Chagasic encephalitis in HIV patients: common presentation of an evolving epidemiological and clinical association

Carlos A DiazGranados, Carlos H Saavedra-Trujillo, Monica Mantilla, Sandra L Valderrama, Carlos Alquichire, Carlos Franco-Paredes

Lancet Infect Dis 2009; 9: 324–30

Emory University School of Medicine, Atlanta, GA, USA (C A DiazGranados MD, C Franco-Paredes MD); **Clínica San Rafael, Bogotá, Colombia, and Universidad Nacional de Colombia, Bogotá** (C H Saavedra-Trujillo MD); **Clínica Jorge Piñeros Corpas (Saludcoop), Bogotá** (M Mantilla MD); **Hospital Militar Central, Bogotá,** (S L Valderrama MD); **Grupo Saludcoop EPS, Bogotá** (C Alquichire MD); **and Hospital Infantil de Mexico Federico Gomez, Mexico** (C Franco-Paredes)

Correspondence to: Carlos DiazGranados, Division of Infectious Diseases, Emory University School of Medicine, 49 Jesse Hill Jr Drive, Atlanta, GA, 30303, USA
cdiazgr@yahoo.com

We present a case of chagasic meningoencephalitis reactivation in an HIV-infected woman with advanced immunosuppression. Prolonged survival was attained with antiparasitic therapy and secondary prophylaxis, in conjunction with the use of highly-active antiretroviral therapy. The geographic expansion of the HIV epidemic around the world coupled with global migration and international travel have created a favourable situation for *Trypanosoma cruzi* and HIV coinfection. The clinical manifestations of Chagas disease in HIV-positive people usually represent reactivation and not acute infection with *T cruzi* (coinfection). Symptomatic reactivation of chronic latent *T cruzi* infection can be triggered by severe immunosuppression associated with HIV infection. In this setting, Chagas disease reactivation often presents as meningoencephalitis resembling toxoplasma encephalitis. We review, in this Grand Round, the clinical manifestations, diagnostic approach, pathogenesis, natural history, treatment, prognosis, and prevention of Chagas disease reactivation among HIV-infected people with an emphasis on CNS manifestations.

Introduction

There is increasing recognition of the concomitant occurrence of HIV infection and tropical infectious pathogens among individuals living in tropical and subtropical regions of the world.[1] This association has also expanded to non-endemic settings as a result of international travel and population migration.[2,3] Indeed, some of these pathogens might act as opportunistic agents in the setting of severe HIV-associated immunosupression.[4]

There are several bidirectional interactions between HIV infection and tropical pathogens that might lead to substantial morbidity and mortality:[1–4] (1) by producing severe cell-mediated immunosuppression, HIV infection might enable latent parasitic infections to reactivate and become clinically apparent; (2) people coinfected with HIV and eukaryotic parasites might represent a clinical diagnostic dilemma due to atypical clinical manifestations; (3) a higher pathogen burden seen among patients with HIV/AIDS might lead to higher morbidity, mortality, and transmissibility;[5] (4) HIV-infected people coinfected with tropical infectious diseases might require longer treatment courses at the expense of more serious side-effects to reduce the possibility of recurrent relapses;[1] and (5) tropical infectious diseases might influence the HIV viral burden with potential consequences for HIV disease progression and HIV transmission.[6]

Like many other tropical diseases, Chagas disease, or American trypanosomiasis, caused by the parasite *Trypanosoma cruzi*, can coexist within HIV-infected people. This coinfection is the result of the geographic overlap of these two pathogens in some areas of Mexico, Central America, and South America and the occurrence of global migration and international travel.[5,7–9] The most important clinical consequence to this dual infection is the reactivation of latent (chronic) *T cruzi* infection triggered by profound HIV-related immunosupression.[5,10] Additionally, coinfection might present as acute Chagas disease among those with AIDS living in Chagas endemic areas and acquiring recent *T cruzi* infection.

HIV-associated immunosuppression influences the clinical manifestations of Chagas disease.[5,9–15] Unlike the classic manifestations of Chagas disease seen in immunocompetent patients,[16] meningoencephalitis dominates the clinical picture in untreated HIV-infected patients. Chagasic myocarditis is considered the second most common presentation that, in some patients, can coexist with meningoencephalitis.[5,8,10–12,14] In this Grand Round we present a case of Chagas disease meningoencephalitis and we review the literature to define the clinical and epidemiological aspects of HIV–Chagas coinfection with an emphasis on CNS manifestations.

Case description

A 26-year-old woman presented to an outpatient clinic in July, 2003, complaining of progressive headache and left-sided weakness. She was born in a rural area of the Department of Quindío in Colombia and had lived for several years at the rural town of Cartagena del Chaira (Department of Caquetá). She had a history of HIV infection, diagnosed in 2001, and had been prescribed zidovudine, lamivudine, indinavir, and ritonavir, but discontinued therapy after 4–8 weeks because of severe gastrointestinal side-effects. She had a history of genital herpes and condylomatosis, and her toxoplasma IgG serology was positive. In May, 2002, her HIV RNA viral load was 222 000 copies per µL and her CD4+ T-lymphocyte count was 189 cells per µL. She was then lost to follow-up until July, 2003.

