ADVANCES AND CHALLENGES IN THE TREATMENT OF CHAGAS DISEASE - A GLOBAL PERSPECTIVE

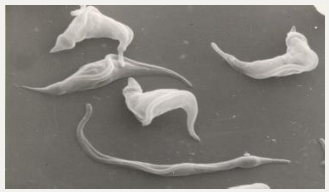
ICID 2018

Sergio Sosa-Estani, PhD

DNDi
Drugs for Neglected Diseases *initiative*

History of Chagas disease

Carlos Chagas



Salvador Mazza

9,000 BC people with *T. cruzi* infection (mummies)

1909 Discovery

1920 Diagnostic

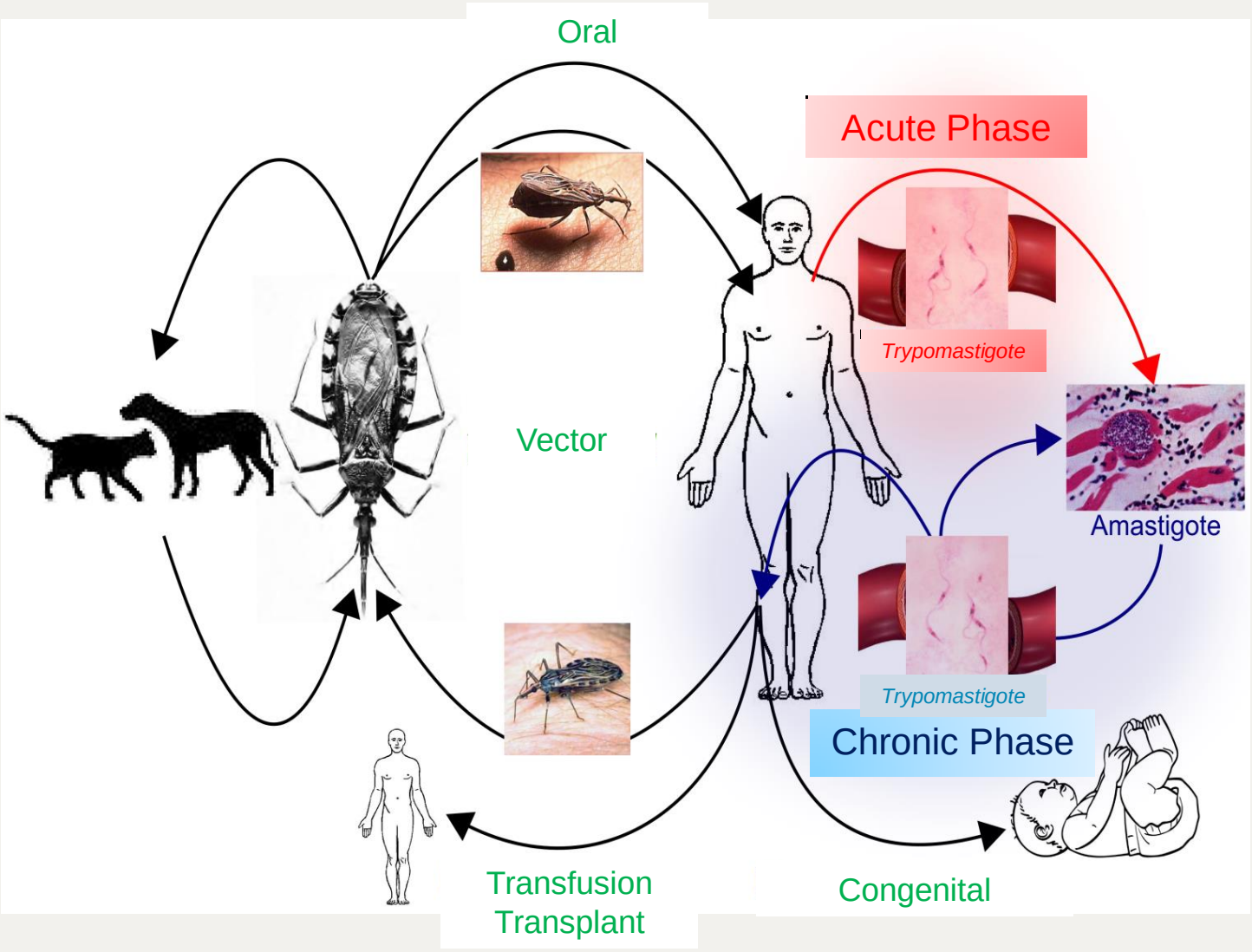
1950 Vector Control

1960-1970
Treatment

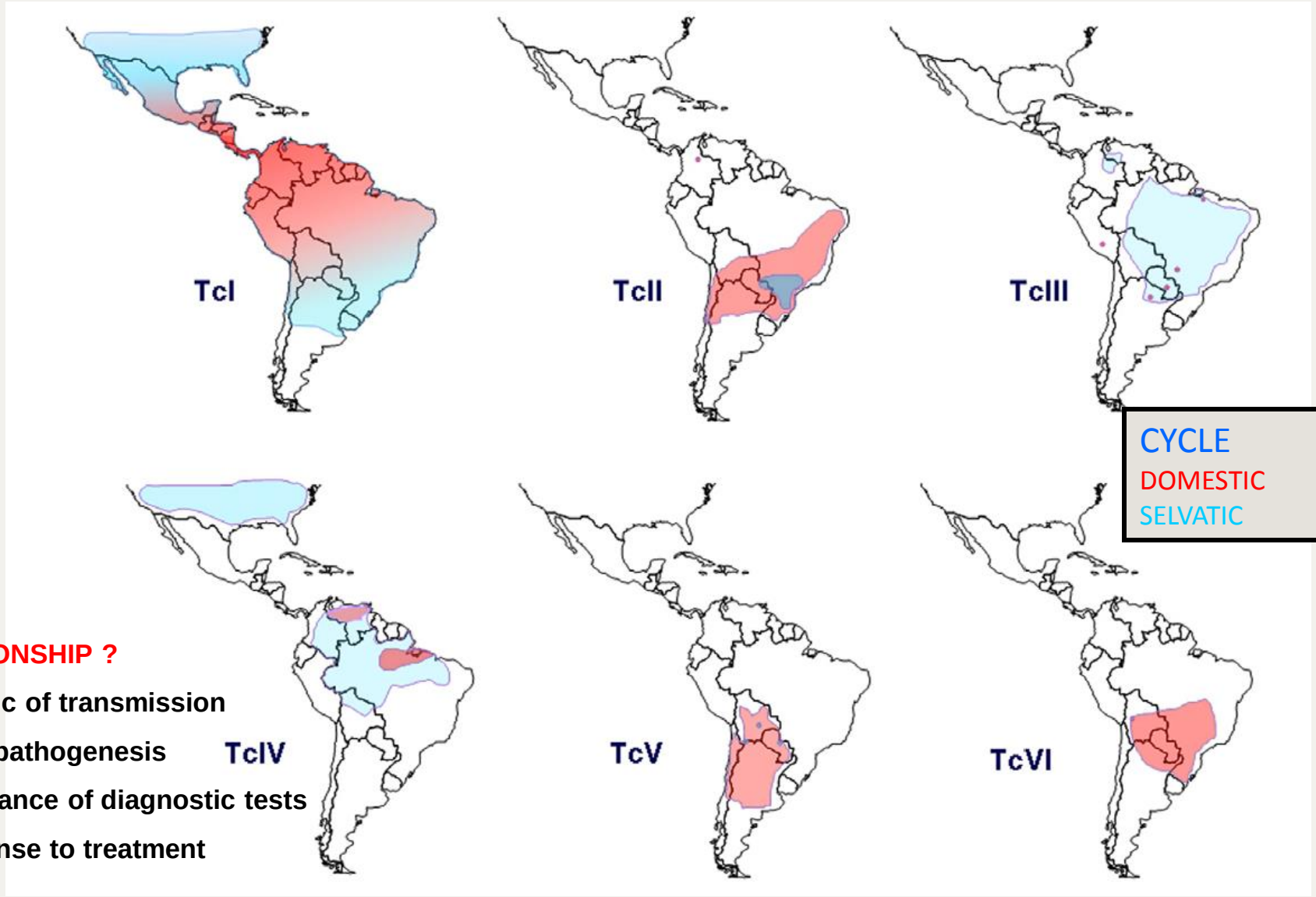
1995-2018 >>>
Treatment – biomarkers

Access

Life cycle of *Trypanosoma cruzi*



GEOGRAPHICAL DISTRIBUTION OF DTU *Trypanosoma cruzi*. Zingales *et al*, 2012.

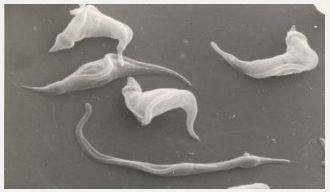


RELATIONSHIP ?

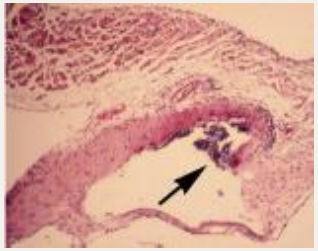
- **Dynamic of transmission**
- **Physiopathogenesis**
- **Peformance of diagnostic tests**
- **Response to treatment**

