Combination therapy for visceral leishmaniasis

Why, what, where ?

Johan van Griensven
Marleen Boelaert
Institute of Tropical Medicine, Antwerp

VL treatment: main options

- Antimonials (Sb^{V})
- Paromomycin (PM)
- Amphotericin B (AmB)
- Liposomal-Amphotericin B (L-AmB)
- Miltefosine (MF)

Why combination therapy ?

- Efficacy
- Toxicity
- Compliance
- Duration of therapy
- Cost
- Resistance
  - SSG
  - MF
    - only oral drug
    - long half-life: risk of resistance

Previous research on combination therapy in Asia

- Sb^V + PM (3 RCT, India)
  - Sb^V 28 days
  - PM 21 days
  - Sb^V + PM 21 days
- Sb^V only ineffective, PM single or in combination effective
- PM 15 mg/kg recommended dose

Thakur et al, 1998-2000

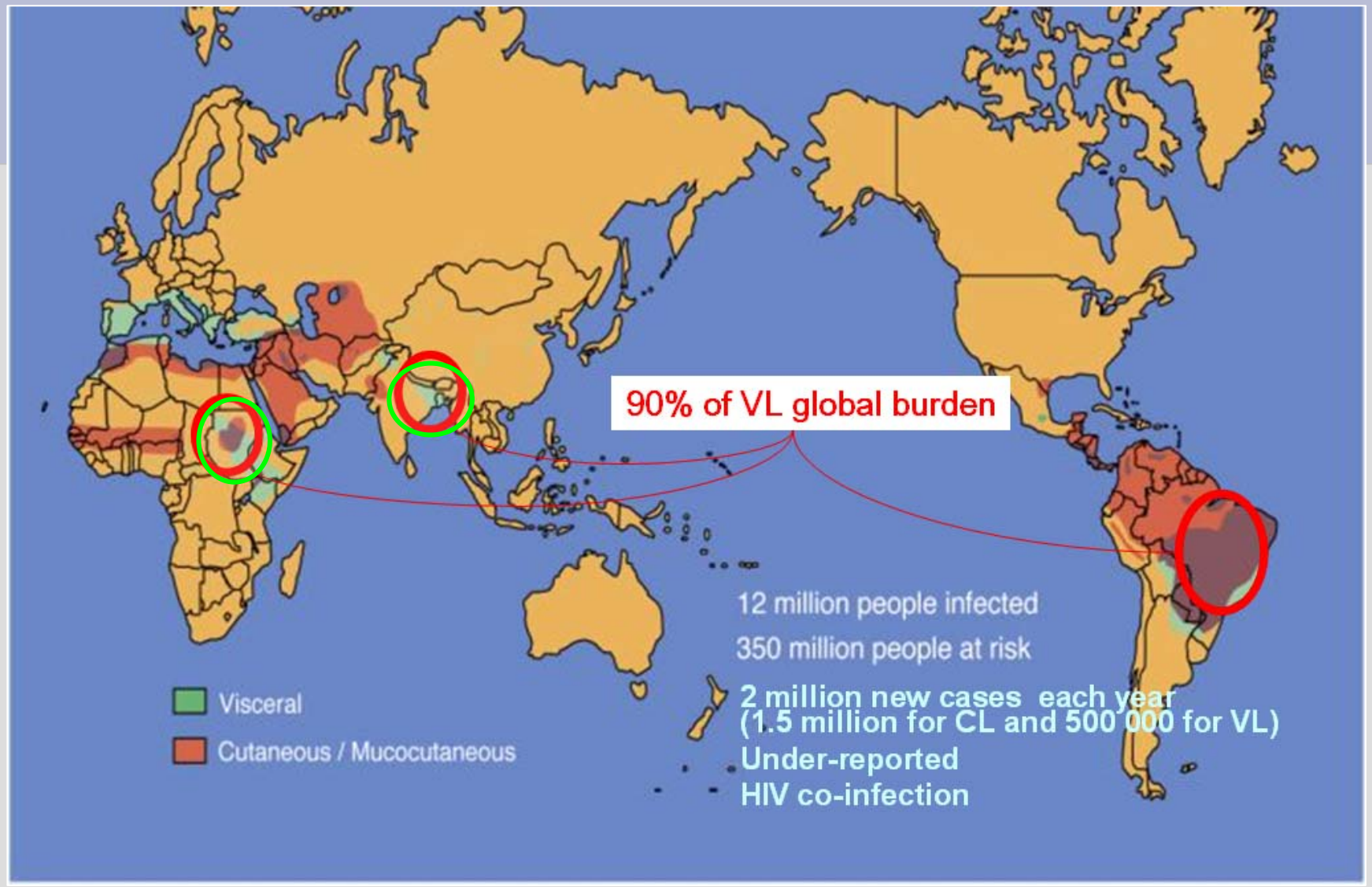
Previous research on combination therapy in Asia

