

Regional Review

History, Current Issues and Future of the Brazilian Network for Attending and Studying *Trypanosoma cruzi*/HIV Coinfection

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Abstract

Introduction: In countries with endemic Chagas disease, coinfection involving *Trypanosoma cruzi* and HIV is expected to become more frequent. There is a clear need to structure a comprehensive care network aimed at dealing with this situation, with mobilization going from primary care to care at the highest level of technological complexity. The objective of this study was to describe the Brazilian response to the challenges of Chagas disease: the history, current issues, and future of the Brazilian Network for attending and studying *T. cruzi*/HIV coinfection.

Methodology: This descriptive study reviewed technical documents relating to the basis and structuring process of the Brazilian network for attending and studying *T. cruzi*/HIV coinfection.

Results: The process of setting up the network was marked by technical and political debates in technical-scientific meetings going back to the 1990s. This process made it possible to expand and focus on different aspects of comprehensive care for Chagas disease in Brazil, regardless of the associated immunosuppressive conditions. These meetings produced a structure of national technical guidelines and standards, health care and research protocols and research priorities, along with mobilization and awareness-raising among HIV/AIDS reference centers regarding occurrences of coinfection.

Conclusions: The creation of the Brazilian network was a milestone for the country in terms of integration of control programs, with the reference point of quality of care and comprehensiveness. The possibility of extending this network to form a Latin American network is seen as a strategy for dealing more effectively with this condition.

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Introduction

In 1908, Carlos Ribeiro Justiniano das Chagas characterized American trypanosomiasis (Chagas disease) by describing its etiological agent, vector, hosts, and animal reservoirs, and was the first to report a human case of the disease [1]. The acute-stage clinical condition (“a new morbid entity among humans”) was described in 1911 [2], while the chronic cardiac form was described a few years later, in 1916 [3]. However, it was only in the 1960s that Latin American institutions demonstrated that the causing agent *Trypanosoma cruzi* might behave as an opportunist pathogen in patients with natural or induced immunosuppression. The cases described included patients with hematological neoplasm such as leukemia and lymphomas (generally treated by means of antineoplastic chemotherapy and

corticotherapy) and patients who had undergone kidney, heart, and bone marrow transplantation, with prolonged use of immunosuppressants to control graft rejection [4]. Despite the clinical relevance of this event, the true epidemiological dimension is unknown. However, this event is recognized as relatively rare [4].

The first record in the literature of AIDS patients with reactivation of Chagas disease was made by Del Castillo *et al.* in 1990 [5]. One case was presented earlier at a congress but only published later on, by Gluckstein *et al.* in 1992 [6]. Interestingly, this first case of reactivation was documented in an AIDS patient in the United States. Subsequently, cases were diagnosed in other countries, mostly in Brazil and Argentina [4,8-10,13]. Since then, there have been several reports from Brazil on cases with severe

clinical expression of Chagas disease reactivation in patients with HIV/*T. cruzi* coinfection at an advanced stage of immunodeficiency [4,11-21].

In a systematic review covering literature up to March 2010, only 267 cases were found to have been published, in periodicals indexed in different health-related databases [7]. In fact, the real frequency of reactivation is not fully known and there are different descriptions of this event in the literature [9]. However, it is recognized that the extent of reactivation could be even greater than that associated with other forms of immunosuppression [4,7].

Reactivation of Chagas disease in coinfecting HIV/*T. cruzi* patients was estimated to occur in approximately 20% of patients in a prospective study [13,14]. As a consequence, coinfecting patients should be prospectively monitored to detect increasing level of parasitaemia. Therefore, even though this rate could be overestimated because it was observed in a major referral center, it shows the need for careful monitoring of HIV-infected patients with *T. cruzi* infection. This prospective study included patients both before the era of highly active antiretroviral therapy (HAART) and since its introduction [13-14]. In most cases, reactivation comprised meningoencephalitis and/or myocarditis.

