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Leishmania/HIV co-infection in south-western Europe 1990-1998: Retrospective analysis of 965 cases

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1. HIV/AIDS statistics and features

According to new estimates from UNAIDS and WHO, 32.4 million adults and 1.2 million children were living with HIV/AIDS at the end of 1999, 95% of them living in the developing world. However, HIV is still a challenge in industrialized countries. Globally, over the course of the year 1999, some 5.6 million people became infected with HIV and 2.6 million died despite the antiretroviral therapy available in the richer countries. The total number of deaths since the beginning of the epidemic is estimated at 16.3 million worldwide.

In western Europe, during 1999, 30 000 adults and children were newly infected with HIV and a total of 520 000 adults and children were living with HIV/AIDS, or 1 in every 400 adults aged 15-49 years (0.25%). The main modes of transmission for adults living with HIV/AIDS were sexual transmission among men who have sex with men and through injecting drug use.

2. Leishmaniasis and *Leishmania*/HIV co-infections statistics and features

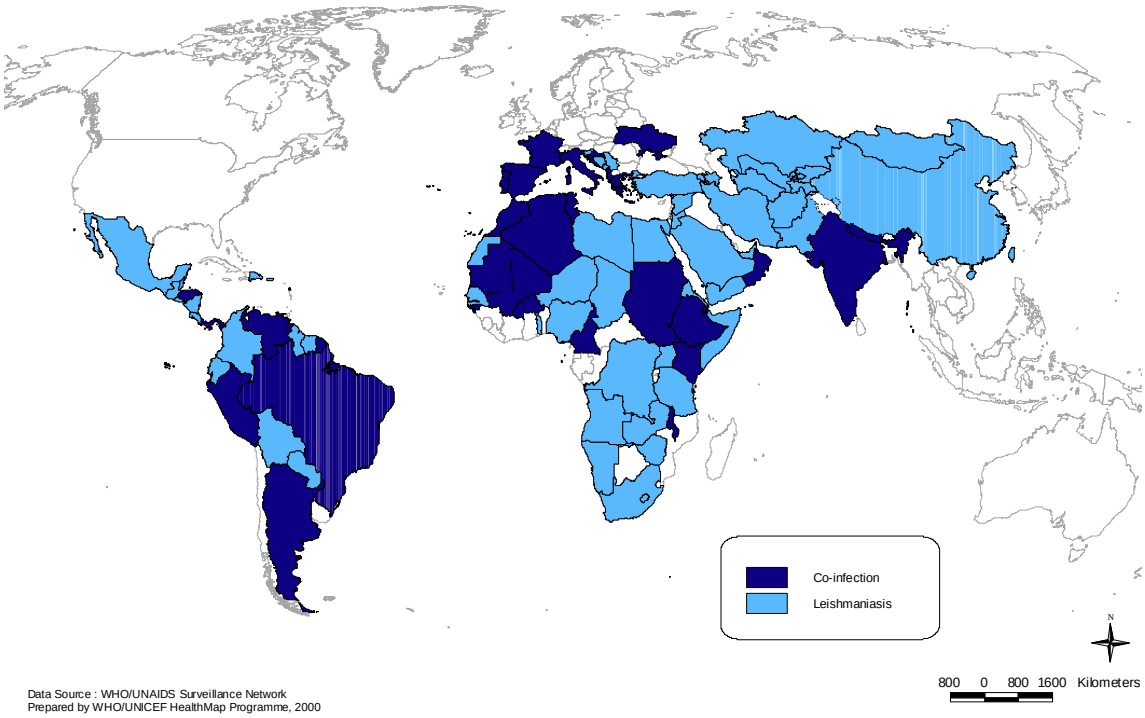
2.1 Leishmaniasis

Leishmaniasis is found in five continents and is endemic in the tropical and subtropical regions of 88 countries: 16 are developed countries, 72 are developing countries and 13 of them are among the least developed (Map 1). There is an overall prevalence of 12 million cases worldwide. Globally the yearly incidence is believed to be 1.5 to 2 million new cases of cutaneous leishmaniasis (CL) and 500,000 new cases of visceral leishmaniasis (VL).

VL is the most severe form of leishmaniasis. Epidemiologically two different situations occur: the zoonotic form, as in the Mediterranean basin, with the dog as the main source of infection for the vector and the anthroponotic form, as in East Africa, Bangladesh, India, Nepal, with man to man transmission through the sandfly vector. In anthroponotic foci severe and deadly epidemics occur.

In immunocompetent patients, infection remains asymptomatic or subclinical in most of the cases. If patients develop the disease after a variable incubation time (weeks to months) they will have fever, severe loss of weight, hepatosplenomegaly (splenomegaly being more frequent) and pancytopenia. If clinically evident and untreated, VL can be fatal especially in developing countries where associated diseases are frequent.

