

# Guidelines on the Treatment of Chronic Coinfection by *Trypanosoma cruzi* and HIV Outside Endemic Areas

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As a result of population migration, Chagas disease is no longer limited to the North and South American continents. In HIV-infected patients, chronic infection by *Trypanosoma cruzi* behaves as an opportunistic infection in severely immunosuppressed patients and is responsible for high morbidity and mortality. Unlike other opportunistic infections, information on the natural history, diagnosis, treatment, and prevention of Chagas disease is scarce. Spain has the highest number of cases of Chagas disease outside the North and South American continents, and coinfection with HIV is increasingly prevalent. In this article, the Spanish Society for Tropical Medicine and International Health (Sociedad Española de Medicina Tropical y Salud Internacional) reviews the current situation of coinfection with HIV and *T. cruzi* infection and provides guidelines on the diagnosis, treatment, and prevention in areas where Chagas disease is not endemic. It also identifies areas of uncertainty where additional research is necessary. **Key words:** Chagas disease, emerging infections, guideline, HIV coinfection, imported infections, opportunistic infections, *Trypanosoma cruzi*

**A**merican trypanosomiasis, or Chagas disease, is a protozoan disease caused by a flagellated parasite known as *Trypanosoma cruzi*. Chagas disease has the fourth highest morbidity and mortality rates of parasitic diseases after malaria, schistosomiasis, and leishmaniasis. It is endemic in several regions in 21 countries on the American continent, from the south of the United States to Argentina.

According to the Pan American Health Organization (PAHO), approximately 108 million people are at risk of contracting this disease in continental America (20% of the population of Latin America), 7.7 million people are infected, and 41,200 new infections are detected annually.

The disease is responsible for 12,500 deaths per year.<sup>1,2</sup> Traditionally, people affected by Chagas disease live in rural areas where they are exposed to bites by the vector (triatomine bugs). Transmission

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from mother to child and by transfusion are also common, especially in urban areas, as a result of migration to cities. Migration outside endemic areas means that many infected persons now reside in countries where this disease has never existed. In nonendemic countries such as the United States, some 325,000 people are infected. In Canada, this figure is 5,500. In Australia, it is 3,000. In Europe, more than 80,000 people are estimated to be infected and more than 4,000 cases have been confirmed.<sup>3,4</sup> With the exception of the United States, Spain is by far the country with the highest number of infected cases outside an endemic area – 2,198,949 people are from Latin American countries considered endemic for Chagas disease<sup>5</sup> – and the number of potentially infected immigrants is estimated to range from 47,000 to 87,000.<sup>4,6</sup> The disease is diagnosed mainly in patients with chronic forms of the disease and has been observed in immunodepressed patients and patients coinfecting with HIV.<sup>7-9</sup>

According to UNAIDS, at the end of 2008 approximately 2 million people were infected by HIV in Central and South America (1.8 to 2.2 million)<sup>10</sup>; and during 2004–2008 in Spain, 14.8% of all new diagnoses of HIV infection were in Latin Americans.<sup>11</sup> Therefore, co-occurrence of both diseases is to be expected in HIV endemic areas such as Spain. However, this association has received little attention. A study carried out in Brazil<sup>12</sup> revealed a prevalence of 1.3%, whereas studies in Argentina<sup>13,14</sup> found percentages of coinfection ranging from 4.2% to 7.14%. Percentages of coinfection were even higher in intravenous drug users (IVDUs; 8.9%). In a recent study in Spain,<sup>8</sup> albeit with a low number of cases, prevalence was 10.5% (2 out of 19 HIV-infected patients). Furthermore, there is no obvious increase in overall prevalence of *T. cruzi* infection in HIV-infected patients (except, perhaps, in IVDUs), because the proportion of patients infected by *T. cruzi* is similar in HIV-infected and HIV-negative patients.<sup>12,14</sup>

Coinfection by HIV and *T. cruzi* in our setting is increasingly prevalent. However, knowledge of the natural history, diagnosis, treatment, and prevention of this coinfection is scarce, and almost no classic cases of Chagas disease have been detected until recently. Consequently, care protocols for HIV-infected patients must be designed in such a way that they can easily adapt to this changing situation.

