Review Article/Artigo de Revisão

Co-infection *Trypanosoma cruzi*/HIV: systematic review (1980 - 2010)

Coinfecção *Trypanosoma cruzi*/HIV: revisão sistemática (1980 - 2010)

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ABSTRACT

Introduction: The co-infection *Trypanosoma cruzi*/HIV has been described as a clinical event of great relevance. The objective of this study was to describe clinical and epidemiological aspects published in literature. **Methods:** It is a systematic review of a descriptive nature from the databases Medline, Lilacs, SciELO, Scopus, from 1980 to 2010. **Results:** There were 83 articles (2.8 articles/year) with a total of 291 cases. The co-infection was described in 1980 and this situation has become the defining AIDS clinical event in Brazil. This is the country with the highest number of publication (51.8%) followed by Argentina (27.7%). The majority of cases are amongst adult men (65.3%) native or from endemic regions with serological diagnosis in the chronic stage (97.9%) and indeterminate form (50.8%). Both diseases follow the normal course, but in 41% the reactivation of the Chagas disease occurs. The most severe form is the meningoencephalitis, with 100% of mortality without specific and early treatment of the *T. cruzi*. The medication of choice was the benznidazole on doses and duration normally used for the acute phase. The high parasitemia detected by direct or indirect quantitative methods indicated reactivation and its elevation is the most important predictive factor. The lower survival rate was related to the reactivation of the Chagas disease and the natural complications of both diseases. The role of the antiretroviral treatment on the co-infection cannot yet be defined by the knowledge currently existent. **Conclusions:** Despite the relevance of this clinical event there are still gaps to be filled.

Keywords: Chagas disease. *Trypanosoma cruzi*. HIV. AIDS. Reactivation. Immunodeficiency.

RESUMO

Introdução: A coinfecção *Trypanosoma cruzi*/HIV vem sendo sistematicamente descrita como um evento clínico de grande relevância. O objetivo deste estudo foi descrever aspectos clínicos e epidemiológicos publicados na literatura científica. **Métodos:** Trata-se de revisão sistemática, de natureza descritiva, a partir da busca nas bases Medline, Lilacs, SciELO, Scopus, de 1980 a 2010. **Resultados:** Identificou-se 83 artigos (2,8 artigos/ano), com um total de 291 casos registrados. A coinfecção foi descrita em 1980 e, no Brasil, tornou-se evento clínico definidor de AIDS. Este é o país com maior número de publicações (51,8%), seguido pela Argentina (27,7%). A maioria dos casos é de homens adultos (65,3%), naturais ou procedentes de regiões endêmicas, com diagnóstico sorológico, na fase crônica (97,9%) e na forma indeterminada (50,8%). As duas doenças evoluem naturalmente, mas em 41% dos casos ocorreu reativação da doença de Chagas. A forma mais grave é a meningoencefalite, com 100% de letalidade nos casos sem tratamento específico e precoce do *T. cruzi*. O medicamento indicado foi benznidazole, nas doses e duração utilizadas na fase aguda em imunocompetentes. O diagnóstico da reativação foi comprovado por alta parasitemia, detectada por métodos diretos ou indiretos quantitativos, sendo a sua elevação considerada fator preditivo para reativação. A menor sobrevida na coinfecção esteve relacionada à reativação da doença de Chagas e às complicações naturais de ambas as doenças. O papel do tratamento antirretroviral sobre a evolução da coinfecção ainda não pode ser definido pelo conhecimento existente. **Conclusões:** Apesar da relevância deste evento clínico, ainda persistem lacunas a serem preenchidas.

Palavras-chaves: Doença de Chagas. *Trypanosoma cruzi*. HIV. AIDS. Reativação. Imunodeficiência.

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INTRODUCTION

The Chagas disease stands as a relevant chronic infectious process from the public health[1] point of view. It is estimated that 14 million people are infected and that 60 million are at risk of infection whereby in Brazil 1.8 to 2.4 million individuals are in the chronic stage of the disease, 1/3 of them are in the cardiac and digestive form, generating a high morbimortality[2]. Despite its relevance there are still major challenges in understanding various aspects of the disease[3,4]. Due to the vectorial transmission control, especially of the main insect *Triatoma infestans,* combined with the transfusional transmission control, the acute phase of the disease is becoming increasingly rare[5], determining that the attention is focused on the population with chronic infection, as well as other changes occurring in the epidemiology of the Chagas disease. This fact is based on increased survival of Chagas disease patients, urbanization of the population amongst other situations and consequently a higher probability of comorbidities, infectious or not[6].

