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# Profile of Patients' Visceral Leishmaniasis-HIV co-infection in Kabylia

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## Abstract

Visceral Leishmaniasis (VL) disease, endemic to Algeria, is a major public health problem for children from rural areas and suffering from malnutrition, this disease currently tends to decrease. However, we found a constant progression in adults over the last twenty years. Indeed, 64 cases of VL in adults were recorded between 1991 and 2010 in Kabylia (Tizi-Ouzou, Bejaia and Bouira) with 18 cases with VL/HIV co-infections. Co-infected men is predominant with 15 cases, a sex ratio of 5 and an average age 35.57 +/- 2.3 years. Typical clinical signs, namely; fever, splenomegaly and hepatomegaly are observed only in 22.2% of the cases; absence of fever (n=4), splenomegaly (n=2), two (n=2) and presence lymphadenopathy (n=5). We also noted the presence of risk factors such as the advanced age of patients and late diagnosis of visceral leishmaniasis usually associated with the advanced stages of HIV infection (III, IV) in mostly multi-infected patients. We also identified five (5) cases of shingles and four (4) cases of digestive candidacies who were the most opportunistic infections observed in our series. Pancytopenia, observed in 2/3 of the cases has been the most consistent biological sign and contributing in the evocation of the VL as the clinical presentation was atypical. The confirmation, by direct examination of bone marrow smears by identifying amastigotes, is observed in all HIV patients (PVIH). Western blot and PCR techniques have allowed better monitoring of patients. In 5 cases, the VL revealed the infection of HIV. The care was difficult because of the numerous observed relapses. The unavailability of Amphotericin B, inherent in different factors, compelled us, in some situations, to use the Glucantime as first-line treatment (n=4). Prophylactic treatment based on Pentamidine (n=2), Glucantime (n=2) and amphotericin B (n=12). The evolution was marked by 5 deaths during the first days of treatment anti-Leishmanial and one after several relapses were observed as well as a resistance perhaps to Glucantime resulting in splenectomy.

**Keywords:** Visceral leishmaniasis; Co-infection VIH; Adults; Kabylian

## Introduction

Leishmaniasis is a group of parasitic diseases constantly expanding and widespread in the world. Almost not controlled because neglected, they particularly affect the poorest populations of the world [1]; the determining factor of the spread is the bite of a sand fly [2]. Global warming and environmental changes also contribute to the expansion of the development of their area [1]. Three active players are essential to maintaining the epidemiological chain and sustainability of this zoonotic disease in endemic areas: the reservoir, the vector and environmental changes [3].

Extremely complex disease characterized in humans by a variety of clinical forms; it is the result of a complex entanglement between the environment, the reservoir hosts, vectors, parasites and a mosaic of genetic and immune factors. Its visceral presentation (VL) is the most serious form because fatal if untreated. Reported mainly in tropical areas, it is also present in temperate regions such as the northern Algeria, one of the most affected countries of Maghreb. It is endemic state, with sub-humid bioclimatic and sub arid [4], with the appearance new outbreaks extending west and arid regions of the south [5].

Algeria is a young country, where the aged under 35 represent 63% of the population estimated at 40,590,000 (2016) with a growth rate of 1.92%. Today, it pursues an expanded monitoring program of vaccination and a strict control of waterborne diseases (MTH). Nevertheless, it remains exposed to emerging diseases including HIV/AIDS as well as zoonoses (leishmaniasis, brucellosis, hydatid cyst and rabies). It is a real public health issue sustained by the involvement of different factors (deterioration of environmental health, increasing number of family farms little or no vaccinated, border movement of illegal and uncontrolled livestock, weakness struggles devices, regression of sanitary measures).

The last two decades, leishmaniasis has become a major public health issue. Traditional households accounted for over 50% of reported cases extend out of Kabylia (large and small) [5,6]. We are witnessing the emergence and geographical redistribution of VL, with appearance of new endemic foci accompanied by an increase in scattered cases in the Dry Areas (Illizi, Tamanrasset, Mila and Tissemsilt) previously unaffected [7]. All this led to epidemiological changes sometimes with the coexistence of two clinical forms (VL and cutaneous zoonotic leishmaniasis) at the same household [4].