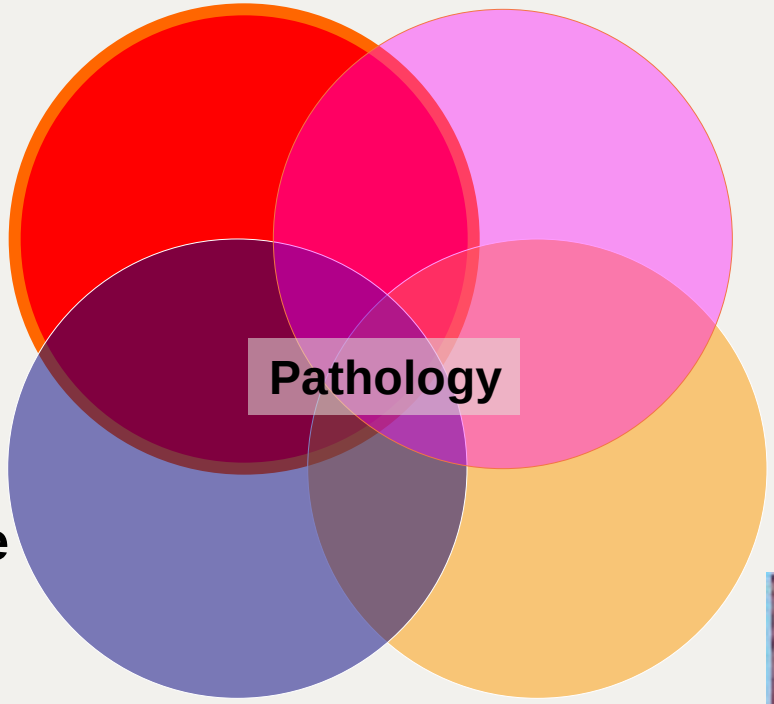
Chagas disease: Physiopathology

Parasite

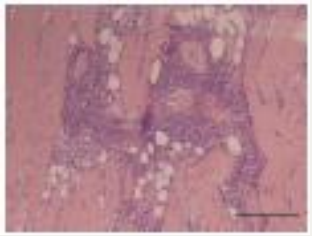


Microvascular

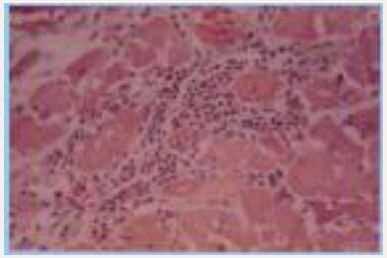




Specific immune response against the parasite

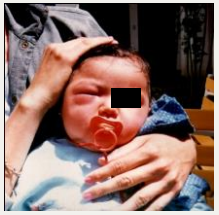


Inflammation

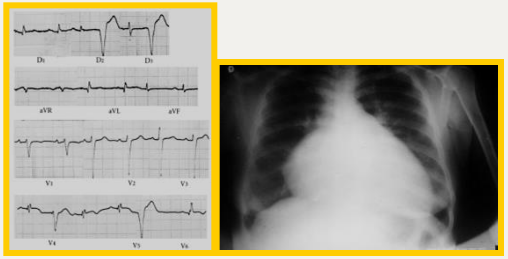


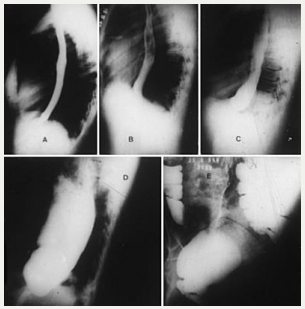
CHAGAS DISEASE
PHASES OF INFECTION AND CLINICAL FORMS

ACUTE PHASE (2 months) Prolonged fever syndrome
- Vector transmission
- Congenital transmission
- Accidents

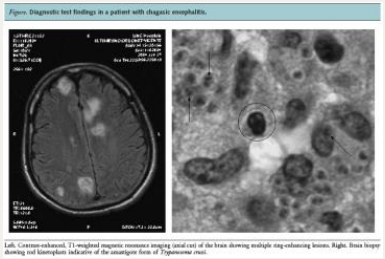


CHRONIC PHASE (decades)
- Without demonstrable disease
- With demonstrable disease
  - Cardiac form
  - Digestive form (megas)
  - Mixed forms and other

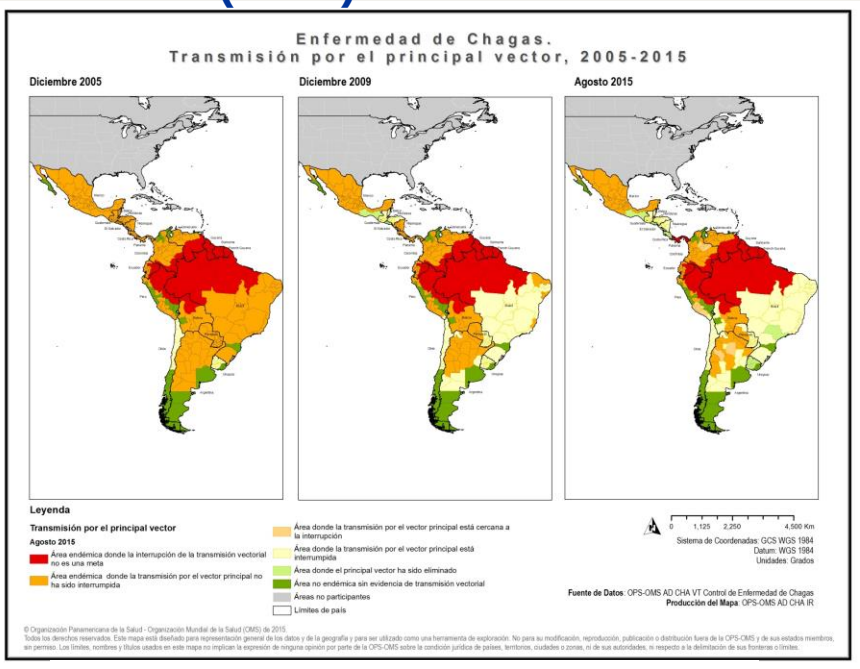


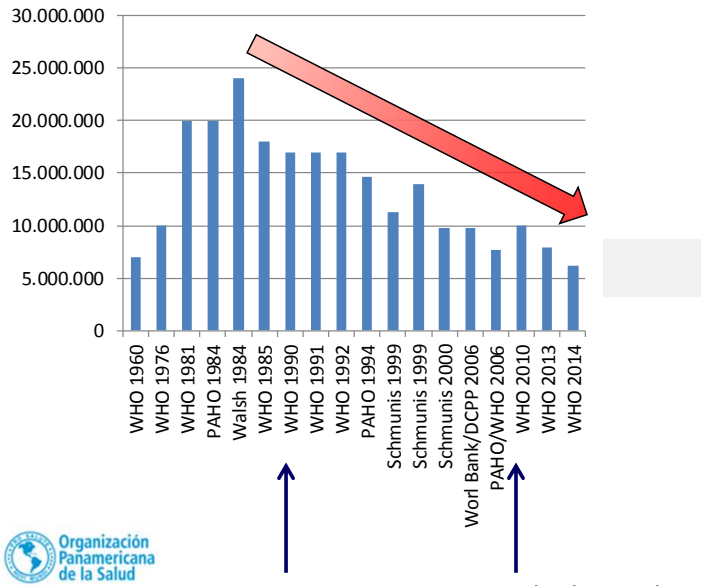


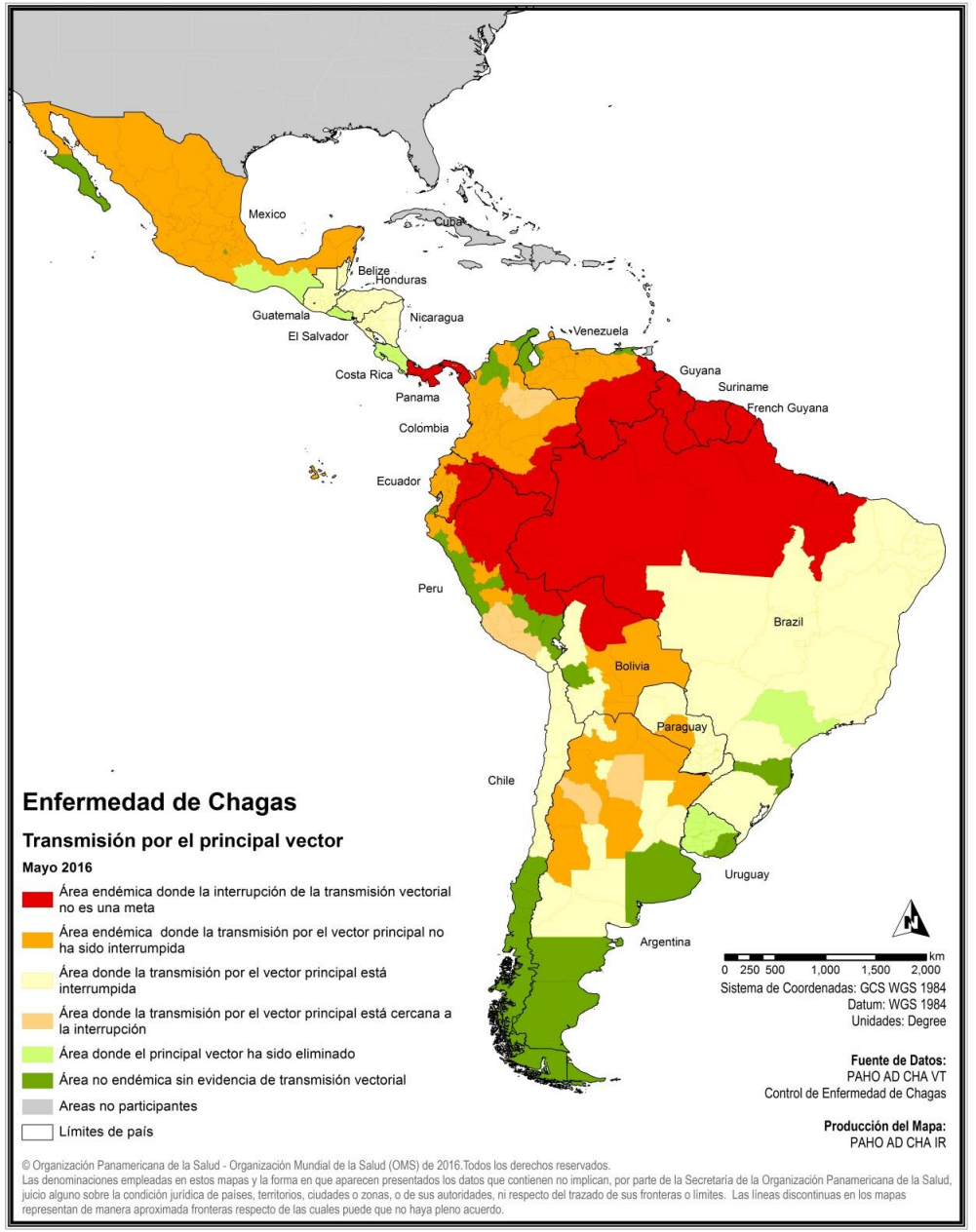
REACTIVATION OF CHRONIC INFECTION (eventual)
- Co-infection (HIV/AIDS)
- Other causes of immunodeficiency (oncology, transplant)



Elimination of intra-domiciliary vectorial transmission of Chagas disease in Latin America (2020)







Organización Panamericana de la Salud
Organización Mundial de la Salud
Américas

Global distribution of Chagas disease cases, based on official estimates, 2006−2017 (WHO, 4th NTD report, 2017)

Around 7,000,000 infected and < 18,000 patients treated/year

- Most common parasitic disease in the Americas
- Leading cause of infectious myocarditis worldwide
- Largest disease burden in chronic indeterminate patients
- 20-30% will evolve to cardiomyopathy with important morbidity and mortality
- Only 2 registered compounds: BZN and nifurtimox

A NEW PARADIGM IN THE 21ST CENTURY

NHEPACHA
Red Iberoamericana

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.

