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EDITORIAL / *ÉDITORIAL*

No, Chagas disease is not the new AIDS of the Americas!

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Abstract Chagas disease and AIDS: the same terminology cannot be used to associate, let alone confuse, these two diseases with one another without distorting reality, as was done in a recent medical article entitled: "Chagas disease: The New HIV/AIDS of the Americas". Even though Chagas disease, like many other "neglected diseases", bears some superficial resemblance to AIDS in certain ways, it nevertheless differs from the latter in many other significant ones.

Keywords Chagas disease · Trypanosomiasis · *Trypanosoma cruzi* · Latin America · HIV · AIDS · Immigrants · Stigmatization · Discrimination · Congenital transmission · Nifurtimox · Benznidazole · Tranfusional risk · Breastfeeding · Abarax®

Résumé Maladie de Chagas et sida ne sauraient être associés, voire confondus sous un même vocable sans distordre la réalité, comme cela a été fait dans un article médical récent intitulé : *Chagas disease : « The New HIV/AIDS of the Americas »*. Si la maladie de Chagas, comme bien d'autres « maladies négligées », présente sur certains points, et en apparence seulement, quelques ressemblances avec le sida, elle s'en différencie sur de nombreux autres qui sont essentiels.

Mots clés Maladie de Chagas · Trypanosomose · *Trypanosoma cruzi* · Amérique latine · VIH · Sida · Immigrants · Stigmatisation · Discrimination · Transmission congénitale · Nifurtimox · Benznidazole · Risque transfusionnel · Allaitement maternel · Abarax®

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Introduction

A North American team recently published an article entitled "Chagas disease: The New HIV/AIDS of the Americas" in the open access journal PLoS Neglected Tropical Diseases [15]. We do not feel that this provocative, if not sensational, title is justified and we would like to say why here. Indeed, even though Chagas disease, like many other "neglected diseases", bears some resemblance to AIDS in certain ways, it nevertheless differs from the latter in many other significant ways that the authors either downplay or ignore.

First of all, Chagas disease is not a new disease as the overtone of the title might suggest. The presence of its causal agent, *Trypanosoma cruzi*, in the mummified tissues of the Chinchorro Indians of the Atacama Desert, some 9000 years before its discovery by the Brazilian Carlos Chagas in 1909 [7], makes this trypanosomiasis one of the oldest scientifically documented disease [2], whereas AIDS only entered the nomenclature of diseases in the 1980s, and according to the most extreme hypothesis, it has only been in existence for around a hundred years at most [36].

Secondly, Chagas disease is an endemic parasitic disease that is essentially vector-borne. It only exists on the American continent, where it was probably prevalent in numerous animal species for millions of years and spread to humans by zoonosis. These animal populations serve as a reservoir, thus ensuring the perpetuity of the disease, come what may. In these respects, human American trypanosomiasis or Chagas disease [26] thus has nothing in common with AIDS, which is a pandemic contagious viral disease without a true animal reservoir, even though it did arise from the accidental crossing of the interspecies barrier between monkeys and humans.

Not enough emphasis was placed on these elementary and fundamental facts in the article by Hotez et al. [15], who instead focus on five "striking similarities" between AIDS and Chagas disease: the presence in both of these diseases of an acute phase, a latent phase, and a chronic phase; the possibility of their respective causal agents being transmitted from mother to child or by blood; the need for a long-term, expensive, and not readily available treatment for both AIDS and Chagas disease; and the fact that these two illnesses

(especially when Chagas disease is compared to the AIDS epidemic of the 80s and 90s) are two diseases that selectively affect impoverished populations, which have great difficulty accessing healthcare structures and suffer stigmatization and discrimination as a result. What exactly is the case?

Poverty, stigmatization, and discrimination

Ever since its discovery, and well before WHO coined the term neglected disease [17], Chagas disease was considered as a disease closely linked to poverty, unsanitary living conditions, ignorance, and underdevelopment of the populations whose members were victims. At one time it was even thought to be responsible for cretinism, thanks to an erroneous link established by Chagas between endemic goiter and human American trypanosomiasis [25]. This pejorative connation of the illness persisted, in fact so much so that many Latin American countries only accept the designation of endemic country with reluctance because they find it degrading. There are still certain individuals or groups of individuals who refuse to accept the very idea that they could be infected and therefore refuse to undergo screening because they are so afraid of discrimination in the event of a positive result. Still others will not call exterminators when they find that their homes are infested with the triatomine bugs ("kissing bugs") that vector the disease for fear of being stigmatized by members of their communities.