The progression of the disease is topical, with an increase in VFL adults [8], the emergence of resistant forms, an urbanization of parasitosis and geographic overlay rural homes of VL and urban areas of co-infections VL/HIV. This risks aggravating the epidemiological situation of tuberculosis and HIV/AIDS [5,9], in the region due to co-infection with an impact in terms of psychological, socio cultural and economic [10] This requires greater vigilance both from clinicians and citizens. That leads us to carry out this work of epidemiological analysis, clinical, biological and therapeutic cases of VL co-infection / HIV / AIDS in Kabylia which remains scarce and little reported in our country [6].

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## Materials and Method

With the waning of a comparative study of two-part, the first retrospective from 1994 to 1999 and the second prospective descriptive from 2000 to 2010: 18 cases of coinfection HIV1/AIDS/VL in adults are diagnosed, all natives and/or residents "in Kabylia" endemic focus which remains the case provider of VL coexisting with canine enzootic in Algeria.

We included in this study all adult patients with HIV-positive serology (2 different ELISA) confirmed by Western blot with identification: direct examination of bone marrow smears of amastigote leishmania or culture (marrow bone), the biopsy (liver, colon and lymph node) and PCR (methods of microscopy and nucleic acid and species identification by sequencing and molecular --other techniques (detection antibody))

For each patient, information was recorded: sociodemographic characteristics (gender, age, occupation, marital status, place of residence), the clinical profile (HIV type, diagnostic delay of the VL to HIV, discovery circumstances, clinical stage according to the WHO classification, clinical symptoms, opportunistic infections have preceded or followed the initiation of treatment, the immunological profile during the VL, the type of treatment established and the evolution of coinfection VL/HIV).

## Objective

Review with epidemiological analysis, immunology, clinical, diagnostic and therapeutic of 18 cases of coinfection VL/HIV in Kabylia.

## Results and Discussion

In Algeria, the first case of co-infection VL/AIDS was reported in 1985 in a native patient of Boussaâda with AIDS stage with an extensive skin leishmaniasis [11]. In 1999, 426 AIDS cases were reported in Algeria [12] including 13 cases (3%) of co-infection VL/AIDS. The majority of patients are from Kabylia, emigrants living abroad where the diagnosis of viral infection was confirmed and VL was incurred during a stay in the country. All patients were men belonging to the age group of 35-50 years.

We report the waning of a comparative study between a kind of retrospective recruitment from patient records in VL n=8 including 4 co-infected VL/HIV, collected from 1991 to 1999 and a prospective recruitment n=56 which 14VL/HIV from 2000 to 2010.

### Demographic - Social data

A total of 64 cases of VL of adult patients are listed in Kabylia in 20 years. Including 18 cases of VL co-infection/HIV/AIDS all natives from the region. Obvious endemic area of visceral leishmaniasis in children and canine enzootic.

### Origin

11 cases are originally from Tizi-Ouzou, 4 from Bejaia and 3 from Bouira. The number of cases is significant in the second period (2P) with 14 cases against 4 to the first (1P).

### Gender and age

The men reached a majority with 15 cases, a sex ratio of 5 and a mean age of 35.57 +/- 2.3 years with an extreme of [18-61 years]. 66.7% (10 men/2 women) belong to the age [6,8,13-30].

### For their marital status

We note 13 married patients among which three HIV-positive women: two of them had lost their husbands due to undetermined causes including one abroad, and the third was diagnosed with the waning of hospitalization for recurrent pneumonia with a history of ABRT and the loss of a child. One patient had multiple wives (n=5, 2 of them died).

### Occupation

The three women of the 18 cases of co-infection VL/HIV were housewives. Two of them lived in the village with their husbands' family who emigrated abroad. The men 2/3, are immigrants, we find professions like; trader (n=4), farmers (n=3), workers (n=4, daily, café owner), officials (n=2) and informal sector (n=2).

High risk factors are reported; such as heterosexuality asserted (11H/3F), bisexuality (2H), an addictive behavior to drug (6H) and a stay in prison in two patients.

All patients in the study were infected with HIV-1. Monitoring their CD4 counts and their viral load was not constant, often not available; nevertheless, we note its frequent feasibility for the prospective study (2P). In the majority of patients (88%) the diagnosis of viral infection was made at a late stage with CD4+ ≤ rate (200/mm<sup>3</sup>). 38.9% of our patients have no assay result of CD4 T cells. 61.1% of patients had CD4 assay (the rate was between 6-135). They were in stage C of the CDC classification and 63.64% of patients were in stages 3 and 4 of the WHO classification.

