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Leishmaniasis and HIV Co-Infection: Review

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Abstract: Leishmaniasis is a parasitic disease caused by obligate intracellular protozoa of the genus leishmania. Leishmania parasites stimulate chronic immune activation, leading to an increased HIV viral load with faster progression to AIDS that reduces life expectancy in HIV infected patients. Leishmaniasis is one of the most neglected tropical diseases, with more than 12 million people worldwide currently infected, with or without apparent symptoms and 2 million new cases reported each year; 350 million people are considered at risk and the number of new cases is increasing. It is endemic in 88 countries of five continents: Africa, Asia, Europe, North America and South America and affects the poorest populations. One-third of all HIV patients worldwide live in regions where leishmaniasis is endemic. The increase in the incidence of Leishmania-HIV co-infection can be attributed in part to the geographicaloverlap of the two diseases. The existence of both Leishmaniasis and HIV in the same cell has been shown to influence the multiplication and expression of either one or both organisms. It is believed that in co-infected patients, there is a symbiotic relationship between Leishmania parasites and HIV. The differences in the clinical pattern are related not only to the type and virulence of the parasite involved but also to the immune response of the infected human. The modern management and control techniques for Leishmaniasis rely upon on reservoir and vector management and the usage of insecticide-impregnated substances and lively case detection and remedy.

Key words: Leishmaniasis · HIV · Co-Infection · Disease · Epidemiology · Diagnosis · Prevention

INTRODUCTION

Leishmaniasis is one of the most neglected tropical diseases, with more than 12 million people worldwide currently infected, with or without apparent symptoms and 2 million new cases reported each year; 350 million people are considered at risk and the number of new cases is increasing. It is endemic in 88 countries of five continents: Africa, Asia, Europe, North America and South America and affects the poorest populations. Two basic clinical forms, namely, cutaneous leishmaniasis (CL), a disfiguring and stigmatizing disease and visceral leishmaniasis (VL) or kala-azar, which is fatal without treatment, are recognized [1-3].

Visceral leishmaniasis (VL) (kala-azar) is a disseminated protozoan infection, transmitted by sand fly bites, in which macrophages of the liver, spleen and bone marrow are preferentially parasitized with intracellular replication. *Leishmania donovani* the primary cause of visceral leishmaniasis in the Indian subcontinent and east Africa. Visceral leishmaniasis is characterized by irregular bouts of fever, substantial weight loss, swelling of the spleen and liver and anemia. If left untreated it is a 100% fatal illness, with the East Africa is one of the most affected regions, second only to south Asia and followed by Brazil, with an estimated annual incidence rate of 29,400, 56,700 and 4000 cases respectively. There is an alarming occurrence of new foci and an increase in the incidence of VL in east Africa [4]. VL is endemic in 70 countries with a total of 200 million people at risk. Worldwide 500,000 new cases of visceral leishmaniasis occur annually, of which 90% are in 5 countries, namely Bangladesh, Brazil, India, Nepal & Sudan. The true incidence of VL is underestimated because surveillance systems are lacking and misdiagnosis, especially with malaria, is common; failure to diagnose the disease leads to an increased case-fatality rate [1, 4-6].

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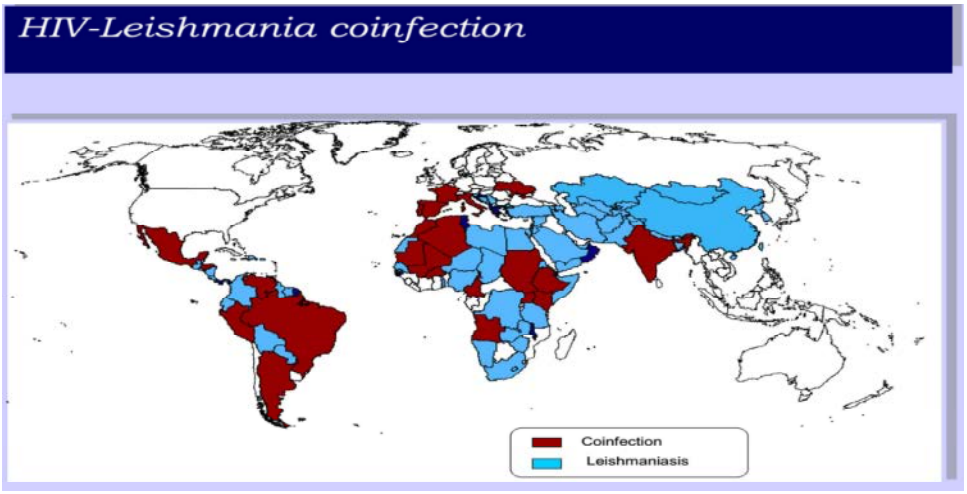