## OBJECTIVES

This article describes the characteristics of Chagas disease in HIV-infected patients and sets guidelines for the diagnosis, treatment, and prevention of this parasitic disease. The end use of the guidelines is to improve the quality of care provided to coinfecting patients in the setting of an emerging infection in Spain and other nonendemic countries.

We performed an electronic search of the published literature, with no language restrictions, until February 2011 in MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, and the Cochrane Clinical Trials Registry. A secondary search was carried out by consulting the bibliographic references of the articles included, as well as reports, conference abstracts, monographic issues, and book chapters on Chagas disease. The key words used in electronic searches were Chagas disease or *Trypanosoma cruzi* and HIV infection or AIDS. To ensure that the recommendations are interpreted correctly, the levels of evidence have been organized according to the strength of the recommendation and the type of design<sup>15</sup> (Table 1).

## CHAGAS DISEASE AND HIV INFECTION

### Clinical Manifestations

Co-occurrence of HIV infection and parasitic diseases can generate bidirectional interactions that increase the morbidity and mortality of both, as follows: (a) reactivation of latent parasitic diseases secondary to cellular immunosuppression; (b) atypical clinical manifestations, including the immune restoration inflammatory syndrome; (c) increased parasitemia in HIV-infected patients compared with other patients; (d) need for longer treatment, with the subsequent increase in side effects; (e) increased transmissibility; (f) increased mortality; and (g) increased replication of HIV due to parasitic diseases and greater likelihood of disease progression.<sup>16-20</sup>

Co-occurrence of Chagas disease and HIV infection has been well documented in the literature since the first case report in 1990,<sup>12,21-26</sup> and the effects of one disease on the other have been studied. Thus, *T. cruzi* parasitemia is more often detectable in HIV-infected patients and can precede the clinical manifestations of the disease. Similarly, increasing parasitemia levels in this group are associated with increased HIV viral load.<sup>18,27</sup>

**Table 1.** Classification of evidence for recommendations<sup>15</sup>

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from >1 properly randomized, controlled trial
II	Evidence from >1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from remarkable results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

The clinical course of Chagas disease is usually divided into 2 phases – the acute phase and the chronic phase.<sup>2</sup> The few symptoms observed during the acute phase include fever, general malaise, inflammation of the inoculation site (inoculation chancre), periocular edema (Romaña sign), enlarged lymph nodes, and splenomegaly. Approximately 5% to 10% of symptomatic cases die of meningoencephalitis, myocarditis, or both. This phase usually resolves spontaneously in 2 to 4 months, after which time the patient is chronically infected if not treated. Between 60% and 70% of patients never develop symptoms (asymptomatic chronic phase). Nevertheless, up to 40% can develop organ involvement 20 to 30 years after acute infection, namely cardiomyopathy, arrhythmia, megaviscera (esophageal achalasia or megacolon), and, more rarely, polyneuropathy. Reactivation of the disease is rare, except in immunosuppressed persons.

As with other opportunistic diseases, HIV infection favors reactivation of Chagas disease, especially in patients with CD4+ counts <200 cells/μL. The clinical picture reflects reactivation of previous chronic disease (whether asymptomatic or symptomatic) in patients who contracted the infection presumably while they were living in endemic areas. In fact, reactivations are considered AIDS-defining disease (WHO class IV) on the continent of America.<sup>28</sup> Such reactivations affect between

15% and 20% of patients, although this figure could reach 35% of coinfecting patients, co-occurring with another opportunistic infection in up to 12%.<sup>12,26,29</sup> According to estimations from Brazil, there are 2.6 cases of coinfection for every reactivation.<sup>30</sup>

Reactivations of chronic Chagas disease in coinfecting patients characteristically present with central nervous system (CNS) involvement (75%–90%), which develops as single or multiple space-occupying lesions (occasionally indistinguishable from toxoplasmosis in their radiographic appearance or clinical manifestations) or as severe necrohemorrhagic meningoencephalitis. The most common clinical manifestations are fever, headache, vomiting, altered consciousness that could progress to coma, focal neurological deficits, and convulsions. Meningeal signs, on the other hand, are uncommon.<sup>12,21,31,32</sup>

