Understanding Chagas Disease in Immunosuppressed Hosts: Lessons from HIV Coinfection

Lígia Camera Pierrotti, MD, PhD
University of São Paulo – São Paulo – Brazil

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IAS

DISCLOSURES

Ligia C Pierrotti, PhD

Infectious Diseases Physician

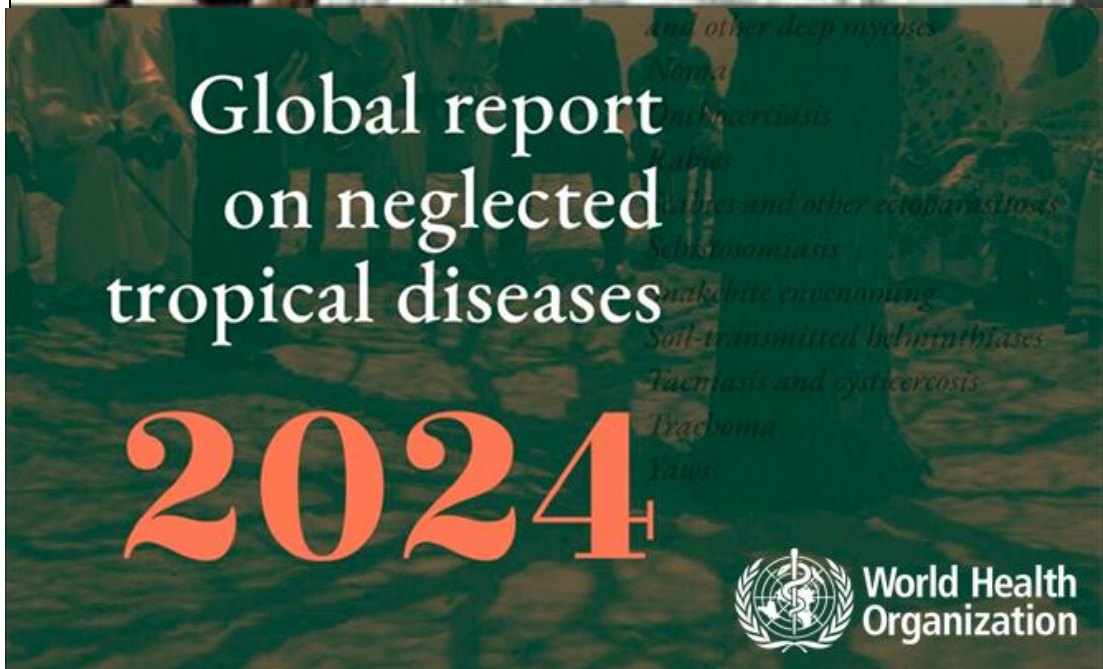
Hospital das Clínicas - University of São Paulo

São Paulo - SP/ Brazil

I, or my spouse/partner *do not have relevant* financial relationship with respect to the content of this presentation /session.

Chagas Disease

More than a century after its discovery, in 1909 [1], Chagas disease remains an infectious condition categorized as a neglected disease by the World Health Organization (WHO) [2]



1. Chagas C. Mem Inst Oswaldo Cruz [Internet]. 1909;1(2):159–218. Available from: https://doi. org/10.1590/s0074-02761909000200008

2. World Health Organization (WHO). Wkly Epidemiol Rec. 2015;90(6):33-43.

2. WHO releases the Global Report on Neglected Tropical Diseases 2024. Available at: https://www.who.int/teams/control-of-neglected-tropical-diseases/global-report-on-neglected-tropical-diseases-2024

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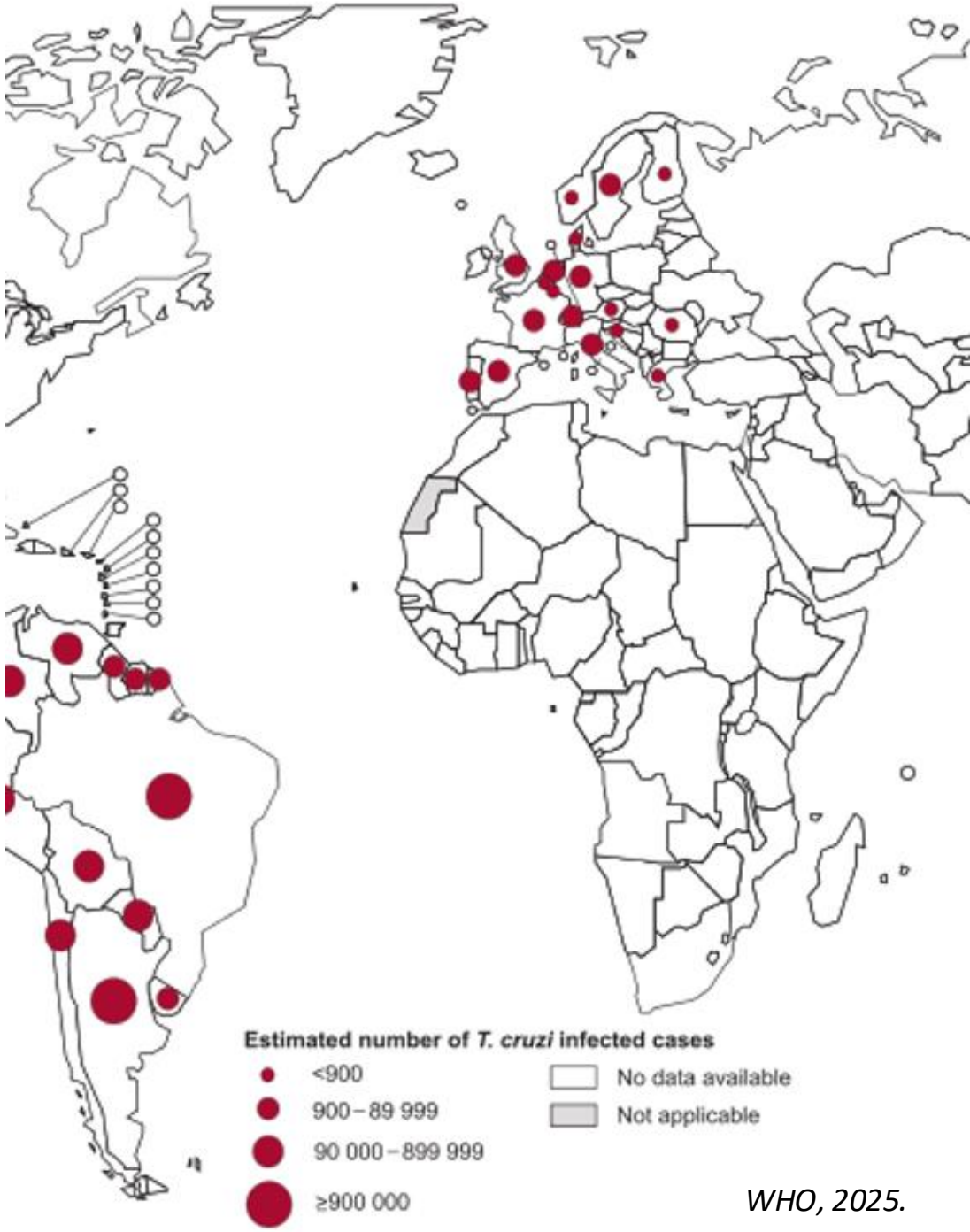
Chagas Disease Landscape

- **Caused by the protozoan *Trypanosoma cruzi***
- Approximately **70 million individuals** residing across 21 endemic countries in the Americas **are susceptible to *T. cruzi* infection.**
- Globally, an **estimated 6-15 million people are infected**, with Latin America accounting for the majority of cases.
- Further, in the Americas alone, **more than 12,000 associated fatalities** are registered each year.



WHO, 2025.

Chagas Disease Landscape

- Approximately 70 million individu endemic countries in the America *cruzi* infection.
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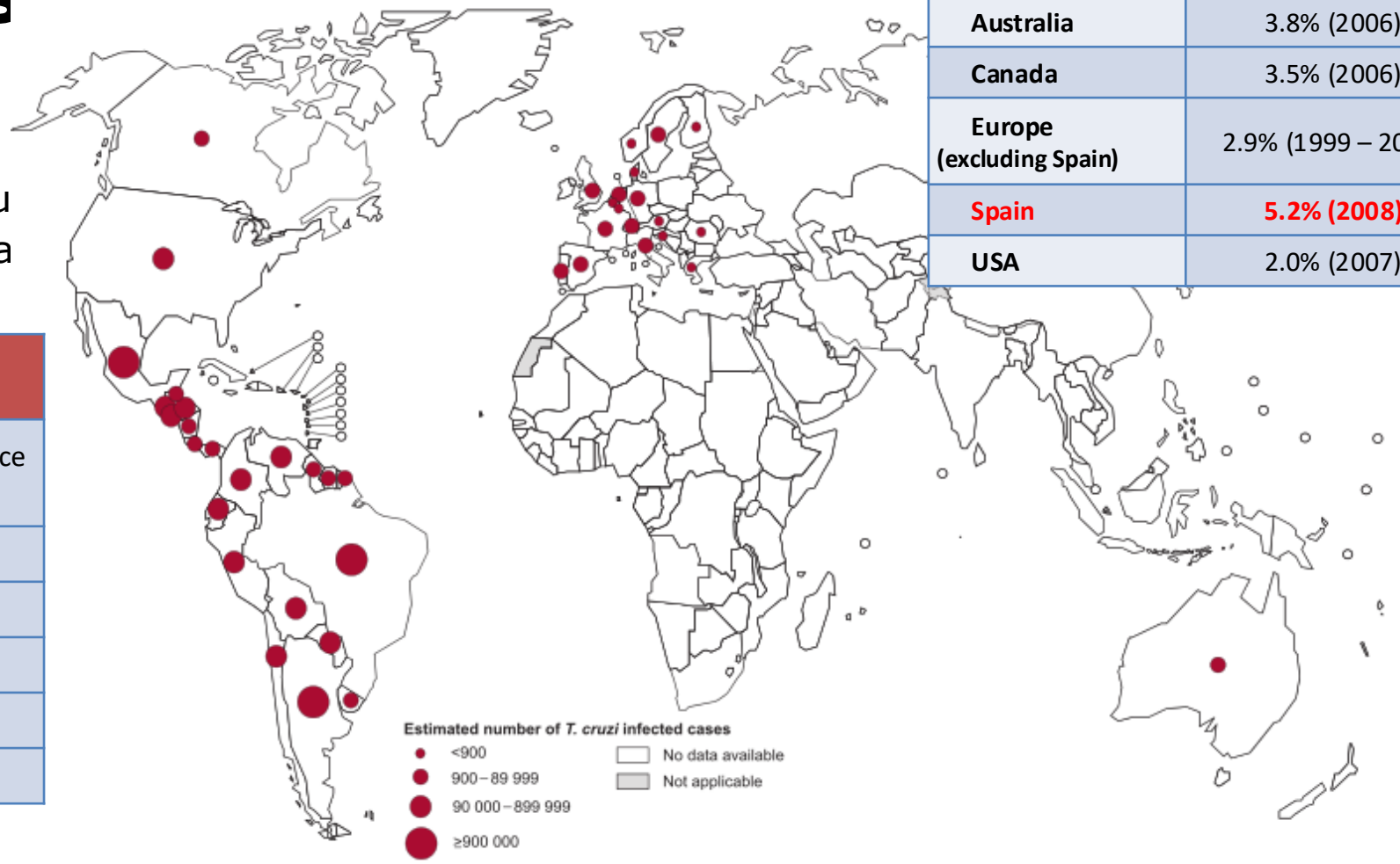
- Furtl asso
- Chag coun expe

