Evolution of Chagas Disease Screening Programs and Control Programs

Historical Perspective

João Carlos Pinto Dias

Belo Horizonte, Brazil

ABSTRACT

Chagas disease remains an important health problem in Latin America, affecting approximately 8 million to 10 million individuals. This disease originated from an ancient enzootic cycle, and human infection has been detected in 4,000- to 9,000-year-old mummies and has expanded with European colonization, reaching its peak prevalence in the 20th century. Discovered in 1909, the disease remained obscure and uncontrolled until the 1950s, when the generalization of serology, the characterization of chronic cardiomyopathy, and effective insecticides began. By the 1960s, national control programs were launched and incidence began to decrease as a result. During this time, scientific improvements became increasingly available to address disease management. Presently, challenges in managing Chagas disease include maintaining sustainable epidemiological surveillance, the spread of the disease to nonendemic countries, the apparent spread of oral transmission, and new symptoms and manifestations. This review discusses the possibilities and challenges in facing Chagas disease in the coming decades.

Human Chagas disease (HCD) is a metaxenic protozoonosis caused by *Trypanosoma (Schizotrypanum) cruzi* and was first described in 1909 by Carlos Chagas in Minas Gerais, Brazil. This brilliant researcher discovered the parasite and its vectors, began the study of the clinical aspects of the disease, and found the first reservoirs [1−3]. Originally enzootic, the parasite circulated among wild mammals and invertebrate vectors for centuries. Much later, the inclusion of humans within the vector chain caused the emergence of HCD as a typical zoonosis or zooanthroponosis in the domestic environment, closely linked to socioeconomic and ecological factors, such as settlements, migration, living standards, landscape, altitude, temperature, and humidity, among others [4,5]. This disease is now endemic in much of Mexico, Central America, and South America and has also spread to nonendemic countries via the migration of thousands of infected individuals in recent decades (Figure 1) [4,6].

In endemic areas, HCD is mainly transmitted by blood-sucking triatomine bugs (*Triatominae*), which thrive in poor housing conditions, making people living in rural areas more susceptible to acquiring infection. The disease can also be transmitted by blood transfusion, organ transplantation, oral and congenital routes (primary and secondary routes), or, more rarely, by alternative exceptional routes such as sexual contact and nontriatomine vectors. The reoccurring nature of *T. cruzi* infections such as HCD is particularly serious in individuals with suppressed immune systems, such as those with acquired immune deficiency syndrome (AIDS) [3,4,7−10].

Since the second half of the 20th century, stringent control measures have largely reduced HCD transmission over a wide endemic region, with infection being concentrated in higher age groups. Nevertheless, in some regions of Argentina, Bolivia, Paraguay, Central America, and Mexico, active vector transmission continues, and young people can become infected [3,4,6].

The clinical management of patients with acute and chronic diseases has progressively improved, providing new avenues for addressing HCD. Currently, the possibility of the 8 million to 10 million *T. cruzi*−infected individuals in various epidemiological contexts continues to warrant the attention of both governments and academic institutions [5,11,12].

In this article, the historical progression of preventative and management measures taken to address human American trypanosomiasis are discussed, with special attention paid to the challenges expected moving forward. An effective system for diagnosing and treating infected individuals must remain at the forefront of additional scientific research.

A BRIEF HISTORICAL OVERVIEW OF CHAGAS DISEASE CONTROL AND MANAGEMENT

The Carlos Chagas era

The discovery of HCD is among the most exciting periods in medical history. Complementing his clinical, epidemiological, biological, and pathological studies, Carlos Chagas believed primarily that disease control is a "duty for the State." His understanding of the problem was based on 3

The author reports no relationships that could be construed as a conflict of interest.

From the Centro de Pesquisas René Rachou, Belo Horizonte, Brazil. Correspondence: J. C. P. Dias (jcpdias@cpqrr.fiocruz.br).

GLOBAL HEART

VOL. 10, NO. 3, 2015
ISSN 2211-8160/$36.00.
http://dx.doi.org/10.1016/j.gheart.2015.06.003

