Chagas disease in the immunocompromised host

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Purpose of review
To highlight recent advances in our understanding of *Trypanosoma cruzi* infection in immunocompromised individuals, a condition that is increasingly recognized as populations shift and use of immunosuppressive medications becomes more commonplace.

Recent findings
Chagas disease screening programs should include people at risk for both Chagas disease and immunocompromise, e.g. people who have resided for ≥6 months in endemic Latin America who have an immunocompromising condition such as HIV or who are planned to start an immunosuppressive medication regimen. The goal of identifying such individuals is to allow management strategies that will reduce their risk of *T. cruzi* reactivation disease. For people with HIV-*T. cruzi* coinfection, strict adherence to antiretroviral therapy is important and antitrypanosomal treatment is urgent in the setting of symptomatic reactivation. People at risk for *T. cruzi* reactivation due to immunosuppression caused by advanced hematologic conditions or postsolid organ transplantation should be monitored via *T. cruzi* qPCR and treated with preemptive antitrypanosomal therapy if rising parasite load on serial specimens indicates reactivation. Reduction of the immunosuppressive regimen, if possible, is important.

Summary
Chronic Chagas disease can lead to severe disease in immunocompromised individuals, particularly those with advanced HIV ($CD4^+ < 200$ cells/mm^3) or peri-transplantation.

Keywords
Chagas disease, HIV, immunocompromise, transplant, *Trypanosoma cruzi*

INTRODUCTION

In patients with chronic Chagas disease, significant dysfunction of one or more of the immune mechanisms important in control of *Trypanosoma cruzi* infection can lead to inability to suppress parasite replication, resulting in *T. cruzi* reactivation [1–4]. Reactivation is most frequently reported in people with HIV (PWH) with low $CD4^+$ cell count and those on immunosuppressive regimens for transplantation. The most frequently used definition of reactivation requires either microscopically detectable parasitemia, or clinical manifestations atypical for chronic Chagas disease plus demonstration of *T. cruzi* in cerebrospinal fluid (CSF) or other normally sterile fluids or tissue [5▪▪]. Patients with positive molecular testing alone are not considered to have reactivation, since positive polymerase chain reaction (PCR) results are seen in blood from patients with chronic Chagas disease. However, evidence of rising blood parasite load by quantitative PCR (qPCR) is increasingly used as an indication for preemptive treatment in posttransplantation monitoring [6], and some researchers suggest qPCR monitoring in HIV-*T. cruzi* coinfection [7▪]. This article will review Chagas disease in these and other immunosuppressed populations.

Trypanosoma cruzi INFECTION IN PEOPLE WITH HIV

PWH who have chronic Chagas disease are at risk for *T. cruzi* reactivation when $CD4^+$ cell count decline, usually <200 cells/mm^3.

Screening for Chagas disease in people with HIV

While the importance of screening for toxoplasmosis – another chronic protozoal infection that can cause similar central nervous system (CNS) reactivation disease – at entry-to-HIV-care is well recognized, screening for Chagas disease has generally

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KEY POINTS

- Chagas disease screening should include people with HIV, hematologic disorders, and impending iatrogenic immunosuppression who have epidemiological risk factors
- Providers caring for these patient populations in regions not typically endemic for Chagas disease should be educated to recognize risk factors and signs of *T. cruzi* reactivation disease
- Knowledge of *T. cruzi* infection status is crucial to management of PWH, but ideal monitoring protocols remain to be identified
- Screening and monitoring recommendations for at-risk transplant patients should be widely implemented

been overlooked. Brazilian guidelines recommend that all PWH be screened at the time of HIV diagnosis or entry-to-care [5▪▪]. US and Spanish guidelines recommend that all PWH with Chagas disease risk factors be screened [8–10]. Screening is usually based on a single *T. cruzi* immunoglobulin G (IgG) assay, with confirmation by a second test based on different antigens (Table 1) [11]. However, *T. cruzi* serology may be negative in patients with severe immunosuppression; molecular methods may be indicated if the index of suspicion is high [12,13].

Epidemiology of chronic Chagas disease and T. cruzi reactivation in people with HIV

Chagas disease prevalence among PWH reflects that of the general population in the same area [14], with reported rates of 0.83–11% in Brazil [5▪▪,15–17], 1.2–4.2% in Argentina [18,19], 7.1% in intravenous drug users in Argentina [20], and 28% in Bolivia [21]. In the United States and Europe, the frequency of HIV-*T. cruzi* co-infection among Latin American immigrants ranges from 0–10%, reflecting the prevalence in their countries of origin [22,23,24▪,25–28]. In longitudinal analyses, the cumulative incidence of reactivation in PWH not on antiretroviral therapy (ART) was 15–21% [5▪▪,14,29,30].

