Leishmaniasis in HIV- infected individuals

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Summary

Leishmaniasis is a zoonotic diseases caused by the protozoa parasites of the genus leishmania, which are transmitted by sand flies. Leishmaniasis constitutes a diverse collection of human diseases ranging from spontaneously healing skin ulcer to overwhelming visceral cases. World wide, two million new cases occur each year and 10^{th} of the world's population is at risk of infection. The complex cell mediated immune responses in visceral infection is likely modulated by a range of innate, natural status of an individual and effectors cells. The leishmania parasites survive hostile host environment through several defense mechanisms such as products of the respiratory bust (hydrogen peroxide $_(H_2O_2)$ supper oxide, hydroxide radicals) and the release of power full lytic enzymes. Leishmaniasis is basically a disease of otherwise healthy children and adults. However severe form of disseminated leishmaniasis has been described in immunocompromized patients. HIV/AIDS and leishmaniasis comprise a mutually reinforcing cycle of infection. Leshmaniasis accelerates the on set of acquired immuno deficiency syndrome (AIDS) by encouraging further opportunistic infections. On the other hand human immuno deficiency virus (HIV) increases the risk of acquiring leishmaniasis by 100-1000 times in endemic areas and encourage development of relapsing and drug resistant leishmaniasis. The over lapping geographical distribution of visceral leishmaniasis (VL)and AIDS is increasing due to the spread of HIV in suburban and rural areas of the world and spread of VL from rural to suburban areas, in consequence an increasing incidence of lishmaniasis/ HIV co-infection. The complication of the problem in leishmania/ HIV co- infection is potentially serious implications in areas where leishmaniasis and HIV co- exist. There fore, this review focuses on the epidemiology, pathogenesis or clinical situations, diagnosis and treatment options of leshmaniasis in HIV co-infections.

1. Introduction

1.1 Leishmaniasis

Leishmaniasis is one of the protozoan diseases caused by groups of parasites belonging to the genus leishmania(L). There are five principal species of leishmania (L-*tropica, L. major, L. donovani* group *L. Braziliensis, L.mexicana)* causing three main forms of the disease in human; they are cutaneous leishmaniasis (CL), visceral leishmaniasis (VL), mucocutaneous leishmaniasis (MCL) (1) and the diseases are transmitted by sand flies.

Five widely accepted genera of sand flies recognized these are phlebotomus and sergentomyia in the old world, and Lutzomyia, Brumptomyia and warileya in the new world. Phlebotomus and Lutzomyia are proven or suspected vectors of leishmania (2). The parasite exists in the sand flies in the form of flagellated promastigotes, but in human hosts the parasites are intra cellular because they usually infect mononuclear phagocytes (3).

CL can produce large number of skin ulcers on exposed parts of the bodies like face, arms, and legs (1). It causes serious disability leaving the patient permanently scarred. Diffuse cutaneous leishmaniasis (DCL) never heals spontaneously and tends to relapse after treatment. The cutaneous forms of leishmaniasis are the most common and represent 50-75% of all new cases. VL is also known as kala azar, which is the most severe form of the disease; and if untreated has a mortality of almost 100 %(1). It is characterized by irregular bouts of fever, substantial weight loss, swelling of the spleen and liver, and anemia. MCL produces lesions which can lead to extensive and disfiguring destruction of mucous membrane of the nose, mouth, and throat cavities.

Post kala-azar dermal leishmaniasis has predominantly been described in Africa and India. The Indian variant occurs several years after recovery form VL .Overtime, these can transform into large plaques and nodules that involve face and trunk. The African variant occurs shortly after treatment of VL and the lesions spontaneously resolve over the course of several months (4).

Leishmaniasis constitutes a diverse collection of human diseases ranging in severity from a spontaneously healing skin ulcer to over wheeling visceral disease. Globally, two million new cases occur each year, and a 10^{th} of the world's population are at risk of infection (5).

Although the disease is highly endemic through out northern Africa, the Middle East, parts of Europe, and central and South America, epidemics are well recognized. For example, in Southern Sudan more than 10% of the population died from VL over the past five years. Out come of infection is determined by introduction between the host and the parasite, which are governed by the genome of the host and the parasite (5).

Leishmaniasis can be found in 88 countries of inter tropical and temperate regions of the world, and visceral leishmaniasis (VL) is endemic in 62 countries (5,6). The World Health Organization reports an annual incidence of 600,000 cases but estimates up to 1.5 million new cases of cutaneous leishmaniasis and 500,000 cases of VL occur each year. An estimated 12 million people are infected from a population of 350 million people who are at risk. Of these infections, approximately 25% are of VL (6).