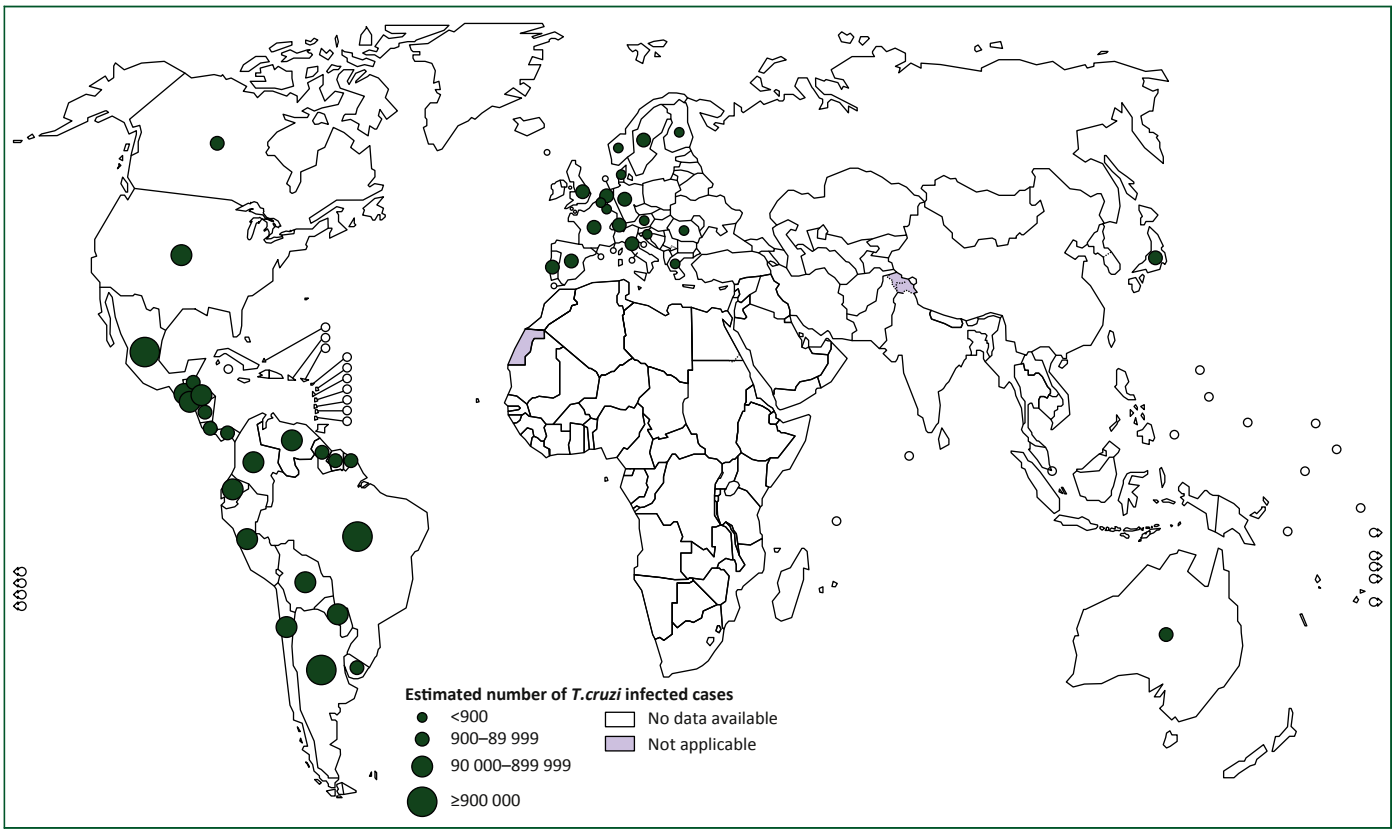

FIGURE 1. Global distribution of human Chagas disease based on 2006 to 2010 official estimates [5].

points: 1) the epidemiological and social impact of the disease would be extremely relevant, considering the very large dispersion of the vector in Brazil and other countries in Latin America; 2) any actions against the disease should be of a preventive nature, because parasite transmission is the most vulnerable point in the epidemiological chain; and 3) the fundamental strategy would involve vector control. Chagas also suspected the existence of other modes of transmission, such as congenital transmission [1,2,13,14].

Chagas noted that HCD primarily affected rural populations of low socioeconomic status, living in poor housing conditions where vector colonization was rampant, and he quickly realized that political factors were involved in disease control: "It is clear that the disease vector is an insect, a constant companion of humans in their houses, and so it is easily destroyable… Sanitary measures, particularly the improvement of living conditions, would certainly be a highly impactful policy action" [1].

Possible strategies for disease control were discussed early in the discovery of HCD. At that time, housing improvement received much attention, because vaccination was not a viable option and there was a lack of specific drugs and effective insecticides. One of Chagas's disciples, Souza Araujo (1919), proposed a law making housing improvement in endemic areas compulsory to prevent insect infestation, but this law was never implemented. As the national director of Public Health, Chagas perceived the major technical and political challenges in HCD control in 1919, and that political change would never occur unless the social and economic impacts of the disease were publicized [2].

An entomological branch of biological studies was implemented at the Oswaldo Cruz Institute in 1910 to map triatomines to provide important information about vector and parasite distribution throughout the continent. However, this was insufficient in promoting the control of the disease, because the basic political subject was not the vector, but human disease. Because of this, Chagas tried to clarify the epidemiology, the diagnosis, and the clinical characterization of chronic disease, but scientific attention remained on the acute phase, reflecting the prevailing trend in microbiological research [2,5].

Another constraint was the lack of interest from European and North American researchers in studying an apparently rare, strictly Latin American pathology. During that time, as Latin American countries were gaining independence and their gold and precious mineral mines were becoming nonproductive, European attention turned to

colonies in Asia and Africa, where classical institutes for tropical medicine were installed. Facing this challenge, Chagas published his works in the United States, Europe, and Argentina, written in English, French, German, and Spanish. He also contacted important figures such as Hartmann, Prowazek, Metchnikoff, Brumpt, Crowell, and Laveran, but focused his efforts on preparing his own group at the national level [2,4,6].

In 1913, he urged his assistants C. Guerreiro and A. Machado to apply the Bordet and Gengou technique to detect anti—*T. cruzi* antibodies in chronic patients. Concurrently, conscious that chronic heart disease was the most relevant aspect of the disease, Chagas focused on this area with the assistance of Eurico Villela and Evandro Chagas [2,5,13,14]. Again, Chagas was proven correct, but he still could not escape from another personal frustration: despite his magnificent descriptions, the clinical and pathological aspects of chronic disease were not appreciated by the majority of scientists in his lifetime.

Chagas remained patient; in his later works and conferences, he still emphasized the chronic aspects of the disease while waiting for confirmation of his findings elsewhere. In 1934 he wrote: "First seen in the hinterland of Minas Gerais, Brazil, this other human trypanosomiasis is not exclusive to our country, since it is also found in other South and Central American countries. In the Tucuman and Catamarca provinces of Argentina, several clinical cases were observed, with verification of the parasite in their peripheral blood. Cases have also been seen in Peru, Venezuela, San Salvador and, recently, in Panamá. However, we still have little knowledge about the endemic index and the social importance of the disease in these other American countries" [15].

Moreover, despite a sad episode in the National Academy of Medicine, where mediocre and jealous enemies aggressively questioned his ideas, Chagas never lost hope in the strength of science in addressing health problems in the tropics: "The European nations, zealous of their colonies in the tropics, have organized the expertise—in their universities and in their great research institutes—to the study and the teaching of pathology in tropical countries. Here, not so much the economic interests, but the most exalted duties and provident nationalism oblige us to study and to research the Brazilian nosology, in order to provide the improvement of our race, of rare native attributes, and to reach, by the prophylactic method, the sanitary redemption of our large territory" [16]. Between 1909 and 1935, despite appeals by its discoverer, HCD remained an invisible and "exceptional" disease. The majority of scientists remained focused on parasite detection, not recognizing chronic cases, and immunological diagnoses would not be used for a long time. On the prevention side, focal attempts that prioritized housing improvement were tried by Rudolf Talice and Salvador Mazza [2].

Chagas died in 1934, but a new era arose from his ideas, taken up by his disciples and scientific followers.