Clinical manifestations of T. cruzi reactivation in people with HIV

CNS disease is the most common clinical manifestation of reactivation and is usually associated with $CD4^+$ cell count <100 cells/mm^3 [13]. In 75–80%, the patient presents with space-occupying cerebral lesions and/or meningoencephalitis [31]. The case fatality rate for CNS reactivation exceeds 75% [13,29,32]. The second most common manifestation is myocarditis in 10–55% of symptomatic patients, also associated with elevated mortality [14,33]. Reactivation also can cause cervicitis [34], peritonitis [35], gastrointestinal [36,37], and dermatologic disease [38,39].

Diagnosis of symptomatic T. cruzi reactivation

Microscopy of blood, CSF, or relevant tissue (e.g. skin) can provide an immediate diagnosis (Table 1). Because *T. cruzi* serologic tests can be insensitive in PWH with $CD4^+$ cell count <200 cells/mm^3 and microscopy of blood and/or CSF may be negative [14], reactivation cannot be ruled out by negative serology and microscopy [12,32,40,41]. PCR of CSF and other relevant fluids and tissues can be a useful tool [5▪▪,10,42,43].

The gray zone between controlled T. cruzi infection and symptomatic reactivation in people with HIV

The loss of immunologic control of *T. cruzi* in PWH represents a spectrum ranging from the asymptomatic patient with elevated parasite load only detectable by PCR, culture, or xenodiagnosis, through an intermediate stage with parasitemia detectable by microscopy, to potentially lethal symptomatic reactivation in the CNS, heart, or other organ systems. Microscopic detection of *T. cruzi* trypomastigotes in centrifuged peripheral blood is common in co-infected PWH presenting with reactivation [29]. In an early cohort, the case-fatality rate among PWH with symptomatic reactivation was high, whereas mortality was much lower among those with asymptomatic patent parasitemia [29].

Recent studies using molecular methods have documented that the distribution of parasite loads is higher in coinfected PWH than immunocompetent people with chronic Chagas disease, showing an inverse correlation with CD4 counts [21,31,38,44]. Thus, PCR sensitivity is generally higher in PWH than immunocompetent people with Chagas disease [21,45,46]. Some experts recommend following *T. cruzi* parasite load using qPCR and treating with antitrypanosomal drugs based on the results [7▪,47]. However, no consensus describes specific qPCR criteria for antitrypanosomal treatment initiation, and immune reconstitution via ART is known to effectively decrease parasite load and reactivation risk [5▪▪]. A randomized clinical trial of ART vs. ART plus antitrypanosomal therapy would be needed to answer the question of whether antitrypanosomal therapy confers added benefit for asymptomatic HIV-*T. cruzi* coinfection.

Table 1. Approach to Chagas disease in persons with current or impending immunosuppression

Scenario	Recommended approach	Laboratory test and monitoring schedule if indicated	Indication for antitrypanosomal treatment
At risk for acute *T. cruzi* infection			
Recipient of blood, organ, or tissue from donor with risk factors for *T. cruzi*	Screening of donor, serial monitoring of recipient	PCR and microscopy weekly for first 2 months, every two weeks from 3-6 months posttransplant, monthly from 6-12 months and at longer intervals thereafter	Confirmed positive PCR or microscopy
At risk for *T. cruzi* reactivation			
PWH with risk factors for *T. cruzi* infection	Screen during entry-to-care or later as catch-up	IgG serology; consider PCR for CD4 cell count < 200 and high index of suspicion	Prophylactic[a] antitrypanosomal treatment controversial due to lack of data; optimization of ART crucial
Transplant candidate (solid organ or HSCT) with risk factors for *T. cruzi* infection	Screen pretransplant	IgG serology	Sparse data suggest pre or posttransplant prophylactic[a] treatment does not eliminate reactivation risk
Solid organ transplant recipient with chronic *T. cruzi* infection	Posttransplant serial monitoring	Quantitative PCR and microscopy of peripheral blood weekly for first 2 months, every two weeks from 3-6 months posttransplant, monthly from 6-12 months and at longer intervals thereafter	Preemptive[b] treatment for rising parasite load in serial blood specimens
HSCT recipient with chronic *T. cruzi* infection	Pre and post-HSCT serial monitoring while immunosuppressed (e.g., ALC ≤ 500)	Quantitative PCR and microscopy of peripheral blood. Ideal monitoring schedule not established but should begin prior to induction chemotherapy and broadly follow that for solid organ transplant patients (5).	Preemptive[b] treatment for rising parasite load in serial blood specimens
Patient on immunosuppressive drugs for neoplasm or rheumatologic disease with risk factors for *T. cruzi* infection	Screen for *T. cruzi* infection prior to immunosuppression	IgG serology; if infected, include reactivation in differential diagnosis for febrile illness and other clinical syndromes consistent with *T. cruzi* reactivation	No data on prophylactic[a] treatment
Symptomatic *T. cruzi* reactivation			
PWH with known or suspected *T. cruzi* infection	Diagnostic testing guided by clinical picture	IgG serology if not previously diagnosed; qPCR and microscopy in blood and other specimens (i.e., CSF) as indicated	Prompt antitrypanosomal treatment can be lifesaving, especially for CNS reactivation; ART crucial
Transplant recipient or patient on immunosuppressive drugs for neoplasm or rheumatologic disease with known or suspected *T. cruzi* infection	Diagnostic testing guided by clinical picture	IgG serology if not previously diagnosed; qPCR and microscopy in blood and other specimens (i.e., CSF) as indicated	Prompt antitrypanosomal treatment; review immunosuppressive regimen

