EPIDEMIOLOGICAL ANALYSIS OF 692 RETROSPECTIVE CASES OF LEISHMANIA/HIV CO-INFECTION
EPIDEMIOLOGICAL ANALYSIS OF

692 RETROSPECTIVE CASES OF

LEISHMANIA/HIV CO-INFECTIONS

This document is not issued to the general public, and all rights are reserved by the World Health Organization (WHO). The document may not be reviewed, abstracted, quoted, reproduced or translated, in part or in whole, without the prior written permission of WHO. No part of this document may be stored in a retrieval system or transmitted in any form or by any means - electronic, mechanical or other - without prior written permission of WHO.

The views expressed in documents by named authors are solely the responsibility of those authors.

Ce document n'est pas destiné à être distribué au grand public et tous les droits y afférents sont réservés par l'Organisation Mondiale de la Santé (OMS). Il ne peut être commenté, résumé, cité, reproduit ou traduit, partiellement ou en totalité, sans une autorisation préalable écrite de l'OMS. Aucune partie ne doit être chargée dans un système de recherche documentaire ou diffusée sous quelque forme ou par quelque moyen que ce soit - électronique, mécanique, ou autre - sans une autorisation préalable écrite de l'OMS.

Les opinions exprimées dans les documents par des auteurs cités n'engagent que lesdits auteurs.
by: Dr P. Desjeux (1), Dr J. Alvar (2), Dr L. Gradoni (3), Dr M. Gramiccia (3), Dr F.J. Medrano (4), Dr M. Deniau (5), Dr M. Portus (6), Dr F. Laguna (2), Dr F. Farault-Gambarelli (7), Dr C. Montalban (8), Dr P. Marty (9), Dr E. Rosenthal (9), Dr T. Gemetchu (10), Dr R. Russo (11), Dr J.P. Dedet (12), Dr Dr S. Matheron (13) and Dr F. Antunes (14).

(1) World Health Organization, CTD/TRY, Geneva, Switzerland
(2) Instituto De Salud Carlos III, Madrid, Spain
(3) Istituto Superiore di Sanita, Roma, Italy
(4) Hospital Universitario Virgen del Rocio, Sevilla, Spain
(5) Centre Hospitalier et Universitaire, Creteil, France
(6) Facultad de Farmacia, Barcelona, Spain
(7) Faculté de Médecine, Marseille, France
(8) Hospital Ramon y Cajal, Madrid, Spain
(9) Centre Hospitalier Universitaire, Nice, France
(10) National Institute of Pathobiology, Addis Ababa, Ethiopia
(11) Istituto di Malattie Infettive, Catania, Italy
(12) Faculté de Médecine, Montpellier, France
(13) Groupe Hospitalier Bichat-Claude Bernard, Paris, France
(14) Hospital de Santa Maria, Lisboa, Portugal
At a Joint Consultative Meeting on *Leishmania/HIV* Co-Infections held in Rome in September 1994 by the Istituto Superiore di Sanità, and the Division of Control of Tropical Diseases (CTD) of the World Health Organization (WHO), a standardized Case Report Form and Guidelines for Diagnosis were finalized and endorsed. At this meeting a recommendation was also made to create a Central Registry to be located in WHO/CTD to collect, process and to periodically rediffuse worldwide basic information.

The overlap of visceral leishmaniasis (VL) and AIDS is on the increase due to the spread of the AIDS pandemic in rural areas and that of VL in suburban areas. Consequently, cases of co-infections are more frequent, with important clinical, diagnostic, chemotherapeutic, epidemiological and economic complications. *Leishmania/HIV* co-infection is regarded as an *emerging disease*, especially in southern Europe, where 25 - 70 % of adult VL cases are related to HIV infection, and 1.5 - 9 % of AIDS cases suffer from newly acquired or reactivated VL.