Acute Phase Acute and Chronic Phase

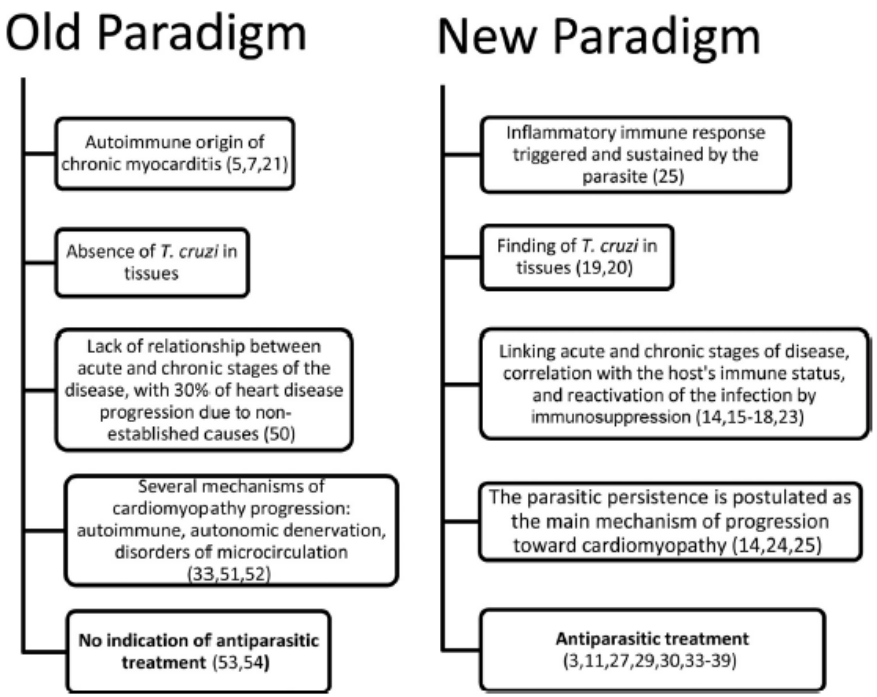
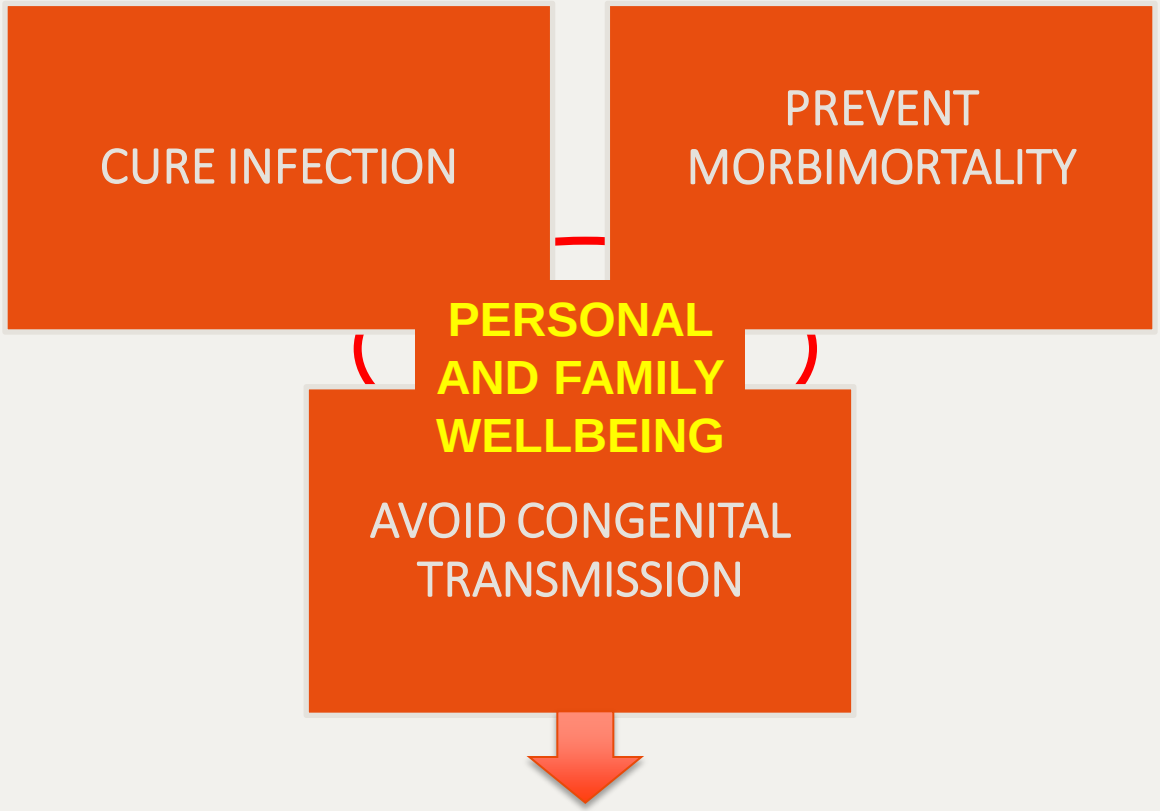


FIG 1 Comparison of concepts belonging to the old and the new paradigms for chronic Chagas disease. Relevant references are given in parentheses.

GOAL OF TIMELY DIAGNOSIS AND TREATMENT



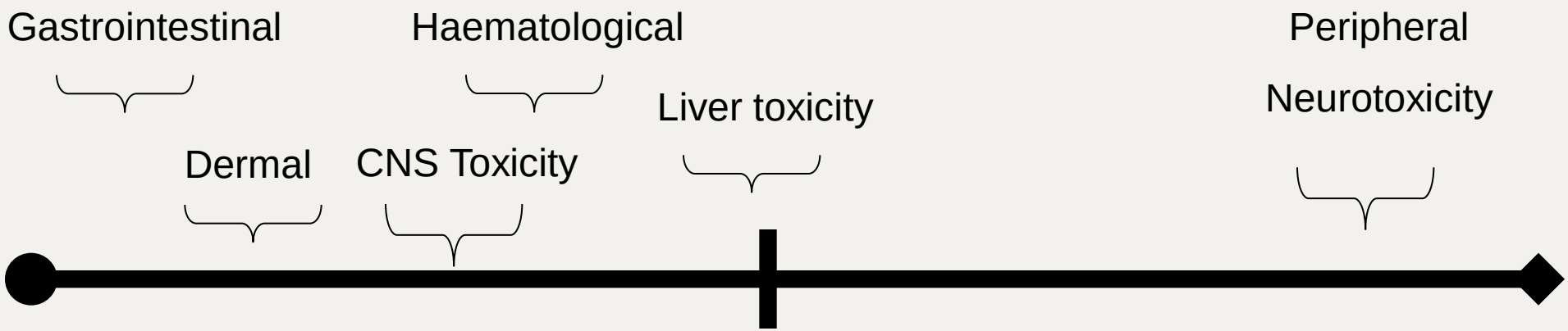
Guidelines for antitrypanosmal treatment with benznidazole or nifurtimox

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

- All patients in the acute phase (A I; A II)
- Children and young adult patients in 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



X X X

Typical completion rates

-adults=83%

-neonates=100%

Monitoring Adverse Events/Drug Tolerance

- Weekly contact with the patient
- Laboratory testing X

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.

TREATMENT
impact again infection

Effects during the acute phase

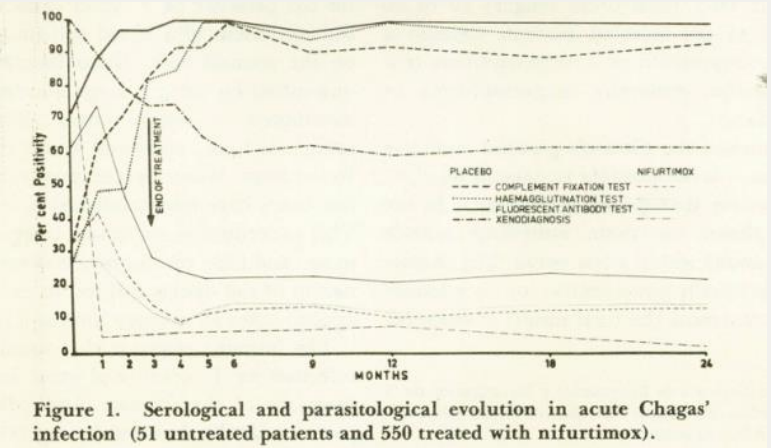
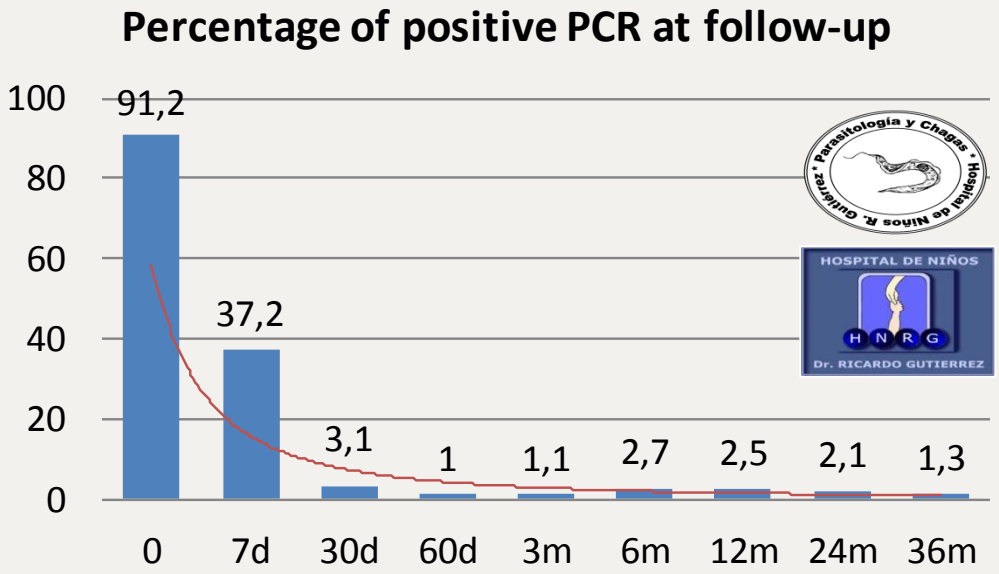


Figure 1. Serological and parasitological evolution in acute Chagas' infection (51 untreated patients and 550 treated with nifurtimox).

Acute Phase: Decrease in antibodies and parasitemia

Cohort of 206 BZN- treated children



Effects during the early chronic phase

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

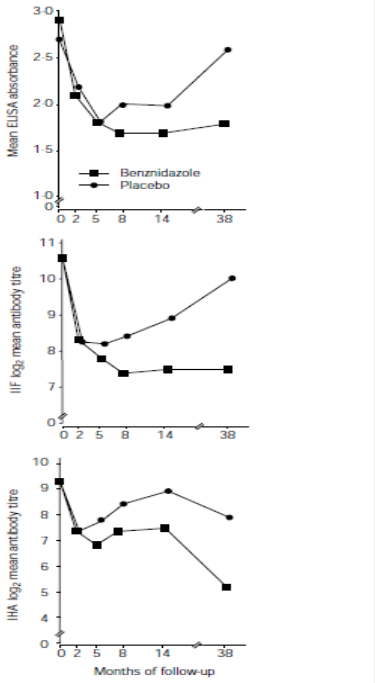


Figure 4: ***T cruzi* serological response in benznidazole and placebo groups by time**
Error bars indicate 95% CI. IIF=indirect immunofluorescence; IHA=indirect haemagglutination.

