Neglected Diseases: Patient Needs From A Clinician's Perspective

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Outline of Presentation

- Introduction to neglected diseases
  - A failed market and a failed public policy
- DNDi's focus on the kinetoplastid diseases
  - Visceral leishmaniasis (kala azar)
  - Sleeping sickness (HAT)
  - Chagas disease

Neglected Tropical Diseases (NTD)

- Diseases of poverty
- 530,000 deaths per year
- Worms, bacteria, viruses, protozoans

Disease	*DALYs
HIV	85.4m
NTD	56.6m
Malaria	39.2m
TB	24.9m

*DALY = disability adjusted life year – a measure of ill-health
Source: World Health Report (WHO 2001)

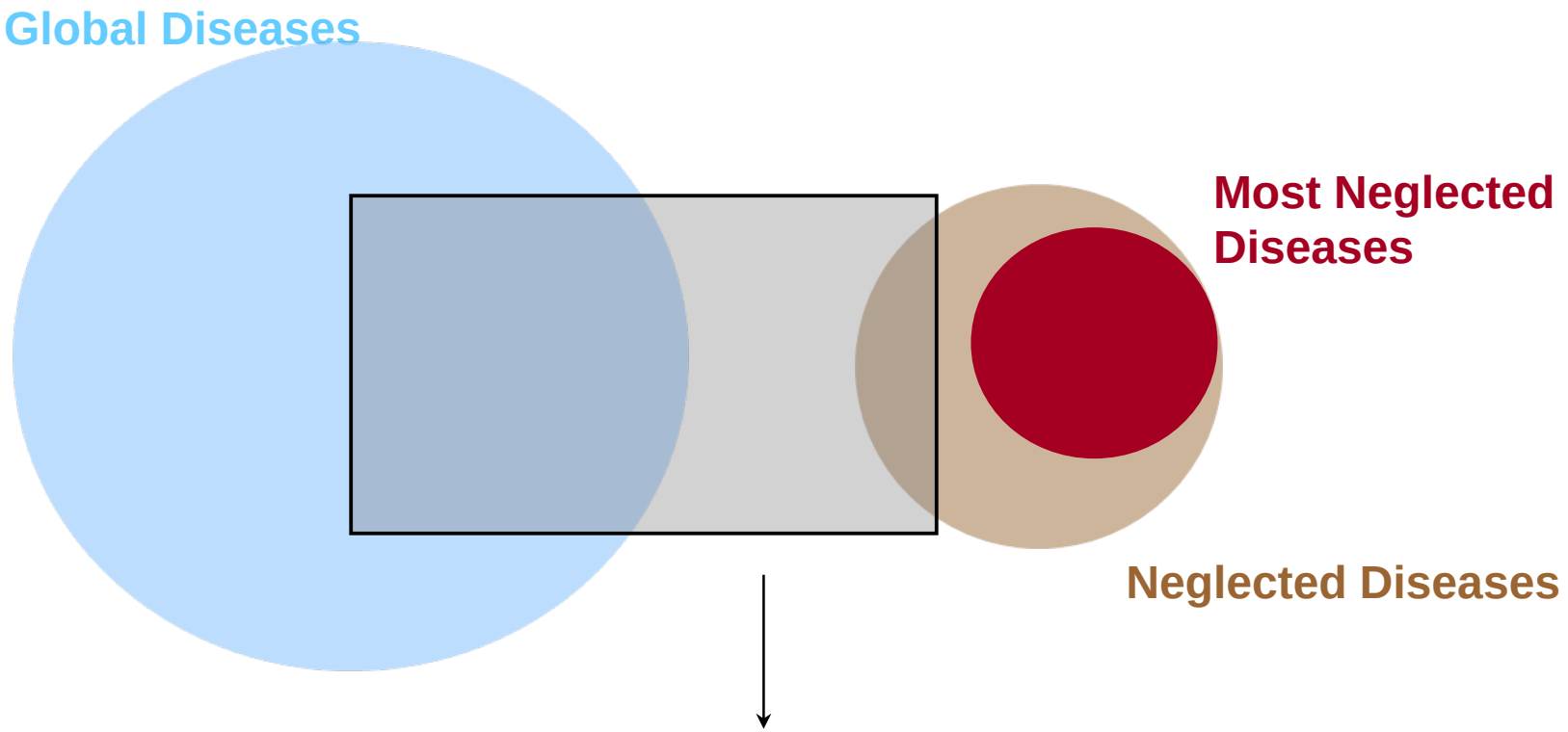
The reality of neglected diseases

Drugs:
inadequate, toxic, parenteral, long courses, resistance patterns

Diagnostics:
invasive, non-predictive, complex, poor biomarkers

Vaccines:
complex, stage dependent

Neglected diseases lie outside the world market



*Source: IMS Health, 26.2.2008

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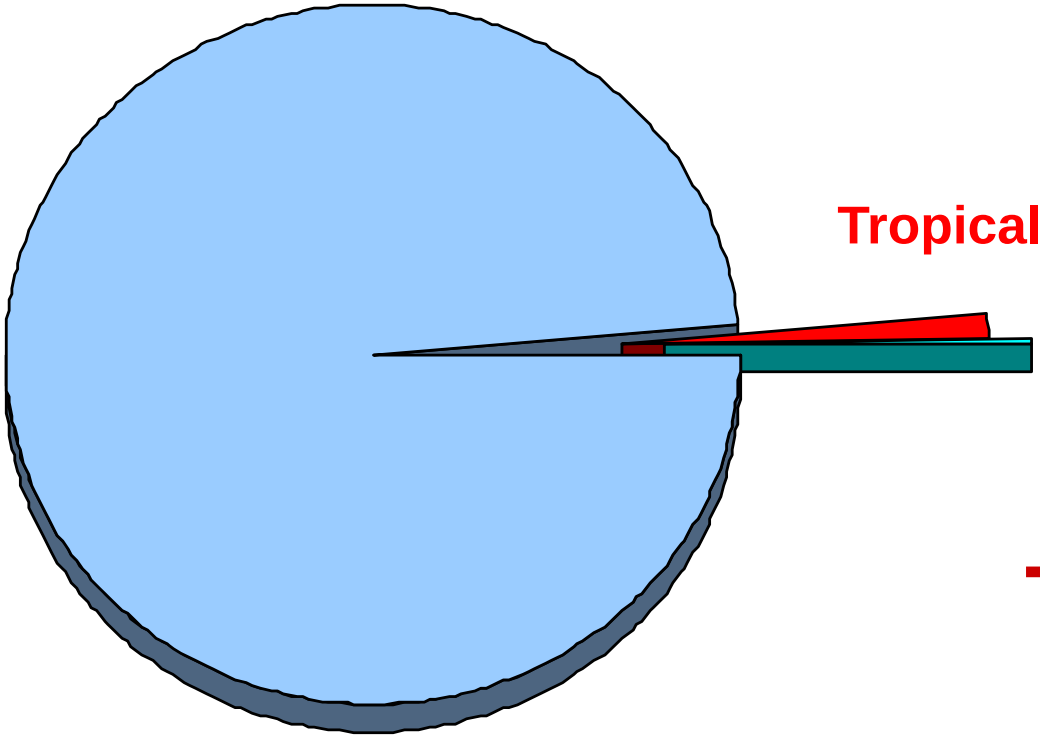
Only 21 New Drugs Developed for Neglected Diseases (1975-2004)