The second most common type of involvement is cardiac (10%–55% of cases), which accompanies CNS involvement in up to 10% of cases.<sup>21,23,26,29,33</sup> Myocarditis may be clinically silent or go unnoticed,<sup>17</sup> but when it manifests, it is acute and accompanied by diffuse or focal involvement of the organ and symptoms of cardiac insufficiency in differing degrees or severe arrhythmia. Given that the clinical manifestations are difficult to distinguish from those of decompensated chronic Chagas heart disease, cardiac reactivations could initially go unnoticed. Autopsy findings suggest

that a significant proportion of coinfecting patients in an apparently asymptomatic chronic phase have silent cardiac involvement with the presence of parasites in the myocardium<sup>26,29,30,33,34</sup>; therefore, the incidence of Chagas myocarditis could be higher than currently thought.

Cases of cervicitis, spontaneous peritonitis, chronic diarrhea, ocular myositis, or skin involvement have been reported anecdotally.<sup>35-39</sup> Furthermore, although reactivations are the most characteristic type of involvement, asymptomatic and paucisymptomatic forms with parasites in peripheral blood smears have also been detected.<sup>17,21</sup>

Administration of oral corticosteroids (prednisone  $\geq 20$  mg/d for more than 21 days) for the treatment of other opportunistic diseases, such as *Pneumocystis jirovecii* pneumonia, can trigger a reactivation.<sup>21</sup> Therefore, the possibility of reactivation should be taken into account in coinfecting patients receiving corticosteroids or other immunosuppressants.

Mortality in coinfecting patients with reactivation is very high, although reported rates vary to a large extent with the degree of immunosuppression, the presence of concomitant opportunistic infections, highly active antiretroviral therapy (HAART), diagnostic delay, or duration of antiparasitic treatment. In general terms, during the pre-HAART era, 80% of patients receiving antiparasitic therapy for less than 20 to 30 days died with a survival period of approximately 1 month. Early antiparasitic treatment for more than 30 days reduced mortality to 20% and significantly improved survival.<sup>12,21,22,26,40-42</sup> Prognosis has improved greatly in the HAART era, with survival periods above 3 to 5 years, although late diagnosis – both of HIV and of reactivations – is still a problem.<sup>17,21,31,43,44</sup>

## Diagnosis

Chronic *T. cruzi* infection should be ruled out in HIV-infected patients who have been exposed to the vector bite, IVDUs from an endemic area, children of mothers born in an endemic area, and recipients of potentially contaminated blood and organs (AIII). For a patient to be considered infected, positive results must be obtained in 2 serology tests with different antigens.<sup>45</sup> However, serology results could be negative due to immunosuppression. Polymerase chain reaction (PCR) could prove useful in diagnosing chronic infection

in these patients and in the evaluation of response to treatment.<sup>46</sup> Nevertheless, no commercial kits are available, and PCR techniques are not uniformly standardized. The high variation in accuracy and lack of international quality controls has precluded its wide application in clinical practice. To overcome this situation, some international standardized PCR methods have been proposed.<sup>47</sup> Finally, it is also necessary to examine the patient to determine the degree of visceral involvement (mainly cardiac and digestive).<sup>48</sup>

Detection of *T. cruzi* in blood using direct methods (microscopy) in the chronic phase of Chagas disease is exceptional (even in coinfecting individuals); therefore, the presence of the parasite is indicative of a reactivation and of the need to initiate specific treatment. Furthermore, high levels of parasitemia can precede the onset of symptoms.<sup>18</sup> In reactivations, 70% to 80% of diagnoses are established by detection of the parasite using direct microscopy in blood, cerebrospinal fluid (CSF), or other body fluids<sup>21,23,26</sup> (ascitic and pericardial fluid). In other patients, a histopathological confirmation based on biopsy specimens or autopsy findings was often the result of a late diagnosis (as coinfection was not suspected) or rapid disease course.<sup>22,32,40,41,49,50</sup>

The most commonly used diagnostic techniques in reactivations are observation of fresh samples (directly or after staining), examination of Giemsa-stained blood smears, microhematocrit, and the Strout method. In the Strout method, 5 to 10 mL of venous blood without heparin is extracted. After spontaneous retraction of the coagulum, the serum is separated and centrifuged at low speed (90–160 g). The supernatant is then transferred to another tube and centrifuged (600–900 g). The sediment is observed under light microscopy for motile *T. cruzi* parasites.

