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An update on leishmaniasis

TREATMENT OF IMMUNOCOMPROMISED HOSTS WITH LEISHMANIASIS

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INTRODUCTION

- *Leishmania* parasites establish chronic intracellular parasitism and survive for an infected person's lifetime (**latency/cryptic infection**).

- **Cryptic infection can be detected** in persons without a previous history of clinical VL by serology, by detection of parasite DNA in blood samples, or by a positive reaction to the leishmanin skin test (LST).

- **The possible evolution of cryptic infections is unclear**. It has been estimated that in endemic areas the proportion of asymptomatic infections is 10-20 times greater than the number of clinically apparent VL cases.

- Conditions of depression of the immune system, such as HIV infection or immunosuppressive treatments in transplant recipients and in patients with autoimmune diseases, impair the capability of the immune response to resolve the infection and allow the **reactivation of the disease** (even years after infection)

- Symptomatic disease can also occur after **primary infection**.

IMMUNOCOMPROMISED
HIV+ HOSTS

TREATMENT OF HIV/AIDS PATIENTS WITH LEISHMANIASIS
Introduction

- **HIV+ patients with VL have**
  - higher mortality rates (13-18% *vs* 1-5% in immunocompetent patients)
  - higher treatment failure rates (≈30%)
  - higher relapse rates than immunocompetent patients (prolonged chronic course)

- **Concomitant opportunistic infections can overlap**

- **Few clinical trials about the efficacy of treatment in HIV+ patients: in Europe (*L.infantum*), in East Africa and India (*L.donovani*)**

- **Effective therapy can be different in different geographical areas:**
  - High rate of resistance to pentavalent antimonials in India, especially in Bihar
  - LAB is effective in Indian HIV/VL, but efficacy is lower in East African HIV/VL patients

- **There are still many unanswered questions**
  - Drug of choice?
  - Dose & Duration?
  - Combined therapies?
  - Drug regimen for relapses?
  - Maintenance therapy / Secondary prophylaxis?
  - Treatment of latent infection / Primary prophylaxis?

TREATMENT OF HIV/AIDS PATIENTS WITH VISCERAL LEISHMANIASIS
Pentavalent antimonials

- Dose: 20 mg Sb^{v+}/kg/day, im or iv for 28-30 days
- Europe: cure rates ≈33%-82% and frequent relapses
- East Africa (Ethiopia): cure rates ≈ 43.5%
- India (Bihar): high rate of resistance
- High toxicity (pancreas, heart)
- High mortality
- **No longer recommended as first line treatment**

Efficacy of Anti-Leishmania Therapy in Visceral Leishmaniasis among HIV Infected Patients: A Systematic Review with Indirect Comparison

Gláucia F. Cota[1,2], Marcos R. de Sousa[3], Tatiani Oliveira Fereguetti[3], Ana Rabello[1]

PLOS Neglected Tropical Diseases | www.plosntds.org 1 May 2013 | Volume 7 | Issue 5 | e2195

17 articles involving 920 VL (76.1% first VL episode) episodes. Only 4 randomized trials involving 279 patients. The efficacy (definition varied among studies) of therapy was assessed by clinical and/or microbiologic criteria. 62.3% (456) of the 732 treated episodes with available information about TOC.49.6% of the patients had AIDS criteria before VL diagnosis. The median or mean baseline CD4 cell counts range from 25 to 204 cells/ml

- AB-deoxycholate similar to AB-lipid formulations
- ABL superior to Sb^{v+}
- Sb^{v+} higher toxicity than AB/ABL
- Sb^{v+} early mortality rate x 3 times in comparison to AB/ABL (18.4.% *vs* 6.1%)
- CD4 count had no influence on efficacy, neither on mortality
- Not possible to asses difference in relapse rate among different treatments

TREATMENT OF HIV/AIDS PATIENTS WITH VISCERAL LEISHMANIASIS

Amphotericin B (AB), amphotericin B lipid complex (ABLC) and liposomal amphotericin B (LAB)

