Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.

Downloaded from https://aidsinfo.nih.gov/guidelines on 10/16/2019

Chagas Disease (Last updated August 8, 2018; last reviewed June 26, 2019)

Epidemiology

Chagas disease (American trypanosomiasis) is caused by the protozoan parasite *Trypanosoma cruzi*, and transmitted to humans by infected triatomine bugs, and less commonly by transfusion, organ transplant, from mother to infant, and in rare instances, by ingestion of contaminated food or drink.[1-4] The hematophagous triatomine vectors defecate during or immediately after feeding on a person. The parasite is present in large numbers in the feces of infected bugs, and enters the human body through the bite wound, or through the intact conjunctiva or other mucous membrane.

Vector-borne transmission occurs only in the Americas, where an estimated 8 to 10 million people have Chagas disease.[5] Historically, transmission occurred largely in rural areas in Latin America, where houses built of mud brick are vulnerable to colonization by the triatomine vectors.[4] In such areas, Chagas disease usually is acquired in childhood. In the last several decades, successful vector control programs have substantially decreased transmission rates in much of Latin America, and large-scale migration has brought infected individuals to cities both within and outside of Latin America.[4,6,7]

Infected triatomine vectors and *T. cruzi*-infected domestic and wild animals are found across the southern half of the United States, and rare cases of autochthonous vector-borne transmission have been documented.[8-10] However, the risk of vector-borne infection within the United States appears to be very low, probably because of better housing conditions and less efficient vectors.[11] *T. cruzi* also can be transmitted in blood; screening of blood donations for anti-*T. cruzi* antibodies was introduced in 2007 after the U.S. Food and Drug Administration approved a serological test for that purpose.[12,13] Currently an estimated 90% of the U.S. blood supply is screened.

For these reasons, the vast majority of the estimated 300,000 individuals in the United States with Chagas disease are thought to be immigrants who acquired the infection while living in endemic areas in Latin America.[14] In patients chronically infected with *T. cruzi* as a result of prior infection, profound immunosuppression (e.g., due to advanced HIV disease) may lead to reactivation disease characterized by parasitemia, associated with increased intracellular parasite replication and lack of immunological control of the infection.[15-17]

Clinical Manifestations

The acute phase of *T. cruzi* infection, which typically goes unrecognized, lasts up to 90 days and is characterized by circulating trypomastigotes detectable on microscopy of fresh blood or buffy coat smears.[2,4] If the portal of infection was the conjunctiva, patients may develop the characteristic Romaña's sign—unilateral painless swelling of the upper and lower eyelids—which usually lasts several weeks. The other symptoms of acute infection are usually limited to a non-specific febrile illness. In a small proportion of patients, however, acute, life-threatening myocarditis or meningoencephalitis may occur.[2,4] At the end of the acute phase, typically 60 to 90 days after infection, parasitemia falls below levels detectable by microscopy, and in the absence of effective etiologic treatment, *T. cruzi* infection passes into the chronic phase.[2,18]

Most patients with chronic *T. cruzi* infection have no signs or symptoms, and are said to have the indeterminate form of the disease. Over the course of their lives, 20% to 30% of them will progress to clinically evident Chagas disease, most commonly cardiomyopathy.[2,18] The earliest manifestations are usually conduction system abnormalities, such as right bundle branch block, alone or in combination with frequent premature ventricular contractions, which may develop years to decades after infection.[4,19] Over time, the disease may progress to higher-grade heart block and complex ventricular arrhythmias. In patients with more advanced cardiomyopathy, congestive heart failure, ventricular aneurysm, and complete heart block are poor prognostic signs, associated with high rates of short-term mortality, including sudden death.[20] Chagas digestive disease is much less common than cardiomyopathy, and seen predominantly in infected patients

in parts of Brazil and Bolivia.[21] Dysphagia is the characteristic symptom of megaesophagus, and prolonged constipation is the most common complaint associated with megacolon.

T. cruzi reactivation during the chronic phase of Chagas disease is characterized by a return to high levels of parasite replication and parasitemia, usually detectable by microscopy, and can occur in the settings of immunosuppressive therapy to prevent transplant rejection and cancer chemotherapy, as well as in HIV-infected patients.[16,22-26] Even in the absence of symptoms, patients with chronic Chagas disease who are HIV-co-infected have significantly higher levels of *T. cruzi* parasitemia than their immunocompetent counterparts.[25] Most cases of clinically apparent reactivation occur in patients with CD4 T lymphocyte cell counts <200 cells/mm^3, a history of prior opportunistic infections, or both.[16]