Endemic Countries *	
T. cruzi-infected people	Estimated prevalence (year)
Argentina	8.2% (1990)
Bolivia	**15.4% (1990)**
Brazil	1.3% (1995)
Guatemala	7.9% (1990)
México	0.7% (1990)



Non-endemic Countries *	
T. cruzi-infected people	Estimated prevalence (year)
Australia	3.8% (2006)
Canada	3.5% (2006)
Europe (excluding Spain)	2.9% (1999 – 2005)
Spain	**5.2% (2008)**
USA	2.0% (2007)

WHO, 2025.
** Adapted from: Schmunis G.A and Yadon Z.E. Acta Tropica 2010.*

ChD Trasmission Routes

Vectorial (infected triatomines, “kissing bugs”)

Oral ingestion

Blood transfusion

Solid organ transplantation

Vertical transmission

Breastfeeding

Acidents in research laboratories

Dias J, Schofield C. Mem Inst Oswaldo Cruz 1999.

Coura JR. Mem Inst Oswaldo Cruz 2015.

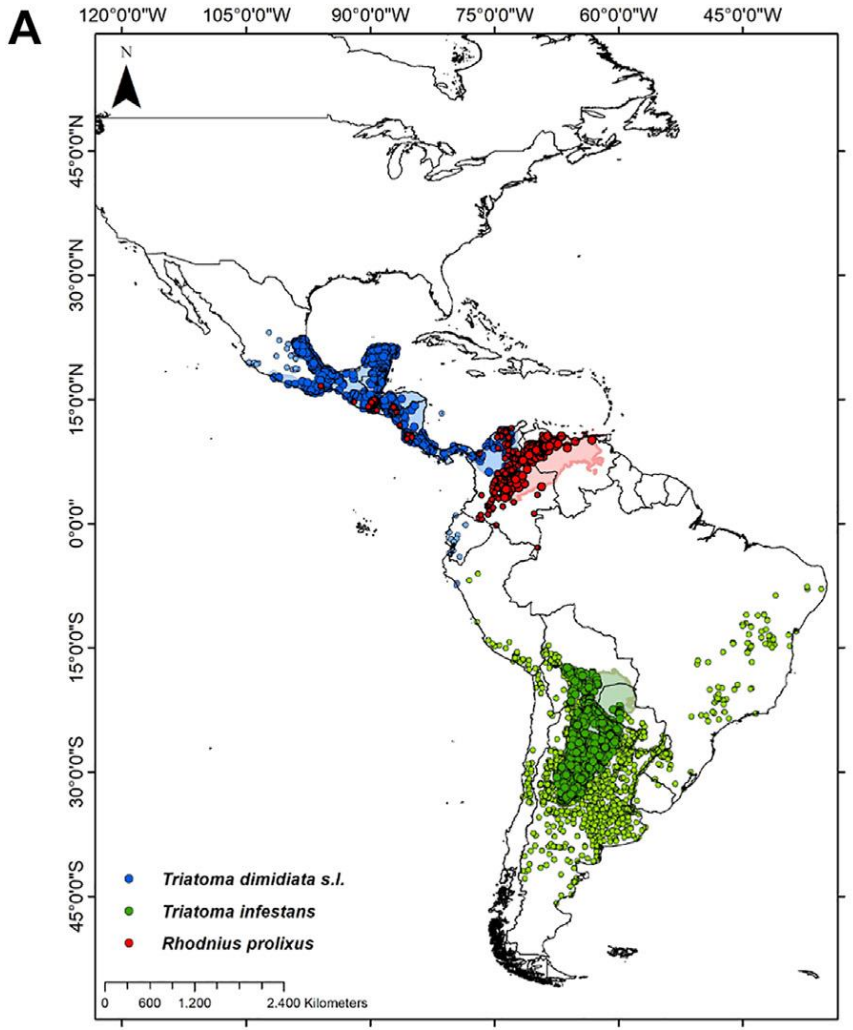
Up to the present, PAHO has issued **certifications of interruption of *T. cruzi* transmission by non-native populations of two vector species**:

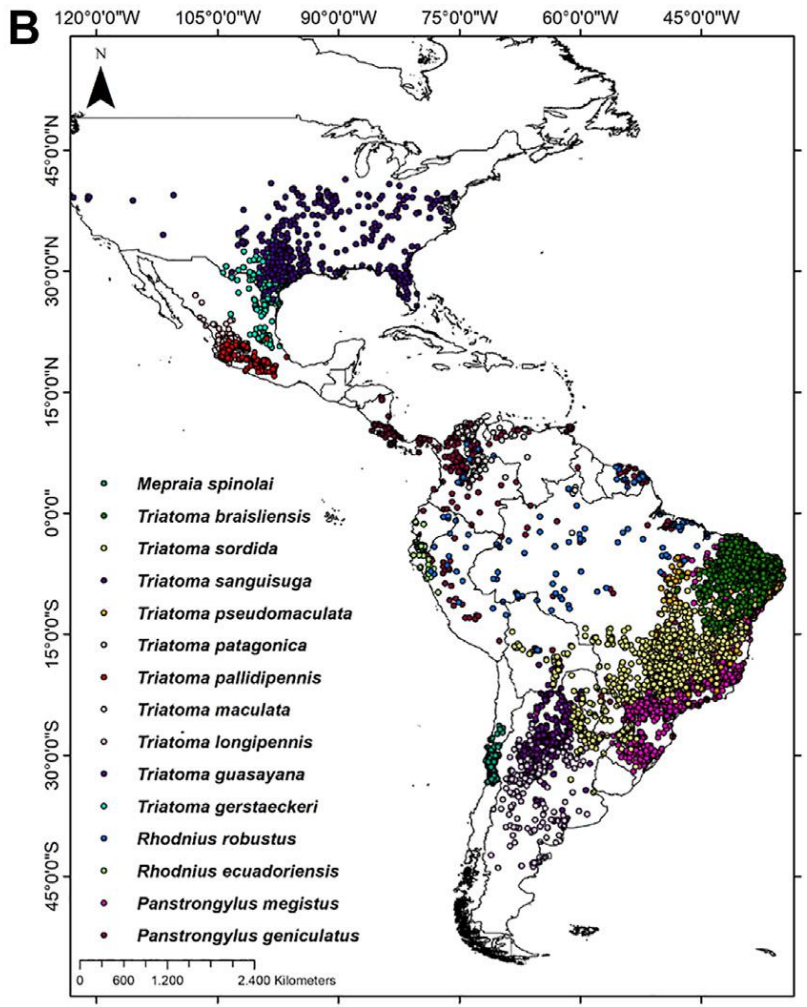
- *T. infestans* in Uruguay, Chile, Brazil, Paraguay, and parts of Argentina, Bolivia, and Peru;
- R. prolixus in Mexico, Guatemala, Belize, Honduras, El Salvador, Nicaragua, Costa Rica, and parts of Colombia.

Organización Panamericana de la Salud. Enfermedad de Chagas – Transmisión por el principal vector. https://www.paho.org/en/ documents/map-chagas-vectorial-transmission-2019-spanish-only; 2019. Accessed June 11, 2024.

Vector transmission is limited to the Americas, involving **more than 150 triatomine species**

Main domiciliated vector species





Other important vector species

Cucunubá ZM et al. The Lancet Regional Health – Americas 2024;37: 100881

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Natural History of Chagas Disease

Acute ChD

- ✓ Mostly asymptomatic
- ✓ High parasitemia
- ✓ Good response to treatment (50 - 100% cure)
- ✓ Resolve with no treatment - chronic infection

Chronic Infection

- ✓ Can be asymptomatic for life
- ✓ Evolve to heart (30%) or GI disease (10 - 15%)
- ✓ Low parasitemia
- ✓ Poor response to treatment (20 - 35% cure)

Reactivation

- ✓ Patients under immunosuppression

Pérez-Molina JA, Molina I. Lancet 2018 Jan;391(10115):82–94.
Echeverria LE, Morillo CA. Infect Dis Clin North Am 2019 Mar;33(1):119–34.