Tropical diseases: 18
TB: 3

1.3%

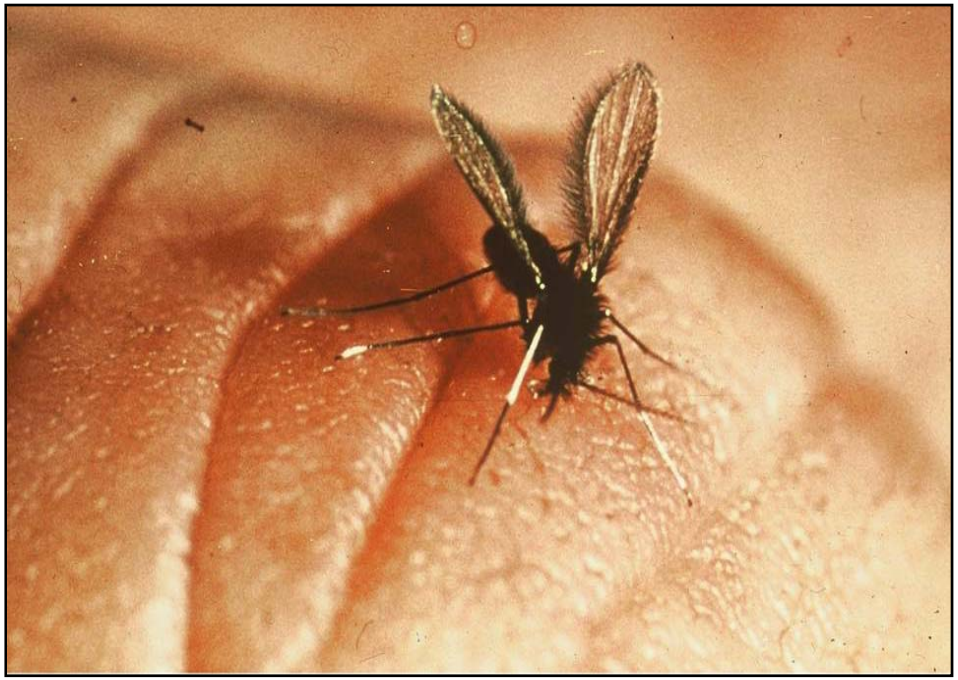
Total: 1,556

Tropical diseases and tuberculosis account for 12% of the global disease burden but only 1.3% of new drugs developed.

Source: Chirac P, Torreele E. *Lancet*. 2006 May 12; 1560-1561.

Leishmaniasis

Transmitted by the sand fly



Leishmaniasis: Disease Burden

- Endemic in 88 countries
- 350 million people at risk
- 12 million people are affected
- 1.5.-2.0 million new cases occurring annually
  - 500,000 cases of VL
- VL is fatal if left untreated