Detection of the parasite by nested PCR or blood culture should not be considered evidence of reactivation, as the results can be positive during the chronic phase, even in immunocompetent patients. However, in immunodepressed patients, real-time PCR can detect an increase in parasitemia (at least 2 determinations are necessary) long before it can be detected using direct parasitological methods or the patient shows clinical symptoms; therefore, early testing could be useful in coinfecting patients.<sup>51</sup> Serology can also be negative (<10%) in cases of reactivation confirmed by histopathology.<sup>21,32,52</sup>

A negative result for *T. cruzi* in blood using direct techniques should not rule out a diagnosis of reactivation. In these patients, the parasite must be sought in other body fluids, if possible (CSF, peritoneal or pericardial fluid), or by biopsy, especially if other concomitant opportunistic infections are suspected (AIII).

The CSF of coinfecting patients with CNS involvement contains the parasite in more than 80% of cases.<sup>21,26,53</sup> If encephalitis is suspected and there are no contraindications for lumbar puncture, examination of CSF has a high diagnostic yield. It generally presents lymphocytic pleocytosis, with moderately increased protein levels and normal or reduced glucose levels.

Necrosis and hemorrhage in tissue and abundant parasites can be observed in patients with meningoencephalitis. The cerebral lobes, cerebellum, and brain stem may be affected. It has been suggested that Chagas disease mainly affects the white matter and subcortical region, unlike toxoplasmic encephalitis, in which the affected areas are the basal ganglia and the cortex<sup>25,54</sup>; however, radiology does not confirm the diagnosis, which must be based on molecular or parasitological techniques. Radiology reveals single or multiple tumor-like lesions, which often show a mass effect and edema, and ring uptake of contrast. The appearance of these lesions may also be similar to that of a brain abscess.<sup>17,21,22,40,41,50</sup> Nuclear magnetic resonance is the most sensitive method for detecting brain lesions compatible with reactivation of *T. cruzi*. The absence of lesions on a computed tomography scan does not rule out a CNS involvement, because this may be normal in 17% of patients.<sup>21</sup>

In reactivations that affect the heart, diffuse or focal myocarditis can be observed, with a mononuclear infiltrate, cardiomegaly, edema, and amastigotes inside the myocyte and in the interstitial tissue.<sup>25,55</sup> In coinfecting individuals with cardiac involvement, it is very important to distinguish between a reactivation and the natural course of heart disease, because treatment differs for each.<sup>56</sup>

### Treatment of Reactivations

Based on data from clinical trials performed in the 1990s and on extensive clinical experience, antiparasitic treatment of Chagas disease has proven efficacious in acute, congenital,

indeterminate, and early symptomatic chronic infections. It is estimated that after treatment with benznidazole, parasitological cure occurs in 60% to 85% of patients in the acute phase and in more than 90% of congenitally infected infants treated in the first year of life, whereas treatment in the early chronic phase was 60% efficacious. However, the usefulness of trypanocidal agents is much more doubtful in patients with late chronic disease. Compared with placebo or no treatment, benznidazole increases 6.3-fold the probability of a response but with a potential marginal effect in the worst scenario (95% CI, 1.6–24.7). This drug probably does not alter the natural history of the disease in patients with advanced organ involvement.<sup>57–61</sup>

Reactivations in coinfecting patients are characterized by acute symptoms and high blood and tissue parasite counts that justify the use of antiparasitic agents<sup>21,25,26</sup> (AIII). Mortality of reactivations is high (up to 70%–80%), even with medication, although early initiation of parasitocidal and prompt antiretroviral therapy seems to improve prognosis.<sup>12,21–23,26,40–42</sup> Drug resistance could be an additional factor leading to a poorer response or increased relapse rate,<sup>62,63</sup> although this mechanism has not been demonstrated in coinfecting patients.