- **LAB is the preferred treatment**. FDA and WHO recommend 40 mg/Kg total dose: 4 mg/kg/d, iv given on days 1-5, 10, 17, 24, 31, 38
- **Amphotericin B lipid complex** at 30-40 mg/kg iv, total dose (3–5mg/kg/d over 10 days or days 1–5, 10, 17, 24, 31 and 38) and **Amphotericin B deoxycholate** at 0.7-1 mg/Kg/d iv, for 28 days, similar to LAB
- Good tolerated. Parasitological failure rates can be about 32% reaching up to 56% in those patients presenting with relapses.
- More effective in India : 20 mg/Kg (4 doses of 5 mg/kg over 4-10 days)
- Less effective in East Africa (Ethiopia)

-Meyerhoff A. Clin Infect Dis 1999
-Laguna F. J Antimicrob Chemother 2003
-WHO. WHO technical report series 949 (2010)
-Sinha PK. Clin Infect Dis 2011;
-Ritmeijer K. Clin Infect Dis 2011
-Burza S. PLoS Negl Trop Dis 2014

TREATMENT OF HIV/AIDS PATIENTS WITH VISCERAL LEISHMANIASIS
Miltefosine

- Limited information about efficacy, tolerance and safety in HIV+ patients
- Approved for *L.donovani* but anecdotally has been used in Europe for *L.infantum*
- Dose: 2.5 mg/kg/day (max 150 mg day), po for 28 days.
- Patients respond with symptomatic improvement but outcomes are suboptimal with high rates of relapse.

-Sindermann H. Clin Infect Dis 2004
-Ritmeijer K. Clin Infect Dis 2006
-Troya J. Scand J Infect Dis 2008

TREATMENT OF HIV/AIDS PATIENTS WITH VISCERAL LEISHMANIASIS
Pentamidine
Paromomycin

- There are no clinical trials with **pentamidine** and experience is limited to clinical cases where on many occasions a combination with other drugs was used.

- The efficacy of **paromomycin** has not been established. The different trials that prove its efficacy are in combined therapies with other drugs have been carried out mainly in HIV negative patients.

TREATMENT OF HIV/AIDS PATIENTS WITH VISCERAL LEISHMANIASIS
Follow up

- Relapses can occur soon after the end of therapy
- Follow up periods for VL treatment should be increased to **12 months** instead of 6 months as have been commonly applied.
- **Monitor clinically** for relapse of symptoms **and confirm** by direct visualization (or culture) of bone marrow aspirate.
- **Low but detectable levels of *Leishmania* DNA in peripheral blood by PCR does not always herald a clinical relapse**.
- **Quantitative real-time polymerase chain reaction (qPCR)** in the blood measures the parasite load and serves as an index for monitoring the response to treatment. **In relapses, qPCR has a 100% negative predictive value**.
- **Serology** is of very limited utility in the diagnosis of relapse.

-Cota GF. Am J Trop Med Hyg 2013

TREATMENT OF HIV/AIDS PATIENTS WITH VISCERAL LEISHMANIASIS
Follow up: predictors of relapse

Predictors of VL relapse in HIV+ (systematic review)

- CD4+ counts <100 cells/mL at the time of primary VL diagnosis
- Previous history of VL relapse
- Absence of an increase in CD4+ cells at follow-up after treatment
  - CD4 cell counts <200 cells/mL at 6 months are a strong predictor of relapse
  - CD4 cell counts <100 cells/mL at 6 months are at a high risk of multiple relapses
- Lack of secondary prophylaxis

-Cota GF. PLoS Negl Trop Dis 2011

TREATMENT OF HIV/AIDS PATIENTS WITH VISCERAL LEISHMANIASIS
treatment of relapse

- **Retreat** with LAB as per initial episode if relapse.

- There are insufficient data regarding the **efficacy of combination therapy** in HIV patients. However, many experts favor combined therapy especially for those patients with multiple relapses.