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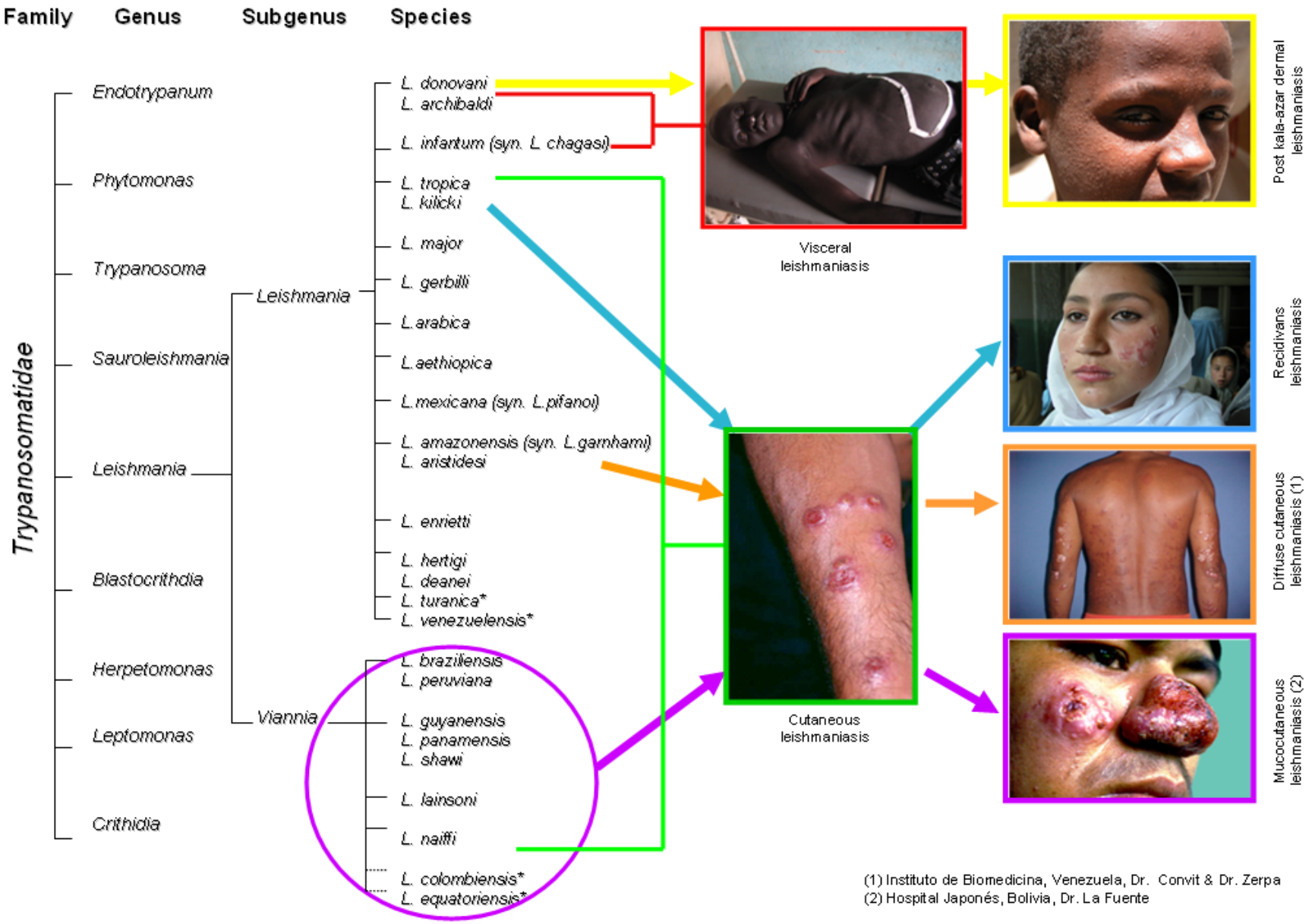
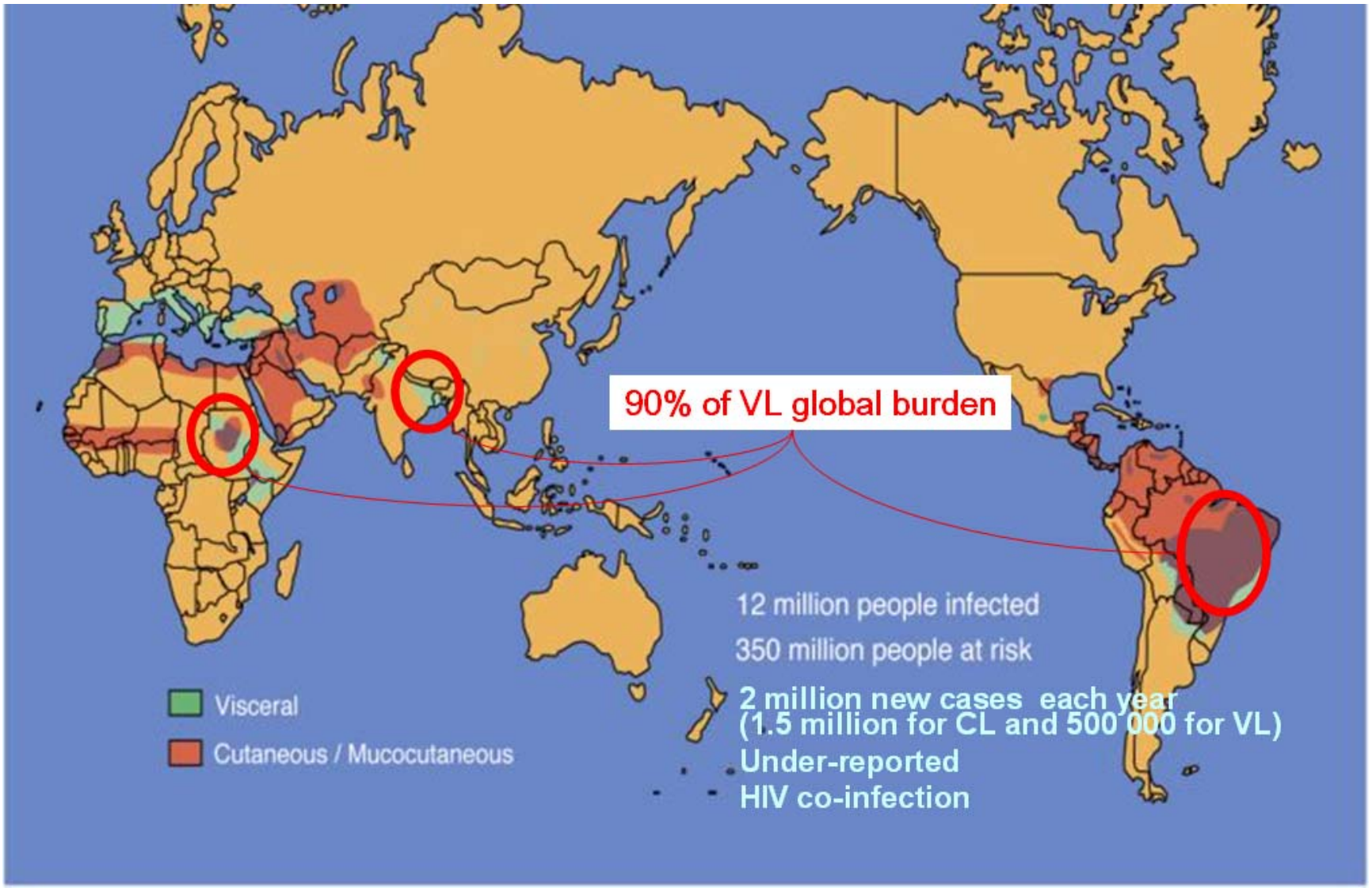
Many Species Cause Leishmaniasis



(1) Instituto de Biomedicina, Venezuela, Dr. Convit & Dr. Zerpa
(2) Hospital Japonés, Bolivia, Dr. La Fuente