Therefore, with the emergence of the human immunodeficiency virus (HIV) and the development of acquired immunodeficiency syndrome (AIDS), the co-infection with the *Trypanosoma cruzi (T. cruzi)* began to be described[7]. As in other infectious diseases, the *T. cruzi* behaves, potentially, as an opportunist microorganism in subjects with immunosuppression of any nature, among them, any generated by HIV, which is predominant in urban areas[8]. In Brazil, the reactivation of the Chagas disease in people with the co-infection was considered as an AIDS defining condition in 2003; therefore, in 2006, the Brazilian Network of Attention and Studies on *Trypanosoma cruzi*/HIV Co-infection[9,10] was established. Although the first case of this association of diseases was reported in the 1980s[11,12], the frequency that it occurs, as well as the reactivation which is clinical and laboratorial profile of the subject with a co-infection, the specific treatment for the *T. cruzi* and antiretroviral and its efficiency, the quantification of survival rates and mortality of this individuals amongst other items are questions that still demand

specific research in order to be clarified. This revision aims to verify the frequency of the records of the co-infection *T. cruzi*/HIV and describe systematically the main clinical and epidemiological aspects found in the literature on the period from 1980 to 2010.

METHODS

The following databases were used for the research: MEDLINE, through PubMed (U.S. National Library of Medicine), Latin American and Caribbean Center on Health Sciences Information (BIREME), Literature in the Health Sciences in Latin America and the Caribbean (LILACS), Scientific Electronic Library (SciELO), SciVerse Scopus and The Library Cochrane, in the period between 1980 and 2010. The terms used as keywords were: 'Chagas disease and HIV and AIDS/*doença de Chagas e* HIV *e* AIDS/Tripanosomiasis and HIV and AIDS/*Tripanosomiase e* HIV *e* AIDS', in order to no lose the articles written in English, Portuguese and Spanish. The studies were recovered in full with no previous selection in terms of the type of the study. Additionally, in order to exclude repeated reports of casuistic or cases based on authors, information about cases previously published and institutions responsible for them, it was decided to consider the more complete article. Only research published in scientific journals were analyzed and abstracts of annals of scientific events or personal information were not considered.

The following data were collected in the research sources: intersection among the used sources, number of published articles during the period, distribution of articles by decade and years in a period, complete citation, country where the research was conducted and type of article. From the article retrieved, the following data were obtained: number of cases, age, gender, stages and clinical forms of the Chagas disease, performance and type of serology for the diagnosis of Chagas disease, *T. cruzi* research realized and method used (xenodiagnosis, blood culture, peripheral blood, liquor and other fluids, histopathology and molecular biology), presence of reactivation of Chagas disease and its location (central nervous system, heart, other organs), if there was specific treatment for *T. cruzi*, medication used, dosage and period of use, survival rate of the patients, imaging exams to diagnose lesions (tomography or MRI), performance and type of antiretroviral treatment, occurrence of death and the necropsy. The analyzed data were presented on a descriptive way.

RESULTS

There were found and recovered 83 articles in the 30 year period researched, corresponding to 2.7 articles per year. Thirty-six (50.7%) articles were found in just one of the databases researched, being PubMed the one with highest number of articles with a single citation (15.5%). Of all the articles, only three were cited in all four databases queried.

Since the first citation took place in 1988[11], there was a 22 year period in which there were publications about the topic; therefore, corresponding to an average of 3.8 articles/year. During the 1980s only two (2.4%) articles were published[11,12]. During the 1990s, there were 37 (44.6%)[13-49] published and during the 2000s, 44 (53%)[53-93], with 1998 having the highest number at 10 (14.1%) articles published. Brazil was the country with the highest number of publications on the topic, with 43 (51.8%) articles, followed by Argentina with 23 (27.7%). This was followed by the United States of America with 7 (8.4%), Chile with 4 (4.8%), Spain with 2 (2.4%) and Jamaica, Germany, Colombia and Switzerland with one (1.2%) citation each. In terms of the types of articles, 63 (75.9%) were clinical studies, 1 (1.2%) related to the anatomical pathology and 1 (1.2%) experimental. In regards to the design of the study, 50 (60.2%) were presented as case reports and 14 (16.9%) as a series of cases. In 13 (15.7%), the form of publication was a topic review, and 3 (3.6%) were letters to the editor and 2 (2.4%) editorials.

The number of co-infected cases obtained from the researched literature was 291, which corresponds to 9.7 cases/year in average. There were 222 (76.2%) cases from Brazil, followed by Argentina with 56 (19.2%) cases, United States of America with 5 (1.7%) cases, Chile with 5 (1.7%) cases and Spain with 3 (1%) cases. It was possible to verify the age in 115 (39.5%) cases ranging between 19 to 66 years, with an average of 37.3 years. There was, however, one record of congenital Chagas disease in a two month old newborn, not being considered to calculate the average. The studies reporting only one case of the co-infection accounted for 50 articles, and the age average of the individuals was of 34.9 years. In regards to the distribution by gender, it was possible to obtain this information in 190 (65.3%) cases, with 126 (66,3%) male case and 64 (33.6%) female cases **(Table 1)**.

