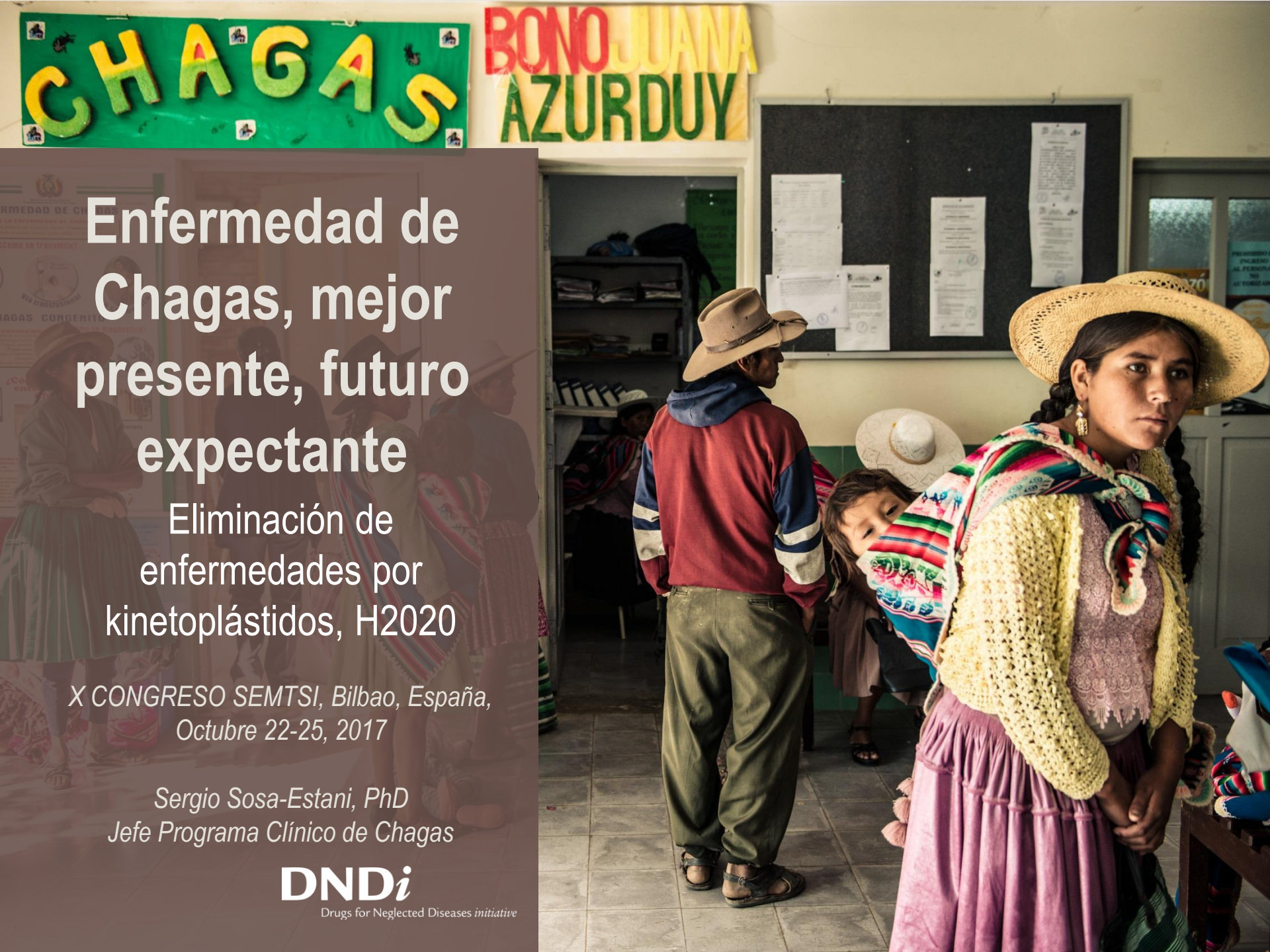


Enfermedad de Chagas, mejor presente, futuro expectante

Eliminación de enfermedades por kinetoplástidos, H2020

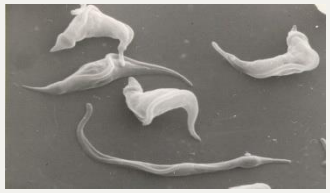
X CONGRESO SEMTSI, Bilbao, España, Octubre 22-25, 2017

Sergio Sosa-Estani, PhD
Jefe Programa Clínico de Chagas

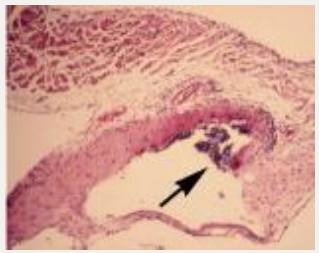
DNDi
Drugs for Neglected Diseases *initiative*