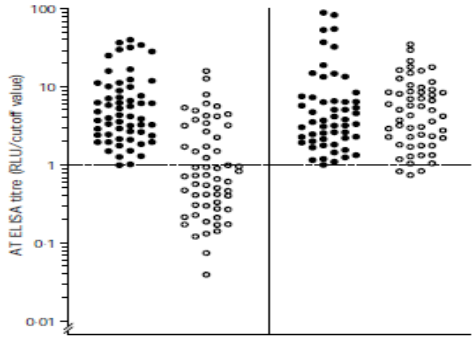


Figure 2: **AT ELISA results at trial entry (●) and at end of follow-up (○) for 58 benznidazole-treated and 54 placebo-treated children who completed trial treatment**
Broken horizontal line=cut-off; values below this indicate seronegativity.

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 ($\log_2$ of two-fold dilutions of serum samples). The EIA values are mean optical densities.

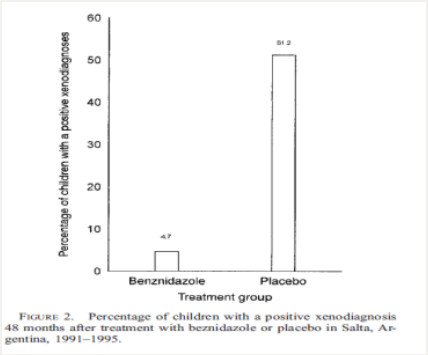


FIGURE 2. Percentage of children with a positive xenodiagnosis 48 months after treatment with beznidazole or placebo in Salta, Argentina, 1991–1995.

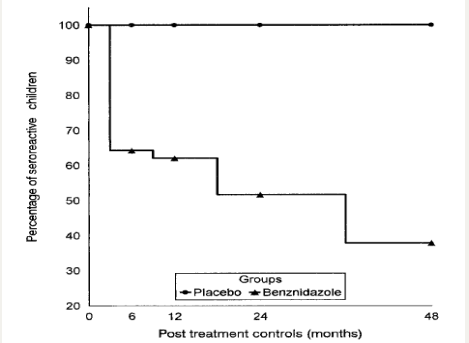
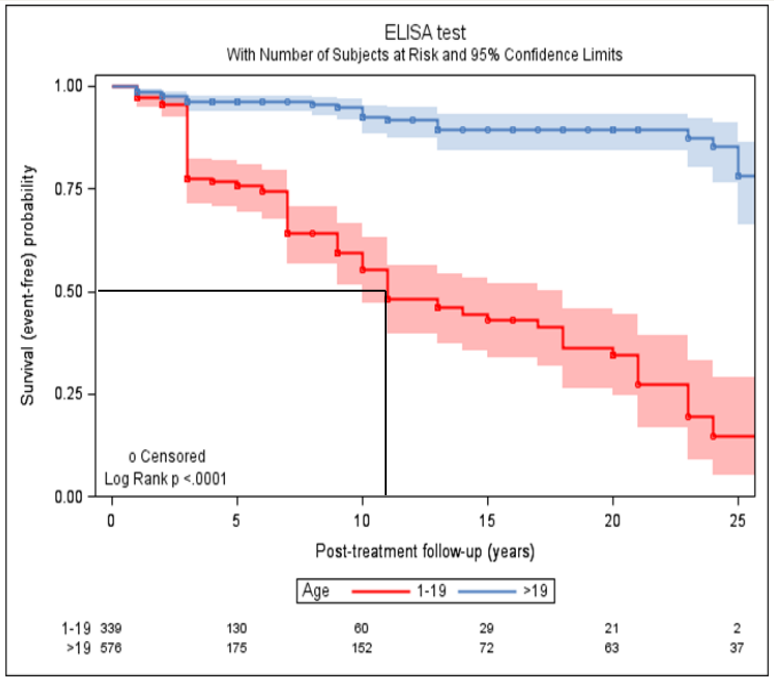


FIGURE 1. Decrease in the percentage of children with reactive serology against *Trypanosoma cruzi* (indeterminate phase of Chagas' disease) by enzyme immunoassay using the F29 protein after treatment with benznidazole or placebo in Salta, Argentina, 1991–1995.

Course of serological outcomes in treated subjects with chronic Trypanosoma cruzi infection: a systematic review and meta-analysis of individual participant data. ELISA test ~ age at treatment



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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]*

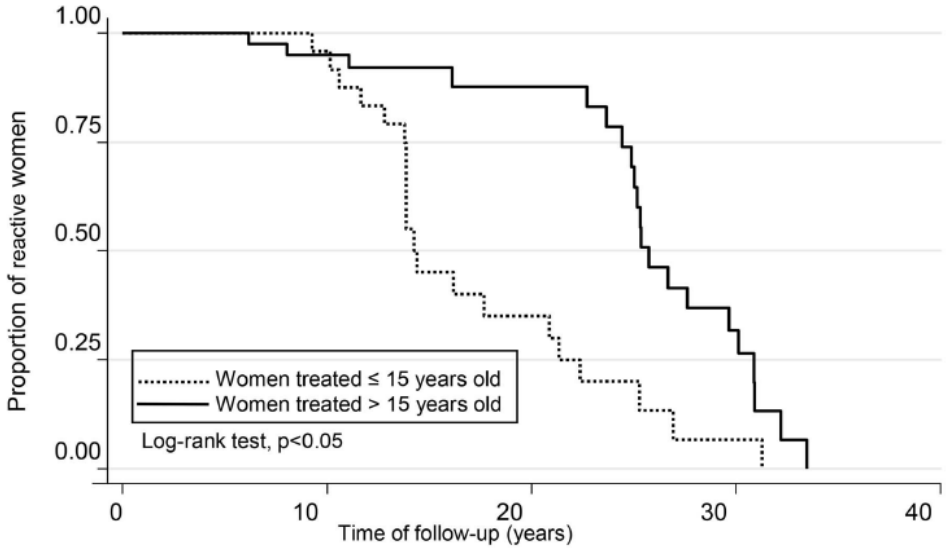

Figure 4. Kaplan-Meier curve showing serological reactivity rate by age during follow-up in 71 treated women.
doi:10.1371/journal.pntd.0003312.g004

Sguassero *et al.* Unpublished

TREATMENT
impact on clinical evolution

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Grupo	N	ACC (n)	ACC (%)	Tpo seguim. (años)	Edad ult. ECG (años)
Tratadas	51	1	1,96	20,6±10,6	44,8±11,6
No tratadas	39	6	15,38	17,9±8,9	47,6±10,5
Total	90	7			

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Evaluation of Parasiticide Treatment with Benznidazol in the Electrocardiographic, Clinical, and Serological Evolution of Chagas Disease

Abilio Augusto Fragata-Filho*, Francisco Faustino França, Claudia da Silva Fragata, Angela Maria Lourenço, Cristiane Castro Faccini, Cristiane Aparecida de Jesus Costa

Table 5. Logistic regression model. Dependent variable: the occurrence of clinical combined outcomes (heart failure, stroke and total mortality) and independent variables: treatment (BZ), follow-up, male, Caucasian and age in years.

		CI (95%) O.R.		
	O.R.	Lower Limit	Upper limit	p
TREATED BZ	0.330	0.115	0.947	0.039
FOLLOW-UP	1.046	0.986	1.110	0.138
MALE	2.264	0.878	5.834	0.091
CAUCASIAN	3.025	0.679	13.480	0.147
AGE	1.021	0.965	1.081	0.463

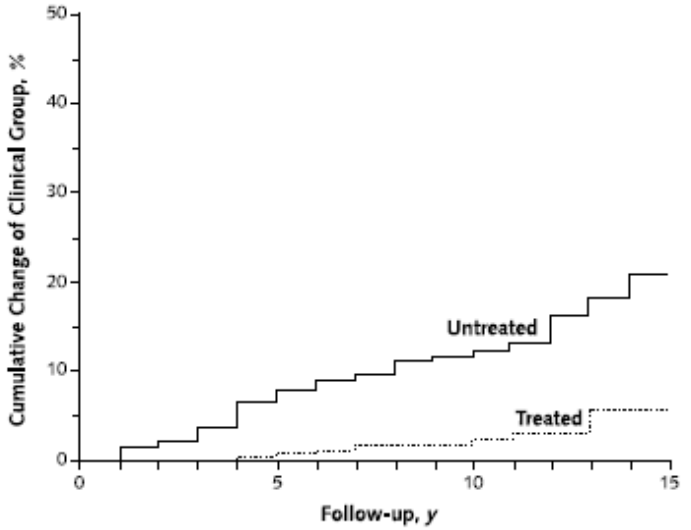
Table 6. Logistic regression model. Dependent variable: normal ECG maintenance and independent variables: treatment with BZ, follow-up, male, Caucasian and age in years.

		CI (95%) O.R.		
	O.R.	Lower Limit	Upper limit	p
TREATED BZ	5.7330	2.5396	12.9420	<0.0001
FOLLOW UP	0.9381	0.8990	0.9789	0.0033
MALE	0.9381	0.8990	0.9789	0.0033
CAUCASIAN	0.9381	0.8990	0.9789	0.0033
AGE	1.0190	0.9886	1.0503	0.2243

