LEISHMANIA & HIV
IN GRIDLOCK

UNAIDS
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Division of Control of Tropical Diseases (CTD)
World Health Organization (WHO)
www.who.ch/ctd
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LEISHMANIASIS IN THE WORLD

For many years, leishmaniasis has been grossly underestimated. Since 1993, it has become apparent that the disease is much more prevalent than previously suspected, with the risk that it will even increase in the future. There is evidence in many countries that urbanization, agricultural development, deforestation, irrigation and more recently HIV, contribute to increased transmission and spread of this disease. There is evidence too that infection with the HIV virus increases the risk of getting leishmaniasis, makes the disease worse and reawakens a latent infection. The converse also occurs with leishmaniasis patients becoming more susceptible to HIV infection. The interaction between the visceral form of leishmaniasis and HIV is rapidly deadly.

Leishmaniasis is found in five continents and is endemic in the tropical and subtropical regions of 88 countries. The geographical distribution of leishmaniasis is limited by the distribution of the sandfly, the carrier of the disease, its susceptibility to cold climates, its tendency to take blood from humans or animals only, and its capacity to support the internal development of specific species of Leishmania. There are an estimated 12 million cases worldwide. Two million new cases occur each year and 350 million people are at risk.
Its Transmission

Leishmaniasis is a parasitic infection transmitted naturally by the bite of an infected female sandfly. There are about 30 species of sandflies in the genera Phlebotomus and Lutzomyia, which can transmit at least 20 different species of Leishmania parasites. The sandfly becomes infected when taking blood from a reservoir host, which may be a human or an animal such as a dog or rodent. This disease can also be transmitted directly from person to person through the sharing of needles, as is often the case among injecting drug users in HIV co-infections.

The cutaneous forms

Cutaneous leishmaniasis is known as “little sister” in countries where the disease is so common that it is part of the family. It produces skin lesions, sometimes as many as 200 on the face, arms and legs, causing serious disability and permanent scars. Ninety percent of the cases occur in Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia and Syria.

The diffuse cutaneous form is less common, chronic in evolution and especially difficult to treat. It produces lesions resembling leprosy, which do not heal spontaneously. There is systematic relapse after treatment, due to deficiency of the immune response.

The mucocutaneous form, also called “espundia” in South America, produces disfiguring lesions to the face, destroying the mucous membranes of the nose, mouth and throat. Most cases of this type (90 percent) are found in Bolivia, Brazil and Peru.

Its Clinical Forms

The disease can present itself in man in four different forms, all with devastating consequences: cutaneous, diffuse cutaneous, mucocutaneous, and visceral. The cutaneous forms are the most common (1.0 to 1.5 million cases per year), representing 50 to 75 percent of all new cases. Visceral leishmaniasis (500,000 cases per year), is the most fatal if untreated, particularly in cases of co-infection with other diseases, such as AIDS.
The visceral form

Visceral leishmaniasis, also known in Asia as “black fever” or “kala azar,” is the most severe and if untreated, usually fatal. It is characterized by irregular fever, substantial weight loss, swelling of the liver and spleen, and anaemia. After recovery, patients sometimes develop chronic cutaneous leishmaniasis and require long and expensive treatment. Ninety percent of visceral cases in the world are in Bangladesh, Brazil, India, Nepal and Sudan.

The visceral form is currently gaining ground, owing to epidemiological changes, such as rural to suburban migration in north-eastern Brazil, and inter-country mass population movements (refugees, returnees and seasonal workers), as in the Horn of Africa. The biggest focus in the world is in eastern India, where almost all districts of Bihar State have been experiencing a pre-epidemic situation with an estimated 200,000 new cases each year. Southern Sudan is another area of concern; with a population of less than one million, there were 100,000 deaths from 1989 to 1994. Also, since September 1997, a severe epidemic has been raging in Gedaref State, in eastern Sudan, with one treatment centre reporting an average of 700 cases per month.