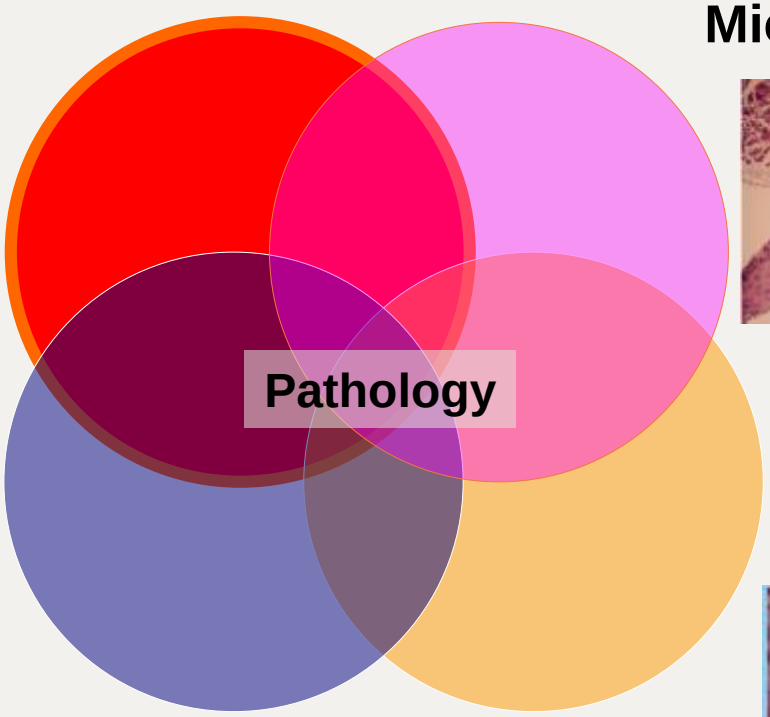
Chagas disease: Physiopathology

Parasite

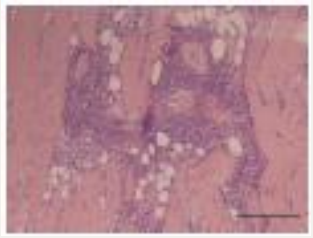


Microvascular

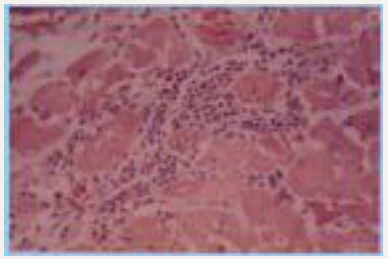




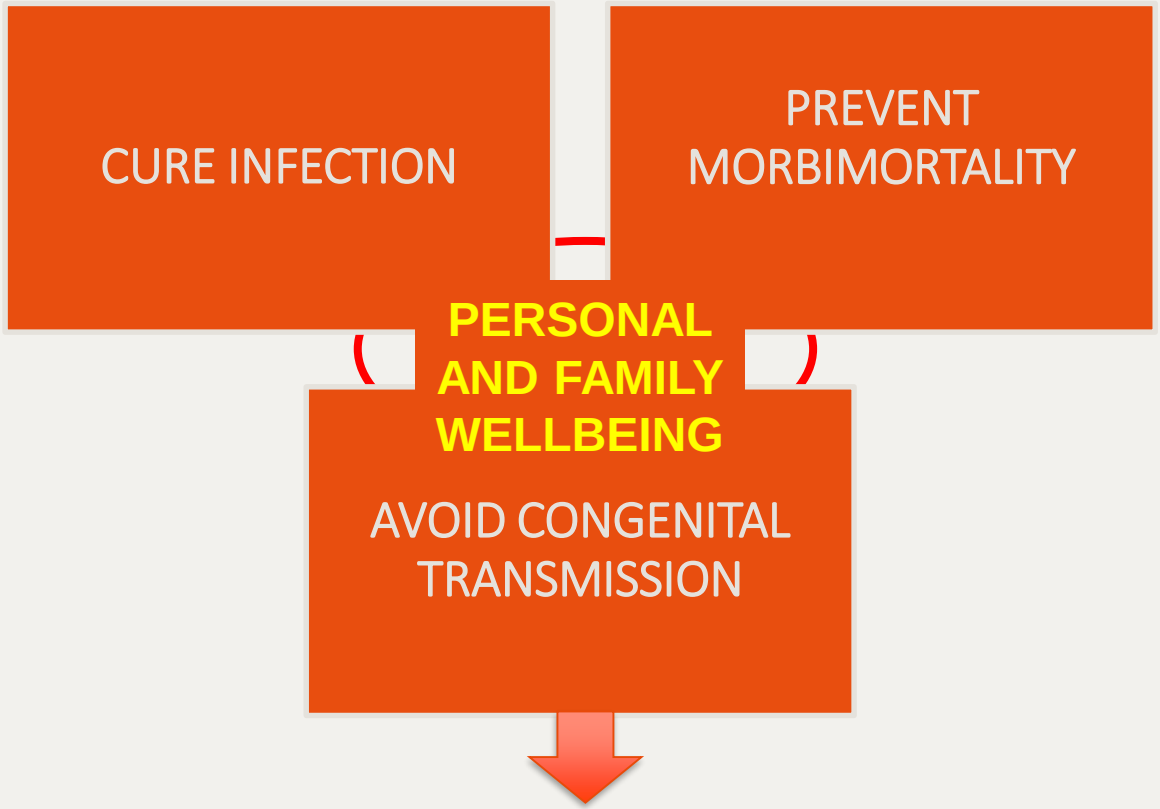
Specific immune response to the parasite



Inflammation



GOAL OF TIMELY DIAGNOSIS AND TREATMENT



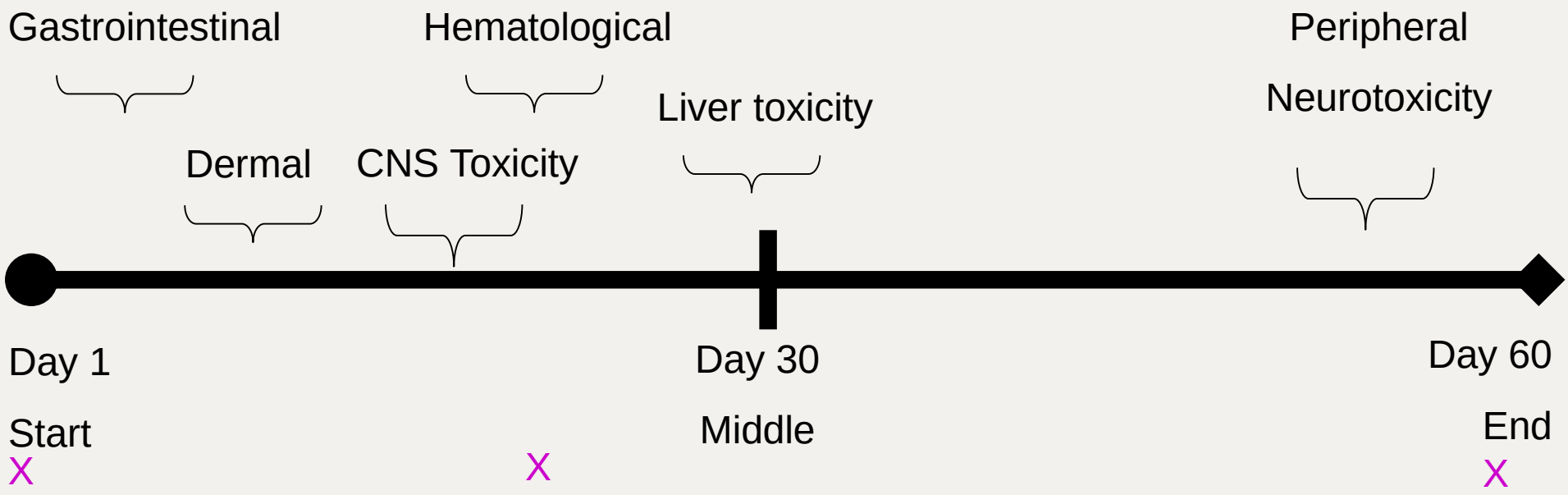
Guidelines for antitrypanosmal treatment with benznidazole or nifurtimox

Varying strengths of recommendation (A-E) and levels of evidence (I-III)

- All patients undergoing the acute phase (A I;A II)
- Children and young adult patients undergoing the chronic phase (A I)
- Women of childbearing age (A II)
- Adults undergoing the chronic phase (B II;C II)
- Laboratory or surgical accidents (B III)
- Organ transplant recipients or donors (A III)

Oral; 60 days

Timeline of side effects of benznidazole and nifurtimox



Monitoring Adverse Events/Drug Tolerance

- Weekly contact with the patient
- Laboratory testing X

Typical completion rates

-adults=83%

-neonates=100%

Sosa-Estani et al. J Trop Med. 2012;2012:292138.

Assessing response to etiological treatment

PRIMARY CRITERIA

- Demonstration of no clinical progression
- Wellbeing (clinical evolution)

SECONDARY CRITERIA

- Failure: Detecting parasite presence using molecular tests (PCR)
  - Time range: end of treatment to month/years post-treatment
- Success: serological negativization
  - Acute phase: Follow-up for 24 months post-tx
  - Chronic phase: Long-term follow-up, every 1-3 years.