  - **LAB (30-60 mg/Kg) + miltefosine (100-150 mg/d for 28 days)**
    Ongoing trial in Ethiopia: LAB (30 mg/kg) + miltefosine (28 days) vs LAB monotherapy

  - Combinations of antimonials with other drugs such as **allopurinol, azole drugs** or **gamma-Interferon** and the **growth factor of rHuGM-CSF colonies** have been used but with insufficient evidence to consolidate the recommendation.

-Monge-Maillo B, López-Vélez R. Drugs 2013

TREATMENT OF HIV/AIDS PATIENTS WITH VISCERAL LEISHMANIASIS
secondary prophylaxis / maintenance therapy

- **Secondary prophylaxis** consistently reduced VL relapse rates in pooled analysis (OR 0.228), but there were insufficient data to compare different regimens.

- **Pentamidine** 4-6 mg/kg infused every 3-4 weeks
  - Ongoing a prospective study in Ethiopia with pentamidine
- **LAB** 3–5 mg/kg every 3-4 weeks
- **Pentavalent antimonials** 20 mg/kg every 3-4 weeks
- Limited experience with **miltefosine** or **azole** drugs.

- **Discontinue prophylaxis** if CD4+ T-cell counts remain >350/mm^3 for at least 3–6 months in response to ART. However, some experts suggest that such prophylaxis should be continued indefinitely because some patients have had relapses despite having CD4 cell counts >200 cells/mm^3.

- *Marques. Scand J Infect Dis 2008*
- *López-Vélez R. J Antimicrob Chemother 2004*
- *Berenguer J. AIDS 2000*
- *NCT01360762*

TREATMENT OF HIV/AIDS PATIENTS WITH VISCERAL LEISHMANIASIS
Screening / primary prophylaxis

- **The risk of developing VL is estimated to be between 100 and 2,300 times higher in HIV-infected than in non-HIV infected individuals**

- High prevalence of **asymptomatic *Leishmania* infection** in HIV-infected patients in endemic areas.
  - 20% of asymptomatic HIV+ in Brazil (serology or PCR)
  - 16.5% of asymptomatic HIV+ in Italy (PCR)

- In North-Ethiopia up to 40% of patients with VL are co-infected with HIV.

- Most HIV/VL have CD4 <200 cells/ml, and <100 cells/ml in up to half of cases.

- *Leishmania* **parasitemia** is higher in patients with **higher HIV loads**

  - *Morales MA. J Infect Dis 2002*
  - *Colomba C.. BMC Infect Dis 2009*
  - *Orsini M. Trans R Soc Trop Med Hyg 2012*

TREATMENT OF HIV/AIDS PATIENTS WITH VISCERAL LEISHMANIASIS
Screening / primary prophylaxis

- **Tackling *Leishmania* infection before disease onset would be a logical approach (as in tuberculosis, cryptococal meningitis, toxoplasmosis, etc)**

- **VL screening and treatment** is not recommended in international guidelines. However, this has never been well studied, and merits further exploration in VL-endemic areas.

- Primary prophylaxis?

- Pre-emtive theraphy?

- Periodic screening for Leishmania by **q-PCR** in HIV-infected subjects to select patients at higher risk of *Leishmania* reactivation?

TREATMENT OF HIV/AIDS PATIENTS WITH CUTANEOUS LEISHMANIASIS

- Immunosuppression is a risk factor for diffuse CL and disseminate CL.
- ML and MCL appear to be more common in immunosuppressed patients.
- Whereas MCL is typically associated with *L. braziliensis*, there are increasing reports of mucosal lesions (with or without concurrent cutaneous or visceral disease) caused by *L.infantum, L.donovani, L.major,* and *L.tropica*.
- Visceralization of dermatotropic species has been reported
- **CL-HIV/AIDS co-infection** is generally **treated with systemic therapy and standard drug regimens.** Higher clinical resistance may be observed with antimonials manifest by an initial response followed by relapse weeks to months later.