Fig. 1: HIV-Leishmaniaco-infection. Source: World Health Organization. Leishmaniasis/ HIVCo-infection. Available: http:// www.who.int/ leishmanias/ leishmaniasis_maps/ en/ index1.htmlaccessed. 20 April 2019.

Several medical forms are viable, relying on the Leishmania species concerned, consisting of localized cutaneous leishmaniasis (LCL), which frequently heals without remedy; diffuse cutaneous leishmaniasis (DCL), which is very tough to deal with; mucocutaneous leishmaniasis (MCL), that's the maximum excessive form, because it produces disfiguring lesions and mutilation of the face and additionally publish- kala-azar paperwork [7].

The disseminated shape (primary diffuse CL) develops in allergic people as considerable nodules and macules, without ulceration or visceral involvement. This variation is characterized with the useful resource of a partial response to treatment and common relapses and the maximum commonplace causal species are *L. amazonensis* and, rarely, *L. aethiopica*. This presentation, with a couple of papules and nodules which may be ulcerated is as an alternative commonplace in patients with HIV co-infection, irrespective of the species of Leishmania concerned. It's far seen in five percent of sufferers getting better from VL in Africa and in 20% of such patients in India. The conversion of leishmaniasis bears a prominent resemblance to lepromatous leprosy and is epidemiologically very necessary, for the source that patients behave as natural reservoirs of *L. donovani* [2].

The simultaneous infection of humans by using HIV and Leishmania almost always results in a ''deadly gridlock,'' as they each have the same deleterious effect at the immune response. the first case of leishmaniasis related to HIV infection become stated in 1985, at the same time as the quantity of instances has eventually increased hastily in southern Europe. Best effective after the introduction of HAART, the extensive kind of co-infected cases in EU countries in which the sickness is endemic fell sharply. With the spread of HIV to other VL-endemic regions of the world, the co-infection is now reported from 35 countries. Because of the alteration of the disease path, the diagnostic demanding situations and the bad treatment reaction(due to multiplied overlap of the two illnesses), VL with HIV co-infection has become a very critical tough trouble and elevated to other predominant foci of leishmaniasis within the globe [3, 5].

HIV infection increases the risk of developing VL by 100 to 2,320 times in areas of endemicity, reduces the likelihood of a therapeutic response and greatly increases the probability of relapse. Both diseases exert a synergistic detrimental effect on the cellular immune response because they target similar immune cells. *Leishmania* and HIV co-infection is currently reported for 2 to 9% of all VL cases in given countries of endemicity, but this proportion is likely to increase dramatically. In selected populations, such as in Humera, Ethiopia, the rate of co-infection in VL patients is 15 to 30%. In general, VL occurs among neglected populations and because it is not on the CDC list of opportunistic infections, so it is rarely reported in AIDS notification systems. The introduction of HAART has totally changed the course of HIV/AIDS infections and the outcome of associated opportunistic infections. However, access to HAART in developing countries remains inadequate. In addition, there are many unresolved questions related to the management of *Leishmania* HIV co-infected patients [3]. Therefore the main objective of this review is to insight leishmaniasis-HIV co-infection, epidemiology, pathogenesis, diagnosis, prevention and treatment of the disease.

Epidemiological Information on *Leishmania*-hivcoinfection: One third of all HIV patients worldwide live in regions where leishmaniasis is endemic [8]. The increase in the incidence of Leishmania-HIV co-infection can be attributed in part to the geographicaloverlap of the two diseases [9]. In visceral leishmaniasis endemic areas, people who are immuno-compromised due to HIV infection are more prone to developing clinical VLcompared to those without HIV co-infection. In fact, *L. infantum* co-infection is now the third most frequentinfection in HIV-infected individuals in VL endemic areas. Furthermore, even non-pathogenic strains of Leishmania and other species of trypanosomatids may cause disease inHIV-infected individuals [9-11].