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

A Nonrandomized Trial

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



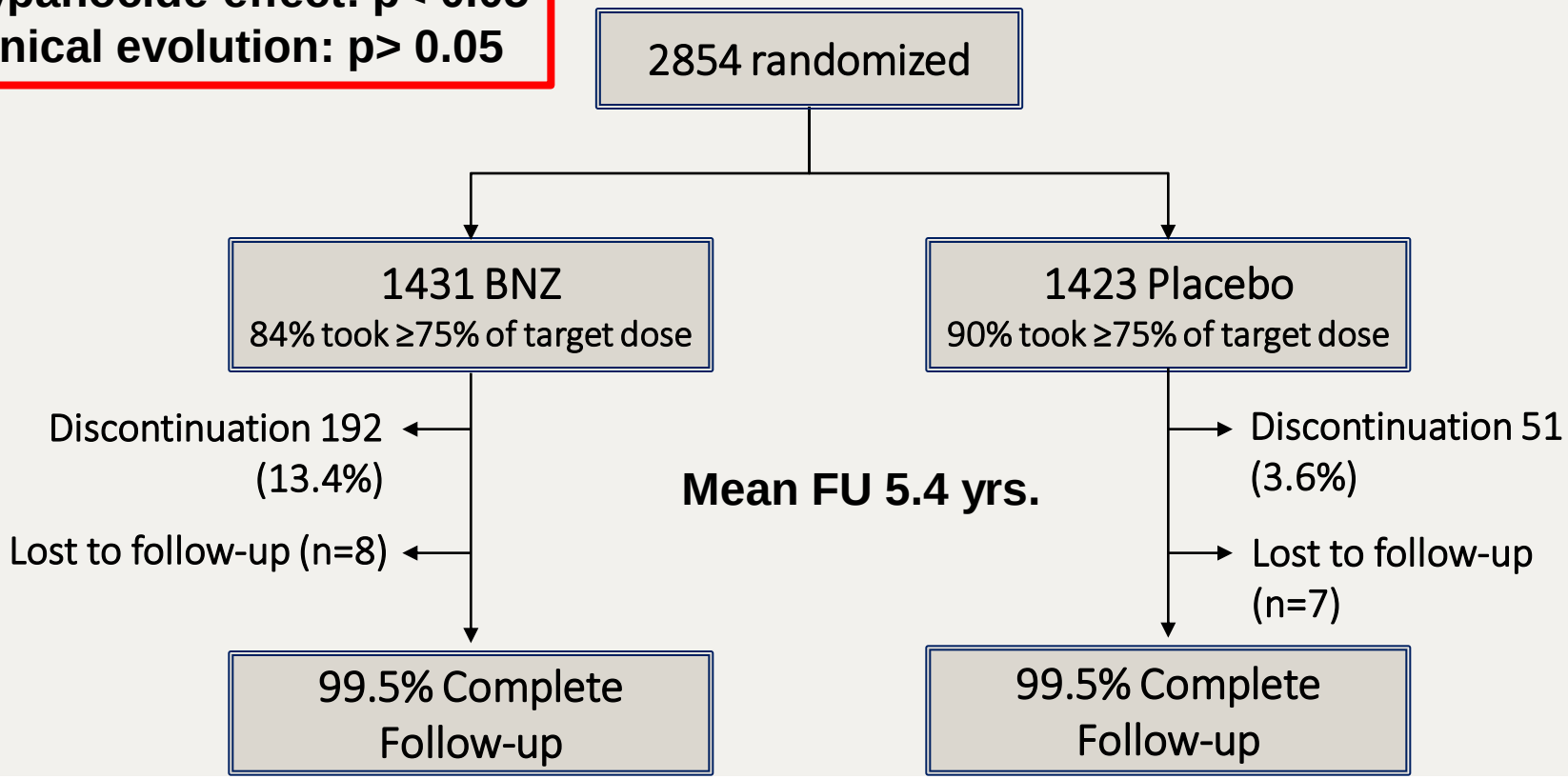
BENEFIT

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:
Trypanocide effect: p< 0.05
Clinical evolution: p> 0.05



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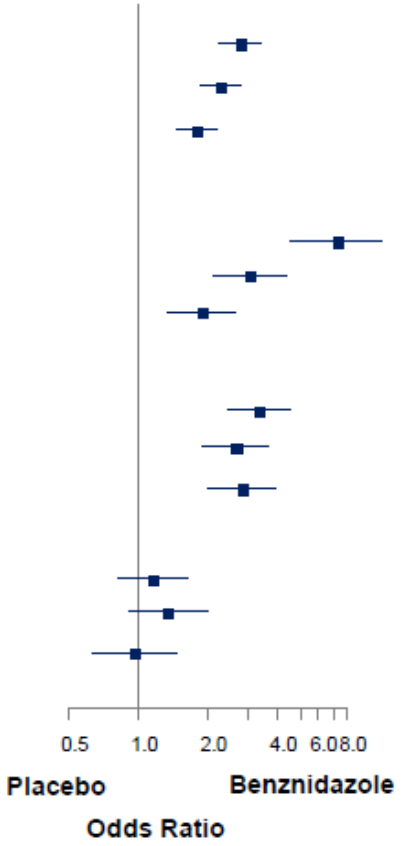
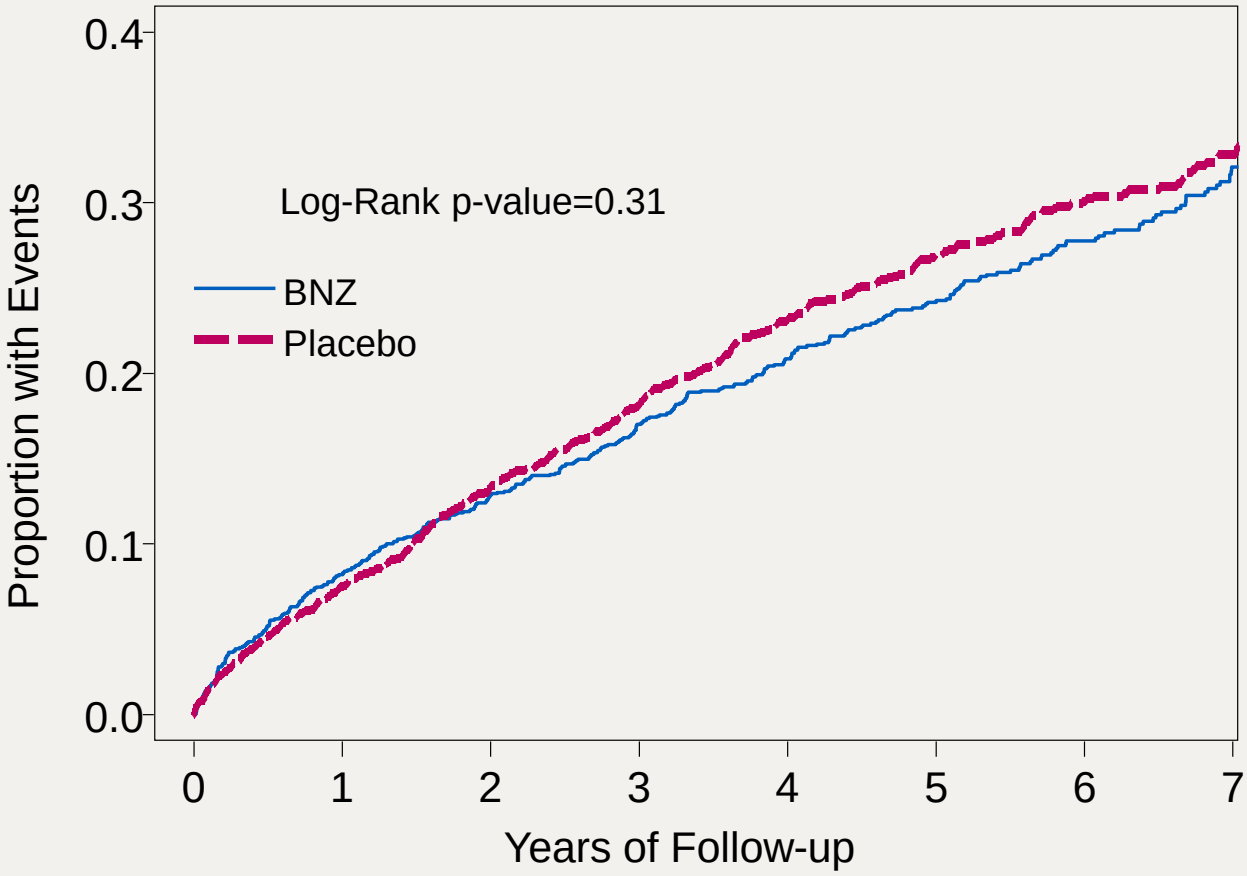
PCR Negativization

	No. of Patients	Placebo (Pts with Events%)	Benznidazole (Pts with Events%)	Interaction P value
Overall				
E.O.T.	918	33.5	66.2	
Year 2	673	35.3	55.4	
>5 Years	647	33.1	46.7	
Brazil				
E.O.T.	213	24.3	86.3	
Year 2	96	31.1	60.8	<0.001
>5 Years	141	27.4	35.3	
Argentina, Bolivia				
E.O.T.	388	28.6	73.0	
Year 2	332	34.1	62.9	
>5 Years	276	30.2	61.4	
Colombia, El Salvador				
E.O.T.	317	45.6	43.9	
Year 2	245	38.5	42.6	
>5 Years	230	40.2	35.4	



Primary Outcome - Overall



# at Risk							
BNZ1431	1312	1246	1178	936	695	484	323
Pl 1423	1316	1233	1155	881	649	459	294

Some of main limitation:

- **Age range**

- Severity of disease (Opportunity of treatment)

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*

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)		—
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)	–1.14)	—
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)	–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)		0.03
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

«Definitive, patient-important outcomes

All results going in the "right direction"...

...but none Statistically significant

N Engl J Med 2015;373:1295-306.

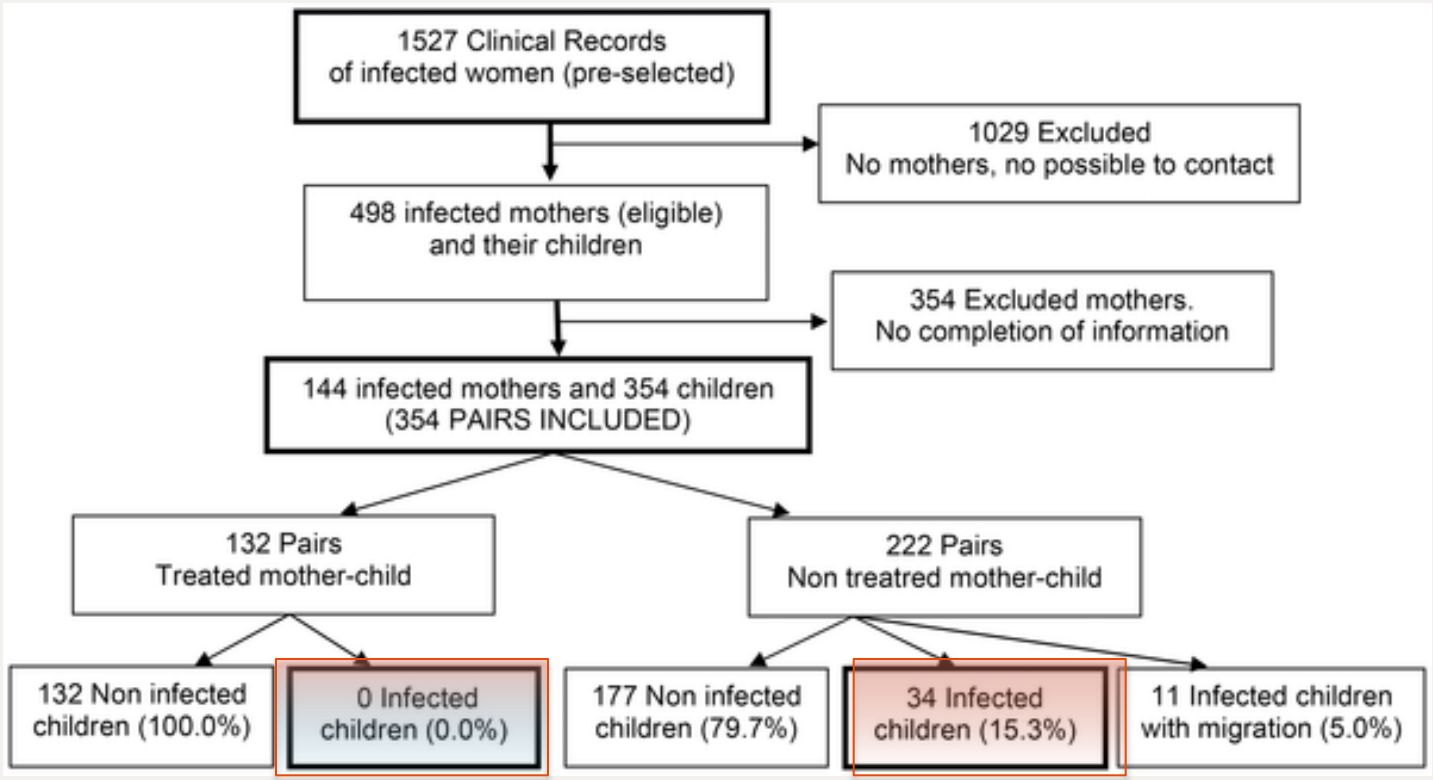
TREATMENT
impact on transmission

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)