HCD visibility over time

HCD became visible as a major public health problem 25 years after Chagas's discovery, relying on specific historic achievements (Figure 2) [2,5,13]:

- The description of the Romaña sign (1934), promoting and facilitating the discovery of hundreds of cases of acute disease in several countries;
- The improvement and availability of serological diagnosis by complement fixation testing, based on research carried out at the Oswaldo Cruz Institute and São Paulo Medicine School between 1944 and 1950;
- The achievement of the first serological screenings of the general population in endemic areas of Minas Gerais and São Paulo (Brazil) in 1946;
- Pioneer studies associating serology and electrocardiography in the same endemic regions in 1947;
- The first serological screening in blood banks, in Belo Horizonte, São Paulo, and Venezuela, in 1949;
- The progressive clarification and systematization of chronic cardiomyopathy, started by Laranja in Bambuí between 1946 and 1955;
- The definitive systematization of Chagas chronic heart disease, published in *Circulation*, 1956 [13];
- The clinical and pathologic studies on the digestive form of chronic HCD, started in 1955 in Ribeirão Preto and Goiás (Brazil);
- The founding of international congresses and meetings on HCD in 1959 (Rio), 1960 (Washington), 1970 (Caracas), 1975 (Belo Horizonte), and 1979 (Rio);
- The improvement of serology since the 1960s, with the development of new modern, easier, and more reliable techniques such as hemagglutination and indirect immunofluorescence;
- The emergence of agencies to stimulate and support researches in HCD from the 1970s, such as Brazil's PIDE/CNPq (Integrated Program on Endemic Diseases/Brazilian National Research Council), the World Health Organization (WHO)'s TDR (Tropical Disease Research), and CONICIT (Science and Technology National Council) in Argentina and Venezuela, among others;
- The national serological surveys of disease prevalence in Sao Paulo, the rest of Brazil, Venezuela, and Argentina, between 1965 and 1985; and
- The first epidemiologic studies on the medical impact of vector control, carried out in São Paulo, Bambuí, and Venezuela, in the 1970s.

In the 1970s, a general framework on the prevalence, distribution, and medical importance of HCD was outlined, incorporating both the arguments and epidemiological data necessary for control programs. Prevalence was estimated at approximately 15 million infected in Latin America. In Brazil, there are an estimated 5 million cases, with an incidence rate of 100,000 new cases annually; chronic cardiomyopathy is found in approximately 30% of infected individuals [4,14,17].

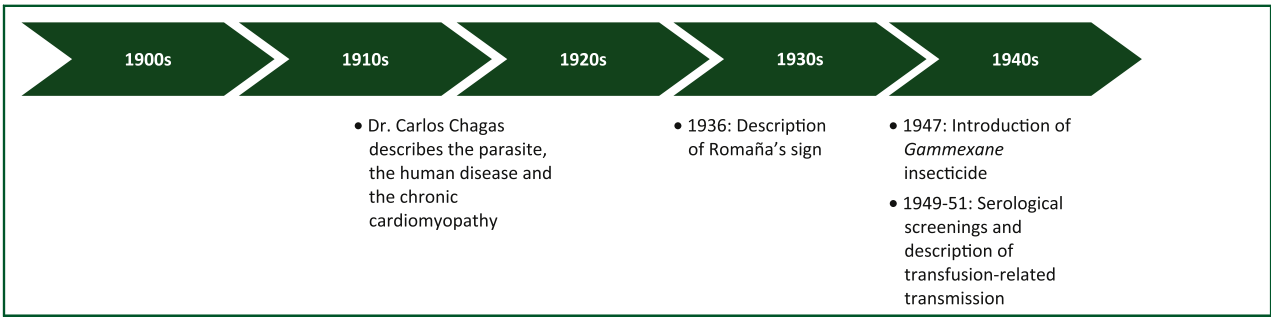

FIGURE 2. Key events in the history of Chagas disease.

The modern era of Chagas disease control and management

In the 1970s, several observations and mathematical models indicated that the social and political development in endemic regions could be sufficient for HCD control. However, this type of work was complicated in less developed regions. Specific technical interventions were carried out in the more vulnerable phases of the parasite cycle, such as on domestic vectors and blood banks, a saga that originated at the end of the 1940s [2,4,18,19].

The beginning and progression of vector control. Vector control measures began when a small branch of the Oswaldo Cruz Institute was established in Bambuí (Brazil) by Emmanuel Dias in the early 1940s. In 1944, Dias surveyed the municipality, finding astonishing epidemiological indicators, including a house infestation rate of 70%, natural infection of insects by *T. cruzi* around 30% to 40%, and positive serology among 45% of rural children under 10 years old. Two research lines were subsequently established to: 1) improve the control of disease transmission, focusing on vector control; and 2) study the clinical manifestations of chronic heart disease [2,13,18,19].

The first line of research began with the use of physical and chemical control measures to address domestic vectors, including housing improvement and intensive health education. A successful insecticide was described in 1946.

The second line of research required the development of a complex research structure, involving cardiologists, serologists, and pathologists; experimental models; and successfully reproducing several aspects of the human disease in dogs and monkeys. In 1956, a classic publication on chronic cardiomyopathy was published in *Circulation*, a work that is still considered to be the definitive description of the characteristics of chronic Chagas heart disease [2,6,13].

In his early attempts, Dias tried everything possible to eradicate triatomines from human dwellings, including boiled water, caustic soda, kerosene, cyano gas, and military flamethrowers. Dichlorodiphenyltrichloroethane is ineffective against *Triatominae*, but good results were obtained with another organochlorine, gamma-hexachlorocyclohexane (γ-HCH), also known as benzene hexachloride, Lindane or Gammexane (used successfully in 1948 by Dias and Pellegrino, in Brazil, and by Romaña and Abalos, in Argentina [2,3,6]). HCH (and/or dieldrin) remained the most widely used compound against domestic *Triatominae* until the late 1970s, when it was replaced with synthetic pyrethroids [2,3,9].

By the end of the 1940s, the main tools and strategies for *Triatominae* control were already available, at least at the experimental or theoretical level [2,4,18]. Nevertheless, large-scale control programs did not begin until the early 1960s due to a lack of political action and the absence of national structures capable of implementing control programs. During the 1960s, the São Paulo state (Brazil) launched its regulatory program, and large-scale trials began soon after in Argentina [2,5,11,19].

National programs were subsequently instituted, using chemical tools against domestic *Triatominae*, with the same rationale and strategies of successful malaria campaigns. In Venezuela, in conjunction with insecticide use, a national program to improve rural dwellings was implemented, capitalizing on the strong economy and public health expertise of the country at that time. Through the 1960s and 1970s, a variety of control approaches were tested (juvenile hormones, insect pathogens, insecticide impregnated traps, etc.), however chemical insecticides remained the most effective and efficient approach [2,3,7,9,11].