The most widely used drug in the treatment of Chagas disease is oral benznidazole (5–8 mg/kg/d in 2 or 3 doses for 30–60 days) (BIII). The most common adverse reactions are gastrointestinal discomfort (heartburn, nausea, vomiting, intestinal pain), cutaneous reactions (pruritus, morbilliform rash, and, rarely, Stevens-Johnson syndrome), hematological toxicity (leukopenia), neuropathy, dizziness, and insomnia.<sup>64,65</sup> Although benznidazole is the drug with which most experience is recorded in HIV-infected patients, the ideal duration of treatment has not been studied<sup>66,67</sup>; nevertheless, some guidelines suggest administering treatment for 60 to 90 days.<sup>34</sup> Data on tolerability in HIV-coinfecting patients are scarce, although up to 50% of patients can present adverse reactions.<sup>21</sup>

Nifurtimox is an alternative to benznidazole and can be administered orally at 8 to 10 mg/kg/d in 2 or 3 doses for 60 to 120 days (CIII). The adverse reaction profile is similar to that of benznidazole, although gastrointestinal tolerability is worse and can lead to anorexia, weight loss,

**Table 2.** Summary of recommendations for patients coinfecting with HIV and *Trypanosoma cruzi*

Situation	Recommendation	Level
<b>Diagnosis</b>		
Screening for chronic infection	Any person exposed to a bite by the vector, intravenous drug users from endemic areas, children of a woman born in an endemic area, recipients of potentially contaminated blood and organs	AIII
Diagnosis of reactivation	Reactivations are detected by visualization of the parasite in peripheral blood. A negative result does not rule out the diagnosis; therefore, other biological fluids should be investigated or biopsies taken, especially if the presence of concomitant opportunistic infections is suspected.	AIII
<b>Treatment</b>		
Reactivation	Antiparasitic treatment should be started early in cases of reactivation.	AIII
	Treatment should preferably be with benznidazole.	BIII
	Early initiation of HAART	AIII
Relapses	Restart antiparasitic treatment.	AIII
Chronic infection	Patients who have had the disease for less than 20 years or who are aged under 50 years, asymptomatic patients, or those with mild visceral involvement should be considered for treatment.	BII
	Consider, particularly if the CD4 T lymphocyte count is <200 cells/ $\mu$ L, the parasite load is high, or both.	CIII
Secondary prophylaxis	After the induction of antiparasitic regimen. Daily administration or 3 times per week (benznidazole)	CIII
	Suspend after reaching a stable CD4 T lymphocyte count >200 or >250 cells/ $\mu$ L and undetectable plasma viral load	CIII
<b>Pregnancy</b>		
Screening	Recommended due to possibility of transmission to the fetus	AIII
Chronic infection	Treatment is contraindicated during pregnancy due to the teratogenic potential of benzimidazoles	DIII
	Recommended after delivery	AIII
Reactivation	Evaluate the risk-benefit ratio of treatment with drugs that are potentially toxic for the fetus but than can save the mother's life.	CIII
	Early initiation of HAART	AIII
Breastfeeding	Breastfeeding is not recommended due to the transmission of HIV.	EIII

and a somewhat higher rate of withdrawal.<sup>64,68</sup> Available data in coinfecting patients are even scarcer than for benznidazole. Information on the use of itraconazole, fluconazole, and ketoconazole in coinfecting patients is anecdotal.<sup>41,69</sup>

These drugs have been useful in some cases where benznidazole cannot be used because of toxicity, by either improving clinical response or causing a decrease in *T. cruzi* parasitemia. Nevertheless, information is too scarce to make

firm recommendations about their use. No clinical trials provide sufficient evidence to warrant routine use of posaconazole. However, if therapy fails or severe adverse effects are observed with benznidazole or nifurtimox and it is impossible to administer conventional treatment, posaconazole is currently an option in immunodepressed patients.<sup>70</sup>

Given that reactivations occur in most patients when the CD4 lymphocyte count is less than 200 cells/ $\mu$ L,<sup>21,26</sup> HAART probably plays a relevant role in disease control and should be initiated when the patient's clinical situation allows (**AIII**). To date, no immune restoration inflammatory syndrome events associated with coinfection have been reported, except possibly 1 case of erythema nodosum.<sup>39</sup>

Although no data are available, antiparasitic treatment should be restarted if a relapse occurs after initially effective treatment (**AIII**). There is no consensus on whether the same or a different drug should be used. Combined therapy with benznidazole and nifurtimox does not seem to be useful, given the poor tolerability profile of both drugs and their similar mechanism of action.