- L-AmB
  - 5-7.5 mg/kg sd: ~90% efficacy

Sundar et al, BMJ 2001/CID 2003

- MF
  - 28 days treatment: ~95% efficacy
  - 14 days treatment: ~89% efficacy

Sundar et al, NEJM 2002/CID 2000


90% of VL global burden
12 million people infected
350 million people at risk
2 million new cases each year
(1.5 million for CL and 500 000 for VL)
Under-reported
HIV co-infection
Visceral
Cutaneous / Mucocutaneous

Previous research on combination therapy in Asia

- Phase II, non-comparative RCT, India
- N=45/arm; > 12 y

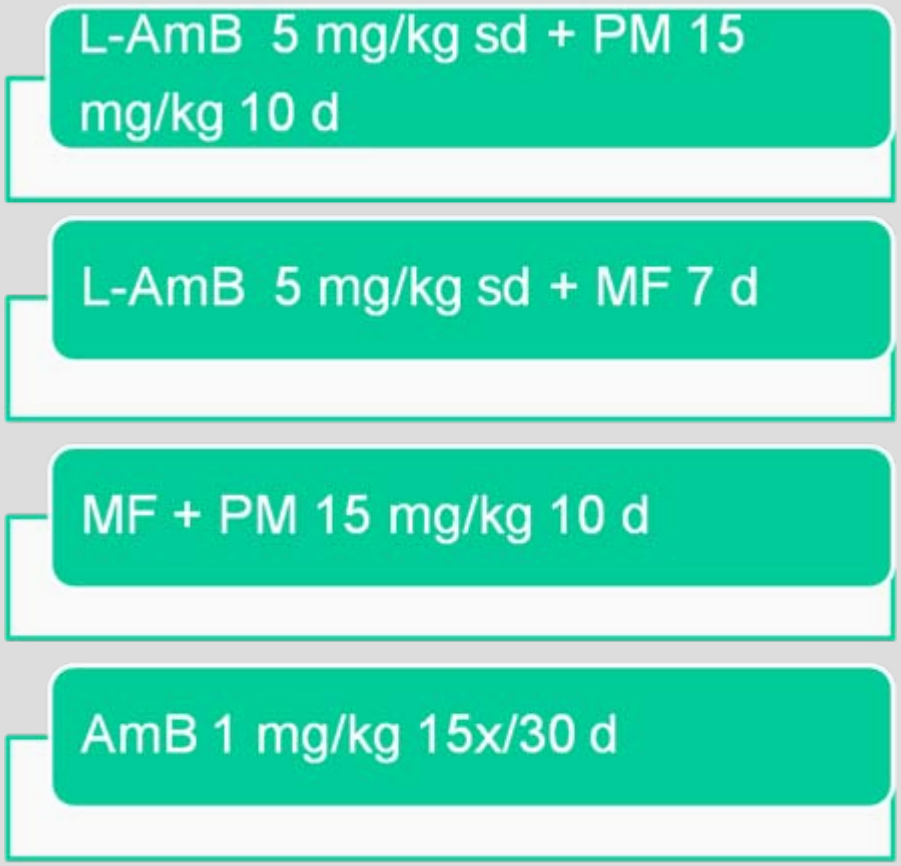
Sundar et al, CID 2008

Planned research on combination therapy in Asia

- WHO/TDR-sponsored trials- Phase II
  - L-AmB 5 mg/kg sd + MF 14 days
  - N=150 (2-65 years)
- India
  - Started Oct 2008
  - Results expected in 2010
- Bangladesh
  - Planned