Southern Europe: Since 1994, the incidence of Leishmania-HIV co-infection has been monitored by a surveillance network consisting of 16 institutions in four countries: France, Italy, Portugal and Spain. Spain consistently recorded the highest number of cases, an observation that may be related to a number of factors including reactivation of asymptomatic infection and greater geographical overlap between leishmaniasis and HIV infections compared to other southern European countries. In this region, many asymptomatic individuals are positive for leishmanin skin test (LST), an indication that they have been actively exposed to Leishmania and may not have developed clinical disease due to effective immune response. Infection with HIV may reactivate latent infections and enhance both anthroponotic (through sand fly bites) and artificial (through needle sharing by intravenous drug users [IVDU]) transmissions. In Spain, 68 % of Leishmania-HIV co-infection is seen among IVDUs. It is important to note that at the time of these studies, Spain had five to seven times more IVDU than the European average. However, the proportion of reactivated leishmaniasis cases in asymptomatic co-infected patients compared to symptomatic co-infected patients due to contaminated needles and syringes has not been established [3, 9].

South Asia: Southeast Asia accounts for 67 % of all leishmaniasis where the disease is spreading fast. As with leishmaniasis, HIV/AIDS epidemic is also spreading rapidly in south East Asia with 4 million people currently living with HIV in 2011. It is estimated that 2.4 million people were living with HIV infection in India, 6300 people in Bangladesh and 64,000 people in Nepal in 2009, Alvar *et al.* [3] and Uzonna [9]. The first Leishmania-HIV co-infection case was reported in 1999 in Kumaon region of India. They either acquire or reactivate latent leishmaniasis due to HIV infection-induced deteriorating immune system. In 2006, a prevalence rate of 2.48 % and 5.7 % for VL was reported among HIV-positive patients in India and Nepal respectively. No data on *Leishmania*-HIV co-infection are available from Bangladesh, but judging by the rates in neighboring India and Nepal, the rate is likely to be high [3, 9].

Sub-Saharan Africa: While most Leishmania-HIV co-infection in Southeast Asia involves VL, both CL and VL are important in Africa due to the geographical spread and distribution of the various Leishmania spp. In Burkina Faso, about 14 % of CL patients were co-infected with HIV and this was characterized by many unusual clinical signs. In French Guyana, co-infected patients had more lesions with a poorer response to treatment and higher recurrence and/or re-infection rates compared to immunocompetent patients. In Ethiopia, both CL/HIV and VL/HIV co-infections have been reported although VL/HIV co-infection appears to be more prevalent. In Humera region of NW Ethiopia, 40 % of VL patients were also co-infected with HIV in 2006, representing an increase of 21.5 % from 1999. More importantly, the case fatality rate of VL/HIV-infected patients was four times higher than those with VL but not HIV infection. In contrast, the incidence of HIV-Leishmania co-infection in Sudan remained basically unchanged for 5 years after the first three cases of Leishmania-HIV co-infection were reported in 1998. The main area of endemicity in Sudan is the southeast of the country, bordering Ethiopia. In Kenya, only 15 cases of VL/HIV co-infection were reported in 2006 and there is no doubt this is a gross under reporting of the real prevalence rate and that the risk of co-infection is increasing. Recent report from Cameroon showed a 4.8 % rate of CL/HIV co-infection in the Mokolo Region (Northern Cameroon) Where CL is endemic. Generally, there is poor data collection and analysis in the region. There are also very limited disease surveillance, reporting and control programs in place in many African countries. Hence, it is conceivable that the few available data may be grossly underestimated and misleading [3, 9, 12, 13]. East Africa is one of the most affected regions, second only to the Indian subcontinent, with an estimated annual incidence rate of 29,400 to 56,700 cases [11, 14].