During the management of four cases of VL, an HIV+ was revealed significantly to the 2nd P against one case to the 1st P. We note that 14 cases of VL were grafted on HIV+ whose diagnosis in 2/3 of cases was done in advanced clinical stages (III and IV of the WHO classification) with opportunistic infections. Their profound immunosuppressant had increased the risk of morbidity and mortality (Table 1).

Clinical subjects with co-infections VL/HIV differs little from the table immunocompetent association with VL. In our series; fever and weight loss were noted in 14 patients (77.8%), splenomegaly in 16 (88.9%), while hepatomegaly is found in only 1/4 of cases (28.57%) and lymphadenopathy recorded in smaller proportion; three cases (21.4%). Beside these classic forms, atypical forms, pauci or asymptomatic are noted, often the cause of delayed diagnosis conditioning prognosis with a discovery of co-infection in polyinfected patients (n=3) at late stages HIV infection (III and IV). This often reflects the ignorance of the

Co-infections VL/HIV/AIDS	1 <sup>st</sup> Period «1991-1999»	2 <sup>nd</sup> Period «2000-2010»
<b>HIV/VL</b>	4/8	14/56
<b>Origin</b> Tizi-Ouzou	4	7
Bejaia		4
Bouira		3
<b>Sex</b>	3♂ 1♀	12♂ 2♀
<b>21-40 years</b>	1♂ 1♀	9♂ 1♀
<b>&gt;50 years</b>	2♂	3♂ 1♀
<b>Risk factors for HIV-1</b>		
Drug addiction	1♂	5♂
<b>Hetero sexuality</b>	3♂ 1♀	8♂ 2♀
Bisexual		2♂
<b>CD4 rate</b>	3 patients	8 patients
200<CD4	[09, 35, 135]	[06, 09, 23, 35, 42, 59,
The Viral load	[1740-55 000]	134, 135]
		[1740-750 000]
<b>Known HIV infection</b>	3/4	10/14

**Table 1:** Epidemiological, clinical and biological characteristics of cases.

association. VL often transplant on the grounds of immuno-deficiency. We noticed the absence of fever in four patients, no increase in spleen size in both cases and the absence of fever and no increase in spleen size in two male patients. The latter finding was observed in two patients which delayed the treatment of VL while patients were HIV+ (Table 2).

### Biological characteristics

We do not find specific hematological characteristics during coinfection VL/HIV; few cases with severe anemia (n=2), a mean hemoglobin  $6.50 \pm 1.3$  g/dl, lymphopenia (n=15), leukopenia (11.1%), thrombocytopenia (5.5%) and neutropenia (5.5%). There are also three cases of bicytopenia and twelve cases of pancytopenia. Nevertheless we note the difficulties encountered in the allocation of these anomalies in VL, to the direct action of HIV itself or the interference of anti-infective drugs multitudes (polyinfected, opportunistic infections) and cytopeniant drugs (as AZT and cotrimoxazol) (Table 3).

The most observed biological association is clinical; pancytopenie with splenomegaly+fever (4 cases) and hepatosplenomegaly+fever (4 times) and to a lesser extent, an isolated lymphadenopathy or splenomegaly or a simple lymphadenopathy and splenomegaly (Table 4).

### Diagnosis of leishmaniasis in HIV-infected patient

In the whole cases (18) of the study, the diagnosis of VL was established by the direct demonstration of amastigotes in the blood and bone marrow. In both cases the diagnosis VL was supported by the positive results of PCR (polymerase chain reaction) specific peripheral blood Leishmania (1 case) and bone marrow samples (2 cases) (an undeniable contribution). Eight patients were diagnosed by serological tests (indirect immuno fluorescence n=4 and Western blot n=4) (Table 5).

Period	1991-1999	2000-2010	Total
Signs	N%	N%	Nb
Fever	3 75	11 78.6	14
Slimming	4 100	11 78.6	15
Splenomegaly	3 75	13 92.8	16
Hepatomegaly	1 25	5 35.7	6
Lymphadenopathy	2 50	3 21.4	5

Table 2: Clinical signs.