Scope

- What is the **risk of reactivation**?
  - How is this affected by type of IS
- What are the **clinical manifestations** of reactivation?
- What is the **definition** of reactivation
- How to make the **diagnosis and treatment**

ChD and Immunossupression

- **About 1 in 50 people globally are immunocompromised** due to a primary disease or as a consequence of immunosuppressive medication [1]
- **Reactivation of chronic Chagas disease** has been described in immunosuppressed patients
  - ✓ **People with HIV/AIDS (PWH)**
  - ✓ **Transplant recipients**
  - ✓ **Patients receiving chemotherapy for hematologic and solid malignancies**
  - ✓ **Patients with autoimmune diseases under IS, including conditions such as systemic lupus erythematosus [SLE], rheumatoid arthritis, dermatomyositis, mixed connective tissue disease, and scleroderma**
- **IS modifies the natural history of *Trypanosoma cruzi* infection** in chagasic patients
- Clinical manifestations of reactivation can result in **more severe presentation** than in acute ChD in immunocompetent individuals
- Early diagnosis and prompt treatment can **reduce morbidity and mortality**
- Healthcare professionals must assess ChD diagnosis in **all patients undergoing immunosuppression who are at epidemiological risk**

1. Harpaz R et al. JAMA. 2016;316(23):2547-2548.
Pinazo MJ et al. PLoS Negl Trop Dis 7(1): e1965.

Risk of reactivation among chronically *T. cruzi*-infected immunosuppressed patients

Populations	Reported rates of ChD reactivation	References
Solid organ transplant recipients	Non-heart tx: 8 – 35% Heart tx: 20 - 90%	Pierrotti, L.C., Ibrahim, K.Y. (2020). Chagas Disease: Coming to a Transplanted Patient Near You. In: Morris, M., Kotton, C., Wolfe, C. (eds) Emerging Transplant Infections. Springer, Cham.
Hematopoietic transplant recipients	17 – 40%	Altclas J et al. Bone Marrow Transplant. 2005.
People living with HIV/AIDS	1 – 28%	Clark EH, Bern C. Trop Med Infect Dis. 2021
Cancer under chemo	Reported cases	Carvalho NB et al. Rev Inst Med Trop Sao Paulo. 2024.
Autoimmune diseases under IS	Reported cases	Czech MM et al. Open Forum Infect Dis. 2021

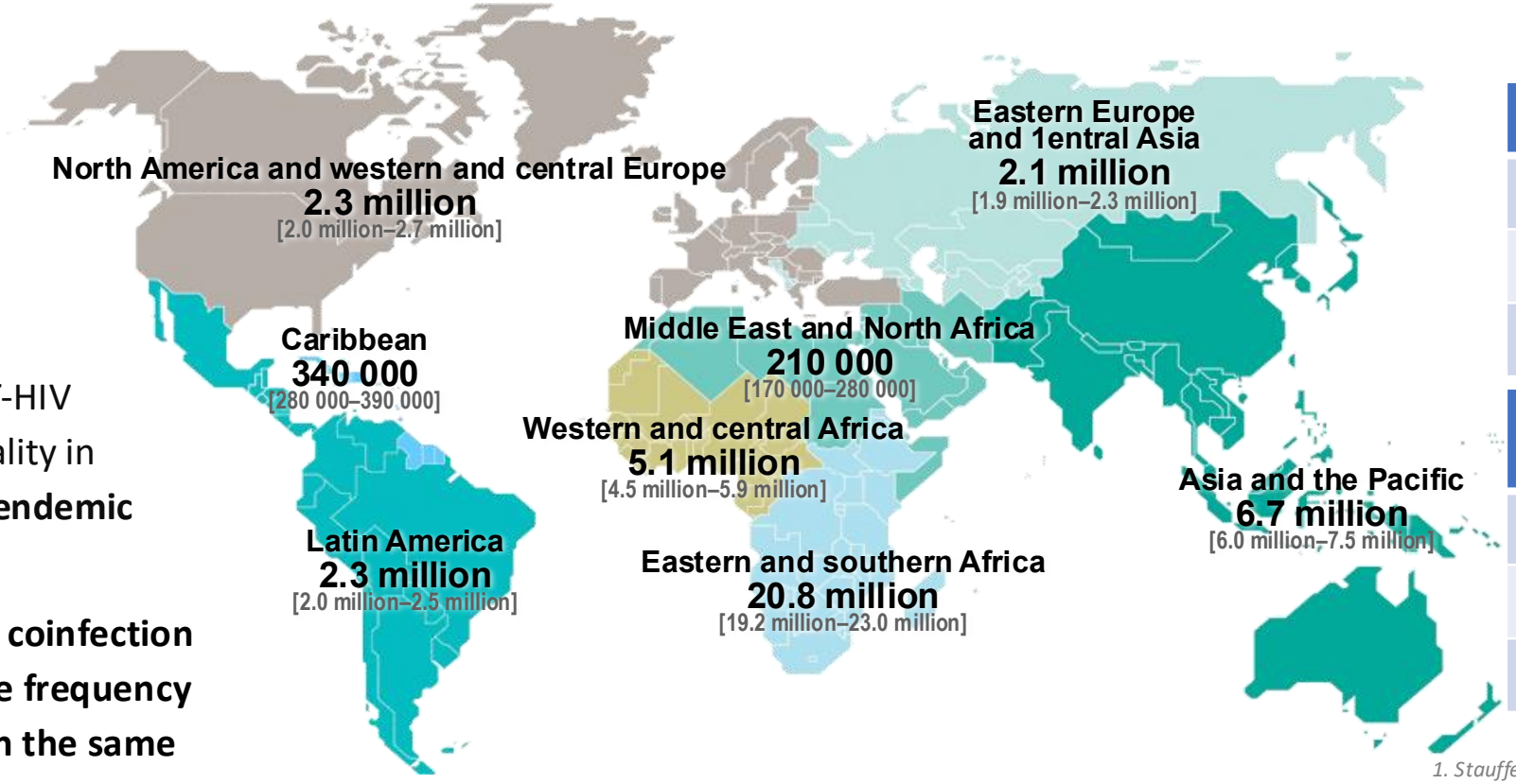
Reactivation rates vary:

- ✓ Intensity of IS
- ✓ Criteria of reactivation used
- ✓ Surveillance protocols
- ✓ *T. cruzi* strains
- ✓ …

Clark EH, Bern C. Curr Opin Infect Dis. 2024 Oct 1;37(5):333-341.

T. cruzi-HIV Coinfection

Adults and children estimated to be living with HIV | 2023



Total: 39.9 million [36.1 million–44.6 million]

https://www.unaids.org/en/resources/documents/2024/core-epidemiology-slides
Acessed on December 2024.

- The risk of *T. cruzi*-HIV coinfection is a reality in **endemic and nonendemic areas**
- The **prevalence of coinfection will depend on the frequency of both diseases in the same location**

Clark EH, Bern C. Trop Med Infect Dis. 2021 Nov 9;6(4):198.

Reported rates of T. cruzi–HIV co-infection

Latin America countries	
Brazil	1.3 – 5% [1]
Argentina	1.2 – 4.2 [2.3]
Bolivia	28% [4]

Latin American PWH living in non-endemic countries	
US	0 [5]
Spain	1.9 – 10.5 [6-8]
Italy	0.5%–1.29% [6 -9]

1. Stauffert D et al. Braz. J. Infect. Dis. 2017. 2. Dolcini G et al. Rev. Argent. Microbiol. 2008 . 3. Scapellato PG et al. Medicina 2006. 4. Reimer-McAtee MJ et al. Am. J. Trop. Med. Hyg. 2021. 5. Hochberg N et al. PLoS Negl. Trop. Dis. 2011. 6. Llenas-García J et al. Eur. J. Clin. Microbiol. Infect. Dis. 2012. 7. Salvador F et al. Am. J. Trop. Med. Hyg. 2013. 8. Rodríguez-Guardado A et al. Epidemiol. Infect. 2010.9. Rodari P et al. Travel Med Infect Dis 2022.

First Reports of Chagas Disease Reactivation in People Living with HIV

Reference	Country	Age (y)/Sex	ME-E	Carditis	CD4 LØ (/mL)	Serological Test	T. cruzi in Blood	T. cruzi in CSF	Treatment	Survival
Del Castilho. 1990	Argentina	19/M	Yes	Yes *	NR	+	NR	NR	Surgery/Nifurtimox	>3 mo
Ferreira MS. 1991	Brazil	37/M	Yes	No	NR	+	No	No	**No**	**No**
Gallo P. 1992	Brazil	26/F	Yes	No	NR	+	NR	Yes	Benznidazole	2 mo
Gluckstein D. 1992	US	32/M	Yes	No	45	+	No	NR	**No**	**No**
Oddó D. 1992	Chile	31/M	Yes	No	35	+	Xenodiagn	NR	Bzn/Itraconazole/Fluconazole	>6 mo
Oddó D. 1992	Chile	40/M	No	Yes	NR	+	Xenodiagn	NR	**No**	**No**
Rosemerg S. 1992	Brazil	40/M	Yes	No	NR	+	NR	Yes	**No**	**No**
Cardozo A. 1992	Uruguay	33/M	Yes	No	NR	NR				
Rocha A. 1993	Brazil	52/M	Yes	Yes	NR	+				
Nishioka SA. 1993	Brazil	33/M	Yes	Yes	382	+				
Metze K. 1993	Brazil	48/F	Yes	No	NR	+				
Sartori AMC. 1995	Brazil	50/F	No	Yes	104	+				
Pimentel PCA. 1996	Brazil	47/M	Yes	No	NR	+				
Ferreira MS. 1997	Brazil	27/M	Yes	Yes*	102	+				
Ferreira MS. 1997	Brazil	48/M	Yes*	No	264	+				
Ferreira MS. 1997	Brazil	39/F	No	Yes **	136	+	No	No	**No**	**No**

Meningoencephalitis/encephalitis = 13/16 (81%)

Carditis = 7/16 (43%)

Diagnostic of ME/E → 6/8 CSF: positive (5 cases, not reported)

CD4 cell count: available only 7 cases (median, 104)

No treatment in 6 cases – 100% lethality

Modified from Ferreira MS et al. Clin Infect Dis. 1997 Dec;25(6):1397-400.

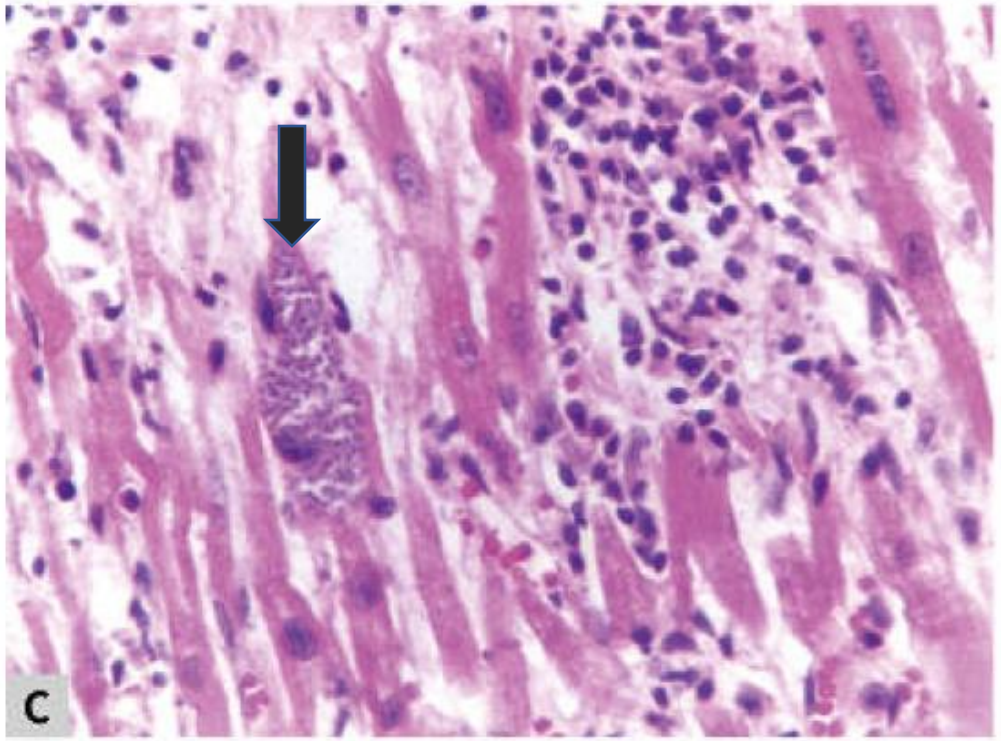
Simultaneous Occurrence of Acute Myocarditis and Reactivated Chagas' Disease in a Patient with AIDS

Ana Marli C. Sartori, Marta H. Lopes, Bruno Caramelli, Maria Irma S. Duarte, Pedro L. da S. Pinto, V. Amato Neto, and Maria A. Shikanai-Yasuda

From the Department of Infectious and Parasitic Diseases, Department of Pathology, and Heart Institute, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

Clin Infect Dis 1995; 21:1297 – 9.