The great challenge is to predict the proportion of individuals presenting natural or induced immunosuppression that will reactivate Chagas disease over time, given that this is currently unknown [4-9]. These questions also arise for other causes of immunosuppression, which present natural history in proportion to the impairment of cellular immunity in these different clinical conditions.

The scenario of increasing life expectancy among populations of all regions of Brazil [22], together with the estimated prevalence of two to three million people infected with *T. cruzi* [23], leads to the possibility and challenge of occurrences of comorbidity and coinfections. The epidemiological situation regarding AIDS needs to be highlighted: up to June 2009, 544,846 cases had been notified in Brazil, and strategic studies have estimated that around 630,000 individuals are infected with HIV [24].

In Brazil, a recent systematic review estimated, on the basis of the prevalence of *T. cruzi* infection in HIV-infected patients and more than 900,000 HIV-infected people in this country, that about 5,000-20,000 HIV/*T. cruzi* infected patients were under risk of Chagas disease reactivation [7].

In this country, reactivation of Chagas disease has been considered a condition defining AIDS for different reasons: 1) high case fatality rate, reaching 100%, without an early intervention with specific therapy with benznidazole; 2) changes in the natural history of Chagas disease and HIV infection due to the severe manifestation of meningoencephalitis and myocarditis; 3) modification of the response to the treatment with recurrence and therapeutic failure; 4) association with CD4 T cells lower than 200/mm³ in the majority of the cases [9,10].

There is therefore a clear need to structure a comprehensive care network aimed at dealing with this situation in Chagas-endemic countries, with mobilization from primary care to care at the highest level of technological complexity.

The present paper aims at describing the historical perspective, current, and future issues relating to the experience of constructing the National Network for attending and studying *T. cruzi*/HIV coinfection, as the Brazilian response to the new challenges of Chagas disease since the control of the most important vector *Triatoma infestans*, in 2006 [9].

Methodology

We reviewed technical documents related to the basis and structuring process of the Brazilian network for attending and studying *T. cruzi* /HIV coinfection. With its establishment, the network began to systematically organize technical discussions at least twice a year during the annual meetings of the *Sociedade Brasileira de Medicina Tropical* (Brazilian Society of Tropical Medicine) (1st semester) and the Annual Meeting of Applied Research in Chagas Disease and Leishmaniasis (2nd semester). Sometimes, extraordinary meetings occurred when new challenges needed decisions.

All reports from technical meetings of this network were reviewed, along with reports from meetings that shaped its construction and national recognition. Furthermore, the future challenges and perspectives are presented, with a view to consolidating the network not only in Brazil but also throughout endemic and non-endemic countries.

Results

Historical background

Since the Brazilian Ministry of Health revised the definition of AIDS cases in 1992, researchers and technical experts have officially indicated from evidence in the national and international scientific

literature that certain infectious and parasitic processes of endemic nature could present opportunistic behavior in individuals with HIV infection at an advanced stage [25].

During the 10th Annual Meeting of Applied Research on Chagas Disease, in Uberaba, Minas Gerais State, in 1994, this discussion was resumed because of the increasing frequency of reports of this nature in the literature, which were also being made in relation to other situations of immunosuppression. The use of the term “reactivation” to indicate the form of Chagas disease expressed under these conditions was recommended [26].

Reactivation of Chagas disease was defined by the identification of trypomastigotes in the peripheral blood or biological fluids or by direct microscopy and/or by the presence of inflammatory infiltrate similar to the acute phase of the disease and the presence of multiple amastigotes. Most common manifestations of reactivation of Chagas disease in HIV-infected patients were reported as meningoencephalitis and myocarditis or meningoencephalitis associated with myocarditis. A few reports registered the involvement of the digestive tract, uterus and pericardium, as well as erythema nodosum and oligosymptomatic cases with febrile illness and phagocytic mononuclear system involvement [9,10,26].