Leishmaniasis Covers 3 Continents



Current treatment options for VL

Drugs available for use & Associated Problems

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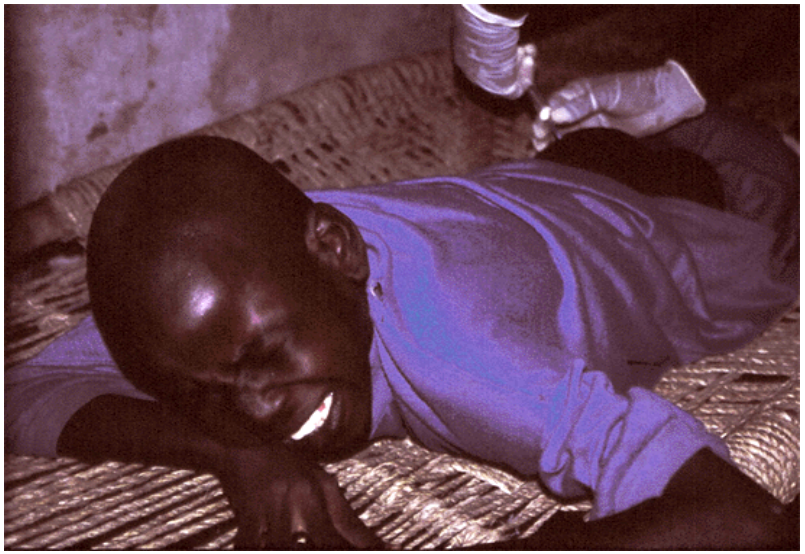
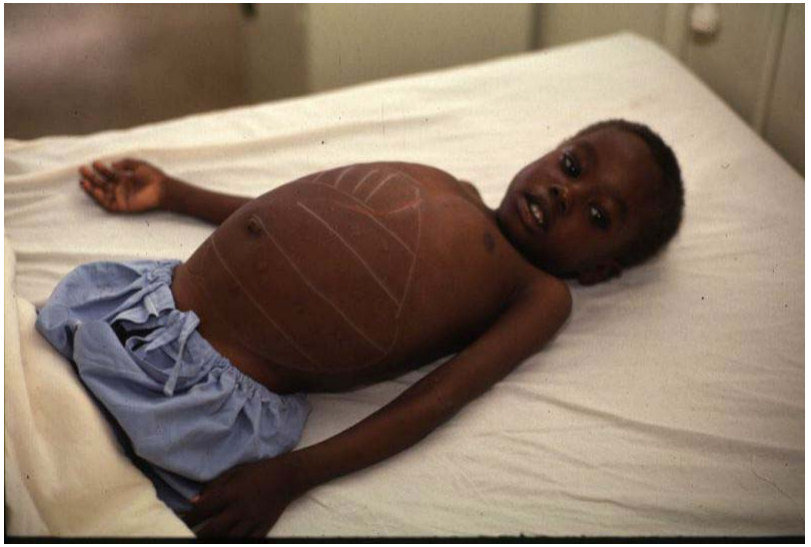
1. **Pentavalent antimonials**
   Toxic, parasite resistance growing, 30-day IV treatment in hospital.
2. **Amphotericin B**
   Used in case of antimonial resistance but dose limiting toxicity, 15-20 day IV treatment in hospital
3. **Liposomal AmphotericinB**
   Less toxic but prohibitively expensive $3,884/treatment except WHO price $840)
4. **Miltefosine**
   Teratogenic, only registered in India, and expensive





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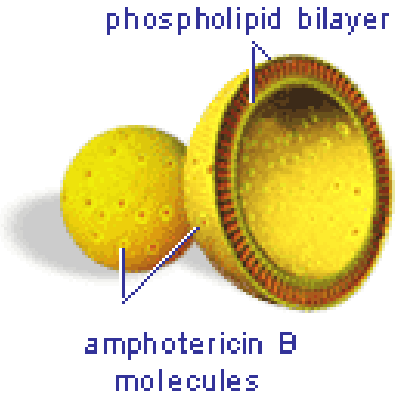


AmBisome is a daily infusion x 6 days

Identified needs of VL patients

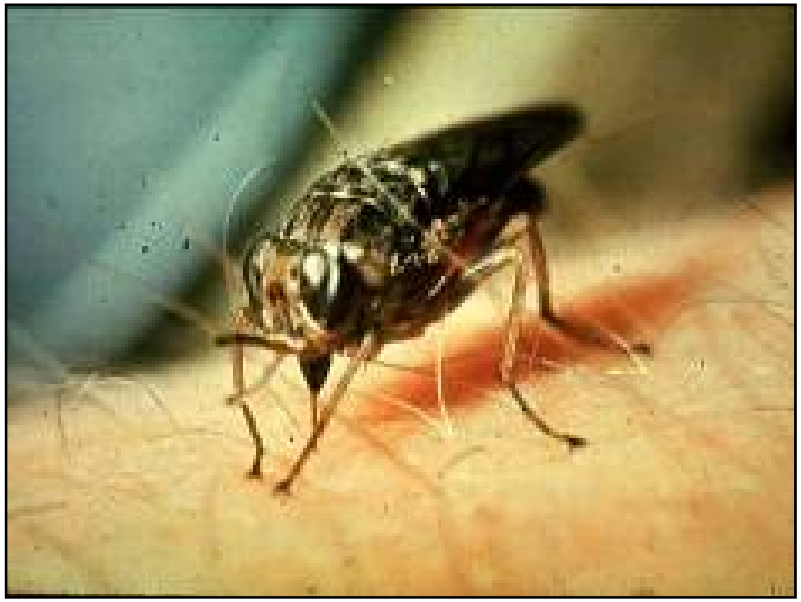
- Simple, effective, easy to deliver, affordable, short term treatment
  - Existing drugs: old, toxic, resistance, difficult to use, expensive
- Easy & field adapted diagnostic tools
- New combinations of existing drugs
- Access to treatment centers/hospital
- Nutrition – lack of food
- Language barriers

Spleen aspirate

Patient being transported to a health center

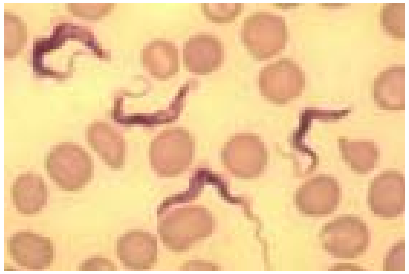
Human African Trypanosomiasis (HAT) or Sleeping Sickness