Its Treatment

Accurate parasitological diagnosis is essential in leishmaniasis to determine the correct treatment, which is often difficult and of long duration. Some infections, especially simple cutaneous lesions due to *L. major*, are often self-healing and induce immunity to reinfection. Owing to the cost and possible toxicity of the available drugs, treatment of these is generally not recommended unless the lesions do not heal within 6-9 months or are facially disfiguring. There is a need for a simplified treatment regimen suitable for outpatient use. Other forms, such as visceral and mucocutaneous infections, can incapacitate, mutilate or kill. First-line treatment relies on the pentavalent antimonial sodium stibogluconate or meglumine antimoniate, which are expensive and need to be given by injection, often for several weeks. The second line drugs - amphotericin B and pentamidine, used in cases unresponsive to antimonials - need careful management to avoid serious side-effects. For visceral leishmaniasis, aminosidine, alone or in association with pentavalent antimonials, has shown good efficacy but it is still under evaluation. Amphotericin B, included in liposomes, has proven to be very efficient but its use is still limited and expensive.
Geographical Distribution of 90 Percent of Cutaneous Leishmaniasis in the World
Geographical Distribution of 90 Percent of Visceral Leishmaniasis in the World
People Living with HIV/AIDS, December 1997

Total: 30.6 million
HIV/AIDS IN THE WORLD

In December 1997, approximately 30.6 million people were living with HIV/AIDS, or one in every 100 adults aged 15-49 years. The sub-Saharan African region has the fastest growing epidemic, with 20.8 million people, or two-thirds of the total world number, with HIV infection or AIDS. Asia has lower infection rates but the epidemic is more recent, and is cause for concern due to the high-density populations. In India, where surveillance remains patchy, an estimated 3 to 5 million people are living with HIV.

While due in part to revised estimates, the HIV/AIDS situation in 1997 proved worse than the year before. 2.3 million people died of AIDS in 1997. 5.8 million people were infected during 1997, a rate of 16,000 infections a day. Ninety percent of the cases occurred in developing countries. About 10 percent were in children under 15 years of age. In western Europe, injecting drug users accounted for 44 percent of the cases of AIDS and HIV infection. If current trends continue, it is estimated that more than 40 million people will be living with HIV in the year 2000.

HIV is transmitted primarily through sexual intercourse, but also through blood, and from mother-to-child. Certain behaviour creates, enhances and perpetuates the risk of catching HIV such as unprotected sex with an infected partner, multiple unprotected sexual partnerships, transfusion with unscreened blood, and sharing needles and syringes, particularly among injecting drug users. More than a decade and a half since the beginning of the HIV/AIDS epidemic, many targeted interventions have helped prevent more persons becoming infected. These include increased information and education campaigns, promotion of condoms, prevention and early treatment of sexually transmitted diseases, needle and syringe exchange programmes among drug-injecting populations, increased safety of medical procedures, including blood transfusion in the health-care setting, as well as programmes to improve women's rights and other societal influences. While these prevention campaigns and vigorous research for a vaccine and cure continue, the epidemic remains, far from over.
### HIV/AIDS Geographical and Regional Statistics, December 1997