Most Leishmaniases are zoonoses and the reservoir hosts are various species of mammals which are responsible for the long-term maintenance of leishmania in nature. Depending on the focus, the reservoirs can be either a wild or a domestic mammal, or even in particular cases human beings. Reservoirs are included in seven different orders of mammals: marsupials, primates, edentates, rodents, carnivores, hyraxes and perissodactyls (2, 7).

1.2 Pathogenesis

Following the bite from infected sand flies human skin can heal spontaneously or develop localized or disseminated disease. Sand flies and leishmania species causing skin disease in human have been classified in geographical terms as old world (*L.major, L. tropical*) and new world (*L.mexicana, L. Braziliensis*) cutaneous leishmaniasis (2). Both can affect an area of exposed thin skin but multiple infective bites or disseminated form may present with lesions on several anatomical regions. Common inoculation sites include facial bone prominent regions, external aspects of wrists and malleolar regions. The bite of sand fly commonly targets exposed areas like the external ankles during sleep or medial regions of when the host is at rest.

After inoculation by sand files, the flagellated promastigotes bind to macrophages in skin. Promastigotes activate complement through the alternative pathway and are opsonized (3).
The most important immunological feature is a marked suppression of the cell mediated immunity to leishman antigens. In persons with asymptomatic self resolving infection, T-helper cells predominate, although immune suppression years later can result in disease (3).

The increase in gamma globulin leads to a reversal of the albumin –globulin ratio commonly seen in this disease. Leishmaniasis is also a disease involving the reticuloendothelial system. Parasitized macrophages disseminate infection to all parts of the body but more to the spleen, liver and bone marrow. The spleen is enlarged with thickening of the capsule, it is soft and fragile, its vascular spacer are dilate and engorged with blood, and the reticular cells of billroth are increased markedly and packed with the amastigote forms of the parasite. However, no evidence of fibrosis is present. In liver, the kupffer cells are increased on size and numbers and infected with amastgote forms of leishmania. Bone marrow turns hyperplasic and parasitized macrophages replace the normal hemopoietic tissue (3).

In immunocompetent cases, infection by the leishmania parasites that can cause VL is not always followed by disease some remain completely asymptomatic, many others have oligosymptomatic infections that resolve on their own, and perhaps only one in every five to ten develops clinical VL (8). Patients, who develop the clinical disease, after an incubation period varying from a few weeks to several months, usually have fever, sever loss of weight, hepatosplenomegaly and pancytopenia. If clinically evident and untreated, VL can be fatal, especially in developing countries, where associated diseases like HIV/AIDS often occur, the two infections have clinical, diagnostic, therapeutic and epidemiological implications (8).A very important aspect in Leishmania /HIV co-infection is the appearance of post treatment relapses, the prognosis of VL in human immuno deficiency virus (HIV) positive patients is very different from that for immuno competent (9). The levels of relapsing and mortality are greater in the cases of co-infection and the majority of co-infected patients display fever, hepatomegaly and or splenomegaly, hypergammaglobulinaemia and pancytopenia. The majority of co-infected patients present some type of heamatological cytopenia, the frequency and grade of anemia, leucopenia, lymphopenia, and thrombocytopenia have been observed to be greater in this type of patient than in the immuno competent (9). Globally, leishmania/ HIV co-infection cases have so far been reported in 35 countries, but most of the cases notified to the world health organization (WHO) are from south Western Europe countries: France, Italy, Portugal and Spain (10).

In addition to the bite from leishmania infected sand flies, leishmaniasis can also be transmitted directly from person to person through the sharing of needles, as is often the cause among intravenous drug users (IVDU) and this group is the main population at risk for co-

infection especially in south western Europe since sharing needles by IVDU can spread not only leishmaniasis but also HIV (10).

1.3 Host immunity against leishmaniasis

Leishmania species alternatively parasitize their sand fly vectors and mammalian macrophages. Parasites are deposited in the mammalian skin by sand flies and there after interact with and over come both extra cellular matrix and basement membrane proteins, to establish infection with in macrophage phagolysosomes (8, 11). Thus, in addition to the effectors the innate immunity plays a role in protection of leishmaniasis.