Map 1: Worldwide distribution of leishmaniasis and countries reporting *Leishmania*/HIV co-infection, 2000.

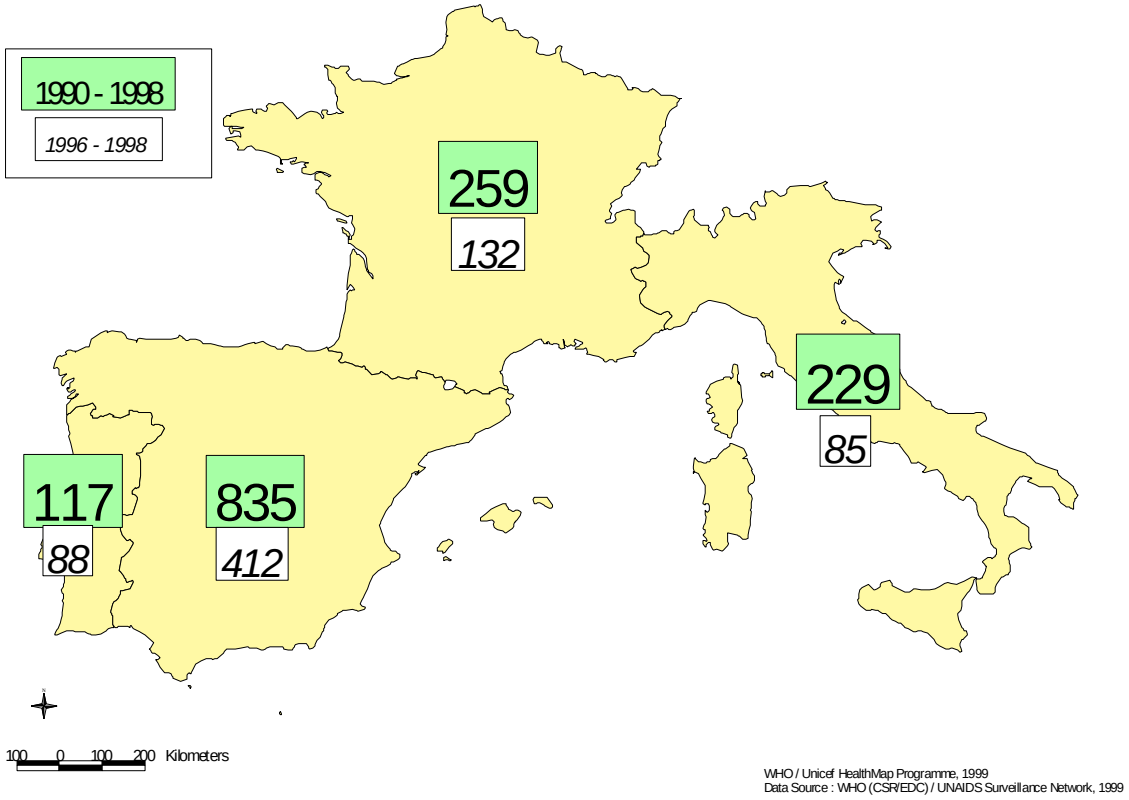


2.2 *Leishmania*/HIV co-infection

VL is the clinical form most frequently associated with HIV/AIDS especially in south-western Europe (although some cases with cutaneous leishmaniasis have been reported). Leishmania/HIV co-infection has emerged as a result of the increasing overlap between VL and AIDS, which is due to the spread of the AIDS pandemic in rural areas and that of VL in suburban areas. This has important clinical, diagnostic, chemotherapeutic and epidemiological implications. Map 1 shows the countries that have reported co-infection cases, as well as those where Leishmaniasis occurs. Although cases of co-infection have so far been reported in 33 countries worldwide, most of the cases have been notified in south-western Europe (France, Italy, Portugal and Spain). The cases reported in these countries between January 1996 and June 1998 represent 49.8% of the total number of cases (1440) reported since 1990 (Map 2).

While *Leishmania*/HIV co-infection is increasing in eastern Africa and the Indian subcontinent, owing to the simultaneous spread and geographical overlap of both diseases as well as periodic epidemics of VL, cases of co-infection are expected to diminish in south-western Europe due to the new combinations of anti-HIV drugs. The number reported to WHO continues to rise however, due to increased awareness and better case definition.