The introduction of synthetic alpha-cyano-substituted pyrethroids in the early 1980s was a major advance in HCD control campaigns. In parallel with pyrethroids, longer residual action and minor ecologic damage, the use of HCH and other chlorine compounds was being banned worldwide. Applied as wettable powder or suspension concentrate formulas, pyrethroids are fast-acting against the target *Triatominae* and also provide transient control of other domestic insect pests such as fleas, cockroaches, and houseflies. New formulas have been tested against triatomines in an attempt to find a more consistent residual effect; these strategies have included microencapsulated

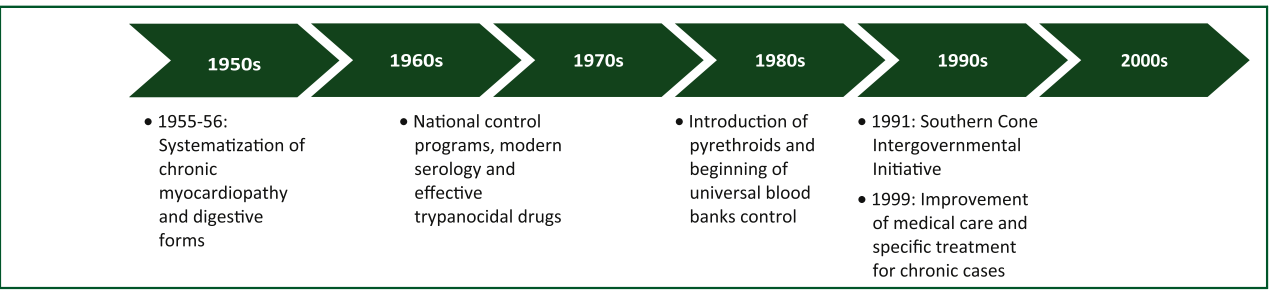

FIGURE 2. Continued.

formulas and slow release polyvinyl chloride matrices [2,9,14].

Control programs against *Triatominae* were organized based on the administrative structures of previous campaigns against yellow fever and malaria, with an operational procedure divided into 3 phases: preparatory; attack; and vigilance. The preparatory phase mainly involved the gathering and organization of resources, personnel recruitment and training, and sketch-mapping of the area to be treated, including baseline population serological studies to determine initial infection rates, where possible. The attack phase involved large-scale spraying of premises in the target area, regardless of the infestation status of individual dwellings. The vigilance phase depended on community participation and was prepared from the start of the campaign through community health education and discussions with local community officials [2,3,9,19].

The results from these types of campaigns have been very satisfactory in Brazil, Uruguay, Chile, and in large regions of Argentina and Venezuela, and parts of Bolivia and Paraguay. Where vector control has been satisfactorily implemented, acute cases of Chagas disease have declined or been eradicated, and serology of young children born since the launch of the control campaigns shows very low prevalence. In addition, infection rates decreased among blood donors and women of childbearing age, thus lowering the corresponding risk of transfusion-based or congenital transmission [2,4,6,20–23].

Since 1991, a new political and technical approach to improve national control programs in endemic areas has been stimulated by the Pan American Health Organization and WHO: the multinational initiatives for vector and blood bank control. The cooperation of efforts, techniques, and epidemiological data in well-defined macro regions (the Southern Cone, Andean Countries, Central America and Mexico, and Amazonian countries) was officially installed by the respective countries, with technical assistance from Pan American Health Organization [2,3,6,9,19].

Other routes of HCD transmission and their possible control. Besides vector transmission, the secondary routes (transfusions, congenital, oral, and accidental) of HCD transmission are considered a major factor in disease occurrence, along with other eventual routes (sexual, through other nontriatomine vectors, etc.). The following paragraphs outline and summarize some considerations and perspectives concerning these secondary routes [4,8,14,24].

The control of transfusion-based transmission. Suspected in the 1930s by Mazza and Dias, transfusion-based transmission of HCD was first recognized in Brazil and other countries in the 1940s. Despite the availability of control procedures at this time, they were not widely used until the 1980s, with the emergence of human immunodeficiency virus (HIV)/AIDS. In endemic countries, the most effective approach for avoiding HCD transmission through blood is the screening of all blood donors via at least 2 technically different serological tests. Seropositive candidates are excluded as blood donors and delivered to a local or regional health system to receive adequate medical and social assistance. In some situations necessitating the use of blood from an infected individual, chemoprophylaxis is administered to stored blood, with the addition of trypanocidal drugs such as gentian violet. The prevalence of infection among blood donors has declined because of systematic vector control and has remained concentrated in older donors [3,5,17,19,21,22].

Preventing congenital HCD. The prevention of congenital HCD remains of significant importance in endemic and nonendemic regions, with a general risk of transmission by infected pregnant women of 0.5% to 7.0%. Infection among pregnant women is decreasing, in a similar trend to that mentioned for blood donors, with a higher concentration of infection in older age groups, due to vector control initiatives. Currently, prevention during pregnancy is not possible because of the toxic and teratogenic effects of the available drugs and the unacceptability of preventative abortion. The best control measure is early diagnosis in the newborn, followed by specific treatment with benznidazole or nifurtimox [9,14,23,24].

Oral transmission. Oral transmission is very common in the sylvatic cycle. It was first suspected as a route of HCD transmission in the 1930s by Mazza and Dias, but has received a lot of interest following 2 community outbreaks

in Teutônia and Belem (Brazil) in the 1960s [2,19]. Besides the rare possibility of ingesting raw meat from infected wild mammals (armadillos, rodents, monkeys), the more common cases of transmission involve the ingestion of contaminated juices and/or raw meals. The most remarkable cases were detected in the Paraiba and Pará states (Brazil) in 1986, involving the ingestion of contaminated sugar cane and other fruit juices [4,7,8,14]. Oral outbreaks are quite unpredictable, but are generally associated with the presence of infected *Triatominae* in the neighborhood. Improved hygiene in meal preparation and environmental management is recommended as the best preventative measure. Detected cases must be treated immediately to avoid disease transmission (known as secondary prevention), and a rigorous epidemiological screen of the area must be undergone to detect other possible cases and to establish the probable transmission route [3,8,24,25].