### MAIN RESULTS

#### 1) GEOGRAPHIC ORIGIN

97.3 % of the cases originate from *southern Europe* with a clear predominance in *Spain*:

- **Spain**: 413 59.7 %
- **Italy**: 130 18.8 %
- **France**: 127 18.3 %
- **Ethiopia**: 19 2.7 %
- **Portugal**: 3 0.5 %

**TOTAL**: 692 100 %

![Graph showing cases by country](image-url)
II) SEX DISTRIBUTION

Most of the cases are males:

- Males: 620 89.6 %
- Females: 72 10.4 %

TOTAL: 692 100 %

III) AGE DISTRIBUTION

Young adults represent 85.7 % of the cases:

- 20 to 30 years old 121 25.8 %
- 31 to 40 years old 281 59.9 %
- 41 to 50 years old 49 10.4 %
- 51 to 60 years old 16 3.4 %
- 61 to 70 years old 2 0.4 %

TOTAL: 469 100 %

The distribution according to age and sex reflects the main population at risk (see below).
IV) RISK GROUPS

There is a predominance among intravenous drug users (IVDU) who are clearly identified as the main population at risk:

- IVDU: 311 71.1%
- Heterosexual: 57 13.1%
- Homosexual: 34 7.8%
- Haemophilic: 13 3%
- Bisexual: 11 2.5%
- Blood transfusion: 11 2.5%

TOTAL: 437 100%

V) MAIN RISK GROUPS BY COUNTRY

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>75</td>
<td>14.7 %</td>
<td>10.7 %</td>
<td>69.3 %</td>
<td>1.3 %</td>
<td>4 %</td>
<td>-</td>
</tr>
<tr>
<td>Italy</td>
<td>128</td>
<td>6.2 %</td>
<td>8.6 %</td>
<td>79.7 %</td>
<td>3.1 %</td>
<td>0.8 %</td>
<td>1.6 %</td>
</tr>
<tr>
<td>Spain</td>
<td>212</td>
<td>7.1 %</td>
<td>9.4 %</td>
<td>73.6 %</td>
<td>1.4 %</td>
<td>3.3 %</td>
<td>5.2 %</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>19</td>
<td>94.7 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There is evidence that the main population at risk is the same (IVDU) in southern France, Italy and Spain. However in Ethiopia, co-infected cases are reported exclusively among heterosexuals.
VI) DATES OF HIV DIAGNOSIS

Yearly distribution of reported HIV cases:

- 1981: 1 0.5%
- 1983: 1 0.5%
- 1984: 1 0.5%
- 1985: 12 6.4%
- 1986: 26 13.9%
- 1987: 26 3.9%
- 1988: 25 13.4%
- 1989: 36 19.3%
- 1990: 13 6.9%
- 1991: 11 5.9%
- 1992: 7 3.7%
- 1993: 11 5.9%
- 1994: 14 7.6%
- 1995:* 3 1.6%

TOTAL: 187 (100%)

* Only first trimester covered

VII) DATES OF LEISHMANIASIS DIAGNOSIS

Yearly distribution of reported leishmaniasis cases:

- 1985: 3 0.6%
- 1986: 3 0.6%
- 1987: 8 1.7%
- 1988: 13 2.7%
- 1989: 16 3.3%
- 1990: 31 6.5%
- 1991: 83 17.5%
- 1992: 67 14.0%
- 1993: 109 22.9%
- 1994: 115 24.2%
- 1995:* 29 6%

TOTAL 477 100%

* Only first trimester covered.

The sharp increase observed in 1993 seems to be the result of increased awareness and implementation of programmes of active medical surveillance of leishmaniasis in HIV- infected individuals.
VIII) CORRELATION BETWEEN LEISHMANIASIS and HIV DIAGNOSIS

HIV was diagnosed before leishmaniasis in two-third of the cases

- leishmaniasis before HIV: 4 2 %
- HIV before leishmaniasis: 132 64.7 %
- Simultaneous: 68 33.3 %
- TOTAL: 204 100 %

IX) IMMUNOLOGICAL PARAMETERS

- CD4 rate

<table>
<thead>
<tr>
<th>CD4 Rate</th>
<th>Value</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;500/mm³</td>
<td>none</td>
<td>0 %</td>
</tr>
<tr>
<td>200 to 499/mm³</td>
<td>31</td>
<td>9.6 %</td>
</tr>
<tr>
<td>&lt;200/mm³</td>
<td>29</td>
<td>90.4 %</td>
</tr>
<tr>
<td>TOTAL</td>
<td>321</td>
<td>100 %</td>
</tr>
</tbody>
</table>

There is a clear association between VL and severe immunosuppression.