Map 2: *Leishmania*/HIV co-infection, total number of reported cases, by country, 1990-1998 and 1996-1998



3. WHO/UNAIDS surveillance network

Until recently, the impact of *Leishmania*/HIV co-infection was not recognized. Some evidence concerning the situation in Europe first emerged after 1994, when a WHO surveillance network was set up, which then included 13 institutions. In 1998, a worldwide WHO/UNAIDS surveillance network was established, which now includes 28 member institutions. In south-western Europe, the surveillance system based on 16 institutions is now well established, creating greater awareness, improved detection of both diseases and better case reporting and management.

The surveillance centres follow standardized guidelines provided by WHO and UNAIDS, to allow a common approach. The systematic use of standardized and recently computerized case-report forms, the central international registry at WHO headquarters, and finally the use of a geographic information system (GIS) for mapping and monitoring co-infections have improved the overall quality of epidemiological data gathering, and as a result, have improved response capability.

Numbers continue to be underestimated however, as case-detection remains mostly passive, and active medical surveillance is inadequate. Closing the gaps in active medical surveillance requires financial support, staff and facilities for diagnosis, as well as an extensive communications network. Equal vigilance for both diseases is also needed. Unfortunately VL is not an “official” opportunistic infection and consequently, it is rarely reported in AIDS notification systems.

A joint consultative meeting held in September 1998 in Spain convened all members of the surveillance network to review epidemiological data, update the guidelines for diagnosis and treatment and reinforce coordination efforts. The surveillance network in southern Europe and improved coordination between hospitals and laboratories have resulted in more accurate epidemiological data for the region.

All member institutions of the network report to WHO on an annual basis. Worldwide information is analysed and periodically disseminated through international publications.

In collaboration with HealthMap[1], a geographic information system (GIS) was established to support surveillance and monitoring of *leishmania*/HIV co-infections. The system integrates epidemiological and demographic datasets and allows for the mapping of co-infection cases down to locality level. The system can be used to easily visualise and analyse the spatial distribution of co-infection cases and to permit monitoring of the evolution of the distribution of the cases over time. In addition, the GIS serves as a common standardised platform for the convergence of country datasets and allows for easy updating and dynamic production of epidemiological maps. Datasets from other countries will be integrated into the GIS.

This document presents a retrospective analysis of 965 cases from the 1440 cases officially reported to WHO.

4. Epidemiological features

4.1 Geographical origin

Among the 965 cases analysed, it was possible to map 793 (Map 3). GIS has been used to visualize the coverage of each member institution of the network and the geographical distribution of the cases, based on the place of residence. This usually corresponds to the place of infection for leishmaniasis, except for those living in non-endemic areas. Patients reported in non-endemic areas, such as Ile-de-france (Paris), seem to be mainly those who have previously lived or travelled in endemic areas (Africa, Asia, Central and South America and southern Europe).

The highest number of cases is found in Spain (835/1440), which may be related to the higher proportion of HIV/AIDS cases among intravenous drug users (IDU) in Spain (68%) compared to France and Portugal, (Table 1) and to the greater geographical overlap between leishmaniasis and AIDS in Spain compared to Italy or France.

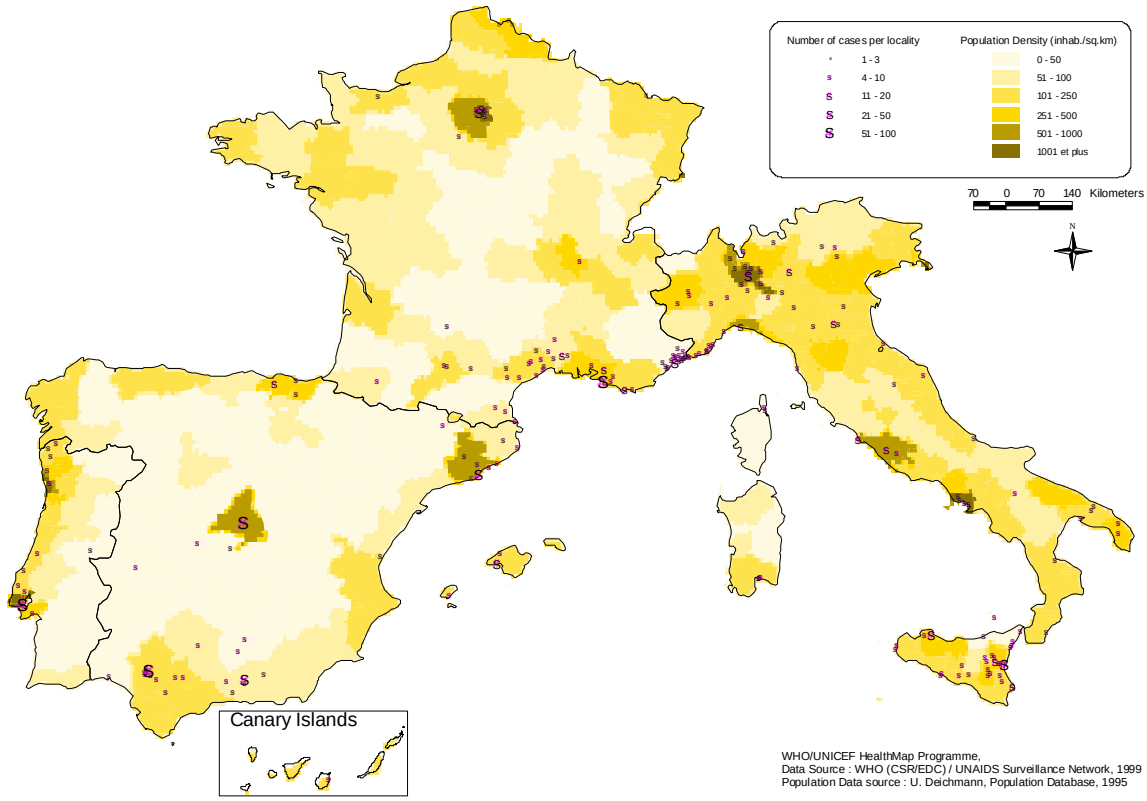
[11] (1) HealthMap is a joint WHO/UNICEF Programme established to support countries in the use of GIS and mapping for public health applications. The Programme is based within the Department of Communicable Disease Surveillance and Response of WHO.