ART, antiretroviral therapy; CNS, central nervous system; CSF, cerebrospinal fluid; HSCT, human stem cell transplant; IgG, immunoglobulin G; PCR, polymerase chain reaction; PWH, people with HIV.
[a]Prophylactic treatment defined as treatment in the absence of evidence of increasing parasite replication.
[b]Preemptive treatment defined as treatment based on rising parasite loads in the absence of symptomatic reactivation.

Management of T. cruzi infection in people with HIV

As in the general population, benznidazole or nifurtimox is used to treat Chagas disease in PWH. Either drug can effectively reduce parasitemia and hasten resolution of clinical symptoms. Treatment follows the standard 60-day regimen, though some experts recommend longer courses [48]. Theoretically, higher benznidazole doses may be needed to achieve adequate CNS levels, but clinical trial data are lacking, tolerance of high dose regimens is poor, and, in practice, clinicians use standard dosing regimens [49,50].

In symptomatic reactivation, especially in the CNS, immediate antitrypanosomal therapy reduces mortality [13,29,32]. Initiation or optimization of ART is an essential component of treatment [13,29,32,47]. No reports of immune reconstitution inflammatory syndrome (IRIS) in HIV-*T. cruzi* coinfection exist in the literature. Brazilian guidelines recommend giving three weeks of antitrypanosomal therapy prior to ART initiation in ART-naïve patients [5▪▪] but the US Opportunistic Infection Guidelines recommend against delaying ART initiation [48]. Benznidazole is usually contraindicated in pregnancy but has been used successfully to treat a PWH with CNS reactivation at 32 weeks' gestation [51].

Co-infected PWH remain at risk for *T. cruzi* reactivation even after receiving a course of antitrypanosomal therapy. Brazilian guidelines recommend blood microscopy weekly during antitrypanosomal treatment until negative then monthly for 3–6 months, and every 6 months thereafter, with additional testing by PCR [5▪▪]. US and European guidelines do not include recommendations for posttreatment *T. cruzi* monitoring but focus on the importance of immune reconstitution [10,48]. After treatment for symptomatic reactivation, many experts recommend secondary prophylaxis (e.g. 2.5–5 mg/kg/day of benznidazole thrice weekly) until $CD4^+$ cell count surpasses 200 cells/mm^3 [5▪▪,52,53].

T. Cruzi INFECTION AND SOLID ORGAN TRANSPLANTATION

People with chronic Chagas disease who are iatrogenically immunosuppressed, such as during solid organ transplantation (SOT), can develop *T. cruzi* reactivation. A distinct scenario may occur when an uninfected person undergoes transplantation with an organ from a *T. cruzi*-infected donor resulting in acute *T. cruzi* infection. Both syndromes are reviewed below. The prognosis of patients with acute or reactivated *T. cruzi* infection after SOT is directly related to how quickly antitrypanosomal treatment is initiated [54–57].

Screening for T. cruzi infection prior to solid organ transplantation

T. cruzi screening of both donors and recipients has long been a standard component of pretransplant guidelines in highly endemic countries [58]. US Organ Procurement and Transplantation Network (OPTN) and European guidelines recommend targeted screening based on Chagas disease risk factors prior to SOT [59–62]. Pretransplant screening is crucial to enable monitoring, rapid diagnosis, and treatment of reactivation or acute *T. cruzi* in the recipient (Table 1).

