Chagas Disease Recommendations for Solid-Organ Transplant Recipients and Donors

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Chagas disease (ChD) is a zoonotic protozoan infection caused by *Trypanosoma cruzi* and naturally transmitted by domestic and sylvatic blood-sucking triatomine bugs, known as "kissing bugs." In the human host, trypomastigotes circulate in the blood stream, whereas intracellular amastigotes appear in tissues, especially muscle (heart) and ganglion cells. *T. cruzi* may be alternatively transmitted to humans congenitally, orally, or via transfusion and organ transplantation.[1,2]

Acute infection from vectorial transmission in endemic areas is mostly asymptomatic with high parasitemia, which generally becomes controlled in immunocompetent hosts after a few months. Without treatment, the infection proceeds to the chronic phase, characterized by low-level parasitemia and poor response to treatment. Although most chronically infected patients do not develop clinical symptoms (a period of clinical latency called indeterminate form), approximately 30% progress to irreversible cardiac, gastrointestinal, and/or more rarely, peripheral nervous system disease characterized by the involvement of the autonomic nervous system and neuritis[2,3] or the central nervous system.[4] Heart disease is characterized by increasing arrhythmias or heart failure; sudden death is a characteristic of chronic ChD occurring in about 40% of patients with or without congestive heart failure.[3] The digestive tract is affected in about 15% to 20% of chronic ChD patients who develop alteration of motility, secretion and absorption in the digestive tract, followed by increased calibre of the organ and increased difficulty in emptying characteristics of megaoesophagus or megacolon.[3]

Endemic in Latin America (LA), ChD is considered a neglected tropical disease, where over 65 million people are at risk of exposure and 6 to 7 million people are infected.[5] Thanks to efforts undertaken to control the vector and test the blood supply, the incidence and prevalence have decreased considerably in the past 20 years. Vector-control policies, screening of blood donors, and the screening and treatment of acute and chronic cases varies greatly among LA countries. Although universal screening of blood donors has been fully implemented in Brazil and Argentina, where the residual risk of infection is calculated to be around 1:200 000 units,[6] in other countries, such as Mexico, there is no consensus on appropriate diagnostic methods for blood bank screening,[7] and less than 20% of units were screened for *T. cruzi* antibodies.[6] A comprehensive ChD surveillance program is not available in all countries. Consequently, there is wide geographic variation in reported infection rates, ranging from 1% to 25%[8] and up to 60% in certain highly endemic Bolivian cities.[6,9]

Risk of acquiring ChD from routine travel to endemic regions is quite low; risk factors include prolonged stays, rural areas, staying in thatched huts, and lower socioeconomic situations. A series of blood donors in the United States found that having spent 3 months or more in Mexico or Central and/or South America was associated with the highest odds of radioimmunoprecipitation assay–confirmed infection.[10]

Imported ChD is increasingly recognized as an emerging problem in the United States and Europe because of the immigration from LA. It is estimated that there are over 80 000 cases in Europe[11] and over 300 000 cases in the United States.[12] The estimated prevalence of *T. cruzi* infection in endemic and nonendemic countries is shown in Table 1.

Transmission of *T. cruzi* via blood and organ donors is a concern in both endemic and nonendemic countries.[9] ChD in transplant recipients can result from organ or blood donor-derived infection, reactivation of chronic latent infection, or de novo infection posttransplant.

RISK ASSESSMENT

Risk of Transmission by the Donor

Donors from endemic regions, or who have spent significant time in endemic regions (more than 3 months), are at risk for potential infection and transmission of ChD.[10] Even if they have no clinical manifestations of the disease, seropositive donors are likely to be chronically infected and able

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TABLE 1.

Estimated prevalence of *T. cruzi*-infected people living in endemic countries and the estimated prevalence of *T. cruzi*–infected immigrants from endemic countries living in nonendemic countries

	Estimated prevalence (year)
T. cruzi–infected people living in endemic countries	
Argentina	8.2% (1990)
Bolivia	15.4% (1990)
Brazil	1.3% (1995)
Chile	2.8% (1990)
Colombia	3.9% (1990)
Costa Rica	4.3% (1990)
Ecuador	1.2% (1990)
El Salvador	6.1% (1990)
Honduras	5.8% (1990)
Guatemala	7.9% (1990)
México	0.7% (1990)
Nicaragua	1.7% (1990)
Panama	9.0% (1990)
Paraguay	9.3% (1990)
Peru	3.0% (1990)
Uruguay	1.2% (1990)
Venezuela	4.0% (1990)
T. cruzi–infected immigrants from endemic countries living in noendemic countries	
Australia	3.8% (2006)
Canada	3.5% (2006)
Europe (15 countries excluding Spain)	2.9% (1999-2005)
Spain	5.2% (2008)
USA	2.0% (2007)

