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Visceral leishmaniasis-HIV coinfection: current challenges and perspectives

The Mediterranean experience: lessons learned and current challenges

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Lessons learned

to learn, no previous experience on co-infected patients

to built up knowledge, to describe and to communicate our experience and findings

to work together, for patient series, for clinical trials and for a surveillance network

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Leishmania and Human Immunodeficiency Virus Coinfection: the First 10 Years

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The Relationship between Leishmaniasis and AIDS: the Second 10 Years

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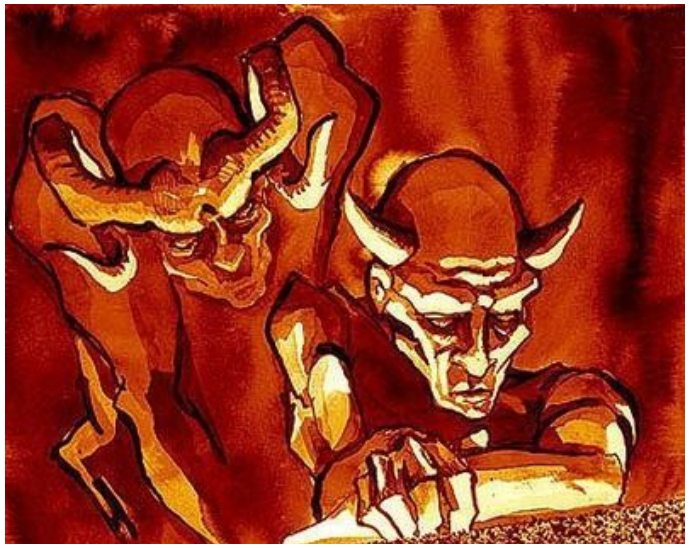
IMPACT

- 1985: first case of HIV/VL co-infection recorded (in Spain)
- Before 1985 (Spain): 70% of VL in children <15 yo; 1997: 75% in adults 29-33 yo (60% HIV+)
- 1990´s (Spain): 15% (7-17%) of febrile HIV: amastigotes in bone marrow
- **1990´s (Spain): collaborative Spanish group for VL/HIV study**
- **1994: WHO dedicated surveillance network (13 reporting sites increased to 16 sites in 1998)**

Leishmania & HIV synergy
Th_2 persistent response

- **HIV increased the risk of VL**
  - By 100-2300 times in endemic areas
  - Reactivation of a latent infection
  - Primary infection
  - Relapse
  - Reinfection



- **VL induces AIDS progression**
  - > HIV load
  - < CD4 count
  - Poor increase in CD4+ in relapsing patients compared with that in non-relapsing patients despite undetectable HIV viral load

WHAT WE HAD AT THAT TIME: passion, bone marrows & antimonials

WHAT CAME YEARS LATTER: knowledge, PCR, liposomal AB & HAART

Incidence trend of HIV/*Leishmania* co-infections

1995 (WHO): 858 cases, 729 from Europe, 450 from Spain (53% of all reported HIV/VL co-infections recorded in the world)