TREATMENT OF HIV/AIDS PATIENTS WITH LEISHMANIASIS
Antiretroviral treatment

- **Antiretroviral therapy (ART)**
  - Improves survival of co-infected patients
  - Effect on relapse is partial, increases the time interval to VL relapse.
  - Dramatic reductions in the incidence of VL–HIV co-infection

- ART should be **started** as soon as the co-infected patient can tolerate it.

- In-vitro studies have consistently documented an **inhibitory effect of specific HIV-1 protease inhibitors** on *Leishmania* parasites

- Leishmaniasis-associated **immune reconstitution inflammatory syndrome** (IRIS) reactions following initiation of ART have been reported occasionally and require treatment with corticosteroids

–Lopez-Velez R. Ann Trop Med Parasitol 2003
–van Griensven J. Lancet Infect Dis 2013

IMMUNOCOMPROMISED NON-HIV HOSTS

Introduction

- Non-HIV related immunosuppressive conditions are becoming increasingly prevalent globally, mainly because of better medical care of patients with chronic illnesses and the therapeutic use of immunosuppressive drugs

- That immunosuppressive conditions pose a real challenge in *Leishmania* endemic regions is illustrated by the recent *L.infantum* outbreak in Madrid.
  - Among the 446 cases detected between 2009 and 2012, 15.2% (n= 68) had immunosuppressive conditions, mostly non- HIV-related.
  - Overall, 31.3% of VL cases and 6.3% of CL cases were diagnosed in immunosuppressed individuals.

Introduction VL

- Experience mostly based on case reports or small case series.
- Initial treatment response is better and recurrence rates are lower than in HIV+ individuals, but not as good as in the immunocompetent population
- Although systematic comparisons are lacking, most authors recommend **LAB**
- Treatment can be complicated by **overlapping toxicity and drug interactions** between some anti-leishmanial and immunosuppressive drugs
- **Maintenance therapy** has occasionally been used. Surprisingly, many patients remained relapse-free without maintenance therapy and despite the ongoing use of immunosuppressive medication

Introduction CL & ML & MCL (1)

- Many cases of CL have been reported.
- ML and MCL appear to be more common in immunosuppressed patients
- Immunosuppression is a risk factor for **diffuse CL**, an anergic form that is notorious for its poor treatment response. In this form, multiple nodular lesions containing large numbers of parasites are seen.
- **Disseminated CL**, presenting with multiple pleomorphic lesions, is another rare form that can be seen
- **Visceralization of dermatotropic** species
- **Skin dissemination of viscerotropic** species

Introduction CL & ML & MCL (2)

- **MCL** is typically associated with *L. braziliensis*, but there are increasing reports of mucosal lesions (with or without concurrent cutaneous or visceral disease) caused by *L.infantum, L.donovani*, *L.major*, and *L.tropica*

- Especially with advanced immunosuppression, **treatment response can be poorer**, with higher rates of recurrence, and the risk of dissemination and concurrent VL and ML is higher.

- Generally speaking is a factor arguing in favour of **systemic treatment** instead of local therapy **for CL.**

- Although some cases of isolated ML have been successfully treated with local treatment, most authors argue in favour of **systemic treatment for ML**, given the risk of subsequent visceralization


Leishmaniasis in immunosuppressed individuals

TABLE 2. Selected reports on cases of visceral leishmaniasis found in non-human immunodeficiency virus-related immunosuppressive conditions[a]