<table>
<thead>
<tr>
<th>Region</th>
<th>Epidemic started</th>
<th>Adults &amp; Children living with HIV/AIDS</th>
<th>Prevalence</th>
<th>% Women</th>
<th>Main mode(s) of transmission for those living with HIV/AIDS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>late '70s – early '80s</td>
<td>20.8 million</td>
<td>7.4%</td>
<td>50%</td>
<td>Hetero</td>
</tr>
<tr>
<td>South and South-East Asia</td>
<td>late '80s</td>
<td>6.0 million</td>
<td>0.6%</td>
<td>25%</td>
<td>Hetero – IDU</td>
</tr>
<tr>
<td>Latin America</td>
<td>late '70s – early '80s</td>
<td>1.3 million</td>
<td>0.5%</td>
<td>19%</td>
<td>MSM – IDU – Hetero</td>
</tr>
<tr>
<td>Established Market Economies*</td>
<td>late '70s – early '80s</td>
<td>1.4 million</td>
<td>0.3%</td>
<td>20%</td>
<td>MSM – IDU – Hetero</td>
</tr>
<tr>
<td>Caribbean</td>
<td>late '70s – early '80s</td>
<td>310 000</td>
<td>1.9%</td>
<td>33%</td>
<td>Hetero</td>
</tr>
<tr>
<td>Eastern Europe - Central Asia</td>
<td>early '90s</td>
<td>150 000</td>
<td>0.07%</td>
<td>25%</td>
<td>IDU – MSM</td>
</tr>
<tr>
<td>East Asia - Pacific</td>
<td>late '80s</td>
<td>440 000</td>
<td>0.05%</td>
<td>11%</td>
<td>IDU – Hetero – MSM</td>
</tr>
<tr>
<td>North-Africa - Middle East</td>
<td>late '80s</td>
<td>210 000</td>
<td>0.1%</td>
<td>20%</td>
<td>IDU – Hetero</td>
</tr>
</tbody>
</table>

* IDU: transmission through injecting drug use – Hetero: heterosexual transmission – MSM: men who have sex with men

* North America, Western Europe, Australia, New Zealand, Japan

UNAIDS

GE-98001/16 – 1 December 1997
(in millions)

- People living with HIV/AIDS: 30.6 million
- Deaths due to HIV/AIDS in 1997: 2.3 million
- Cumulative number of deaths due to HIV/AIDS: 11.7 million

New HIV Infections per day in 1997:

Age Distribution of New HIV Infections
- Age below 15: 10%
- Age over 24: 44%
- Age between 15-24: 46%

Sex Distribution of New HIV Infections
- Adult women: 41%
- Adult men: 59%
Annual Number of New HIV Infections Projected to the year 2000, in Selected Regions

- sub-Saharan Africa
- South & South-East Asia
- East Asia & Pacific
- Latin America & Caribbean
- Established Market Economies*

* Western Europe, North America, Australia, New Zealand, Japan

GE-98001/14 – 1 December 1997
EMERGING CO-INFECTION

The co-infection with *Leishmania* and HIV is emerging as a new and frightful disease and is becoming increasingly frequent. Cases have been reported in 25 countries and are currently considered an ominous threat in Spain, Italy, France, and Portugal. In these countries, up to 70 percent of adult cases of visceral leishmaniasis are associated with HIV infection and, up to 9 percent of people with AIDS suffer from newly acquired or reactivated visceral leishmaniasis. Cases have also been reported in Algeria, Brazil, Cameroon, Costa Rica, Djibouti, Ethiopia, Greece, Guadeloupe, Guinea-Bissau, India, Kenya, Malawi, Mali, Malta, Morocco, Panama, Peru, Sudan, Sultanate of Oman, Tunisia, Ukraine and Venezuela.

The number of cases of co-infection with *Leishmania* and HIV is expected to rise in South Asia, sub-Saharan Africa, South America and Southern Europe, owing to the simultaneous spread of both diseases and their increasingly overlapping geographical distribution - an urbanization of visceral leishmaniasis and a ruralization of HIV/AIDS. The incidence of AIDS in Brazil, for example, has risen from 4.3 cases per 100,000 inhabitants in 1986, to 18.4 in 1997. India is particularly vulnerable, with one-half of the world’s visceral leishmaniasis cases, and HIV/AIDS on a sharp increase. East Africa is also of great concern, with the continued spread of AIDS and sporadic epidemics of visceral leishmaniasis.
Countries Reporting Leishmania & HIV Co-infection
Areas of Increased Risk of Leishmania & HIV Co-infection

