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Recent HIV-VL clinical research initiatives in East-Africa

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VL-HIV coinfection

- Limited concerted clinical research activities on VL/HIV in East-Africa
- Research collaboration
  - DND*i*/LEAP
  - MSF
  - Addis Abeba University
  - Gondar University
  - ITM-Antwerp

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VL-HIV clinical research

- Secondary prophylaxis to reduce **relapse rate**
- RCT aiming to increase **initial cure rate**
- "Low hanging fruits": HIV-1 PIs
- Perspectives

Secondary prophylaxis of visceral leishmaniasis relapses in HIV co-infected patients using pentamidine as a prophylactic agent: a prospective cohort study

Partners: MSF, AAU, GU, DND*i*/LEAP, ITM-A

Legal sponsor: ITM-A

Secondary prophylaxis: zoonotic transmission

- "Secondary prophylaxis is recommended, particularly when CD4+ counts <200 cells/μL **(AII)"**
- "Existing data are insufficient to recommend a specific regimen" – Centers for Disease Control (CDC)

WHO: anthroponotic transmission

- "In anthroponotic VL, the risk of resistance development means that HIV-coinfected patients may become an important reservoir of drug-resistant *L. donovani. " WHO*
- "Drugs used to treat relapse should therefore be avoided for secondary prophylaxis" *WHO*

Fifth Consultative Meeting on *Leishmania*/HIV Coinfection

Options for secondary prophylaxis

Antimonials

Amphotericin B lipid formulations

Pentamidine

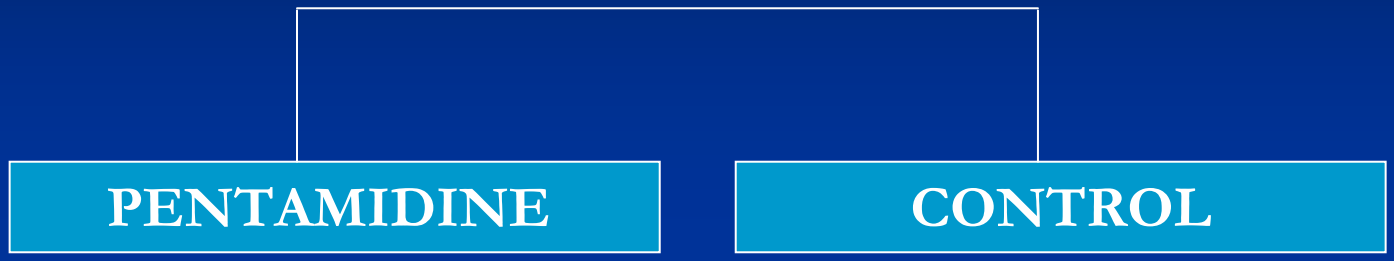
USED FOR TREATMENT

NOT USED
REGISTERED FOR VL in Ethiopia
DONATION (Sanofi)

Pentamidine secondary prophylaxis

- Pentamidine secondary prophylaxis (PSP) used in high-income countries (monthly)
  - Safety isues as treatment (daily)
  - Prophylactic use: limited toxicity (monthly)
- Operational challenges and issues when implementing in Ethiopian health-care system
  - Safe?
  - Feasible ?
  - Effectiveness?

Study design



- No documented experience implementing in remote areas – E-African context
  - "Recommended intervention": no placebo
  - No alternative: no comparator
- Pilot project with need of careful documentation
  - Safety, feasibility and effectiveness
- Inform policy and guidelines

Pentamidine 4 mg/kg iv (im)/60 min

Multicentric prospective cohort (GoU –Abderafi)

One month after end of VL treatment + TOC(-)

72 adults with VL/HIV
- High relapse risk: any of
  - relapse
  - CD4<200 cells/µL
  - WHO stage IV
- Negative TOC

Exclusion criteria:
- Renal, cardiac dysfunction,
- Diabetes,
- Pregnancy/lactation

Start October 2011 – 4 years

Main analysis: 12M data

CD4<200

Monthly PSP 12M

(PSP – 6M)

Extended FU 12M

Evaluation for safety/relapse

Relapse (rebound?)
Long-term toxiciy

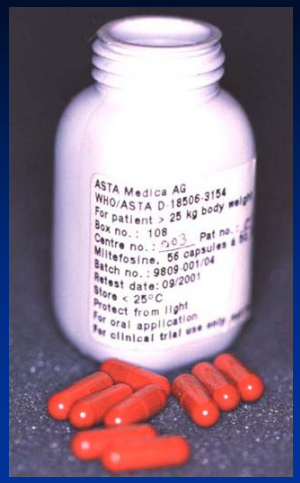
VL-HIV clinical research

- Secondary prophylaxis to reduce **relapse rate**
- RCT aiming to increase **initial cure rate**