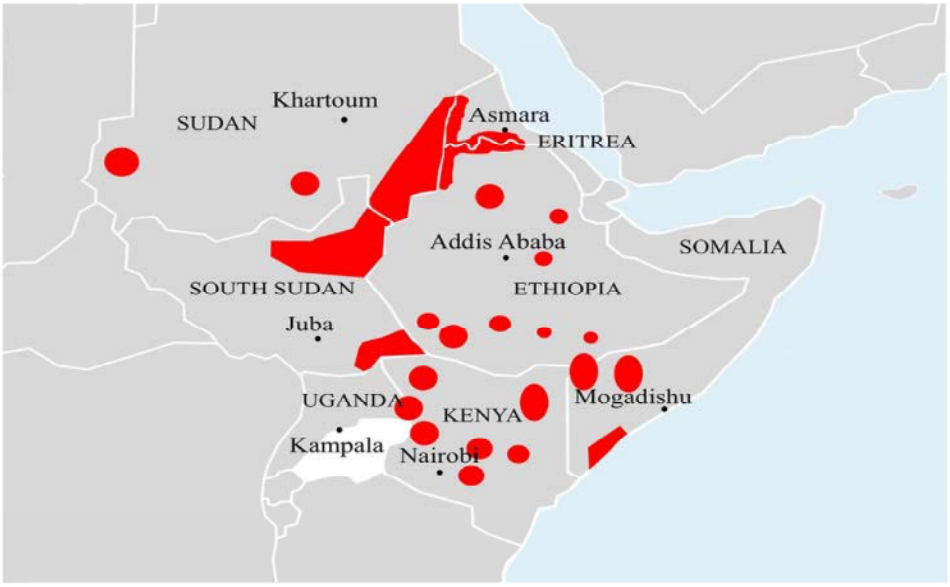

Fig. 2: Map of East Africa showing the distribution of Visceral Leishmaniasis [14]

South America: As in Africa, data on the prevalence of HIV-Leishmania co-infection in South America are also scanty and may be misleading. Of the 315 estimated cases of VL/ HIV co-infection between 2001 and 2005, 78 % were males with a median age of 38 years. This is in agreement with more recent studies, which showed that 86.6 % and 88 % of co-infected individuals were males. A study showed that most (66.6 %) of the individuals co-infected with VL and HIV were from the rural areas and included different occupations like hair dressers, doormen, salesmen, office assistants, maids, farmers and unemployed. According to the Brazilian Ministry of Health, the rate of HIV-VL co-infection is currently estimated to be in the order of 6.5 %. Despite the reduction in the number of VL and HIV/VL cases in 2009 and 2010, the proportion of HIV/VL continues to increase and in 2010 was 17.4 %. Because 57 % of patients in Brazil have HIV diagnosis after VL manifestations, the Ministry of Health has recommended that all patients with VL be tested for HIV [3, 9,15].

Microbiology: A total of 1,037 *Leishmania* strains have been isolated and identified from HIV-positive patients, which represents the largest sample studied around the world. The majority of the isolates came from VL cases in southwest Europe and a few isolates were obtained from other foci and other leishmaniasis forms Alvar *et al.* [3].

Leishmania Infantum Identification During Co-Infection: Using isoenzyme electrophoresis, 695 isolates were identified as *Leishmania infantum* in southern Europe, mainly from patients infected in Spain, France, Italy and Portugal, with a few isolates from patients in Algeria, Tunisia, Greece and Morocco. Almost all of the leishmaniasis clinical forms were VL (99.6%), with occasional cases of CL(3). VL occurring during HIV infection cannot be cured, even after extensive anti-leishmanial treatment. The likelihood of a relapse occurring is dependent on the level of $CD4^+$ cells in the patient. In patients (n = 80) from southern Europe, two or three stocks were isolated from each patient following successive episodes of relapse, with time intervals of 1 to 4 years and were subsequently identified by enzymatic electrophoresis. All of the isolates were *L. infantum* and 18 zymodemes were found repeatedly during the various episodes. More recently, *L. infantum-L. Major* hybrid strains were described for HIV co-infected patients from Portugal, by sequencing of the gene for polymerase II RNA and by isoenzymatic identification [3,16].