VL-Combo Asia (DNDi)

- Phase III, non-inferiority trial
- India
  - Started 06/2008; children planned
  - Results expected early 2010
- Bangladesh/Nepal
  - Start 2009; Results 2010



Ongoing research on combination therapy in Africa: LEAP-0104A/B (DNDi)

- Phase III, non-inferiority trial
  - Kenya, Sudan, Ethiopia, Uganda
  - LEAP0104A: start 2004
    - High failure rate with PM 15 mg/kg in certain sites (Sudan)
      - Pharmacokinetics ? Parasite strain ?
  - LEAP0104B with PM 20 mg/kg
  - Results early 2010

Combination therapy in Africa: experience with MF and L-AmB

- Miltefosine vs SSG (Ethiopia)
  - HIV-: safe and effective
  - HIV+: safer and but less effective
- L-AmB

Ritmeijer et al, CID 2006

  - Dose-finding multi-continent study
    - Brazil > Kenya > India
    - Kenya 10 mg/kg TD

Berman et al, WHO Bulletin, 1998

  - Sudan
    - High dose needed for complicated cases (20-30 mg/kg)
    - High treatment failure rate
      - Co-morbidity ? Strain-effect ?

Seaman et al, CID 1995; Mueller et al, TRSTMH 2007

Combination therapy in Africa Planned studies (DNDi):

- AmBisome VL – E. Africa
  - Start Jan 2009
  - L-AmB monotherapy
    - Single dose 7.5 – 15 mg/kg vs standard 21 mg/kg over 21 days (7x3 mg/kg)
  - Registration purposes
- Combination studies (phase II)
  - Start planned in 2009
  - Treatment arms
    - L-AmB 10 mg/kg sd + MF 2.5 mg/kg 10 days
    - L-AmB 10 mg/kg sd + SSG 20 mg/kg 10 days
    - MF 2.5 mg/kg 28 days

Combination therapy: options

- Several trial data becoming available
  - Africa
    - SSG + PM
    - L-AmB + MF
    - L-AmB + SSG
  - Asia
    - L-AmB + MF
    - L-AmB + PM
    - MF + PM
- What can we expect from combination therapy ?
- Which factors will determine our choice ?

Efficacy and safety

- Minimum efficacy
  - Initial Cure > 95%
  - Definitive Cure > 90% (6 months)
- Special populations/Effectiveness
  - HIV
  - Co-morbid conditions (excluded in RCT)
  - Pregnancy
- Toxicity

Compliance

- MF
  - 28-day treatment (ambulatory) is challenging
    - Phase IV study
      - End of treatment: 95.5%
      - 6 months of FU: 85.6%
  - 7-10 days treatment more feasible

Cost-effectiveness

- Data Filip Meheus

Feasibility and acceptability

- Health infrastructure: Capacity
  - IV/IM treatment
  - Monitoring for ambulatory treatment
    - MF, PM
  - MF: contraception
- Disease burden
- Reliable drug availability (cost)
- Second line options (HIV, relapse)

Resistance

- Limited understanding of dynamics of development and spread of drug resistance
  - Rational design of resistance-prevention strategy ?
- Short, well tolerated and effective combination therapy as strategy to prevent resistance

Regional factors

- Resistance pattern
- Strain susceptibility ?
  - PM ? L-AmB ?
- Pharmacokinetics
  - PM ?
- Co-morbidity
  - HIV, tuberculosis, malnutrition
- Health systems

Future challenges

- Resistance
  - Most effective way to prevent resistance ?
- Regional factors
- Pharmacovigilance
- Complexity
  - Stable delivery of one drug is already challenging