Chagas disease in the United States

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Outline

Principles of diagnosis and disease management

Epidemiology, Access to Care in the US & the Strong Hearts Pilot

Carlos Chagas, discovered Chagas disease in 1909

Principles of diagnosis and disease management

8 – 10 million people are infected with Chagas disease

- **Concentrated in Latin America**
- **Increasing in US due to migration**

Estimated 300,000+ cases in the United States

The parasite and vector

Trypanosoma cruzi parasite

Triatoma vector

Image Credits: agsci.oregonstate.edu; cals.ncsu.edu

Disease transmission and treatment

Disease Transmission

Vector-borne Transmission

- *R. Prolixus (Guatemala)*
- *T. dimidiata (Guatemala)*
- *T. infestans (Peru, S. Cone)*
- *T. pallidipennis (Mexico)*

Mother to Child Transmission

Blood/Organ donation

Contaminated Food

Disease Course

Acute (6-8 weeks):

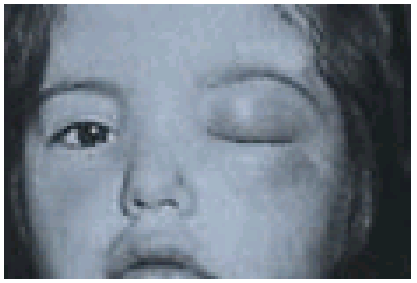
- Romana's sign, flu-like symptoms

Indeterminate (5–20 years):

- Reservoir for transmission
- Possible subtle morbidity

Chronic (lifetime):

- 10-30% develop cardiac form
- 10-15% develop digestive form



Romana's Sign

Treatment

Diagnosis: serological test (ELISA, IIF, IHA) in any stage

Two Available Drugs:

- Benznidazole (Exeltis)
- Nifurtimox (CDC/Bayer)
- BID dosing for 60 days
- Weekly Lytes/LFTs

Common AEs include dermatitis, nausea/anorexia & peripheral neuropathy

Lack of RCTs, especially for nifurtimox

A few detailed clinical pearls regarding presentation

Category	Clinical Symptoms	Diagnostic Findings	Differential Dx
Acute Chagas (Vector 5-14 d after, Transfusion 30-110 d after, Oral 5 d after)	Romana's sign, Chagoma, LAD malaise, fever, HF symptoms	ECG: T-wave changes, conduction defect, anemia, transaminitis	CMV, primary HIV, Toxoplasmosis
Chronic Chagas (Cardiac)	Palpitations, Syncope, HF symptoms, Stroke	**RBBB**, LAFB, NSVT, AF/flutter, dilated CM,	Dilated CMP of other origin
Chronic Chagas (GI)	esophageal (dysphagia, cough, weight loss) or colonic (constipation, volvulus, pseudo-obstruction)	Barium Swallow (dilated esophagus), Nanometry (non-relaxing sphincter) or barium enema	Achalasia, neurodegenerative disorder, Amyloidosis, Systemic Sclerosis
Chagas & HIV	Meningoencephalitis, fever, HF	CSF w/ lymphocytosis, Imaging: hemorrhagic lesions w/ ring enhance	Toxo, Lymphoma, PML, Cryptococcosis
Chagas & Transplant	Nodular rash, myocarditis, meningoencephalitis	EKG, Echo, Head CT	Other transplant-related infections

FDA-approved tests for screening + diagnosis

Test	Sensitivity	Specificity	Specimen origins	Pearls
Abbott PRISM chemiluminescent immunoassay	100 (preselected); 98.5 (high risk)	99.86 (US donors); 98.7 (high risk)	Argentina, Bolivia, Brazil, Guatemala, Panama, Peru; RIPA-confirmed US blood donors	Only used in blood donation labs, FDA-approved for screening
Ortho *T. cruzi* ELISA	100 (preselected); 98.9 (high risk)	99.99 (US donors); 99.0% (high risk)	US blood donors, Mexico, Guatemala, Nicaragua, Bolivia, Colombia	Only marketed for screening but approved for screening + dx
InBios Chagas Detect Plus	95 (WB); 99 (serum)	98 (WB); 96 (serum)	Bolivia, Chile	Point-of-care testing
Hemagen ELISA	100	98.7	Unclear; comparator = specimens with IFA $\geq$1:80	Used in many commercial labs (i.e. Quest)
Wiener recombinant ELISA	99.3	98.7	Argentina, Brazil, Chile	No US distributor, better evidence