Treatment of women before pregnancy *Conclusions*

- No case was detected among the offspring of mothers treated before pregnancy
- Specific treatment of young women is useful at the level of secondary prevention
- Etiological treatment in girls and women of childbearing age is helpful at the primary prevention level to avoid congenital *T. cruzi* transmission

TREATMENT
new challenges

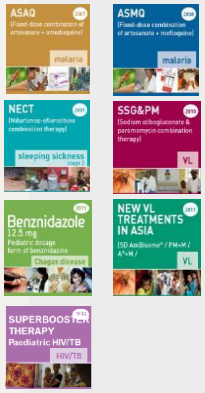
DND*i*'s success is only possible through innovative partnerships

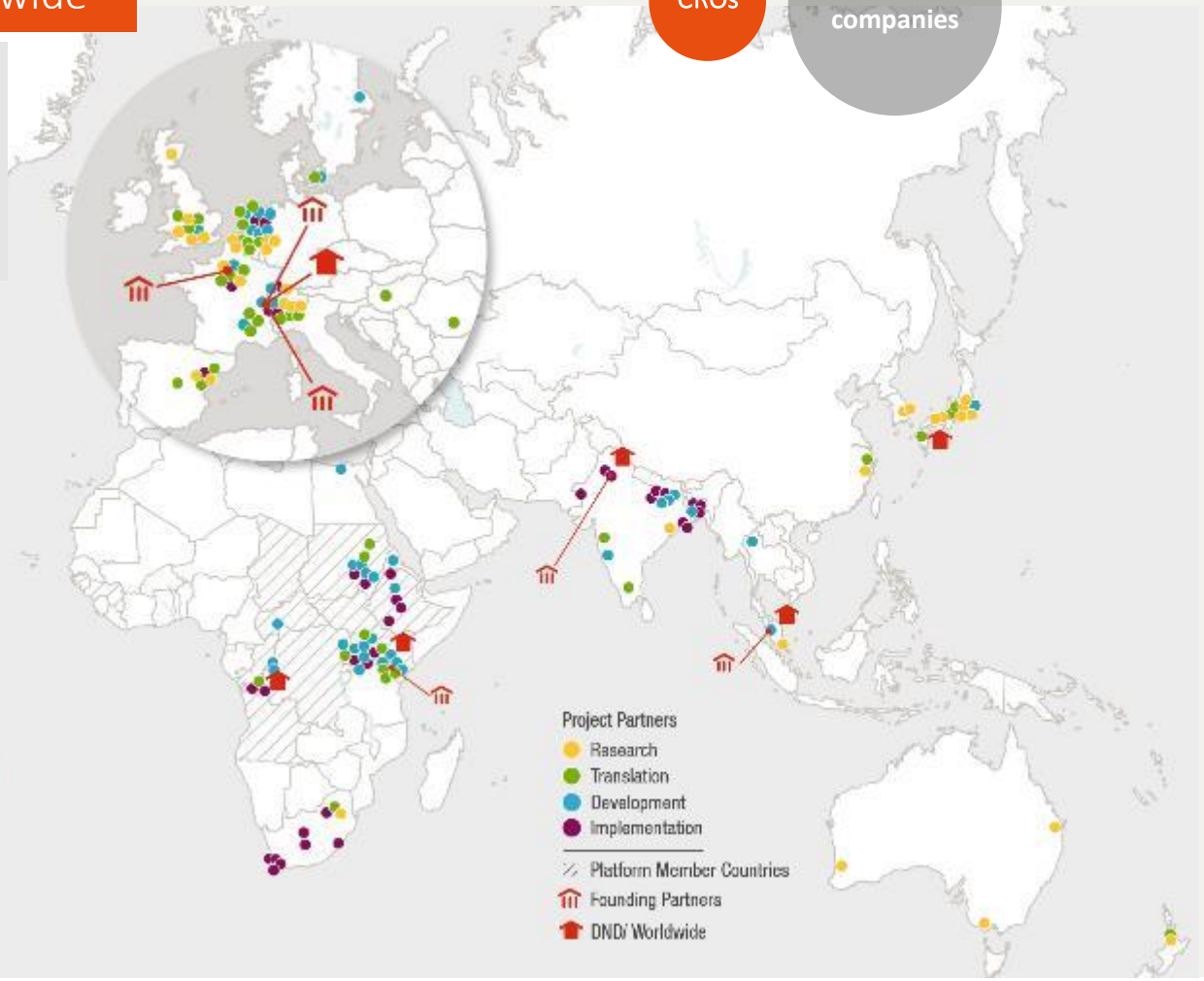
PDPs
Int. Org. & NGOs
Universities & Research Institutes
Biotechs
CROs
Pharmaceutical companies

Over 160 partnerships worldwide

CRITERIA FOR SUCCESS

- ✓ Share the same vision
- ✓ Mutual understanding
- ✓ Involvement throughout the whole process





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

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 VOL. 69, NO. 8, 2017
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER 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

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

OPEN ACCESS Freely available online PLOS | NEGLECTED TROPICAL DISEASES

Population Pharmacokinetic Study of Benznidazole in Pediatric Chagas Disease Suggests Efficacy despite Lower Plasma Concentrations than in Adults

Jaime Altcheh[1], Guillermo Moscatelli[1], Guido Mastrantonio[2], Samanta Moroni[1], Norberto Giglio[1], Maria Elena Marson[2], Griselda Ballering[1], Margarita Bisio[1], Gideon Koren[3], Facundo García-Bournissen[1,3]*

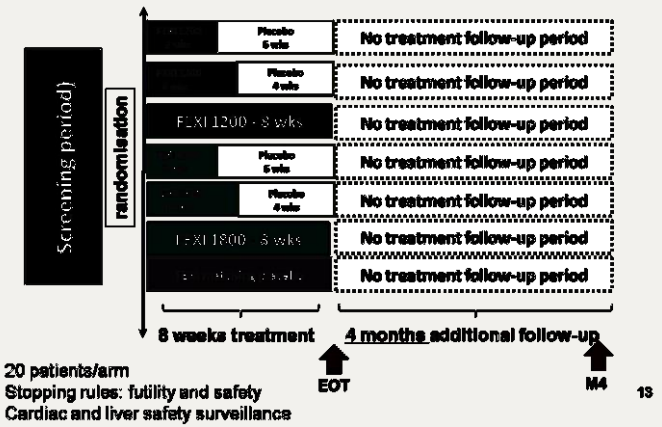
Treatment of adult chronic indeterminate Chagas disease with benznidazole and three E1224 dosing regimens: a proof-of-concept, randomised, placebo-controlled trial

Faustino Torrico*, Joaquim Gascon*, Lourdes Ortiz, Cristina Alonso-Vega, María-Jesús Pinazo, Alejandro Schijman, Igor C Almeida, Fabiana Alves, Nathalie Strub-Wourgaft, Isabela Ribeiro, on behalf of the E1224 Study Group†

Fexnidazole Phase II

DND*i*

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



Antimicrobial Agents and Chemotherapy

Systematic Review and Meta-analysis of the Pharmacokinetics of Benznidazole in the Treatment of Chagas Disease

Matthew O. Wiens,[a,b] Steve Kanters,[a] Edward Mills,[a,c] Alejandro A. Peregrina Lucano,[d] Silvia Gold,[e] Dieter Ayers,[a] Luis Ferrero,[e] Alejandro Krolewiecki[f]

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 x 60 days (suspended for safety issues) was effective during treatment with sustained response (PCR negative 100%) at 12 months FUP

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

- Pharmacokinetic studies suggest that doses of benzidazole could be reduced

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

Treatment of adult chronic indeterminate Chagas disease with benznidazole and three E1224 dosing regimens: a proof-of-concept, randomised, placebo-controlled trial

Faustino Torrico, Joaquim Gascon*, Lourdes Ortiz, Cristina Alonso-Vega, María-Jesús Pinazo, Alejandro Schijman, Igor C Almeida, Fabiana Alves, Nathalie Strub-Wourgaft, Isabela Ribeiro, on behalf of the E1224 Study Group†*

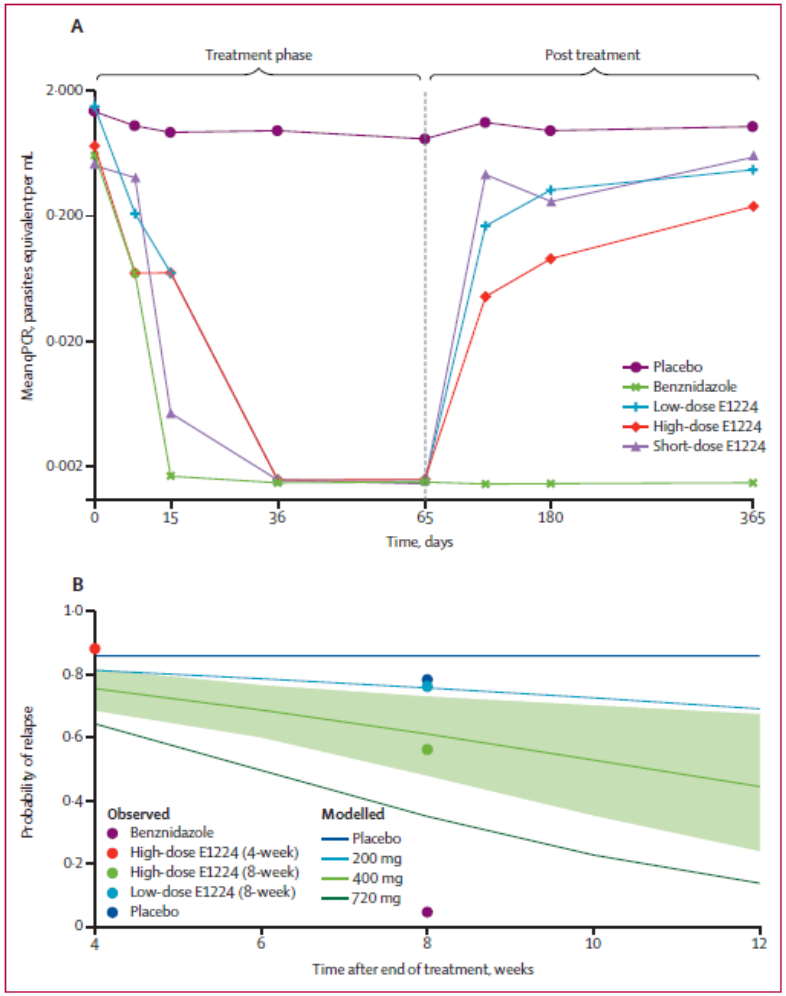
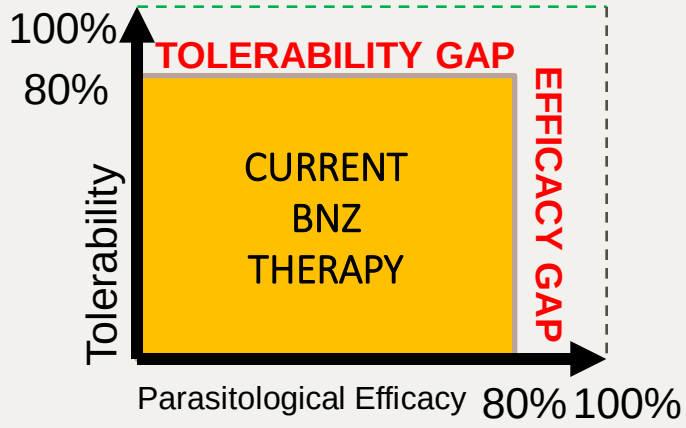