Clinical studies in the 60's and 70's

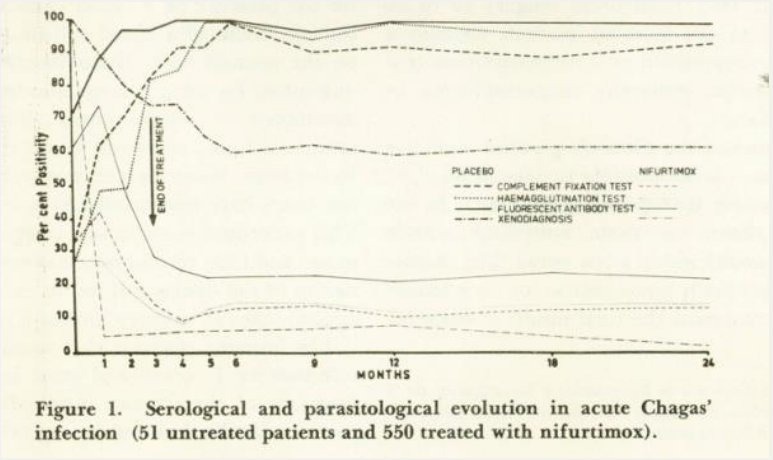


Figure 1. Serological and parasitological evolution in acute Chagas' infection (51 untreated patients and 550 treated with nifurtimox).

Acute Phase: Decrease antibodies and parasitaemia

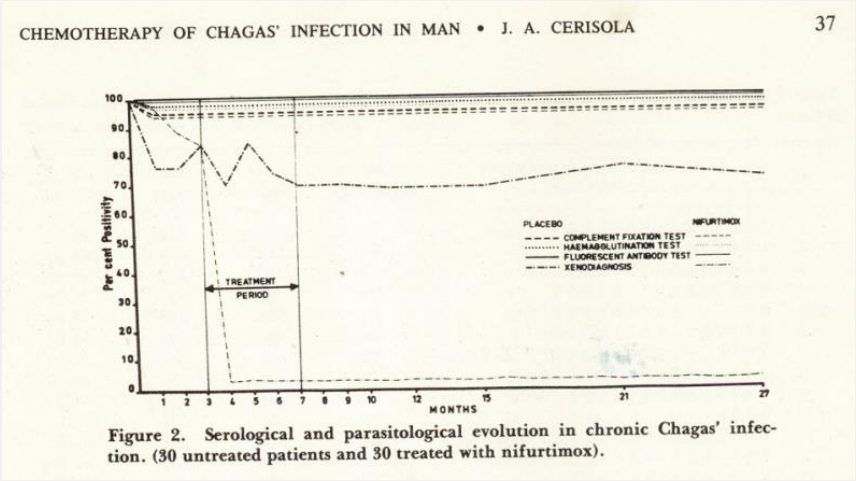


Figure 2. Serological and parasitological evolution in chronic Chagas' infection. (30 untreated patients and 30 treated with nifurtimox).

Chronic Phase: Remain antibodies and Decrease parasitaemia

Table 11. Chronic Chagas' infection. Nifurtimox. Summary of results as per duration and site of treatment.

Site	90-120 days			30-60 days		
	Failures	Cured	%	Failures	Cured	%
Argentina	1	18	94.7	1	9	90.0
Chile	1	8	88.9	1	5	83.3
Pôrto Alegre	0	13	100.0	2	15	88.2
Brasília	5	4	44.4	2	4	66.7
Total	7	43	86.0	6	33	84.6

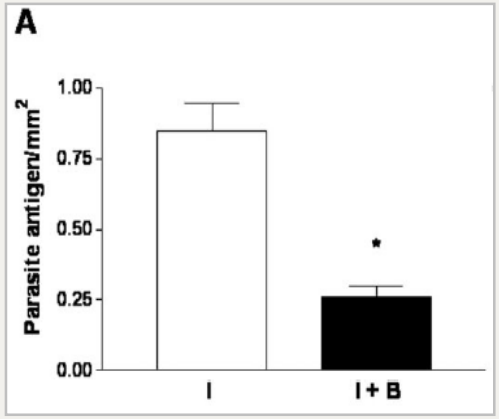
Between treatments $p > 0.10$ not significant
Between Argentina, Chile, and Pôrto Alegre $p > 0.10$ not significant
Between Brasília and the rest $p < 0.005$ very significant

Chronic Phase: Better response on the south than Central west of Brasil

Preclinical and Clinical studies in the 90's

Treatment with Benznidazole during the Chronic Phase of Experimental Chagas' Disease Decreases Cardiac Alterations

Simone Garcia,[1,2] Carolina O. Ramos,[1] Juliana F. V. Senra,[1] Fabio Vilas-Boas,[3] Maurício M. Rodrigues,[4] Antonio C. Campos-de-Carvalho,[2] Ricardo Ribeiro-dos-Santos,[1] and Milena B. P. Soares[1]*



Revista da Sociedade Brasileira de Medicina Tropical 40(1):.jan-fev, 2007 ARTIGO/ARTICLE

Trypanocide treatment among adults with chronic Chagas disease living in Santa Fe city (Argentina), over a mean follow-up of 21 years: parasitological, serological and clinical evolution.

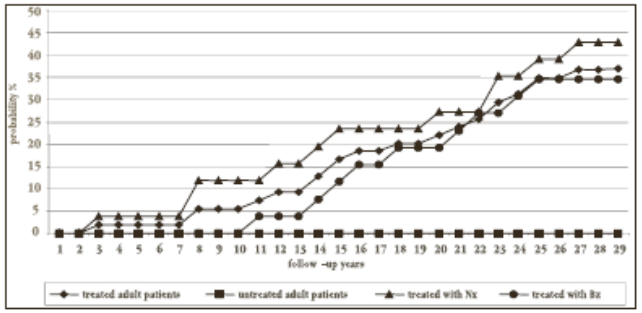
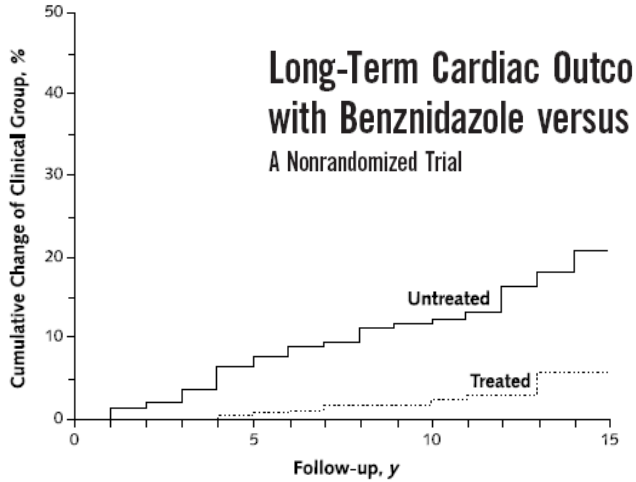


Figure 2 - Probability of negative seroconversion in adult patients with chronic Chagas disease, treated with nifurtimox and/or benznidazole and untreated, over the course of time.

Figure 2. Kaplan–Meier curves of cumulative percentage of patients who changed clinical group.