Her physical examination revealed a temperature of 38·5°C and left-sided hemiparesis. She was admitted to the hospital, and a head CT showed a space-occupying lesion in the right basal ganglia with some areas of enhancement with surrounding vasogenic oedema (figure 1). A presumptive diagnosis of toxoplasma encephalitis was made, and she was started on a regimen of clindamycin and pyrimethamine. The patient was discharged home, but despite 5 weeks of antitoxoplasma therapy, she developed worsening headaches, inability to

ambulate, and seizures. She was readmitted to the hospital and underwent craniotomy with cerebrospinal fluid (CSF) sampling and brain biopsy. The CSF analysis revealed lymphocytic pleocytosis (23 white blood cells per µL, 60% lymphocytes, 40% neutrophils), elevated protein (320 mg/dL), low glucose (22 mg/dL), and flagellated parasites consistent with trypomastigotes. Although no parasitic forms were described, histopathology of the brain biopsy revealed acute and chronic inflammation with areas of necrosis, haemorrhage, and astrocytic gliosis. *T cruzi* serology (indirect immunofluorescence IgG) was positive. An electrocardiogram revealed non-specific T-wave changes and transthoracic echocardiogram reported normal valves and mildly depressed systolic function with an ejection fraction of 48%. The patient was started on a daily regimen of benznidazole 5 mg/kg. She also received phenytoin and carbamazepine for seizure prevention and co-trimoxazole for *Pneumocystis jirovecii* pneumonia prophylaxis.

After a 15 day hospital stay, she was subsequently discharged to a long-term care facility, where she continued to receive benznidazole, anticonvulsant drugs, and co-trimoxazole. Benznidazole 5 mg/kg per day was given for 60 days and then continued as secondary prophylaxis (5 mg/kg three times per week). Additionally, she was started on a highly-active antiretroviral therapy (HAART) regimen that included stavudine, lamivudine, and efavirenz, and received scheduled physical therapy. With this HAART regimen, she achieved virological suppression and substantial immune recovery (table). The frequency of convulsive episodes progressively decreased. A follow-up CT scan done in January, 2004, revealed a small calcification and an area of encephalomalacia (figure 1). The patient showed slow but steady neurological improvement. After 10 months of medical and physical therapy she was able to walk independently with a cane. She developed leucopenia as the most serious side-effect of chronic benznidazole maintenance, but did not require discontinuation of therapy (absolute neutrophil count remained above 500 cells per µL). After 2 years of secondary prophylaxis and given consistent immune reconstitution and virological control, benznidazole was discontinued in September, 2005. As a result of her substantial neurological and radiological improvement, we considered it unnecessary to repeat parasitological analyses of the CSF. To date, the patient has not had any evidence of chagasic encephalitis reactivation or evidence of Chagas cardiomyopathy. After more than 5 years of follow-up, she remains alive and well.

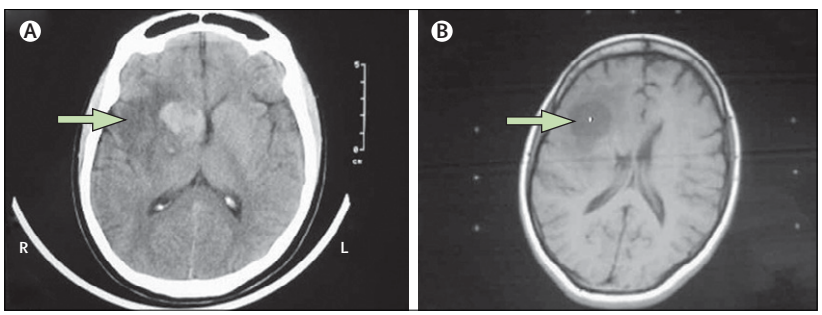

Figure 1: **CT scans of the patient's head**
Initial tomography (A) showing a space-occupying lesion in the right basal ganglia with some areas of enhancement and surrounding vasogenic oedema. Follow-up tomography (B) after therapy showing a small calcification and an area of encephalomalacia. Affected aread indicated by arrows.