Epidemiology of Chagas disease and T. cruzi reactivation in solid organ transplantation

In Brazil, Chagas cardiomyopathy is a frequent underlying disease in those awaiting heart transplantation (13–35% (15)), and survival posttransplant for Chagas disease patients is the same or better than for those receiving heart transplants for other etiologies [5▪▪,63]. Reported reactivation rates postcardiac transplantation range from 5 to 86% [64,65▪]. However, case definitions vary widely across these published cohorts; those that defined reactivation based on peripheral blood microscopy were associated with lower incidence and a higher proportion of clinical disease [6], while those with prospective monitoring by qPCR show higher rates overall with nearly all detected and treated preemptively while still asymptomatic [65▪,66–71].

Longitudinal data for reactivation after transplantation of organs other than the heart are sparse [72▪]. Reported reactivation rates are lower among kidney and liver recipients (22 and 33%, respectively) compared to heart recipients [73–77].

Clinical manifestations of T. cruzi reactivation post-solid organ transplantation

Reactivation symptoms range from fever, malaise, and hepatosplenomegaly [69,71] to graft failure and severe disseminated disease. The most frequent specific manifestations are skin lesions [69,78]. Reactivation myocarditis is usually diagnosed via endomyocardial biopsies during postcardiac transplant rejection monitoring [64,66,79–84] and can range from asymptomatic [66] to acute heart failure [6]. CNS disease is much less frequent in the transplantation setting than in HIV-*T.cruzi* coinfection [6,83].

Laboratory monitoring for T. cruzi reactivation post-solid organ transplantation

Because patients with chronic Chagas disease can have positive PCR results in peripheral blood, a positive PCR result alone is insufficient to diagnose reactivation. Serial blood monitoring using qPCR allows the early detection of rising parasite loads, triggering early initiation of antitrypanosomal treatment and thereby preempting symptomatic reactivation [54–57].

Recommended reactivation monitoring schedules mandate serial testing of peripheral blood by qPCR and microscopy [85] (see Table 1 and [72▪]). More frequent monitoring is recommended after heart transplantation than for other organs, given the higher degree of immunosuppression. Additional testing is warranted if the patient develops symptoms or when immunosuppression is increased for suspected organ rejection [9]. For cardiac transplant patients, because the symptoms of reactivation and organ rejection may be similar, endomyocardial tissue should be examined to distinguish between the two entities [85,86].

Management of T. cruzi reactivation in solid organ transplantation recipients

Reactivation post-SOT can occur in people treated with a full course of antitrypanosomal medication prior to immunosuppression [69,71]. The frequent adverse effects of the prolonged antitrypanosomal drug course also make prophylactic treatment less attractive. Thus, most experts recommend against giving antitrypanosomal treatment prior to SOT, and instead recommend laboratory monitoring and preemptive treatment at the first sign of rising parasitemia [6,69,71,87,88]. No published data describe the use of secondary prophylaxis for transplant recipients at risk for reactivation.

Antitrypanosomal treatment should be instituted at the first sign of reactivation (rising parasitemia levels or clinical symptoms). Poor outcomes are due to delayed recognition and treatment of reactivation. To the extent possible, immunosuppression should be minimized [69]. Brazilian guidelines recommend avoiding induction with thymoglobulin and using basiliximab or daclizumab when possible [5▪▪]. Factors associated with higher reactivation risk include the number of organ rejection episodes and, in some analyses, the use of mycophenolate mofetil (MMF) [62,65▪,68,89].

Donor-derived T. cruzi infection

When an uninfected person receives an organ from an infected donor, acute *T. cruzi* infection may occur. Transmission is not universal and varies by organ. Transplantation of heart or bowel from an infected donor is contraindicated due to *T. cruzi*'s known tissue tropism for these organs [5▪▪,90]. Four of six recipients of hearts from infected donors developed *T. cruzi* infection [91–93]. Transplantation of other organs from donors with Chagas disease can be undertaken with appropriate informed consent and posttransplantation monitoring [58,60–62,90]. Data from kidney transplant cohorts demonstrate transmission rates from 12 to 19% [74,91,94▪▪], while liver transplant cohorts show transmission rates from 0 to 36% [91,94▪▪,95,96]. No systematic data describe transmission rates for recipients of other organ types.

Clinical manifestations vary by degree of immunosuppression and speed of detection and treatment. Syndromes include myocarditis, renal graft dysfunction, and CNS disease [92,93,97,98]. Donor screening is essential; poor outcomes and death have occurred when donor status was unknown and the recipient was not monitored [56,91–93]. For the recipients of organs from infected donors, experts recommend using PCR in serial blood specimens, with antitrypanosomal treatment only if *T. cruzi* infection is detected (Table 1) [74,91,94▪▪,99▪▪].