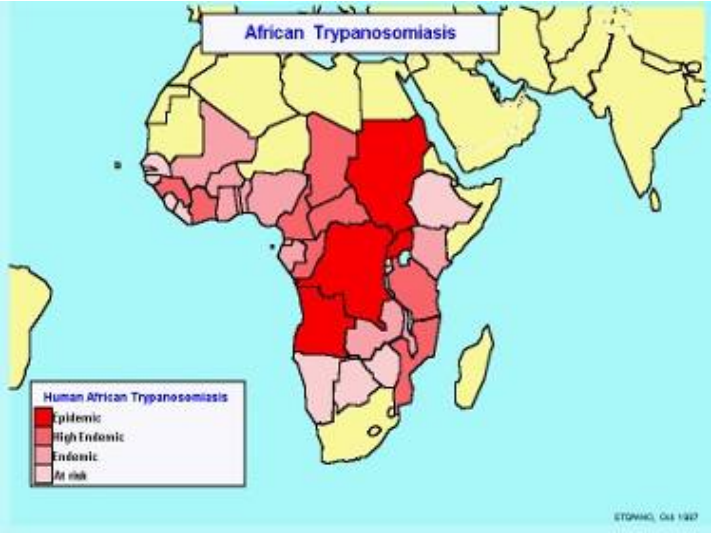
Transmitted by the tsetse fly

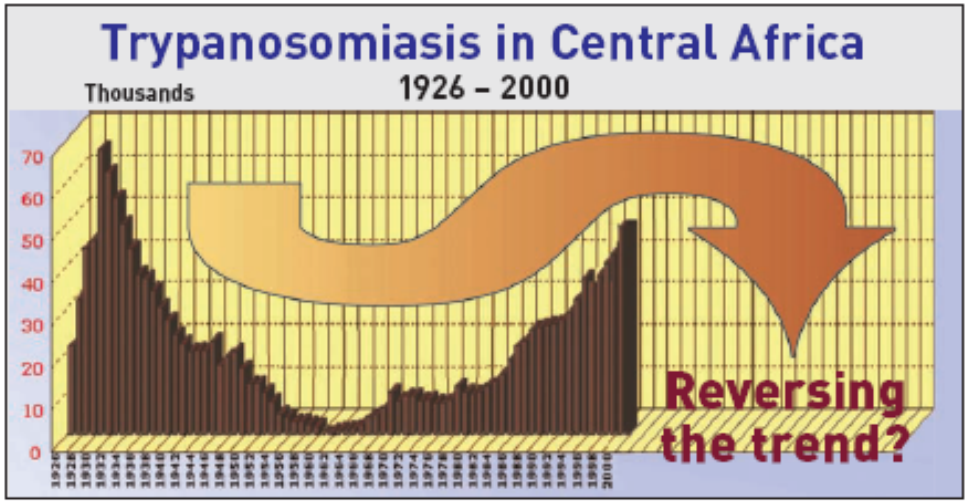


Sleeping Sickness
Fatal if Untreated

- Caused by protozoal parasites *Trypanosoma brucei*:
  - *T. brucei gambiense: Chronic disease, progresses during 1-2 years, 95% of cases*
  - *T. brucei rhodesiense: Acute disease, kills within weeks*
- An estimated 50-70,000 infected (WHO)
- 55 million at risk in sub-Saharan Africa
- Difficult to diagnose







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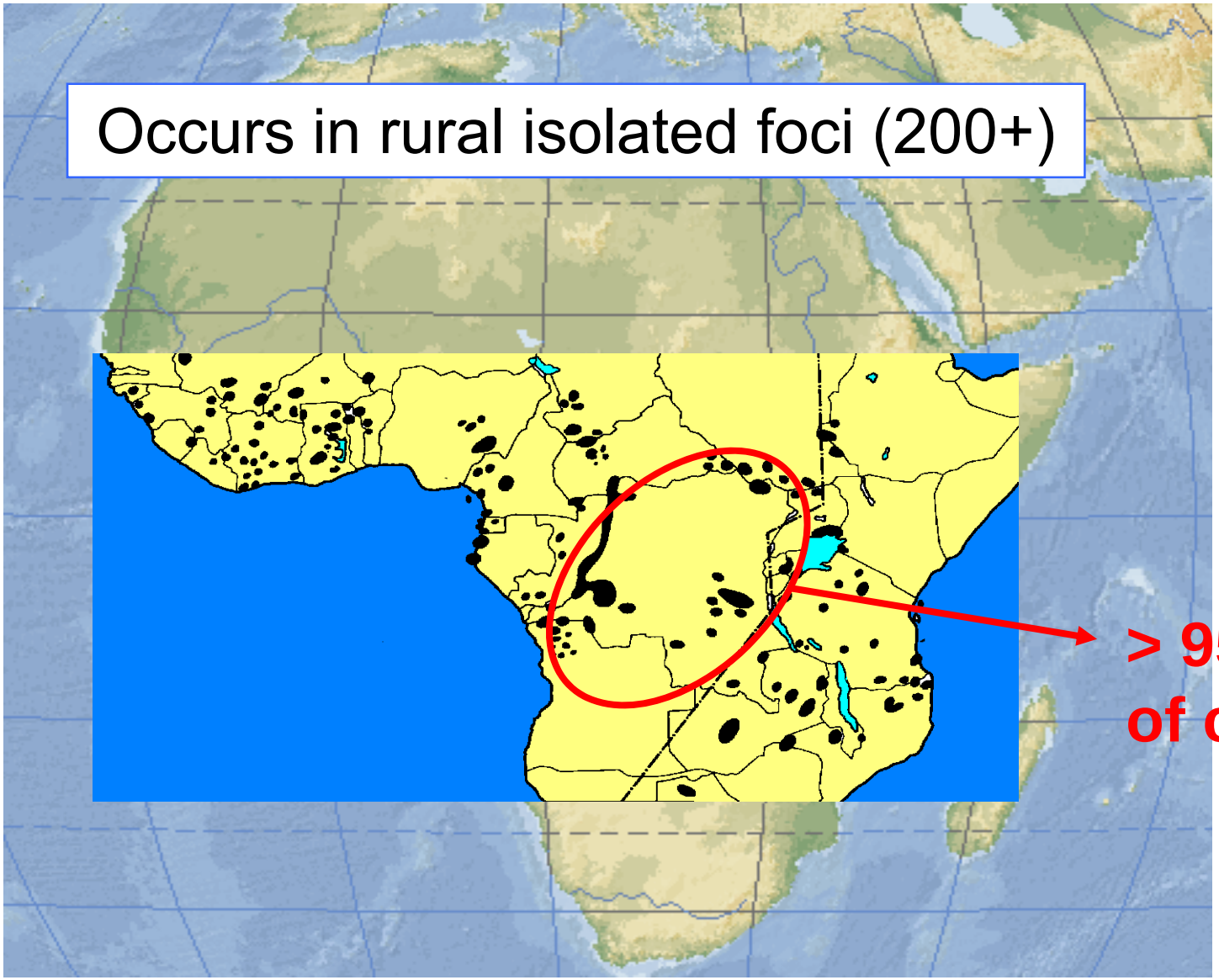