In contrast, AIDS is not strictly speaking a disease of poverty because it affects rich and poor alike on every continent. The real difference between these two categories of victims lies in the fact that during the first 20 years of the pandemic, the rich in prosperous countries benefited from the steady advance of knowledge and development of therapies plus a more favorable environment for survival, whereas impoverished populations often remained ignorant of the risks and had no access to treatments for lack of sufficient financial resources and adequate healthcare infrastructures. Poverty and the ignorance of the methods of transmission nearly always associated therewith have therefore played and are still playing a significant role in the epidemiology of both of these diseases as well as that of many other neglected diseases, but in very different ways. The stigmatization that AIDS victims have experienced and still do experience was and is of an entirely different nature than that experienced by Chagas disease victims. First of all, the former was linked to the sexual orientation of the first victims and then to an irrational fear of the contagion, thus making AIDS victims into the lepers or plague carriers of the twentieth century for the remainder of what little time they had left to live.

Even today we still encounter traces of this fear in the restrictions to which AIDS patients are subjected when they attempt to obtain a visa or residence permit in one of the 48 countries that still practice such discrimination, which violates the Convention on Human Rights. Obviously there is nothing like this for Chagas disease patients, who are free to go and live anywhere in the world that they wish, although it is true that they may encounter other forms of discrimination. In certain endemic countries it is not uncommon for an employer to ask a job applicant to present a certificate of seronegativity for Chagas disease out of fear that a seropositive individual is less fit for work, or would be absent more often due to health reasons, or would develop progressive heart disease during his or her employment for which the employer would then be obligated to assume part of the treatment costs. In other cases, an employee who tests positive after hiring (and is most likely not a union member) is simply fired [12].

The exportation of more and more Chagas disease cases [30] outside of Latin America, while it does constitute a public health problem that must not be ignored and that we do need to learn how to manage [4,16], does not pose a threat to the host populations, European, American, Australian, or other, as long as the necessary preventive measures are taken at blood transfusion and transplant units. It therefore must not be presented in such a way that could lead to such an interpretation.

The discrimination to which Chagas disease patients would be subjected in non-endemic countries in terms of access to care is primarily linked to their frequent status as illegal immigrants, where prudence prevents them from coming forward and getting care [19], except in cases of serious cardiac complications. This type of discrimination can hardly be placed on the same level as that which AIDS patients of the 80s experienced owing to the unique sexual connotation of the disease in the early days of the pandemic.

Long, expensive, and hard-to-obtain treatments

The "treatment" of AIDS is a lifelong thing. It is still not capable of curing, but it does slow the progress of the disease considerably and allow patients to lead relatively normal lives. Were it not for an unprecedented research effort on the part of the prosperous countries directly affected by the pandemic, which under the pressure of humanitarian organizations and facilitated by the drop in the price of antiretrovirals between 2000 and 2002 was reinforced by a likewise unprecedented financial effort to provide poor populations access to this treatment, this progress would not have been possible.

The picture for the treatment of human American trypanosomiasis is entirely different. Nifurtimox and benznidazole permanently cure ca. 80% of the Chagas disease

patients in the acute phase, although the price is certain side effects that can be severe and require the treatment to be stopped. For a long time, however, it was thought that these two molecules had no effect on the chronic (indeterminate phase and late complications) phase of the infection, and it was not until 1990 that these molecules were found to have activity for this indication in children under 12 [9,32]. Consequently, several somewhat controversial studies demonstrated a slower progression of the disease in certain treated adults, with a possible later onset of the complication phase and, when chronic myocarditis did occur, it was less severe [35]. Numerous other studies followed, but they were conducted under highly variable conditions and according to protocols so different that it is very difficult to make comparisons among them. According to the most recent meta-analyses of these studies, the results are contradictory and far too inadequate in every way for recommending a treatment for all chronic Chagas disease patients [11,20,27]. According to one of these studies, the parasitological cure rate of patients 15–70 years old in whom treatment was delayed was a mere 5.9% [13]. This is a far cry from the rate of efficacy of the antiretroviral tritherapy (ART) prescribed for AIDS. This is one of the reasons why decision makers in endemic countries continue to prioritize vector control and the prevention of all other modes of transmission, and have their reservations concerning a treatment which seems less than promising and which would involve the estimated 9–10 million chronic Chagas disease patients on the Latin American subcontinent. On the other hand, there is a consensus as to how to treat all seropositive patients younger than 18 years, although the results are quite variable from one region to another [38]. Only the development of a test for confirming a cure within a reasonable timeframe would be likely to bring about progress in this area. At present, the only way to truly confirm a cure, at least in theory, is by a seroreversion that remains stable for 5 years and which generally does not occur until much later (18 months to 15 years after the treatment, plus there is the possibility of reinfection in endemic zones). Developing such a test is a priority, but it is not easy. The existence of this test would also have a "booster effect" on the search for new, more active and better tolerated molecules. Contrary to what many may have heard, this search has never stopped [1] but thus far has failed to generate any concrete results. Nor has it been encouraged by the spectacular decline in the incidence and prevalence of the disease recorded in the last 20 years thanks to the vector control programs [10,37].