Prevention in organ transplantation. Theoretically, transmission of *T. cruzi* can occur during the transplant of virtually any organ from an infected donor to a susceptible recipient. However, most reported cases were the result of kidney transplants, with rare cases attributed to heart, pancreas, and bone marrow transplants. Pre-surgery serological assessments of both the donor and recipient should be mandatory in endemic areas, or when parasite contact is suspected in either individual. In the case of a positive donor and a susceptible recipient, it may be best to discharge the donor. Nevertheless, in urgent or specific cases of histocompatibility, where the transplant must proceed, the best strategy is to provide treatment to the donor (ideally 10 days prior to the surgery) and to the recipient 1 day prior to surgery and for the following 9 days [6,8,9,24].

Preventing laboratory accidents. Laboratories dealing with *T. cruzi* must incorporate a very stringent routine of personal training and protective regulations under periodic supervision of reference centers to avoid infection of research personnel. The laboratories should have a restricted entrance, and technicians working directly with the parasite should be required to use gloves, protective eyeglasses, masks, closed shoes, and long-sleeved gowns. Periodical serological tests on staff are also highly recommended [4,8,10].

Immediate local sterilization is necessary in cases of accidents involving the skin or mucosa. For example, silver nitrate wash is recommended in cases involving the eyes. If a person seems likely to have been infected, immediate treatment should be administered for a period of at least 10 days [8,14].

Vaccination and chemoprophylaxis. While no vaccination exists for HCD, several forms of immunization against *T. cruzi* have been tested using attenuated strains, fractionated parasites, antigenically similar trypanosomatides, and synthetic molecules. None has yet been effective. "Live" vaccines may not be safe, and "killed" vaccines may not offer complete protection, and so, further research on this subject is discouraged [9,11,26]. Similarly, there is currently no effective prophylactic drug, for example, those that protect travelers to endemic areas. In this context, however, it is worth emphasizing that travelers' infection risk is extremely low [5–7,14].

Reactivation of HCD. As mentioned in the cases of organ transplants, some other situations involving immunological depression can cause the reactivation of the *T. cruzi* infection. The most common occurrence is in patients with HIV who have previously been infected with HCD, particularly when the CD4 cell count is <300 cells/mm^3, generally resulting in severe neurological outcomes. More than 40 such cases are known, most of them with fatal progression. Adequate treatment with antiretroviral drugs is able to prevent *T. cruzi* reactivation in these cases. Recently, the administration of benznidazole at a dose of 5 mg/kg/day was suggested as an appropriate way to maintain a low number of circulating parasites [4,7,10,27].

Managing infected individuals

Until the 1960s, the clinical management of HCD was a difficult task, because effective drugs and treatment procedures were not available. Therefore, there was little interest regarding HCD from medical professionals for many years. Nevertheless, a great medical advance took place in the 1970s, with the advent of new drugs, medical interventions, and diagnostic tools (e.g., specific, functional, and topographic) [2,6,19,28–31]. The progressive indications for specific treatments received stronger input after the 1990s, with special attention paid to the chronic indeterminate form of HCD, and to younger infected individuals [4,12,19,32].

Currently, the management of acute cases and chronic patients is based on 3 main pillars of public health: 1) the epidemiological and clinical situation; 2) the existence of appropriate technologies; and the general conditions of the health system, including access, conditions, expertise, and drug availability [12,29,30]. In general, HCD patients are of low socioeconomic standing and illiterate, and so they depend on aid from state public health measures and philanthropic or university institutions [4,11,31]. Private or complementary health systems should also be engaged. The major disease management goals are as follow: to cure the infection by means of specific treatments; to avoid mortality in acute cases and premature death in chronic cases; early detection of chronic infection, particularly in younger individuals; minimizing congenital transmission; and diagnosis and clinical management for all infected individuals [7,12,28–30].

Accordingly to their epidemiological profiles, cases of HCD should be handled at different health care levels [12]. The consensus is that early diagnosis and correct treatment and management measures are the best way to ensure a positive outcome for patients [5,14,30]. The general rule is

that adequate and continuous management of chronic HCD patients requires suitable expertise and available drugs. Among other barriers and challenges, limited early diagnostic opportunities are remarkable, and are potentially due to a lack of symptoms and/or incorrect diagnosis from physicians, limited health care access by patients in several regions, and the lack of regional laboratories [12,29].

Social security benefits are also an extremely important factor in the effective management of HCD, mainly in cases of severe Chagas cardiomyopathy [20]. For instance, in Brazil, there are approximately 2 million chronically infected individuals, and 20% of them will develop an HCD-related cardiac disease (400,000 individuals). Among those individuals, 5% to 10% (20,000 to 40,000) will develop a severe heart disease [20]. In nonendemic areas, the social and macropolitical aspects of globalization, underemployment, and immigration of people from endemic countries have been the main causes behind the detection of thousands of infected individuals. This relatively new situation is creating serious problems regarding the need for medical attention, as well as labor affairs, and the possibility of transmitting the disease via blood transfusion, or other secondary mechanisms [4,5,17]. Related problems include medical expertise and the undocumented situation of thousands of individuals who remain socially unprotected [5,6,29,31].

It is unrealistic to hope that all individuals with HCD will be treated by specialists, chiefly cardiologists; many of these specialists are not available or accessible in endemic regions, and general clinicians are also able to treat a large number of chronic and acute patients. In reality, most of the cases depend on the available primary health care services, because these cases are in the indeterminate or initial/benign chronic forms [4,6,12]. A secondary level of health care must also be available, including adequate etiological, topographical, and syndromic diagnoses, as well as more complex medical interventions, mainly in the case of complex arrhythmias and heart failure [14,28,31]. Again, the expertise of physicians is a related problem, along with flexibility in referring patients to higher health care levels and counter-reference to the primary care level [12,24,29].

Approximately 3% to 5% of all infected individuals will require tertiary level care, involving high levels of medical expertise and specialization, and very specialized hospital facilities. These cases are typically characterized by severe heart failure, advanced digestive "megas," and the combination of HCD with advanced AIDS, all of which require precise diagnoses and intensive care units [12,27]. Access, high costs, and low rates of disease resolution have been the most frequent constraints at this health care level. In the last 2 decades, a great effort was made by Latin American heart societies to improve the knowledge, diagnosis, and treatment of HCD-caused cardiomyopathy [4,6,12,28].

Regarding research and policy, concurrent with the need for novel safer and more effective anti–*T. cruzi* drugs is the need for better clinical procedures and national health systems able to address HCD. It is important to remember that the vast majority of people with HCD do not have the means to face the social and medical burdens of the disease. Over the next couple of decades, besides new research and better-equipped health systems, the medical attention toward HCD will also depend on political will and permanent advocacy, as outlined by the WHO [5,9,19].

