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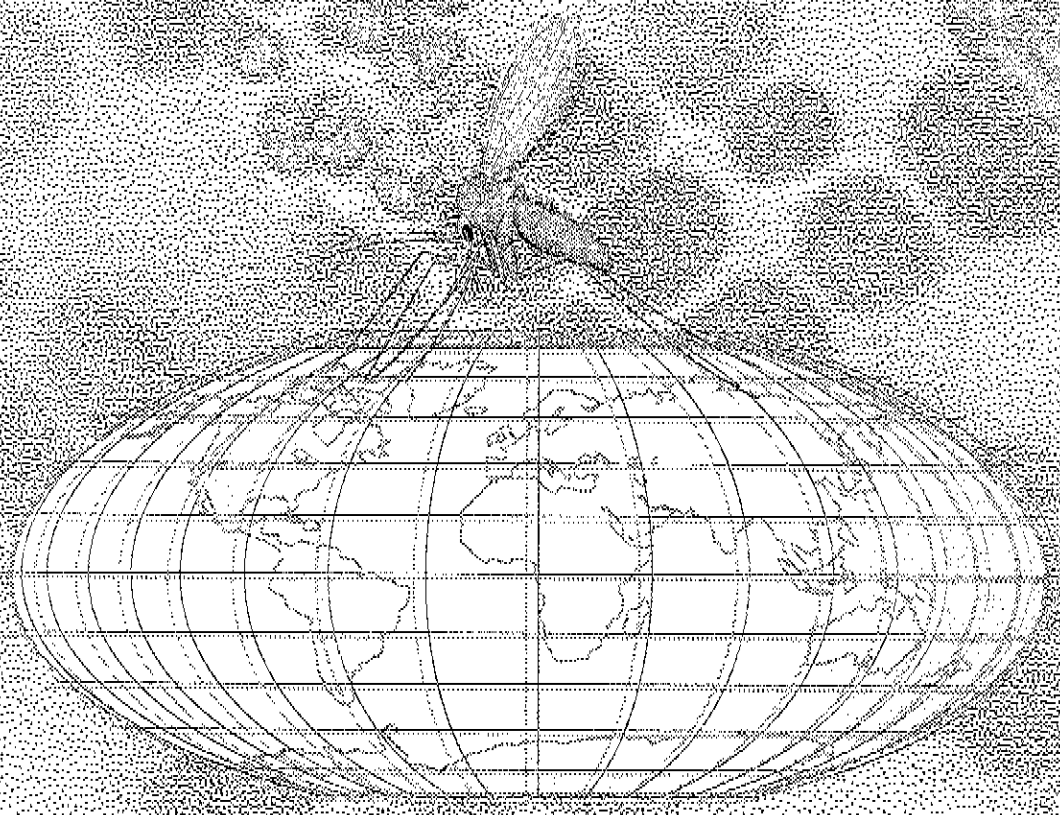
LEISHMANIA / HIV CO-INFECTION



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REPORT ON THE CONSULTATIVE MEETING ON *LEISHMANIA*/HIV CO-INFECTIONS CO-SPONSORED BY THE ISTITUTO SUPERIORE DI SANITA AND THE WORLD HEALTH ORGANIZATION, ROME, 6-7 SEPTEMBER 1994

The meeting was opened by Dr G. Majori, Director of the Department of Parasitology of the Istituto Superiore di Sanitá (ISS) on behalf of Dr G. Vicari, Director General of ISS, who welcomed all participants.

Dr P. Desjeux of the Division of Control of Tropical Diseases, Trypanosomiasis and Leishmaniasis Unit (CTD/TRY), WHO/Headquarters, Geneva, gave figures highlighting the spread of the AIDS pandemic in the world as a whole, where there are roughly estimated to be 4 million AIDS cases and 17 million HIV positive subjects in 1994. And more particularly in Asia, where more than 1.5 million people are currently infected with HIV and AIDS cases are increasing dramatically (30,000 in 1992; 250,000 in 1993). The current situation in Asia is similar to that in Africa ten years ago.

Visceral leishmaniasis (VL) is spreading in several areas of the world owing to epidemiological changes, such as urbanization in Brazil, or to mass migrations as in the Indian subcontinent.

Overlapping of the two diseases is also increasing sharply and ***Leishmania***/HIV co-infections are being reported more and more frequently. **It is estimated that in southern Europe between 25 and 70% of adult VL cases are related to HIV and 1.5 to 9% of AIDS cases suffer from newly acquired or reactivated VL.** On the other hand, the number of VL cases in immunocompetent patients remains relatively stable. That is why ***Leishmania***/HIV co-infections are now among the priorities for CTD. Anticipating an increase in the severity of the problem, WHO wants to take timely action to deal appropriately with this situation.