- In the case reported herein, **fatal acute myocarditis** developed in a patient with **AIDS and chronic Chagas' disease who had not previously had cardiac abnormalities**; its development was simultaneous with the **detection of *Trypanosoma cruzi* via direct microscopic examination of the buffy coat, blood cultures, and xenodiagnosis.**



A nest of Trypanosoma cruzi amastigotes (arrow) in the cytoplasm of one myocardial cell (stain, hematoxylin and eosin; original magnification, x 630; bar = 16.6 pm).

Image Source: Doenças Infecciosas: Visão Integrada da Patologia, da Clínica e dos Mecanismos Patogênico. Organizadores, Maria Irma Seixas Duarte...[et al]. – [São Paulo]: Editora dos Editores; Porto Alegre: Artmed ; 2024. E-pub.

HOSPITAL DAS CLÍNICAS FMUSP

T. cruzi- HIV coinfection

- *T. cruzi* reactivation has been classified as an **AIDS-defining opportunistic disease since 2000s**
- Typically occurs with **low CD4 counts (<200 cels/mm3)** and poor virologic control

  15 – 35% of co-infected PWH with reactivation ChD are not being treated with antiretroviral therapy
- The mortality rate of symptomatic reactivation is high (> 75%)

- **In endemic countries, all PWH need be screened for *T. cruzi* infection at the time of HIV diagnosis**
- **Patients under follow-up for ChD should be tested for HIV (recommendation)**

Chronic ChD diagnosis criteria:

***T. cruzi* IgG serologic assay**

Two positive results with different serological methods: ELISA, IFA, HAI

✓ *Accurate diagnosis in > 95%*

✓ *If discordant, "confirmatory" tests*

WHO Consultation on International Biological Reference Preparations for Chagas Diagnostic Tests (WHO, Geneva, July 2007).

Clark EH, Bern C. Trop Med Infect Dis. 2021 Nov 9;6(4):198. Diazgranados CA et al. Lancet Infect. Dis. 2009. Gluckstein D et al. Am. J. Med. 1992. Gomez CA; Banaei N. NEJM 2018 Lambert N et al. Ann. Intern. Med. 2006. Yasukawa K et al. Am. J. Trop. Med. Hyg. 2014. Bern C et al. Clin. Microbiol. Rev. 2019.

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Clinical Manifestations of ChD Reactivation

- **Subcutaneous nodules**
- **Panniculitis**
- **Myocarditis**
- **Meningitis/ Encephalitis**
- **Nonspecific febrile illness (fever, anemia, fatigue, anorexia, diarrhea)**

Kidney Tx recipients

<u>Cutaneous lesions</u> have been reported as diagnostic indicator of ChD reactivation in at least 50% of the KT recipients

Riarte et al., Clin Infect Dis 1999. de La Fuente et al., Transplant 2010; Suppl 23rd International Meeting Abstracts, TTS 2010. Schiavelli et al. Am J Transplant 2006. Suppl 2 Intern Meeting Abstracts, WTC 2006.

Heart Tx recipients

<u>Frequent cardiac manifestations</u>: myocarditis, ventricular dysfunction, arrhythmias, new atrioventricular/intraventricular blocks on ECG

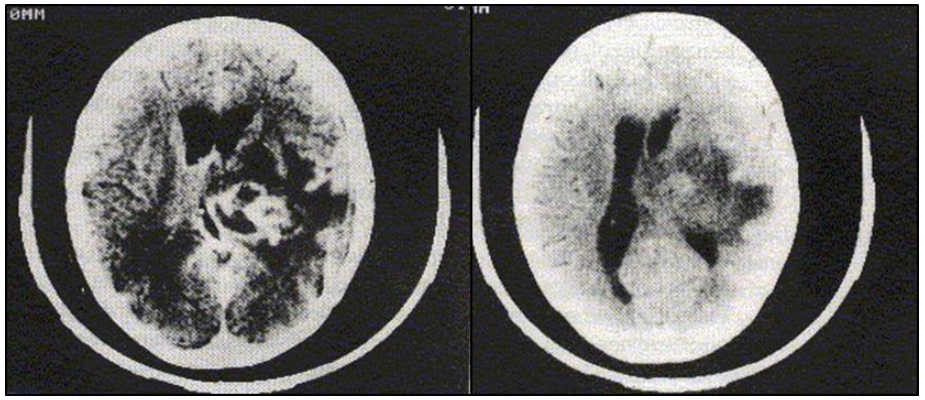
Marin-Neto JA et al. Arq Bras Cardiol. 2023 Jun 26;120(6):e20230269.

HIV/AIDS

Reactivation mostly presents as:
- central nervous system (approx. 70%) [1-5]
- acute myocarditis (10 – 55%) [6]

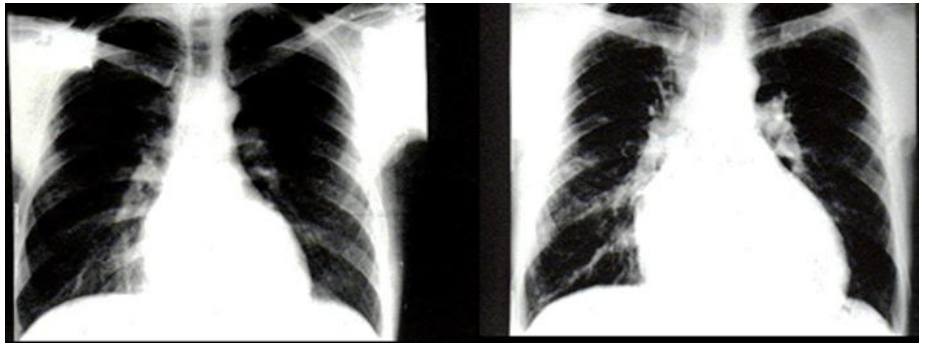
1. Diazgranados CA et al. Lancet Infect. Dis. 2009. 2. Gluckstein D et al. Am. J. Med. 1992. 3. Gomez CA; Banaei N. NEJM 2018 4. Lambert N et al. Ann. Intern. Med. 2006. 5. Yasukawa K et al. Am. J. Trop. Med. Hyg. 2014. 6. Bern C et al. Clin. Microbiol. Rev. 2019.

Clinical Manifestations of ChD Reactivation in HIV patients



80% of reported cases

- Unifocal or multifocal lesions
- Most common in PWH with CD4 cell counts < 100 cells/mm^3
- in the absence of antiparasitic treatment, letality rate is close to 100%



30 – 40% of cases

- Underestimated in mild cases
- Typically manifest as acute myocarditis – tachycardia, dyspnea, cyanosis, edema, jugular stasis, pulmonary congestion, hepatomegaly, arrhythmias
- Distinguish cardiac reactivation from the progression of pre-existing chronic cardiomyopathy poses diagnostic challenges

Other Manifestations

- Peritonitis, pericarditis, pleuritis, erythema nodosum

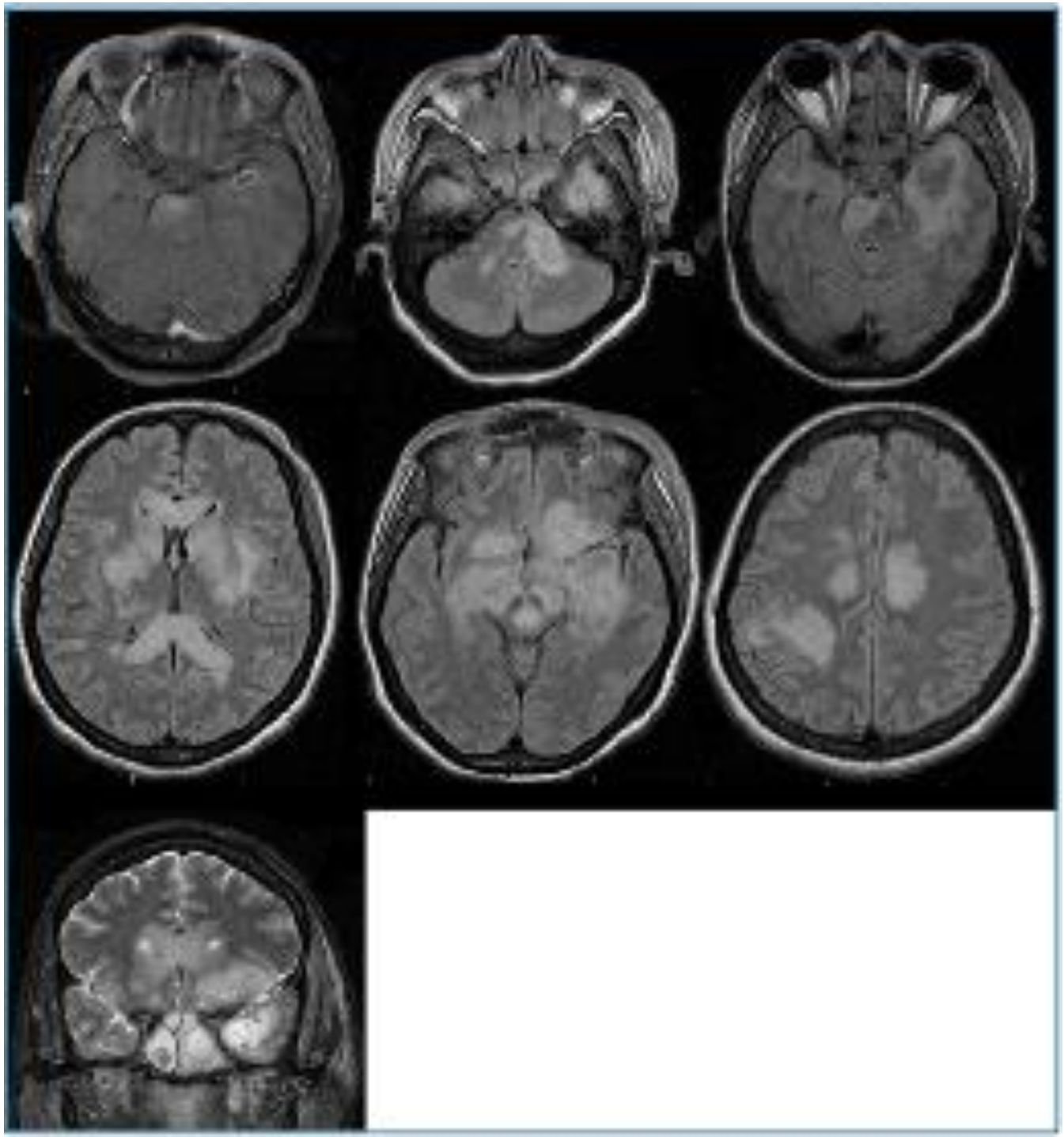
Marin-Neto JA et al. Arq Bras Cardiol. 2023; 120(6):e20230269.
Almeida EA et al. Rev Soc Bras Med Trop. 2023 Dec 8;56:0549.
Clark EH, Bern C. Curr Opin Infect Dis. 2024 Oct 1;37(5):333-341.