Complex cell mediated immune response in visceral infection is likely modulated by a range of innate and environmental factors (example nutrition) and also effectors cells (natural killer cells, $CD8^+$ cells, and perhaps neutrophils). However, most evidence points to a mechanism of resistance which is T($CD4^+$) cell dependent and involve T-cell co- stimulatory pathways required secretion of regulatory, activating Th 1-cell associated cytokines, including interleukin 12 (IL-12) and gamma interferon (INF-γ) induces adhesion molecule and chemokine-mediated recruitment of inflammatory monocular cells into infected tissue and within assembled granulomas and culminates in activation of leishmanicidal mechanisms in parasitized resident macrophages and in fluxing blood monocytes. If this response develops fully, the likely outcome is killing of most intracellular parasites, induction of quiescence in residual organism and maintenance of low level infection in life-long, asymptomatic states (12).

1.4 Mechanisms of immune evasion

Successful mammalian infection by leishmania species depends on the abilities of the parasite to evade non specific host defenses (13). The bite of an infected sand fly results in the intra dermal inoculation of metacyclic forms. Their establishment in the mammalian host is facilitated in a remarkable way by sand fly saliva delivered at the same time, which enhances leishmania infectivity. Sand fly saliva contains various pharmacologically active substances, which prevent haemostatic mechanisms of hosts, and cause vasodilation and local immune suppression (13). With in the dermis of mammalian skin the metacyclic promastigotes use their surface components mainly lipophosphoglycan and glycoprotein to escape complement activation. They are then phagocytosed by macphages which they transform in to amastigotes,

and have the capacity to resist intracellular digestion .The survival in these cells is the result of several factors related to the cell it self (decreased in the production of oxidative and nitrogenic derivatives triggered by the presence of the parasite) and the amastigot's ability to resist lysosomal hydrolases, a property probably related to surface glylco- inositol phospho lipids (2).

When an infected sand fly takes blood meal it infects the host with promastigote metacyclic forms. With in short time the promastigotes are taken up by macrophages, the first line of defense of the immune system. During the process of up take by the macrophage, the promastigote loses its flagella and transforms in to the amastigote form. Once internalized in a phagosome the macrophage lysosome fuses with the phagosome to form a phagolysosome containing the parasite (11, 14).

The parasites survive hostile host environment such as products of the respiratory burst like hydrogen peroxides, super oxide, hydroxyl radicals and the release of power full lytic enzymes through several defense mechanisms. Detoxification with antioxidant enzymes such as Trypanothione peroxidase is a unique antioxidant enzyme which can detoxifies hydrogen peroxides, down regulation lipophosphoglycans on the surface of the promastigote interfere with signal transduction pathway, specifically inhibits protein kinase C, which trigger the respiratory burst in response to the parasite, and hydrolytic enzymes posses surface glycoproteins that are refractory to host lysosomal enzymes and may also destroy then. Thus leishmania parasites unlike other intra cellular protozoans, which either inhibit lysosomal fusion with the phagosole or escape the parasitophorous vacuole, depend on their defense mechanisms to survive (5).

Salivary gland material from *Lutzomyia longipalis* has an inhibitory effect on the abilities of macrophage to present parasite antigens to specific T cells and can down regulate the ability of these cells to produce H_2O_2 in response to an activating stimulus form gamma interferon (INF -γ) (13).

2. Leishmania/HIV co- infection

Leishmania parasites exist with in macrophages as round to oval non-flagellated amastigotes, but in the sand flies the parasites exist as elongated flagellated promastigotes. For many years, leishmaniasis has been grossly underestimated but since 1993 it has become apparent that is

much more prevalent than previously suspected, with the risk that it will even increase in the future (15). There is evidence in many countries that HIV contributed to increased transmission and spread of the disease (16, 17). Infection with HIV virus increases the risk of getting leishmaniasis, thus it makes the disease worse, and reawakens a latent infection. The converse also occurs with leishmaniasis patients becoming more susceptible to HIV infection (16). Therefore, co- infection of leishmaniasis and HIV is emerging as a new and frightful disease and is becoming increasingly frequent with important clinical, diagnostic, chemotherapeutic, and epidemiological implications. Although people are often bitten by infected sand flies, most do not develop the disease. However, among individuals who are immunosuppressed due to advanced HIV infection cases, the disease has shown to evolve quickly to a full clinical presentation of severe leishmaniasis (15).