Review and discussion

Overview of Chagas disease

Chagas disease, also known as American trypanosomiasis, is an anthropozoonotic tropical disease caused by the protozoal parasite *T cruzi*.[16,17] Millions of inhabitants of rural Mexico and Central and South America continue to be affected by this neglected tropical disease.[18–21] In addition, as the trend for global migration increases, the scope of Chagas disease is spreading from rural to urban areas and endemic to non-endemic areas.[19,22] The life cycle of *T cruzi* is amplified by employing more than 150 species of wild and domestic animals as reservoirs, including dogs, rodents, armadillos, and raccoons.[17,19] The main mode of transmission is by inoculation of the parasite present in the faeces of the insect vectors—reduviid bugs belonging to different genera (*Triatoma infestans*, *Rhodnius prolixus*, and *Panstrongylus* spp). The vectors acquire the parasite after feeding on blood from an infected animal. The inoculation of the microorganism present in faeces can occur directly on mucosal membranes or through skin breaks. Poorly constructed dwellings with wall or ceiling defects and cracks facilitate transmission because they create an appropriate habitat for reduviid bugs.[16,17,19] Transmission of the urban form of the disease results from transfusion of contaminated blood products, sharing of contaminated needles (ie, intravenous drug users), or transplantation of infected organs. Mother-to-child transmission can occur in both rural and urban settings secondary to transplacental infection. Ingestion of contaminated food has been implicated as the mechanism of transmission in some reports.[19,23]

Among otherwise immunocompetent individuals, the clinical course of Chagas disease is usually divided into three stages: acute, indeterminate, and chronic. The indeterminate phase usually lasts 10–20 years, but it might last a lifetime.[16–20,24,25] In some individuals, the acute phase can lead to symptoms produced by parasite-mediated injury of cardiac muscle or brain, manifesting as acute myocarditis or meningoencephalitis.[22,26] If left untreated, the acute phase progresses to a subclinical latent period after several weeks (indeterminate phase).[17,19,27,28] About 10–30% of seropositive individuals progress to symptomatic chronic disease 10–20 years after persistent *T cruzi* infection, characterised by unceasing inflammation in the myocardium that disrupts

	Viral load (copies per μL)	CD4+ T-lymphocyte count (cells per μL)
May 2002	222 000	189
June 2005	Less than 400	359
December 2006	Less than 400	316

Antiretroviral therapy was started on September, 2003.

Table: **Virological and immunological response to antiretroviral therapy of case patient**

the cardiac conduction system and produces structural abnormalities. These events lead to cardiac arrhythmias, congestive heart failure, thromboembolism, and sudden cardiac death. In other cases, destruction of visceral autonomic neurons in the digestive and urinary tract can lead to progressive enlargement of visceral organs leading to the megasyndromes.[19,25,29]

Clinical manifestations

The most relevant clinical manifestations of *T cruzi* infection in HIV-infected individuals result from reactivation as a consequence of progressive HIV-associated immunosupression.[5,10] In the context of reactivation of Chagas disease, several syndromes, which might or might not coexist, have been recognised. The most common syndrome and the focus of our discussion is that of neurological involvement, which occurs in 70–85% of cases.[5,9–13,15,30–32] The second most common manifestation is cardiovascular involvement, documented in 10–55% of cases.[8–11,14,15,33] According to a recent longitudinal series, the incidence of chagasic myocarditis in HIV-infected patients might be higher than previously thought, with new estimates showing similar occurrence for both neurological and cardiac reactivation.[15] There have been anecdotal reports of peritoneal or cutaneous involvement.[34,35] The neurological presentation is usually consistent with a space-occupying lesion, encephalitis, or meningoencephalitis.[5,9–11,30] The cardiac form is characterised by myocarditis,[14,15] which can be clinically silent. Our patient presented with neurological involvement characterised by a syndrome consistent with a space-occupying lesion. Additionally, given the decreased ejection fraction identified in our patient she might have developed cardiac involvement due to myocardial reactivation or chronic *T cruzi* myocardial infection.

Diagnosis

The diagnosis of Chagas disease reactivation in patients infected with HIV requires a high index of suspicion. The neurological form of Chagas disease should be included in the differential diagnosis of HIV-infected individuals who present with focal neurological signs.[5,9–11,36] The nature of the process should be further investigated, when possible, by doing imaging studies, specifically CT scanning or MRI.[5,9–11,36,37] These studies characteristically report space-occupying lesions similar to those described for toxoplasma encephalitis. Although some researchers[30,31] have proposed that lesion location can suggest the aetiological agent (with toxoplasma encephalitis more likely to cause cortical or basal ganglia lesions and chagasic encephalitis more often causing white matter or subcortical lesions), radiological images alone are clearly insufficient for a definitive diagnosis.[5,9,10,36] Rarely, Chagas disease and toxoplasmosis can coexist in the same patient.[10]

Two epidemiological criteria are useful to suspect chagasic encephalitis at the time of initial presentation in patients with HIV with space-occupying lesions: the patient comes from or has lived in areas endemic for Chagas disease, and the patient has a history of blood transfusions or intravenous drug abuse (IVDA).[12] If one or both criteria are documented at the time of presentation, further work-up for Chagas disease reactivation is warranted.[10,36] Serological studies (ELISA, indirect immunofluorescence, and indirect haemagglutination) allow the diagnosis of recent or remote parasite infections (usually by reactive results of at least two of three serological assays),[36] but are not sufficient to confirm disease reactivation and, in some cases, can be negative despite pathological evidence of reactivation.[10,37] Therefore, parasitological studies or histopathology are the ultimate confirmatory diagnostic tests. Useful parasitological studies include thick smears or Strout's concentration method, and CSF smears (ideally after centrifugation).[9,10,12] These methods allow the direct visualisation of the trypomastigote stage of the parasite—the flagellated and elongated form of the parasite. Identification of the trypomastigotes in CSF is sufficient criteria for a definitive diagnosis of chagasic encephalitis. In a case series from Argentina, the parasite was detected in the CSF in 11 of 13 patients.[12] Strout's concentration method has been found to be positive in the majority of patients with chagasic encephalitis.[10]