At a meeting held in São Luís, Maranhão State, in 2000, during the Congress of the Brazilian Society of Tropical Medicine, a group of specialists drafted recommendations relating to coinfection with *T. cruzi* and HIV. These recommendations included: compulsory notification of patients presenting Chagas disease reactivation; establishment of criteria for Chagas disease reactivation and definition of such reactivation as a defining condition for AIDS; creation of a work group for establishing a national network for studies on coinfection and reactivation; compilation of a manual for clinical and laboratory approaches for reactivation; and organization of a national network for coinfection-specific blood monitoring. This meeting became an important reference point for all following discussions.

During meetings of the Advisory Epidemiological Committee of the National STD/AIDS Program in 2003 to revise the definition of AIDS cases in Brazil based on the scientific evidence available, it was decided to include Chagas disease reactivation. Subsequently, in January 2004, this condition became officially recognized as a defining condition for AIDS. This important decision

required a response from the professionals within the care network of the Sistema Único de Saúde -SUS [National Unified Health System] [27].

The importance of this initiative by the Brazilian Ministry of Health needs to be emphasized. It had immediate international repercussions and, at a consultancy meeting on clinical staging of HIV infection and AIDS case definitions for the purposes of epidemiological surveillance organized by the World Health Organization [WHO] and the Pan-American Health Organization [PAHO], in Washington [United States] in October 2005, it was recommended that “...national cohorts or other databases should be used to evaluate whether additional conditions [for defining AIDS] could be included, while currently the only additional condition proposed and accepted at this meeting is Chagas disease reactivation” [28].

In meetings and workshops in 2004 and 2005, important issues that would serve as the basis for forming the network were defined. A workshop on “Reference centers for Chagas disease and research priorities for investigating questions of care for Chagas disease patients”, at the 20th Annual Applied Research Meeting on Chagas Disease and Leishmaniasis, provided the first forum for joint participation by representatives from the Brazilian Ministry of Health’s National Programs for both Chagas disease and STD/AIDS control. General issues and challenges relating to the care network for people living with Chagas disease, in addition to the question of organizing the care network and the need for structuring the Brazilian Consensus on Chagas disease as a strategic technical foundation were raised. One of the questions to be considered was the association between Chagas disease and AIDS, which had become a demand on the National Epidemiological Surveillance System [9,27-29].

A further series of meetings was held, culminating in a meeting in Brasília in June 2005, at which researchers and clinicians were brought together to prepare consensus guidelines. These guidelines were published within the same year and formed a reference point [28]. During this process in 2005, the idea of forming a national network for attending and studying *T. cruzi*/HIV coinfection was presented as a Brazilian response to the challenge of providing comprehensive care and developing research within this field that had been posed earlier.

Recommendations of the National Network for Attending and Studying T. cruzi/HIV Coinfection

Since the first meeting of the network, which was held during the 22nd Annual Meeting of Applied Research on Chagas Disease and Leishmaniasis, in October 2006 [31], six further formal technical-scientific meetings have been held. These meetings included participation by health care professionals and key researchers in Brazil within the field of Chagas disease and HIV/AIDS infection, and by representatives from different sectors within the Ministry of Health, such as care provision, epidemiological surveillance, sanitary surveillance (including blood monitoring) and health education [31-36].

Since the beginning, the central proposal for the network was supposed to be of a broader scope, encompassing not only the organizational issues relating to service networks within the country's healthcare system, but also linking the already existing international groups in this field, thereby stimulating new groups within an international network [31,32].

The strategic missions of the network were defined as follows: 1) to contribute toward structuring the comprehensive care network for people living with Chagas disease in its different forms, in association with states of immunosuppression; 2) to contribute toward developing actions of this network through evidence obtained from scientific research, conducted in accordance with ethical standards, including clinical, epidemiological, immunological and laboratory factors; 3) to contribute toward structuring a continuing education network for health care professionals involved in management of Chagas disease in its different forms, in association with states of immunosuppression; 4) to contribute toward identifying priorities for research in Brazil on this subject.