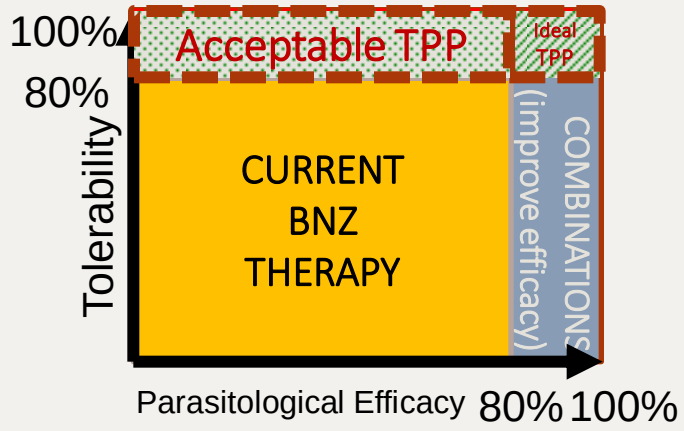
Figure 2: **Sequential qPCR measurements of *Trypanosoma cruzi* DNA and pharmacokinetic-pharmacodynamic model of predicted probability of relapse**

Strategies for Improving Efficacy and Tolerability

Current situation



Opportunities



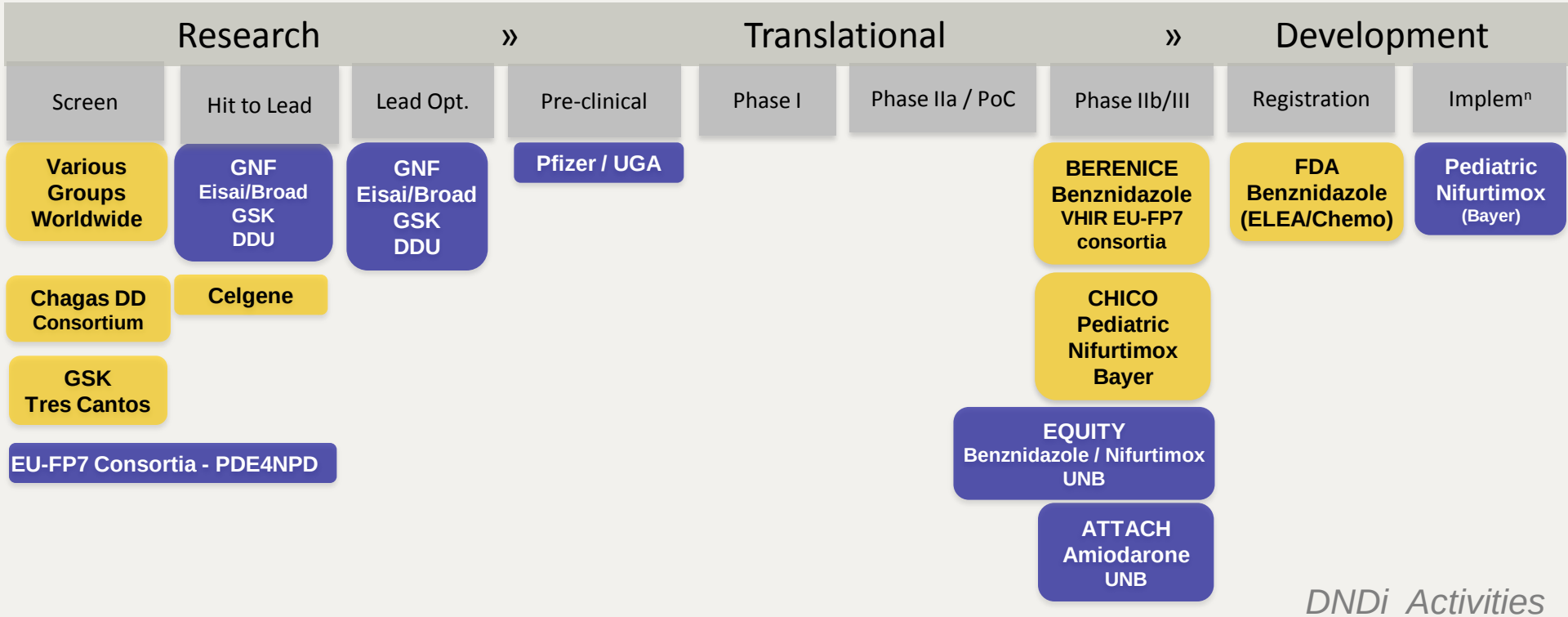
- BNZ is an effective drug

… but

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

- 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

Chagas Landscape 2018



LSHTM
STPH
LMPH

IPK
Dundee
Eskitis

LOAUS-LOUS-LOLA
Series from partners and sources
-Abbvie
-GSK "Chagas" Box
-Sanofi
-Celgene
-others

Fexinidazole

Benznidazole New Regimen / Comb
Forsavuconazole

Pediatric Benznidazole
LAFEPE Bra
ELEA Arg

Biomarkers

DNDi only *DNDi in collaboration* *other*

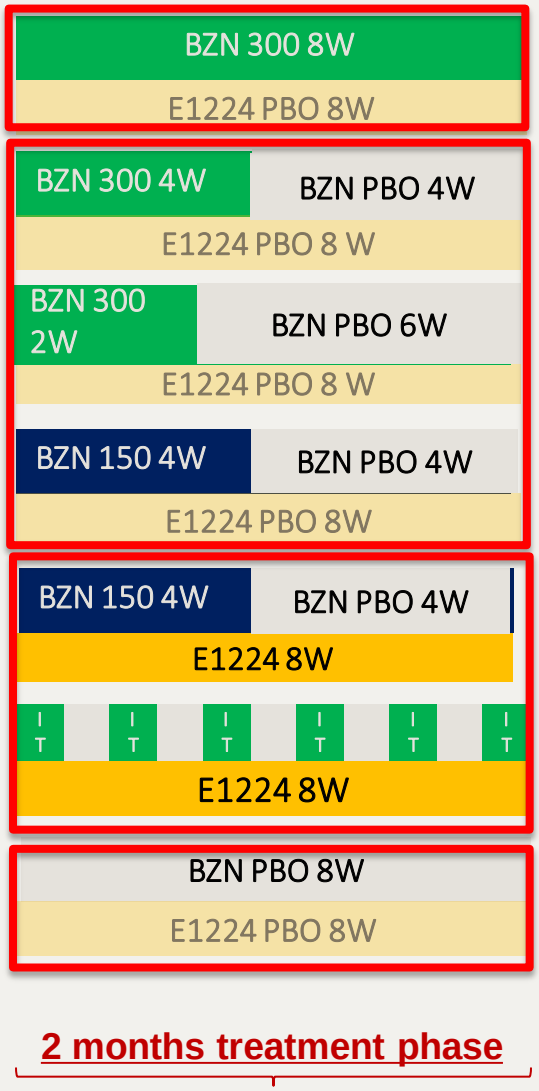
BENDITA overall design Bolivia

Partners
CEADES
ISGlobal
INGEBI
INP

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

Screening period

randomisation



2 months treatment phase

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)**

ClinicalTrials.gov Identifier: NCT03378661

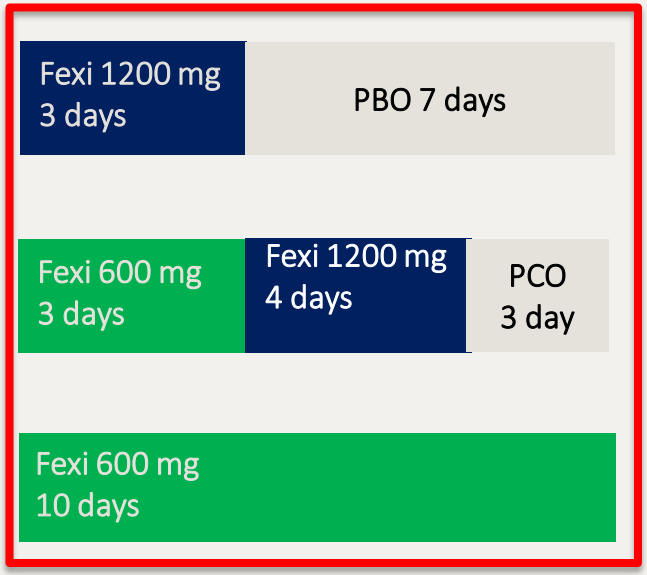
FEXI 012 overall design Spain

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

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

Screening period

randomisation



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

Primary endpoint at 4M

Follow-up until 12M

10 day treatment phase

Historical Control

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

Partners
Hosp Vall d´Hebron
ANLIS-INP; ICC
FIOCRUZ
FCI
ELEA
DNDi

MULTIBENZ overall design
Argentina, Brazil, Colombia, Spain

Screening period

randomisation

BZ 300 mg
60 days

BZ 150 mg
60 days

BZ 400 mg
15 days

PLACEBO
45 days

- **Adults (18 – 50 years old) at Chronic Indeterminate CD stage**
- **240 subjects - 80 patients/arm**

Follow-up at 4; 6; 8; 12 M

Follow-up until 12M

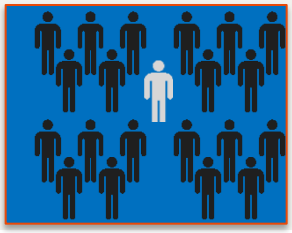
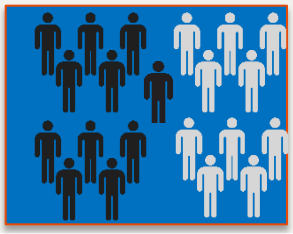
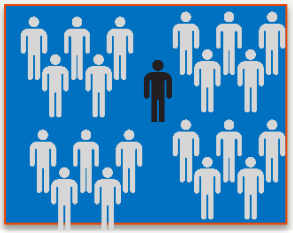
60 days treatment phase

BERENICE Phase I and II WIHP FP7 UC

ClinicalTrials.gov Identifier: NCT03191162

Current alternatives under evaluation

- Different old courses of benznidazole and nifurtimox (30 vs 60 days)
- New regimens of benznidazole in monotherapy (low dose and/or short regimen or intermittent): Next step, policy change ?
- NCE: New regimen of Bz in combination with E1224: Next step, Move to Phase 3 ?
- NCE: Fexinidazole, short course of treatment: Next step, Move to Phase 3 ?