Although the diagnosis can be pursued from the time of the patient's initial presentation, as a consequence of the relatively low frequency of chagasic encephalitis most cases are initially misdiagnosed and treated erroneously as toxoplasma encephalitis. If not considered initially, clinicians should suspect the possibility of chagasic encephalitis in a patient that comes from or has lived in Chagas-endemic areas or has a history of blood transfusions or IVDA, and has an inadequate response to appropriate antitoxoplasma therapy. Patients for whom a definitive diagnosis remains unclear, despite less invasive techniques, should be considered candidates for a brain biopsy.[9,31] Figure 2 shows an algorithm of the proposed diagnostic approach for neurological reactivation of Chagas disease in HIV-infected patients.

Mechanism of Chagas disease reactivation

Patients with acute *T cruzi* infection usually achieve high levels of parasitaemia regardless of their immune status. If the patient is not immunocompromised, the parasite

load decreases after the acute infection but persists at low levels.[5,10,16] Chronically infected immunocompetent individuals might go on to develop chagasic cardiomyopathy, megacolon, megaureter, or megaoesophagus, possibly as a result of persistent infection and chronic immune activation.[16,29] Many individuals, however, remain asymptomatic for several years.[27,28] If a chronically infected individual becomes immunocompromised, the parasite load can increase and parasitaemia might ensue.[9–12,38,39] Among immunosuppressed patients, such as those with AIDS, high-level parasitaemia is related to the development of acute organ damage, predominantly involving the CNS and heart. However, the relation between *T cruzi* parasitaemia and organ damage among immunocompromised individuals is not absolute, and sometimes severe disease presents without detectable parasitaemia.[4,10,16] In these cases, tissue specimens might be required for a definitive diagnosis.

The immunological abnormalities leading to increased parasite load are poorly understood, but likely to include quantitative as well as qualitative dysfunction. Most HIV-infected patients with a Chagas disease reactivation have a CD4+ count below 200 cells per μL.[5,9,12,39,40] Although unknown, the risk of reactivation for HIV-infected patients has been estimated at around 16% over a 15-month period[41] and 21% over a 58-month period.[15] Several studies suggest an imbalance in the T-helper (Th) immune responses, with Th2 predominating over Th1 responses (and therefore interleukin-4 production predominating over interferon-γ production).[5,42]

Chronology and natural history

Most cases of the manifestations of Chagas disease in HIV-infected patients are the result of the development of immunosuppression in a person chronically infected with *T cruzi* leading to its reactivation. It is generally assumed that individuals become infected with *T cruzi*, while living in endemic rural areas, years before becoming infected with HIV.[10–12] Travel and migration between urban and rural areas facilitates the subsequent acquisition of HIV infection in the latently *T cruzi*-infected patient, which, after years of progressive immune suppression, would allow parasitaemia to increase and organ damage to develop (figure 3).[5,10,15,39]

Some patients might acquire both HIV and *T cruzi* via exposure to contaminated blood, as might happen in injection drug users and patients who receive improperly-screened blood transfusions.[5,12] When the route of transmission of *T cruzi* is percutaneous or via contaminated blood products the chronology of the coinfection is unclear. Patients might become infected with HIV and *T cruzi* at the same time, or they might have chronic HIV infection and subsequently become infected with *T cruzi*.

Finally, given the changes in travel and migration patterns, some patients that are chronically infected with HIV might acquire *T cruzi* infection while travelling.[1,3]