Early Data on Treatment Outcomes

- De Andrade et. al. 1996, *The Lancet*: 130 children, 58% of benznidazole group and 5% of the placebo group seroconverted at 3 years

- Sosa-Estani et. al. 1998, *AJTMH:* 106 children, 62% of benznidazole group and 0% of the placebo group seroconverted at 2 years

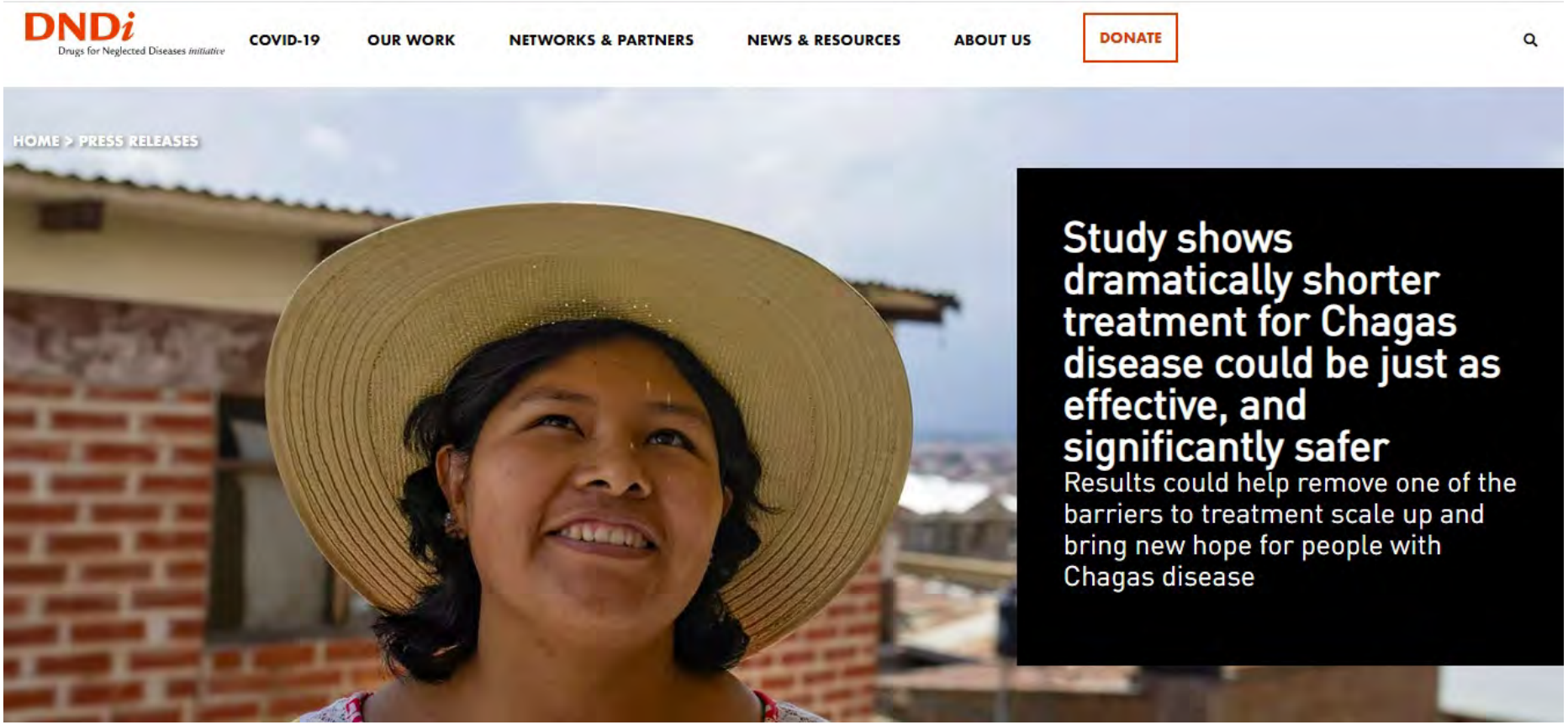
- Viotti et. al. 2006, *Annals of Internal Medicine:* cohort study w/ 283 adults given benznidazole & 283 untreated, followed for 9.8 years; found decreased cardiomyopathy (4.2% treated v.14.1% untreated, adjusted hazard ratio of 0.24, P = 0.002) and decreased mortality (1.1% vs. 4.2%; adjusted hazard ratio of 0.2, P = 0.09).