The difficulties in gaining access to nifurtimox and benznidazole are paradoxical and due to a situation that is both dramatic and "ludicrous". The solutions for getting out of it should therefore be a matter of simple common sense. But thus far this has not been the case, and some treatment campaigns in course have even had to be stopped for lack of medication [21]. Up until the last few months, the license for manufacturing benznidazole was held by the Brazilian state of Acre in association with the Pharmaceutical Laboratory of the State of Pernambuco (LAFEPE), which subcontracted the production of the raw material to the private laboratory Nortec Quimica, all under the aegis of the Brazilian Ministry of Health. For reasons that are not exactly clear, thus far these different entities have proven to be incapable of coordinating with one another in order to meet their commitments and thus ensure not only steady and adequate production of the medication in response to a growing demand, but also the distribution thereof [23]. Today the situation is improving with the arrival on the scene of two Argentinian laboratories (Maprimed and Elea), which have joined together, under the aegis of the Argentinian ministry of health and the Mundo sano foundation presided over by the owner of Elea, to produce a generic form of benznidazole under the name of Abarax® (100 mg and 50 mg tablets readily breakable into four sections and dissolvable for pediatric use) [18,22]. At the same time, Brazil claims that it is ready to resupply the market and also to sell a pediatric form of benznidazole, but production according to the standards and market approval of these 12.5 mg tablets is still not a sure thing. The case with nifurtimox is different but paradoxically just the same. This molecule is deemed, and rightly so, to have an activity similar to that of benznidazole, although there are no comparative studies of the spectrum of activity of these two trypanocides, especially on the different strains of trypanosome. Nevertheless nifurtimox is hardly used at all by South American doctors, who prefer benznidazole, often without any convincing reasons, even when the latter cannot be obtained! Meanwhile, Bayer Laboratories (the manufacturer of nifurtimox) had supplied several hundreds of thousands of tablets at no charge to the majority of the endemic countries in 2003. These tablets have hardly been used at all [29].

As is the case with nifurtimox therapy, the average length of benznidazole therapy is 2 months, which really is not that long compared to the lifelong therapy for AIDS, or even to the 6–12 month therapy for a mycobacteriosis. The cost of a benznidazole therapy, assuming that this medication is available, can vary greatly (between US $50 and 600, or apparently even more) depending on the country, the poverty level, and the sector: private, public, humanitarian, etc. The anticipated price increase of the raw materials needed for synthesizing the molecule should not affect the sales price of Abarax® (fixed at US $120 for the treatment of an adult), if the promise of the manufacturers is to be believed (J. Jannin, personal communication). Even if this turns out not to be entirely the case, the price of a benznidazole therapy would still be much lower than that for a lifelong ART. Nifurtimox, which is also used to treat sleeping sickness in the neurological phase, can still be obtained free of charge

from WHO thanks to a long-term donation on the part of Bayer Laboratories.

The costs for managing the cardiac and digestive complications of Chagas disease are obviously much higher than those for its etiological treatment. Between 1992 and 2000, the costs to the southern cone countries alone for treating the symptoms, palliative care, number of years of work, and loss of life (DALYs) would have amounted to US $1140 million. This cost, both real and theoretical, was the main motivation behind the involvement of Latin American countries in the major regional initiatives implemented between 1991 and 1997 for eliminating the vector-borne transmission of the disease. A very rapid return on investment, at least on paper, was almost a sure thing [31].

Mode of progression of the two diseases

In the absence of treatment, the way in which AIDS and Chagas disease progress is probably where these two illnesses show the most "false" similarities. Both diseases start with a generally paucisymptomatic acute phase that is often unnoticed. With Chagas disease, however, complications in the form of fatal, acute myocarditis or meningoencephalitis can develop within the first few weeks in young children, who are the most likely victims of vector-borne transmission. In both children and adults, the disease can be expressed as rather characteristic chagomas or a unilateral, bipalpebral, pathognomonic, periorbital violate edema known as Romaña's sign. The latent phase that follows the acute phase is extremely variable in length between the two diseases. In less than one out of three Chagas disease cases, it ends with delayed complications of varying severity, with an annual mortality rate of 1–1.5 per 1000. In nearly all AIDS cases, however, the latent phase leads to severe immunodeficiency which is always fatal within a relatively short term. In the first case, it is a matter of complications. In the second, it is a question of the natural progression of the disease.