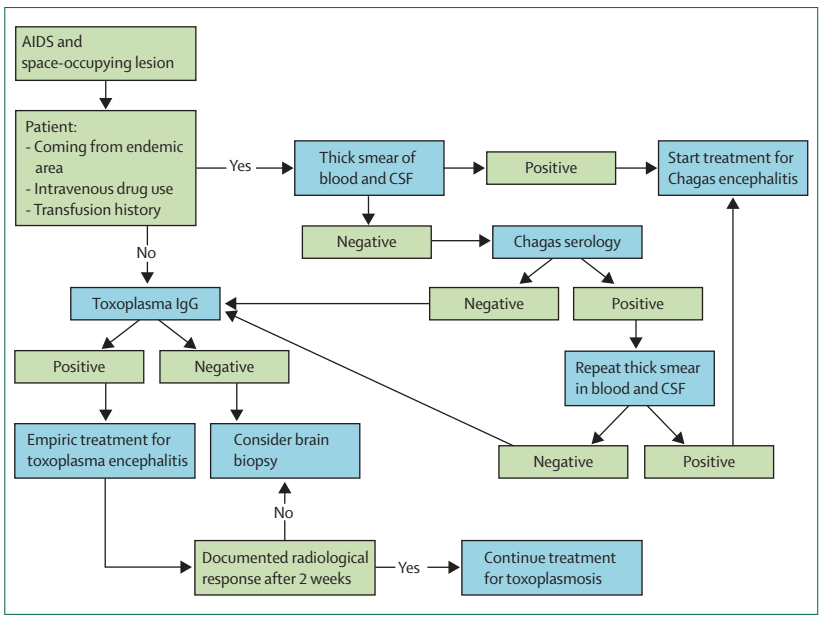

Figure 2: **Diagnostic approach to the neurological reactivation of Chagas disease in HIV-infected patients**

Treatment

The recommended treatment for Chagas disease reactivation in HIV-infected patients is benznidazole 5 mg/kg daily divided in two doses for 60–90 days.[4,9,10,22,40] Nifurtimox 8–10 mg/kg daily divided in three doses for 60–120 days is considered an alternative, although clinical experience is more limited.[9,10] The use of agents like fluconazole, itraconazole, allopurinol, and interferon is unknown,[43–46] and their clinical activity remains anecdotal until further studies become available. Once patients have completed the induction phase of therapy, secondary prophylaxis with benznidazole 5 mg/kg administered three-times per week is recommended.[9] Patients should also be initiated on antiretroviral therapy in a timely fashion to favour immune reconstitution for further parasite control.[9,40]

It is unknown whether it is safe to discontinue secondary prophylaxis in patients with a history of Chagas disease reactivation with immune recovery; when practiced, it is done as an extrapolation from the management of other opportunistic infections. Secondary prophylaxis was discontinued in our patient once CD4+ lymphocytes were consistently above 200 cells per μL and persistent viral suppression was confirmed. Follow-up for longer than 3 years without evidence of reactivation anecdotally suggests that discontinuation of secondary prophylaxis might be safe. However, there is a need for further studies to address this issue. Although there are no data available, retreatment with either benznidazole or nifurtimox is recommended for HIV-infected patients who fail to respond or who relapse after initial antiparasitic therapy.[4]

Currently, it is recommended that all HIV-infected people with epidemiological risk factors for Chagas

disease be tested for antibodies to *T cruzi* to detect latent infection.[4] If asymptomatic HIV-infected individuals screen positive for *T cruzi*, and they are likely to have been infected for less than two decades, a single course of treatment with benznidazole or nifurtimox might be beneficial.[22,28] However, there is a lack of consensus on this issue because of the absence of controlled studies. Initiation or optimisation of HAART might be helpful in preventing Chagas reactivation since most cases have been reported among HIV-infected patients who were not receiving HAART.

Prognosis

Before the advent of HAART the prognosis of Chagas disease reactivation in HIV-infected patients was poor. Median survival was estimated to be as short as 10 days,[11] and mortality was consistently within 6–8 months of the diagnosis.[10] Prognosis during the HAART era is better, with survival times reported of as long as 3 years.[40] To our knowledge, our case constitutes the patient with longest survival after diagnosis of chagasic encephalitis in HIV, with survival beyond 5 years.

Prevention

Appropriate measures for the prevention of *T cruzi* infection depend on the predominant mechanism of transmission. For the rural form of Chagas disease, prevention is based on vector control and improvement of living conditions.[17,47] For the urban form of the disease, prevention strategies must concentrate on blood-product quality and screening, and needle-exchange programmes and behaviour-changing interventions for IVDA.[12,17,47,48]

Patients infected with HIV that are coinfected with *T cruzi* should be started on HAART as indicated by the degree of immunosuppression and the presence of symptoms or comorbidities.[4,40] There is no consensus on the role of primary prophylaxis for coinfected patients that have not developed Chagas reactivation.[9] Some experts suggest considering primary prophylaxis for individuals with a CD4 count lower than 200 cells per μL,[10] predominantly if the level of parasitaemia is higher than 50% by xenodiagnosis—ie, the identification of trypanosomes in the gut contents of laboratory-reared triatomine bugs fed on the patient's blood.[39] Although the scarcity of data mandates extreme caution, prophylactic agents to be considered can include benznidazole, itraconazole, fluconazole, ketoconazole, or allopurinol. There is at least one case reported that suggests a possible role for ketoconazole in primary prophylaxis.[33]