- SEROLOGY OF LEISHMANIASIS

- positive 257 57.8 %
- negative 188 42.2 %

TOTAL 445 100 %

- POSIVITY / TEST USED

- IFI 235 / 434 54.1 %
- ELISA 75 / 129 58.1 %

The humoral response is frequently negative (42.2 %) due to a global reduction of sensitivity of the serological tests.
X) PARASITOLOGICAL DIAGNOSIS

- POSITIVITY / TEST USED:

<table>
<thead>
<tr>
<th>Test</th>
<th>Positivity</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A- bone marrow</td>
<td>634 / 647</td>
<td>98 %</td>
</tr>
<tr>
<td>B- blood</td>
<td>119 / 159</td>
<td>74.8 %</td>
</tr>
<tr>
<td>C- skin</td>
<td>44 / 50</td>
<td>88 %</td>
</tr>
<tr>
<td>D- gastrointestinal tract</td>
<td>25 / 26</td>
<td>96.2 %</td>
</tr>
<tr>
<td>E- spleen</td>
<td>24 / 24</td>
<td>100 %</td>
</tr>
<tr>
<td>F- liver</td>
<td>18 / 26</td>
<td>69.2 %</td>
</tr>
<tr>
<td>G- xenodiagnosis</td>
<td>13 /22</td>
<td>59.1 %</td>
</tr>
<tr>
<td>H- pleural liquid</td>
<td>11 / 11</td>
<td>100 %</td>
</tr>
<tr>
<td>I- lymph nodes</td>
<td>7 / 7</td>
<td>100 %</td>
</tr>
</tbody>
</table>

Bone marrow aspirate remains the most frequently used technique for parasitological diagnosis and is among the most sensitive techniques (98 %).

XI) CLINICAL DIAGNOSIS STAGE

- first onset: 443 91.7 %
- relapse: 40 8.3 %

TOTAL: 483 100 %
XII) CLINICAL FEATURES

- typical: 400 84.2 %
- atypical: 40 15.8 %
TOTAL 440 100 %

XIII) AIDS DEFINING DISEASES *

Number of patients suffering from specific AIDS defining diseases:

A- Oesophageal candidiasis 65
B- Tuberculosis (pulmonary and cerebral) 59
C- Pneumonia (Pneumocystis carinii) 41
D- Toxoplasmosis cerebral 28
E- Retinitis CMV 17
F- Kaposi 11
G- Lymphoma 8
H- Cryptococcosis cerebral 6
I- Cryptosporidiosis intestinal 5
J- Sarcoidosis intestinal 4
K- Leucoencephalopathy 4
L- Herpes 1
M- Hodgkin 1
N- Syphilis 1

*Associations are frequent
DISCUSSION OF MAIN RESULTS

In addition to the five countries included in this study, cases of co-infections have also been reported in Africa from: Algeria, Cameroon, Djibouti, Guinea Bissau, Kenya, Malawi, Morocco, Sudan, Tunisia; in America from: Brazil, Panama, Peru, Venezuela; in Asia from: India, Sri Lanka; in the Arab Peninsula from Saudi Arabia and in Europe from Greece, making a total of 22 countries.

Southern Europe is definitely a high priority area for Leishmania/HIV co-infections. Epidemiological changes such as the increased population density in suburban areas where the vector is widespread and dogs are abundant, have facilitated a growing overlap of VL and AIDS. In this area, traditional patterns of zoonotic VL are changing. VL is no longer a children’s disease, as the main population at risk now includes young male adults who are frequent intravenous drug users (IVDU). Based on available data, it can be concluded that the population at risk in Ethiopia is drastically different as all the cases reported so far are heterosexuals.

In two-thirds of the cases, a diagnosis of HIV was made before that of leishmaniasis as HIV detection is considered a priority especially in high risk groups whereas leishmaniasis infections are more chronic and clinical manifestations appear months or even years after leaving endemic areas. Concerning the sequence of acquisition, earlier reports notably by Italian investigators based on serological results indicated that in co-infection cases, leishmaniasis was more frequently a newly acquired infection rather than a reactivated old one. However, more studies are still required to allow a final conclusion.

The progressive yearly increase in the number of VL cases is probably related to both, an increase in HIV infections and a more systematic detection of leishmaniasis due to more awareness and implementation of active epidemiological surveillance programmes.