Period	1991-1999	2000-2010	Total
Anomaly	N	N	
Anemia $\leq 5$ gr/dl	1	1	2
Leucopenia	1	2	2
Bicytopenia	0	2	3
Pancytopenia	2	10	12

Table 3: Biological characteristics.

Period	1991-1999	2000-2010	Total
Clinical association	N	N	Nb
Spg+F+Pcp		4	4
Spg+F+Lp		1	1
Spg+F+An	1	1	2
Spg+F+Adp+Pcp	1	1	2
Spg+F+Adp+Bcp		1	1
Hpg+Spg+F+Pcp	1	3	4
Hpg+Adp+Pcp		1	1
Hpg+Spg+Pcp		1	1
Adp+Spg+Lp		1	1
Adp+Lp	1		1

\* F: Fever; Spg: Splenomegaly; Hpg: Hépatomegaly; Adp: Adenopathy; An: Anemia; Lp: Leucopenia; Bcp: Bicitopenia; Pcp: Pancytopenia

Table 4: The most biological/clinical association.

\* Opportunistic infections frequency Zona (3), hepatitis C (2), cryptococcosis (2), Pneumocystis pneumonia (2), a tubercular disease (2), and hairy leukoplakia.

### Opportunist infections

The mean opportunistic infections noted in our patients were cutaneous (10), digestive (12), neurology (2) and pulmonary (4) (Table 6).

\* Thirteen of our HIV patients were at an advanced stage of the disease when antiretroviral therapy was initiated. Two have not been treated, they were at an advanced stage of coinfection VL/HIV complicated with polyinfection and died the first days of hospitalization. Glucantime was established first intention in 4 patients and fourteen cases with amphotericin B. The prophylaxis was initiated in all patients (n=16), both with Pentamidine twelve with amphotericin B and too with Glucantime. 3 patients presented relapses among which a patient in treatment failure requiring splenectomy (Table 7).

### The evolution

The evolution of the disease is marked by the frequency of relapses observed in three patients all supported at the P2 of the study and two of which died.

In a recent study, we noted five deaths: one during the P1 study, three during the P2 and one during the follow-up in April 2016. Two are lost to follow-up and the others are still under surveillance, two of which are no longer receiving maintenance treatment.

### Comments

The World Health Organization estimates that about 900,000 to 1.3 million new cases of leishmaniasis are reported per year, of these, approximately 0.2-0.4 million are of visceral leishmaniasis (VL) [3].

Exams	1994-1999	2000-2010	Total
Born marrow	4	14	18
PCR+	NF	3/5	2
Culture+	NF	0/3	0
Serology IFI+	2/4	2/5	4/9
WB+	2/4	2/5	4/9

Table 5: Diagnoses.

Period	1991-1999	2000-2010	Total
Opportunist	N %	N %	
Hepatitis C	/	4 28.6	4
Hepatitis B	/	1 7.2	1
Tuberculosis Pneumonia	1 25	1 7.2	1
Zona	/	5 35.9	5
Seborrheic dermatitis	2 25	3 21.8	3
Meningitis cryptococcosis	/25	2 14.3	2
Pneumonia pneumocystis	1 25	1 7.2	1
Hairy leukoplakia	/	2 14.3	2
Colonic Lymphoma	/	1 7.2	1
Digestive candidiasis	2 50	4 28.6	2

Table 6: Opportunist infections.

	Glucantime*	Amphotericin B*	Pentamidine*	Total
1 <sup>st</sup> intention	4	14		18
2 <sup>nd</sup> intention	2	14		16
Interview	2	12	2	16

Table 7: Therapeutic lines.

Visceral Leishmaniasis is the most severe form of a parasitic disease transmitted by insects prevalent in 98 countries [26]. HIV infection is a major public health problem. Globally, 36.9 million people living with HIV with 2.0 million new infections per year [31]. 35 countries currently report cases of co infection (Leishmania/HIV) in in 2-12% of all cases of VL, This proportion increases dramatically [16].