Generalities about the treatment of HCD. Although the primary emphasis in controlling Chagas disease is on interrupting transmission, the need to treat infected people remains. This applies not only to specific cases such as transfusions, transplant surgery, congenital transmission, and accidents as described previously, but also to those individuals infected in rural settings prior to the implementation of large-scale vector control interventions. Even if all causes of transmission were eradicated immediately, 14 million to 16 million people will require medical attention over the next 30 years. In the context of the broader HCD control strategy, the treatment of infected individuals is the secondary intervention level, designed primarily to halt disease progression [12,14,29,30].

Specific treatments. There are 2 drugs that can be used to specifically treat a *T. cruzi* infection: nifurtimox manufactured by Bayer (Whippany, NJ) under the trade name Lampit; and benznidazole, manufactured by LAFEPE (Recife, Brazil) and ELEA (Buenos Aires, Argentina) laboratories. Treatment with either drug is recommended in acute or recent infections, and in congenital cases with a good chance of radical cure. Side effects are dosage-dependent and include malaise, anorexia, loss of both appetite and concentration, erythema, pruritus, and peripheral neuritis. In some cases, agranulocytosis and/or anemia have been observed, requiring the interruption of treatment. In general, children tolerate treatment much better than do adults [6,29,30].

Nifurtimox and benznidazole have given variable results in different countries, which may reflect differences in parasite strains. However, a complete cure can generally be expected with immediate treatment of congenital cases and accidental infections, and a 30% to 70% cure can be achieved for treatment of acute infections. Even if a radical cure is not achieved, there is now strong evidence that early treatment can prevent mortality during the acute phase of infection, and that it can reduce the progression of disease in the subsequent chronic phase—particularly in relation to cardiac lesions. Results in the chronic phase are variable according to different observations made across different regions and age groups. Both drugs were effective at the tissue level, and the inflammatory response (and even initial fibrosis) is reversible when the parasite is killed during treatment. Specific treatment of chronic infections should therefore be considered on a case-by-case basis, depending on the age of the patient, because treatment is better tolerated in younger individuals, as well as the length

of infection, as the greatest treatment success is more likely in individuals with relatively recent infections [7,9,24,32]. The modern tendency is to give to the patient the "benefit of the doubt" when treating indeterminate cases and those involving initial cardiac and digestive chronic forms of HCD [5,12,28,29].

Symptomatic treatment. Symptomatic or supportive treatment for patients in the chronic phase has advanced greatly in recent years. Effective treatment presupposes adequate access to medical attention, with periodic clinical checks. Patients with indeterminate, asymptomatic chronic infections need to be followed up annually, whereas those with severe arrhythmia or heart failure should be hospitalized, receiving weekly or monthly clinical examinations. In general, approximately 85% of chronic phase patients can be followed through the primary health care system, with periodic medical consultations, serology, and electrocardiograms [10,12,14,19,24,28]. Particularities and advances in the management of principal clinical manifestations can be found in other sections of this issue of *Global Heart*.

Reintegrating chagasic patients into the community. The reintegration of patients into the community is the last stage in the classical sequence of preventive medicine. Often, a patient will experience anxiety or depression following a positive HCD diagnosis, even in the absence of clinical manifestations [12,14]. The public perception of Chagas disease is commonly associated with sudden mortality and/or irreversible heart disease, an image that has been widespread due to inappropriate and sensationalist reporting of a minority of severe cases. Nevertheless, a person with positive serology must be informed of this result in order to begin treatment and avoid becoming blood donors. Clinicians and health workers must give a realistic and objective explanation about HCD, outlining its natural history and providing a balanced view of the patient's clinical prognosis. Most patients are apparently healthy and have little likelihood of serious manifestations in the short and medium terms. Moreover, available medical resources for disease management are continuously improving, and the patient must be made aware of the need for regular medical consultation and checks [7,14,28].

A rarely discussed problem is the psychological behavior of chagasic individuals, because most will suffer parasympathetic denervation, becoming hyper-reactive to common ambient stimuli; they thus experience sustained anxiety [14,33]. At the operational level, a present tendency is to provide additional psychological care in the health services where people with HCD receive care [10,14,33].

At the community level, correct and balanced information must be given, particularly that which emphasizes the noncommunicable nature of Chagas disease and that the prognosis for infected individuals is generally good. This is particularly important to protect the basic rights of the chagasic individual, especially the right to work (which is often refused to individuals merely because of a positive serological test), and the right to social security (which is sometimes denied in cases of advanced heart disease). These factors require well-trained clinicians and health care workers, clear practical guidelines, and effective social security systems. In practice, medical decisions must take into account the clinical state, the profession, and general living conditions on a case-by-case basis, trying to avoid distress and false expectations in the patient [14,31,33].

HCD IN 2015

According to WHO and the World Bank, the incidence and social impact of HCD have significantly decreased since the beginning of the 21st century, compared with previous decades [3,5,19,20,22]. The driving factors behind this change are of a social nature (urbanization, improved living standards, modernization of agriculture, etc.), which complement specific interventions (e.g., vector and blood bank control, and better conditions for medical care). The new scenery of Chagas disease programs is replacing the classical vertical versus horizontal approach, because most of the countries are turning their public health systems toward a decentralized model. In the 1990s, globalization and market-controlled economies imposed the general tendency to deliver resources and responsibilities to the periphery, in order to improve small and efficient central and national structures. In fact, considering the general conditions in endemic regions, the transition to decentralization can be considered another new challenge, as low-income municipalities and counties tend to have a lack of sufficient expertise, organization, and political will to carry out the programs [2,3,11,34,35].

There are currently no major technical problems regarding the eradication of domestic triatomines: the results of various initiatives are considered successful in those regions where they have been conducted meeting the minimum quality, coverage, and continuity requirements [2,9,35].

Nevertheless, a century after its discovery, Chagas disease still represents a major public health challenge in Latin America. In the last decades, several interventions encompassing the primary, secondary, and tertiary prevention levels of Chagas disease have been attempted. The control of both vector and blood transfusion-based transmission of *T. cruzi* (primary prevention) has been successful in many endemic regions, but early detection and etiological treatment of asymptomatic subjects have been largely underutilized [3,5,12,19].