The acute phase of the Chagas disease was reported in only six (2%) cases, the remaining (97.9%) were considered to be in the chronic phase, distributed in the following clinical forms of 118 cases: 60 (50.8%) undetermined cases, 44 (37.3%) cardiac cases, 6 (5.1%) digestive cases and 8 (6.8%) mixed cases **(Table 2)**.

The serology for the diagnosis of Chagas disease was informed in 185 (63.6%) cases, 175 (94.6%) positive. The techniques used were enzyme-linked immunoabsorbent assay (ELISA), immunofluorescence and indirect hemagglutination and complement fixation. Among the methods for identification of the parasite, the

TABLE 1 - Number of cases, age and gender of individuals with the co-infection *T. cruzi*/HIV and distribution by country in the period from 1980 to 2010.

	Cases				Cases	
Country	**n**	**%**	**Age (years)**	**Gender**	**n**	**%**
Brazil	222	76.2	minimum 19	male	126	66.3
Argentina	56	19.2		female	64	33.7
USA	5	1.7	maximum 66	not informed	101	34.7
Chile	5	1.7				
Spain	3	1.0	average 37.3			
Total	**291**		**115 (39.5%)**		**190**	**65.3**

HIV: human immunodeficiency virus; **USA**: United States of America.

TABLE 2 - Phase and clinical forms of the Chagas disease in individuals with the co-infection *T. cruzi*/HIV and published in the period from 1980 to 2010.

	Cases	
Phase/form	**n**	**%**
Acute	6	2.0
Chronic	285	97.9
Undetermined	60	50.8
Cardiac	44	37.3
Digestive	6	5.1
Mixed	8	6.8
Not informed	173	59.5
Total	**291**	

HIV: human immunodeficiency virus.

direct research was performed in the peripheral blood in 92 (31.6%) cases with positivity in 51 (54.4%) and also in the liquor in 64 (22%) of the cases, with positivity in 50 (78.1%) cases and negativity in 14 (21.9%). On the other hand, in regards to the indirect methods for research of the *T. cruzi*, the xenodiagnosis was used in 104 (35.7%) cases with positivity in 97 (93.3%) of them, while the blood culture was used in 95 (32.6%) cases with positivity in 75 (78.9%) cases. The research by molecular biology utilizing the polymerase chain reaction (PCR) was reported in only 7 (2.4%) cases being that in four of them, the parasite was recognized from the study of the duodenal biopsy by occasion of a high digestive endoscopy. In addition to the duodenum, there was identification of the parasite in the skin in three (1%) cases, and one (0.3%) case each in the pericardium fluid, ascites, cervix and stomach. The histopathological evaluation was reported in 44 (15.1%) cases with parasite finding and inflammatory lesion suggesting Chagas disease, with 31 (70.4%) in the central nervous system, six (13.6%) in the myocardium, four (9%) in the duodenum, three (6.8%) cases in the skin and in the cervix and stomach were reported one (2.3%) case each.

There were 120 (41.2%) reported cases of reactivations of Chagas disease, 89 (74.2%) cases in the central nervous system, and 20 (16.7%) in the myocardium. Other places with reports of reactivation included the duodenum with four (3.3%) cases, skin with three (2.5%) and one (0.8%) in the cervix, peritoneum, pericardium, stomach and eye tissue **(Table 3)**.

TABLE 3 - Number of cases and places of reactivation of Chagas disease in individuals with the co-infection *T. cruzi*/HIV and published in the period from 1980 to 2010.

Places	Cases	
	n	%
Central nervous system	89	74.2
Heart	20	16.7
Others	11	9.2
Total	**120**	**41.2**

HIV: human immunodeficiency virus.

The count of CD4 + T cells was reported in 59 (20.3%) cases varying from 1 cell/mm^3 to 1,949 cells/mm^3, with an average of 340 cell/mm^3. In the reactivated cases, the count varied from 1 cell/mm^3 to 551 cells/mm^3, with an average of 98 cells/mm^3. In the cases where there was no reactivation, the count of CD4 + T cells varied from 44 cells/mm^3 to 1,949 cells/mm^3 with an average of 562 cells/mm^3 **(Table 4)**.

TABLE 4 - Number of CD4+ T Cells in individuals with the co-infection *T. cruzi*/HIV and published in the period from 1980 to 2010.

Number	CD4+ T cells	CD4+ T cells – non reactivation	CD4+ T cells – reactivation
Minimum	1 cell/mm^3	44 cells/mm^3	1 cell/mm^3
Maximum	1949 cells/mm^3	1949 cells/mm^3	551 cells/mm^3
Average	339,5 cells/mm^3	561,5 cells/mm^3	98,4 cells/mm^3

HIV: human immunodeficiency virus; **CD4:** cluster of differentiation 4.

The etiologic treatment of the infection by *T. cruzi* was reported in 100 (34.4%) cases, having the benznidazole being used in 87 (87%) cases, the nifurtimox in 14 (14%) cases, the fluconazole in three (3%), the itraconazole in two (2%) and the ketoconazole in two (2%) cases. The dosage used was 5mg/kg for the benznidazole and 7mg/kg for the nifurtimox, in a time period equal to immunocompetent individuals.