The main objectives of the meeting were emphasized, as follows: to evaluate the real extent of the problem and identify the main populations at risk; to issue guidelines for diagnosis and treatment; to set up a network of institutions that can promote systematic detection of both infections and improve the management and follow up of co-infected patients; to set up in CTD at WHO Headquarters a central registry to centralize, analyze, and

periodically rediffuse the basic epidemiological information concerning *Leishmania*/HIV co-infections; and, finally, to secure the recognition of VL as an AIDS-defining disease.

Dr G. Rezza, Director of the AIDS Unit in ISS, spoke on the current status and trend of HIV infection, explaining its chronic and multi-stage nature and how all risk groups are now showing an identical progression to AIDS. He highlighted the particular situation of HIV infection in Italy, where so far 23,000 AIDS cases have been reported. Finally he provided some information on the modification of the transmission pattern (heterosexual behaviour becoming progressively more important).

Speaking of the current status and trends of the leishmaniases, Dr P. Desjeux explained the extreme diversity and complexity of the epidemiological entities around the world. He provided a worldwide overview noting that out of 88 leishmaniasis endemic countries, 72 of these are developing countries, of which 13 are among the least developed. The increase in the number of cases and the wider geographical distribution currently observed seem to be related to environmental and economic development factors bringing non-immune people into contact with the zoonotic cycle, for example through mass migrations, man-made environmental changes, building of dams, urbanization, reduction of insecticide spraying for malaria and the emergence of new immunosuppressive factors such as HIV infection.

Only 30 countries list leishmaniasis as a compulsorily notifiable disease. The overall prevalence of the leishmaniases is estimated at 12 million cases, with 0.5 million new VL cases per year, and 1 to 1.5 million new cutaneous leishmaniasis (CL) cases per year. The population at risk totals 350 million and the DALYs (disability-adjusted life years) lost are estimated at 2,060,000 (World Development Report, 1993).

Zoonotic cutaneous leishmaniasis (ZCL) is mainly associated with sylvatic transmission cycles requiring animal reservoirs. New irrigation schemes, together with climatic changes in countries such as Senegal, Saudi Arabia or Tunisia have led to rodent pullulation and epidemics of ZCL in human populations. In some areas of Morocco rodents have become adapted to eating human garbage (synanthropism), increasing the risk of leishmaniasis transmission.

For anthroponotic cutaneous leishmaniasis (ACL), most foci are urban and the number of cases is growing at an ever higher rate, for example in Aleppo (Syria), Kabul (Afghanistan), Bam (Iran) etc. *Leshmaniasis recidivans* CL cases, being infective for sandflies, act as an important residual reservoir between epidemics of ACL.

Zoonotic visceral leishmaniasis (ZVL) which is normally rural, has recently been identified in the suburbs of cities, such as Bahia, Joa Pessoa, Natal (Brazil) sharply increasing the risk of transmission. The epidemiology of VL in southern Europe was moving away from infantile VL even before the HIV epidemic and this trend has continued: in some areas of France and Italy about 50% of HIV negative cases are now adults.

Anthroponotic visceral leishmaniasis (AVL) occurs in the Indian subcontinent and East Africa. An epidemic situation has been reported from Bangladesh owing to a four-year

interruption of DDT spraying, as also in north-eastern and southern Sudan owing to war and cumulative risk factors. In Bombay "sex workers", many of whom are Nepalese, frequently become HIV positive (25 % after 3 years), and then return to Nepal where VL is endemic (the low plains of Terai). WHO is concerned at the risk that will be posed by the increasing overlap between ***Leishmania*** and HIV infections in those countries.

Dr L. Gradoni (ISS), reviewed the literature on ***Leishmania***/HIV co-infections. The fact that out of the 443 cases published by early 1994, 403 were from Mediterranean countries, including 245 in Spain, may be due to good case-finding, a high degree of overlap and the markedly opportunistic behaviour of ***L. infantum***. Out of 412 cases, 72% occurred in AIDS patients and 28% in asymptomatic HIV positive subjects. Thus, leishmaniasis should be considered as an AIDS-defining disease. Of the 443 patients, 429 (97%) had VL and 36 patients (8%) also had skin, gastric, rectal, pulmonary or laryngeal involvement. Only 14 patients (3%) had limited lesions: CL (10), MCL (2), rectal (1) and laryngeal (1). Serology was positive in 53% of the co-infected patients, compared with over 90% in immunocompetent subjects. Treatment with antimonials, alone or in combination, was administered to 96% of the patients and 4% received other drugs.