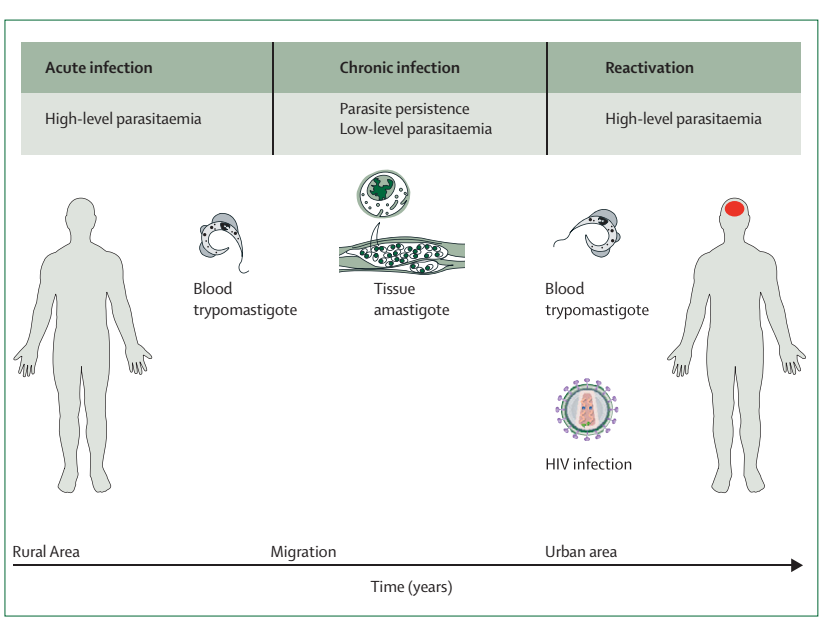

Figure 3: **Chronology and natural history of HIV and Chagas disease co-infection**

Public-health implications

The evolving clinical and epidemiological association of Chagas disease in patients with HIV/AIDS needs to be further delineated. Chagas disease affects more than 10 million people in Central and South America, distributed from the southern USA to some areas of Argentina and Chile.[17,18,20,21,47] The burden of disease caused by Chagas disease in Latin America is therefore substantial. On the other hand, the number of new HIV infections in 2007 totalled an estimated 140 000, bringing to 1·7 million the number of people currently living with HIV infection in this region of the world.[49]

Although much emphasis has been placed in the prevention and management of opportunistic infections that commonly occur in patients with AIDS in Latin America, there is increasing recognition that Chagas disease can lead to substantial morbidity and mortality.[4,17,28,32] Given this geographic overlap, it has become clear that the prognosis and clinical outcomes of HIV-infected patients with Chagas disease is worse than in patients who are not coinfected.[9,10,32,38,40] In fact, it has been shown that reactivation of Chagas disease is associated with increases in HIV RNA load,[6] which potentially could lead to an accelerated clinical course of HIV-associated immunosuppression and increased risk of HIV transmission. Similarly, HIV infection favours higher levels of parasitaemia,[38] which not only facilitates end-organ damage but also might increase the likelihood of further *T cruzi* transmission.

Conclusion

More efforts should be placed on screening programmes to identify latent *T cruzi* infection among HIV-infected individuals in Chagas-disease endemic areas. In non-endemic settings it is crucial to identify latent *T cruzi* infection among those with substantial exposure to endemic areas, blood products, or engaged in intravenous drug use, particularly, if not receiving HAART. More importantly, preventing new HIV infections and controlling the existing burden of *T cruzi*

Search strategy and selection criteria

Data for this review were identified using Medline and the following search strategies: (["*Trypanosoma cruzi*" OR "Chagas disease"] AND "Encephalitis"), and ("HIV" AND ["Chagas disease" OR "*Trypanosoma cruzi*"]). The search was limited to articles published after 1985 in English, Spanish, or Portuguese. Relevant articles resulting from these searches and relevant manuscripts cited as references were included in this review.

infection in Latin America continues to be a major medical and socioeconomic challenge within the context of the UN Millennium Development Goals in the region.[50]

Conflicts of interest

We declare that we have no conflicts of interest.

References

1 Harms G, Feldmeier H. The impact of HIV infection on tropical diseases. *Infect Dis Clin North Am* 2005; **19:** 121–35.

2 Karp CL, Auwaerter PG. Coinfection with HIV and tropical infectious diseases, II: helminthic, fungal, bacterial, and viral pathogens. *Clin Infect Dis* 2007; **45:** 1214–20.

3 Karp CL, Auwaerter PG. Coinfection with HIV and tropical infectious diseases, I: protozoal pathogens. *Clin Infect Dis* 2007; **45:** 1208–13.

4 National Institutes of Health, Centers for Disease Control and Prevention, and the HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. http://aidsinfo.nih.gov/contentfiles/Adult_OI.pdf (accessed Feb 17, 2008).

5 Vaidian AK, Weiss LM, Tanowitz HB. Chagas' disease and AIDS. *Kinetoplastid Biol Dis* 2004; **3:** 2.

6 Sartori AM, Caiaffa-Filho HH, Bezerra RC, do S Guilherme C, Lopes MH, Shikanai-Yasuda MA. Exacerbation of HIV viral load simultaneous with asymptomatic reactivation of chronic Chagas' disease. *Am J Trop Med Hyg* 2002; **67:** 521–23.