HAT: 2 stages of disease

- **Stage 1**: lymphovascular, few specific symptoms
  - Patients often go undiagnosed
- **Stage 2**: with CNS involvement, progressive neurological disturbances including behavioural changes, ending with coma and death if left untreated
  - Social stigma

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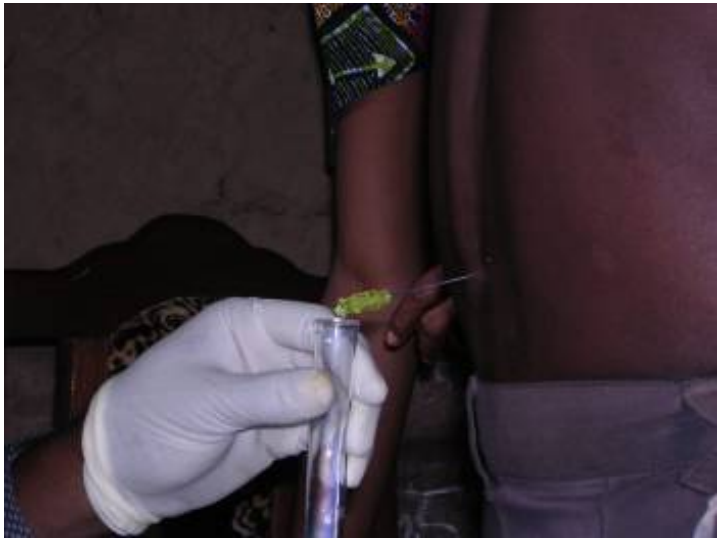
Field Challenges
Human African Trypanosomiasis (HAT)



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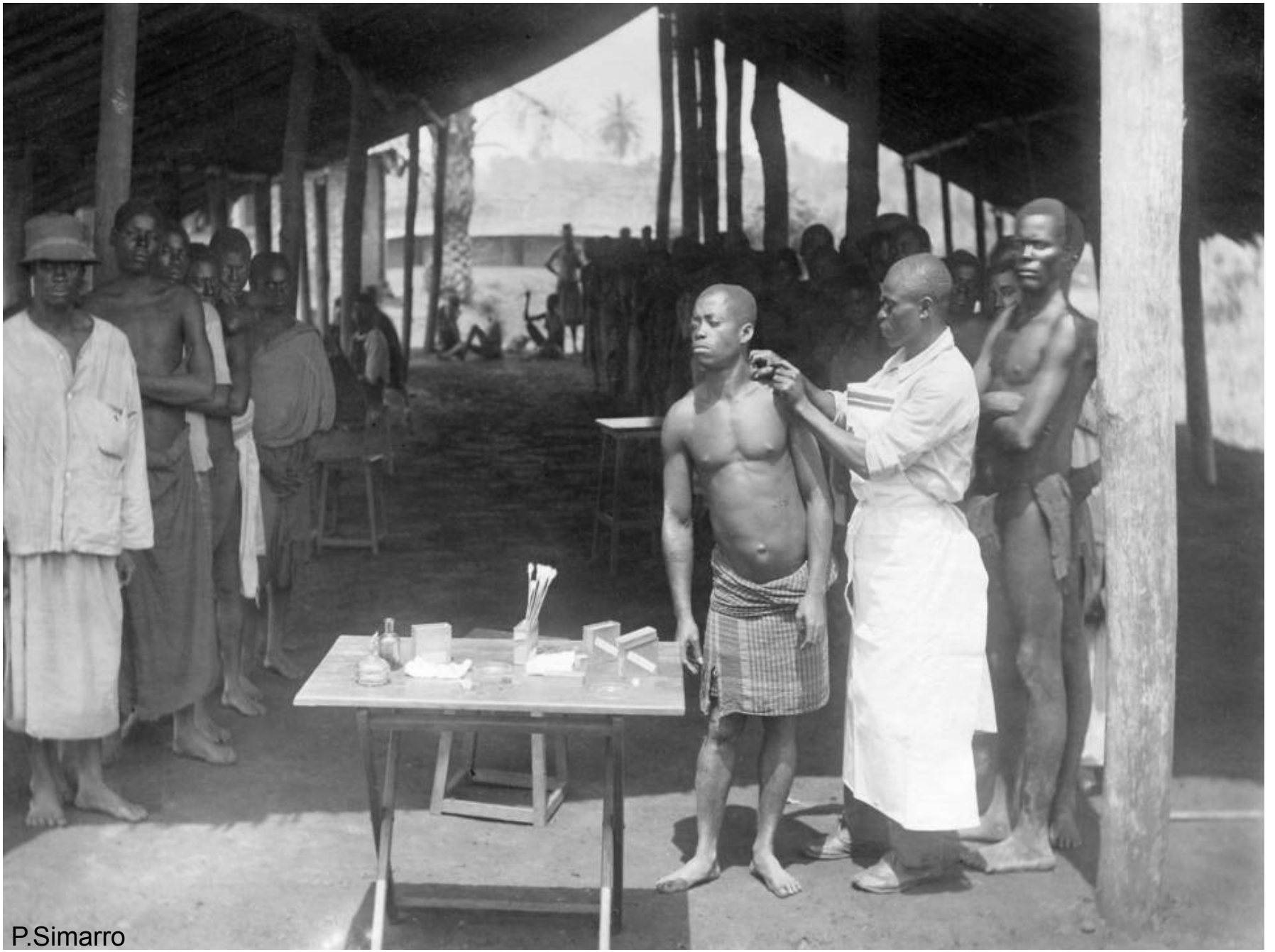