The minimum survival was one day to a maximum of 11 years, the average being 626 days. In the co-infected individuals with reactivation of Chagas disease, the survival rate ranged from one day to five years and five months, with an average of 10.6 months, and that the highest survival rate of reactivation in the central nervous system was five years and four months, and in the heart of five years. In the individuals where the reactivation did not happen, the survival rate varied from two months to 11 years, with an average of 2.8 years **(Table 5)**.

TABLE 5 - Survival in individuals with the co-infection *T. cruzi*/HIV and published in the period from 1980 to 2010.

Survival	General	Non-reactivation	Reactivation
Minimum	1 day	2 months	1 day
Maximum	11 years	11 years	5 years
Média	1,7 years	2,8 years	10,6 months

HIV: human immunodeficiency virus.

The computerized tomography was registered in 66 (22.7%) cases, evidencing pseudotumoral lesions in 59 (89.4%) cases, similar lesions to that found in toxoplasmosis in two (3%) cases and hydrocephalus, meningoencephalitis and calcifications in one (1.6%) case. In two cases, the brain tomography was reported as normal. The magnetic resonance was registered in 22 (7.6%) cases, the type of lesion being found in the pseudotumoral (100%).

The antiretroviral therapy was reported in 65 (22.3%) cases. In five cases, it was reported the use of highly active antiretroviral therapy (HAART).

Progression to death was reported in 86 (29.6%) cases, being that in 63 (73.3%) of them the reactivation of Chagas disease occurred. Amongst this cases, 56 (88.9%) happened in the central nervous system and 12 (19%) in the heart. The necropsy was performed in 25 (29.1%) cases.

DISCUSSION

This article represents the first systematic evidence of publications on the *T. cruzi* co-infection and HIV. From this analysis is reinforced that even though the co-infection Chagas disease/HIV has expanded its importance since the advent of AIDS in the 1980s[10,11], the subject has not been the object of systematic scientific-technical publications by what is shown in the number of articles published in the past 30 years. In this sense, combined with underreporting of this event, there are still gaps in terms of clinical and epidemiological aspects, comprising prevention, diagnosis, treatment and follow up. This observation is not only based on the low amount of articles, but also on the type of published studies, mostly case reports, often of single ones.

The other frequent kind or article found is the series of cases addressing the reactivation of Chagas disease in the central nervous system as a rare and unusual event since the brain is not a usual place for lesions in the course of the chronic evolution of this disease. The exception to these types of publication was the analysis of a series of cases from Brazilian authors[81,93] where the topic was discussed in a broad way with detailed description of cases of individuals with the co-infection, clinical and evolutive profile. Also, the majority of articles were published in Latin American countries, led by Brazil, reflecting the regional importance of Chagas disease as an endemic in this region. The lack of studies with a higher number of follow-up cases, with cohorts, as those that have been carried addressing ischemic cardiomyopathy, high blood pressure, diabetes and other clinical events so far hinders the understanding of the co-infection in many aspects.

In almost all the records, the topic is addressed from the clinical description of cases, antomopathological aspects and due to the particularities of the HIV infection the non occurrence of studies with laboratory animals. As expected, with the publication of the first articles about the co-infection, the topic became more explored as it occurred with the other diseases, mainly the infectious and neoplasic associated with HIV[11] infection. Over the last years, despite the higher number of publications about the co-infection, there were no modifications on the modality of the studies found. One of the aspects not yet completely recognized and of extreme relevance, refers to the frequency that the co-infection occurs. The approach used on this systematic review of the literature may reflect an underestimation of this event, since not all the cases can be published, or yet, are in different indexing databases of scientific-technical researches from the ones utilized in this study.

It is likely that other cases were reported in scientific events, such as congresses, meetings, dissertations in graduate programs or simply were not reported. However, the analysis only of the data published in journals, in the way it was done, brings more reliability to the interpretations. Therefore, as far as it was possible to revise the literature, for the first time the number of cases with the co-infection *T. cruzi* and HIV has been systematized worldwide with 291 subjects.

Brazil has a concentrated AIDS epidemic, considering that the prevalence rate of HIV infection is less than 1% in the general population and above 5% in population subgroups with higher risk to infection including, men who have sex with men, injectable drug users and sex workers. In 2004, it was estimated an overall prevalence of 0.6%[98]. Based on this estimate, the country had in 2009 approximately 642,601 infected people. On the other hand, as from the epidemiological surveillance based on the notification of cases of AIDS, from July 1980 to June 2010, were reported in the country 592,914 cases (adults and children). Regarding the Chagas disease, it is estimated the existence of approximately 2 million infected individuals[10,11].