Pathological and clinical aspects were reviewed by Spanish physicians : Dr C. Montalbán and Dr R. López-Vélez from Madrid, Dr A. Salas from Majorca and Dr J. Medrano from Seville. They highlighted the various possible causes of immunosuppression other than HIV, including haematological diseases, corticoid therapy, organ transplants, and autoimmune diseases. Most of the co-infected cases (about 70%) were associated with intravenous drug use and the rest with homosexual behaviour (20%), heterosexual behaviour (8%) and haemophilia (2%). It was noted that intravenous transmission could be of major importance among drug abusers, but reactivation of latent infection has to be taken into consideration for other population groups at risk. The average age of the patients is about 30 years and the male/female ratio is 8:1. **It was reported that in Spain, as also in France, 1.5 to 9% patients meeting the definition of AIDS have newly acquired or reactivated VL. Between 25 and 70% of VL adult cases are related to HIV infection.** Clinically the major manifestations are fever (95%), splenomegaly (92%) and hepatosplenomegaly (80%); biologically, pancytopenia is very common, and immunologically CD4 values are below normal (77 to 90% of patients had fewer than 200 lymphocytes per cubic mm, 7 to 22% had 200 to 500, and 0 to 3% had more than 500).

The mean survival time of co-infected patients under treatment is 12 months. At the two extremes, Dr López-Vélez added, a third of the patients die during or within a month of the first episode, and 16% are still alive 3 years later.

Dr J. Alvar, from Madrid, reviewed the status of laboratory diagnosis. Serology in VL/HIV co-infection shows 20 to 40% less sensitivity than in immunocompetent VL patients; it therefore has partial value. Among the different serological techniques, Dot-ELISA seems to be more sensitive (78%) than IFAT (68%). In parasitological diagnosis, bone marrow aspirate (BMA) is of major value since BMA staining shows a sensitivity of 94% in the first episode and 64% in relapses. BMA is needed not only for diagnostic purposes but also in epidemiological studies for further characterization of the parasite. When BMA culturing is done in NNN medium, the sensitivity increases even more. However, BMA is an invasive

method difficult to perform in relapses. There is a need for alternative non-invasive diagnostic techniques, such as blood samples. By simple smear staining, 50% of the co-infected cases can be detected, and even more (70%) when white cells are cultivated in NNN medium. Indirect xenodiagnosis by using colonized sandflies, under the strict conditions of security necessary when manipulating infectious material, can resolve the diagnosis of some difficult cases, as it is an extremely sensitive technique owing to the constant presence of parasites in the peripheral blood. Dr F. Faraut-Gambarelli, from Marseille, reported findings as to the efficacy of PCR in the diagnosis of 73 immunocompromised patients, including 70 with HIV infection and 10 with proven visceral leishmaniasis. This technique has high sensitivity but false positives are seen. PCR on bone marrow aspirate becomes negative on treatment but reverts to positivity in relapse cases. Professor M. Portús reported on the diagnostic value of three polypeptide fractions of 72, 75 and 123 KDa detected in the urine of 24 patients with HIV/VL co-infection : at least one fraction was always found in parasitologically and/or serologically confirmed VL patients.

Dr R. Russo (Italy), emphasized the main objectives of treatment in immuno-compromised patients, namely : clinical and parasitological cure, prevention of relapses and minimization of drug side-effects. It is generally accepted that in such patients treatment failure, unresponsiveness related to drug resistance, and drug toxicity are more frequently observed. In follow-up studies after treatment with meglumine antimoniate at a dosage of 20 mg/sb5^{+}/kg/day for 28 days or even longer, several authors concurred in recording a positive response in 83% of cases, 16% of the patients failing to respond at all, and 52% relapsing (from one to four times between one month and 36 months after treatment). Acute disease is considered a dangerous syndrome. Clinical response is difficult to achieve because of the presence of other opportunistic infections, adverse events, persistent VL, HIV infection, and atypical clinical presentation of VL. The reasons for failure are lack of synergy between medicament and cellular immunity, high parasite loads, unusual host cells and primary drug resistances. Among alternative drugs suggested were pentamidine at 4 mg/kg/day on alternate days for 4 to 11 weeks, and amphotericin B at 0.5 to 1 mg/kg on alternate days for 4 to 8 weeks, both drugs, however, showing high toxicity. Amphotericin B encapsulated in liposomes at 1.5 mg/kg/day for 21 days or 3-4 mg/kg/day for 10 days resolves most of the side-effects, though relapses still occur and the drug remains extremely expensive. As regards aminosidine, allopurinol, azoles, INF-gamma, etc, their efficacy needs to be evaluated more thoroughly. Maintenance therapy for life, to prevent relapses, has been suggested by administering pentavalent antimonials at a dose of 850 mg of antimony monthly, pentamidine every two weeks (2 mg/kg) or monthly (4 mg/kg), allopurinol daily (300 mg total), amphotericin B in liposomes every 15 days (3 mg/kg), or itraconazol daily (400 mg total dose). In the current unsatisfactory chemotherapy situation, the most important objectives are to maintain a good quality of life for the patients, prevent relapses and avoid life-threatening infections. Multicentre randomized drug trials using different multitherapy schedules are needed.