A randomized trial of AmBisome® monotherapy and combination of AmBisome® and miltefosine in patients with visceral leishmaniasis co-infected with HIV in Ethiopia

Partners: AAU, GU, DND*i*,/LEAP, MSF, LSHTM, ITM-A

Legal sponsor: DND*i*



NOT FOR PROFIT

AmBisome™

Liposomal Amphotericin B 50 mg

Antimonials
Effective but **highly toxic**

Miltefosine
Safe but less effective

Ambisome 30 mg/kg
Excellent tolerance, high initial failure rate

COMBINATION THERAPY

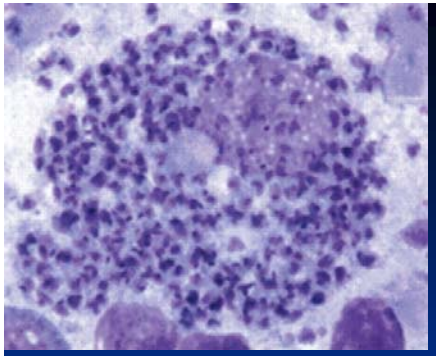
Preliminary data

AMBISOME 40 mg/kg

FDA/Mediterranean/WHO

Objectives

- **Overall objective**
  - To identify a safe and effective treatment for VL in VL/HIV coinfected pts in Ethiopia
- **Primary Objective:**
  - To evaluate the end of treatment efficacy of a AmBisome® + miltefosine and AmBisome® monotherapy in high dose
- **Secondary Objectives:**
  - To evaluate survival at 12 months
  - To assess safety of the regimens



Study design

NOT FOR PROFIT
AmBisome™
Liposomal Amphotericin B 50 mg

Primary VL + HIV coinfected patients
5-60 years

Exclusion if child bearing potential, TB

Randomization

Open-label
Proof of concept

Group sequential design (2x63 max)

Primary end-point:
End of treatment cure

Secondary end-point:
VL-free survival - 12M
Safety

Ambisome high dose
Ambisome 40 mg/kg - 24d
(8x5mg/kg)

Combination therapy
Ambisome 30 mg/kg - 11d
(6x5mg/kg)
Miltefosine 150 mg - 28 d

HIV-1 Protease inhibitors

Evidence overview of anti-leishmanial effects - potential for VL/HIV coinfection

HIV-1 protease inhibitors

- Pillar of combination therapy
- Currently 10 PIs approved by FDA (>1995)
- Lopinavir/ritonavir
  - Extensive clinical experience/evaluation
  - Second-line ARV treatment (WHO)
  - Widely available in VL-endemic regions (VL/HIV)

Intracellular Survival of *Leishmania* Species That Cause Visceral Leishmaniasis Is Significantly Reduced by HIV-1 Protease Inhibitors

Effect of PIs on Leish: summary

- Inhibitory effect of HIV-1 PIs on L donovani/infantum
  - Macrophage model, including (resistant) field strains and co-infection
- Effective concentration of PIs borderline levels for clinical use
- NFV most well studied/most active
- Limited data with LPV in *L infantum/donovani*
  - Unpublished data: no effect
- Screening of additional PIs through DND*i*

VL-HIV clinical research: perspectives

- Initial parasitological cure: findings by 2014
- Pentamidine secondary prophylaxis: by 2013
- Major knowledge gaps regarding VL/HIV
- Addressing key questions: novel therapeutic approaches + better control
  - Substudies nested in clinical trials

VL-HIV research priorities?

- Parasite: molecular, susceptibility ?
- Drug: PK, ARV drug interactions
- Immunological
- Prevention of overt disease
  - Asymptomatic Leish infection in HIV+ pts
  - Natural" evolution of *L donovani* co-infection
    - Early start of ART
    - Primary prophylaxis

VL-HIV clinical research: perspectives

- VL/HIV clinical research consortium or partnership?
  - Join forces/complementary expertise
  - Funding
  - Applied/clinical and basic research
- International linkage
  - Multi-regional studies
  - Exchanges of knowledge, expertise
  - Pro-active reflection on how to maximally exploit studies at the global level

Thank you