7 Pacheco RS, Ferreira MS, Machado MI, et al. Chagas' disease and HIV co-infection: genotypic characterization of the *Trypanosoma cruzi* strain. *Mem Inst Oswaldo Cruz* 1998; **93:** 165–69.

8 Rocha A, de Meneses AC, da Silva AM, et al. Pathology of patients with Chagas' disease and acquired immunodeficiency syndrome. *Am J Trop Med Hyg* 1994; **50:** 261–68.

9 Ferreira MS, Borges AS. Some aspects of protozoan infections in immunocompromised patients—a review. *Mem Inst Oswaldo Cruz* 2002; **97:** 443–57.

10 Corti M. AIDS and Chagas' disease. *AIDS Patient Care STDS* 2000; **14:** 581–88.

11 Ferreira MS, Nishioka Sde A, Silvestre MT, Borges AS, Nunes-Araujo FR, Rocha A. Reactivation of Chagas' disease in patients with AIDS: report of three new cases and review of the literature. *Clin Infect Dis* 1997; **25:** 1397–400.

12 Cordova E, Boschi A, Ambrosioni J, Cudos C, Corti M. Reactivation of Chagas disease with central nervous system involvement in HIV-infected patients in Argentina, 1992–2007. *Int J Infect Dis* 2008; **12:** 587–92.

13 de Oliveira Santos E, dos Reis Canela J, Gomes Moncao HC, Guedes Roque MJ. Reactivation of Chagas' disease leading to the diagnosis of acquired immunodeficiency syndrome. *Braz J Infect Dis* 2002; **6:** 317–21.

14 Sartori AM, Lopes MH, Caramelli B, et al. Simultaneous occurrence of acute myocarditis and reactivated Chagas' disease in a patient with AIDS. *Clin Infect Dis* 1995; **21:** 1297–99.

15 Sartori AM, Ibrahim KY, Nunes Westphalen EV, et al. Manifestations of Chagas disease (American trypanosomiasis) in patients with HIV/AIDS. *Ann Trop Med Parasitol* 2007; **101:** 31–50.

16 Marin-Neto JA, Cunha-Neto E, Maciel BC, Simoes MV. Pathogenesis of chronic Chagas heart disease. *Circulation* 2007; **115:** 1109–23.

17 Maguire JH. Chagas' disease—can we stop the deaths? *N Engl J Med* 2006; **355:** 760–61.

18 Cruz-Reyes A, Pickering-Lopez JM. Chagas disease in Mexico: an analysis of geographical distribution during the past 76 years—a review. *Mem Inst Oswaldo Cruz* 2006; **101:** 345–54.

19 Pinto Dias JC. The treatment of Chagas disease (South American trypanosomiasis). *Ann Intern Med* 2006; **144:** 772–74.

20 Anez N, Crisante G, Rojas A. Update on Chagas disease in Venezuela—a review. *Mem Inst Oswaldo Cruz* 2004; **99:** 781–87.

21 Coura JR, Junqueira AC, Giordano CM, Funatsu RK. Chagas' disease in the Brazilian Amazon, I—a short review. *Rev Inst Med Trop Sao Paulo* 1994; **36:** 363–68.

22 Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of Chagas disease in the United States: a systematic review. *JAMA* 2007; **298:** 2171–81.

23 Gus I, Molon ME, Bueno AP. Chagas disease—review of 8 simultaneous cases of acute Chagas myocarditis: 25 years later. *Arq Bras Cardiol* 1993; **60:** 99–101 (in Portuguese).

24 Teixeira AR, Nascimento RJ, Sturm NR. Evolution and pathology in Chagas disease—a review. *Mem Inst Oswaldo Cruz* 2006; **101:** 463–91.

25 Sanchez-Guillen Mdel C, Lopez-Colombo A, Ordonez-Toquero G, et al. Clinical forms of *Trypanosoma cruzi* infected individuals in the chronic phase of Chagas disease in Puebla, Mexico. *Mem Inst Oswaldo Cruz* 2006; **101:** 733–40.

26 Shikanai-Yasuda MA, Lopes MH, Tolezano JE, et al. Acute Chagas' disease: transmission routes, clinical aspects and response to specific therapy in diagnosed cases in an urban centre. *Rev Inst Med Trop Sao Paulo* 1990; **32:** 16–27 (in Portuguese).

27 Dias JC. The indeterminate form of human chronic Chagas' disease: a clinical epidemiological review. *Rev Soc Bras Med Trop* 1989; **22:** 147–56.

28 Viotti R, Vigliano C, Lococo B, et al. Long-term cardiac outcomes of treating chronic Chagas disease with benznidazole versus no treatment: a nonrandomized trial. *Ann Intern Med* 2006; **144:** 724–34.

29 Herbella FA, Aquino JL, Stefani-Nakano S, et al. Treatment of achalasia: lessons learned with Chagas' disease. *Dis Esophagus* 2008; **21:** 461–67.

30 Lazo J, Meneses AC, Rocha A, et al. Chagasic meningoencephalitis in the immunodeficient. *Arq Neuropsiquiatr* 1998; **56:** 93–97.