The first case of leishmaniasis associated with HIV has been reported in Algeria in 1985 and in the region of Kabylia in 1991 [14]. Visceral leishmaniasis (VL) and HIV (HIV) co-infection has emerged as a model of severe disease [32]. Between 1991 and 2010, 64VL cases were recorded in three regions of Kabylia (Tizi-Ouzou, Bejaia and Bouira) with 18 cases of coinfection VL/ HIV/AIDS. In Algeria very few cases of VL/HIV coinfections are reported (less than 35 cases). The historical entity of infantile VL cases is not current. The endemic Kabylia region is the bigger provider of infantile cases in our country, but faces a constant increase in the adult form and VL/HIV co-infections these two last decades. This work is a comparative study between two periods P1 retrospective study with 8 cases of which 4 co-infections VL/HIV and P2 exploratory study with 56 cases adult of which 14 cases of co-infections.

The presumed parasite infestation place corresponds to areas of endemic diseases known to VL (Tizi-Ouzou, Bejaia and Bouira), which is also the birthplace and/or patient residence. As for literature, it reduces the frequency of occurrence of this association (parasitic diseases-HIV) in case of travel and/or stay in immunocompromised patients of endemic area can be up to 2 or 3 years later [11,28,33,34].

VL is an opportunistic parasitosis emerging since 1980 on the southern shore of Europe [3,20,35], where nearly 1500 cases of HIV/ Leishmania co-infection are reported by Alvar [3]. In the last decade in the Maghreb, its incidence in HIV+adults is steadily increasing.

By 2015, 51% of all adults living with HIV (approximately 17.8 million) are women (aged 15 years and older) [25]. In the Maghreb, women account for 38% of newly infected adults, nearly half (48%) of whom are between the ages of 15 to 24. In our study the incidence of HIV infection remains generally higher in men than in women 15 versus 3 [17,36,37].

The sexual contamination remains in our country the most common mode of transmission. Contamination via heterosexual intercourse is 88.9% of cases (18.7% women). Men who have sex with men (MSM) are the only group whose HIV-positive findings increased between 2003 and 2011 [36,38]. However, in Europe, the use of IV drugs is a major risk factor [36], affecting 76% of cases in a study of 781 cases between 1990-1998 and 67% of cases on a study of 95 cases performed between 2001-2006 [5,11].

The role of substance abuse (injectable way) in the transmission of the parasite is reported respectively 92.5% and 50% of cases by Montalban and Cabier [22,39]. Desjeux and Alvar in a series of 1911 cases, patients between 31-50 years are reported in 77,3% of cases, for the most part male (85%) with 70% of injecting drug users, for whom serology was falsely negative in 40% of cases [32,40].

This mode is not noted in our series and there is a decline in its incidence since the awareness of populations at risk with the use of sterile single material. In two of our patients with drug addiction (acquired during stays abroad), we find the concept of needle exchange with people unknown serological profile and anarchic sexual behavior. Therefore it was difficult to determine the mode of contamination. For the women of our series who contracted the infection, they were

not aware of the disease of their spouses; moreover their status was only discovered during a hospitalization for opportunistic infection (pneumocystosis, dermatosis mucocutaneous and candidiasis) and advanced stages of the disease. This indicates unconsciousness infected patients, who often hide their disease especially for societal considerations (taboo).

In a series of 965 cases studied between 1990 to 1998, the average age of patients was 38.6 years and 38.9 years in another series of 253 cases studied between 2001 to 2006 [11,41]. The average age of our series 35.57 +/- 2.3 years (18-61) is close to the averages quoted and below the average (37 to 48 years) reported by the [WHO].

Many studies suggest that VL will gladly transplant in patients with evidence of immunosuppression with a CD4 count <200/mm<sup>3</sup> (2). In our study, this assay was performed only in 61% of cases (n=11), with an average CD4 of 40/mm<sup>3</sup> with extremes of 6 to 135/mm<sup>3</sup>. In a few cases, viral loads were performed (n=4) [39]. All this leads us to screenings when acquired immunosuppression, if stays of recent or old travel or transit through traveler from increased traffic to airports from endemic areas.

In two patients, the diagnosis of co-infection was made at admission, in 10 cases of HIV infection had been known for at least 2 years and one year in one case. In all five cases (27.8%), or VL revealed HIV-seropositive (Montalban 10%) [22], we find the notion of pets (particularly dogs) in the immediate vicinity associated with a permanent residence in endemic areas [15]. 11 patients classified as stage C AIDS CDC classification have proven track record of opportunistic infections before or during the first episode of VL [36].