THE "POST CONTROL" WORLD AGENDA FOR HCD

The present global HCD situation, particularly its incidence and morbidity, is indeed much better than it has been. Infections transmitted by vector and blood transfusions

have significantly reduced in several countries, but new modes of transmission and disease spreading have been observed.

Vector control has been implemented in several endemic regions, but there is a lack of initiatives in others. *Triatoma infestans* was eliminated in large geographic areas, but it remains the focus in the Chaco region. A similar situation exists in some Andean and Central American regions for *Rhodnius prolixus*. Fortunately, it appears that the Amazon region will not to be invaded and colonized by allochthonous species such as *T. infestans, T. brasiliensis, T. dimidiata*, and *Panstrongylus megistus*. At the same time, the encroaching of native species into human homes remains very rare in this region [3,4,35].

Levels of domestic infestation are not recovering to their former elevation in those areas where surveillance is maintained. Native wild species naturally remain, but their domestic density tends to decrease when control activities and surveillance are maintained. Pyrethroid resistance has been detected in some situations, but has been addressed using alternative insecticides, such as carbamates. The existence of sylvatic *T. infestans* in some areas of the Southern Cone region requires attention. Conversely, the progressive (sometimes slow) modernization of rural activities and living standards are contributing to the reduction of vector domiciliation [11,22,34,35].

The greatest challenges in vector control are undoubtedly the dismantling of regular programs, mainly due to untimely decentralization, and the move away from HCD as a priority area. Because in several regions of Brazil, Venezuela, Central America, and Mexico, native secondary species such as *T. brasiliensis, T. maculata, T. dimidiata, T. pseudomaculata,* and *P. megistus* will remain in their natural habitats and may eventually invade human dwellings, a permanent surveillance system is necessary. Furthermore, the current trend in health care decentralization, which has removed HCD as a priority in some municipalities found in endemic areas, may jeopardize the maintenance of vector control. It is therefore crucial that control programs in endemic areas continue to receive priority at the local, national, and international levels. Regarding vector control, the 4 main challenges in the 21st century can be summarized as follows: 1) maintaining political interest and action, including allocating the necessary resources in those regions where the disease impact has decreased; 2) objectively facing the irreversible tendency to centralization, in other words, maintaining the minimum central and regional reference structures to improve the efficacy and continuity of activities at the peripheral level; 3) controlling secondary and ubiquitous species at the peri-domestic level; and, 4) maintaining a high and sustained level of community participation in order to ensure continuous epidemiological surveillance [3,5,11,19,35].

Almost all blood banks are being controlled in endemic countries, and so it is anticipated that in the next 20 years, only exceptional cases of blood-based HCD transmission will occur. A similar trend is also anticipated for congenital transmission, because the current generations of women in endemic areas are becoming free of *T. cruzi* infection [6,11,14,21,23].

The prevalence of HCD is expected to decrease progressively in the next 3 decades, including a reduction in both incidence and mortality. Morbidity has also been decreasing due to improved medical care and the specific treatment in chronic individuals. At this point, the next step is the tremendous challenge of using a universal, specific treatment to manage the illness of the millions of individuals with HCD [12,29].

As stated by Morel [36], we are now at a crossroads regarding Chagas disease research, and tension is mounting due to opposing views among researchers, health authorities, and policy makers. We must remain realistic, remembering that throughout the history of HCD, the scientific community has been the principal protagonist in disease management initiatives [2,19,31]. In this sense, underestimating the possibility of resurgence of this "controlled" disease can be a fatal mistake, as was seen with resurgences of both tuberculosis and malaria. However, it is also true that many predicted epidemics ended up as false alarms.

FINAL REMARKS

Many accounts of HCD still present a fatalistic picture of an incurable infection affecting millions of rural, ignorant Latin American individuals of low socioeconomic standing, and as a neglected disease with no or very little possibility of being treated or prevented. Thankfully, this image has changed in recent years. Advances in disease control, diagnosis, and clinical attention have led to much better management, and to a progressive awareness that transmission can be halted and the clinical course of the infection attenuated. A subtle change from the classical paradigm of a neglected disease to a disease of neglected populations is arising all over the world, stimulating hope and providing dignity to those infected with *T. cruzi*.

Political and scientific challenges to governmental and academic institutions are becoming clear, and new possibilities for HCD control and treatment are available, with the help of policy implementations and involvement of regional public health organizations. Transfusion and congenital transmission are decreasing and expected to disappear in the next 20 or 30 years. However, vector control must be maintained in endemic areas, which are still largely dependent on regional and local decentralized health systems by means of an adequate epidemiological surveillance. Oral transmission will likely continue to appear in eventual outbreaks, which may be managed in a focalized manner, depending chiefly on social advances and better environmental management.

In the future, infected individuals will be seen in increasingly higher age groups, consistent with the progressive reduction in universal infection prevalence. Nevertheless, optimistic epidemiological data, together

with other social priorities such as underemployment, violence, the global market, dengue fever, HIV/AIDS, degenerative diseases, etc., have the potential to decrease the priority of American trypanosomiasis in public health, and so, the reduction of human and financial resources for HCD is predicted. As a whole, the great challenge now and for the future is to maintain HCD as a minimal government and academic priority for the next 2 to 3 decades.