31 Lazo JE, Meneses AC, Rocha A, et al. Toxoplasmic and chagasic meningoencephalitis in patients with human immunodeficiency virus infection: anatomopathologic and tomographic differential diagnosis. *Rev Soc Bras Med Trop* 1998; **31:** 163–71 (in Portuguese).

32 Madalosso G, Pellini AC, Vasconcelos MJ, et al. Chagasic meningoencephalitis: case report of a recently included AIDS-defining illness in Brazil. *Rev Inst Med Trop Sao Paulo* 2004; **46:** 199–202.

33 Galhardo MC, Martins IA, Hasslocher-Moreno A, et al. Reactivation of *Trypanosoma cruzi* infection in patients with acquired immunodeficiency syndrome. *Rev Soc Bras Med Trop* 1999; **32:** 291–94 (in Portuguese).

34 Sartori AM, Sotto MN, Braz LM, et al. Reactivation of Chagas disease manifested by skin lesions in a patient with AIDS. *Trans R Soc Trop Med Hyg* 1999; **93:** 631–32.

35 Iliovich E, Lopez R, Kum M, Uzandizaga G. Spontaneous chagasic peritonitis in a patient with AIDS. *Medicina (B Aires)* 1998; **58:** 507–08 (in Spanish).

36 Montero A, Cohen JE, Martinez DP, Giovannoni AG. Empirical anti-toxoplasma therapy in cerebral AIDS and Chagas disease. Presentation of 2 cases, review of the literature and proposal of an algorithm. *Medicina (B Aires)* 1998; **58:** 504–06 (in Spanish).

37 Pagano MA, Segura MJ, Di Lorenzo GA, et al. Cerebral tumor-like American trypanosomiasis in acquired immunodeficiency syndrome. *Ann Neurol* 1999; **45:** 403–06.

38 Sartori AM, Neto JE, Nunes EV, et al. *Trypanosoma cruzi* parasitemia in chronic Chagas disease: comparison between human immunodeficiency virus (HIV)-positive and HIV-negative patients. *J Infect Dis* 2002; **186:** 872–75.

39 Perez-Ramirez L, Barnabe C, Sartori AM, et al. Clinical analysis and parasite genetic diversity in human immunodeficiency virus/Chagas' disease coinfections in Brazil. *Am J Trop Med Hyg* 1999; **61:** 198–206.

40 Corti M, Yampolsky C. Prolonged survival and immune reconstitution after chagasic meningoencephalitis in a patient with acquired immunodeficiency syndrome. *Rev Soc Bras Med Trop* 2006; **39:** 85–88.

41 Sartori AM, Shikanai-Yasuda MA, Amato Neto V, Lopes MH. Follow-up of 18 patients with human immunodeficiency virus infection and chronic Chagas' disease, with reactivation of Chagas' disease causing cardiac disease in three patients. *Clin Infect Dis* 1998; **26:** 177–79.

42 Rodrigues DB, Correia D, Marra MD, et al. Cytokine serum levels in patients infected by human immunodeficiency virus with and without *Trypanosoma cruzi* coinfection. *Rev Soc Bras Med Trop* 2005; **38:** 483–87.

43 Araujo MS, Martins-Filho OA, Pereira ME, Brener Z. A combination of benznidazole and ketoconazole enhances efficacy of chemotherapy of experimental Chagas' disease. *J Antimicrob Chemother* 2000; **45:** 819–24.

44 Sanchez G, Coronado X, Zulantay I, et al. Monitoring the efficacy of specific treatment in chronic Chagas disease by polymerase chain reaction and flow cytometry analysis. *Parasite* 2005; **12:** 353–57.

45 Rassi A, Luquetti AO, Rassi A Jr, et al. Specific treatment for *Trypanosoma cruzi*: lack of efficacy of allopurinol in the human chronic phase of Chagas disease. *Am J Trop Med Hyg* 2007; **76:** 58–61.

46 Stoppani AO. The chemotherapy of Chagas disease. *Medicina (B Aires)* 1999; **59** (suppl 2)**:** 147–65 (in Spanish).

47 Dias JC, Silveira AC, Schofield CJ. The impact of Chagas disease control in Latin America: a review. *Mem Inst Oswaldo Cruz* 2002; **97:** 603–12.

48 Scapellato PG, Bottaro EG, Scapellato JI, Vidal GI. Can Chagas disease be transmitted by sharing syringes in HIV+ drug addicts?. *Medicina (B Aires)* 2006; **66:** 595–96 (in Spanish).

49 UNAIDS. Country Responses: Latin America. http://www.unaids.org/en/CountryResponses/Regions/LatinAmerica.asp (accessed Sept 22, 2008).

50 Franco-Paredes C, Von A, Hidron A, et al. Chagas disease: an impediment in achieving the Millennium Development Goals in Latin America. *BMC Int Health Hum Rights* 2007; **7:** 7.