The BENEFIT Trial (2015)

Table 2. Primary Outcome and Its Components, Hospitalizations, and Deaths.

Outcome	Benznidazole (N=1431)	Placebo (N=1423)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary composite outcome	394 (27.5)	414 (29.1)	0.93 (0.81–1.07)	0.31
Death	246 (17.2)	257 (18.1)	0.95 (0.79–1.13)	—
Resuscitated cardiac arrest	10 (0.7)	17 (1.2)	0.58 (0.27–1.28)	—
Sustained ventricular tachycardia	33 (2.3)	41 (2.9)	0.80 (0.50–1.26)	—
New or worsening heart failure	109 (7.6)	122 (8.6)	0.88 (0.68–1.14)	—
Pacemaker or implantable cardioverter–defibrillator	109 (7.6)	125 (8.8)	0.86 (0.66–1.11)	—
Stroke or transient ischemic attack, systemic embolism, or pulmonary embolism	54 (3.8)	61 (4.3)	0.88 (0.61–1.26)	—
Cardiac transplantation	3 (0.2)	9 (0.6)	0.33 (0.09–1.22)	—
Hospitalization				
Any	358 (25.0)	397 (27.9)	0.89 (0.77–1.03)	0.11
For cardiovascular causes	242 (16.9)	286 (20.1)	0.83 (0.70–0.98)	0.03
Death from cardiovascular causes	194 (13.6)	203 (14.3)	0.94 (0.77–1.15)	0.55
Death from or hospitalization for cardiovascular causes	348 (24.3)	380 (26.7)	0.89 (0.77–1.03)	0.13

Shorter courses of benznidazole efficacious?



Benznidazole New Doses Improved Treatment & Associations (BENDITA)

Epidemiology and access to care in the United States

Background

According to prevalence estimates for the U.S., more than 300,000 people are infected with *T. cruzi* and at least 300 babies are born with congenital Chagas disease each year[1]

Limited information exists on how many patients receive clinical care, including diagnosis, treatment and clinical follow-up as appropriate

[1]*Bern and Montgomery, 2008 CID*

Chagas in the United States

Comments by Sheba Meymandi at UCLA on Chagas in the United States

https://www.youtube.com/watch?v=GUq_mDIdJrk

Data on access

Estimated total cases calculated with data from the American Community Survey (US Census) and WHO sending country prevalence estimates

Confirmed cases of Chagas disease (2007-2013) from AABB (formerly American Association of Blood Banks)

Number of benznidazole and nifurtimox drug releases to individuals from the United States Centers for Disease Control and Prevention (CDC)

Estimated cases, confirmed cases in donors, and drug releases

STATE	TOTAL CASES	AABB CASES	DRUG RELEASES
CALIFORNIA	70700	707	141
TEXAS	37000	176	41
FLORIDA	18000	260	23
NEW YORK	17400	160	32
ILLINOIS	9300	22	12
NEW JERSEY	8600	32	7
VIRGINIA	7300	103	30
ARIZONIA	6400	28	1
MARYLAND	5900	29	4
GEORGIA	5600	37	4
NORTH CAROLINA	5400	41	16
NEVADA	3700	25	2
MASSACHUSETTS	3300	9	21
COLORADO	3200	4	6
WASHINGTON	3100	18	2

>300,000 Estimated Cases, <2000 AABB Confirmed Cases

Manne-Goehler et al, 2016 PLOS NTDs

Drug releases before and after FDA approval of benznidazole

	Oct 2011-May 2018		May 2018-Feb 2019	
Age group (yrs)	No	%	No	%
<2	1	0.3	0	0.0
2–12	2	0.5	5	3.9
13–18	29	7.9	2	1.6
19–50	236	64.7	80	62.0
>50	97	26.6	42	32.6
Total	**365**	**100**	**129**	**100**