Table 1: HIV/AIDS patients and *Leishmania*/HIV co-infection patients, risk groups, south-western Europe, 1998

	Homosexual		Heterosexual		IDU		Blood Transfusion	
	HIV/AIDS	Co-Inf.	HIV/AIDS	Co-Inf.	HIV/AIDS	Co-Inf	HIV/AIDS	Co-Inf.
Italy	15	8.14	14	12.22	68	75.11	2	0.45
France	48	15.23	19	15.89	26	62.25	5	1.99
Portugal	24	4.41	27	19.12	44	70.59	4	0.00
Spain	17	12.44	11	7.87	68	72.34	2	2.28

(Source: UNAIDS, Report on the global HIV/AIDS Epidemic, June 1998)

Map 3: *Leishmania*/HIV co-infection cases per locality and population density

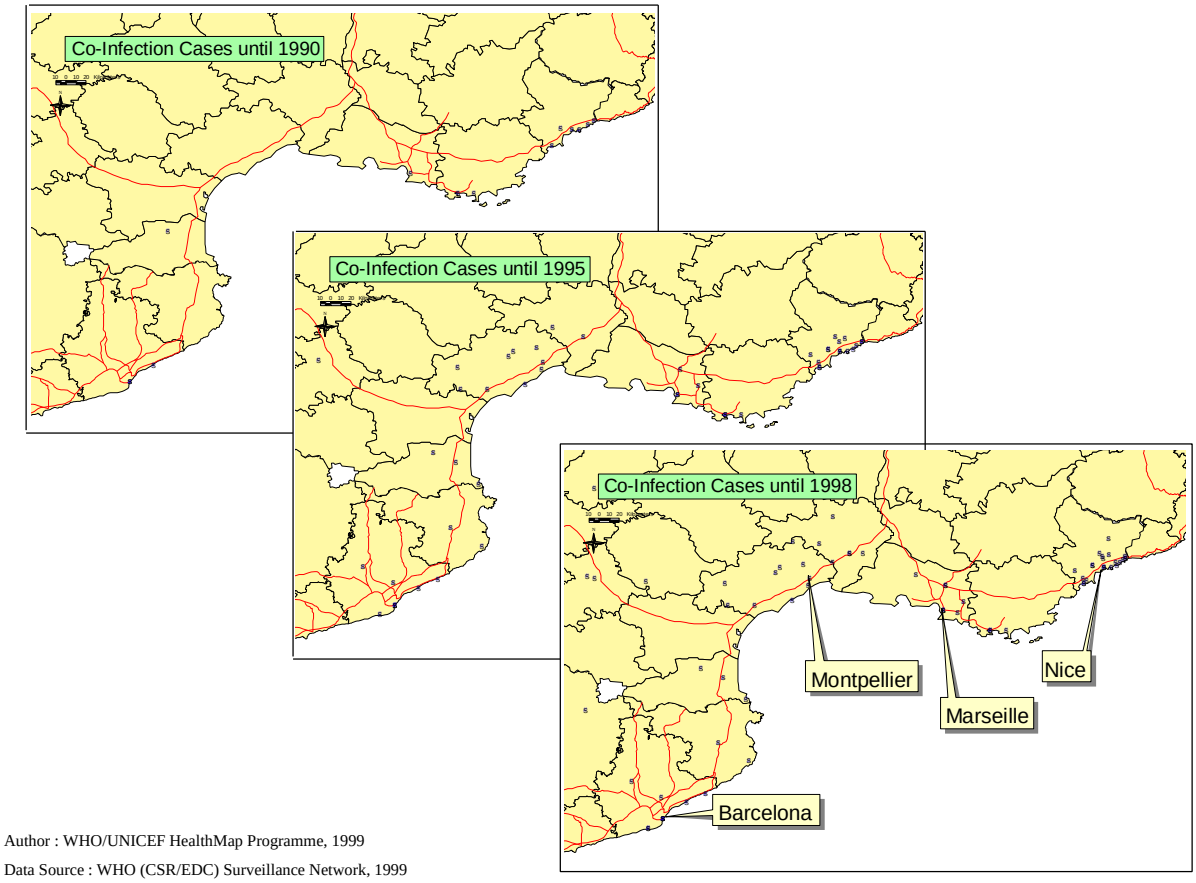


In south-western Europe, approximately 80 % of the cases are from urban areas: the main cities are Lisboa and Porto in Portugal, Barcelona, Granada, Madrid and Sevilla in Spain, Montpellier, Nimes, Marseille, Cannes and Nice in France, Genoa, Milano and Catania (Sicily) in Italy. Most of the cases are reported from the most populated departments and provinces, and there is a predominance of cases in coastal areas (75%). This pattern of distribution seems directly related to the epidemiology of both diseases: geographic distribution of sandfly species vectors of