The clinical features of reactivated Chagas disease in patients with HIV infection differ from those observed in individuals who are immunosuppressed for other reasons. The most common manifestations consist of *T. cruzi* meningoencephalitis, with or without brain abscesses (chagomas).[15,16,27,28] The presentation may be confused with central nervous system (CNS) toxoplasmosis and should be considered in the differential diagnosis of AIDS patients with CNS symptoms or mass lesions on imaging. The second most frequently reported manifestation of reactivation in HIV-infected patients is acute myocarditis, sometimes superimposed on pre-existing chronic Chagas heart disease.[16,17] Patients may present with new arrhythmias, pericardial effusion, acute cardiac decompensation or rapid progression of existing chronic cardiomyopathy.[16,29] Less frequent manifestations of reactivation include skin lesions, erythema nodosum, and parasitic invasion of the peritoneum, stomach or intestine.[16,29]

Diagnosis

Most patients infected with Chagas disease, including those in the United States, are in the chronic phase and typically unaware of their infection. Screening for infection in patients with the indeterminate or early clinical forms of chronic Chagas disease is important to identify those who might benefit from antiparasitic treatment and counseling regarding potential transmission of *T. cruzi* to others (e.g., blood donation, organ donation). This is particularly important for HIV-infected patients because of the risk of reactivation disease. Diagnosis of chronic infection relies on serological methods to detect immunoglobulin G antibodies to *T. cruzi*, most commonly enzyme-linked immunosorbent assay (ELISA) and immunofluorescent antibody assay (IFA). No available assay has sufficient sensitivity and specificity to be used alone; a single positive result does not constitute a confirmed diagnosis. Two serological tests based on different antigens (i.e., whole parasite lysate and recombinant antigens) and/or techniques (e.g., ELISA and IFA) are used in parallel to improve the accuracy. In some cases, the infection status remains difficult to resolve even after a third test, because there is no true gold standard assay for chronic *T. cruzi* infection.[30,31] Data suggest that the sensitivity of serological assays varies by geographical location, possibly because of *T. cruzi* strain differences and resulting antibody responses.[32,33] Options for *T. cruzi* serological testing in the United States include diagnostic ELISA kits based on parasite lysate or recombinant antigens.[30,34] In general, polymerase chain reaction (PCR) is not a useful diagnostic test for chronic *T. cruzi* infection. The sensitivity is highly variable and depends on patient characteristics as well as PCR primers and methods.[35,36]

In HIV-infected patients with epidemiologic risk factors for Chagas disease, co-infection with *T. cruzi* and reactivation disease should be considered in the differential diagnosis of CNS mass lesions, meningoencephalitis, arrhythmias or heart failure.[16,26,27] The imaging pattern of brain chagoma is similar to that of cerebral toxoplasmosis, although chagomas tend to be larger than Toxoplasma lesions.[17,27,28] Computed tomography and magnetic resonance imaging show subcortical hypodense lesions that enhance with contrast or gadolinium. These lesions most often involve brain white matter. Histopathology shows inflammation and the presence of *T. cruzi* amastigotes in glial cells, and less often, in neurons. Cerebrospinal fluid (CSF) shows a mild pleocytosis (lymphocyte predominance), increased protein, and *T. cruzi* trypomastigotes.[16,17,27,28] In a case series that included 15 HIV and *T. cruzi*-co-infected patients with clinical meningoencephalitis, trypomastigotes were visualized in CSF in 85%.[15,16,27,28]

A definitive diagnosis of re-activation is established by identification of the parasite or its products in tissue, such as on brain biopsy, in CSF or in blood.[16] Circulating parasites are rarely detected microscopically in immunocompetent patients with chronic Chagas disease or in HIV-co-infected patients in the absence of reactivation.[25] If observed in an HIV-*T. cruzi*-co-infected patient, circulating parasites suggest reactivation and the need for treatment. Blood concentration techniques, such as capillary centrifugation, can improve sensitivity.[37] In centrifuged blood, *T. cruzi* trypomastigotes are found just above the buffy coat. Centrifugation and microscopic examination of CSF also can be employed for patients with suspected CNS Chagas disease. Parasites also may be observed in lymph nodes, bone marrow, skin lesions, or pericardial fluid. Hemoculture is somewhat more sensitive than direct methods, but takes 2 to 8 weeks to demonstrate parasites.