From a technical point of view, important researchers within this field in Brazil have been mobilized with the aim of systematizing the information, with a view to structuring clinical protocols. Consequently, standardized instruments using follow-up protocols structured by the network have been tested. These have the function of supporting clinical and laboratory data records in the medical files, and simplified protocols for key information aimed at monitoring this clinical event are at the test stage.

The proposed criteria defined for identifying health care service networks that could make up the national network are as follows: attendance of Chagas disease cases; attendance of coinfection cases (HIV/*T. cruzi*); attendance of Chagas disease reactivation cases (due to AIDS or other forms of immunosuppression); attendance of cases of HIV infection and/or AIDS at clinics close to services providing Chagas disease management.

According to data from the National Program for Chagas disease control presented in 2010, 38 reference centers in Brazil were registered within the National Network for Attending and Studying HIV/*T. cruzi* coinfection. Most of these were reference centers for managing HIV infection and/or Chagas disease. More than 166 cases of *T. cruzi*/HIV coinfection were registered by means of the specific clinical-epidemiological instrument devised by professionals within the network. Out of this total, around 26 cases consisted of Chagas disease reactivation that were notified by the referral centers of the Universities of São Paulo, Triângulo Mineiro, Campinas, Brasília, Porto Alegre, and the Instituto Evandro Chagas (Fundação Oswaldo Cruz).

The network has defined the following potential and priority lines of research: 1) retrospective study to determine the prevalence of *T. cruzi*/HIV coinfection from 1980 onward; 2) retrospective study to determine the prevalence of Chagas disease reactivation in cases with immunosuppression from 1980 onward; 3) seroprevalence of *T. cruzi*/HIV coinfection in clinics that perform serological screening on blood donor candidates; 4) building up a cohort of new cases of *T. cruzi*/HIV coinfection from 2007 onward, with definition of a more specific follow-up protocol [to evaluate its application in certain centers or in all centers in which such cases are identified]; 5) studies to define predictive factors for disease reactivation; 6) studies to estimate the incidence of disease reactivation; 7) studies to estimate the percentage recurrence among patients who were treated during parasitological remission; 8) studies to evaluate the efficacy of secondary prophylaxis and its relationship with CD4+ T lymphocyte levels, HIV viral load and HAART therapy; 9) studies to evaluate the potential use of primary prophylaxis among coinfecting patients with high levels of parasitaemia and/or persistent parasitaemia; 10) studies to estimate the congenital transmission rate among the fetuses of coinfecting pregnant women and the morbidity-mortality rate among newborns; 11) studies on the genotypic

characteristics of subpopulations of the parasite at the time of reactivation; 12) studies on the influence of the HIV-1 and HIV-2 subtypes on reactivation, and their interaction with different subpopulations of *T. cruzi*; 13) study on the physiopathogenesis and immunopathogenesis of reactivation; 14) study on the validation of molecular methods for quantifying parasitaemia as a prognostic factor for reactivation [34,35].

Discussion

Over the century since the first studies by Carlos Chagas, there have been advances in combating *T. cruzi* transmission throughout endemic countries [23,37,38] as a result of vector and transfusion control measures developed in all parts of endemic countries, along with the social transformations created by the urbanization process in large proportions, thereby giving rise to a significant reduction in the incidence of the disease [39]. However, these results emphasize the need for sustainable actions, with the further need to consolidate a surveillance stage, in conjunction with appropriate care for the needs of millions of infected individuals [40-41]. In addition to the determinants of biological or ecological nature, those of economic and social nature are fundamental to Chagas disease [39]. Although Chagas disease incidence is decreasing in many endemic countries, trypanosomiasis is also an imported disease in high income countries, due to the immigration of infected people from endemic areas.