leishmaniasis, and major incidence in urban areas for HIV/AIDS. It may also be related to the current location of the surveillance centres,which suggests that, although some regions have not reported any cases, for example the Spanish coast between Barcelona and Andalucia, cases probably do exist. In order to get a better idea of the geographic distribution of *Leishmania*/HIV co-infection, more institutions should be included in the network of surveillance.

The spatial pattern of co-infections has been mapped for southern France and north-eastern Spain (Map 4).

Map 4: Spatial evolution of co-infection cases in southern France and north-eastern Spain:

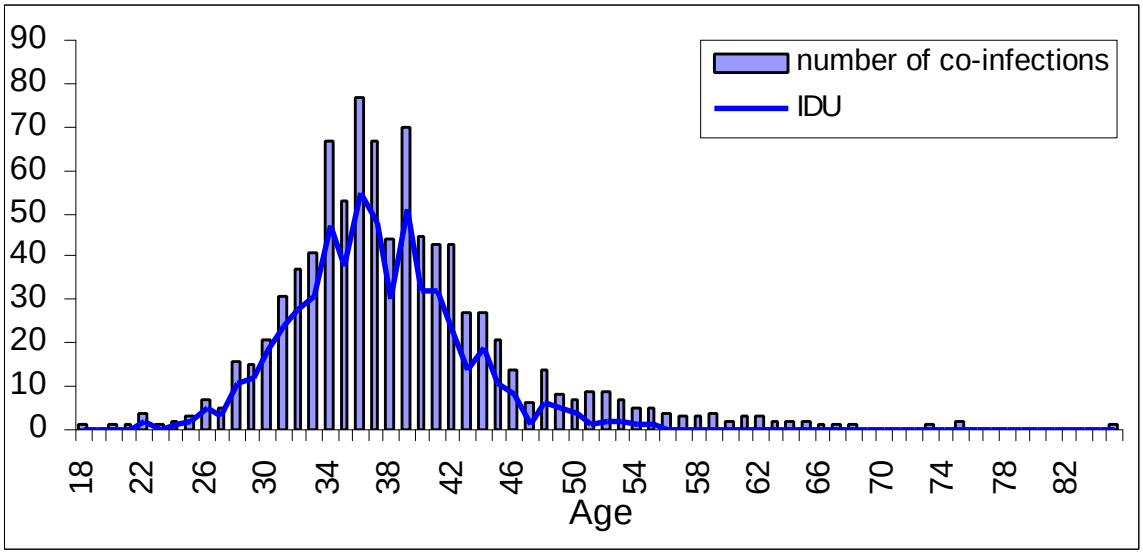


Until 1990, only a few cases were reported and almost exclusively from Provence-Côtes d'Azur. During the second period, up to 1995, cases were recorded from Languedoc-Roussillon and in the area of Barcelona. Simultaneously the distribution became progressively more rural and more widely distributed. Finally during the third period up to 1998, this pattern of distribution was confirmed. It reflects the increased geographic overlap between both diseases but it has also been influenced by the implementation of the WHO/UNAIDS surveillance network established in 1994-1995.