Europe
VL: 1,000 cases
HIV/AIDS: 530,000 cases

India
VL: 200,000 cases
HIV/AIDS: 3 to 5 million cases

Brazil
VL: 3,000 cases
HIV/AIDS: 600,000 cases

Sudan
VL: 5,000 cases
HIV/AIDS: 130,000 cases

VL: Incidence in 1997
THE CONCERNS

AIDS and visceral leishmaniasis are locked in a vicious circle of mutual reinforcement. Visceral leishmaniasis accelerates the onset of full blown AIDS, and shortens the life expectancy of HIV-infected people, while HIV spurs the spread of visceral leishmaniasis. The gridlock produces cumulative deficiency of the immune response, as Leishmania parasites and HIV destroy the same cells, exponentially increasing disease severity and consequences. A person with HIV infection whose immune system is suppressed and is bitten by a sandfly infected with Leishmania, will develop severe cutaneous leishmaniasis, or the visceral form. Visceral leishmaniasis, once developed in the HIV-infected person, impairs the patient’s condition by further suppressing more of the same immune response cells. As a consequence of this severe immunosuppression, the subject quickly becomes an AIDS patient with associated diseases, otherwise known as opportunistic diseases such as tuberculosis, often found in co-infected patients.

CASE STUDY

Case No. 1.

A blood sample from a patient with suspected Plasmodium falciparum malaria, sent to a laboratory, proved negative microscopically, and by immunofluorescent antibody test (IFAT). Serological tests for leishmaniasis were positive (IFAT titre: 1:160). A diagnosis of visceral leishmaniasis was confirmed by histological examination of a bone marrow smear. Because the patient was a male heroin addict aged 26 years old and had spent some time in endemic areas, he was tested for HIV infection. The serological tests for HIV were positive. The condition of the patient deteriorated and he died.

A 32 year old male bisexual dancer presented with a Kaposi's sarcoma lesion on the leg. He had been positive for HIV infection since 1986 and had recently been treated for an atypical pneumonia. He had travelled to several endemic countries over the past 10 years. On examination he had mild oral candidosis. A tender liver and spleen were palpable one cm below the costal margin. Routine biopsy of the Kaposi's lesion revealed typical Kaposi's sarcoma histology plus Leishmania amastigotes. Further investigations confirmed visceral leishmaniasis involving skin, bone marrow and spleen. The patient was treated with sodium stibogluconate and stilbgrubine. After 4 weeks, spleen aspirates became negative. The patient was treated for a further 3 weeks and at the time of discharge from the hospital, was well.
Difficult Diagnosis and Treatment

The diagnosis of visceral leishmaniasis in leishmania/HIV co-infected patients is particularly difficult. The usual clinical features such as fever, weight loss, swelling of the liver, spleen, and lymph nodes, are not always present and may be hidden by other associated opportunistic infections mimicking the same symptoms. In AIDS patients, moreover, the cells responsible for the immune response are severely destroyed, impairing the capacity of the immune system to react to the invasion of any new pathogen including Leishmania. Consequently, blood tests in the diagnosis of visceral leishmaniasis, are in more than 40 percent of the cases, falsely negative, especially at an advanced stage or during relapses, making the detection of Leishmania in biopsy material, all the more crucial. Patients infected with HIV and who have fever, swelling of the spleen, liver, or lymph nodes and anaemia, must have their travel history checked for any visits to leishmaniasis endemic areas. Similarly, patients with leishmaniasis, who are unresponsive to treatment, relapsing, or developing opportunistic diseases, should be checked for HIV.

The best that patients with co-infection can expect, is that their treatment will help them maintain a good quality of life and prevent relapses, or life-threatening infections. However, the treatment of leishmaniasis often fails. Failure is due to several factors including a destroyed immune response system, drug resistance, drug toxicity, and an over abundance of Leishmania in the digestive tract, skin, pleura, lung, brain, and other sites. Despite the use of polychemotherapy, relapses remain frequent - more than 50 percent compared to 10 percent in immunocompetent subjects. While most patients will die from AIDS-related causes (mainly opportunistic diseases), visceral leishmaniasis is considered a major contributor to the fatal outcome. It is the use of a combination of three different drugs (tritherapy) that has, however, improved the prognosis of HIV/AIDS patients, by reducing the virus load, increasing the number of cells responsible for the immune response and preventing the appearance of opportunistic diseases.
Changing Epidemiology in Europe