The initiative to form the National Network for Attending and Studying *T. cruzi*/HIV Coinfection is a strategic action, not only for Brazil but also for the entire region in which Chagas disease is endemic. This initiative is fully justified by the specific nature of this disease in relation to Latin America, in which Brazil is one of the areas of greatest epidemiological importance; the imprecision of the estimates regarding the numbers of people living with Chagas disease; the increasing prevalence of HIV/AIDS infection in Brazil in areas of high endemicity of Chagas disease; the many gaps in the knowledge of this topic, in epidemiological, clinical, anatomopathological, immunological and laboratory terms etc.; and the severity of clinical conditions of Chagas disease reactivation.

The gaps that exist in aspects of the full care provision for individuals with *T. cruzi* and HIV coinfection introduce the need for a network-integrated response in Brazil, with repercussions for

all other endemic areas because of the flow of migrants. The technical debates over these five years of constructing the network grounded in the technical recommendations have been published in technical manuals and scientific papers. Moreover, this strategic initiative can be considered to be a movement towards opening people's eyes to care provision for Chagas disease, and not just in endemic countries, thus bringing back its visibility and channels for publicizing the status of disease control and funding.

It has been estimated that there are approximately 12 to 15 million infected individuals worldwide, and Brazil is believed to account for two to three million individuals with Chagas disease [23]. These statistics make it necessary to take a longitudinal and integrated approach to this chronic condition [42]. In addition, there are high morbidity and mortality rates in many regions that have been studied, particularly among socially marginalized populations of rural origin, with a lack of options for efficacious and effective specific treatment [37-38].

Despite this context, Chagas is still a neglected tropical disease of large magnitude in endemic areas. Moreover, it even extends to non-endemic countries, given the migratory dynamics of human populations infected by *T. cruzi* who become the source of infection in blood banks, organ transplants, and congenital transmission [43-44]. Setting up coinfection networks in different countries and their states presents more possibilities for combating it and discussing the real context of control, including all modalities of immunosuppression.

There have been suggestions that excessive optimism from the advances achieved through control has given rise to increased indifference toward the disease and its control among health authorities. Loss of visibility and priority are negative signs of this attitude [40]. Emphasis on associations with HIV infection and AIDS may represent a strategy for boosting the mobilization toward studies and actions relating to Chagas disease. Most of these patients presented chronic Chagas disease, generally in the indeterminate form, and developed clinical reactivation of the disease through the presence of immunosuppression. Conditions of acute transformation of *T. cruzi* infection have been found to have repercussions of greater severity on the organism than those usually observed in the acute forms resulting from transmission by triatomine bugs or from transfusion, especially the meningeal-encephalic and cardiac forms. Because of this clinical

particularity, it has become an event indicative of AIDS in Brazil [27-28,45]

Since its creation in 2006, inclusion of Latin American countries and other countries around the world has been considered a strategic objective to internationalize this network for attending and studying *T. cruzi*/HIV coinfection [46]. At a meeting of the Pan-American Health Organization in Belém (Pará State, Brazil) in March 2009, the network was presented officially to the member countries, which were invited to participate fully in an International Network for Attending and Studying *T. cruzi*/HIV coinfection and other immunosuppression conditions.

We consider that information and communication strategies are key points for developing the network and expanding its scope and the spaces occupied by its members within the national and international scientific community and in relation to the Ministry of Health [46]. Technical legitimacy constitutes a strong point of the network. From this perspective, one of the issues to be faced is the shaping of the service network, which necessarily involves primary care. For this, one of the current action points of the network is to boost continuing education actions in all forums that can be followed up.

Conclusion

Despite the advances towards the control of Chagas disease in Brazil and other endemic countries, *T. cruzi* infection in immunocompromised patients represents a public health problem, especially in association with HIV. Despite the small number of new Chagas cases reported, it is estimated that thousands of people in endemic and non-endemic areas are under risk for reactivation of Chagas disease. The structuring of the Brazilian network represents an organized way to stimulate specific initiatives of research and health education. The challenges associated with management and epidemiological surveillance of Chagas disease in cases with associated immunosuppression reinforce the need for organized and evidence-based responses.

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