Other Leishmania *Species during HIV Co-infection*: In the sub-Saharan Sahelian zone of Africa, several *L. major* isolates obtained from patients in Mali (n= 4), Burkina Faso (n =7), Senegal (n =1) and Mauritania (n =1) belonged to zymodemes MON-26 and its small editions, MON-seventy four and

MON-117, a collection of zymodemes extending from west Africa to central Asia [17]. Furthermore, numerous New global Leishmania dermotropic species, including *L. braziliensis*, *L. mexicana* and *L.amazonensis*, had been diagnosed as causes of VL in HIV-positive patients, even as conversely, viscerotropic editions of *L. infantum*/*L.chagasi* were observed in cutaneous lesions or even within the healthy skin of HIV-positive patients [3, 17].

Pathogenesis

VL-HIV Co-Infection: The existence of both Leishmania and HIV in the same cell has been shown to influence the multiplication and expression of either one or both organisms. Leishmania parasites stimulate chronic immune activation, leading to an increased HIV viral load with faster progression to AIDS that reduces life expectancy in HIV infected patients. However, a recent study showed that the immune system can be highly activated without a concomitant increase in HIV viral load in co-infected patients. Whereas immunological disturbances caused by HIV are particularly favorable for the uncontrolled multiplication of the parasite [9, 18, 19].

Mechanisms That Are Involved in the Immunopathogenesis of *Leishmania*-HIV Co-Infection: Preliminary reports proved that Leishmania can upregulate virus expression in 2 monocytoid mobile strains latently inflamed with HIV-1. Leishmania parasites and HIV infect and interact with both dendritic cells and macrophages. The consequences of this interaction are yet to be fully determined. However, it has been suggested that Leishmania and HIV-1 can exploit DCs by modulating several cell surface molecules, inhibition of DC function, production of soluble factors, delayed lysosomal fusion and intracellular killing activities. When DCs and macrophages encounter antigens, they process and display their peptides on their surfaces and migrate to the nearest draining lymphoid organs where they present these peptides to nave T cells. Infection of dendritic cells and macrophages with Leishmania and HIV has been shown to alter the physiologic functions of these cells, particularly their antigen processing and presentation capacities. HIV-1 infection has also been shown to affect phagocytosis and replication of Leishmania parasites by macrophages. In addition to altering the activation states of infected macrophages and dendritic cells, HIV infection also alters their physiologic response leading to production of immunomodulatory molecules [9].

Following phagocytosis, the promastigotes are engulfed within the phagolysosomes in antigen-presenting cells (APCs), especially macrophages, where they transform to the intracellular (amastigote) forms. In the phagolysosome, the LPG molecule is shed leaving only the phosphatidylinositol anchor. Evidence was provided that *Leishmania* promastigotes (LPG) and the intramembrane structural component of LPG (core-PI) present in amastigotes were both capable of promoting virus replication in T cells through complex biochemical pathways that involve the translocation of the transcriptional factor NF-kβ to the nucleus. Despite the fact that the exact mechanism remained uncertain, it changed into concept that LPG molecules could engage with the HIV-inflamed T cell during antigenic presentation between the Leishmania-inflamed macrophage and the T cell. Furthermore, *Leishmania* may induce HIV replication in infected cells through antigen-specific and non-antigen-specific mechanisms in which tumor necrosis factor alpha (TNF-a) plays a key role [9].

Now a days, it's been shown that Leishmania does no longer directly have an effect on virus gene expression but alternatively modulates the existence cycle of HIV-1 through an oblique phenomenon this is connected to the induction or elevation of TNF- o and interleukin-1a (IL-1a) and that can characteristic in an autocrine/paracrine way to up regulate virus gene expression mediated thru induction of NF-kβ [20, 21].

Human immunodeficiency virus infection also negatively impacts on the outcome of Leishmania infection. Although not yet demonstrated in vivo, it is conceivable that the high parasitemia in AIDS patients may be related to the observed impairment in macrophage effector functions in vitro which could also account for the increased disease recurrence and reactivation seen in HIV Patients co-infected with Leishmania [9].

Recent findings in mice suggest that mechanisms other than IL-10 may be responsible for the immunopathology. The fact that HIV and Leishmania (VL) cause immunosuppression on their own suggests that there could be more pronounced immunosuppression in Leishmania/HIV co-infected individuals [9, 20].