4.2 Age distribution

There have been major epidemiological changes in VL patterns in Europe in recent years. In south-western Europe, VL was traditionally a childhood disease, whereas today the co-infection mainly strikes adults : 76.9% of co-infected patients are aged between 31 and 50 years. The age distribution of co-infected patients is consistent with that of intravenous drug users (Figure 1). Compared to our previous analysis (WHO/LEISH/96.39), the mean age has risen slightly.

Fig.1: Age distribution of co-infection patients and intravenous drug users



4.3 Sex distribution

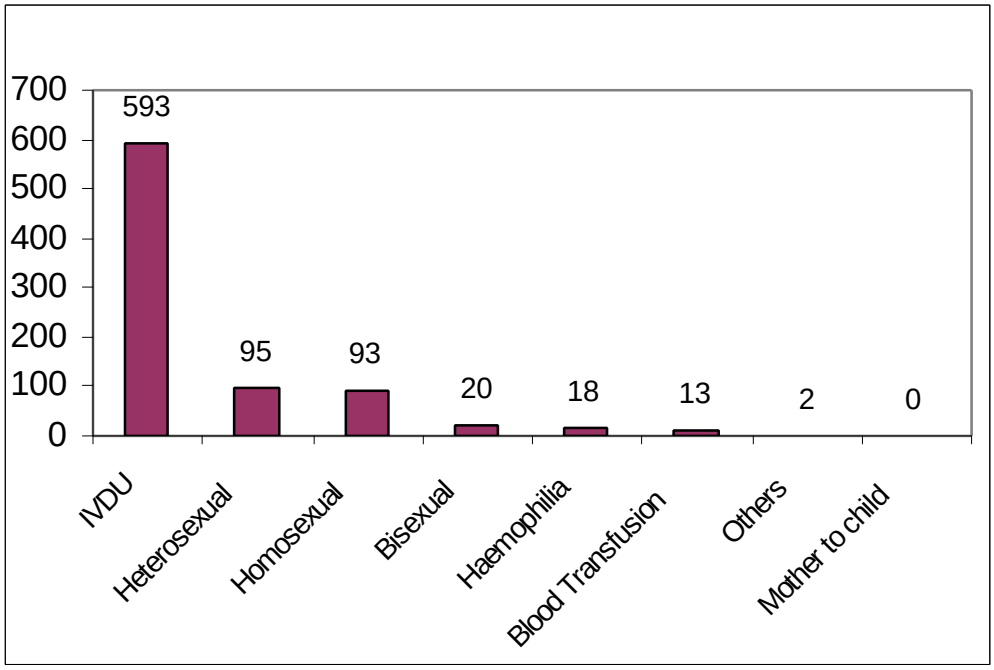
Most of the patients (83.2%) are males, which is consistent for all age groups.

4.4 Population at risk

In south-western Europe, there is a clear predominance of intravenous drug users (IDU) among the co-infection cases (593/965) (71.1%) who are the main population at risk (Figure 2). When data obtained from co-infection cases are compared to those from HIV/AIDS (Table 1), it is clear that the proportion of IDU among the co-infection patients is almost the same from country to country but that the proportion of these patients is higher than in HIV/AIDS cases in the same countries especially in France and in Portugal.

Globally the proportion of homosexuals (93/965) (11.1%) is almost the same as that of heterosexuals (95/965) (11.4%), but at country level there are significant differences. In contrast with IDU, these two risk groups are less important in co-infection cases than in HIV/AIDS patients.

Figure 2: Distribution by risk group of *Leishmania*/HIV co-infection, south-western Europe, 1990-1998



4.5 Immunological status/opportunistic diseases

AIDS increases the risk of VL by 100-1000 times in endemic areas. Moreover, a person with HIV infection whose immune system is suppressed, and who is bitten by a sandfly infected with *Leishmania*, will develop severe leishmaniasis. VL, once developed in the HIV-infected person, accelerates HIV replication and impairs the patient's condition by further immunosuppression. As a consequence, most of the patients (91.5%) have less than 200 CD4/mm3 (Table 3). The subject quickly becomes an AIDS patient with opportunistic diseases such as tuberculosis, candidiasis, pneumonia due to *Pneumocystis carinii* or toxoplasmosis (Table 2).