HIV/AIDS and Leishmaniasis comprise a mutually reinforcing cycle of infection. Leishmaniasis accelerates the onset of ADIS by encouraging further opportunistic infections and thus reduces the life expectancy of people with HIV infection. HIV related immunosuppression has shown to increase the risk of acquiring leishmaniasis by 100-1000 times in endemic areas and encourages the development of relapsing and drug resistance leishmaniasis (18).The overlapping geographical distribution of VL and AIDS is increasing due to two main factors. The spread of AIDS in sub urban, rural areas of the world and simultaneous spread of VL from rural to sub urban areas were shown to result the emergence of leishmania/ HIV co-infection (10).

2.1 Epidemiology

Mainly *Leishmania donovani* is causing visceral leishmaniasis (kala azar). VL is distributed all over the world but is predominantly encountered in India, South America, central Asia, Middle East, and Africa (3). Although the number of leishmaniasis cases are increasing mainly due to man made environmental changes that increase human exposure to sand fly vectors, poverty and malnutrition but co-existence of leishmaniasis with HIV in persons added a serious dimension to the problem of leishmaniasis spread in several areas of the world as a result of the rapidly spreading endemic of AIDS (3, 6). The immunodeficiency has lead to increased susceptibility to infections including leishmaniasis. Co-infection with HIV has lead to the spread of leishmaniasis, typically a rural disease in to urban areas. In infected patients with HIV, leishmaniasis accelerates onset of AIDS by cumulative immunosuppression and by stimulating the replication of the virus. It also may change

asymptomatic leishmania infections in to symptomatic ones and sharing of needles by IVDU can spread not only HIV but also leishmaniasis.

The clinical forms of VL are most frequently associated with HIV/AIDS especially in South Western Europe although some cases with CL have been reported (10). This implicated that leishmaniasis is being recognized as an important opportunistic disease among person with HIV infection. Almost all cases of leishmania/HIV co-infection have been described in southern regions of Spain, France and Italy, where 25% to 70% of patients with leishmaniasis are concurrently infected by HIV (8, 17). Some case reports in Bologna, Italy the typical patient with HIV- leishmania co-infection was shown in young men who were intravenous drug abuser (IVDU). The higher disease prevalence among IVDU a possible parasite transmission by contaminated syringes, in addition to the usual vector-borne infection; indeed, this group of patients often presents detectable parasitemia.

Cutaneous manifestations of leishmaniasis-HIV co-infection have up until now been observed in a very small number of patients and they may represent the primary site of infection or a secondary involvement, after the visceral disease. Few cases of cutaneous and mucocutaneous HIV- related leishmaniasis have been reported from southern America (Brazil), where as this disease manifestation is very uncommon in Europe. *L-infantum* is potentially responsible for most of cutaneous cases occurring in Mediterranean countries (8).

AIDS and VL therefore are locked in a vicious circle of mutual reinforcement. VL accelerates the onset of full blown AIDS and shortens the life expectancy of HIV infected people, while HIV encourages the spread of VL (17). The grid lock produces cumulative deficiency of the immune response as leishmania parasites and HIV destroy the same cells, exponentially increasing disease severity and consequences. If a sand fly that is infected with leishmania parasites bites a person who is already infected with HIV and already exhibits a suppressed immune system, this person will develop several leishmaniasis in the visceral form. VL, once developed in the HIV infected person, impairs the patient's condition by further suppressing more of the same immune response cells. In sex distribution, there are far more male cases of co infection recognized in Europe than female. Of all the European cases reported, with the gender of the case, by early 2001, 85% were male. In south Western Europe, the main population at risk of co- infection appears to be that of IVDU more than 70% of the known cases had used intravenous drugs (10, 19). Investigations of twenty immunocompromised patients in Madrid Spain with VL showed about 12 (60%) HIV infected patients, out of which

8(40%) had other immunosappressive conditions such as hematologic neoplasia, corticosteroid therapy (3 patients) and renal transplantation (2 patients). All HIV infected patients were men, with median age of 43.7 years (range 22-65 years). Seven were drug abusers and five were homosexual men. All those patients had full-blown AIDS with a medium CD_4^+ count or Lymphocyte of $81.2^{\pm}46$ cells per micro liter (20).

In Ethiopia, HIV co-infection in some endemic areas of VL ranges from 15% to 40% and was known to be much higher in hospitals of big cities. European patients of HIV/ VL co-infection were reported to have CD4 cell counts of less than 200 x 10^6/L, however in Ethiopia most patients were found dying before reaching such low CD_4 counts (21). For example, among 199 VL patients in an area with high prevalence of HIV co -infection in Ethiopia, twenty-seven patients had confirmed co-infection with HIV (22).