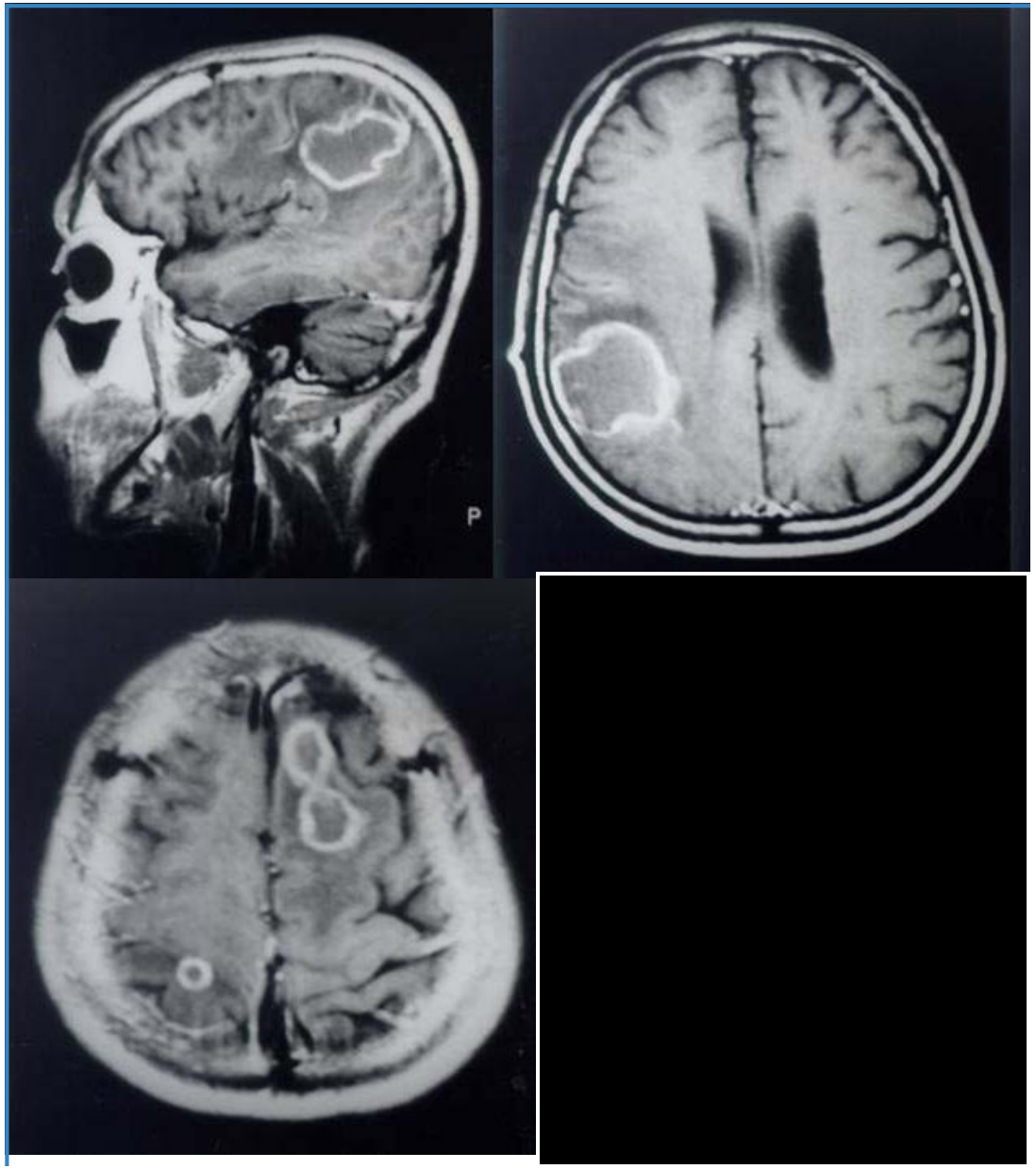
ChD Reactivation in the Central Nervous System in HIV patients

- Main manifestation: **symptoms and signs of intracranial hypertension**

headache, vomiting, altered sensorium → may progress to coma

- **Other findings**: seizures, focal motor/ sensory deficits
- **Less frequent**: meningeal signs, cranial nerve or spinal cord involvement
- **Imaging**: MRI and CT recommended for assessing brain involvement
- **CSF exam**: most reliable for confirming chagasic origin
  - Mild pleocytosis (< 100 cells per mm^3), lymphomononuclear predominance
  - Hyperproteinorrhea (mild-moderate), glycorrhea normal or low
  - Detection of *T. cruzi*
- *T. cruzi* often detected in the peripheral blood → **check parasitemia**
- PCR in CSF: may **detect *T. cruzi* DNA even when direct exam is negative**





Source: Eros A. Almeida, GEDOCH UNICAMP

Scope

- What is the **risk of reactivation**?
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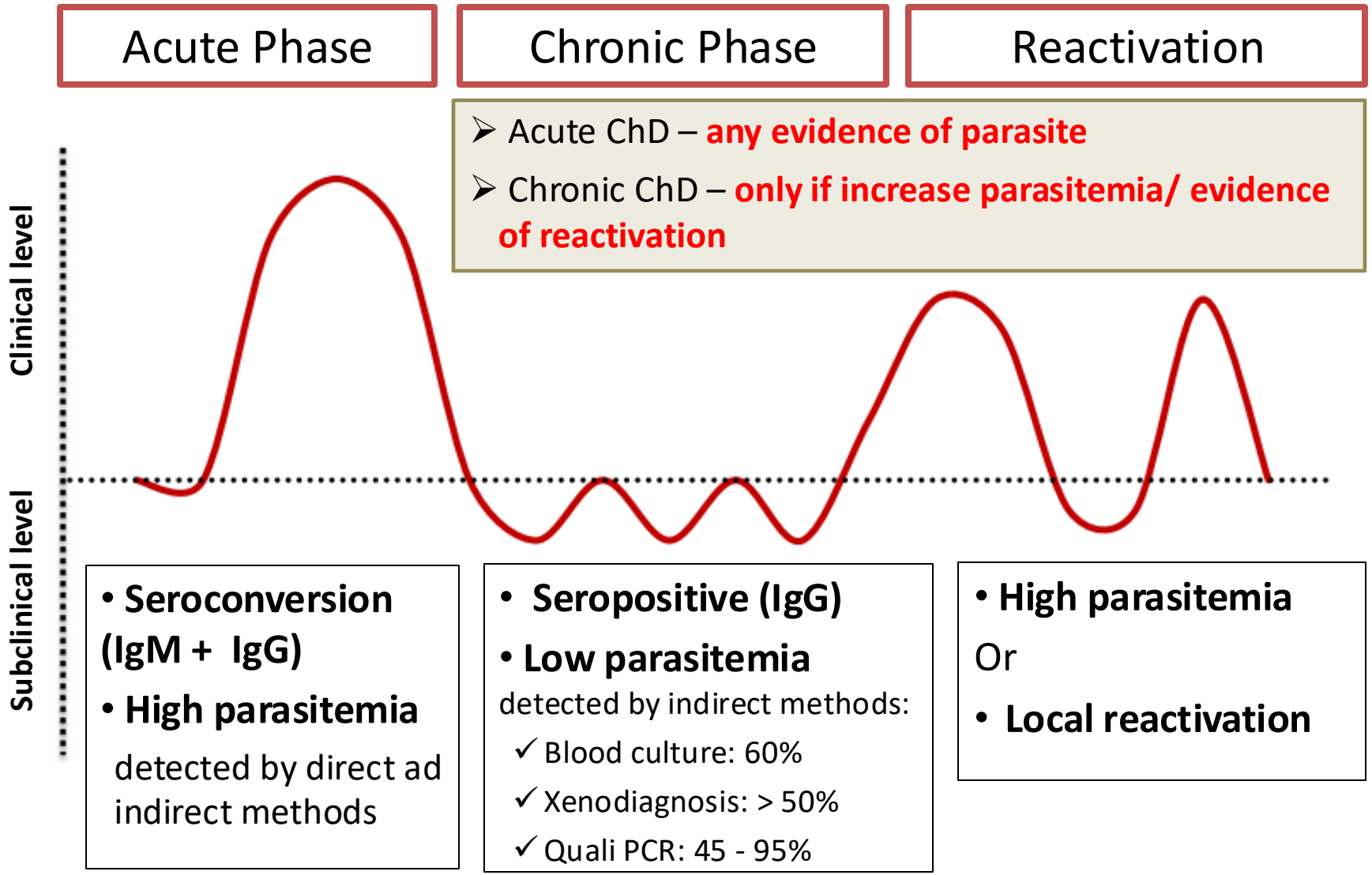
- **What is the definition of reactivation**
- **How to make the diagnosis and treatment**

Definition of ChD Reactivation

- ChD reactivation is defined as **increased parasitemia regardless of clinical symptoms**
  - ❖ **Direct parasitological methods**
  - ❖ **qPCR**
- Reactivation **may remain entirely asymptomatic**, evidenced solely by parasitemia



Pierrotti LC et al. Transplantation. 2018 Feb;102(2S Suppl 2):S1-S7.

Diagnosis of ChD Reactivation

- ➢ High level of clinical suspicion
- ➢ Laboratory investigation

Detection of *T. cruzi* by direct examination is the gold standard for diagnosis of ChD reactivation.