Table 2: CD4 rates, patients with *Leishmania*/HIV co-infection, south-western Europe, 1990-1998

CD4	Number	Percentage
< 200/mm3	624	91.50
200 to 499/mm3	51	7.47
> 500/mm3	7	1.03
total	682	100

Table 3: AIDS-defining diseases in patients with *Leishmania*/HIV co-infection, south-western Europe, 1990-1998

Aids-defining diseases		Number
A	Tuberculosis	136
B	Oesophageal candidiasis	118
C	Pneumocystes carinii	96
D	Toxoplasmosis	68
E	Retinitis CMV	38
F	Kaposi	36
G	Cryptosporodiosis	14
H	Cryptococcosis	10
I	Lymphoma	10
J	Herpes	5
K	Leucoencephalopaty	4
L	Syphilis	2
M	Sarcoidosis	1
	Not specified	576

4.6 Clinical diagnosis

The diagnosis of VL in *Leishmania*/HIV co-infected patients is particularly difficult. The usual clinical features of VL such as fever, weight loss, and swelling of the liver, spleen and lymph nodes, are not always present or may be hidden by other associated opportunistic infections with similar symptoms. However most of the co-infected patients who participated in the study (84.9%) showed the usual clinical features (Table 5).

Patients infected with HIV and who have fever, swelling of the spleen, liver or lymph nodes, and anaemia, should have their travel history checked for any visits to areas where leishmaniasis is endemic.

Table 4: Clinical features, patients with *Leishmania*/HIV co-infection, south-western Europe, 1990-1998

Clinical features	number	%
Visceral - typical	736	84.89
Visceral - atypical	82	9.46
Cutaneous	36	4.15
Others	6	0.69
Mucocutaneous	4	0.46
Mixed	3	0.35
	n = 867	

4.7 Serological diagnosis

There is a negative humoral response in 42.6% of co-infected patients. However, there are major differences between the tests and the laboratories. It is recommended to use 2 or more serological tests and antigens freshly prepared in the laboratory to increase sensitivity. Patients who develop VL after AIDS have difficulty building a humoral response (Figures 3 and 4).

Figure 3: Sensitivity of serology, 941 patients tested, south-western Europe, 1990-1998

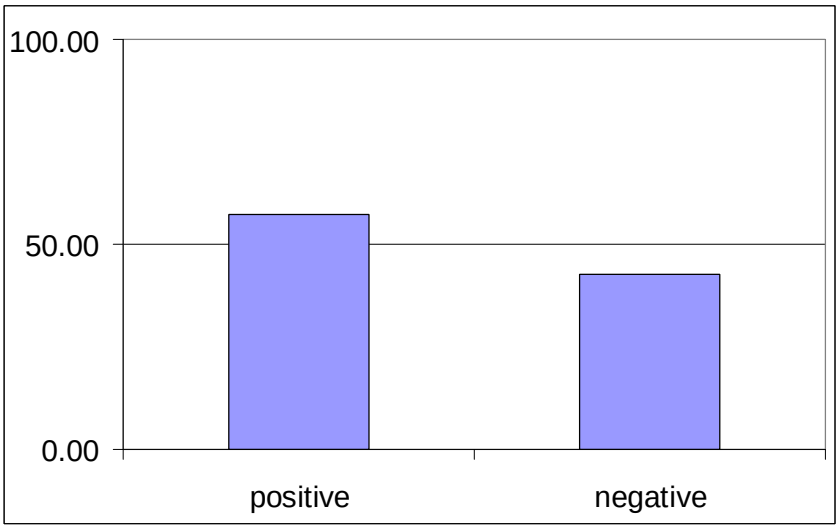
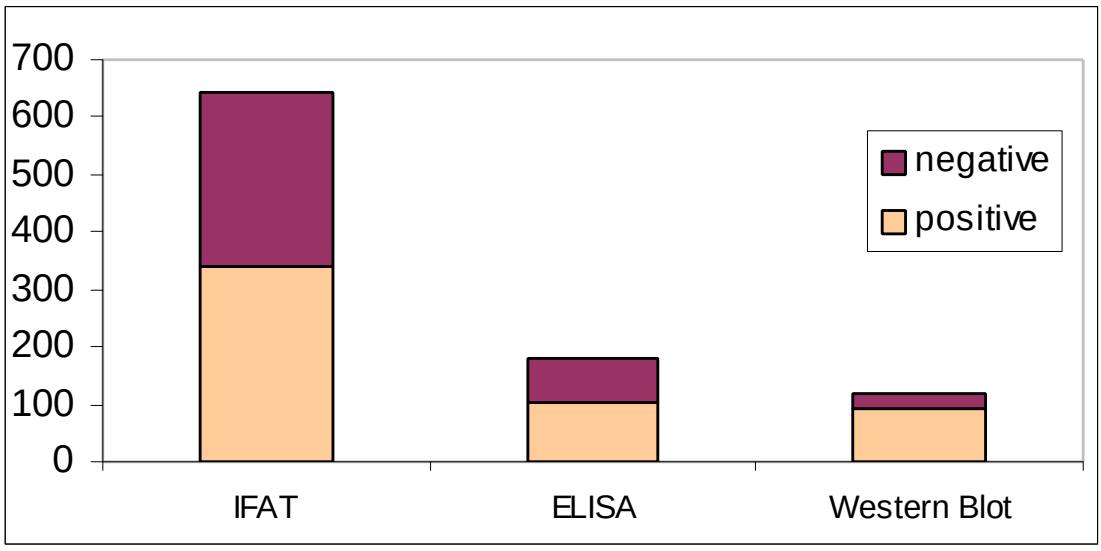