There have been major epidemiological changes in Europe in recent years that give cause for further concern. In southern Europe, visceral leishmaniasis used to be traditionally among children, whereas today 73 percent of the co-infected patients, are injecting drug users, and almost all are more than 15 years old. Similarly, in the Mediterranean area, where visceral leishmaniasis was traditionally zoonotic (the dog being the only source of infection for the sandfly), cases have recently arisen where transmission has been from person to person, either through the vector, or through syringes. Co-infected patients can serve as human reservoirs, harbouring numerous Leishmania in their blood and becoming a source of infection for the vector. Co-infected patients, who are often injecting drug users, can also transmit the Leishmania among themselves, through needle sharing. If the number of co-infected patients continues to increase, the risk of epidemics in the Mediterranean basin is likely to increase accordingly.

Leishmania and HIV co-infections are not exclusive to the developing countries.

Imported Cases of Leishmania & HIV Co-Infections in Non-Endemic Countries

Cases reported to WHO
Transmission Cycles in South-Western Europe

Zoonotic and anthroponotic cycles in southwestern Europe.
Gaps In the Reporting System Worldwide

While becoming progressively more realistic, the number of cases reported in the world is still considered an underestimation. A lack of awareness, rare systematic detection, limited access to HIV tests, absence of notification, non-compulsory notification of leishmaniasis, and limited number and coverage of the surveillance centres, all contribute to an under-reporting of HIV-related cases. In 1998, in Brazil, India, Kenya, Nepal and Sudan, where there is co-infection, the numbers reported are disproportionately low. In Nepal, for instance, it is estimated that 25 percent of the Nepalese sex workers become HIV positive after three years of activity in a neighbouring country. Their return to their native rural areas - highly endemic for visceral leishmaniasis, creates the conditions for co-infection. But, surveillance systems have only just been set up with financial support. Similarly, the surveillance centres in India have just recently been financed and staffed, because the leishmaniasis/HIV overlap is increasing in the Bihar and West Bengal States. Ethiopia is a good example, however, of a country where the detection, management and reporting of co-infection cases is already well organized. The number of cases reported in the two and a half years between 1996-1998 was three times that of the number of cases reported between 1990-1995. On the other hand, there is no leishmaniasis surveillance system in West Africa, as this disease is not a public health problem there.

In Europe, a surveillance system is now well established creating greater awareness, improved detection of both diseases and better case reporting. Overall case detection, however, remains passive. Closing the gaps in active medical surveillance requires financial support, staff, and facilities for diagnosis, as well as an extensive communication network. Equal vigilance of the two diseases is also needed. Visceral leishmaniasis is not an "official" opportunistic infection and consequently, it is rarely reported in AIDS-notification systems.
The reported cases in Spain, France, Portugal and Italy, from 1996 to June 1998, represent 48 percent of the total number reported in the Mediterranean since 1990.

The reported cases in Africa are a modest estimation. Surveillance was set up in Kenya and Sudan, only in 1998. The numbers are expected to rise owing to factors such as increasing mass migration, displacement, civil unrest, war, and sex work. In West Africa, there is yet no official surveillance system.
In the Americas, co-infections have been reported to WHO, mostly from Brazil, where the incidence of AIDS has more than quadrupled in 11 years. The ruralization of HIV transmission and a simultaneous urbanization of visceral leishmaniasis, especially in north-eastern Brazil and the resulting overlap of the two diseases, should increase the incidence of co-infections. For the rest of South America, single cases of co-infection have been reported in Guadeloupe, Panama, Peru and Venezuela.