Long-Term Cardiac Outcomes of Treating Chronic Chagas Disease with Benznidazole versus No Treatment

A Nonrandomized Trial

Viotti R, et al. Ann Intern Med 2006;144:724-34

DNDi Drugs for Neglected Diseases *initiative*

Randomized clinical trials to assess treatment against *T. cruzi* infection in the 90s

THE LANCET

Randomised trial of efficacy of benznidazole in treatment of early *Trypanosoma cruzi* infection

Ana Lucia S Sgambatti de Andrade, Fabio Zicker, Renato Mauricio de Oliveira, Simonne Almeida e Silva, Alejandro Luquetti, Luiz R Travassos, Igor C Almeida, Soraya S de Andrade, João Guimarães de Andrade, Celina M T Martelli

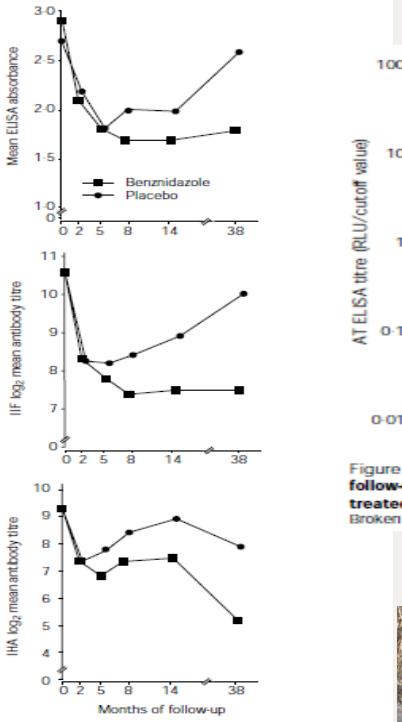


Figure 4: ***T cruzi* serological response in benznidazole and placebo groups by time**
Error bars indicate 95% CI. IIF=indirect immunofluorescence; IHA=indirect haemagglutination.

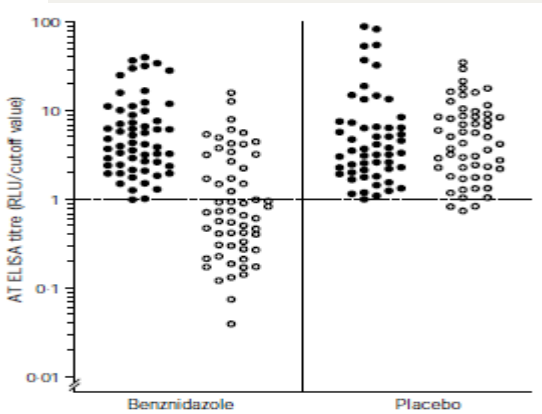


Figure 2: **AT ELISA results at trial entry (●) and at end of follow-up (○) for 58 benznidazole-treated and 54 placebo-treated children who completed trial treatment**
Broken horizontal line=cut-off; values below this indicate seronegativity.

Am. J. Trop. Med. Hyg., 59(4), 1998, pp. 526–529

EFFICACY OF CHEMOTHERAPY WITH BENZNIDAZOLE IN CHILDREN IN THE INDETERMINATE PHASE OF CHAGAS' DISEASE

SERGIO SOSA ESTANI, ELSA LEONOR SEGURA, ANDRES MARIANO RUIZ, ELSA VELAZQUEZ, BETINA MABEL PORCEL, AND CRISTINA YAMPOTIS

Centro Nacional de Diagnóstico e Investigación de Endemo-Epidemias/Administración Nacional de Laboratorios e Institutos de Salud (ANLIS) Dr. Carlos G. Malbrán, Buenos Aires, Argentina; Instituto Nacional de Parasitología Dr. Mario Fatala Chaben/ ANLIS, Secretaría de Salud, Ministerio de Salud y Acción Social de la Nación, Buenos Aires, Argentina; Hospital San Roque, Ministerio de Salud de la Provincia, Embarción Salta, Argentina

Serologic follow-up of children treated with benznidazole or placebo to 48 months post-treatment in Salta, Argentina, 1991–1995*

		IHA				IFA				EIA			
Treatment	n	Mean	SD	Test		Mean	SD	Test		Mean	SD	Test	
Benznidazole													
Pretreatment	51	7.98	1.82	7 DF	1 DF	7.05	1.12	7 DF	1 DF	0.467	0.099	7 DF	1 DF
End of treatment	47	7.68	2.14		NS	6.57	1.58		NS	0.433	0.110		NS
3 months	45	7.26	2.33		NS	6.27	1.28		$P<0.01$	0.409	0.112		$P<0.01$
6 months	45	7.00	2.53		$P<0.05$	6.11	1.57		$P<0.001$	0.371	0.115		$P<0.001$
12 months	48	7.00	2.27		$P<0.05$	5.87	1.56		$P<0.001$	0.369	0.107		$P<0.001$
18 months	47	6.53	2.62		$P<0.001$	5.80	1.82		$P<0.001$	0.358	0.120		$P<0.001$
24 months	46	6.80	2.26		$P<0.01$	5.32	2.03		$P<0.001$	0.330	0.098		$P<0.001$
48 months	44	5.93	2.11	$P<0.001$	$P<0.001$	5.65	2.18	$P<0.001$	$P<0.001$	0.343	0.094	$P<0.001$	$P<0.001$
Placebo													
Pretreatment	50	8.00	1.16	7 DF	1 DF	6.80	1.22	7 DF	1 DF	0.472	0.095	7 DF	1 DF
End of treatment	45	8.11	1.21		NS	6.80	1.07		NS	0.492	0.090		NS
3 months	44	8.11	1.10		NS	6.54	1.15		NS	0.489	0.098		NS
6 months	39	7.87	1.34		NS	6.61	1.60		NS	0.477	0.101		NS
12 months	47	8.08	1.26		NS	6.40	1.13		NS	0.476	0.113		NS
18 months	48	7.93	1.17		NS	6.47	1.16		NS	0.464	0.108		NS
24 months	49	7.77	1.22		NS	6.34	1.54		NS	0.479	0.104		NS
48 months	44	7.47	0.95	NS	$P<0.05$	6.97	2.21	$P<0.05$	$P<0.05$	0.501	0.115	NS	NS

* IHA = indirect hemagglutination assay; IFA = indirect immunofluorescence assay; EIA = enzyme immunoassay; Test = analysis of variance or Kruskal-Wallis test; df = degrees of freedom; NS = not significant ($P > 0.05$). The IFA and IHA values are means (log, of two-fold dilutions of serum samples). The EIA values are mean optical densities.

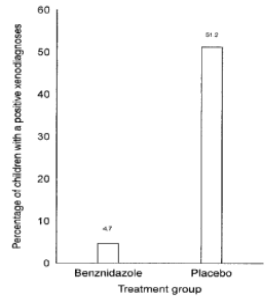


FIGURE 2. Percentage of children with a positive xenodiagnosis 48 months after treatment with beznidazole or placebo in Salta, Argentina, 1991–1995.

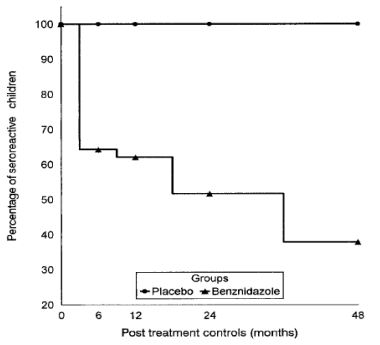


FIGURE 1. Decrease in the percentage of children with reactive serology against *Trypanosoma cruzi* (indeterminate phase of Chagas' disease) by enzyme immunoassay using the F29 protein after treatment with benznidazole or placebo in Salta, Argentina, 1991–1995.

A NEW PARADIGM IN THE 21ST CENTURY

Antimicrobial Agents and Chemotherapy

Towards a Paradigm Shift in the Treatment of Chronic Chagas Disease

R. Viotti, B. Alarcón de Noya, T. Araujo-Jorge, M. J. Grijalva, F. Guhl, M. C. López, J. M. Ramsey, I. Ribeiro, A. G. Schijman, S. Sosa-Estani, F. Torrico and J. Gascon
Antimicrob. Agents Chemother. 2014, 58(2):635. DOI: 10.1128/AAC.01662-13.
Published Ahead of Print 18 November 2013.