2.2 Leishmaniasis -hiv co-infection complications

The leishmaniasis cases in association with HIV infections possess several principal characteristics like parasitic dissemination via the reticuloendothelial system. It has been suggested that almost any organ that contains phagocytic cells could become infected. (10).Typical locations are affected as a consequence of parasite's spread and deficiency in the cellular immunity, chronic progress and relapse, with each patient experiencing between two and three relapse independently of the treatment received; poor response to classic therapy, low presence of anti-leishmania antibodies and also gastrointestinals implication are among the most frequent complications in HIV positive patients. Leishmania has been identified in the gastrointestinal tract of 50 percent of HIV-patients with VL (9).

2.3 Diagnostic problem of leishmania /HIV co infection

In HIV positive patients, clinical diagnosis of VL has more limited value since in the AIDS patients; leishmaniasis can first appear in an unusual way and with not very specific clinical signs (23). An important point to be noted is in about 68 percent of the cases of co-infection other opportunistic infections were shown to be associated with HIV also appears with displayed clinical and biological signs similar to those of VL (18). There are different laboratory techniques to diagnose the leishmania/HIV co infection. Microscopic examination is fundamental, since they might need to recognize Histoplasma or other organisms that could infect these patients and lead to false positive results. For the Microscopic observation of bone

marrow sensitivity has been described to be between 67 and 94 percent. In the case of false negatives, it could be presented for several reasons, as for example, the presence of low number of leishmania-infected cells as a consequence of pancytopenia. Another parameter that can affect the parasitic load is if the patients have been treated with pentamidine or amphotericin B against mycosis or pneumocystosis. Amastigotes can be found in the peripheral blood of approximately 50 percent of HIV positive patients and occasionally, the parasites can also be observed in unusual locations such as the lungs, larynx, gastro intestinal tract, rectum and spinal fluid and others (9). In co-infected patients of leishmania /HIV, the culture of mononuclear peripheral blood cells has a sensitivity of 67 percent and the culture of splenic aspirate can reach a greater sensitivity (63-100%). However, when using culture for diagnosis, one should remember that some special precautions are required in the routine handling of leucocytes samples form AIDS patients (6).

In leishmania /HIV-co-infection, the humoral specific response to leishmania turns out to be partial, weak or absent, due to the fact that the cellular immunity is affected after infection by HIV causing decrease of total lymphocytes in the production of antibodies.

Leishmania infection affects the appearance of antigens to the B- cells as much as does HIV. Thus the process,of antibodies production remains blocked. This has been confirmed the level of specific anti-leishmania antibodies in patients with AIDS is 50 times lower than in patients with an intact immune system. Therefore, it is recommended that at least two different serological techniques are used in the diagnosis of every patient. (6,9).Enzyme immuno assay most assays performed on HIV positive samples where by using rk-39 antigen, rk-39 dipstick is rapid diagnostic test and detects antibodies of leishmania causing VL, however it is supposed to detect only active VL cases (24). This assay has a sensitivity of 20 present for patients co-infected by leishmania HIV. Direct agglutination test (DAT) is also a simple technique with high specificity and sensitivity thus is a suitable for both field and laboratory use (24). The test can be carried out using plasma or serum. The major disadvantage of DAT is the relative long incubation time of 18 hours and the need for serial dilutions of blood or serum. Also DAT has no prognostic value for evaluating the parasitological cure of the disease as the test may remain positive for several years after cure. DAT remains the first line diagnostic tool for VL in many developing countries. Polymerase chain reaction (PCR) has been shown to be a great utility in the diagnosis of co-infected patients. Analyzing samples of bone marrow, obtained a sensitivity of 82 percent for the PCR, where as other studies showed 100 percent. Although the classic PCR technique is very useful as a diagnostic tool it has

some disadvantages, such as the need to analyze the amplified products using electrophoresis, and it has limited utility when the parasitic load needs to be monitored precisely as it is not able to quantify the obtained deoxyribonucleic acid (DNA) (25).

2.4 Control problems

While becoming progressively more realistic, the number of cases reported in the world is still underestimated. Lack of awareness, rare systematic detection, limited access to HIV tests, absence of notification, non compulsory notification of leishmaniasis, and a limited number and coverage of the surveillance centers contributed to an under reporting of HIV-related case. In 1998 in Brazil, India, Kenya, Nepal, and Sudan where there is co-infection the reported cases are disproportionately low. In Nepal, for instance, it is estimated that 25% of the Nepalese sex workers become HIV positive after 3 years of activity in a neighboring country (17). Their return to their native rural areas, highly endemic for VL, creates the condition for co-infection. But, surveillance systems have been set up. Similarly, the surveillance centers in India have been financed and staffed, because leishmaniasis /HIV overlap is increasing. In Europe, a surveillance system is well established creating awareness, improved detection of both diseases, and better cases of reports. In Africa, VL is mainly transmitted in rural area either from a zoonotic source or human to human in secondarily anthropotic foci. Owing to the complexity and diversity of transmission patterns but also absence of health care settings, control of VL in African endemic countries has shown to be challenging (21) Therefore lack of integral component of VL control program through out the world creates a problem to leishmania HIV co-infections.