In Brazil, in a service of macro-regional scope and reference to 50% of the cases of HIV/AIDS patients it was verified that the frequency of co-infection was of 1.3%[56,93]. Based on this study, for the total of individuals infected with HIV without AIDS[98], it is estimated the existence of approximately 8,354 people with the co-infection in Brazil. Considering the cases of AIDS, the country should have an additional number of 7,708 co-infection cases, totaling 16,062 cases. As of the 291 cases described around the world, 222 are in Brazil. It is very likely that this number is truly underestimated, with the majority of the cases not being reported or in a worst scenario, not diagnosed. In the Latin America, only Brazil, Argentina and Chile described cases. Following the same reasoning previously used for Brazil, there are 1.7 million individuals with HIV/AIDS in the Latin America[99], the estimate for the frequency of co-infection in this region would be of 21,420.

There is controversy regarding the first description of the co-infection. Argentinean authors[7] refer to as the first description of a case of Chagas disease in the central nervous system published in June 1990, mimicking a tumor in an individual with AIDS. However, in 1992, authors in the United States of America[18] published a case describing the Chagas disease as another cause of brain mass in AIDS patient, emphasizing this to be the first of co-infection since the Argentinean authors did not confirm the trypanosomiasis for not having performed culturing on brain fragments for the identification of *T. cruzi.* The controversy prompted the exchange of mail between the authors with justifications and addition of information, confirming that this is the first case of a person with acquired immunodeficiency and chagasic encephalitis. However, published on two occasions by Brazilian authors[12,13], prior to the controversy already mentioned, proven cases of the presence of *T. cruzi* in the liquor of individuals with HIV infection in which the denomination reactivation of Chagas disease had been used before. In none of these two studies, the Argentinean or the American[6,15], the Brazilian studies were cited. The fact that the articles were published in Brazilian journals and in Portuguese may justify their non citation. For the diagnostic of the co-infection, it is sufficient the concurrence of both diseases in the same individual, regardless of place of affection by the *T. cruzi* infection. The different locations of it within the organism only reflect the cosmopolitan distribution of the Protozoa. Thus the first description of the co-infection is of Brazilian authorship, as well as the cerebral damage by *T. cruzi* in this situation.

The age group in which co-infected individuals are found is broad, but the average age found shows that these are young adults for the most part. This reflects the variation of the epidemiology of the HIV/AIDS epidemic since its description in the 1980s[94]. The epidemiology of the Chagas disease also suffered changes in the last decades in view of the control of its main vector, *T. infestans*, the controlling of the transmission through transfusion, generating the aging of the infected population[1,10,11]. This reflected on the profile of the co-infected individual, since the description of the co-infection on a pediatric population was not registered with the exception of the cases of congenital infection in neonates from mother with the co-infection[29]. In this way, so far this population expresses more the behavior of the HIV/AIDS infection epidemic in relation to the age than that of the Chagasic endemic, and thereafter accompanying the aging tendency of the HIV infected individuals in view of the epidemiological changes in relation to the transmission mechanisms of the virus and in response to the HAART. The higher frequency of men amongst the co-infected individuals, as well as the age, reflects the epidemiological profile of the infection by HIV[94].

The almost total prevalence of co-infected individuals in the chronic phase of the Chagas disease (98%) reflects the control of the disease in its main means of transmission[11]. This is particularly true in Brazil, where the transmission of *T. cruzi* by *T. infestans* was considered interrupted since 2006 by the World Health Organization (WHO)/Pan American Health Organization (PAHO)[5]. Although the same wasn't observed in all Latin America, the higher amount of cases related by Brazilian studies must be responsible for the result found. Operational aspects of national health systems of different countries in terms of timely diagnosis of both infections certainly fall within this perspective[11]. The distribution of the cases on the different clinical forms of the chronic phase, predominantly of the indeterminate form, followed by the cardiopathy, digestive and mixed corresponds to the natural history of this phase of the Chagas disease[95]. Therefore, on the series of cases published in Brazil[81,93] the occurrence of the different clinical forms overlaps that found in this revision of all the cases, there being no report of any in the acute phase.

The diagnostic of the Chagas disease was serologic and followed the WHO[96] criteria, been used the methods most recently employed, such as the ELISA, indirect immunofluorescence and passive hemagglutination in the detection of antibodies for *T. cruzi.* Positivity was reported on the majority of the cases. However, the finding of 5.4% nonreactive serological proof may result in misdiagnosis and