Adapted from: Schmunis G.A and Yadon Z.E.[9]

to transmit infections. Lack of recognition of potential for chronic infection in donors and the concomitant need for donor screening have resulted in transmission and numerous deaths over the years, especially in nonendemic regions. In a survey of all United States organ procurement organizations, only 19% were performing either universal or targeted donor screening for *T. cruzi* infection.[13]

The risk of transmission using kidneys and livers from chronically infected donors varies across different series, but ranges from roughly 10% to 20%, as shown in Table 2. Rates of transmission after heart transplant are much higher, at 75% or more. Although some programs and guidelines support the use of kidneys and livers from chronically infected donors, most specifically defer from use of intestine and hearts in such situations, based on the augmented risk of transmission (with use of lungs rarely or not mentioned).[16,21-26]

Rates of transmission from infected donors in nonendemic regions would be assumed to be like those seen in endemic regions. In a series of 32 transplant recipients in the United States who unintentionally received organs from 14 *T. cruzi* seropositive donors from 2001 to 2011, transmission was confirmed in 9 recipients from 6 donors, including 3 (75%) of 4 heart transplant recipients, 2 (20%) of 10 liver recipients, and 2 (13%) of 15 kidney recipients[16]; these rates are similar with those reported from South America.

It is important to mention that, because for some cases in this series, donor seropositivity was only identified retrospectively after transplant, because of the disease being identified in 1 or more recipients, there is likely to be some ascertainment bias in the rate of transmission in these figures, and the true risk of infection after receiving an organ from a seropositive donor is likely to be lower.

The decision to accept an organ from an infected donor is a balance between urgency of need for the organ and the acceptance of the risk of possible infection in the recipient, both by the medical team and the recipient through informed consent, along with the ability to diagnose and treat infection if it occurs.

Infected living donors should receive trypanocidal treatment for 30 to 60 days before the procedure and donation should take place as soon as possible after completion of treatment.[23,27] In special situations requiring transplantation before completing treatment, the transplant can be performed but if possible, not before 14 days of treatment has been completed.[27] Such recommendation is not supported by data but is most supported by the rational goal to decrease the parasitemia and consequently the risk of parasite transmission.

Donors with symptomatic acute disease (albeit rare) should be temporarily deferred and organs from donors who died of acute disease should be excluded.

TABLE 2.

Transmission from *T. cruzi* seropositive donors to seronegative recipients; each series include at least 2 patients

	Rate of transmission					
Organ	N[a]	%	Prophylaxis	Parasitemia or molecular screening after transplant	Country of transplant	Reference
Kidney	3/16	19%	No	Yes	Argentina	14
Kidney	0/9	0	Yes	No	Brazil	15
Kidney	2/15	13%	No	Yes	United States	16
Kidney	0/6	0	No	Yes	Argentina	17
Liver	0/2[b]	0	Yes	Yes	Spain	18
Liver	2/9	22%	No	Yes	Argentina	19
Liver	0/6	0	Yes	Yes	Brazil	20
Liver	2/10	20%	No	Yes	United States	16
Heart	3/4	75%	No	Yes	United States	16

[a] Recipients with transmission detected/Total recipients.
[b] One seroconverted but without disease and no molecular test was positive.

Risk of Reactivation of Infection in the Recipient

The risk of reactivation in chronically infected recipients is highest in the first year after transplant, and subsequently with intensification of immunosuppression. The risk of reactivation is highest after heart transplant, ranging from 27% to approximately 50%, and sometimes as high as 90%; although, overall transplant outcomes are usually similar to those without ChD.[25,26,28,29] The incidence of reactivation in kidney transplant recipients varies across transplant programs, and is estimated at 8% to 22%.[14,25] Reactivation after liver transplant has not been well described, perhaps because the intensity of immunosuppression is often lower,[25] with less induction therapy. The reactivation risks with specific induction treatments or maintenance immunosuppression protocols are variable across different studies, and definitive conclusions have not been reached.