2.5 Treatment problems

VL occurring in HIV infected patients appear globally as non-responsive to the classical anti leishmania drugs, with incomplete cure and frequent relapses (2). Experiment studies have shown that after effective treatment, the parasite remains quiescent in several organs after induction of immune system depression in the host, the parasite can be reactivated and cause new disease(24,25). The persistence of leishmania in blood for many years after recovery and the recrudescence of the infection in immunodepressed patients following effective treatment as a result HIV- Positive patients with VL have very frequent recurrence, probably due to the reactivation of the process caused by inability of the immune system to help control of the infection. Therefore treatment for co-infected patients aimed at clinical and parasitological cures and prevention of relapses is important. As it is explained above, unfortunately in such

patients, treatment failure, relapses due to drug resistance and drug toxicity are very common. For example in south western Europe, follow up studies using pentavalent antimonials, the first line drug used to treat classic leishmaniasis show a positive response in 83% of case. However, 52% of patients relapse with in a period of one month to three years, with the number of relapse ranging for one to four (6). So the first drug for treating VL is sodium stibogluconate (pentavalent antimonials) 20mg/kg by intramuscular injection for 30 days. Despite poor tolerance of this treatment among patients co-infected with HIV and VL (18).

In a series of 51 treatment courses in Spanish HIV positive VL patients, antimonials were frequently toxic, causing hyperamylasaemia, acute pancreatitis, renal failure and leucopenia (22) but thanks to technology the implementation of highly active antiretroviral therapy (HAART) has modified the incidence of most opportunistic diseases related with HIV infection. HAART seems to prevent the development of overt kola-azar in patients with sub-clinical VL (26).

A recent report of Ethiopian cases showed that HIV-co-infected VL patients had higher mortality during treatment. 33.3% mortality during treatment among HIV-Positive patients and 3.6% mortality in HIV negative patients and at 6 month follow-up time patients had a higher relapse rate of up to 16.7% in co-infected patients with HIV and 1.2% in patients negative in HIV (22).

Treatment of VL in HIV positive patients using pentavalent antimonials or amphotericin B desoxycholate were shown to be useful, but resulted in high toxicity and therapy takes a long time (9, 12, 27). The new lipidic formulations of amphotericin B offer greater to tolerability and can be used in short treatments and the improvement of treatment of leishmaniasis in HIV- positive patients should be based on both the development of new regimes based on already tested drugs and the experimentation with oral drugs such as miltefosine.

2.6 Treatments options

There have been no significant changes in the treatment of leishmaniases for many years. Since the 1920s, treatment has been based on pentavalent antimonial compounds. Following the increasing incidence of VL cases in immunocompromised patients and the rise of acquired resistance to antimonials, amphotericin B, mainly in its liposomal form, which is less toxic drugs, has joined the antimonials as a first line drug (2, 18). Alternative drugs are investigated for many years with out passing the step of clinical trials, Miltefosine is a new oral compound

tested during the last few years, has shown promising results, and could change completely the therapy of leishmaniasis in the near future (2).

3. Conclusions

Leishmaniasis is an opportunistic infection that is particularly troublesome for HIV patients, because attacks the immune system and there by worsens a patient's already compromised ability to resist other infections. Therefore leishmania /HIV co-infection remains a serious public health problem in many countries of the world. The possibility of leishmania as well as HIV transmission among IVDU who share blood-contaminated needles has been confirmed. This indicates IVDU are the main risk group for the co-infection and the emergence of drug resistance represents one of the most serious problems in the control of leishmania /HIV co-infection. To improve leishmania /HIV co-infection, control tools like providing alternative new drugs for safer, shorter and cheaper treatments are important. Identification and quantification of risk factors to better focus the control activities and prevent epidemics. Strengthen disease and vector surveillance, integrated vector management, social mobilization and networking, and research are also helpful to accessing early diagnosis. Therefore by integration of different control methods it is possible to prevent the leishmania/HIV co-infection.

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