2-9% AIDS patients in Southern Europe will develop VL

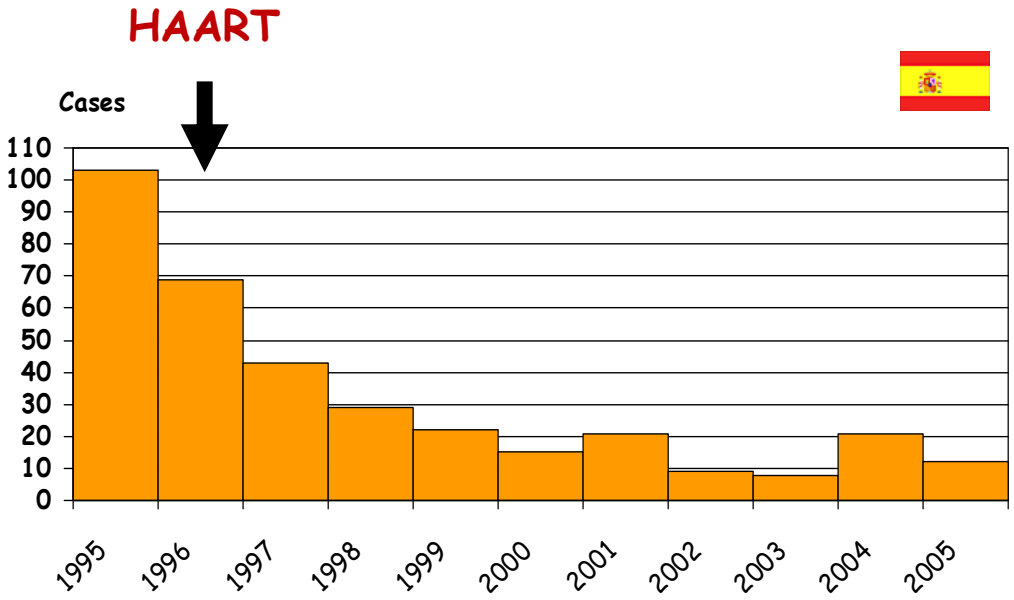
1990-2006: 2210 cases in southern Europe (57% in Spain)