P.Simarro

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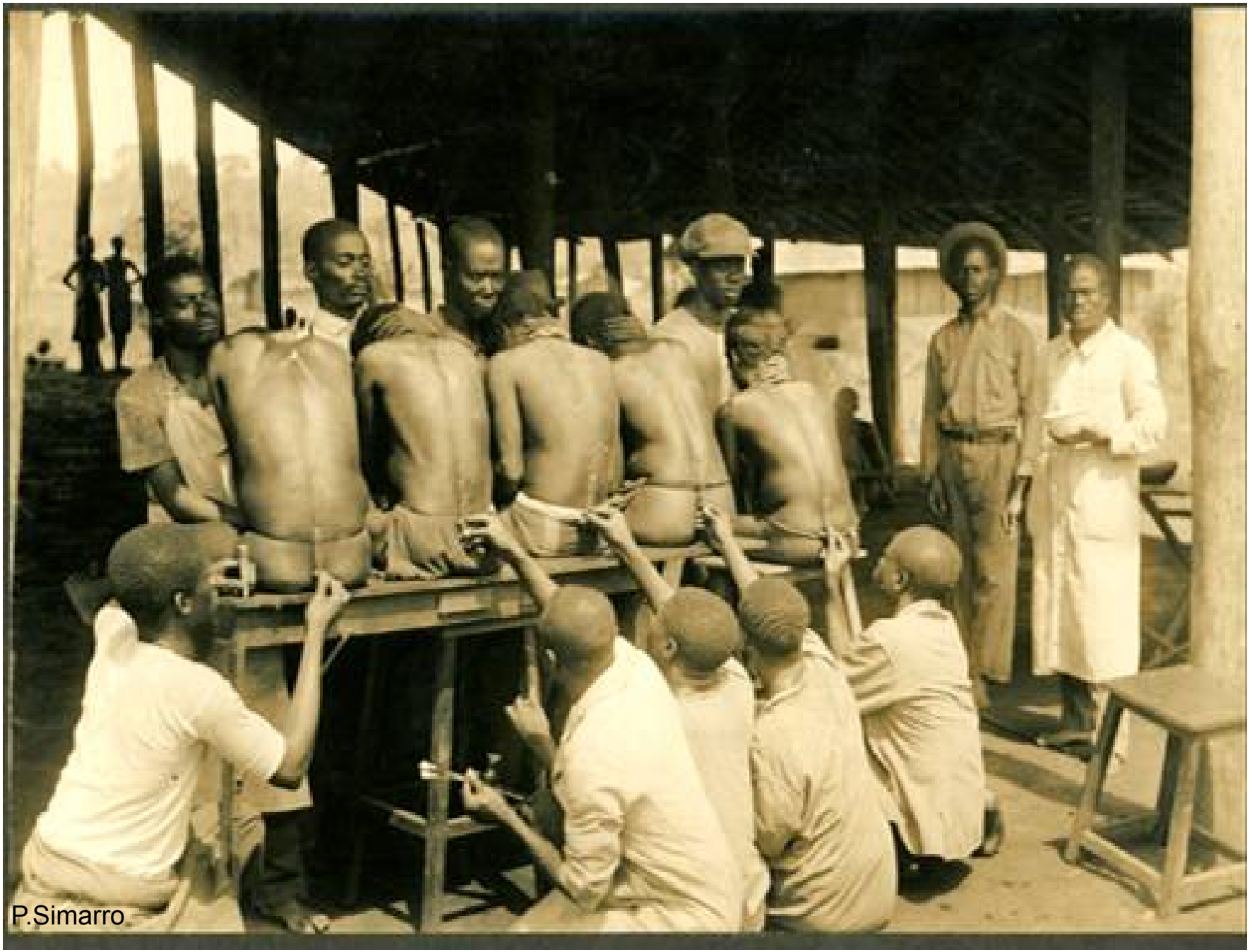


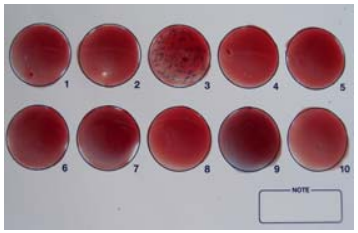
Limitations With Current Treatments for HAT

Existing drugs:
old, toxic, resistance, difficult to use, expensive

HAT	Drug	Associated Problems
Stage 1	Pentamidine (1940)	7-10 daily intramuscular injections; only efficacious for stage 1
	Suramin (1920s)	Used primarily for stage 1 **T.b. rhodesiense** HAT
Stage 2	Melarsoprol (1949)	10 painful daily intravenous injections; highly toxic, with ~5% treatment-related mortality Increasing number of treatment failures (up to 30% in some regions)
	Eflornithine (1981)	Administration difficult – 4 intravenous infusions per day required for 14 days; not active on **T.b. rhodesiense** HAT;
	Nifurtimox (1970s)	Oral drug developed for Chagas disease, not registered for HAT; sometimes used compassionately after melarsoprol relapse – probably ~70% efficacy