Resolution of both cutaneous and visceral leishmaniasis is usually associated with a strong Th1 response because it ensures the production of macrophage-activating cytokines, especially IFN-λ and its mediated expression of TNF and inducible nitric oxide synthase (iNOS) with production of NO and parasite killing. Conversely, susceptibility has been attributed to

the over production of Th2-associated cytokines (including IL-4, IL-5 and IL-10), which inhibit Th1 cytokines and deactivate macrophages leading to parasite proliferation and survival. However, in VL, the role of Th1 or Th2 cytokines in the resistance and susceptibility, respectively, is not very obvious because both Th1 and Th2 cytokines have been detected in VL patients showing different clinical disease manifestations [9, 22].

Studies suggest that HIV infection could alter the responsiveness of T cells to Leishmania. For example, it has been shown that HIV influences the responsiveness of peripheral blood mononuclear cells (PBMC) to Leishmania antigens. The inhibitory effect of HIV and VL on IFN-λ production may not be solely dependent on the anti-inflammatory effect of IL-10, but may be related to the effect of HIV in regulating IFN-λ inducing factors, such as IL-12 and IL-18. In addition, patients with VL and HIV-1 infection have decreased circulating levels of IL-15, a cytokine that enhances the Th1 response and potentiates the immune response to intracellular human pathogens and could play a critical role in Leishmania/HIV co-infection. Proinflammatory cytokines have also been implicated in the pathogenesis of Leishmania/HIV co-infection. The pathologic effect of TNF-a in coinfected patients could provide explanation for increased viremia, decreased $CD4^+$ T cell numbers and enhanced seroconversion. It is suggested that opportunistic infections during HIV infection could lead to the production of proinflammatory cytokines during the stage of immunodeficiency, thereby accelerating disease progression [3, 9, 22].

CL-HIV Co-Infection: HIV co-infection has the potential to negatively affect the course of CL as immunosuppression progresses by promoting parasite dissemination, atypical localization, unusual and more severe clinical presentations, delayed healing, poor responses to treatment, more frequent recurrences and difficulty in diagnosis, irrespective of the etiologic species of *Leishmania* involved. The major pathophysiologic basis for this appears to involve an enhanced shift to a predominant Th2 response driven by the HIV-mediated immune dysregulation in the human host, which undermines the mainly Th1 response that is characteristic of CL in patients who are not immune-compromised. On the other hand, CL might be unmasked or show deterioration during the course of immune recovery following HAART in HIV co-infected patients [3].

Diagnosis: Atypical presentations of leishmaniasis can easily be confused with several other opportunistic conditions that occur in HIV patients and therefore cause a diagnostic challenge for the physicians. So Laboratory diagnosis is crucial.

Diagnosis of Cutaneous and Mucocutaneous Leishmaniasis: Parasite detection by direct identification of amastigotes in Giemsa-stained lesion smears of biopsies, scrapings, or impression smears. Amastigotes are observed as round or oval bodies, 2-4 μm in diameter, with characteristic nuclei and kinetoplasts. The material from the ulcer base usually has the highest yield; however, conventionally, three to five aspirates from different lesions or portions of lesions are dissected. The first samples should be used for microscopy and the last for culture to minimize the risk of contamination. A combination of microscopy and culture increases diagnostic sensitivity to more than 85% [3, 5].

Diagnosis of Visceral Leishmaniasis

Parasite Detection: The visualization of the amastigote form of the parasite by microscopic examination of aspirates from lymph nodes, bone marrow or spleen is the classical confirmatory test for VL. Although the specificity is high, the sensitivity of microscopy varies, being higher for spleen (93-99%) than for bone marrow (53-86%) or lymph node (53-65%) aspirates. However, spleen aspiration can be complicated by life-threatening hemorrhages in ~0.1% of individuals and therefore requires considerable technical expertise, as well as facilities for nursing surveillance, blood transfusion and surgery. Moreover, the accuracy of microscopic examination is influenced by the ability of the laboratory technician and the quality of the reagents used [1, 5].