Some antiretroviral drugs, mainly nonnucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI), present pharmacokinetic interactions due to their ability to induce or inhibit specific enzyme systems.<sup>71</sup> There are no studies on interactions between benznidazole and antiretroviral drugs, and available information is anecdotal.<sup>17,31,43,72</sup> Nevertheless, as benznidazole is metabolized in its active form mainly in the liver by the cytochrome P450 system,<sup>64</sup> simultaneous administration with antiretroviral agents can increase its toxicity (by enzyme induction and therefore accelerated transformation to the active form) or reduce its efficacy (by enzyme inhibition). In addition, joint use of these drugs could give way to additive toxicity: cutaneous reactions with NNRTI, fosamprenavir, and abacavir, hematologic toxicity with NRTI (especially zidovudine); peripheral neuropathy with didanosine or stavudine; and CNS toxicity with efavirenz.<sup>73</sup>

In the case of integrase inhibitors, raltegravir is a drug whose main metabolic pathway is via glucuronidation. It acts neither as a substrate of cytochrome P450 nor as an inducer of CYP3A4; therefore, no significant interactions are to be expected with benznidazole.<sup>72</sup>

### Prevention of Infection, Treatment of Chronic Infection, and Secondary Prophylaxis

Vector transmission in endemic regions usually takes place in rural areas with buildings that facilitate colonization (adobe walls and palm or straw roofs). Triatomine bugs bite at night, mainly indoors, but they can also bite outdoors.<sup>2</sup> Bites can be prevented by not sleeping in the open air or in colonized houses. A mosquito net should be used if necessary. Although oral transmission is rare in endemic areas, acute infection has high morbidity and mortality; therefore, potentially contaminated fruit or cane juices should be avoided.<sup>74</sup> Blood transfusions from infected persons should be avoided. If no compatible organs are available, organs from donors infected with *T. cruzi* can be considered for transplantation in HIV-positive patients, except for heart or intestine transplants. However, this recommendation deserves a more thorough follow-up because of the theoretical increased risk of *T. cruzi* reactivation.<sup>75,76</sup>

Treatment of chronic *T. cruzi* infection in HIV-infected patients has 2 objectives: preventing long-term complications (as in the non-HIV-infected population) and preventing reactivation. In the first case, treatment is indicated mainly in patients who have been infected for less than 20 years and who are asymptomatic or have mild visceral involvement<sup>57,58,77</sup> (**BII**). Reactivations have been reported in up to 35% of coinfecting patients; in 80% of patients experiencing reactivation, the CD4 lymphocyte count is <200 cells/ $\mu$ L (almost 50% have <100) and is generally associated with a high parasite load.<sup>21,25,26,29,78</sup> The presence of some or all of these factors simultaneously could be evaluated alongside the general recommendations for treatment of chronic *T. cruzi* infection in the general population (**CIII**). Furthermore, in this phase, optimization of HAART probably reduces the risk of reactivation.

Although the literature provides little information on long-term follow-up of patients after a reactivation, in theory there is a risk of relapse, especially if the CD4 lymphocyte count does not recover well. The regimen administered has been secondary prophylaxis with benznidazole (200 mg/d or 5 mg/kg/d, 3 times per week)<sup>17,21</sup> and with ketoconazole (400 mg/d)<sup>79</sup> (**CIII**). It is not possible to establish firm recommendations on the ideal duration of treatment or when to discontinue

it; however, a CD4 lymphocyte count of >200 or >250 cells/ $\mu$ L should be reached with a stable HAART regimen for at least 6 months (CIII).