Conventional PCR is not useful for diagnosing re-activation, because the method can yield a positive result in chronic *T. cruzi* infection in the absence of re-activation.[35,36] However, quantitative PCR assays (real-time PCR) performed on serial blood specimens that show rising parasite numbers over time provide the earliest and most sensitive indicator of reactivation.[38,39] Few published data exist on PCR of CSF, but it would be expected to have high sensitivity for the diagnosis of reactivation in the CNS.[40]

Preventing Exposure

Travelers to endemic countries may be at risk for infection with *T. cruzi* if they visit rural areas and stay in rustic lodging. The triatomine vector typically infests cracks in walls and roofing of poor-quality buildings constructed of adobe brick, mud, or thatch.[41] Because the insects feed at night, individuals who live in or visit Chagas disease-endemic areas should avoid sleeping in such dwellings or outdoors. Control programs in endemic areas rely on spraying infested dwellings with residual-action insecticide. If sleeping outdoors or in suspect dwellings cannot be avoided, sleeping under insecticide-treated bed nets provides significant protection.[42]

Most blood products in the United States are screened routinely for *T. cruzi* but screening is not universal in the United States or in others areas, including parts of Latin America.[43]

Although transfusion-acquired cases have been uncommon in the United States, transfusion with infected blood products remains a risk for acquiring Chagas disease. No drugs or vaccines for preventing *T. cruzi* infection are available.

Preventing Disease

Clinical manifestations of Chagas disease in HIV-positive patients usually represent reactivation and not acute infection with *T. cruzi*. All HIV-infected patients with epidemiologic risk factors for Chagas disease should be tested for antibody to *T. cruzi* to detect latent infection.[18] A single course of treatment with benznidazole or nifurtimox can be considered for *T. cruzi*-infected individuals who have not been previously treated and who do not have advanced Chagas cardiomyopathy **(CIII)**. However, the efficacy of currently available drugs in the chronic phase is suboptimal, there is no useful test of cure, and treated individuals are still considered at risk for reactivation.[31,44] Although direct data are lacking, optimization of antiretroviral therapy (ART) may help prevent Chagas reactivation in co-infected patients **(BIII)**. Most symptomatic reactivation cases have occurred in patients who were not taking ART.[16]

Treating Disease

Chemotherapy for Chagas disease with benznidazole or nifurtimox is effective in reducing parasitemia and preventing clinical manifestations or slowing progression in patients with acute, early-chronic, and re-activated disease.[44,45] These drugs have limited efficacy, however, in achieving parasitological cure. Consultation with a specialist should be sought. Benznidazole (5 to 8 mg/kg/day for 30 to 60 days) is the initial treatment most commonly recommended **(BIII)**. Nifurtimox (8 to 10 mg/kg/day, administered for 90 to 120 days) is an alternative **(CIII)**. The duration of therapy with either of these agents has not been studied in patients co-infected with HIV. Mortality is high for symptomatic reactivated *T. cruzi* infection,

even in patients who receive chemotherapy.[16,27] Limited data suggest that early recognition and treatment of reactivation may improve prognosis.[16]

Benznidazole is approved by FDA for use in children 2–12 years of age and is commercially available at http://www.benznidazoletablets.com/en/. Nifurtimox is not currently FDA approved and is available from the Centers for Disease Control and Prevention (CDC) Drug Service for use under an investigational protocol. Consultations and nifurtimox requests should be addressed to Division of Parasitic Diseases and Malaria Public Inquiries line (404-718-4745); parasites@cdc.gov), the CDC Drug Service (404-639-3670), and for emergencies after business hours, on weekends, and federal holidays through the CDC Emergency Operations Center (770-488-7100).

Special Considerations with Regard to Starting Antiretroviral Therapy

As with other parasite infections that localize in the CNS, the decision to initiate antiretroviral therapy (ART) must be carefully considered in HIV-infected patients with reactivated *T. cruzi* infection involving the brain. Only anecdotal information exists on the consequences of starting ART after a diagnosis of CNS Chagas disease, but there are no cases of Chagas-related immune reconstitution inflammatory syndrome (IRIS) that have been well described. Therefore, there is no known contraindication to starting or optimizing ART in patients with CNS Chagas disease as soon as their CNS disease is clinically stable **(AIII)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients undergoing treatment should be monitored closely because both benznidazole and nifurtimox are associated with significant toxicities.[46] Benznidazole causes peripheral neuropathy, rash, and granulocytopenia. Nifurtimox causes anorexia, nausea, vomiting, abdominal pain and weight loss, restlessness, tremors, and peripheral neuropathy. The adverse effects of both drugs wane when the drugs are discontinued.

As stated above, no reports are available regarding *T. cruzi* infection and IRIS.