should not be undervalued when the Chagas disease diagnostic seems likely by other methods. The immunological disorders involving the pathogenesis of the HIV infection, especially in the presence of AIDS, may be responsible for these non-reactive serological proofs in the presence of Chagas disease[97]. This way the finding of the parasite by direct or indirect methods is pointed as the sure diagnosis of Chagas disease, while the positive serology configures the safety diagnosis[12,13]. The xenodiagnosis was the most utilized indirect research method of *T. cruzi*, with high (93%) positivity, followed by the blood culture which showed lower (79%) positivity although high. It was not observed in all the reports uniformity on the indirect methods, although for the xenodiagnosis the Schenone[98] was the most used technique. The results however were positive or negative for most of the cases reported, showing that the analyses was conducted in a group of nymphs, making the examination of qualitative nature. As for the blood culture, although the mean of culture reported has been the LIT (liver infusion tryptose), the same kind of interpretation is subject to be made, since usually the amount of blood used for this purpose is one milliliter. Although both exams reflect an increased parasitemia when positive, along the qualitative lines it can be found in immunocompetent hosts on the natural course of the Chagas disease. More recently both exams have been receiving special care in order to make them quantitative. Therefore, 30ml of blood distributed in vials with five milliliters have been used for the *T. cruzi* culture, as well as the xenodiagnosis started to be analyzed quantitatively through the individual examination of the nymphs, obtaining the proportion of parasitized nymphs, as reported by Brazilian authors in a series of cases[81]. This way was possible to quantify the parasitemia and suggest a classification of very high when the parasites could be identified by microscopic examination of the peripheral blood, high when more than 20% of the utilized nymphs on the xenodiagnosis were infected and, low, when less than 20% of those were found parasitized by *T. cruzi*.

The molecular biology by means of the polymerase chain reaction technique, is already well studied in Chagas disese[101], but has not been a frequently utilized method for indirect research of *T. cruzi* in the presence of the co-infection with HIV/AIDS. However, it was described in two (0.7%) cases used for diagnostic confirmation in peripheral blood[92], and on the study of the parasite in duodenal biopsies in four co-infected individuals[51]. The samples were positive and in all of them were found nests of amastigote forms of *T. cruzi* on histological examination. This values the PCR method of the indirect study of the parasite in individuals with the co-infection. In only one case, the real time PCR technique was utilized as cure criteria in a case of reactivation of Chagas disease of long survival, serving as criteria to interrupt the etiologic treatment, once the result was negative[90]. Other authors utilized the PCR for lineage specifications of the parasite isolated by other methods[62,64,73].

The study of the parasite on a direct way took as reference, mainly, the peripheral blood and liquor. However, the utilized method was not specified in some articles[29,30,32,70]. Yet, the research between slide and cover slip of fresh material, thick smear with May-Grunwald-Giemsa coloration, Strout, microhematocrit and buffy-coat was reported in several studies in order to increase the sensitivity when verifying the presence of the protozoa[23,33,39,42,45,46,63,68,81], not having, however, in any of those reference to the superiority of this methods compared to the study of the parasite directly on fresh material. The peripheral blood was the site where the parasite was most searched, but the liquor was where the largest proportion of positivity on the *T. cruzi* research (78%) occurred, which shows that it is indispensable the use of this evaluation during the investigation of cerebral impairment in patients with the co-infection, considering the feasibility of the exam. The study on the liquor of co-infected individuals, but without evidence of alterations in the nervous system, was not related in the researched literature. The finding of the parasite in other organic fluids was related in the pericardial[32] and ascetic[40] fluid which shows that in situations of high parasitemia, the *T. cruzi* can spread, and during the co-infection it must be searched systematically in all organic fluids. The histopathological evaluation was reported in only 15% of the cases, with the places most studied the central nervous system (70%) and the myocardium (14%), places where the Chagas disease usually has its most severe forms during the acute phase[96]. Also, were described histopathological evaluations in the stomach[32], duodenum[51], skin[48,61,81] and uterine cervix[55]. In all this locations were found parasites and inflammatory reaction suggestive of the Chagas disease. Apart of the myocardium, the other locations are not those where these anatomopathological findings are often described on Chagas disease. Therefore, they must be considered as enhanced parasitemia dependents in immunosuppressed individuals and are data considered by the authors as indications of reactivations of Chagas disease, understanding that reactivation comprises the presence of the acute disease and high parasitemia in the course of the chronic phase, and may be more or less severe, depending on the stricken place in the organism. It is emphasized that in Brazil, this reactivation condition is considered for the definition of an AIDS[9] case.

The majority of the articles report the reactivation in the central nervous system and in the myocardium, usually severe cases, with fatal outcome[38]. However, just as there are difficulties to know the exact number of individuals co-infected, this also occurs regarding the frequency that these reactivate the Chagas disease, a pathognomonic clinical event. However, when the parasitemia is analyzed by xenodiagnosis or blood culture, the co-infected individuals have a higher chagasic parasitemia than patients without the co-infection with the HIV, suggesting that this reactivation may occur asymptomatic, with a higher frequency[44,60,61]. In this revision, it was reported the occurrence of 41,2% of reactivations, this percentage higher than the ones related in series of cases, which varies between 10 and 15%[81,93,97], reflecting that, probably, the more severe cases must have been diagnosed and related. Considering the estimates presented in this review, the occurrence of reactivations of Chagas disease in the co-infection with HIV is underestimated[99,100].