Source: Herwaldt et al. [9], Exeltis USA

https://doi.org/10.1371/journal.pntd.0008398.t001

Yoshioka et al., 2020 PLOS NTDs

Barriers and facilitators to benznidazole access in the US

Stream	Barriers	Facilitators	Actions to Address Challenges
Architecture	- Lack of a national level network for multi-sector coordination.	- Existence of two networks (Chagas Consortium and Texas Chagas Task Force).	- Create a national platform as a mechanism for multi-sector coordination.
Availability	- Providers' failure to send a specific order form to a specialty pharmacy when they prescribe BNZ. - Lack of an express delivery system for emergency situations.	- BNZ production and importation controlled by the single corporate group. - Forecasting leading to adequate supply of benznidazole, compared to the current demand level. - A specialty pharmacy providing logistic assistance for domestic delivery of BNZ.	- Increase provider awareness about the order form. - Develop an emergency BNZ delivery system.
Affordability	- Costs of medical services for uninsured patients.	- Exeltis USA's low-cost/free drug program. - Some of the major public and private insurers covering BNZ.	- Establish financial sustainability of the Exeltis USA's low-cost/free drug program. - Expand public and private insurance coverage for BNZ.
Acceptability	- Narrow indications for BNZ approved by the FDA. - Lack of a clinical practice guideline for CD treatment. - Limited number of physicians offering CD treatment. - Obstacles for patients to make medical appointments.	- FDA approval of BNZ. - Existence of treatment centers.	- Expand the FDA-approved indication of BNZ. - Establish a clinical practice guideline for CD treatment. - Organize a physician network. - Organize a patient peer support network.
Appropriate use	- Providers not confirming diagnosis or inadequately evaluating patient eligibility for CD treatment.	- Clinical guidance available from CDC	- Educate prescribers on how to confirm diagnosis and evaluate patient eligibility for BNZ treatment. - Understand treatment practices (dosage and management of adverse effects).

BNZ: Benznidazole, CD: Chagas disease

Source: Authors

https://doi.org/10.1371/journal.pntd.0008398.t002

Interest in testing and treatment in affected populations

TABLE 3

Opinion of Chagas disease by country of birth (participants who have heard of Chagas disease)*

Variable	No. (%) Mexico (n = 188)†	El Salvador (n = 81)	Guatemala (n = 38)	Other (n = 45)	Total (n = 352)	P‡
Do you think Chagas disease is a problem in your country of origin?						0.15
Definitely/probably no	36 (20)	13 (16)	2 (5)	8 (18)	59 (17)	
Maybe/not sure	42 (23)	17 (21)	4 (11)	9 (20)	72 (21)	
Definitely/probably yes	105 (57)	50 (63)	31 (84)	28 (62)	214 (62)	
Do you think Chagas disease is a problem in the Latino community in the USA?						0.55
Definitely/probably no	43 (23)	13 (16)	10 (26)	13 (29)	79 (22)	
Maybe/not sure	46 (25)	16 (20)	8 (21)	10 (22)	80 (23)	
Definitely/probably yes	99 (53)	52 (64)	20 (53)	22 (49)	193 (55)	
If you could get tested for Chagas disease by a doctor, would you get tested?						NA
Definitely/probably no	7 (4)	2 (3)	0 (0)	0 (0)	9 (3)	
Maybe/not sure	1 (1)	1 (1)	0 (0)	0 (0)	2 (1)	
Definitely/probably yes	178 (96)	78 (96)	38 (100)	43 (100)	337 (97)	
If you had Chagas disease, would you take the medication for it?						NA
Definitely/probably no	0 (0)	0 (0)	1 (3)	0 (0)	1 (0)	
Maybe/not sure	2 (1)	0 (0)	1 (3)	0 (0)	3 (1)	
Definitely/probably yes	184 (99)	81 (100)	36 (95)	45 (100)	346 (99)	
Do you think Chagas disease is a disease that is: _____						0.35
Not serious	152 (82)	59 (76)	30 (79)	38 (88)	279 (81)	
Serious	33 (18)	19 (24)	8 (21)	5 (12)	65 (19)	

* NA = not applicable (chi-square test invalid because of low expected counts).
† Subtotal affected by missing data for each response.
‡ By chi-square test for independence.

Sanchez et al., 2014 AJTMH

The Strong Hearts Pilot: a screening program for Chagas in MA

Time is running out…

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Treatment of Chagas' Disease — Time Is Running Out

James H. Maguire, M.D.