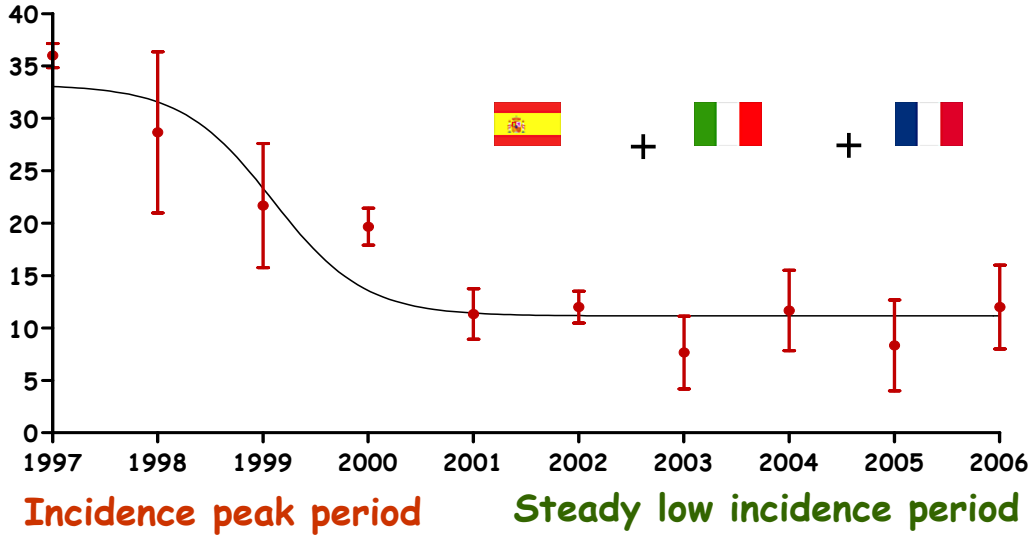
-Incidence peak during 1996-1998

-1996-1997: HAART

-Steadily decrease during 1998-2001

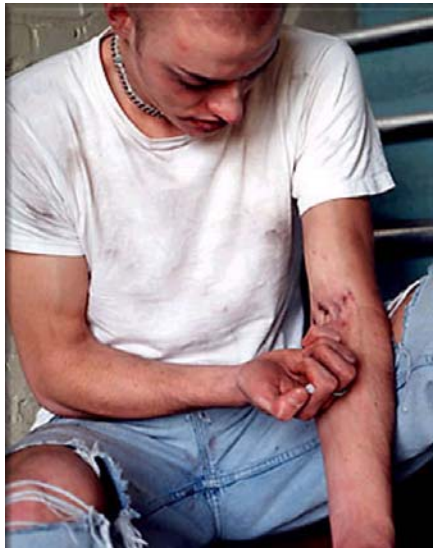
-Low incidence plateau after 2006

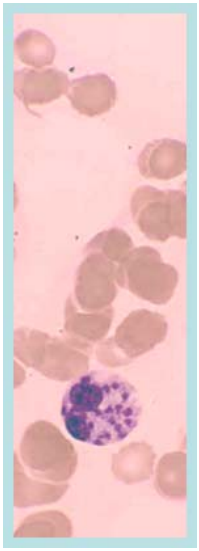




DEMOGRAPHICS

- Mean age: 38-39 yo adults
- Gender: 83-85% male
- IVDU ++ affected: from 76% (1990-8) to 67% (2001-6)
  - live in peri-urban environment
  - transmission sharing syringes (artificial-epidemic-anthroponotic cycle)
  - secondary reservoirs: +++ parasites in the peripheral blood (50% in monocytes; 67% in buffy-coat culture, 100% by xenodiagnosis)



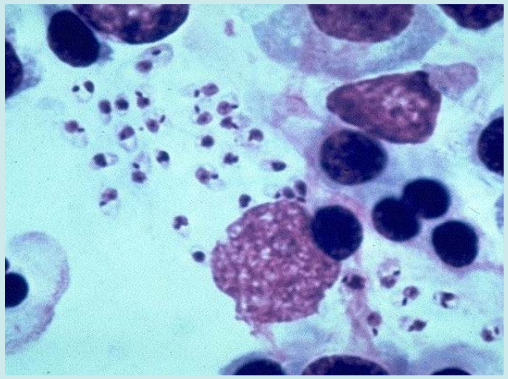



THE PARASITE

- **3 main cryobanks/identification centers were designed**
- *Leishmania infantum*
- Enzymatic characterization of VL cases
  - extreme variability (28 different zymodemes): MON-1 (66%), MON-24 (13%)
  - new zymodemes never described
  - low-virulence dermotropic variants
  - recombinative variants
  - no correlation with clinical expression
  - *L.infantum-L.major* hybrid strains
  - *Leishmania*-like flagellates (nonhuman trypanosomatids)
- PCR + RFLP analysis for *Leishmania* characterization

VL DIAGNOSIS

- **Serology**
  - 40% one test serology is negative
  - 15-20% all test serology (CIE, IFAT, ELISA, WB) are negative
  - serology +ve in reactivations and –ve in primary infections?
- **Bone marrow aspirate and biopsy staining & culture**
  - 74-98% in first episode
  - 64% in relapses
  - Culture increases sensitivity
- **Lymph node & spleen & liver biopsy or aspirate staining & culture**
  - Spleen: 95-96%
  - Liver: 77-91%
  - Lymph node: 52-59%
- **Peripheral blood staining & culture**
  - Staining: 50-53%
  - Buffy-coat culture: 67%



- **Can be found in any place**
  - mouth, larynx, gastrointestinal tract, rectum, pleura, lungs, mediastinum, pericardium, suprarenal glands, CSF…

CLINICAL MANIFESTATIONS

- **CD4 count**
  - <200/mm^3 in 80-99%
  - 200-500/mm^3 in 7-22%
  - >500/mm^3 in 0-3%

- 42-72% **AIDS defining criteria** before/during 1st episode of VL

- 42-68% **concomitant opportunistic infection** during any episode of VL
  - disseminated tuberculosis
  - atypical mycobacteriosis
  - lymphoma
  - salmonellosis
  - disseminated CMV
  - toxoplasmosis
  - pneumocystosis
  - cryptococosis…

SPECTRUM OF THE DISEASE

- **Broad spectrum:** from asymptomatic disseminated and fatal cases
- **Cutaneous CL (4%)**
  - Healthy skin
  - Exclusive cutaneous
  - Mucocutaneous: nasal, oral, pharynx and larynx
  - Diffuse cutaneous: non-ulcerated papulonodular, dermatomyositis-like…
  - Concomitant with Kaposi's sarcoma, herpes, varicella-zoster, tattoos…
- **CL + VL**
  - CL (ulcer) can precede (even months) VL
  - CL concomitant with VL
  - CL after VL treatment (diffuse cutaneous)
- **Typical VL: bone marrow, spleen, lymph nodes (94%)**
  - Not significantly different from those HIV-
  - Fever (80-95%), constitutional syndrome, splenomegaly (54-90%), hepatomegaly (34-85%), pancytopenia (35-77%), thrombocytopenia (52-93%), adenopathies (12-57%)
- **“Atypical” VL**
  - Digestive tract: chronic diarrhea
  - Respiratory tract: pleural effusion, pneumonitis, mediastinal adenopathies
  - Multiorgan dissemination