NHEPACHA
Red Iberoamericana

Review Article

Therapy of Chagas Disease: Implications for Levels of Prevention

Sergio Sosa-Estani,[1,2,3] Lisandro Colantonio,[4] and Elsa Leonor Segura[1,2]

[1] *Instituto Nacional de Parasitología "Dr. Mario Fatala Chaben" y Centro Nacional de Diagnóstico e Investigación de Endemo-epidemias (CeNDIE), ANLIS "Dr. Carlos G. Malbrán", Ministerio de Salud, Avendia Paseo Colón 568, 1063 Buenos Aires, Argentina*
[2] *Consejo Nacional de Investigaciones Cientificas y Técnicas (CONICET), Avendia Rivadavia 1917, 1033 Buenos Aires, Argenti*
[3] *Instituto de Efectividad Clínica y Sanitaria (IECS), Dr. Emilio Ravignani 2024, 1414 Buenos Aires, Argentina*
[4] *Departamento de Salud Pública, Facultad de Medicina, Universid*

Acute Phase

Old Paradigm

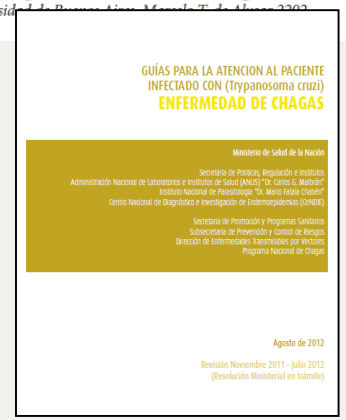
- Autoimmune origin of chronic myocarditis (5,7,21)
- Absence of *T. cruzi* in tissues
- Lack of relationship between acute and chronic stages of the disease, with 30% of heart disease progression due to non-established causes (50)
- Several mechanisms of cardiomyopathy progression: autoimmune, autonomic denervation, disorders of microcirculation (33,51,52)
- **No indication of antiparasitic treatment** (53,54)

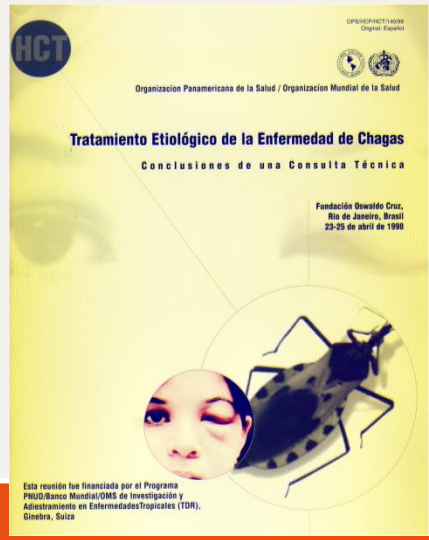
Acute and Chronic Phase

New Paradigm

- Inflammatory immune response triggered and sustained by the parasite (25)
- Finding of *T. cruzi* in tissues (19,20)
- Linking acute and chronic stages of disease, correlation with the host's immune status, and reactivation of the infection by immunosuppression (14,15-18,23)
- The parasitic persistence is postulated as the main mechanism of progression toward cardiomyopathy (14,24,25)
- **Antiparasitic treatment** (3,11,27,29,30,33-39)

FIG 1 Comparison of concepts belonging to the old and the new paradigms for chronic Chagas disease. Relevant references are given in parentheses.





Chagas Disease –TPP 2015

	Acceptable	Ideal
Target population	Chronic indeterminate	Chronic indeterminate and Acute
Geographic Distribution	All regions	All regions
Efficacy	Non-inferior to benznidazole standard dose* in all parasitological areas	Superior to benznidazole standard dose in different phases of disease (acute and chronic) (parasitological)
Safety	Superior to benznidazole* in the frequency of definitive treatment discontinuations due to medical indication (clinical and laboratory)**	Superior to benznidazole* in the frequency of definitive treatment discontinuations due to medical indication (clinical and laboratory)**
Contraindications	Pregnancy	No contraindications
Precautions	No genotoxicity**; no pro-arrythmic potential	No genotoxicity; no teratogenicity; no pro-arrythmic potential
Interactions	No clinically significant interaction with anti-arrythmic and anticoagulant drugs	No clinically significant interaction with other drugs
Presentation	Oral/Parenteral (short POC)*** Age-adapted	Oral Age-adapted
Stability	3 years, climatic zone IV	5 years, climatic zone IV
Dosing regimen	Oral - any duration Parenteral - <7 days	<30days
Cost	Lowest possible	≤ current treatment cost

* As per WHO recommendation; ** No genotoxicity is a condition only for NCEs; *** Need for parenteral treatment for severe disease