Clinical Aspects

- ✓ Asymptomatic
- ✓ Mono-like
- ✓ Dermatological lesions
- ✓ Meningitis, encephalitis
- ✓ Myocarditis

Parasites on tissues and fluids

- ✓ Tissue biopsies: amastigotes
- ✓ Body fluids (CSF): trypomastigotes

High parasitic load

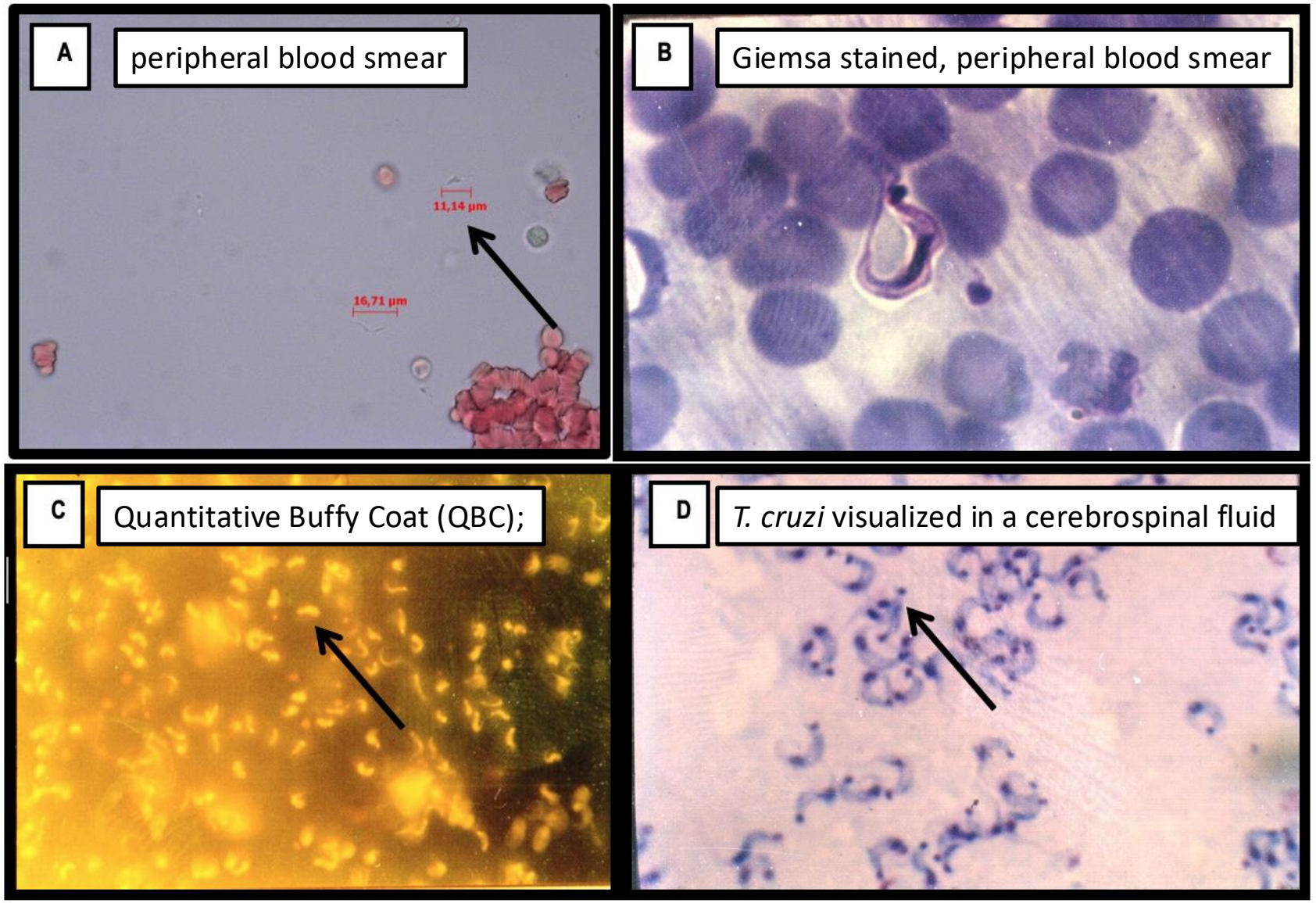
- ✓ **Direct methods:** microscopy, Buffy coat, QBC, Strout, microhematocrit
- ✓ **Indirect methods:** Blood culture, xenodiagnosis, qualitative PCR: not able to distinguish between high and low parasitemia of chronically infected patients

Serology

- ✓ Not useful for reactivation diagnosis

2º Brazilian Consensus on Chagas Disease, 2015. Rev Soc Bras Med Trop 2016.
Pierrotti, L.C., Ibrahim, K.Y. (2020). Chagas Disease: Coming to a Transplanted Patient Near You. In: Morris, M., Kotton, C., Wolfe, C. (eds) Emerging Transplant Infections. Springer, Cham.

Parasitemia detection by direct methods



Courtesy of Vera Lúcia Teieira de Freitas and Laboratório de Investigação Médica –Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

The distinction between chronic parasitemia and reactivation is particularly difficulty among immunocompromised patients

Immunocompromised individuals have higher parasitic load compared to immunocompetent individuals, with no reactivation

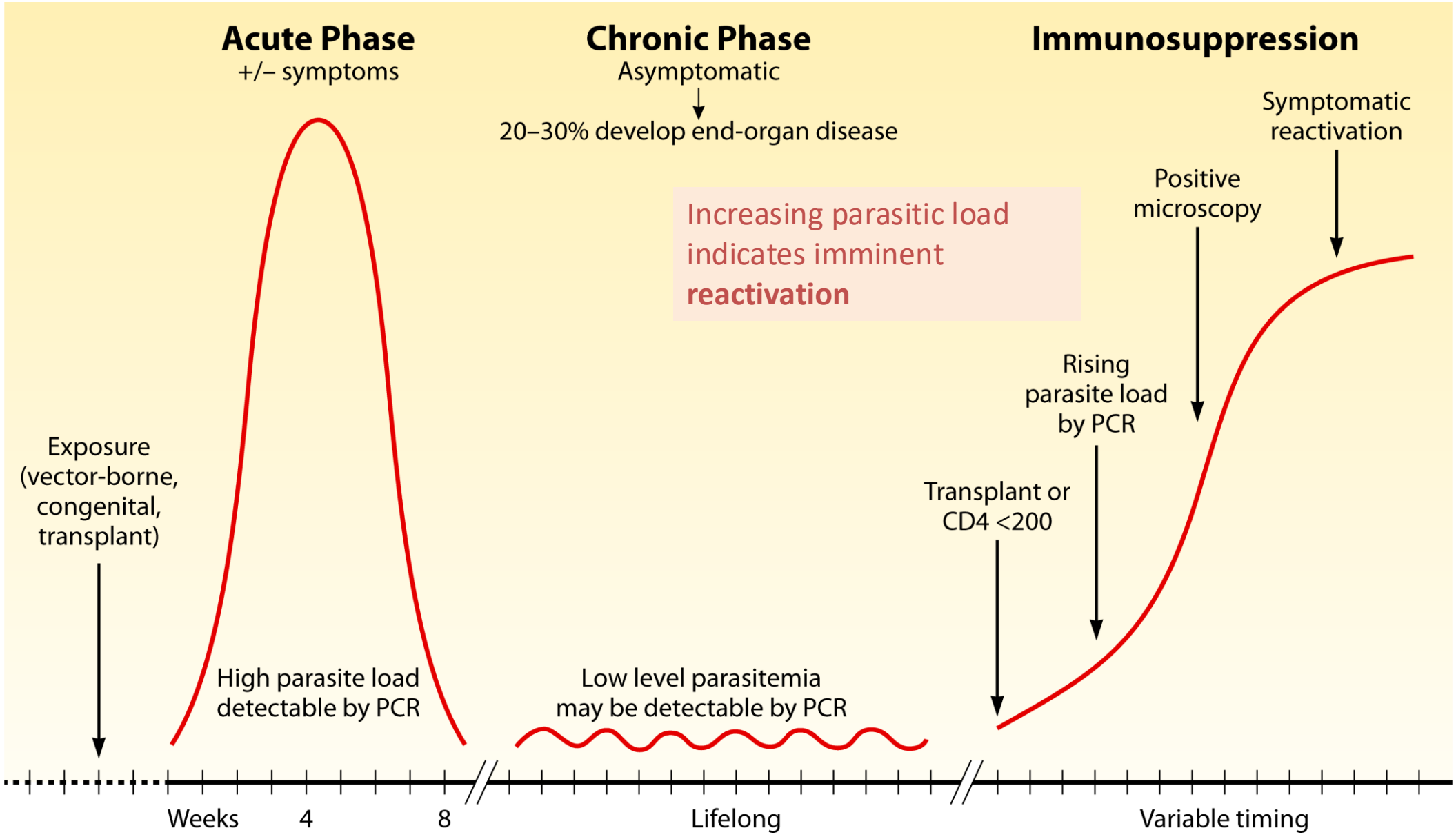
	Xeno diagnosis	Blood Culture	Qualitative PCR	qRT-PCR (mediam)
Chronic ChD (N = 57)	50.9%	31.6%	50.9%	0.00
Chronic ChD- HIV coinfection (N=29)	44.8%	35.7%	89.7%	1.57
Chronic ChD- HIV coinfection with reactivation (N = 5)	60%	100%	100%	1428.90

- ✓ Sensitivity and specificity of noncommercial PCR tests are highly variable
- ✓ Lack of standardized protocol

AIDS Outpatient Unit, São Paulo - Brazil

De Freitas VLT et al. PLoS Negl Trop Dis. 2011;5:e1277.

The natural history of ChD and impact of HIV-induced or iatrogenic immunosuppression



Clark EH et al. Clin Microbiol Rev. 2024 Jun 13;37(2):e0009923.

Asymptomatic ChD Reactivation

- Asymptomatic ChD reactivation was **first reported in an HIV-infected patient in Brazil** [1]
- The direct detection of *T. cruzi* is often not positive during the initial phase of reactivation, which can delay diagnosis
- Parasite DNA can be detected in the blood approximately **30 days before the parasite detection** in IS patients [2-5]
- Pre-emptive treatment in IS patients has been proposed for ChD [6]

Quantitative PCR

✓Provides a correlation of higher parasitic load with clinical significance in chronically infected recipients

Maldonado C, et al. J Heart Lung Transplant 2004; Diez et al., AM J Tx, 2007; Schijman AG et al., PLoS Negl Trop Dis 2011; Cura CI et al., AJT 2013.

qRT-PCR needs cut-off definition to distinguish between REACTIVATION and INCREASED PARASITEMIA in chronic ChD recipients.