The reactivation was described in the majority of the articles as occurring in the central nervous system, responsible by 74% of the events, followed by heart, 17%, clinically characterized by signs of acute disease being fever the main manifestation. In relation to the clinical focus of each organ affected, this was nonspecific, ranging to the central nervous system from headache, signs of intracranial hypertension, seizures, motor location and coma, generating diagnostic confusion, mainly with toxoplasmosis and tumors of the central nervous system[37,65,66,75,84]. For the heart, it consists of triggering or exacerbating congestive heart failure, arrhythmias, atrioventricular, heart and fascicular blocks[22,27,34,42]. The fact that the clinical picture presented in the reactivation in the heart, usually occurred in the natural evolution of the chronic chagasic cardiopathy[88,102] making the diagnosis difficult, unlike the central nervous system which does not present exuberant symptomatology in the chronic phase of the disease. Other less common locations of reactivations cited were the pericardium[32], peritoneum[40], skin[48], intestine[32,51] and cervix[55]. Although the reactivation has been described in the extrinsic eye

muscles in a case of co-infection with reactivation of the Chagas disease in the brain[47], parasites were not found at the lesion site, only myositis. It is a constant in all articles published, that the identification of *T. cruzi* at the place where the reactivation occurred has been essential for this diagnosis. Thus, although likely in the described case, this possibility should not be considered as ocular reactivation of Chagas disease.

A concern expressed by various authors regards the predictive factors that may occur before the reactivation, allowing a preventive action strategy or mainly the specific treatment. Such factors have had the parasitemia as its main predictor[7,81]. The parasitemia must be identified by direct methods in blood or other organic fluids, always reflecting high intensity. For the indirect methods, xenodiagnosis and blood culture, there is a need that they are quantitative for the same purpose. However, in some cases the high parasitemia occurs for a long time without a reactivation happening, demonstrating that other deterrent factors of reactivation might exist[81]. The immunosuppression expressed by the levels of CD4 T cell bellow 200 cells/mm^3 would be another predictive factor, since the reactivation is described most of the times in individuals with AIDS. However, in the researched literature the Chagas disease reactivation occurred in individuals with the CD4 T cells of up to 382 cells/mm^3[3,23]. Other similar reports with CD4 T cells above 200 cells/mm^3 and confirmed reactivation by high parasitemia with *T. cruzi* detected on peripheral blood, pericardial fluid, myocardial and quantitative xenodiagnosis have been described[34,42]. The opposite is also found, that is, CD4 T cells count bellow 200 cells/mm^3 without reactivation[35]. However in this cases the average count of CD4 T cells was much higher, 562 cells/mm^3, than on those reactivated, 98 cells/mm^3. But some few non reactivated cases present a very low CD4 T cells count[42]. Although there are discrepancies amongst the published studies, the majority of the reactivated cases, occurred in individuals with the CD4 T cells count inferior to 200 cells/mm^3 and the average value of these cells are well below this parameter, so, it is acceptable to consider this data as predictive to reactivation. The same has been observed in relation to the viral load that as the lymphocyte count reflects the degree of immunosuppression of the HIV infected patient. The data revised of the researched literature head to the fact that, in the infected individual, the monitoring of the reactivation must be based on the evaluation of the parasitemia by *T. cruzi*, taking into account the degree of immunity: the more immunosuppressed, the greater should be the monitoring of the parasitemia. The degree of immunity in the co-infected individual would be given mainly by the CD4 T cells count, but also by the viral load.

As to the diagnosis of Chagas disease reactivation, it involves the clinical approach, the imaging exams and the observation of the parasite in the reactivated place, for most of the times. The clinical condition is nonspecific for including reactions from the acute phase: fever, poor general condition, disorientation, hepatosplenomegaly, lymphadenopathy, among others[22,23,32,42,81,93]. Specifically, the clinical condition refers to the place of the reactivation. Therefore, the neurological condition draws more the attention[25,52,65,66,87] that in most of the times has toxoplasmosis as the main diagnosis in view to the frequency that this condition happens in HIV infected individuals[33,37,68]. In the heart, the symptomatology and the physical aspects overlap those seen on the natural evolution of the chronic chagasic cardiopathy, hindering the diagnosis[22,27,34,42,88].

This way, the imaging exams have great importance in the identification of lesions, mainly in the central nervous system. There is no substantial difference between the findings on the computed tomography (CT) of the head and those observed on magnetic resonance imaging (MRI), whereas the lesion most often found is the pseudotumoral. These lesions, usually, are hypodense, single or multiple, with or without ring reinforcement when using contrast. White matter of the brain hemispheres happened more frequently. Some authors have searched for aspects in the tomographic images and on the MRI of the brain capable of defining the chagasic etiology, as the prevalence of these in the subcortical areas[33,37,68]. The purpose would be to make a differential diagnosis with the toxoplasmosis, whose involvement of the thalamus and the basal ganglia happen more frequently. However, the chagasic lesions are widely distributed in the central nervous system and this should not be generalized, and the Chagas disease diagnosis should be among those differentials, especially in the cases where the epidemiological history is predictive. In two cases, there was description that the CT of the brain was normal[32]. In one of them, the reactivation happened in the heart and on the other, although there was a detection of parasites in the peripheral blood and hemiparesis, it was not possible to define the etiology of the involvement of the brain. The patient died and the brain could not be examined.