REFERENCES

1. Chagas CRJ. Moléstia de Carlos Chagas: segunda conferência realizada na Academia Nacional de Medicina, em agosto de 1911. In: Prata A, editor. Carlos Chagas, coletânea de trabalhos científicos. Brasília, Brazil: Universidade de Brasília ED; 1981. p. 167–92.
2. Dias J, Schofield C. The evolution of Chagas disease (American trypanosomiasis) control after 90 years since Carlos Chagas discovery. Mem Inst Oswaldo Cruz 1999;94(Suppl 1):103–21.
3. Coura JR, Dias JC. Epidemiology, control and surveillance of Chagas disease: 100 years after its discovery. Mem Inst Oswaldo Cruz 2009; 104(Suppl 1):31–40.
4. Miles MA, Yeo M, Gaunt MW. Epidemiology of American Trypanosomiasis. In: Maudlin I, Holmes PH, Miles MA, editors. The Trypanosomiasis. Oxfordshire, UK: CAB International; 2004. p. 243–52.
5. WHO. Chagas Disease. Available at: neglected.diseases@who.int; 2014. Accessed September 12, 2014.
6. Coura JR, Viñas PA, Junqueira AC. Ecoepidemiology, short history and control of Chagas disease in the endemic countries and the new challenge for non-endemic countries. Mem Inst Oswaldo Cruz 2014; 109:856–62.
7. Centers for Disease Control and Prevention. Chagas Disease. Available at: http://www.cdc.gov/parasites/chagas/. Accessed August 26, 2015.
8. Dias JC, Amato Neto V, Luna EJ. Alternative transmission mechanisms of *Trypanosoma cruzi* in Brazil and proposals for their prevention. Rev Soc Bras Med Trop 2011;44:375–9.
9. WHO. Control of Chagas Disease. Second Report of the WHO Expert Committee, WHO Technical Report Series 905. Geneva, Switzerland: WHO; 2002.
10. Carlier Y, Dias JCP, Luquetti AO, et al. Trypanosomiase américaine ou maladie de Chagas, Enciclop. Médico-Chir 2002;8:505–20.
11. Dias JC, Prata A, Correa D. Problems and perspectives for Chagas disease control: in search of a realistic analysis. Rev Soc Bras Med Trop 2008;41:193–6.
12. Rassi A Jr, Dias JC, Marin-Neto JA, Rassi A. Challenges and opportunities for primary, secondary, and tertiary prevention of Chagas' disease. Heart 2009;95:524–34.
13. Dias E, Laranja FS, Miranda A, Nóbrega GC. Chagas' disease: a clinical, epidemiologic, and pathologic study. Circulation 1956;14: 1035–60.
14. Dias JCP, Pereira JB, Macedo VO. Doença de Chagas. In: Coura JR, editor. Dinâmica das Doenças Infecciosas e Parasitárias. 2nd ed. Rio de Janeiro, Brazil: Guanabara Koogan; 2013. p. 606–41.
15. Chagas CRJ. Estado actual da Trypanosomiase americana. Rev Biol Hyg 1934;5:58–64.
16. Chagas CRJ. Aula inaugural da Cadeira de Medicina Tropical. In: Prata A, editor. Carlos Chagas, coletânea de trabalhos científicos. Brasília, Brazil: Editora Universidade de Brasília; 1981. p. 832–60.
17. Dias JCP. Epidemiologia. In: Brener Z, Andrade ZA, Barral-Neto M, editors. *Trypanosoma cruzi* e doença de Chagas. 2nd ed. Rio de Janeiro, Brazil: Guanabara Koogan; 2000. p. 48–74.
18. Dias E. Profilaxia da doença de Chagas. Hospital 1957;51:485–98.
19. Sosa-Estani S. Epidemiología de la enfermedad de Chagas en los paises endémicos. In: Viotti RJ, Vigliano CA, editors. Enfermedad de Chagas: un enfoque práctico basado en la investigación médica. Buenos Aires, Argentina: Editorial Panamericana; 2014. p. 45–56.
20. Organización Panamericana de la Salud. Estimación cuantitativa de la enfermedad de Chagas en las Américas. Washington, DC: OPS/HDM/CD/425-06; 2006.
21. Moraes-Sousa H, Ferreira-Silva MM. Control of transfusion transmission of Chagas disease in different Brazilian regions. Rev Soc Bras Med Trop 2009;42(Suppl 2):103–5.
22. Dias JC, Silveira AC, Schofield CJ. The impact of Chagas disease in Latin America: a review. Mem Inst Oswaldo Cruz 2002;97: 603–12.
23. Torrico F. Chagas congénito. In: Viotti RJ, Vigliano CA, editors. Enfermedad de Chagas: un enfoque práctico basado en la investigación médica. Buenos Aires, Argentina: Editorial Panamericana; 2014. p. 117–28.
24. Ministério da Saúde, Secretaria de Vigilância em Saúde. Brazilian consensus on Chagas disease. Rev Soc Bras Med Trop 2005;38(Suppl 3):7–29 [in Portuguese].
25. Aguillar HM, Abad-Franch F, Dias JC, Jungueira AC, Coura JR. Chagas disease in the Amazon Region. Mem Inst Oswaldo Cruz 2007;102-(Suppl 1):47–56.
26. Camargo EP. Perspectives of vaccination in Chagas disease revisited. Mem Inst Oswaldo Cruz 2009;104(Suppl 1):275–80.
27. Ferreira MS. Infecções no hospedeiro imunocomprometido. In: Coura JR, editor. Dinâmica das Doenças Infecciosas e Parasitárias. 2nd ed. Rio de Janeiro, Brazil: Guanabara Koogan; 2013. p. 209–19.
28. Andrade JP, Marin-Neto JA, Paolo AA, et al., for the Sociedade Brasileira de Cardiologia. I Diretriz Latino-Americana para o Diagnóstico e Tratamento da Cardiopatia Chagásica [I Latin American guidelines for the diagnosis and treatment of Chagas cardiomyopathy]. Arq Bras Cardiol 2011;96(Suppl 1):1–48 [in Portuguese].
29. Albajar-Viñas P, Dias JC. Advancing the treatment of Chagas' disease. N Engl Med 2014;370:1942–3.
30. Viotti RJ, Vigliano CA. Tratamiento etiológico. In: Viotti RJ, Vigliano CA, editors. Enfermedad de Chagas: un enfoque práctico basado en la investigación médica. Buenos Aires, Argentina: Editorial Panamericana; 2014. p. 253–62.
31. Dias JCP, Briceño-León R, Storino R. Aspectos sociales, económicos, políticos, culturales y psicológicos. In: Storino R, Milei J, editors. Enfermedad de Chagas. Buenos Aires, Argentina: Doyma; 1994. p. 527–48.
32. de Andrade AL, Zicker F, de Oliveira RM, et al. Randomised trial of efficacy of benznidazole in treatment of early Trypanosoma cruzi infection. Lancet 1996;348:1407–13.
33. Oliveira W Jr. All-around care for patients with Chagas disease: a challenge for the XXI century. Mem Inst Oswaldo Cruz 2009;104-(Suppl 1):181–6.
34. Dias JCP, Coura JR. Globalization and Chagas disease. In: Delic Z, editor. Globalization and Responsibility. Rijeka, Croatia: InTech Ed; 2012. p. 153–66.
35. Schofield CJ, Jannin J, Salvatella R. The future of Chagas disease control. Trends Parasitol 2006;22:583–8.
36. Morel CM. Chagas disease, from discovery to control— and beyond: history, myths and lessons to take home. Mem Inst Oswaldo Cruz 1999;94(Suppl 1):3–16.