It has been reported that in southern Europe, Leishmania/HIV co-infections occur in severely immunosuppressed patients (90.4% have CD4<200/mm3). Moreover, the consequences of such a co-infection lead to a sharp reduction of the mean survival (13 months) compared to other AIDS patients, the response to treatment is worse than in HIV negative patients, and there is a quicker evolution from infection to disease (up to 20-25% of the global population living in endemic areas). There are also reports of frequent severe VL caused by Leishmania strains with low or no virulence in HIV-negative individuals. The information collected so far indicates that Leishmania may behave as an opportunistic agent in HIV-infected patients, and should be included among the “AIDS-defining” diseases. The proposed definition of leishmaniasis as an “AIDS-defining” disease is: “Any patient with co-existing HIV-infection and visceral leishmaniasis”.
As evidenced in the study, diagnosis of Leishmania/HIV co-infections implies specific difficulties:

- **Clinical:** although most of the patients were seen during the first onset (91.7%) 15.7% evidenced atypical clinical features due to the frequent association of other opportunistic infections and atypical localizations of the *Leishmania*. Several other AIDS-defining diseases are often associated to VL the most frequent being candidosis oesophageal, pulmonar and cerebral tuberculosis, pneumonia due to *Pneumocystis carinii* and cerebral toxoplasmosis.

- **Sero logical:** 42.2% of the co-infected patients evidenced a negative humoral response due to a global reduction of the sensitivity of the serological tests. Nevertheless it is important to emphasize that there were great differences between the results of the different laboratories which were apparently related to the different tests and qualities of antigens used. Hence the recommendation of the Consultative Meeting in Rome to combine two or more serological techniques and to use preferably fresh “laboratory-made” antigens to increase the sensitivity of the tests is highly relevant. The most frequently used tests are Indirect Immunofluorescence (IFI) and ELISA. It seems that it is more difficult for patients to build a humoral response when they are seen at a late stage after many relapses.

- **Parasitological:** bone marrow aspirate (BMA), especially when repeated and used during the first onset of the disease, seems to be one of the most sensitive methods (98% in the study). During the Consultative Meeting in Rome, it was stated that the sensitivity of the method could be increased, especially for treated patients or during relapses if BMA is cultivated. BMA should be the first-line technique in relapses. It is the most frequently used technique especially in the Mediterranean area. Recently, excellent results were reported on the use of leukocytoconcentration which is considered to be an easy, fast and inexpensive technique.

Multiple visceral localizations outside the reticuloendothelial system are frequent during co-infections viz., in the blood, normal skin, gastrointestinal tract, lungs and central nervous system. **The frequency of Leishmania in the peripheral blood is particularly noticeable.** As buffy-coat staining and culture was used in some of the cases in the study, the sensitivity reached 74.8%. The search for *Leishmania* in blood can be an alternative when BMA cannot be performed.

Positive cultures from BMA or blood can be used for biochemical and/or molecular identification of the *Leishmania* involved.

As recently suggested by Spanish investigators, the possibility of an occasional transmission through the sharing of syringes has to be taken into account due to:

- the frequency of the *Leishmania* in the peripheral blood of co-infected patients;
- the possibility of positive xenodiagnosis with a quantity of blood from IVDU co-infected patients less than the content of a needle;

- the focus of a population at risk (IVDU):

- the dispersed geographical pattern of clusters and the identification of new zymodemes isolated from IVDU co-infected patients. Such variability is not observed in immunocompetent patients and neither in dogs.

A further important question is whether co-infected patients are infective for sandflies and can become true reservoirs of the disease as in the anthropoponic foci of East Africa and Asia.

**CONCLUSION**

The burden of *Leishmania*/HIV co-infections is likely to increase over the coming years. The existing network must therefore be strengthened in order to cope with the problems this development will bring.

The epidemiological analysis of 692 retrospective cases of *Leishmania*/HIV co-infections was made possible thanks to the provision of basic information by the investigators and institutions who are official members of the network of surveillance.

The risk of IVDU co-infected patients to act as reservoirs should be taken into consideration at two levels:

- by transmitting the parasite when sharing needles with contaminated blood

- by being directly infective for the sandfly during blood meal.