Managing Treatment Failure

Although no efficacy data are available, retreatment with benznidazole or nifurtimox is recommended for HIV-infected patients with *T. cruzi* reactivation who fail to respond or who relapse after initial antitrypanosomal therapy **(AIII)**. A publication documents a single case of a *T. cruzi*-infected patient on immunosuppressive therapy for systemic lupus erythematosus who had a good response to posaconazole after failure of benznidazole treatment; failure of benznidazole and response to posaconazole were documented by real-time PCR assays in serial specimens.[47] However, the results of a randomized clinical trial comparing the efficacy and safety of low and high dose posaconazole to that of benznidazole demonstrated that posaconazole was not efficacious for treatment of chronic Chagas disease.[48]

Preventing Recurrence

Patients with HIV infection are at risk for recurrent or relapsing clinical manifestations because of intermittent reactivation of chronic infection.[16] The drugs are only partially effective in the chronic phase of *T. cruzi* infection and may be suppressive rather than curative.[44] Because the drugs are toxic and experience with their use in HIV-infected patients is limited, expert advice should be sought.[45] Whether secondary prophylaxis or chronic maintenance therapy should be used in HIV-infected patients with latent Chagas disease is unclear, particularly when potent ART is used.

Special Considerations During Pregnancy

As recommended for all individuals with epidemiological risk of Chagas disease, screening of pregnant women who have lived in endemic areas should be considered to identify maternal infection and possible risk of infection in their offspring. In pregnant women in areas where the disease is endemic in Latin America, the seroprevalence of *T. cruzi* infection can be as high as 30%.[14,49] In the United States, a 1999 study of 3,765 pregnant women in Houston, Texas, confirmed antibody to *T. cruzi* in 0.4% of Hispanic women and 0.1% of

non-Hispanic women and a 2013 study of 4,000 predominantly Hispanic women in the same city found 0.25% with confirmed infection.[50,51]

From 1% to 10% of infants of *T. cruzi*-infected mothers are born with acute *T. cruzi* infection.[14,49] Most congenital *T. cruzi* infections are asymptomatic or cause non-specific signs; laboratory screening is required for detection of these cases. Studies from the 1980s suggest that congenital transmission of *T. cruzi* may increase the risk of spontaneous abortion, stillbirth, and low birthweight.[52] In a small proportion of patients, congenital infection causes severe morbidity, including low birthweight, hepatosplenomegaly, anemia, meningoencephalitis, and/or respiratory insufficiency, with high risk of mortality.[49] Limited data suggest that the rate of congenital transmission is higher for HIV-infected women than in immunocompetent mothers.[16,53] Infants co-infected with HIV and *T. cruzi* also may be more likely to have symptoms, especially neurologic symptoms.[54,55]

Minimal data are available on potential reproductive toxicity of benznidazole and nifurtimox, although both drugs have been associated with increased detection of chromosomal aberrations in children being treated for Chagas disease.[56,57] Benznidazole crosses the placenta in rats and covalently binds to fetal proteins.[58] Because of the toxicity and limited experience with use of these drugs in pregnancy, treatment of acute *T. cruzi* infection in pregnant women should only be undertaken in consultation with a specialist in this area, and treatment of chronic disease should be considered only after completion of the pregnancy. For HIV-infected pregnant women with symptomatic reactivation of *T. cruzi* infection, ART should be initiated **(AIII)** as initial treatment. Two cases of treatment of Chagas disease in pregnancy with benzdidazole have been reported. One report was of an acute infection with treatment continued for the first few weeks of an subsequently diagnosed pregnancy, with normal infant outcome,[59] and one was of treatment of an HIV-infected woman with severe immunosuppression with Chagasic encephalitis in the third trimester of pregnancy.[60] The infant was small for gestational age but otherwise healthy and without evidence of *T. cruzi* infection. All infants born to *T. cruzi*-infected women should undergo appropriate testing for congenitally acquired *T. cruzi* infection and be treated promptly if infection is confirmed.[14,61]

Recommendations for Preventing and Treating Chagas Disease (American Trypanosomiasis)

Preventing Clinical Disease

Indication

- Individuals with epidemic risk factors for Chagas disease and tested positive for antibody to *T. cruzi*, have not been previously treated, and do not have advanced Chagas cardiomyopathy.
    - A single course of benznidazole or nifurtimox can be considered (doses and duration same as for treatment of disease) **(CIII)**. However, the efficacy of this therapy is suboptimal, and treated patients are still at risk of reactivation.
    - Initiation or optimization of ART may prevent reactivation of Chagas disease **(BIII)**

Treating Chagas Disease

Note: Treatment is effective in reducing parasitemia and preventing clinical manifestation or slowing progression in patients with acute, early-chronic, and re-activated disease. They have limited efficacy, however, in achieving parasitological cure.

Preferred Therapy for Acute, Early Chronic, and Re-Activated Disease:

- Benznidazole 5–8 mg/kg/day PO in 2 divided doses for 30–60 days **(BIII)** (commercially available at http://www.benznidazoletablets.com/en/).