The Strong Hearts Program

Screening at East Boston Neighborhood Health Center in East Boston, MA

Screening Test: Hemagen Chagas ELISA at Quest Labs

Confirmatory Test: US CDC

Time Period: 03/2017 – Present

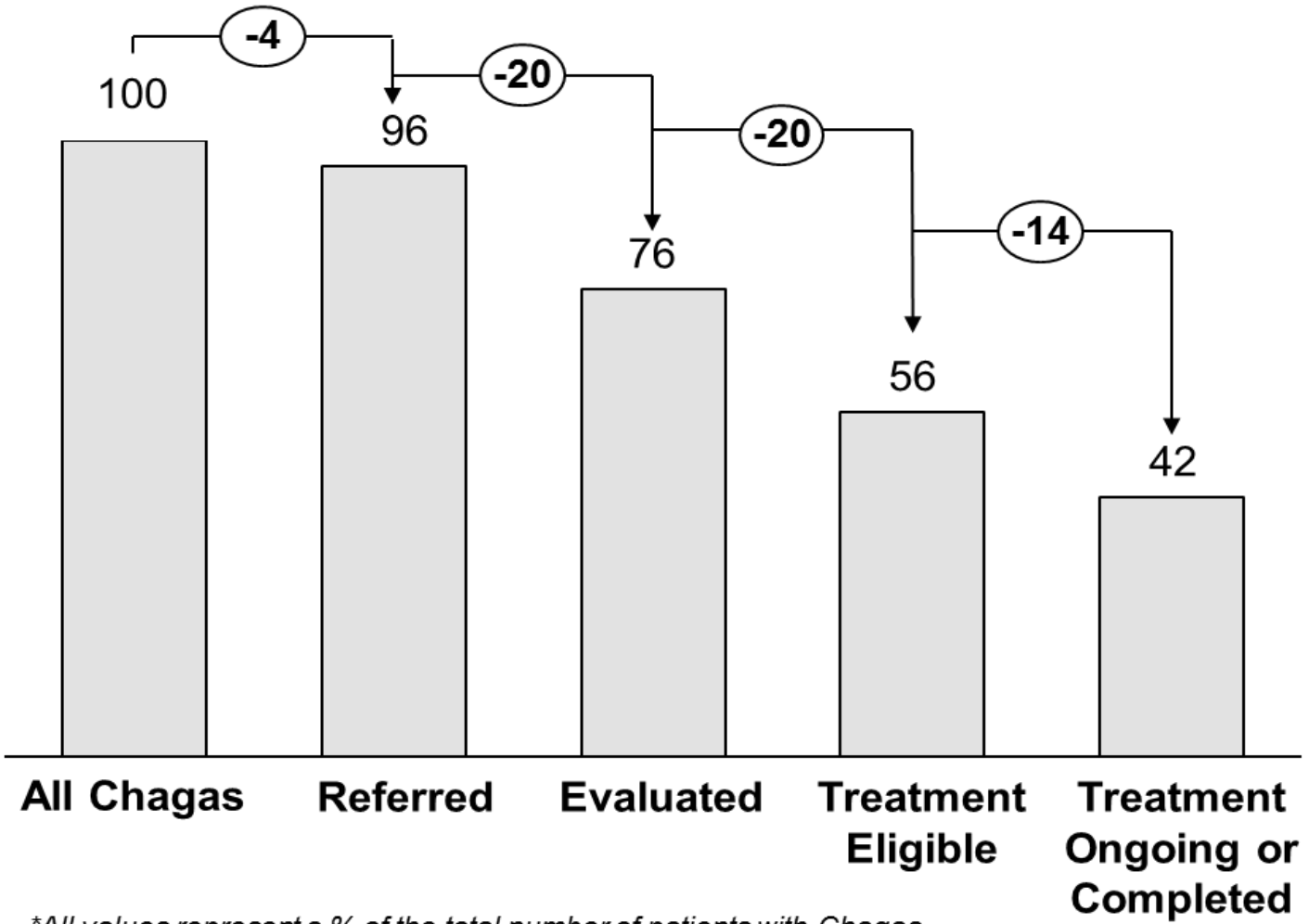
Screening Recommendation: all people [≤50 years old] who lived in Mexico, South or Central America for ≥6 months