### Care of Coinfected Pregnant Women and Children

In Spain, the prevalence of *T. cruzi* infection in women of childbearing potential from endemic areas is 3.4% to 4.8% and has been reported to be as high as 17% to 27% among Bolivian women.<sup>80-82</sup> The rate of mother-to-child transmission is 7.3%.<sup>80</sup> There are no data in Spain on mother-to-child transmission in coinfecting women, although information from Latin America shows that women with frank parasitemia or parasitemia that can be detected by PCR transmit the disease more frequently and that the percentage of transmission in coinfecting mothers is >75%.<sup>26,83-89</sup> Therefore, screening for the parasite in coinfecting pregnant women is highly recommended (AIII). By contrast, it seems that infection by *T. cruzi* could make mother-to-child transmission of HIV more difficult, either by inhibiting HIV-1 replication at several replication stages in macrophages or through a deleterious effect of *T. cruzi* on HIV-1 transduction in placental cells.<sup>90,91</sup>

There are few data on the teratogenic potential of benzimidazoles (benznidazole and nifurtimox). Nevertheless, benzimidazoles are contraindicated during pregnancy, due to their mechanism of action, the fact that they cross the placenta to bind with fetal proteins in animal models,<sup>92</sup> and the detection of chromosomal diseases in children treated with benznidazole<sup>64,93,94</sup> (DIII). In the case of a reactivation, clinicians should evaluate the risk-benefit ratio of drugs that are potentially toxic for the fetus but could save the mother's life (CIII). Although there is no published experience, another potential therapeutic option in this setting could be the use of azoles (itraconazole, fluconazole, and posaconazole) to suppress and partially treat reactivations, although this increases the risk for the fetus, given that most azoles are at least class "C" drugs (CIII). This constitutes a sensitive area for future research.

In the case of a reactivation in a pregnant woman, HAART should be initiated to maximize the immune response (AIII). Treatment of chronic infection is recommended after delivery, with the same indications as for other patients. It has been postulated that antiparasitic treatment in women

can reduce the rate of mother-to-child transmission in future pregnancies, although controlled studies evaluating this objective are necessary in order to be able to make a firm recommendation on treatment of women of childbearing potential<sup>57,84,85</sup> (AIII).

Breastfeeding should not be suspended as a consequence of *T. cruzi* infection, as the parasite has not been detected in breast milk. It should only be suspended during the acute phase with frank parasitemia or due to severe injuries on the nipple.<sup>95,96</sup> Nevertheless, in Spain as well as in the majority of developed countries, breastfeeding is not recommended for HIV-infected women<sup>97</sup> (EIII).

The children of coinfecting mothers more often present symptoms or even severe forms of the disease, with neurologic or cardiac involvement.<sup>86,87</sup> In addition, the proportion of spontaneous abortions, stillborns, and low-weight babies has increased.<sup>96</sup> In children born with HIV and *T. cruzi* infection, there is insufficient information to recommend a different care approach to that indicated for each disease separately. A greater degree of suspicion should be maintained with regard to mother-to-child transmission of Chagas disease.

### CONCLUSIONS

In nonendemic areas, *T. cruzi* can be transmitted from mother to child or accidentally through blood transfusions and organ transplants. In severely immunodepressed HIV-infected patients, chronic infection by *T. cruzi* behaves as an opportunistic disease and is responsible for high morbidity and mortality. Therefore, screening for this parasite is necessary in HIV-infected patients from endemic areas and in children of infected mothers. Reactivation of Chagas disease must be included in the differential diagnosis of diseases affecting coinfecting patients, especially when the heart or CNS are involved, as late initiation of specific treatment worsens prognosis.

Many areas of uncertainty have yet to be clarified if we are to optimize treatment of HIV-infected patients with Chagas disease. For example, we need to establish a more accurate description of the epidemiology of the disease in Spain and other nonendemic areas and improve our knowledge of its natural history in the HAART era. In addition, the ideal therapeutic

regimen must be determined and the toxicity and interaction profiles of currently used drugs must be analyzed. Finally, if secondary prophylaxis is necessary, dosing and duration must be determined.

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J.A.P.M., A.R.G., A.S.A., and J.G.B. designed the study, carried out the bibliographic search, and prepared the first draft. The rest of the authors revised the first draft and contributed to the subsequent versions until the final version. J.A.P.M. was responsible for coordinating the manuscript and for preparing the final version.

The authors declare that they have no competing interests.

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