Alternative Therapy

- Nifurtimox 8–10 mg/kg/day PO for 90–120 days **(CIII)** (not commercially available in the United States. Contact the CDC Drug Service at 404-639-3670 or drugservice@cdc.gov; for emergencies, call 770-488-7100)

Note:

- Optimal duration of therapy has not been studied in HIV-infected patients.
- Initiation or optimization of ART in patients undergoing treatment for Chagas disease, once the patient is clinically stable **(AIII)**
- Even with treatment, mortality is high in patients with symptomatic reactivation.

Key to Acronyms: ART = antiretroviral therapy; CDC = Centers for Disease Control and Prevention; PO = orally

References

1. Bittencourt AL. Congenital Chagas disease. *Am J Dis Child*. Jan 1976;130(1):97-103. Available at http://www.ncbi.nlm.nih.gov/pubmed/813519.
2. Maguire J. Trypanosomoa. In: Gorbach S. BJ, Blacklow, N; ed. Infectious Diseases: Lippincott, Williams & Wilkins; 2004:2327-2334.
3. Benchimol Barbosa PR. The oral transmission of Chagas' disease: an acute form of infection responsible for regional outbreaks. *Int J Cardiol*. Sep 10 2006;112(1):132-133. Available at http://www.ncbi.nlm.nih.gov/pubmed/16600406.
4. Rassi A, Jr., Rassi A, Marin-Neto JA. Chagas disease. *Lancet*. Apr 17 2010;375(9723):1388-1402. Available at http://www.ncbi.nlm.nih.gov/pubmed/20399979.
5. Organización Panamericana de la Salud. Estimación cuantativa de la enfermedad de Chagas en las Américas. Montevideo, Uraguay, Organización Panamericana de la Salud. 2006.
6. Gascon J, Bern C, Pinazo MJ. Chagas disease in Spain, the United States and other non-endemic countries. *Acta Trop*. Jul-Aug 2010;115(1-2):22-27. Available at http://www.ncbi.nlm.nih.gov/pubmed/19646412.
7. Moncayo A. Chagas disease: current epidemiological trends after the interruption of vectorial and transfusional transmission in the Southern Cone countries. *Mem Inst Oswaldo Cruz*. Jul 2003;98(5):577-591. Available at http://www.ncbi.nlm.nih.gov/pubmed/12973523.
8. Dorn PL, Perniciaro L, Yabsley MJ, et al. Autochthonous transmission of Trypanosoma cruzi, Louisiana. *Emerg Infect Dis*. Apr 2007;13(4):605-607. Available at http://www.ncbi.nlm.nih.gov/pubmed/17553277.
9. Herwaldt BL, Grijalva MJ, Newsome AL, et al. Use of polymerase chain reaction to diagnose the fifth reported US case of autochthonous transmission of Trypanosoma cruzi, in Tennessee, 1998. *J Infect Dis*. Jan 2000;181(1):395-399. Available at http://www.ncbi.nlm.nih.gov/pubmed/10608796.
10. Kjos SA, Snowden KF, Craig TM, Lewis B, Ronald N, Olson JK. Distribution and characterization of canine Chagas disease in Texas. *Vet Parasitol*. Apr 15 2008;152(3-4):249-256. Available at http://www.ncbi.nlm.nih.gov/pubmed/18255233.
11. Navin TR, Miller KD, Satriale RF, Lobel HO. Adverse reactions associated with pyrimethamine-sulfadoxine prophylaxis for Pneumocystis carinii infections in AIDS. *Lancet*. Jun 8 1985;1(8441):1332. Available at http://www.ncbi.nlm.nih.gov/pubmed/2860516.
12. Centers for Disease C, Prevention. Blood donor screening for chagas disease--United States, 2006-2007. *MMWR Morb Mortal Wkly Rep*. Feb 23 2007;56(7):141-143. Available at http://www.ncbi.nlm.nih.gov/pubmed/17318113.
13. Bern C, Montgomery SP, Katz L, Caglioti S, Stramer SL. Chagas disease and the US blood supply. *Curr Opin Infect Dis*. Oct 2008;21(5):476-482. Available at http://www.ncbi.nlm.nih.gov/pubmed/18725796.
14. Bern C, Verastegui M, Gilman RH, et al. Congenital Trypanosoma cruzi transmission in Santa Cruz, Bolivia. *Clin Infect Dis*. Dec 1 2009;49(11):1667-1674. Available at http://www.ncbi.nlm.nih.gov/pubmed/19877966.
15. 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*. Mar 1994;50(3):261-268. Available at http://www.ncbi.nlm.nih.gov/pubmed/8147485.
16. Sartori AM, Ibrahim KY, Nunes Westphalen EV, et al. Manifestations of Chagas disease (American trypanosomiasis) in patients with HIV/AIDS. *Ann Trop Med Parasitol*. Jan 2007;101(1):31-50. Available at http://www.ncbi.nlm.nih.gov/pubmed/17244408.
17. Vaidian AK, Weiss LM, Tanowitz HB. Chagas' disease and AIDS. *Kinetoplastid Biol Dis*. May 13 2004;3(1):2. Available at http://www.ncbi.nlm.nih.gov/pubmed/15142278.
18. Committee WHOE. Control of Chagas disease. *World Health Organ Tech Rep Ser*. 2002;905:i-vi, 1-109, back cover. Available at http://www.ncbi.nlm.nih.gov/pubmed/12092045.
19. Rassi A, Jr., Rassi A, Little WC. Chagas' heart disease. *Clin Cardiol*. Dec 2000;23(12):883-889. Available at http://www.ncbi.nlm.nih.gov/pubmed/11129673.
20. Rassi A, Jr., Rassi SG, Rassi A. Sudden death in Chagas' disease. *Arq Bras Cardiol*. Jan 2001;76(1):75-96. Available at http://www.ncbi.nlm.nih.gov/pubmed/11175486.
21. de Oliveira RB, Troncon LE, Dantas RO, Menghelli UG. Gastrointestinal manifestations of Chagas' disease. *Am J Gastroenterol*. Jun 1998;93(6):884-889. Available at http://www.ncbi.nlm.nih.gov/pubmed/9647012.
22. Campos SV, Strabelli TM, Amato Neto V, et al. Risk factors for Chagas' disease reactivation after heart transplantation. *J Heart Lung Transplant*. Jun 2008;27(6):597-602. Available at http://www.ncbi.nlm.nih.gov/pubmed/18503957.