Clinical manifestations were mostly atypical, suggesting different infections, which resulted in delay in initiating treatment. The weight loss reported in both VL and HIV infection is multifactorial. This weight loss is noted in 83.3% and has often been the reason for consultation in our series. Fever and weight loss were associated with 14 cases in more than 3/4 of the cases (77.8%) and splenomegaly in almost all cases 16% (88.9%), whereas hepatomegaly was only noted in six patients: 1/3 of cases (33.3%), and lymphadenopathy in a lesser proportion: five cases (21.8%). The clinic observed in our patients merges with the literature. Alvar in 2002 noted the presence of fever in all patients as well as splenomegaly and paleness [40]. Other authors state that the clinical features are not always present and that non-specific signs are often confused with those of other opportunistic infections, parasitic, fungal, bacterial or viral (data observed by Cabier, Montalban, Pagliano) [22,28,39].

The absence of major signs: fever (22.2%), splenomegaly (11.1%) or both were particularly observed in the second study period (P2). Inconstancy of these signs is observed in the series but has been little reported [42].

The classic triad splenomegaly, anemia and fever is little reported in the literature in patients co-infected VL/HIV, as well as in our series 11.2% (n=2) [18].

\* Different hematologic events are reported individually to the waning of the VL and/or HIV. When co-infection, abnormal blood counts are almost constant, often compounded by the side effects of multiple therapeutic: ARVs and anti-infective (antibiotics, antifungal and antiparasitic) conditioning an already diminished prognosis co-infection.

Pancytopenia is the most observed biological perturbation, reported in the literature [36] and noted in more than 3/4 of the cases



(80%) in our series. The first observations of pancytopenia associated with AIDS have been described since 1983 [21]. Two patients presented severe anemias  $<5$  g/dl at admission and died within a few days. The lymphopenia observed in 83.3% of our patients testifies to the evolution of the HIV infection (advanced stages of infection with multiple opportunistic infections), hence the consequent collapse of the value of total lymphocytes. The cytopenias noted at variable frequency (leukopenia  $n=2$  and thrombocytopenia  $n=1$ ) in our series reflect peripheral and/or central (bicytopenia) involvement.

\* The diagnosis of VL whether in an immunocompetent or immunocompromised based on identification from bone marrow smears, lymph node aspiration or puncture splenic amastigote arranged in clusters in all cases by the Giemsa or Leishman staining [43]. Puncture aspiration of the marrow is an examination of choice and high sensitivity (62-94%), safely and privileged over the splenic puncture is not without risk. Unfortunately suction by aspiration is not practiced in the Maghreb countries [18] (With regards to the diagnosis of VL, parasitological tests of bone marrow aspirates have proved to be the most sensitive test in HIV-infected patients).

The techniques of IFI, Western blot and PCR were an undeniable contribution in the P2 study. And the PCR is an excellent criterion for assessing the evolutivity of parasitosis in subjects at risk of relapse. In our series, at the time of diagnosis of VL, our patients were in severe immunosuppressive stages (advanced AIDS stage). They had already made at least one other HIV-related opportunistic infection. 11 had CD4 lymphocyte counts  $<135/\text{mm}^3$  (Data reported by Alvar and Paintado 42% to 72%) [2,39].

The main opportunistic infections observed in our work are: Cutaneous localization (3); Zona (5), mouth candidiasis (2), hairy leukoplakia (2), digestive with hepatitis C (2), neurology; cryptococcal meningitis (2), pneumonia with *Pneumocystis pneumonia* (1) and tuberculosis (1) [24,27].

\*Treatment and follow-up, the care of our patients with established treatments and scalable monitoring was consensual. The strength of the series studied is small ( $n=18$ ) making it impossible to draw statistical conclusions. During VL/HIV co-infection, the two pathogens target the same cells and exert a synergistic deleterious effect on the cellular immune response, hence the more rapid evolution of the retroviral infection and the difficulties encountered during treatment; Two patients received only a few days of anti-VL (Amphotericin B) treatment before they died, they were at an advanced stage of VL/HIV and poly-infected co-infection.

13 co-infected patients had a classic response to treatment Leishmaniasis (with maintenance) and a conventional monitoring to date; 9 were undergoing ARV therapy to discover VL. 5 had CD4  $<135/\text{mm}^3$  at diagnosis of VL with an HIV viral load at more than 50,000 copies/ml ( $n=2$ ), 11 were under Amphotericin B in 1st intention and maintenance, was vitiated by any side effects related to treatment, only two patients had a change of ART for the treatment of co-infection.

