

532 patients´ health status; and (ii) to promote a more active role of the people affected by

533 the disease in the decision-making processes. But these associations face many

534 difficulties (dispersion of objectives, multiplicity of voices with different requirements,

535 little real mobilization in many countries, and lack of resources) to achieve their

536 objective of having an effective role in the health policies makings of their countries.

537   The WHO global strategy on integral health services centered on people could

538 be a way through which these associations can play an important practical role [77]. In

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539 fact one of the goals of such program is to empower individuals, families and
540 communities by including in it some well-known activities led by patients such as
541 community education, groups of patients for mutual support, expert patients to engage
542 and help others, etc. [77]. In addition, this WHO program goes beyond a single disease
543 and has the virtue of encompassing other actors with decisive roles in health systems
544 performance, like governmental policy-makers, municipalities, donors, and providers.

545   Overall, the strategy is thus envisaged to allow the community and patients to
546 actively participate in the decision-making process, together with other involved actors,
547 in issues regarding their health. By doing so, they also play a role on the way the health
548 system is organized, for instance ensuring that community and primary healthcare are
549 prioritized. Therefore, patients associations should look after the implementation and
550 compliance with this WHO strategy as it underlies the activities they are already taking
551 on.

552

553 **7. The R&D Agenda: clinical trials for new drugs or new strategies of treatment**
554 **with current drugs.**

555 *7.1. Results from recently completed trials.*

556   Upon the questioned efficacy of currently available therapies (BNZ and NFX)
557 against the chronic symptomatic stage of the disease, clinical testing of new drugs
558 and/or of new regimens of BNZ and NFX is being pursued. Nonetheless, some major
559 obstacles are in the way to getting more adequate treatments, including the poor
560 understanding of the infection pathophysiology leading to the disease clinical
561 progression, and the lack of biomarkers to determine prognosis and cure (see review by
562 Pinazo et al., [19]). Particularly the latter hinders the follow-up of treated patients both
563 in the daily clinic and in clinical trials. At present, an absence of molecular
564 amplification of *T. cruzi* DNA from periphery blood is used as surrogate of "treatment
565 success". But this approach is far from optimal, especially at the chronic stage of the
566 disease when the parasitemia is low and intermittent. A negative result obtained at a
567 determined time point does not exclude the possibility that a positive one will be
568 obtained in the next visit. A false-negative PCR, i.e., a negative PCR result ("treatment
569 success" event) in the patient follow up is then less informative than a positive
570 determination, as this one will indeed define a case of treatment failure.

571   Despite this limitation, several clinical trials have been completed in the last
572 years, and there are several more currently ongoing. This advance represents a major

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573 shift in the research landscape of this historically forgotten NTD. The vast majority of

574 the performed trials have been Phase 2 randomized, multi-centric, double-blinded,

575 efficacy and safety studies to evaluate oral dosage schemes for the treatment of adult

576 patients at indeterminate (asymptomatic) chronic stage (see Table 1). Amongst them,

577 CHAGASAZOL [78], STOP CHAGAS [79] and E1224 [31] have evaluated for the first

578 time two triazole anti-fungal drugs (posaconazole (POS), and the ravuconazole

579 precursor E1224) for their anti-*T. cruzi* properties. In addition, the BENEFIT trial that

580 evaluated the use of BNZ for chronic stage treatment must also be highlighted as it has

581 been the largest Phase 3 Chagas disease trial performed so far [47].

582   CHAGASAZOL and E1224 trials entailed a direct comparison of POS and

583 E1224 monotherapy at a high and a low dose to a BNZ standard dosage group (5

584 mg/kg/day orally divided in two daily doses for 60 days) [31,78]. In addition to

585 monotherapy branches, STOP CHAGAS trial also included a study group that received

586 POS and BNZ as combined therapy [79]. In the latter, treatment success was defined as

587 a negative PCR value at the day 180 follow-up visit [79], whereas parasitological cure

588 in CHAGASAZOL was determined by a negative PCR result at 12 months follow-up

589 [78]. The most stringent success criteria was that of E1224 trial, which involved serial

590 negative PCR results (3 negative PCR results from 3 samples collected over 7 days) at

591 65 days after end of treatment and a further negative PCR outcome at 12 months follow-

592 up [31].

593   Although both POS and E1224 drugs showed good safety and efficacy profiles

594 at end of treatment in the three studies, the suppressive effect on parasite clearance after

595 12 months was much reduced in comparison to BNZ, which showed early and sustained

596 efficacy until 12 months of follow-up (Table 1). Thus, neither POS nor E1224 were as

597 good as BNZ and could not substitute it as monotherapies.