23. Kohl S, Pickering LK, Frankel LS, Yaeger RG. Reactivation of Chagas' disease during therapy of acute lymphocytic leukemia. *Cancer*. Sep 1 1982;50(5):827-828. Available at http://www.ncbi.nlm.nih.gov/pubmed/6807527.

24. Riarte A, Luna C, Sabatiello R, et al. Chagas' disease in patients with kidney transplants: 7 years of experience 1989-1996. *Clin Infect Dis*. Sep 1999;29(3):561-567. Available at http://www.ncbi.nlm.nih.gov/pubmed/10530448.

25. 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*. Sep 15 2002;186(6):872-875. Available at http://www.ncbi.nlm.nih.gov/pubmed/12198628.

26. Sartori AM, Lopes MH, Benvenuti LA, et al. Reactivation of Chagas' disease in a human immunodeficiency virus-infected patient leading to severe heart disease with a late positive direct microscopic examination of the blood. *Am J Trop Med Hyg*. Nov 1998;59(5):784-786. Available at http://www.ncbi.nlm.nih.gov/pubmed/9840598.

27. 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*. Nov 2008;12(6):587-592. Available at http://www.ncbi.nlm.nih.gov/pubmed/18337139.

28. Diazgranados CA, Saavedra-Trujillo CH, Mantilla M, Valderrama SL, Alquichire C, Franco-Paredes C. Chagasic encephalitis in HIV patients: common presentation of an evolving epidemiological and clinical association. *Lancet* Infect Dis. May 2009;9(5):324-330. Available at http://www.ncbi.nlm.nih.gov/pubmed/19393962.

29. 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*. Dec 1997;25(6):1397-1400. Available at http://www.ncbi.nlm.nih.gov/pubmed/9431385.

30. Leiby DA, Wendel S, Takaoka DT, Fachini RM, Oliveira LC, Tibbals MA. Serologic testing for Trypanosoma cruzi: comparison of radioimmunoprecipitation assay with commercially available indirect immunofluorescence assay, indirect hemagglutination assay, and enzyme-linked immunosorbent assay kits. *J Clin Microbiol*. Feb 2000;38(2):639-642. Available at http://www.ncbi.nlm.nih.gov/pubmed/10655360.

31. Tarleton RL, Reithinger R, Urbina JA, Kitron U, Gurtler RE. The challenges of Chagas Disease-- grim outlook or glimmer of hope. *PLoS Med*. Dec 2007;4(12):e332. Available at http://www.ncbi.nlm.nih.gov/pubmed/18162039.

32. Sosa-Estani S, Gamboa-Leon MR, Del Cid-Lemus J, et al. Use of a rapid test on umbilical cord blood to screen for Trypanosoma cruzi infection in pregnant women in Argentina, Bolivia, Honduras, and Mexico. *Am J Trop Med Hyg*. Nov 2008;79(5):755-759. Available at http://www.ncbi.nlm.nih.gov/pubmed/18981518.