The identification of ***Leishmania*** isolated from co-infected patients was reviewed by Dr M. Gramiccia from the ISS in Rome. She provided information on the different techniques currently used and their respective levels of definition, isoenzyme characterization being the most widespread method and regarded as the "gold" standard. So far, several species have been identified from immunocompromised patients, in particular ***L. infantum*** (122 typed strains from 133 reported) and much less frequently ***L. braziliensis***, ***L. donovani***, ***L. tropica***

and ***Leishmania sp.*** With regard to ***L. infantum***, information was provided from several countries, all having in common a higher variability of zymodemes among co-infected patients. Zymodeme one (MON-1) is reported in 65% of samples and 13 other zymodemes in percentages ranging from 1 to 9%. Eight zymodemes never isolated from HIV negative patients have already been identified. Possible explanations of these results could be exacerbation of some non-virulent zymodemes, recombination among certain zymodemes or transmission of such zymodemes by syringes.

*Table - **L. infantum** zymodemes in co-infected patients and geographical distribution (information provided by M. Gramiccia, J. P. Dedet, M. Portús, J. Alvar and P. Abranches).*

	Algeria	France	Italy	Portugal	Spain	Tunisia
MON-1	✓	✓	✓	✓	✓	✓
MON-18				✓		
MON-24	✓	✓	✓	✓	✓	
MON-28					✓	
MON-29		✓	✓		✓	
MON-33		✓	✓		✓	
MON-34			✓		✓	
MON-77					✓	
MON-78	✓		✓			
MON-136			✓			
MON-183		✓			✓	
New zymodemes without definitive codes *			✓			
*			✓			
*					✓	

Dr L. Gradoni, reviewing different surveillance methods, emphasized the difficulties of VL surveillance in immunocompetent people : the diagnosis is sometimes not easy, VL is compulsorily notifiable in only 30 out of 88 endemic countries and, finally, the notification system is frequently inadequate. Surveillance in immunocompromised people is even more problematic: diagnosis is more difficult, "unusual" medical institutions are involved and, as it is not yet an "official" opportunistic infection, VL is rarely reported in AIDS notification systems. He stressed the value of active medical surveillance, which allows the detection of a more realistic number of patients; for example, in Campania, Italy, from 1991 to 1994, 42 VL cases were notified by active surveillance and only three by passive case detection; during the same period, 88 cases of co-infection were notified by active surveillance and only

21 by passive detection. Good medical surveillance implies adequate financial support, competent scientific institutions at regional or national level, an effective communication network and a high-quality diagnostic service. Active medical surveillance is usually based on retrospective and prospective studies.

The second part of the meeting was devoted to reviewing the *Leishmania*/HIV co-infection situation country by country.

Dr L. Gradoni explained the uneven distribution of leishmaniasis foci in **Italy**, the north of the country, which is free of that disease, being precisely where most of the cumulative total

of AIDS cases occur. Moreover, transmission of HIV is urban and that of VL rural and periurban, so the two diseases do not overlap extensively, though migration increases the risk. In all, 98 VL/HIV co-infections have been detected in Italy, but only 24% of this total have been notified in AIDS reports. Thirty-one of these co-infections occurred in Sicily, where the estimated population at risk of leishmaniasis is over 40% and the cumulative total of AIDS cases per 100,000 inhabitants (1982-1993) is between 10 and 20. From what is known of the incidence/ prevalence of HIV and VL, it appears that the majority of co-infection cases are new infections rather than reactivations.