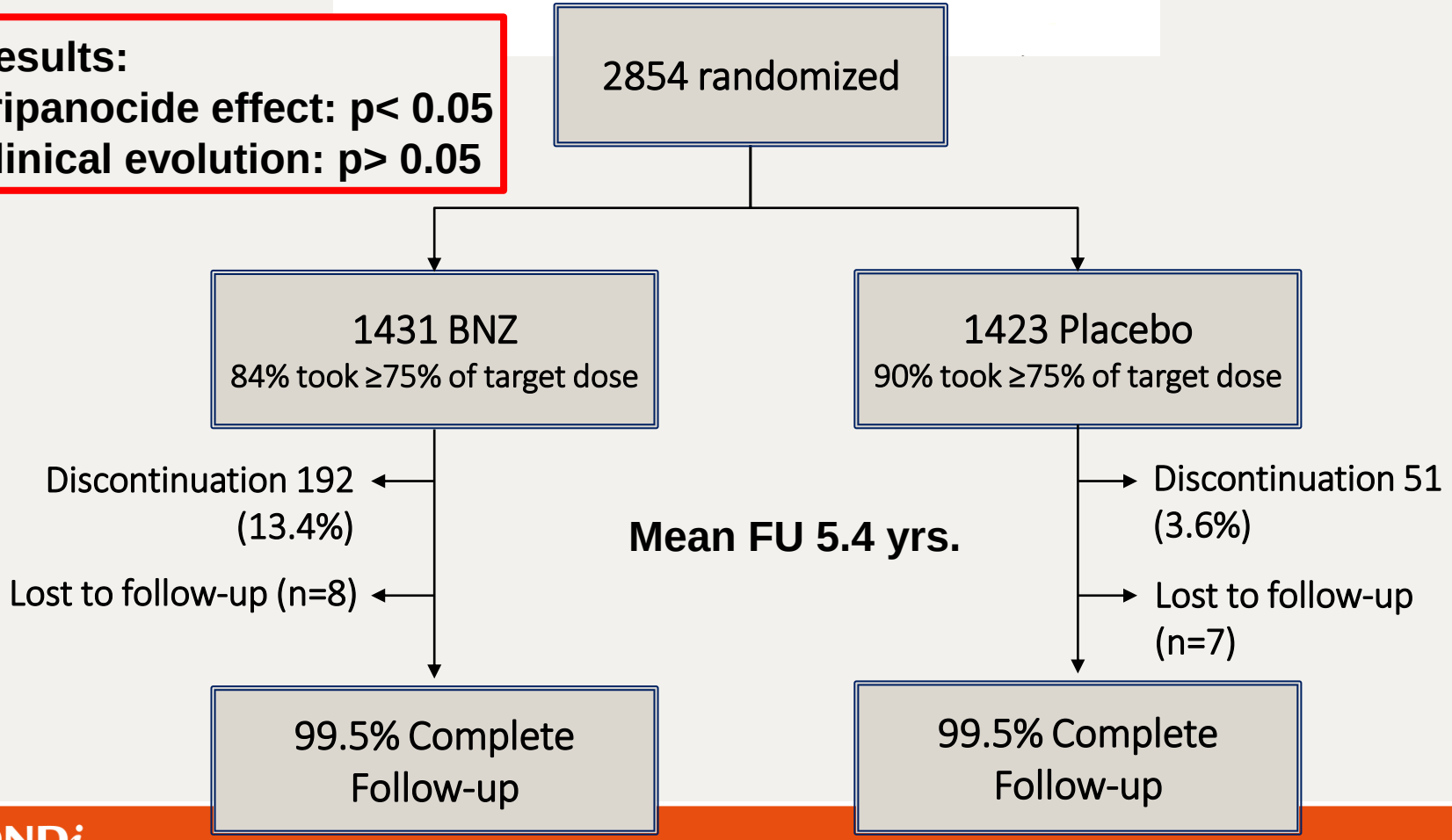
BENEFIT

ORIGINAL ARTICLE

Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy

C.A. Morillo, J.A. Marin-Neto, A. Avezum, S. Sosa-Estani, A. Rassi, Jr., F. Rosas, E. Villena, R. Quiroz, R. Bonilla, C. Britto, F. Guhl, E. Velazquez, L. Bonilla, B. Meeks, P. Rao-Melacini, J. Pogue, A. Mattos, J. Lazdins, A. Rassi, S.J. Connolly, and S. Yusuf, for the BENEFIT Investigators*

Results:
Tripanocide effect: p< 0.05
Clinical evolution: p> 0.05

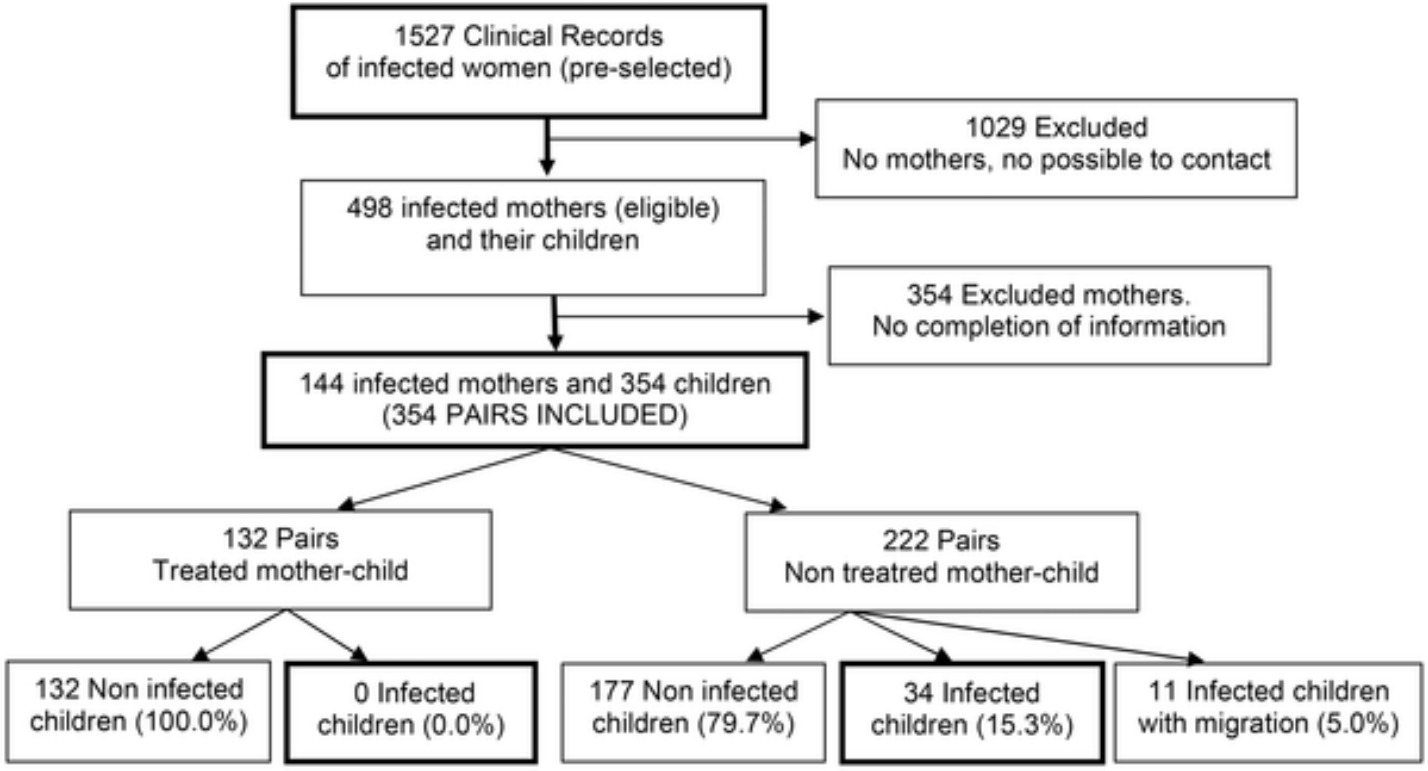


OPEN ACCESS Freely available online

PLOS | NEGLECTED TROPICAL DISEASES

Trypanocide Treatment of Women Infected with *Trypanosoma cruzi* and Its Effect on Preventing Congenital Chagas

Diana L. Fabbro[1], Emmaria Danesi[2], Veronica Olivera[1], Maria Olenka Codebó[3], Susana Denner[1], Cecilia Heredia[2], Mirtha Streiger[1], Sergio Sosa-Estani[2,3]*



(RR congenital transmission in treated mothers = 0.04, IC:95%: 0.012 - 0.166; p<0.05)

CD Clinical Landscape

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Posaconazole and Benznidazole for Chronic Chagas' Disease

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER
VOL. 69, NO. 8, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.12.023

Benznidazole and Posaconazole in Eliminating Parasites in Asymptomatic *T. Cruzi* Carriers

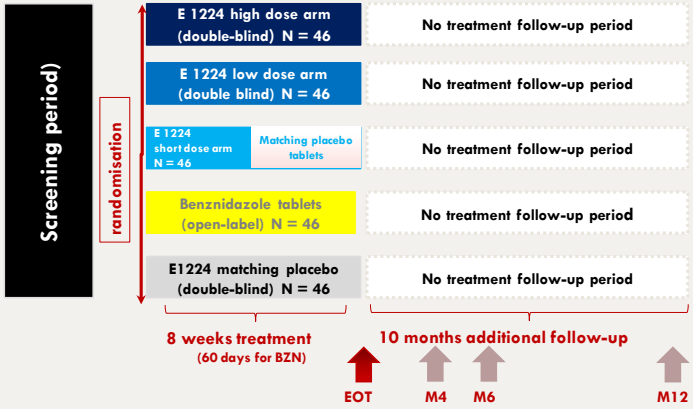
The STOP-CHAGAS Trial

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

New Scheme of Intermittent Benznidazole Administration in Patients Chronically Infected with *Trypanosoma cruzi*: a Pilot Short-Term Follow-Up Study with Adult Patients