Risk of "De Novo" Infection Posttransplant

Outside of the transplant event, de novo acquisition can occur from travel or residence in endemic regions and blood transfusions. Before travel to such areas, immunocompromised hosts should be educated about the risk of bites from reduviid (kissing) bugs, and postbite management should include screening for acute active disease in transplant recipients. Oral transmission has been reported from unpasteurized products (ie, contaminated guava juice, açaí products); safe food precautions should be observed in endemic regions.

DIAGNOSIS AND FOLLOW-UP

Diagnosis of Acute Infection

Acute ChD can increase morbidity and mortality in immunosuppressed individuals, especially if there is cardiac and/or central nervous system involvement. If acute ChD is suspected, any seroconversion or positive parasitologic test for *T. cruzi* in a previously negative recipient confirms infection, even before the onset of symptoms.[25] Methods such as the direct parasitologic examination (Strout, buffy coat, blood smear) in peripheral blood, spinal fluid or pericardial fluid, histopathological examination of biopsy specimens, and molecular tests (the sensitivity of polymerase chain reaction (PCR) detection of *T. cruzi* in blood samples approaches 100%) are widely used, whereas indirect parasitologic methods, such as xenodiagnosis and blood culture, are labor-intensive and time-consuming.[25]

Based on the data on transmission and clinical course, safe kidney and liver transplantation using positive donors is possible if strict posttransplant *T. cruzi* monitoring can be done to establish early diagnosis and treatment.[14,19,30] The time interval between transplant and diagnosis of acute infection varies from 3 to 29 weeks, with a mean of 8 weeks.[16]

Diagnosis of Chronic Infection

Chronic ChD is defined by having a positive epidemiology and serology, using at least 2 serological methods.[31] Conventional serological techniques are enzyme-linked immunoabsorbent assay (ELISA), indirect immunofluorescence and indirect hemagglutination. In case of inconclusive serology (ie, both a positive and a negative test), a third test is required. Cross-reaction with *Leishmania* sp and *T. rangeli* resulting in false-positive serology may occur. Thus, immunoblotting with trypomastigote excreted-secreted antigen blot can be useful to distinguish these infections; trypomastigote excreted-secreted antigen blot can also be useful in the confirmation procedure for inconclusive tests.[32] In some cases, conventional serology may not detect chronic infection because of impaired humoral immunity or the inability to detect low antibody titers to *T. cruzi*; the possibility of inconclusive or false-negative donor or recipient serology results should be considered.[33,34] Inconclusive serologic results can be confirmed by PCR, which can detect low parasitemia in chronic patients. PCR should not be used as a screening test in chronic patients; however, because its sensitivity ranges between 50% and 90% in chronic phase because of the intermittent parasitemia, a negative PCR result does not exclude the possibility of ChD.[35]

Negative seroconversion (defined as conversion from positive to nonreactive testing results) in individuals with chronic ChD has been reported after transplant, related to the immunosuppressed status.[14]

Diagnosis of Reactivation of Chronic Infection

Manifestations of clinical reactivation can include febrile illnesses, atypical skin lesions, myocarditis, or meningoencephalitis. In heart transplantation, reactivation more commonly occurs as myocarditis because of the tropism of *T. cruzi* for cardiomyocytes, causing the risk of graft dysfunction. More than 1 episode of reactivation per patient is common in heart transplantation (from 1 to 8 episodes), and an endomyocardial biopsy is essential for early diagnosis of reactivation.[36]

Positive xenodiagnosis, blood culture, or PCR results do not necessarily imply reactivation, because asymptomatic low-level parasitemia may occur in chronic disease. Therefore, a quantitative method is recommended. On the other hand, in patients with clinical suspicion, a negative blood smear does not exclude the possibility of acute disease or reactivation and bears repeating. In immunosuppressed patients, a very high parasitemia detected by blood cultures, or by xenodiagnosis, was shown to be a risk factor for reactivation.[37] The most sensitive method seems to be the dynamics of *T. cruzi* parasitemia measured by real-time PCR (RT-PCR). Quantitative RT-PCR distinguish individuals with reactivation from those without reactivation, proving to be an important tool in the prospective monitoring of parasitemia and assisting in decision making regarding preemptive therapy in transplant recipients.[38,39] However, quantitative RT-PCR needs a cutoff definition to distinguish reactivation from increased parasitemia in chronic ChD patients. An additional challenge is the *T. cruzi* genetic diversity influencing parasitemia level in infected individual from different regions of Latin America.[40]

Serology has no utility in the diagnosis of reactivation. Other diagnostic methods, discussed above in the section on acute infection, could be used to diagnose reactivation infection.