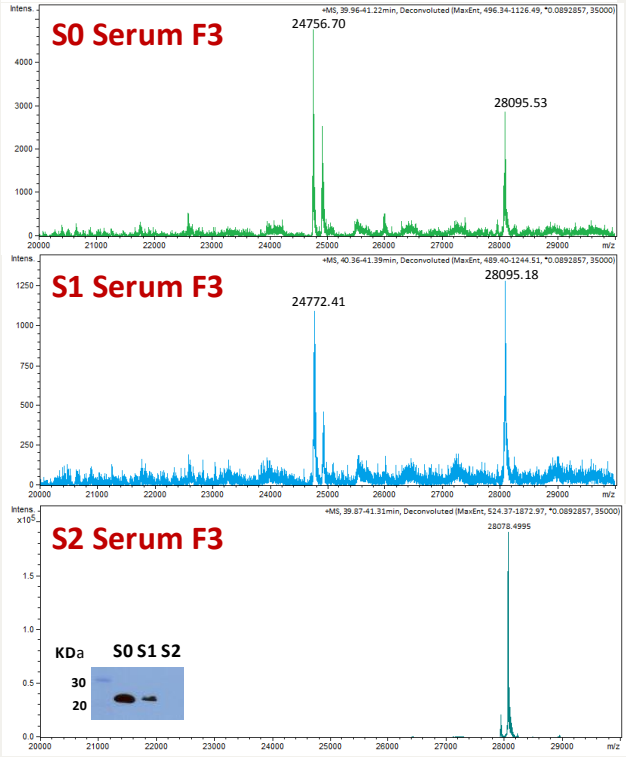
Biomarkers to improve assesment of response of etilogical treatment

POTENTIAL BIOMARKER. SECONDARY SURROGATES
NHEPACHA Pilot Study 2017-2018

NHEPACHA
Red Iberoamericana

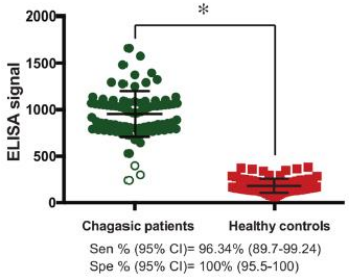
PARASITE ANTIGENS	Expression level in % (vs no *T. cruzi*)	% of decreasing after treatment	Elapsed time to decrease
CoML **anti rTc24 ab**	80 100	38 – 19 38 – 19 // 80*	6-24m/ 24-36m
KMP11	100	74-67	6m -24m
HSP70	100	74-50	6m-9m
F29	80	35– 62	6m - 48 m
Ab 3	NP	NP	NP

Apo1 New markers through Proteomic platforms
DND*i*-McGill University



Next-generation ELISA diagnostic assay for Chagas Disease based on the combination of short peptidic epitopes

Juan Mucci[1©], Santiago J. Carmona[1©¤], Romina Volcovich[2], Jaime Altcheh[2], Estefanía Bracamonte[3], Jorge D. Marco[3], Morten Nielsen[1,4], Carlos A. Buscaglia[1], Fernán Agüero[1]*



Sen % (95% CI)= 96.34% (89.7-99.24)
Spe % (95% CI)= 100% (95.5-100)

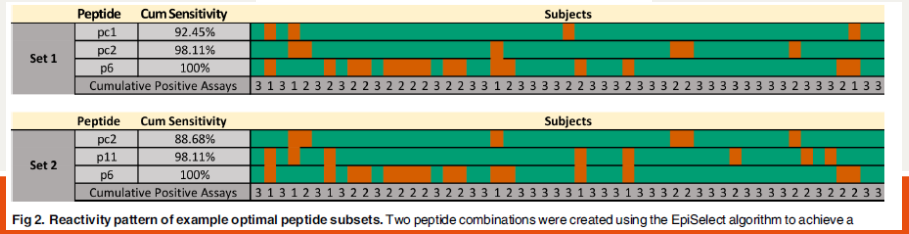
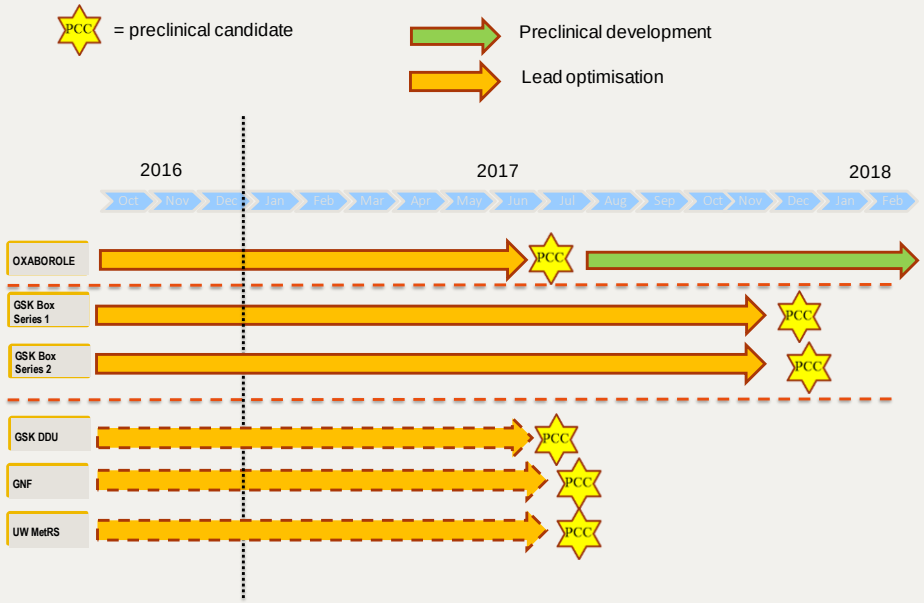


Fig 2. Reactivity pattern of example optimal peptide subsets. Two peptide combinations were created using the EpiSelect algorithm to achieve a

Progress in developing NCEs for Chagas disease



DNDi
Drugs for Neglected Diseases *initiative*

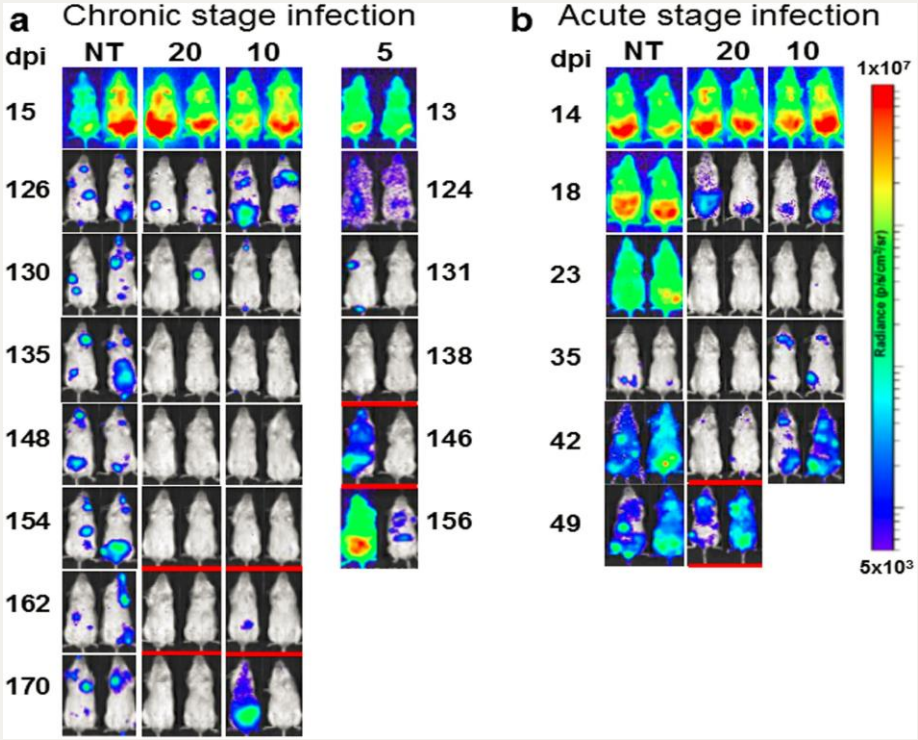
SCIENTIFIC REPORTS

OPEN

Nitroheterocyclic drugs cure experimental *Trypanosoma cruzi* infections more effectively in the chronic stage than in the acute stage

Received: 04 August 2016
Accepted: 28 September 2016
Published: 17 October 2016

Amanda Fortes Francisco[1], Shiromani Jayawardhana[1], Michael D. Lewis[1], Karen L. White[3], David M. Shackleford[3], Gong Chen[3], Jessica Saunders[3], Maria Osuna-Cabello[4], Kevin D. Read[4], Susan A. Charman[3], Eric Chatelain[2] & John M. Kelly[1]



OUTLOOK FOR 2020 BEYOND….

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

Chagas Access Plan: Current Outlook

Regional Initiatives
Ministries of Health
INCOSUR, IPA,
IPCAM, IAMAZON,
NonEC

OPS OMS

DNDi Drugs for Neglected Diseases *initiative*

Mundo Sano

Registration of Bz in NA (FDA-USA and COFEPRIS-Mexico) 2017

USA

Mexico

Guatemala

Colombia

Brazil

Gran Chaco
ARG, BOL,
PAR

IDRC | CRDI Canadá

USAC TRICENTENARIA

MinSalud Ministerio de Salud y Protección Social

Ministério da Saúde BRASIL UM PAÍS DE TODOS GOVERNO FEDERAL

Colombian Pilot Project, initial Y1 results:

Increase in screening:	900%
Coverage of dx confirmation:	100%
Reduction in delays, dx confirmation:	from > 1 year to <2 weeks

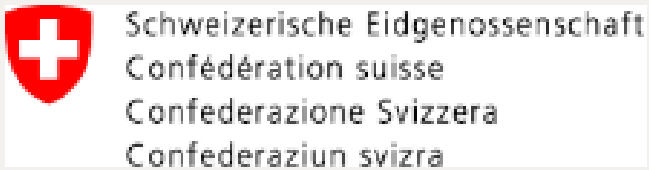
Available Medication:
BZ 12,5; 50; 100 mg
NFT 30; 120 mg

World Health Organization

International Federation of Associations of People Affected by Chagas disease - FINDECHAGAS

http://www.youtube.com/watch?v=t3yVr8N3XmU

Acknowledgements



by

THANK YOU!!!

https://www.dndi.org/
ssosa@dndi.org