33. Verani JR, Seitz A, Gilman RH, et al. Geographic variation in the sensitivity of recombinant antigen-based rapid tests for chronic Trypanosoma cruzi infection. *Am J Trop Med Hyg*. Mar 2009;80(3):410-415. Available at http://www.ncbi.nlm.nih.gov/pubmed/19270291.

34. Gorlin J, Rossmann S, Robertson G, et al. Evaluation of a new Trypanosoma cruzi antibody assay for blood donor screening. *Transfusion*. Mar 2008;48(3):531-540. Available at http://www.ncbi.nlm.nih.gov/pubmed/18067497.

35. Junqueira AC, Chiari E, Wincker P. Comparison of the polymerase chain reaction with two classical parasitological methods for the diagnosis of Chagas disease in an endemic region of north-eastern Brazil. *Trans R Soc Trop Med Hyg*. Mar-Apr 1996;90(2):129-132. Available at http://www.ncbi.nlm.nih.gov/pubmed/8761570.

36. Wincker P, Telleria J, Bosseno MF, et al. PCR-based diagnosis for Chagas' disease in Bolivian children living in an active transmission area: comparison with conventional serological and parasitological diagnosis. *Parasitology*. Apr 1997;114 (Pt 4):367-373. Available at http://www.ncbi.nlm.nih.gov/pubmed/9107023.

37. Feilij H, Muller L, Gonzalez Cappa SM. Direct micromethod for diagnosis of acute and congenital Chagas' disease. *J Clin Microbiol*. Aug 1983;18(2):327-330. Available at http://www.ncbi.nlm.nih.gov/pubmed/6413530.

38. Duffy T, Bisio M, Altcheh J, et al. Accurate real-time PCR strategy for monitoring bloodstream parasitic loads in chagas disease patients. *PLoS Negl Trop Dis*. 2009;3(4):e419. Available at http://www.ncbi.nlm.nih.gov/pubmed/19381287.

39. Schijman AG, Vigliano C, Burgos J, et al. Early diagnosis of recurrence of Trypanosoma cruzi infection by polymerase chain reaction after heart transplantation of a chronic Chagas' heart disease patient. *J Heart Lung Transplant*. Nov 2000;19(11):1114-1117. Available at http://www.ncbi.nlm.nih.gov/pubmed/11077230.

40. Qvarnstrom Y, Schijman AG, Veron V, Aznar C, Steurer F, da Silva AJ. Sensitive and specific detection of Trypanosoma cruzi DNA in clinical specimens using a multi-target real-time PCR approach. *PLoS Negl Trop Dis*. 2012;6(7):e1689. Available at http://www.ncbi.nlm.nih.gov/pubmed/22802973.

41. Mott KE, Muniz TM, Lehman JS, Jr., et al. House construction, triatomine distribution, and household distribution

of seroreactivity to Trypanosoma cruzi in a rural community in northeast Brazil. *Am J Trop Med Hyg*. Nov 1978;27(6):1116-1122. Available at http://www.ncbi.nlm.nih.gov/pubmed/103445.