In Figure 1, there is a summary of ChD diagnosis in acute, chronic, and reactivation phase.

Posttransplantation Follow-Up

Careful monitoring during the first 6 to 24 months posttransplant for chronically infected recipients and for seronegative recipients from infected donors is recommended, because acute manifestations and reactivations predominantly occur within this period and when immunosuppression is intensified.[23] There is no study to validate a specific

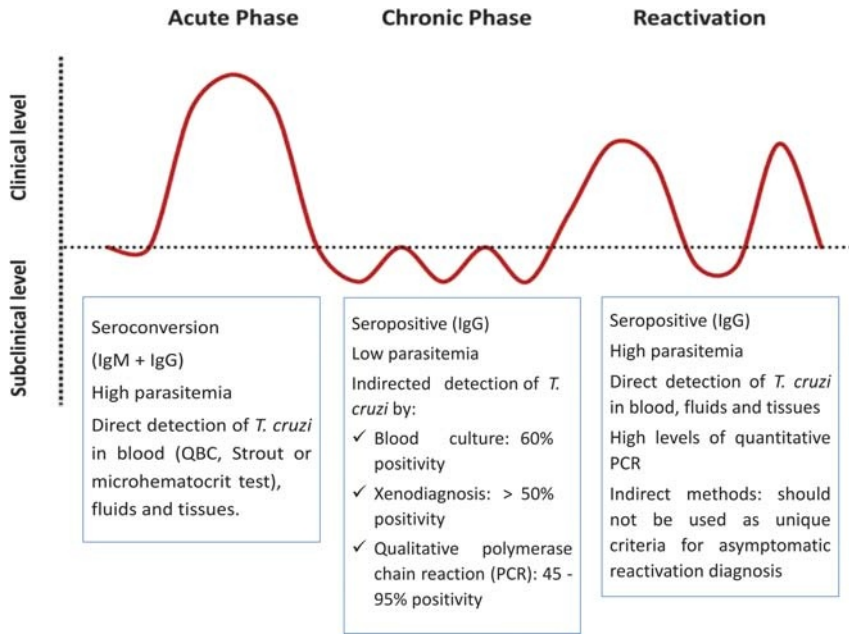

FIGURE 1. Chagas disease diagnosis in acute, chronic and reactivation phase. Red line: parasitemia levels of *T. cruzi*.

monitoring program, but most studies monitor the patients during the first 2 years after transplant.

Monitoring may detect subclinical infection before any symptoms or organ dysfunction occurs.

Monitoring Recipients of Nonheart Solid Organ Transplantation From an Infected Donor or Infected Recipients

All transplant recipients from positive donors or positive recipients should be monitored for Chagas transmission or reactivation in the posttransplantation period as follows: weekly during the first 2 months, every 2 weeks through months 3 to 6, and annually thereafter or at any time after an intensification of immunosuppression.[41] Parasitological testing should be done according to the protocol, or sooner if there is clinical suspicion for acute disease[16,23,41]; such testing includes direct parasitemia analysis (ie, Strout method), molecular methods, pathological detection of parasites in tissues, and serology. Reactivation and primary infection can appear similar; however, with reactivation, an increase in parasitic load as measured by RT-PCR can allow an earlier identification of reactivation parasitemia.[25] If transmission or reactivation occurs, tests should be performed weekly while on treatment until (at least) 2 negative results are obtained.[23]

Monitoring Seropositive Recipients After Heart Transplantation

For the diagnosis of acute chagasic myocarditis in the graft, close parasitologic monitoring, including immunohistochemistry on endomyocardial biopsies, is recommended with the following proposed schedule: weekly during the first 2 months, every 2 weeks through months 3 to 12, every 3 months through the months 13 to 24, and every 6 months thereafter.[26,42]