598   In the BENEFIT trial, the treatment response was evaluated in a sub-group of

599 1,896 subjects who had PCR results at baseline (60.5% of them were positive) by PCR

600 conversion at the end of treatment, and at two and five years post-treatment [47]. Being

601 a large multi-national study, the PCR conversion rates varied geographically with

602 Bolivia and Argentina showing the best results, though it must be noticed that such

603 conversion did not correlate with clinical outcome [47]. BENEFIT was devised to study

604 whether BNZ administration to patients at the chronic stage of the disease would widely

605 have a clinical benefit for them [22,47]. Sadly, its conclusions, far from reassuring the

606 role of BNZ turned out to be a setback, as they suggested not-to treat patients with

18

607 advanced cardiac disease [47]. As it has been criticized elsewhere, this devastating

608 conclusion drains from the fact that many subjects with advanced cardiac involvement

609 were enrolled in the study [3,22]. Despite its negative outcome due to a rather

610 questionable study protocol design [22], the BENEFIT trial involved ample cooperation

611 between multiple study sites opening the door to the performance of multi-national

612 Phase 3 Chagas disease trials in South America [47].

613

7.2. Ongoing clinical trials of anti-T. cruzi drugs.

615 There are now some active and/or ongoing clinical trials. Some test alternative

616 BNZ dosing regimens to reduce exposure, improve tolerability and maintain efficacy as

617 described elsewhere [52], based also on the description of BNZ pharmacokinetics (PK)

618 in Chagas disease adult patients [80]. In others the evaluation of NFX has gained

619 prominence under the promotion of Bayer, NFX producer. The use of fexinidazole, a

620 nitroimidazole drug like BNZ that is being trialed for human African trypanosomiasis

621 and leishmaniasis (respectively caused by *T. cruzi* closely related Kinetoplastid

622 parasites *T. brucei gambiense* and *T. brucei rhodensiense,* and by *Leishmania* spp.), and

623 the antiarrhythmic drug amiodarone are also being clinically assessed for the first time

624 against *T. cruzi* based on their anti-parasitic capacities [81,82]. These ongoing trials

625 range from smaller Phase 1 to larger Phase 2 and 3 efficacy studies. There are: (1) a

626 Phase 1 safety, tolerability and bioavailability assessment of new NFX tablets and

627 another Phase 1 study to determine NFX PK in relation to dietary habits; (2) a Phase 2

628 study to evaluate different BNZ regimens (MULTIBENZ); (3) another Phase 2 study to

629 evaluate reduced and intermittent BNZ regimens, either given alone or in combination

630 with E1224 (BENDITA); (4) two more Phase 2 studies evaluating fexinidazole to

631 respectively determine dosing regimens and the minimal efficacious and safety dose; (5)

632 a Phase 2-3 trial to compare safety and efficacy of NFX and BNZ (EQUITY); (6) a

633 Phase 3 study to assess amiodarone, a commonly used antiarrhythmic with selective

634 anti-*T. cruzi* properties, administered over 6 months to individuals with mild-to-

635 moderate Chagas cardiomyopathy (ATTACH); (7) a Phase 3 study of a pediatric

636 formulation of NFX (CHICO); and (8) a very recently added Phase 3 study to evaluate a

637 short dose of BNZ in child-bearing age women (BETTY) (Table 2).

638 All Phase 2 or above trials in Table 2 but CHICO involve the evaluation of

639 drugs in chronically infected adult patients, and the measurement of treatment success

640 will rely on molecular detection of the parasite DNA. In contrast, in CHICO, designed

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641   to assess NFX performance in Chagas disease infant population, the way to measure

642   cure is seroconversion a year after treatment because this is much easier to timely occur

643   in children than in adults and its readout is less ambiguous than the PCR output. All

644   these studies are currently in the recruiting stage, except FEXI NCT02498782 and

645   CHICO which are active but not recruiting, and BETTY that is not yet recruiting

646   (https://clinicaltrials.gov). Regarding the latter, benefits of treating *T. cruzi*-infected

647   women before pregnancy have been described by several smaller studies [23–26].

648   Hopefully BETTY´s outcome will serve to enforce treatment administration to all child-

649   bearing age women as soon as possible.

650

651   **Conclusion.**

652   Increasing the awareness on the prevalence and health impact of Chagas disease

653   among patients, health practitioners and political health authorities may eventually

654   translate to enhanced population-based diagnostic screening and treatment

655   interventions. The tools needed to facilitate this activity are being tested currently in the

656   field and incorporate more practical and point-of-care diagnostics, new drugs regimens,

657   and the standardization of daily clinical care routines. In addition, efforts to obtain

658   biomarkers of disease prognosis and early assessment of treatment are also being

659   pursued and will probably yield results soon.

660   Upon failure of azoles, the majority of presently ongoing Chagas disease clinical

661   trials either evaluate alternative regimens of current drugs or other chemical entities

662   distinct from azoles (e.g., fexinidazole, amiodarone) with the aim to identify dosages

663   with lower toxicity and at least equal efficacies compared to present chemotherapy with

664   either benznidazole or nifurtimox. There is certain optimism on that a new treatment for

665   Chagas disease can be scheduled in the next few years. Further complementing the new

666   anti-parasitic drugs is a new therapeutic biologic, a vaccine, now advancing to the

667   clinic. However, access to these new drugs and innovations will require enhanced

668   policies and advocacy activities. In parallel, it will be essential to shape and disseminate

669   pharmacovigilance protocols so that the drugs performance can be closely monitored,

670   and patients´ and healthcare providers´ confidence on these therapies is promoted and

671   maintained.