TREATMENT

- **Sb5+: 20 mg/Kg/d/iv/28 d**
  - Resistance after repeated treatment
  - Toxicity: pancreatitis and heart toxicity (Q-Tc, AV-block)

- **AB: 0.7 (0.5-1) mg/kg/d/iv/28 d (15-25 mg/kg total dose)**
  - Toxicity: fever, chills, veins inflammation, thrombophlebitis, kidney failure and anemia

- **LAB: 4mg/kg/d daily or intermittently for 10 doses (40 mg/kg total dose)**
  - Similar to AmB deoxicolate in its efficacy
  - Less toxic than AmB deoxycholate
  - Recurrences could be treated with LAB as not described resistance

- **Pentamidine: 4 mg/Kg/d /iv/14-21 d**

- **Allopurinol; Ketoconazole; Fluconazole; Itraconazole, Miltefosine oraly combined or combined with parenteral treatment.** No good data on the efficacy of combination therapy

- **Interferon gamma (IFNγ) 100 µg/m2/d x 28 days**

- Selective splenectomy

- Systematic parenteral treatment for CL to prevent dissemination

CLINICAL COURSE

- **Co-infection is characterized by**
  - Lower cure rates
  - Higher drug toxicity
  - Higher relapse rates (up to 9% can be re-infections)
  - Higher mortality rates

- **Initial cure** rate 56-90%

- **Adverse effects**
  - Sb^{5+}: 56% (SAE: 28%, fatal AE: 12%), mainly pancreatitis and arrhythmias
  - AB: renal toxicity (18-36%), anemia

- **Relapsing course** after a correctly treated 1st VL episode
  - 60% relapse at 6-9 months
  - 90% relapse at 12 months
  - Relapsing time is shorter with future relapses
  - Clinical features of relapses are comparable with initial episodes

MAINTENANCE TERAPHY

- Primary prophylaxis was not indicated

- Antimonials: 20 mg/Kg/d/21-28d
- LAB or ABLC: 3-5 mg/Kg/21-28d
- Pentamidine: 4 mg/Kg/21-28d

- Miltefosine (100-150 mg/d)
- Itraconazole + Allopurinol
- Itraconazole + Miltefosine

- Once the patient had recovered his immune function with HAART (CD4+ >200/µl for >6 months) and the VL was quiescent, suspension of the prophylaxis can be considered.

TEST OF CURE/FOLLOW UP

- A parasitological cure is not indicative of an absence of future relapse
- A clinical cure does not necessarily indicate parasitological clearance

- **Bone marrow** aspirate/biopsy performed at 1 month and 6 month. Patients refuse successive bone marrow aspirate/biopsy: is an invasive and painful technique

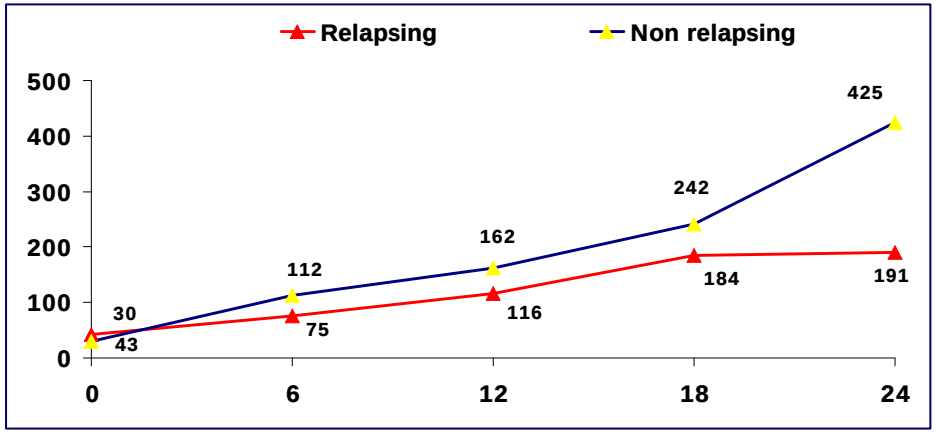
- **Urine latex** agglutination antigen detection test (no relapse if repeatedly negative)