The survival of the patients was highly variable and was related to some factors, the main one being the reactivation of the Chagas disease in the central nervous system, where the mortality reaches 100% in the cases without specific treatment[81,93]. When the reactivation does not occur or is controlled, the survival is directly related to the complications found in the natural evolution of the Chagas disease and, mainly, of the infection by HIV/AIDS. In the cases with reactivation the studies, in general, consider the survival severely reduced in the following conditions: when there is compromising of the central nervous system, the late diagnosis of chagasic etiology of the neurological lesion and the late introduction of the specific therapy for the *T. cruzi*[81,93]. The last two situations are those that can modify and influence the prognosis of the patients. When such interventions don't occur, there is no description of spontaneous resolution of the chagasic meningoencephalitis. Thus, by separating the reactivated cases from the non reactivated, the average survival rate of the first group was 11 months. As for the non reactivated cases, the survival rate was of 34 months, in other words, three times longer. The longest survival amongst the reactivated cases was of approximately six years and it happened in the heart[27,35]. When the reactivation was in the central nervous system, the longest survival was three years[14,81] happening in two cases. In both, there was specific treatment of the infection by *T. cruzi* with benznidazole, itraconazole and fluconazole in one and only with benznidazole in another, and that on this last one it was utilized secondary prophylaxis. In the cases with higher survival where there was reactivation in the heart, the patients were treated with benznidazole[35].

The influence that the immunological reconstitution reached by the antiretroviral treatment determines the natural evolution of the co-infection Chagas/HIV/AIDS is not yet found defined in the researched literature[77,81]. In theory, once this is established, mainly by the medications of the HAART in the control of the viral replication and recovering the immunological system, the Chagas disease should follow its natural course as in the immunocompetent individual. For the other infectious diseases associated to the HIV infection this seems to occur[8,50]. However, the few cases already reported about the co-infection Chagas/HIV/AIDS and the incomplete information about the antiretroviral treatment, as drug specifications, length of use, compliance with treatment, intolerance, side effects, response of the patient to the immunological recovery, makes it difficult to

establish in this revision the real impact of this treatment on the reactivation of Chagas disease in co-infected patients. In the largest series of cases with the co-infection published by Brazilian authors[81], is where the best reports about the antiretroviral treatment were, being used in the period of monitoring of the patients receiving single, double and triple therapy, with 28 cases using HAART. Although the authors have not discussed in detail the subject, the antiretroviral therapy did not change significantly the *T. cruzi* parasitemia in the cases where it was classified as high, even when an increase of the CD4 T cells takes place. In the cases where the parasitemia was low, the evolution was the usual of immunocompetent chagasic patients. Therefore, efforts should continue to be made to establish the role that the medicinal immunological reconstitution would have in the control of the Chagas disease reactivation in individuals co-infected with HIV/AIDS.

Although the overall mortality verified was 30%, it occurred in 73% of the cases in which there was reactivation of Chagas disease. Of these deaths, 89% had reactivation in the central nervous system, reinforcing what was previously discussed and the necessity of monitoring this reactivation.

The co-infection *T. cruzi*/HIV has not been systematically evaluated in the majority of the endemic countries for Chagas disease.

The topic has been published, mainly as case reports or small series of it, with incomplete information and diverse codes of conduct.

Probably, the number of subjects co-infected and published on the literature until now is underestimated.

The epidemiological profile of the co-infected subjects is: adult male, native or from endemic regions, with serological diagnosis in the indeterminate form of the chronic phase and reactivation of the Chagas disease.

The reactivation diagnosis its suspected when the subject with the co-infection presents a clinical profile of acute disease or clinical decompensation of the natural evolution of the chronic phase, clinical profile of organic impairment uncommon in Chagas disease or presence of pseudotumoral brain lesions on imaging exams.

The high parasitemia is recognized as the main predictive factor of the Chagas disease reactivation.

In the presence of co-infection, the count of T lymphocytes CD4+ bellow 200 cells/mm^3 or the high HIV viral load are indicating factors for the monitoring of the parasitemia.

The reactivation diagnosis is verified when there is a high parasitemia detected by direct or indirect quantitative methods.

The specific treatment for the *T. cruzi* is a formal recommendation on reactivation, starting as early as possible with benznidazole on the doses and length of use as indicate on the acute phase of natural evolution of the Chagas disease. Other medications, as nifurtimox, azole derivatives and allopurinol should be considered on the treatment of the reactivation when there is impediment for the use of the benznidazole.

The lower survival rate of subjects with the co-infection is related to the presence of the reactivation of Chagas disease and the natural complications of both diseases.

The role of the antiretroviral treatment on the evolution of the patient with the co-infection cannot yet be determined by the knowledge currently existing.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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