Antigen-Detection Tests: In principle, antigen-detection tests need to be more precise than antibody-detection assessments as they avoid move-reactivity and may distinguish active from past infections. The detection of polypeptide fractions of kDa and 123 kDa of Leishmania antigen in the urine of patients with VL is 96% sensitive and 100% specific; furthermore, these antigens is not detectable after three weeks of treatment, suggesting a good prognostic value [9, 20].

Antibody-Detection Tests: Several tests that detect specific anti-leishmanial antibodies have been developed, but all have major limitations. VL relapse and cure cannot be diagnosed by serology. Similarly, patients with

unusual immune systems (e.g., HIV infection) could have false-negative assessments. An excessive sensitivity (95%) of the direct agglutination check (DAT) for Ethiopian VL-HIV co-infected patients has additionally been mentioned. Few studies have assessed the performance of the main serological tests in HIV-positive patients in East Africa. Compared to HIV negative individuals, sensitivity of the rK39 RDT was lower (77% versus 87%) [3, 5, 23].

The rK39 dipstick test is a simple, fast, noninvasive serological method that has shown high sensitivity and specificity in the diagnosis of immune-competent VL patients from different countries. But Studies didn't done well on Leishmania HIV co-infected patients from different countries [3].

Culture: The culture of splenic aspirates has shown a high sensitivity (63 to 100%) for Leishmania-HIV co-infected patients, but due to the risk of internal bleeding, bone marrow aspiration is recommended because it is safer and has a similar sensitivity (50 to 100%). Cultures of bone marrow aspirate specimens represent an increase in sensitivity of approximately 7% compared to direct examination.

The culture of mononuclear peripheral blood cells reaches a sensitivity of 64 to 67%. And Cultures have to be examined every week by light microscopy, looking for promastigote forms and subculture into fresh medium. Cultures are considered negative if no flagellates are observed after 4 weeks. In case of cutaneous and mucocutaneous to lessen the possibility of dissemination and relapse in CL-HIV and MCL co-infected patients, systemic remedy is suggested over nearby remedy, with near tracking and comply with-up of the patient [3].

Molecular Technique: Molecular diagnoses involving PCR combine several advantages: PCR is minimally invasive, has a high sensitivity and specificity and is capable of identifying relapses and re-infections in treated VL patients. Leishmania PCR assays the use of bone marrow samples and peripheral blood as medical specimens proved to be a dependable tool for the diagnosis of VL in HIV-positive patients. Having sensitivity for bone marrow samples varies from 82 to 100%, however these techniques remain restricted to referral hospitals and studies facilities. Real-time quantitative PCR (RTQ-PCR) is recently applying to the diagnosis and monitoring of Leishmania infections. Its main advantages include a reduction in the time needed for the assay and the possibility to quantify the parasitic load of the clinical sample.The existence of both Leishmania and HIV in the same cell has been shown to influence the multiplication and expression of either one or both organisms; it is believed that in co-infected patients, there is a symbiotic relationship between Leishmania parasites and HIV. Leishmania parasites stimulate chronic immune activation, leading to an increased HIV viral load with faster progression to AIDS [4].

Leishmania Treatment in Hiv Co-Infection: In case of cutaneous and mucocutaneous to lessen the possibility of dissemination and relapse in CL-HIV and MCL co-infected patients, systemic remedy is suggested over nearby remedy, with near tracking and comply with-up of the patient. Pentavalent antimonial drugs, sodium stibogluconate (SSG) and Meglumine antimoniate is using for CL-HIV and MCL-coinfected patients following treatment with L-AMB & Miltefosine for patient failing antimonial treatments [3]. Access of HAART, HAART has reduced the risk of relapse in CL &MCL infections in HIV-positive patients' and also decrease frailer rates but not clear the parasites [4, 8].

Treatment of Visceral Leishmaniasis and HIV Co-Infection: Pentavalent antimonial drugs, sodium stibogluconate (SSG) and meglumine antimoniate have been used for past decades as first line drugs for treatment because of their low cost and availability in most countries. Currently, this option has been sidelined due to their unacceptable toxicity and high rate of treatment failure and mortality. It has been repeatedly shown that antimonials are poorly tolerated among patients co-infected with HIV and VL in Europe The 6-fold higher odds of mortality associated with SSG treatment, in comparison with miltefosine treatment, among patients who had been both HIV positive or whose HIV status changed into something strange strongly indicates that lots of the mortality amongst HIV-infected patients became resulting from the SSG remedy itself [24].