Epidemiology of Chagas disease in East Boston

Prevalence	Overall (%)	Men (%)	Women (%)	p*
Region				
North America	1/205 (0.5)	1/75 (1.3)	0/130 (0.0)	p=0.001
Central America	45/3262 (1.4)	18/1142 (1.6)	27/2120 (1.3)	
South America	4/1574 (0.3)	3/603 (0.5)	1/971 (0.1)	
Age				
<20 years old	0/192 (0.0)	0/59 (0.0)	0/132 (0.0)	p<0.001
20 – 29 years	9/1561 (0.6)	3/460 (0.7)	6/1101 (0.5)	
30 – 39 years	12/1834 (0.7)	5/640 (0.8)	7/1194 (0.6)	
40 – 49 years	11/1065 (1.0)	6/490 (1.2)	5/575 (0.9)	
50 – 59 years	11/285 (3.9)	7/128 (5.5)	4/157 (2.6)	
60+ years	7/130 (5.4)	1/55 (1.8)	6/75 (8.0)	
Overall	**50/5065 (1.0)**	**22/1831 (1.2)**	**28/3234 (0.9)**	**p=0.246**

Cascade of care for Chagas disease in East Boston

East Boston
Prevalence = 1.0%
(95% CI: 0.7 – 1.2%)



**All values represent a % of the total number of patients with Chagas*

References & Resources

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- Dr. Michael R. Reich, Harvard School of Public Health
- Dr. Colin Forsyth, Drugs for Neglected Diseases Initiative
- Dr. Sheba Meymandi, UCLA Olive View Medical Center
- Dr. Susan Montgomery, US CDC

Appendix

Chagas Control and Treatment: a global perspective

Ongoing global efforts to prevent, control and treat Chagas

Prevention

Southern Cone Initiative reduced incidence of infection by 60-95% between 1983 and 2000

With Southern Cone model, programs have been started in Central America, the Andean Region and Amazon

Treatment

In 2009, estimated that less than 1% of those infected with *T. cruzi* received treatment for the disease globally

Increase in evidence for antitrypanosomal treatment has put pressure on countries to diagnose + treat

Prevention has several approaches

Vector control through house spraying

Education

In addition, many countries screen blood products or donated organs

Results of prevention efforts in the Southern Cone

Country	Incidence Rate (1983)	Incidence Rate (2000)	% Reduction
Argentina	5.8	1.2	80
Brazil	5	0.28	95
Chile	5.4	0.38	94
Paraguay	9.3	3.9	60
Uruguay	2.5	0.06	99

Source: WHO 2002

Prevention effective in reducing incidence of disease

Diagnosing and treating Chagas Disease?

Diagnosis

Treatment

#1

#2

The BENEFIT Trial (2015)

Table 3. Adverse Events and Laboratory Abnormalities.*

Cohort and Event	Adverse Events Leading to Drug Interruption			Serious Adverse Events Leading to Drug Interruption		
	Benznidazole (N=1431)	Placebo (N=1423)	P Value	Benznidazole (N=1431)	Placebo (N=1423)	P Value
	no./total no.(%)			*no./total no. (%)*		
Patients completing follow-up visits through end of study-treatment period	1429/1431 (99.9)	1422/1423 (99.9)		1429/1431 (99.9)	1422/1423 (99.9)	
Any adverse event	342/1429 (23.9)	135/1422 (9.5)	<0.001	119/1429 (8.3)	20/1422 (1.4)	<0.001
Cutaneous rash	137/1429 (9.6)	18/1422 (1.3)	<0.001	58/1429 (4.1)	2/1422 (0.1)	<0.001
Gastrointestinal symptoms	112/1429 (7.8)	41/1422 (2.9)	<0.001	26/1429 (1.8)	9/1422 (0.6)	0.004
Nervous system symptoms including peripheral neuropathy	52/1429 (3.6)	19/1422 (1.3)	<0.001	14/1429 (1.0)	6/1422 (0.4)	0.07
Leukopenia†	2/1429 (0.1)	2/1422 (0.1)	1.0	1/1429 (0.1)	0	NA
Permanent treatment discontinuation	192/1429 (13.4)	51/1422 (3.6)	<0.001	96/1429 (6.7)	15/1422 (1.1)	<0.001
Patients completing 60-day visit‡	1123/1431 (78.5)	1194/1423 (83.9)		0	0	NA
Alanine aminotransferase >2× ULN	55/1123 (4.9)	19/1194 (1.6)	<0.001	0	0	NA
Alanine aminotransferase >3× ULN	20/1123 (1.8)	9/1194 (0.8)	0.03	0	0	NA

* NA denotes not applicable, and ULN upper limit of the normal range.
† Leukopenia was defined as a neutrophil count of less than 1900 cells per cubic millimeter.
‡ Data are shown for patients who completed the 60-day study visit and had available values for alanine aminotransferase at that visit.