SCREENING OF DONORS AND RECIPIENTS

Systematic screening for donors and recipients is required for those at risk for *T. cruzi* infection before transplant. The sensitivity of those methods varies among the different phases of the disease and the immunologic status of the patient. For screening purposes, several serological techniques are used: ELISA, indirect hemagglutination assay, and indirect immunofluorescence assay. The current *T. cruzi* infection diagnosis criterion is that at least 2 different serologic tests are positive. All serologic testing has excellent sensitivity in the chronic phase but lower specificity.[43] ELISA and indirect immunofluorescence assay have sensitivity of greater than 94% in the chronic phase.[43] The serological studies perform less well in the immunosuppressed population. Molecular studies (ie, PCR) show wide variations across different studies, with a sensitivity that ranges between 45% and 95% in the chronic phase with a reported specificity of 100%, making it a very useful diagnostic tool[35,43-46] Because of the genetic variability of *T. cruzi* strains, a combination of 2 or more PCR assays with different target genes has been recommended to increase accuracy.[47] Other parasitologic diagnostics for the chronic phase have low sensitivity: 13% for xenodiagnosis and 31% for blood culture.[31]

PROPHYLAXIS AND TREATMENT

Antiparasitic Prophylaxis

Systematic data on the efficacy of prophylaxis (defined when the drug was administered in the absence of a documented acute or reactivation scenario, independently of the duration) for recipients after transplant to prevent *T. cruzi* transmission from positive donors to negative recipients are lacking. In some cases, and series published on KT, no prophylaxis has been administered, whereas others do report prophylaxis, primarily with benznidazole. When prophylaxis was not administered, parasite transmission has been reported in some or all the patients evaluated. In cases where prophylaxis was given, no cases of disease transmission have been reported, nor have any complications been observed in relation to the treatment,[15,20] although those studies included a small number of patients with no control group.

In addition, prophylactic therapy may mask signs of infection. Taking these considerations and the potential for drug toxicity into account, monitoring for evidence of transmission infection is generally preferred over the use of prophylactic therapy.[14,48]

Similarly, there is no prospective randomized trial supporting prophylaxis to prevent reactivation for positive candidates or positive recipients. In addition, because it is impossible to determine whether the patient remains at risk for subsequent reactivation, prospective monitoring of positive recipients is recommended, independent of whether they were given prophylaxis.[49]

Treatment of Chagas Disease in Solid Organ Transplantation

Immunosuppressive Treatment and Chagas Disease

There are no randomized clinical studies that evaluate the relationship between immunosuppressive treatment and transmission or reactivation of ChD. Studies carried out in heart transplant recipients support strategies to reduce ChD reactivation after transplant by altering the immunosuppression, specially replacing mycophenolate mofetil with azathioprine or using lower doses of mycophenolate.[50,51] In a retrospective study, the number of reactivations of ChD was significantly lower in patients who received lower doses of cyclosporine (5-10 mg/kg vs 3-5 mg/kg).[52]

Rapamycin appears to inhibits the in vitro growth of *Trypanosoma brucei*,[53] suggesting that mTOR inhibitors could be a good alternative to MMF. Overall, insufficient evidence exists for recommending specific immunosuppression for these cases; although, it is recommended that the use of antithymocyte globulin should be avoided and the use of MMF should be minimized, in addition to maintaining immunosuppression therapies at the lowest tolerated doses.

Antiparasitic Treatment

At any time if acute or reactivation ChD is detected, trypanocidal therapy should be started immediately. Monitoring may detect subclinical infection before any symptoms or organ dysfunction occurs. In such scenario, trypanocidal therapy is recommended as a preemptive therapy.[54]

In general population, the average cure rate among acute cases is 80%, whereas it is less than 20% among chronic patients.[55] There are no data about the cure rate among immunocompromised patients.

Among general population antiparasitic treatment is indicated for all cases with indeterminate chronic form or initial cardiac and digestive ChD.[27] There is no experience, however, on treatment of indeterminate chronic form among SOT recipients, and ChD treatment studies in this population are limited to monitoring and treatment of acute or reactivation. Theoretically, this population would be the advantage of treating the chronic condition in posttransplantation similar to general population, which would be to suppress parasitemia (for at least some time) to avoid or to slow up the progression of the disease.[8,56] The balance between the benefit of treatment of chronic ChD and the risk of adverse effects and drug interactions among SOT recipients should be addressed.