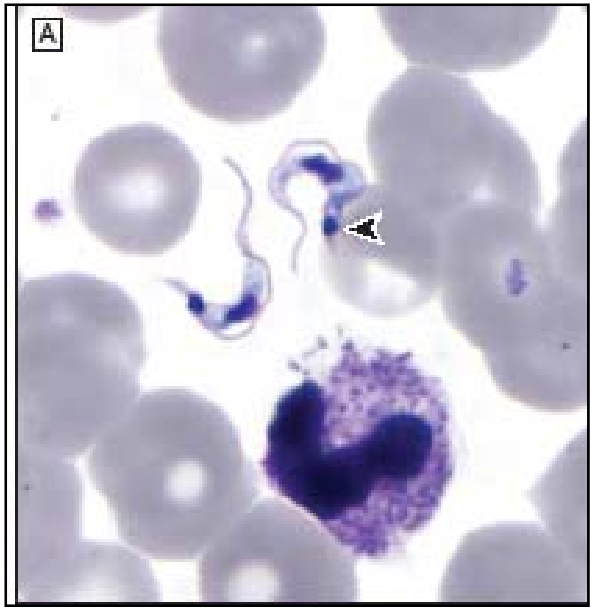
Identified needs of HAT patients

- Improved diagnostics:
  - Simple, rapid, specific diagnostic test
  - Non-invasive staging (no LP)
- Improved treatment:
  - Easy to use (oral?)
  - Short course
  - Affordable
  - Safe
  - Effective in both stages 1 and 2



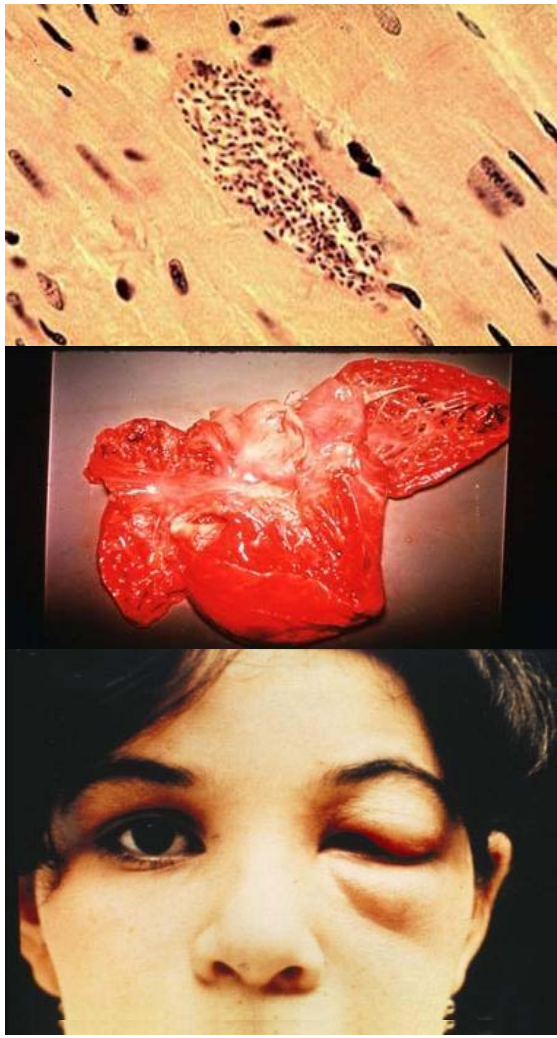
Chagas Disease

caused by *Trypanosoma cruzi* infection

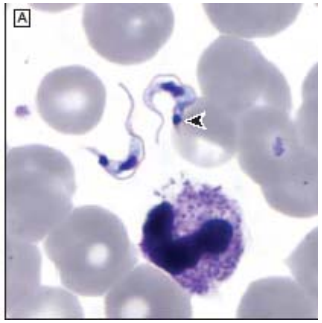


Chagas Disease (South American Trypanosomiasis)

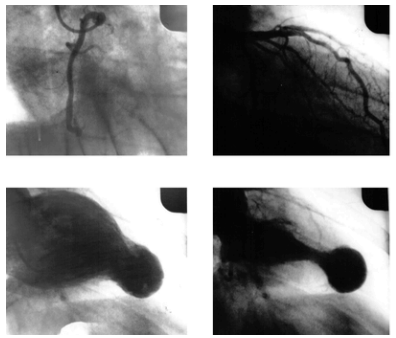
- ~8M infected & 100M at risk in Central & South America
- Bloodstream invasive form, intracellular in macrophages, muscle and nerve cells

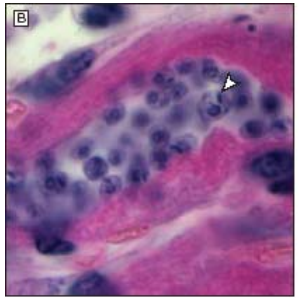


Chagas: 3 stages of disease



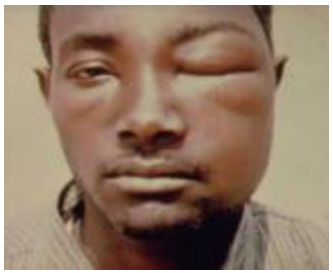
- 10 years - decades
- Asymptomatic
- Positive serology
- Xenodiagnosis ?
- PCR ?





Acute → Indeterminate → Chronic

- 2 - 4 months
- Asymptomatic or oligosymptomatic
- Direct examination
- ≤5% mortality rate



- Positive serology
- Heart disease (mild to severe)
  20 – 30% indet. patients
- GI tract disease
- Neurological disease
- Life expectancy ↓9 years (av.)

DNDi
Drugs for Neglected Diseases *initiative*

Current Treatment Limitations for Chagas Disease

- Only 2 drugs currently available:
  - Benznidazole, nifurtimox (primarily acute & early indeterminate)
    - Long treatment period (30-60 days)
    - Dose-dependent toxicity
    - High rate of patient non-compliance
    - No paediatric formulations
  - No treatment for indeterminate and chronic disease

Current Treatment Needs for Chagas Disease

- Drugs for acute and chronic diseases
- Safer and more effective drugs adapted to patient needs
  - Paediatric formulations
- Improve diagnosis and test of cure

Neglected Diseases: Current Treatment Limitations

- Ineffective (resistance)
- Toxic
- Expensive
- Painful when delivered
- Difficult to follow
- Not adapted to the health system capability
- Not registered in endemic regions
- Restricted by patents

A Step Together in the Right Direction

"In leaps and bounds, DNDi has moved forward with activities in the region."

Prof AM El-Hassan, Leishmaniasias expert with over 30 years experience, Institute for Endemic Diseases, University of Khartoum, Sudan

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ASANTE SANA

DNDi