T. cruzi INFECTION, HEMATOLOGIC CONDITIONS, AND HEMATOPOIETIC STEM CELL TRANSPLANTATION

People with chronic Chagas disease who develop a hematologic malignancy or nonmalignant bone marrow dysfunction can develop reactivation due to cellular immunosuppression caused by their underlying disease, chemotherapeutic agents, immunosuppressive regimens for hematopoietic stem cell transplantation (HSCT), or from a combination of these factors.

T. cruzi reactivation in hematological malignancy

All cases of reactivation associated with hematologic malignancy in the absence of HSCT have been reported in patients with leukemia or lymphoma (total $N = 17$; eight acute lymphocytic leukemia, one acute myelocytic leukemia, one chronic lymphocytic leukemia, two Hodgkin's lymphoma, and five non-Hodgkin's lymphoma) [100–112]. The most frequent clinical manifestations of reactivation were CNS disease ($n = 5$) and myocarditis ($n = 4$) [103,109].

A Brazilian case series described nine Chagas disease cases with multiple myeloma, of whom seven underwent autologous HSCT [104]. All were

monitored with microscopy, hemoculture, and qPCR. Several received preemptive antitrypanosomal treatment based on qPCR results, but none were diagnosed with reactivation. Notably, benznidazole treatment is not recommended for asymptomatic patients with hematologic disease due to its potential to cause myelotoxicity [5▪▪].

T. cruzi reactivation during and after hematopoietic stem cell transplantation

In the only published cohort study of patients with chronic Chagas disease who underwent HSCT, four (44%) of nine allogenic and one (8%) of 12 autologous HSCT patients developed reactivation detected by peripheral blood microscopy [87]. Notably, reactivation was detected in the autologous HSCT patient 20 days prior to HSCT, during chemotherapy. In those with reactivation, all underlying diseases were hematologic but not necessarily malignancies (one each with non-Hodgkin's lymphoma, chronic myelocytic leukemia, aplastic anemia and 2 with bone marrow dysplasia). All received preemptive benznidazole treatment and had no adverse effects related to Chagas disease.

Laboratory monitoring for *T. cruzi* reactivation before and after hematopoietic stem cell transplantation

Serial qPCR monitoring for reactivation should begin prior to HSCT for patients with chronic Chagas disease [5▪▪,6,82,104]. Specific pre-HSCT monitoring protocols have not been defined but should be tailored to the immunosuppressive regimen. The only published post-HSCT laboratory monitoring guidelines, from Brazil, recommend weekly monitoring for 60 days, then every 2 weeks during the third month, followed by monthly as long as the patient is immunosuppressed; methods similar to those used for other transplant recipients should be employed [5▪▪]. Preemptive antitrypanosomal treatment should be given for signs of rising parasitemia [87].

T. cruzi INFECTION IN PATIENTS ON IMMUNOSUPPRESSIVE AGENTS FOR RHEUMATOLOGIC DISEASE

Data describing *T. cruzi* infection in patients with rheumatologic diseases are sparse and heterogeneous with respect to underlying diseases and immunosuppressive regimens [113,114]. Six patients (three systemic lupus erythematosus, one each with rheumatoid arthritis, psoriatic arthritis, and systemic sclerosis) developed symptomatic reactivation, two with skin nodules, one with panniculitis, and three with CNS lesions; two others had fever and arthralgias which might have been related to reactivation or their underlying diseases [113–118]. Their regimens variously included cyclophosphamide, methotrexate, hydroxychloroquine, MMF, and/or azathioprine. Reactivation risk was higher in patients on >20 mg of prednisone-equivalent corticosteroid daily [113]. Rising parasite loads by qPCR were reported in two patients on TNF-alpha inhibitors [119,120].

CONCLUSION

T. cruzi reactivation disease is the most feared consequence when people with chronic Chagas disease become immunosuppressed. Severe sequelae are preventable by screening prior to immunosuppression, thereby enabling laboratory monitoring during immunosuppression. If symptomatic reactivation occurs, giving antitrypanosomal medications and reducing immunosuppression are the mainstays of treatment. Future directions include expanding access to Chagas disease screening in at-risk populations and improving management of reactivation through less toxic drugs and effective prophylactic drug regimens.

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- ▪ of special interest
- ▪▪ of outstanding interest

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This document constitutes formal recommendations by the US advisory body for screening and monitoring organ donors and recipients for *T. cruzi* (among other pathogens).

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