The BENEFIT clinical trial, which evaluated the long-term potential benefit of benznidazole therapy in patients with chronic Chagas cardiomyopathy, showed that trypanocidal therapy significantly reduced serum parasite detection but did not significantly reduce any severe related cardiac events evaluated through 5 years of follow-up.[57]

Current treatment options for ChD are limited to only 2 old nitro-heterocyclic drugs: benznidazole and nifurtimox (Table 3). Both drugs are metabolized via cytochrome P450 reductase and may increase calcineurin inhibitors, tacrolimus and cyclosporine blood levels, and cause tremors.[58] There is an urgent need for safe and efficacious new drug treatments or combination of drugs for both acute and chronic phases of the disease.[59]

Benznidazole is the generally preferred option for treatment given its better tolerability, although there are few studies of drug interaction with immunosuppressant drugs. The standard dose is 5 to 7 mg/kg per 24 hours divided in 2 doses, and the treatment is usually 60 days. No adjustment is needed in renal or hepatic failure patients. The most common secondary side effects of this drug are the appearance of cutaneous rashes associated with photosensitivity, peripheral neuropathy, and an unexpected high rate of angioedema.[60] It is also important to monitor for bone marrow

TABLE 3.

Current treatment options for Chagas disease

	Benznidazole	Nifurtimox
Action	Inhibition of protein and RNA synthesis in *T. cruzi*	Free oxygen radical formation
Administration	Oral	Oral
Dose for adults	5-7 mg/kg per day divided in 2 doses	8-10 mg/kg per day divided in 3 doses
Duration of treatment	60 d	90 d
Renal/Hepatic dose adjustment	No	No
Most frequent adverse effects	Rash (30%) Peripheral Neuropathy (30%, usually late)	Gastrointestinal (30-70%) Central nervous (irritability, insomnia)
Less common adverse effects	Myelosuppression Gastrointestinal	Peripheral neuropathy (usually early) Myelosuppression
Blood monitoring	Blood cell count and liver transaminases levels every 2-3 wk	Blood cell count every 2-3 wk
Immunosuppressive drug interactions	Possible increase in cyclosporine or tacrolimus levels (not studied)	Possible increase in cyclosporine or tacrolimus levels (not studied)
Other interactions	Alcohol: disulfiram-like effects	
Contraindications	Pregnancy	Pregnancy

suppression, including leukopenia and thrombocytopenia. Simultaneous alcohol intake may trigger antabuse-like symptoms.

The second-line treatment is nifurtimox, at a dose of 8 to 10 mg/kg per day in 3 divided doses, and the treatment is usually prolonged for 90 days. No adjustment is needed in renal or hepatic failure patients. The most frequent adverse effects are gastrointestinal (anorexia, nausea), weight loss, and headache. The majority is mild and can be managed with dose reduction and/or temporary suspension of medication. Potentially severe symptoms, including depression, rash, and anxiety, may appear early during the treatment.[61]

Treatment duration and dose used for benznidazole and nifurtimox were determined empirically rather than based on data. Moreover, treatment with these drugs is associated with side effects, and it is difficult to assess their efficacy given the different methods used and the lack of test-of-cure or treatment efficacy.

Regarding new drugs, a randomized controlled trial compared benznidazole with posaconazole delivered at 2 doses for 60 days.[62] Posaconazole failed to maintain a sustained response during follow-up after end of treatment as determined by PCR. Conversely, all but 1 patient treated with benznidazole showed sustained response (ie, no relapse). Azoles are not efficacious as monotherapy for the treatment of ChD patients in the indeterminate phase of the disease and benznidazole has been shown to be an efficacious drug to maintain sustained clearance of parasite even 1 year later. The azoles E1224 trial investigated the potential of E1224 (ravuconazole prodrug) as a treatment for chronic ChD: 12 months after treatment, 8% to 31% of patients treated with E1224 maintained parasite clearance compared with 81% with benznidazole, and 8.5% placebo.[63]

After treatment, transplant recipients should be followed up by clinical and laboratory testing annually for an indefinite period, because it is difficult to certify the cure after treatment.[64] Positive parasitological assays mean treatment failure, whereas negative results are insufficient to ensure cure. In addition, serology can remain positive for years after treatment in a large number of patients, which do not necessarily indicate failure of treatment.[65] Negative seroconversion after treatment usually takes months to occur after treatment of acute ChD and several years (usually 10-20 years) after treatment of chronic disease.[66] Furthermore, persistent negative results over years are necessary to indicate cure. Thus, it has been proposed to consider significant reduction in the anti–*T. cruzi* antibody titer as being similar to seronegative,[64] although this concept may not be valid for immunocompromised patients.

Several molecules and techniques have been proposed as biomarkers in *T. cruzi*-infected patients to assess whether trypanocidal therapy with is effective,[67] such as cellular injury and inflammatory markers, metabolic biomarkers, and biomarkers and thrombotic markers derived from parasite antigens. Some of them have been demonstrated to be useful for this purpose, but need to be further assessed.[68]

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