672   The functional deployment of counter-reference circuits fully integrated in the

673   national health services will be required to scale up the attention to Chagas disease

674   patients. In this regards, improved coordination between vector control authorities and

20

675   sanitary authorities needs strengthening in those regions with active vector transmission

676   of the infection. Widespread access to diagnosis and treatment will not yield the desired

677   outcome unless chances to get re-infected are minimized or eliminated. This approach

678   also requires maintaining blood screening and programs to stop congenital transmission.

679   An improved maternal diagnosis and treatment protocol would in itself reduce

680   congenital transmission.

681   Despite recently achieved advancements, Chagas disease management and

682   control is still a huge challenge. Therefore, to succeed in this matter it will be

683   paramount the continued involvement of key actors, including patients associations,

684   health authorities at regional and national levels, governmental and non-governmental

685   institutions, basic and clinical researchers, and of course financial partners.

686

Expert Opinion.

687

688   A huge drawback in the management of Chagas disease has traditionally been

689   the lack of awareness of the disease and its impact by both health professionals and the

690   patients themselves, as well as by governmental institutions with the power to dictate

691   health policies. However, Chagas disease awareness is gradually increasing, so that

692   efforts to combat this neglected tropical disease now need to shift in order to address its

693   often insidious onset and silent clinical progression. These features currently complicate

694   the access to timely diagnosis and treatment, which is also ballasted by the very limited

695   resources available for research and development of improved treatment and disease

696   prevention methodologies.

697   After so many years of neglecting Chagas disease, new efforts at R&D have the

698   potential for high returns on investment. However, the R&D needs for Chagas disease

699   are pervasive and span requirements for both basic and applied research, as well as new

700   drugs, diagnostics and vaccines. With the ultimate goal of controlling the disease in

701   endemic and non-endemic regions, the consequences of widening our understanding on

702   Chagas disease and the pathogen that causes it will have an impact on the lives of

703   millions of people. For instance, research on parasite-host interactions is needed to fully

704   comprehend the pathogenic processes that lead to the life-threatening symptomatology

705   characteristic of chronic *T. cruzi* infections. Furthermore, considering that in the

706   absence of treatment ~30% of those chronically infected will develop cardiac and/or

707   digestive tract disruptions, studies on both parasite and host genomics (and other omics)

708   are required to determine the key factors leading to the development of pathogenesis.

21

709 Deeper understanding of the parasite biology and of its interactions with the host is
710 fundamental for the discovery of safer drugs or vaccines. Another challenge is the
711 dearth of public policies and advocacy that so far has mostly failed to attract requisite
712 funding.

713 　　Currently the most urgent needs include an expansion in clinical studies to test
714 an enlarged portfolio of new drugs, together with improved biomarkers to monitor
715 disease progress. There is also urgency for inexpensive and accessible point-of-care
716 diagnostics, especially for mass screenings as well as for the early assessment of
717 treatment responses. Their availability will widen access to treatment because they
718 would introduce a more accurate picture of the disease epidemiology, as well as the
719 ability to acknowledge cure upon treatment.

720

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Table 1. List of the most relevant anti-*T. cruzi* clinical trials recently completed.

Name	NCT number[1]	Drug tested	No. Patients	Outcome[2]	Ref.
CHAGASAZOL	01162967	POS	78	>80% (POS) 38.4% (BNZ)	[77]
STOP CHAGAS	01377480	POS POS-BNZ	120	>86% (POS) 14.3% (BNZ) 20% (POS+BNZ)	[78]
E1224	01489228	E1224	231	≥81% (E1224) 18% (BNZ)	[30]
BENEFIT	00123916	BNZ	2854 (1896)[3]	44.6% (BNZ)[4]	[46]

[1]Clinical trial identification number (check it out at https://clinicaltrials.gov).
[2]Study outcome shown as treatment failure measured by PCR; STOP CHAGAS entry also includes the failure rate in the POS+BNZ group.
[3,4]Number in parenthesis stands for the number of patients with a PCR result at baseline of which 60.5% were positive. The outcome shown indicates the % of initially PCR positive patients who were reported PCR positive again at two years.

Table 2. List of currently ongoing clinical trials of anti-*T. cruzi* drugs.

Name	NCT number[1]	Drug tested	Study type	No. Patients (estimated)	Promoter
-	03350295	NFX	Phase 1	48	Bayer
-	03334838	NFX	Phase 1	36	Bayer
MULTIBENZ	03191162	BNZ	Phase 2	240	Hospital Vall d´Hebron (Spain)
BENDITA	03378661	BNZ and E1224	Phase 2	210	DNDi
- -	02498782 03587766	FEXI	Phase 2	140 45	DNDi
EQUITY	02369978	NFX and BNZ	Phase 2-3	500	Autonomous University of Bucaramanga (Colombia)
ATTACH	03193749	AMD	Phase 3	200	Fundación Cardioinfantil - Instituto de Cardiología de Bogotá (Colombia)
CHICO	02625974	NFX	Phase 3	330	Bayer
BETTY	03672487	BNZ	Phase 3	600	Tulane University (USA)

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