Congenital transmission

Congenital transmission of AIDS affects 25–45% of the children born of infected mothers in developing countries. This term generally includes transmission *in utero*, transmission during birth, and, somewhat improperly, transmission by breastfeeding, which accounts for slightly less than half of the cases of mother-to-child transmission. A well-managed preventive treatment lowers the frequency of these types of transmission to less than 5% and in theory could reduce it to almost zero [34]. In contrast, only 5% of mothers with Chagas disease transmit it to their children *in utero*. Unlike AIDS, there is no preventive treatment for mother-to-child transmission. If infected, however, the child can be permanently cured in nearly 100% of the cases if he or she is treated before the age of 6 months, and with no side effects if the treatment takes place within the first few weeks of life. Thereafter, the efficacy of the treatment and the ability to tolerate it decline over the course of months and years [6]. Screening of women of child-bearing age and pregnant women inside and outside of endemic countries is therefore a tremendous challenge that needs to be addressed and overcome in order to make Chagas disease a thing of the past.

Oral route

Despite some suspicions, the transmission of *T. cruzi* in mother's milk has never actually been proven. Hence there are no restrictions as far as a mother with Chagas disease breastfeeding her child is concerned. We just mentioned the significance of the role of breastfeeding in the transmission of AIDS. Implying that "the absence of transmission by the oral route" in AIDS is one of the three cardinal points that differentiate AIDS from Chagas disease [15] is therefore inaccurate. Both diseases can indeed be transmitted orally, but only through mother's milk in the case of AIDS and apparently never this way in the case of Chagas disease. However, Chagas disease is transmitted orally through food or drink contaminated by the waste of infected kissing bugs, by the urine of certain reservoir animal such as opossums, or by fragments of infected insects accidentally introduced in food or drink [8,33]. Cases of Chagas disease contracted in this manner are particularly serious in children as well as adults.

Probably in an attempt to reinforce the idea that Chagas was a neglected disease among the general public, not a single word [15] was said about the vast number of research projects conducted on human American trypanosomiasis since the start of the century in the majority of endemic countries and elsewhere. Every day, however, these projects give rise to a dozen or so international scientific publications, and have been doing so for several decades. Nor were the large-scale regional initiatives (INCOSUR for the countries of the Southern cone, IPCA for the countries of Central America, IPA for the Andean countries) conducted under the aegis of PAHO for controlling, even eliminating vector-borne transmission mentioned or even cited [14,24,28,37]. But thanks to these initiatives, the prevalence of the disease has been reduced by more than 50% and its incidence by almost 90% in less than 20 years [26]. Even though there is still a great deal to be done, particularly in terms of early detection and treatment of new cases, whether congenital or acquired, there is no reason not to point out and acknowledge these successes. To portray Chagas disease as a forgotten disease that was suddenly rediscovered is to

cheapen the dedication and efforts of the doctors, researchers, nurses, and public health agents in South America who have devoted themselves to Chagas disease for a century, with or without the help of NGOs.

As one might expect with such a title, "Chagas disease: the new HIV/AIDS of the Americas" found a resonance in the media (including the very serious New York Times) that is unusual for an article appearing in a medical journal, no doubt owing to the very large number of chronic Chagas disease patients now living in North America and who are presented, with a certain degree of ambiguity, as a potential danger even though North American blood banks have had strict monitoring measures in place since 2006 [4]. Meanwhile, hundreds of internet sites have seized upon the title in question. Most of them exaggerate in a manner that often borders on the caricature, for example by talking about the "disease that causes your heart and even your kidneys to burst" [3], or about the extremely limited number of individuals who are able to get treatment because of the high cost of the medications, or even about a new version of AIDS recently discovered by American researchers, and so forth. Googling the combination AIDS/Chagas disease is truly enlightening.

Given that another autoimmune syndrome with AIDS-like clinical symptoms but different in terms of its physiopathological mechanism and epidemiology is being defined and described in Asia [5], now is not the time for controversial and dubious amalgams and comparisons that can only generate anxiety and confusion among the general public.

AIDS and Chagas disease are two diseases that differ from one another in fundamental ways and in fact have only a certain number of "false" similarities in terms of their secondary modes of transmission, their mode of progression, the problems in treating them, and the socioeconomic characteristics of the populations that they target.

No, not even for "good cause" and for effective communication (which we hope was the reason behind it) should Chagas disease be presented under the guise of AIDS, a disease that so tragically and wrongly connotes deviant behavior, sex, and death.

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