Medical condition	Immunosuppressive drugs	Reference
Transplantation		
Bone marrow/ haematopoietic stem cells	Various, including steroids, cyclosporine,	[37–40,183]
Solid organ: mainly kidney; more rarely liver, heart, lung, and kidney–pancreas	azathioprine, tacrolimus, and mycophenolate mofetil	[27–36,184]
Rheumatological/connective tissue diseases/vasculitis		
Rheumatoid arthritis	Various, including steroids, methotrexate,	[44,46,47,51,98, 99,185–189]
Systemic lupus erythematosus	cyclophosphamide,	[43,45,99]
Wegener's granulomatosis	anti-TNF-α agents	[48]
Idiopathic juvenile arthritis		[80,190]
Ankylosing spondylitis		[149,190]
Giant cell arthritis		[149]
Psoriatic arthritis		[51, 111, 191]
Other chronic inflammatory or iatrogenic immunosuppressive conditions		
Asthma	Steroids	[56]
Asthma/dermatitis	Steroids	[168]
COPD	Steroids	[58]
Cheilitis granulomatosa	Steroids	[56]
Ulcerative colitis	Azathioprine/cyclosporine	[59]
Sarcoidosis	Steroids	[57]
Myasthenia gravis	Steroids	[56]
Oncology		[61]
Haematological malignancies	Various (chemotherapy)	[60,192–195]
Solid tumours		[61]

COPD, chronic obstructive pulmonary disease; TNF-α, tumour necrosis factor-α.
[a]Non-exhaustive, with priority given to more recent or particularly interesting cases.


Leishmaniasis in immunosuppressed individuals

TABLE 4. Treatment recommendations for leishmaniasis in immunosuppressed individuals.

Organization	Target group	Preferred therapy	Alternative therapy
VL			
American Society of Transplantation and American Society of Transplant Surgeons [141]	Organ transplant	Liposomal amphotericin B 21 mg/kg total dose 3 mg/kg IV days 1–5, 14, 21	Amphotericin B deoxycholate 1.0 mg/kg daily for 15–20 days or a pentavalent antimony compound[a]
Centers for Disease Prevention and Control [128]	HIV	Liposomal amphotericin B 20–60 mg/kg total dose 2–4 mg/kg IV daily or interrupted schedule (e.g. 4 mg/kg days 1–5, 10, 17, 24, 31, 38)	Other amphotericin B lipid complex dosed as for liposomal amphotericin B Amphotericin B deoxycholate 0.5–1.0 mg/kg IV daily (total dose of 1.5–2.0 g) SSG 20 mg Sb5+/kg IV/IM daily for 28 days Miltefosine 100 mg PO daily for 4 weeks
Food and Drug Administration [126]	Immunosuppression (HIV and non-HIV)	Liposomal amphotericin B 40 mg/kg total dose 3–5 mg/kg IV days 1–5, 10, 17, 24, 31, 38	
WHO [127]	HIV	Liposomal amphotericin B 40 mg/kg total dose 3–5 mg/kg IV daily or days 1–5, 10, 17, 24, 31, 38	
CL and MCL			
American Society of Transplantation and American Society of Transplant Surgeons [141]	Organ transplant	Pentavalent antimonials[a] 20 mg Sb5+/kg IV/IM daily CL: 21 days MCL: 28 days	Conventional or liposomal amphotericin B, miltefosine, paromomycin, pentamidine, and fluconazole, based on species and availability
Centers for Disease Prevention and Control [128] (only for CL, not for MCL/ML)	HIV	Liposomal amphotericin B as for VL SSG 20 mg Sb5+/kg IV/IM daily for 28 days	Miltefosine PO, topical paromomycin, intralesional SSG, or local heat therapy

CL, cutaneous leishmaniasis; HIV, human immunodeficiency virus; IM, intramuscular; IV, intravenous; MCL, mucocutaneous leishmaniasis; PO, per os; SSG, sodium stibogluconate (pentavalent antimony); VL, visceral leishmaniasis.
[a]Stibogluconate or meglumine antimoniate.

TREATMENT OF ORGAN TRANSPLANT PATIENTS WITH LEISHMANIASIS
Introduction

- Most cases after **renal transplantation** (the most commonly tx organ)
- Some after **hematopoietic stem cell/bone marrow transplantation**.

- By the bite of a sand fly
- By reactivation of dormant infection
- By an infected organ or transfusion/blood product.