Lattes R and Lasala MB. Clin Microbiol Infect 2014.
Pierrotti LC et al. Transplantation. 2018.

1. *Sartori AM et al., Am J Trop Med Hyg 2002. 2. Maldonado C, et al. J Heart Lung Transplant 2004; 3. Diez et al., AM J Tx, 2007. 4. Schijman AG et al., PLoS Negl Trop Dis 2011. 5. Cura CI et al., AJT 2013. 6.* Altclas J et al., Bone Marrow Transplant 2005

Prevalence of Chagas disease among people living with HIV (PWH) in Cochabamba, Bolivia

- **Cross-sectional study** conducted in 2011.
- **116 HIV patients** were recruited from hospitals and clinics.
- **32 (27.6%)** of HIV patients had positive *T. cruzi* serology (indicative of chronic Chagas).
  - ✓ **50%** of seropositive patients were qPCR-positive (parasitemia detected).
  - ✓ **12.5%** showed reactivation by direct microscopy (all had CD4 < 100).
  - ✓ Symptoms like headache, fever, and weight loss were more common in qPCR-positive patients.

TABLE 5
Clinical characteristics of patients with positive quantitative polymerase chain reaction divided by estimated parasite load

	Parasite load > 100 parasites/mL (*n* = 7)	Parasite load < 100 parasites/mL (*N* = 9)	*P* value
Median HIV viral load	63,494 (4,698–237,684)	7,711 (68–317,789)	0.668
Median CD4+ count	48 (8–393)	284 (92–430)	0.164
Hospitalized (vs. ambulatory)	4 (57%)	2 (22%)	0.152
Fever	6 (85.7%)	2 (22%)	0.012
Headache	5 (71%)	6 (67%)	0.838
Weight loss	5 (71%)	4 (44%)	0.280
Body mass index < 20	4/6 (67%)	0 (0%)	0.011

Reimer-McAtee MJ et al. Am J Trop Med Hyg. 2021 Aug 16;105(3):643-650.

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- 116 HIV patients were recruited from hospitals and clinics.
- **32 (27.6%)** of HIV patients had positive *T. cruzi* serology (indicative of chronic Chagas).

50% of seropositive patients were qPCR-positive (parasitemia detected).

12.5% showed reactivation by direct microscopy (all had CD4 < 100).

Symptoms like headache, fever, and weight loss were more common in qPCR-positive patients.

TABLE 5

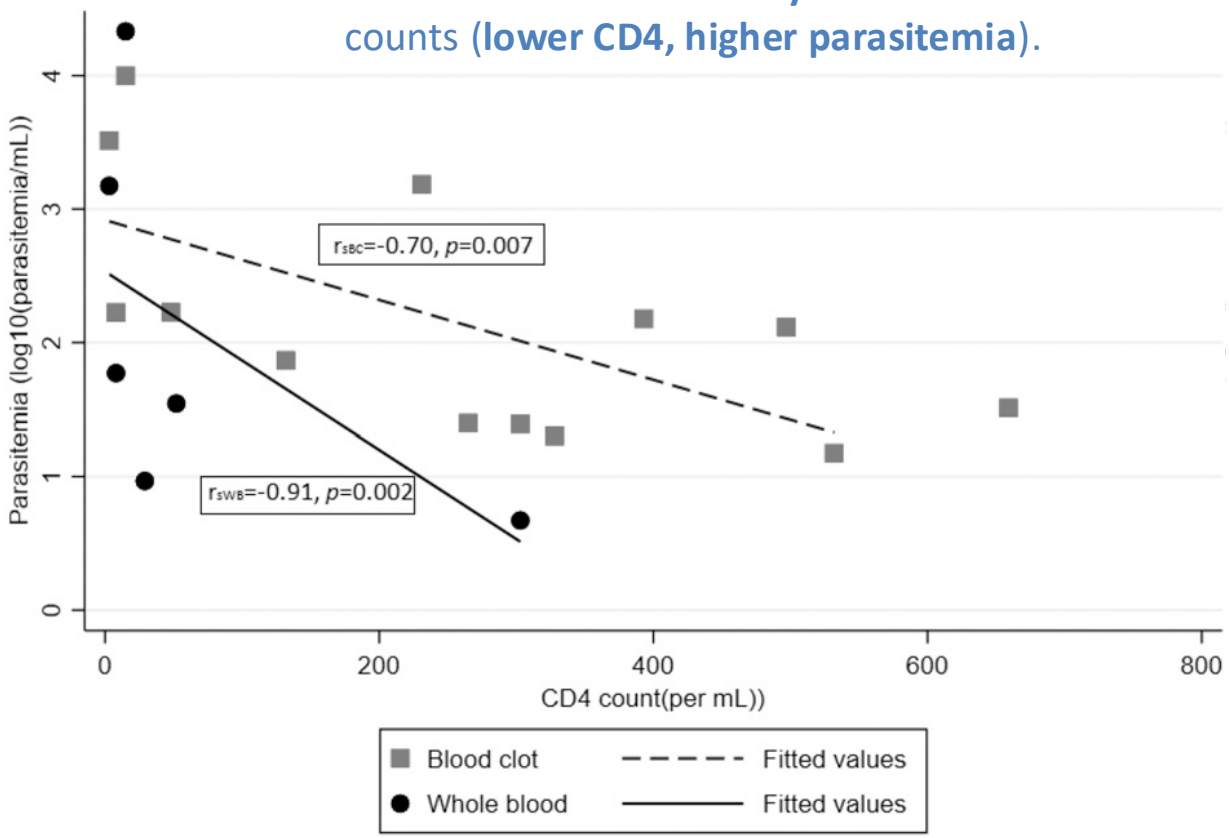
Clinical characteristics of patients with positive quantitative polymerase chain reaction divided by estimated parasite load

	Parasite load > 100 parasites/mL (n = 7)	Parasite load < 100 parasites/mL (N = 9)	P value
Median HIV viral load	63,494 (4,698–237,684)	7,711 (68–317,789)	0.668
Median CD4+ count	48 (8–393)	284 (92–430)	0.164
Hospitalized (vs. ambulatory)	4 (57%)	2 (22%)	0.152
Fever	6 (85.7%)	2 (22%)	0.012
Headache	5 (71%)	6 (67%)	0.838
Weight loss	5 (71%)	4 (44%)	0.280
Body mass index < 20	4/6 (67%)	0 (0%)	0.011

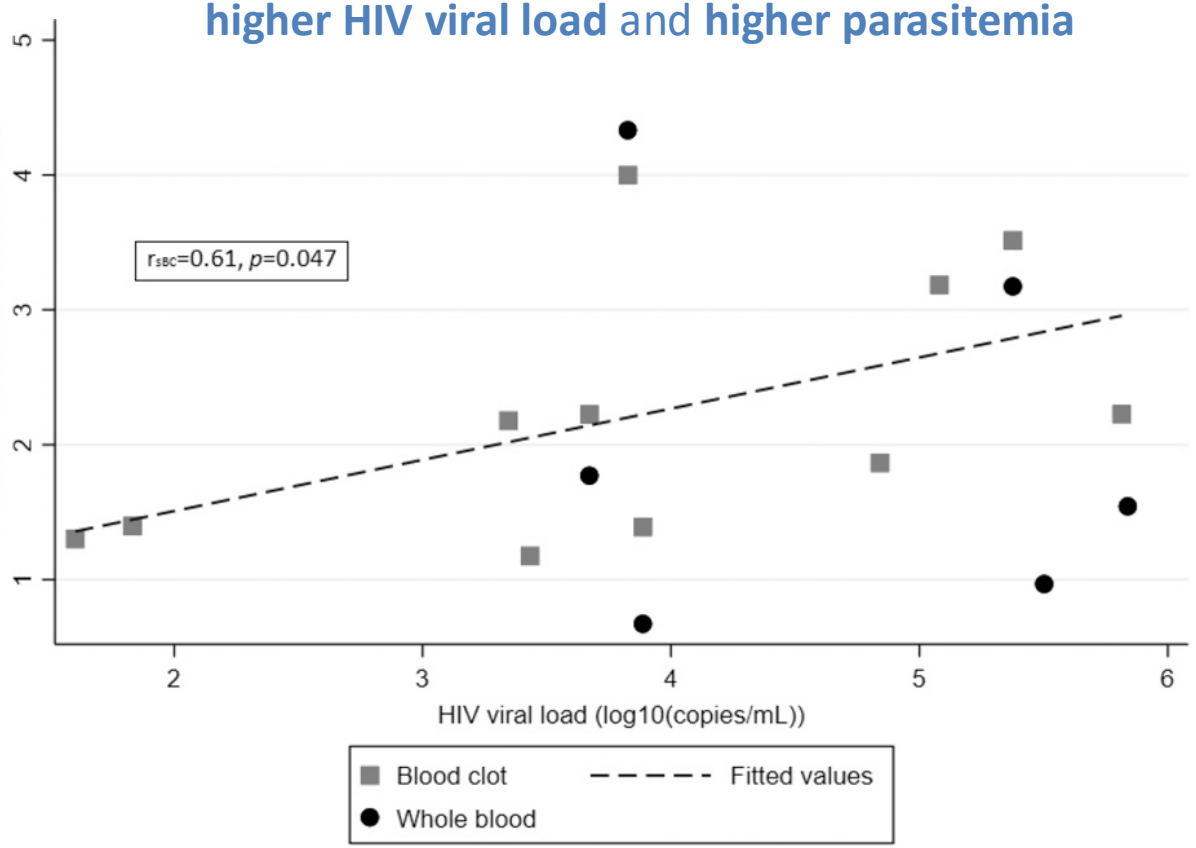
Reimer-McAtee MJ et al. Am J Trop Med Hyg. 2021 Aug 16;105(3):643-650.

Scatterplot of estimated parasitemia by quantitative polymerase chain reaction (blood clot and whole blood) by CD41 count and HIV viral load.

Parasitemia levels **were inversely correlated** with CD4 counts (**lower CD4, higher parasitemia**).



higher HIV viral load and **higher parasitemia**



Reimer-McAtee MJ et al. Am J Trop Med Hyg. 2021 Aug 16;105(3):643-650.

Treatment of ChD Reactivation among T.cruzi– HIV Coinfection

- **Specific treatment for *T. cruzi* is imperative**, despite of clinical symptoms
- **Lethality rate of up to 100%** if delayed or no treatment
- Completing more than 30 days of specific treatment **decreases lethality to approximately 20%**

- **Patients who are not on ART should receive it as soon as possible.**

However, **treatment with benznidazole should be made for at least three weeks prior ART due to the risk of immune reconstitution syndrome**.