In a recent Ethiopian study, high parasitologically, confirmed treatment-failure rates (30%) were observed in HIV infected patients treated with antimonials. Currently available evidence suggests superiority of amphotericin B in the treatment of HIV infected patients with visceral leishmaniasis (VLHIV) because recent literatures show that the higher mortality rate among VL-HIV patients treated with SSG than among patients treated with amphotericin B. It could be due to the low efficacy or the toxic effects of antimony; however the risk

of death seems to be related to the increase in SSG dose, suggesting that toxicity is the most important factor [5, 23, 24].

Combination treatment with Ambisome +Miltefosine is the recommended option of treatment or miltefosine, paromomycin and liposomal amphotericin B), preferably to be used in combination. and enhance treatment effectiveness and may delay on set of drug unresponsiveness [23].

Antiretroviral: Access HAART, HAART has reduce the risk of relapse in VL infections in HIV-positive patients and also decrease frailer rates but not clear the parasites [23].

Prevention and Control: The modern manage techniques for Leishmaniasis relies upon on reservoir and vector management, the usage of insecticide-impregnated substances and lively case detection and remedy; anti-leishmanial vaccines are nevertheless now not developed [5].

Reservoir Control: Dogs are the main reservoir of *L. infantum* in zoonotic VL. following serological screening of dogs and killing of sero-positive animal is seems better because; Treating infected dogs isn't an valuable treatment approach as relapses are frequent and puppies can regain infectivity weeks after remedy, in spite of being clinically cured. Moreover, the widespread veterinary use of VL drugs might lead to resistance in parasites. But still, the efficiency and acceptability of this control strategy is increasingly being debated [5, 11, 25].

Vector Control: Sand flies are susceptible to the same insecticides as Anopheles mosquitoes, the malaria vector. Residual insecticide spraying of houses and animal shelters are better mechanisms.

Insecticide-Impregnated Materials: The use of insecticide-treated bed nets (ITNs) could concomitantly prevent VL and other vector-borne diseases, such as malaria. Scale up community awareness by Continuous Health education programme [5].

CONCLUSION

The expanding and overlie of each and every leishmaniasis and HIV infections within the major foci of leishmaniasis (India, Brazil and eastern Africa) make VL-HIV co-infection a critical international problem. The mobility of people, such as seasonal migrant laborers, urban migration from rural areas, resettlement activities from areas where the disease is non-endemic to those where it is endemic and the presence of refugees and internal population displacements due to war and conflicts constitute major factors for the spread of both diseases. Both HIV and *Leishmania* infections induce a deficit in host humoral and cellular responses that limits the diagnostic value of serological tests for co-infected patients. Only 40 to 50% of VL-HIV co-infected patients have detectable specific antibody levels against *Leishmania*.

The high parasitic burden of leishmaniasis in HIV-infected individuals permits the detection of *Leishmania* antigens, but there is only one technique currently available for antigen detection (KAtex, used for urine samples). It is crucial to try to restore cell-mediated immunity with HAART as soon as possible to prevent further relapses of VL, even though HAART alone is not enough to prevent VL relapse.

All anti-leishmanial therapies are less effective in HIV-positive patients. There is a high mortality rate due to concurrent illness, complications and drug toxicity. Pentavalent antimonies and AMB are greater noxious to HIV patients, who require close tracking for pancreatitis, cardio toxicity and nephrotoxicity and those drugs need to be prohibited if effective drugs, inclusive of liposomal formulations of AMB, are existing. Miltefosine is a safer drug for co-infected patients, although there are still problems of teratogenicity and adherence to consider. In general, patients who fail to clear the parasite will relapse, independent of the drug used. Relapses should be treated appropriately and combination therapy may represent the best approach to avoid drug resistance while balancing benefit with drug toxicity and should be administered sequentially (with the safest given first) rather than concurrently.

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