- VL can occur as an early of 17 days or late of 18 months

- Classic form of VL
- Atypical cases of CL and ML caused by viscerotropic strains

- May simulate other infections: misdiagnosis

- Can cause graft dysfunction and loss of the organ

-Antinori S. Lancet Infect Dis 2008

TREATMENT OF ORGAN TRANSPLANT PATIENTS WITH LEISHMANIASIS
Antiparasitic drugs

- Most authors recommend **LAB**: 4 mg/kg/d given on days 1-5, 10, 17, 24, 31, 38 (total dose 40 mg/kg).

- An alternative could be a sequential combination of **LAB + miltefosine** (2.5 mg/kg/day, maximally 150 mg po daily, for 28 days).

- A few renal transplant patients have been successfully treated with **fluconazole or ketoconazole + allopurinol**

- **Overlapping toxicity and drug interactions**. When possible, doses of immunosuppressive drugs should be decreased during VL treatment.

-Antinori S. Lancet Infect Dis 2008
-Murray HW. Am J Trop Med Hyg 2012
-Schwartz BS. Am J Transplant 2013
-Llorente S. Transplantation 2000
-Halim MA. Clin Infect Dis 1993
-Hueso M. Nephrol Dial Transplant 1999

TREATMENT OF ORGAN TRANSPLANT PATIENTS WITH LEISHMANIASIS
Follow up

- **Relapse**: 6 months after liver transplantation and 19 months after renal transplantation (higher immunosuppression in liver transplantation)

- **Monitoring** for *Leishmania* reactivation (microscopy and/or qPCR of serial peripheral blood or biopsy specimens) is recommended. Rising numbers of blood parasites measured by **qPCR assays over time** provide the earliest and most sensitive indicator of VL reactivation.

- **Presumptive antileishmanial treatment is not recommended** without evidence of reactivation.

- The indications for **secondary prophylaxis** remain to be defined (exceptionally used). Many patients remain relapse-free without maintenance therapy and despite the ongoing use of immunosuppressive medication.

TREATMENT OF ORGAN TRANSPLANT PATIENTS WITH LEISHMANIASIS
Routine screening

- Routine screening of **donors** from endemic areas is not recommended. If a donor is seropositive: accept the organ, and perform close monitoring of the recipient in the post-transplant period

- Serological screening or qPCR or specific interferon-gamma release assays of **recipients** with a history of potential exposure to *Leishmania* may be considered before transplantation.

- If **recipient** is asymptomatically infected or has a history of VL, close monitoring is warranted. Pre-emptive treatment is currently not recommended.

- **In a recent Brazilian study, none of the liver transplant recipients who were found to be *Leishmania*-PCR positive at the time of transplantation or received a PCR-positive organ developed VL over a median follow-up of 24 months, without any prophylaxis being given.**

-Martin-Davila P. Clin Microbiol Rev 2008
-Clemente WT. Am J Transplant 2014

TREATMENT OF PATIENTS ON IMMUNOSUPPRESSIVE DRUGS WITH LEISHMANIASIS

- Asthma, sarcoidosis, myasthenia gravis, IBD; rheumatologic diseases…
- Azathioprine, methotrexate, steroids, cyclosporine, cyclophosphamide…
- Tumor necrosis factor-a (TNF-a) antagonist drugs
  - There are a substantial number (several tens) of reports
  - Occurring after many months of use
  - Increases x16 times the risk in patients receiving infliximab or adalimumab than in patients receiving etanercept x8 times

- Most of cases are VL, but CL and MCL also observed.

- There are insufficient data for **guideline treatment** recommendations

- **Screening** for asymptomatic VL if history of travel to endemic regions in the past is not currently recommended
- If an immunosuppressed individual is known or found to be asymptomatically infected or has a history of VL, close monitoring is warranted.

- **Pre-emptive treatment** is currently not recommended.

-Neumayr AL. Travel Med Infect Dis 2013

TREATMENT OF CANCER PATIENTS WITH LEISHMANIASIS

- Several **cancer-related cases** (mainly haematological malignancies and after haematopoietic stem cell/bone marrow transplantation) of VL have been reported, associated with the use of various chemotherapeutic regimens or monoclonal antibodies.

- There are insufficient data for guideline recommendations at this time.

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