- **First choice: BZD**
  - 5 – 7 mg/kg/day for adults
  - 10 mg/kg/day for children
  - Every 8 - 12 hours, for a minimum of 60 days and possibly extended up to 90 days
  - Total daily should not surpass 300 mg
- **Use nifurtimox if intolerant to BZN**
  - 8 – 10 mg/kg/day, for 60 – 120 days
- **Alternative: azole antifungals**

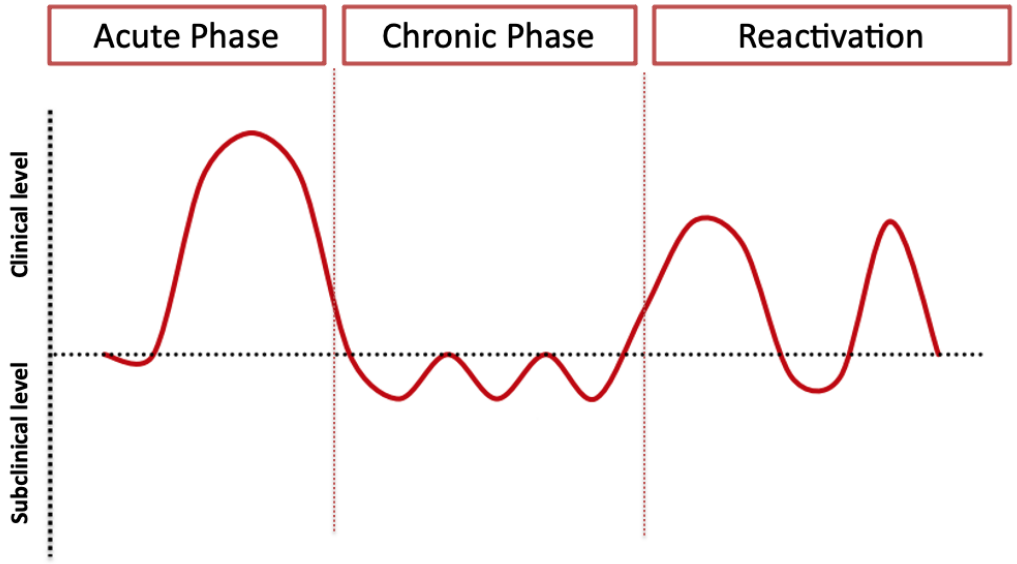
  Posaconazole, itraconazole, fluconazole, and ketoconazole
  - If BZD and nifurtimox CI, adverse reactions, therapeutic failure

Almeida EA et al. Rev Soc Bras Med Trop. 2023 Dec 8;56:0549.

Follow-up during and after antitrypanossomal treatment

- Direct parasitological tests should be conducted **weekly during treatment with benznidazole, until negative**
- After negative results, perform **monthly parasitological tests until 6 months**, then **every 6 months thereafter**
- If acute infection signs appear (especially fever), prompt parasitological tests are essential to rule out the possibility of **Chagas disease reactivation recurrence**

Risk of recurrent ChD reactivation under IS



Pierrotti LC et al. Transplantation. 2018.

- **Negative seroconversion after treatment (the current criteria of cure) takes months-years**

Almeida EA et al. Rev Soc Bras Med Trop. 2023 Dec 8;56:0549.

Prophylaxis for ChD Reactivation among *T. cruzi*– HIV Coinfection

- **Primary prophylaxis is not recommended** (as for other forms of IS)
- **Secondary prophylaxis is recommended** when CD4+ T lymphocyte levels are **below 200 cells/mm^3** (similar to that for other opportunistic infections)
- Medication and dosage for secondary prophylaxis: **BZD 2.5 mg/kg/day every 8 hours, three times a week**

Almeida EA et al. Rev Soc Bras Med Trop. 2023 Dec 8;56:0549.

Chronicically chagasic-HIV coinfected patient

Treatment of ChD

- Recommended for the indeterminate form (WHO) in patients up to 50 years old, or for the determined form without advanced cardiomyopathy (Brazilian Chagas Consensus).
- For coinfected patients, potential additional benefit of flare-up prevention (WHO).

OMS https://www.who.int/health-topics/chagas-disease#tab=tab_1. Accessed in January 2024.
Dias JC et al. II Consenso Brasileiro em Doença de Chagas, 2015. Epidemiol Serv Saude. 2016 Jun;25(spe):7-86. Portuguese.

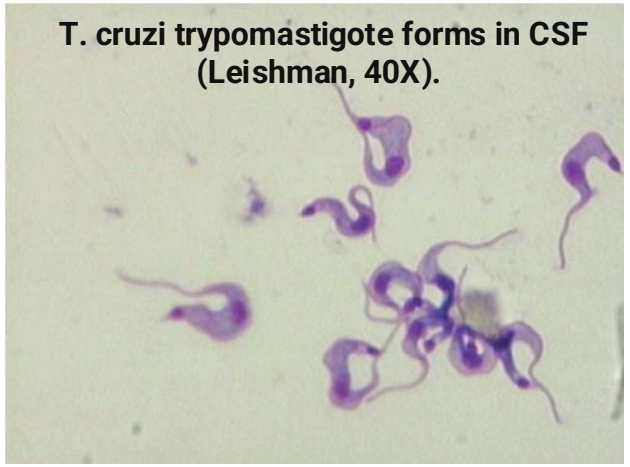
Outpatients HIV-Clinic – Hospital das Clínicas – University of São Paulo

- 22 chronically chagasic-HIV coinfected patients
- Total 3,500 patients under follow-up (prevalence 0.6%)
- Routine protocol
  - **Follow-up visits every 2–4 months**
  - **ECG annually**
  - **Echocardiogram, chest X-ray, and Holter every 2 years if asymptomatic**
  - **Barium swallow and contrast enema at baseline and later if symptoms or X-ray changes**
  - **Parasitemia tests every 8 months if asymptomatic, with high CD4 and suppressed VL**

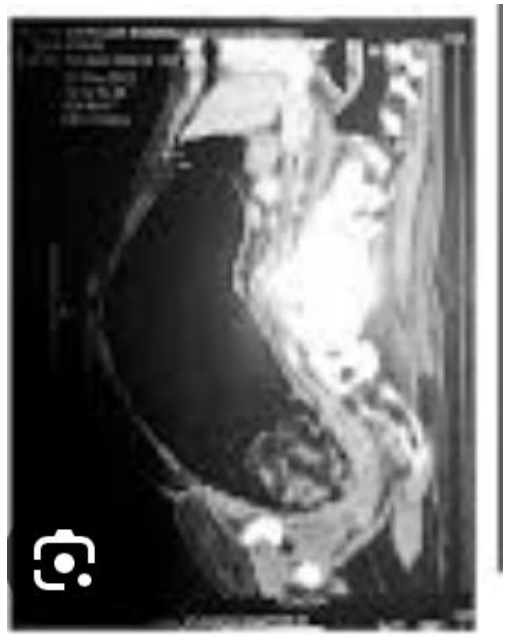
Data: SEAP (Courtesy: Christina T. Gallafrio Novaes)

Case Study

- **1996 – HIV+ diagnosis** (uveitis investigation); initial CD4 = 121; started ART the same year; irregular use; persistently high HIV viral load.
- **2005 – Chagas disease diagnosis** by posit serology (negative parasitemia: XD, HMC, PD); normal ECG and echocardiogram (indeterminate form).



Brazilian Consensus 2015



DOI: 10.1590/s0036-46652004000400005

12.Nov 2008

Extra appointment for **lower limb weakness and numbness.**

04.Dec 2008

Emergency consultation: decreased muscle strength and balance issues. **CSF direct exam: *T. cruzi* trypomastigotes. Diagnosis: Chagas disease reactivation (myelitis)**

08.Dec 2008

Treated with **benznidazole**; stopped due to **optic neuritis**. Other adverse events: neutropenia (managed with granulokine), rash.

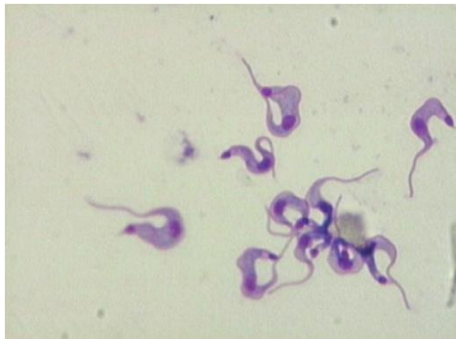
Abril. 2009

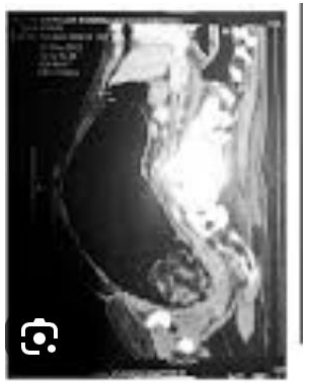
ART switched to **3TC + DRV/rtv + RAL + T20**. First undetectable VL achieved. CD4 recovery up to 442 cells/mm^3 (Feb/2010).

Sept. 2009

Courtesy: Christina T. Gallafrio Novaes (SEAP - HCFMUSP

Case Study





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Abril. 2009

ART switched to 3TC + DRV/rtv + RAL + T20. First undetectable VL achieved. CD4 recovery up to 442 cells/mm^3 (Feb/2010).

Sept. 2009

to Sept 2013

VL < 40 from

2014 onward

Virological failure; progressive CD4 decline, reaching <10 cells/mm^3.

April 2019

Negative *T. cruzi* parasitemias up to April 2019. **Lost to follow-up.**

August 2022

New ChD myelitis reactivation; treated with nifurtimox

2025

CD4 < 50; VK > 100,000
Start fostensavir.
No new ChD reactivation

Courtesy: Christina T. Gallafrio Novaes (SEAP - HCFMUSP

IAS

Summary

- Clinicians should bear in mind the **risk of ChD reactivation in HIV-infected patients**
- Severe immunossupression, especially with CD4 counts below 200 cells/mm3, is the main driver of life-threatening Chagas reactivation
- Reactivation primarily affects the CNS and hear, and early diagnosis is essential
- **Direct *T. cruzi* detection** is the gold standard for diagnosis
- There is **no definitive evidence-based recommendations** for the approach and management of chronic ChD in this population

ChD Working Group –
Noemia Carvalho
Vera Freitas
Maria Aparecida Shikanai-Yasuda
Marta Heloisa Lopes

ligia.pierrotti@hc.fm.usp.br