Figure 4: Main tests used for serological diagnosis, *Leishmania*/HIV co-infection, south-western Europe, 1990-1998

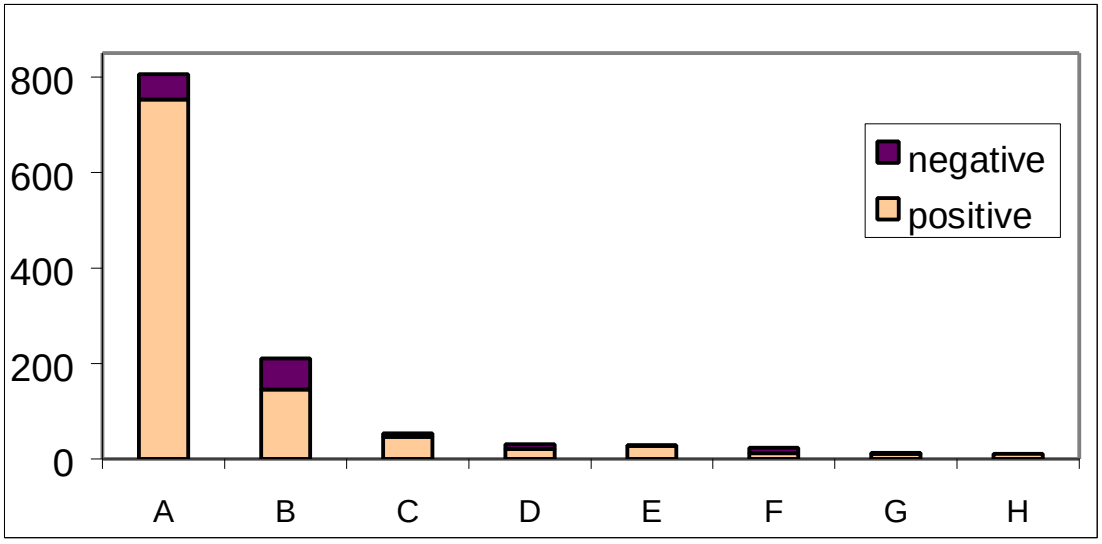


4.8 Parasitological diagnosis

Parasitological diagnosis through the detection of *Leishmania* in organs is crucial. Bone-marrow aspirate (BMA), especially when repeated and used during the first onset of the disease, is one of the most sensitive methods (93.5% in the study) (Figure 5).

The sensitivity of the method can be increased, especially for treated patients or during relapses, if BMA is cultivated. The frequency of *Leishmania* in the peripheral blood is particularly noticeable. Buffy-coat staining and culture increase sensitivity. Leukocytoconcentration is considered as an easy, fast and inexpensive technique.

Figure 5: Main tests used for parasitological diagnosis, *Leishmania*/HIV co-infection, south-western Europe, 1990-1998



	test*	Total	Positive	pos.%	Negative	neg.%
A	Bone marrow	805	753	93.54	52	6.46
B	Blood	211	145	68.72	66	31.28
C	Skin	53	47	88.68	6	11.32
D	Liver	31	21	67.74	10	32.26
E	Gastrointestinal tract	29	28	96.55	1	3.45
F	Lymph nodes	24	12	50.00	12	50.00
G	Spleen	13	11	84.62	2	15.38
H	Pleural liquid	11	11	100.00	0	0.00
	*tests used at least 10 times					

5. Conclusion

In the future, the risk of co-infected patients, as carriers of *Leishmania* in the blood, should be carefully taken into consideration as a source of infection for the sandfly during the blood meal. In addition intravenous drug users should also be considered as they transmit contaminated blood through the sharing of needles. As a result, the distribution of co-infection cases may no longer be restricted to endemic areas and it is anticipated that co-infection will spread. This is illustrated by the recent report of the first cases from Albania. The evolution of *Leishmania*/HIV co-infection should be closely monitored by extending the geographic coverage of the surveillance network and by improving the case reporting. An active medical surveillance of the main population at risk (IDU) should be encouraged.

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