E1224: DNDi

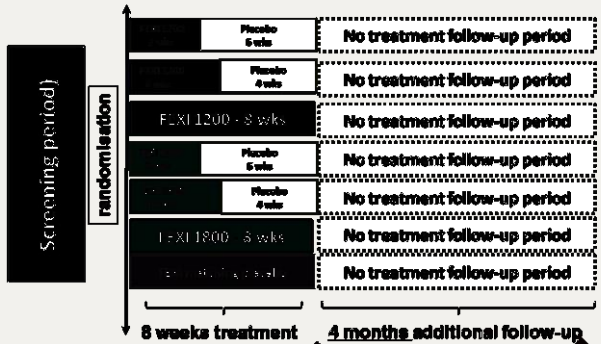
Proof of Concept for a Safe, Effective and Affordable New Therapy for Chagas Disease



Fexnidazole Phase II

DNDi

Proof-of-Concept Dose Ranging Study Evaluation of Dose and duration



20 patients/arm
Stopping rules: futility and safety
Cardiac and liver safety surveillance

SUMMARY OF RECENT RCTs

- Posaconazole (monotherapy or in combination) and E1224 (monotherapy) were effective during treatment and relapsed after EOT (demonstrated by PCR Positive)

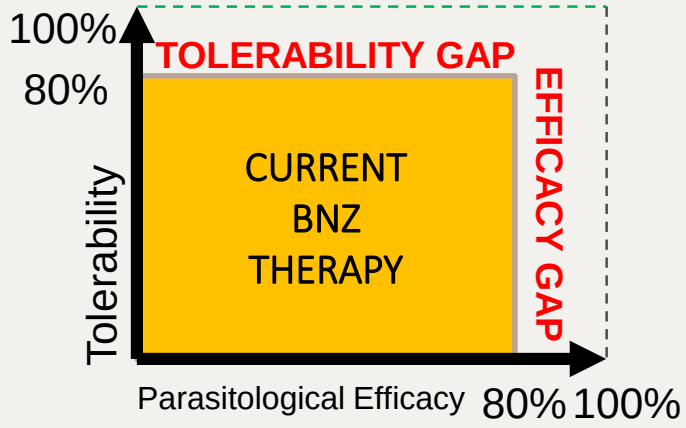
- Fexinidazole (suspended for safety issues) was effective during treatment with sustained response (100%) at 12 months FUP

- Benznidazole was effective during treatment with sustained response (~ 80%) at 12 months FUP

- PCR proved useful for assessing treatment response to anti-trypanosomal drugs

Strategies for Improving Efficacy and Tolerability

Current situation

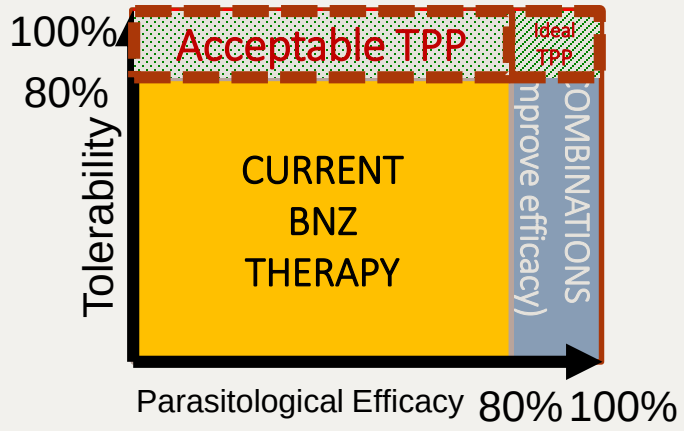


- BNZ is an effective drug

… but

- Efficacy gap
  - About 80% exhibit sustained response on PCR at 12 months
- Tolerability gap
  - 15-20% do not complete treatment
    - Majority due to ADRs

Opportunities



- Reduce BNZ exposure
  - Improve tolerability while maintaining efficacy
  - *Does not address the efficacy gap
- Combination therapy
  - Improve efficacy while maintaining or improving tolerability
  - *May not address the tolerability gap

BENDITA overall design

Partners
CEADES
ISGlobal
INGEBI
INP

- **Adults (18 – 50 years old) at Chronic Indeterminate CD stage**
- **210 subjects - 30 patients/arm**

Screening period

randomization

BZN 300 8W
E1224 PBO 8W

BZN 300 4W | BZN PBO 4W
E1224 PBO 8 W

BZN 300 2W | BZN PBO 6W
E1224 PBO 8 W

BZN 150 4W | BZN PBO 4W
E1224 PBO 8W

BZN 150 4W | BZN PBO 4W
E1224 8W

IT IT IT IT IT IT
E1224 8W

BZN PBO 8W
E1224 PBO 8W

Follow-up at 10 wk, 12 wk, 4M, 6M, 12 M

Primary endpoint at 6M

Follow-up until 12M

- **Futility stopping rule**
- **10 and 12-week interim analysis (safety and efficacy)**

2 months treatment phase

Partners
ISGlobal
Hosp Vall d´Hebron
Hop Clinic
Hop Moises Broggi
Hosp Univ Valencia
INGEBI

FEXI 012 overall design

- **Adults (18 – 50 years old) at Chronic Indeterminate CD stage**
- **45 subjects - 15 patients/arm**

Screening period

randomization

Fexi 600 mg
10 days

Fexi 1200 mg
3 days

PBO 7 days

Fexi 600 mg
3 days

Fexi 1200 mg
4 days

PCO
3 day

Follow-up at 1-4; 6; 10; 12 wk, 4M, 6m, 12 M

Primary endpoint at 4M

Follow-up until 12M

10 days treatment phase

- **Futility stopping rule**
- **12-week interim analysis (safety and efficacy)**

Chagas Disease – R&D strategy

POC PHASE 2 studies
BENDITA (N: 210)
3 Arms New Reg Bz
2 Arms Combo New Reg Bz-E1224
LPI 29/7/17 : 210

FEXI 012 (N: 45)
3 Arms new Reg Fexinidazole
FV/FP OCTOBER 2017

BMK

Go/No-Go

PHASE 3 study
Select best NCE (**1-2 among 5 arms**)
Efficacy and Safety – Confirmatory

- New Regimen BZN in combination E1224, and/or
- Fexinidazol

- Using a new Set of BMKs

Registration in Endemic Countries
(US and EMA)

Chagas Disease – R&D strategy
New Regimen of BZ monotherapy

PHASE 2 studies

POA and POC – Exploratory in adult, chronic indeterminate CD

- BENDITA Study (DNDi),N: 210 (assesing 3 new regimens of bz monotherapy)
  - Bolivia
- **LPI 29/7/17 : 210**

- BERENICE Study (EU FP7), N:240 (assesing 2 new regimens of bz monotherapy)
  - Argentina
  - Brasil
  - Colombia
  - Spain
- **FV/FP JULY 2017**