- Nested-**PCR in peripheral blood** (+ does not mean relapse, but excellent negative predictive value). RTQ-PCR sensitivity of 0.001 parasites/ml

PREDICTORS OF VL RELAPSE

- CD4+ count <100 cells/µL at the time of 1st VL episode
- Previous history of VL relapse
- Lack of secondary prophylaxis
- Absence of an increase in CD4+ treated with ARV

Relapsing patients show a lower CD4 count increase



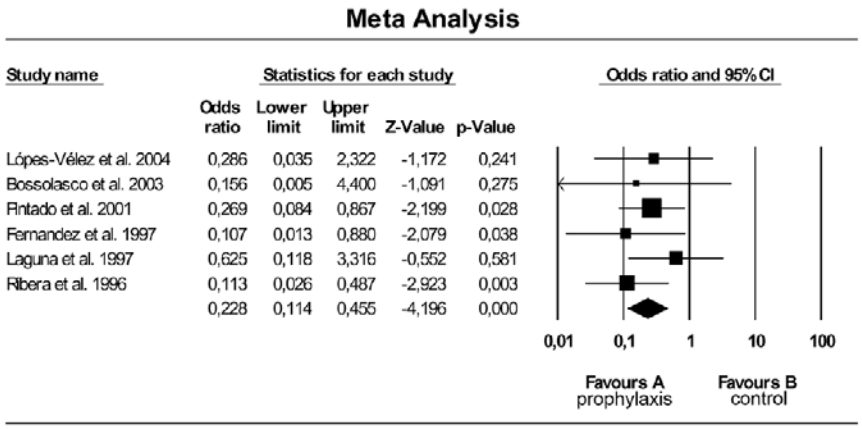


Figure 3. Meta-analysis of secondary prophylaxis results. Footnote: $I^2 = 0\%$ Egger test for publication bias was negative, $p = 0.76$.
doi:10.1371/journal.pntd.0001153.g003

(Cota GF. PLoS Negl Trop Dis 2011)

SURVIVAL

- Mortality rate during 1st episode was 10-19% and can reach up to 24% during the month following termination treatment, mainly because drug-toxicity and opportunistic infections

- Mean survival time is 4-12 months, and the mortality rate at 12 months of 1st episode is 60%

- **Predictive survival factors**
  - **HAART**
  - **High CD4+**
  - **Maintenance therapy**

HAART

- 1996-7: introduction in Europe
- Reduces morbidity and mortality
- Greatly reduces the incidence of symptomatic first episode of VL
- Reduces the risk of relapse. VL relapse even with undetectable viral load (81% had undetectable viral load at the time of VL relapse)
- The period between relapses is prolonged
- Some cases of immune-reconstitution-disease (IRD): VL, diffuse cutaneous, PKDL…

- **Leishmaniasis is an AIDS-defining disease (WHO) and a reason to start HAART independent of the CD4 count**
- **Protease inhibitors have in vitro activity against *Leishmania***

Current challengers

Immigration and travel

Non-HIV immune suppressed patients

- Transplant
- anti-TNF drugs

Climate change

REVIEW ARTICLES

Leishmaniasis emergence in Europe

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Mediterranean Chef´s recommendations for VL/HIV co-infection

- To suspect VL in any febrile HIV patient
- To diagnose *Leishmania* infection promptly: bone marrow/ spleen/ liver/ blood samples by staining/ culture/ PCR
- To treat with liposomal AB (40 mg/Kg), combination of drugs?
- To start ARV treatment
- Test of cure?
- To initiate secondary prophylaxis just after treatment
- To follow up patients closely & quantitative PCR in blood
- To be aware of atypical relapses