In **southern France** three areas are of major interest. For Languedoc-Roussillon information was provided by Professor J.P. Dedet, from Montpellier. Between 1983 and 1993, among the 2,110,000 inhabitants living in this area, 952 AIDS cases were reported, giving a prevalence of 458 per million, 4,500 HIV positive subjects were also notified. Between 1989 and 1993, 25 VL cases were detected, including 10 (40%) co-infected, all in adults. Over the same period 139 HIV subjects with unexplained fever were notified; consequently, a 7.2% rate of co-infection is estimated for this area. In the Marseille area, over the period 1993-1994, Dr Faraut-Gambarelli recorded 29 cases of VL, including 21 in co-infected patients (70%) and 8 cases of VL only (7 children and one renal transplant patient). For the Alpes-Maritimes, Dr P. Marty reported on the epidemiological situation: 1,000,000 inhabitants, 1,718 cases of AIDS and 26 cases of co-infection (a 1.5% co-infection rate). 70% of all VL cases were adults, and among them 32% were HIV positive.

The VL/HIV co-infection situation in **Spain** was reported by several participants. Professor M. Portús, from Barcelona, reviewed the information from 12 hospitals in Catalonia which, during the period 1986-1993, recorded 3,617 AIDS cases, representing 70% in that region, and including 83 co-infection cases (66 in intravenous drug users) giving a 2.3% ratio. She estimated the real figure as 145 co-infected patients for the whole of Catalonia. Dr A. Salas, from Majorca, reported on a retrospective study of 30 co-infected patients among 362 AIDS cases, which represents a ratio of 8.2% (67% of the co-infected cases being in intravenous drug users). Dr J. Alvar reported the figures for Madrid and Castilla-La Mancha. Madrid, with almost 4 million inhabitants, had 6,532 AIDS cases as of March 1994, and 143 co-infected cases - a ratio of 2.2%. Castilla-La Mancha, with 1.9 million people, has 360 AIDS cases and 13 known co-infected patients, which represents a ratio of 3.3%. Dr J. Medrano, from Seville, reported the experience of three hospitals in

Andalusia where 550 AIDS cases have been recorded: 50 co-infected patients are known (a ratio of 9%) and 70% of adult VL cases are HIV positive. In a prospective study carried out in his hospital between 1990 and 1994, 67 cases of co-infection were recorded out of 450 AIDS cases. The present situation regarding co-infection in Spain is of major concern since most of the cases reported occur there.

The epidemiological situation in **Portugal** was reviewed by Professor P. Abranches who noted that there are three major foci : Alto Douro, Lisbon and Algarve. The traditional pattern of Mediterranean VL, affecting mainly children (80%) still prevails there, in contrast with Spain. Professor F. Antunes gave the basic information on co-infection in Portugal : from 1983 to 1994, 1,958 AIDS cases were notified, mainly from the Lisbon area (57%), while over the same period 26 cases of co-infection were reported for the whole country, but 73% of them from the Lisbon area. Among the 26 co-infected cases, 24 were VL and 2 combined VL and DCL.

Professor M.S. Ben Rachid provided the information for **Tunisia,** where VL is still a children's disease with an average of 200 new cases per year. Between 1986 and 1994, 488 HIV/AIDS cases have been reported, 78% in intravenous drug users and 32% in heterosexuals. In a serological study, 28 out of 132 HIV seropositive samples (21%) were positive for leishmaniasis but only two were parasitologically proven as co-infection cases.

Professor C.P. Thakur (**India**), reported the situation in Bihar State where there is an average of 250,000 new VL cases per year. No co-infection has been reported yet owing to the absence, so far, of overlapping between the two infections (AIDS is restricted to urban areas like Madras, Calcutta and Bombay). With an increasing number of drug abusers and mass migrations there is a potential risk for the near future.

Co-infection in **Brazil** was reported on by Dr R. Badaró, who noted that the incidence of AIDS had risen from 4.3 cases per 100,000 inhabitants in 1986 to 18.4 in 1994. In the period 1980 to 1993, 224,000 leishmaniasis cases (80% in the northern and northeastern regions) and 51,942 AIDS cases (70% from Sao Paulo and Rio de Janeiro, in the south) were officially reported. While there is not as yet any marked overlapping of the two infections, fast urbanization of VL in Brazil has been demonstrated (Bahia, Natal, Pará, Paraiba, Sao Luis, Rio de Janeiro and Teresina States) and simultaneously ruralization of HIV transmission is reported in the same areas, creating a real risk. In a prospective study 25 VL/HIV co-infections (17 of them proved) have been put down to ***L. brasiliensis***, ***L. amazonensis*** and *L. chagasi* with different clinical patterns (CL, DCL, MCL, VL) but all with bad prognoses