Consistent/ Inconsistent Results

IMPLEMENTATION NEW REGIMEN OF BENZNIDAZOLE

BERENICE Phase I and II WIHP FP7 UC

DNDi
Drugs for Neglected Diseases *initiative*

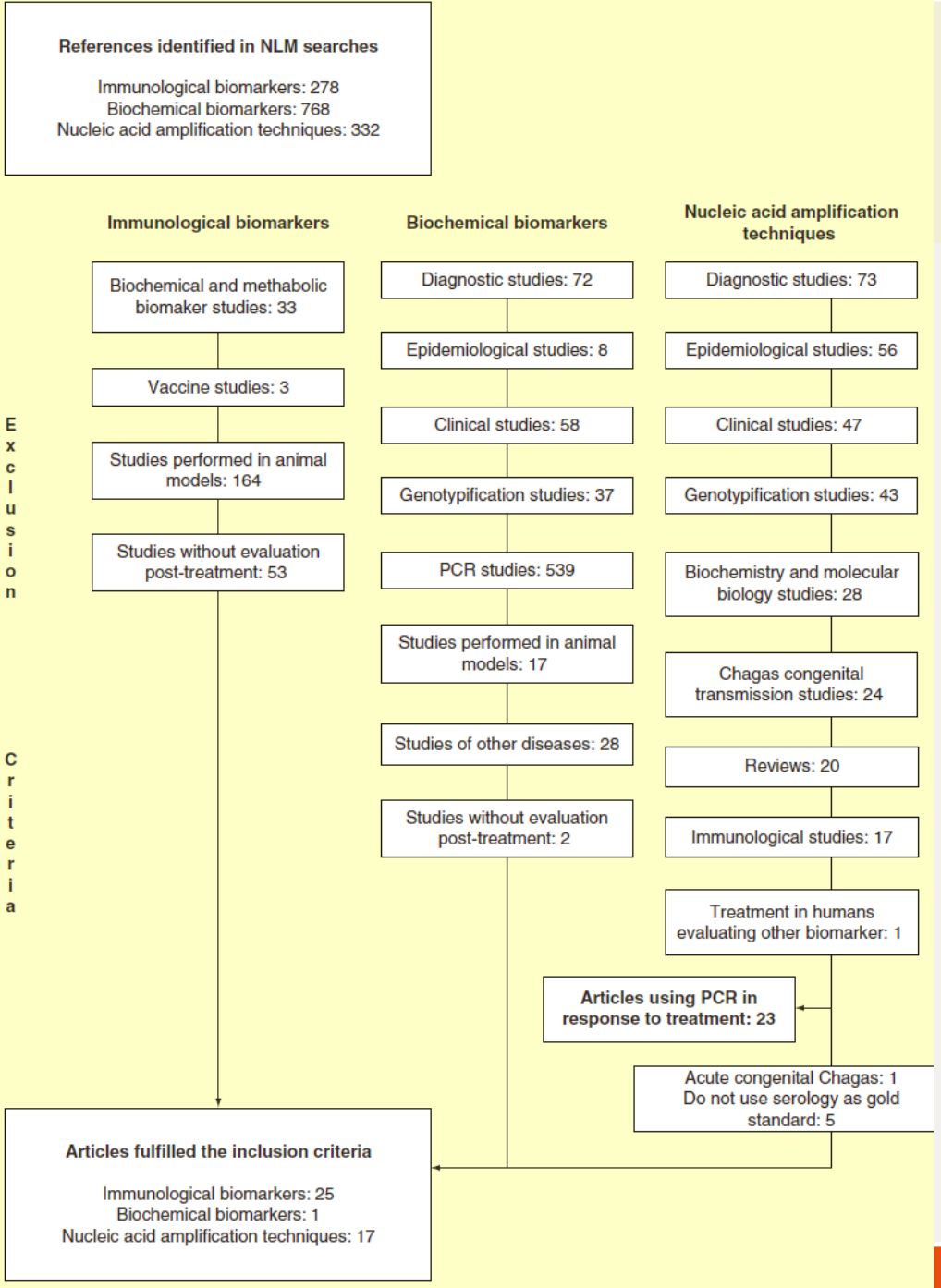


Figure 1. Flow of inclusion of studies on biological markers for evaluating.

EXPERT REVIEWS

Biological markers for evaluating therapeutic efficacy in Chagas disease, a systematic review

Expert Rev. Anti Infect. Ther. 12(4), 479–496 (2014)

Maria-Jesús Pinazo*, M Carmen Thomas, Jacqueline Bua, Alina Perrone, Alejandro-Gabriel Schijman, Rodolfo-Jorge Viotti, Janine-M Ramsey, Isabela Ribeiro, Sergio Sosa-Estani, Manuel-Carlos López and Joaquim Gascon

Articles fulfilled the inclusion criteria

Immunological biomarkers: 25
Biochemical biomarkers: 1
Nucleic acid amplification techniques: 17

NHEPACHA
Red Iberoamericana

Chagas Disease – R&D strategy - Biomarkers

- Non-human primates
  - PCR (TBRI)
  - Anti-alpha-GAL Ab (TU)
  - Multiplex Recomb Ag (UGA)
- Humans
  - PCR Clinical Validation
  - ApoA1 fragments (Proteomic platforms. McGill U)
  - Multiplex Recomb Ag (UGA)
  - F29 (NHEPACHA)
  - K11-H70 (NHEPACHA)
  - PFR2-peptido 3973 (NHEPACHA)
  - Anti-alpha-GAL Ab (NHEPACHA)
  - Ab3 Ag (InfYnity Biomarkers)

Assessment of treatment failure

Selection of a minimum set of BMKs among 7 candidates to assess treatment success

- Protocol LT FUP RCTs
- Set Biomarkers Phase 3

OUTLOOK FOR 2020 BEYOND….

- NEW TRYPANOCIDE CHEMOTHERAPY
- TRYPANOCIDE CHEMOTHERAPY PLUS IMMUNOTHERAPY (?)
- TRYPANOCIDE CHEMOTHERAPY PLUS MODULATION OF PHYSIOPATHOGENESIS (?)
- TRIPANOCIDE CHEMOTHERAPY PLUS IMMUNOTHERAPY PLUS MODULATION OF PHYSIOPATHOGENESIS (?)

R&D and Access

H 2 2018	H 1 2019	H 2 2019	H 1 2020	H 2 2020	H 1 2021

Increased access to current regimens based on benznidazole and nifurtimox

POC FEXI 012
P 2: 3 arms

POC BENDITA
P 2: 6 arms

POC BERENICE
P 2: 3 arms

New Treatment
P 3: 1-2 among 5 arms

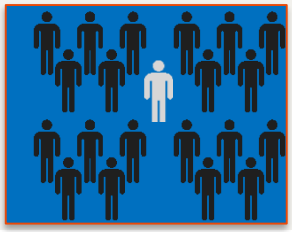
New regimen bz monotherapy
P4: 1 among 4 arms

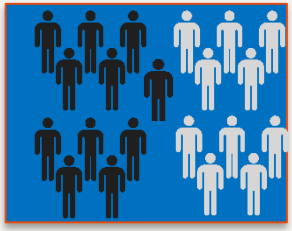
New treatment
P 4:1 among 1-2 arms

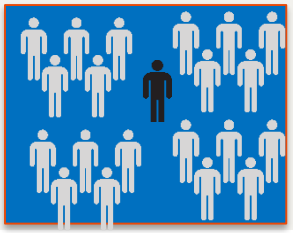
New regimen bz monotherapy
Implementation

NCE

Phase 1 NCE







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THANK YOU!!!

https://www.dndi.org/