42. Kroeger A, Villegas E, Ordonez-Gonzalez J, Pabon E, Scorza JV. Prevention of the transmission of Chagas' disease with pyrethroid-impregnated materials. *Am J Trop Med Hyg*. Mar 2003;68(3):307-311. Available at http://www.ncbi.nlm.nih.gov/pubmed/12685636.
43. Schmunis GA, Cruz JR. Safety of the blood supply in Latin America. *Clin Microbiol Rev*. Jan 2005;18(1):12-29. Available at http://www.ncbi.nlm.nih.gov/pubmed/15653816.
44. Rodriques Coura J, de Castro SL. A critical review on Chagas disease chemotherapy. *Mem Inst Oswaldo Cruz*. Jan 2002;97(1):3-24. Available at http://www.ncbi.nlm.nih.gov/pubmed/11992141.
45. Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of chagas disease in the United States: a systematic review. *JAMA*. Nov 14 2007;298(18):2171-2181. Available at http://www.ncbi.nlm.nih.gov/pubmed/18000201.
46. Castro JA, de Mecca MM, Bartel LC. Toxic side effects of drugs used to treat Chagas' disease (American trypanosomiasis). *Hum Exp Toxicol*. Aug 2006;25(8):471-479. Available at http://www.ncbi.nlm.nih.gov/pubmed/16937919.
47. Pinazo MJ, Espinosa G, Gallego M, Lopez-Chejade PL, Urbina JA, Gascon J. Successful treatment with posaconazole of a patient with chronic Chagas disease and systemic lupus erythematosus. *Am J Trop Med Hyg*. Apr 2010;82(4):583-587. Available at http://www.ncbi.nlm.nih.gov/pubmed/20348503.
48. Molina I, Gomez i Prat J, Salvador F, et al. Randomized trial of posaconazole and benznidazole for chronic Chagas' disease. *N Engl J Med*. May 15 2014;370(20):1899-1908. Available at http://www.ncbi.nlm.nih.gov/pubmed/24827034.
49. Torrico F, Alonso-Vega C, Suarez E, et al. Maternal Trypanosoma cruzi infection, pregnancy outcome, morbidity, and mortality of congenitally infected and non-infected newborns in Bolivia. *Am J Trop Med Hyg*. Feb 2004;70(2):201-209. Available at http://www.ncbi.nlm.nih.gov/pubmed/14993634.
50. Di Pentima MC, Hwang LY, Skeeter CM, Edwards MS. Prevalence of antibody to Trypanosoma cruzi in pregnant Hispanic women in Houston. *Clin Infect Dis*. Jun 1999;28(6):1281-1285. Available at http://www.ncbi.nlm.nih.gov/pubmed/10451166.
51. Edwards MS, Rench MA, Charles TW, et al. Perinatal Screening for Chagas Disease in Southern Texas. *J Ped Infect Dis*. 2015;4(1):67. Available at http://jpids.oxfordjournals.org/content/early/2013/10/03/jpids.pit056.1.full.
52. Bittencourt AL. Possible risk factors for vertical transmission of Chagas' disease. *Rev Inst Med Trop Sao Paulo*. Sep-Oct 1992;34(5):403-408. Available at http://www.ncbi.nlm.nih.gov/pubmed/1342103.
53. Scapellato PG, Bottaro EG, Rodriguez-Brieschke MT. Mother-child transmission of Chagas disease: could coinfection with human immunodeficiency virus increase the risk? *Rev Soc Bras Med Trop*. Mar-Apr 2009;42(2):107-109. Available at http://www.ncbi.nlm.nih.gov/pubmed/19448923.
54. Freilij H, Altcheh J. Congenital Chagas' disease: diagnostic and clinical aspects. *Clin Infect Dis*. Sep 1995;21(3):551-555. Available at http://www.ncbi.nlm.nih.gov/pubmed/8527542.
55. Freilij H, Altcheh J, Muchinik G. Perinatal human immunodeficiency virus infection and congenital Chagas' disease. *Pediatr Infect Dis J*. Feb 1995;14(2):161-162. Available at http://www.ncbi.nlm.nih.gov/pubmed/7746707.
56. Gorla NB, Ledesma OS, Barbieri GP, Larripa IB. Assessment of cytogenetic damage in chagasic children treated with benznidazole. *Mutat Res*. Oct 1988;206(2):217-220. Available at http://www.ncbi.nlm.nih.gov/pubmed/3140001.
57. Gorla NB, Ledesma OS, Barbieri GP, Larripa IB. Thirteenfold increase of chromosomal aberrations non-randomly distributed in chagasic children treated with nifurtimox. *Mutat Res*. Oct 1989;224(2):263-267. Available at http://www.ncbi.nlm.nih.gov/pubmed/2507913.
58. de Toranzo EG, Masana M, Castro JA. Administration of benznidazole, a chemotherapeutic agent against Chagas disease, to pregnant rats. Covalent binding of reactive metabolites to fetal and maternal proteins. *Arch Int Pharmacodyn Ther*. Nov 1984;272(1):17-23. Available at http://www.ncbi.nlm.nih.gov/pubmed/6440493.
59. Correa VR, Barbosa FG, Melo Junior CA, D'Albuquerque e Castro LF, Andrade Junior HF, Nascimento N. Uneventful benznidazole treatment of acute Chagas disease during pregnancy: a case report. *Rev Soc Bras Med Trop*. May-Jun 2014;47(3):397-400. Available at http://www.ncbi.nlm.nih.gov/pubmed/25075496.
60. Bisio M, Altcheh J, Lattner J, et al. Benznidazole treatment of chagasic encephalitis in pregnant woman with AIDS. *Emerg Infect Dis*. 2013;19(9):1490-1492. Available at http://www.ncbi.nlm.nih.gov/pubmed/23965334.
61. Oliveira I, Torrico F, Munoz J, Gascon J. Congenital transmission of Chagas disease: a clinical approach. *Expert Rev Anti Infect Ther*. Aug 2010;8(8):945-956. Available at http://www.ncbi.nlm.nih.gov/pubmed/20695749.