In Asia the first three cases of co-infection were reported in India, in Uttar Pradesh State, where a sharp increase can be expected. There has been a recent increased overlap in the States of Bihar and West Bengal. Co-infection risk is increasing not only in India but also in Nepal.
THE RESPONSE

Up until recently, the impact of *Leishmania* and HIV co-infection was not recognized. The evidence that has been compiled since 1994 through the surveillance networks in 13 countries, has determined, however, a few predictions. The number of co-infection cases is likely to increase substantially in south Asia, sub-Saharan Africa, South America and southern Europe. India is especially vulnerable, as is East Africa. To cope with this emerging problem, the Division of Control of Tropical Diseases of the World Health Organization and UNAIDS decided to join efforts in setting up better surveillance networks, improved case detection and management, and coordinated preventive measures.
Better Surveillance and Coordination

In 1994, the Division of Control of Tropical Diseases established a Central International Registry in WHO headquarters, Geneva, to collect, process and diffuse information on leishmaniasis and co-infections worldwide. During the same year, an international meeting held in Rome helped set in place a surveillance network which has since become 28 institutions and is increasing. These centres have been set-up to include central laboratories and hospitals with an infrastructure capable of diagnosing and caring for co-infected patients.

The surveillance centers follow standardized guidelines provided by WHO and UNAIDS, to allow a common approach. The systematic use of standardized and computerized case report forms, the central international registry at the WHO headquarters, the improvement of data entry and analysis, and finally the use of a Geographic Information System (GIS) for mapping and monitoring co-infections, are measures expected to improve the overall quality of epidemiological data gathering, and as a result, improve response capability. (GIS is a computer-aided information system that permits visualization and analysis of epidemiological data in map form, and within a geographical context.)

The surveillance network in southern Europe and the coordination between the hospitals and laboratories have resulted in more accurate epidemiological data for that region. However, active medical surveillance of the injecting drug users, the main population at risk, continues to be inadequate. Outside Europe, the surveillance network has only just begun, and therefore the available information is less representative of reality. Hospitals and laboratories still need equipment for diagnosis, and drugs for treatment, to become more responsive to the actual and potential needs. It is expected that the number of Leishmania and HIV co-infections will continue to rise in the coming years, particularly in developing countries, and the existing surveillance network will consequently need to be further expanded. For this reason, WHO and UNAIDS are inviting all willing partners to participate in the joint initiative.
Better Case Management

AIDS and leishmaniasis are locked in a vicious circle of reinforcement which can be unlocked by a dual strategy of visceral leishmaniasis control, based on early detection and treatment, and simultaneous HIV prevention. Diagnosis of co-infected patients should be at the earliest stages (parasitological for leishmaniasis and serological for HIV). Where feasible it should be followed by immediate treatment of both diseases. Currently, however, there is no satisfactory scheme for leishmaniasis treatment of co-infected patients. Although patients respond positively to the first course of chemotherapy, more than 50 percent relapse. It is therefore important to explore new treatment schemes including multidrug therapy and secondary prophylaxis in order to reduce the frequency of relapses and the appearance of resistance in co-infected patients. It is a priority for WHO to design and carry out a number of clinical trials in co-infected people. Although this activity is not included in the current joint initiative, external support is being sought.

A joint consultative meeting held in September 1998 in Spain, will convene all members of the surveillance network to review epidemiological data, update the guidelines for diagnosis and treatment and reinforce coordination efforts.

Prevention of Co-Infections

Among the global strategies to curb the prevalence of co-infections is a coordinated effort of prevention. Early detection, early treatment by first-line drugs (antimonials) and notification of leishmaniasis cases and availability of these drugs in health centres, particularly in remote rural areas are key, as is close vigilance over populations at greatest risk, the injecting drug users. All this has to be coupled with health education and awareness for HIV infection, among all populations and those at risk, the sex workers, truck drivers and drug users.

It is believed that, only through concerted efforts of individuals, communities, country members of the surveillance network, WHO and UNAIDS, as well as other new partners, that the battle to quell this emerging disease will succeed.
Surveillance Centres for Leishmanina & HIV Co-Infections