During the long follow-up of our patients, many relapses were managed in 3 patients.

The first case was 23 years old when he was diagnosed with VL, he was originally from Bejaia and had been on antiretroviral therapy since 2007 and he was diagnosed with co-infection at the end of 2008 and was given Glucantime and then Amphotericin B with maintenance of therapy. Immune reconstitution is slow, during follow-up, several relapses are noted. In spite of the splenectomy carried out in 2014,

the marrow remains rich in parasites, indicating either the presence of a parasitized zone inaccessible to the treatment or the absence of immune restoration or the resistance of the parasite. Intolerance and adverse effects of treatments (cardiac toxicity, renal and hypocalcemia), unavailability of therapeutic alternative (such as Amphotericin B liposomal not ATU) make the patient therapeutic escape and died in April 2016.

The second patient ( $n=6$  relapses), Glucantime\* was used as first-line treatment and maintenance but not observing, 2<sup>nd</sup> cure with Amphotericin B then relay maintained at 2 mg/kg per month. Despite the reduction in viral load that decreased to the point of becoming undetectable (more assiduous patient) with a CD4 count  $>200/\text{mm}^3$ , the patient continued to relapse, switching to maintenance dose of 10 mg/Kg/week with Amphotericin B\* was effective.

The third unruly patient, relapse ( $n=3$ ), multiple addictive behavior; addict (IV and oral, ethyl), with CD4 counts at diagnosis of VL  $09/\text{mm}^3$  received amphotericin B\* (first-line and maintenance) and then lost sight of not observing its treatment modification ARV therapy in the treatment of coinfection, dies in a clinical picture suggestive of encephalitis meningoencephalitis with polyinfection (meningeal cryptococcosis, hepatitis C, digestive candidiasis) after stopping treatment. Davidson reports 80% recidivism in the case of co-infection [44] and Alvar reported an increase in this frequency when using DP as in co-infections [45]. The unavailability of other therapeutic alternatives in Algeria (no ATU), (Ambisome\*, Pentamidine\*, Itraconazole\* Allopurinol\*) explains the absence of molecular association in our treatments especially in cases with repeated relapses). This could enhance the effects of drugs, reduce the duration and reduce the risk of resistance development (mentioned in both cases) [46,47].

From these examples we can see that the factors that maintain relapse and determine the prognosis is the fact of living in a high endemic areas, the support of delay, advanced co-infection stadiums, immunosuppression Profoundness during the first episode of VL, the attainment of different organs (high parasitic load), the delay or lack of restoration of immunity and the chronicity of evolution.

Although there is a theoretical consensus in the management of patients co-infected with HIV and visceral leishmaniasis, driving in practice it is not always easy and often put in check. The atypical clinical manifestations wander the diagnosis of visceral leishmaniasis. That often constitutes a circumstance of discovery of HIV infection and often at a late stage of immunosuppression. The frequency of stibio-resistance, drug toxicity molecules (Glucantime\*, amphotericin B), the unavailability of lipid amphotericin B drift (excessive cost) and the long duration of treatment (processing) complicate the observation and monitoring of patients and promote relapse.

Factors influencing the choice of our therapeutics that was not so wide that this view, we do not have the ATU for other molecules in the cost of treatment and the duration of hospitalization. The price of amphotericin B lipid formulations is inaccessible in developing countries.

## Conclusion

This study shows the complexity of the management of HIV/visceral Leishmaniasis co-infection. The diagnosis is difficult because the clinical forms are atypical. The pathogenic effects of HIV infection and VL are potentiated in patients co-infected with HIV/VL, increasing morbidity/mortality, with less effective first-line therapy. The risks of relapse are linked to "sanctuary zones" inaccessible to the treatments or

resistances of the parasite to the molecules used despite their toxicities in monotherapy in the first line therapeutic due to lack of molecular alternatives (not ATU, excessive cost). Immune restoration by ARVs is essential but insufficient for healing.

In the last decade, the association of visceral leishmaniasis and HIV is often brought to the banks of the Mediterranean. In Algeria, VL is a public health problem and the incidence of co-infection has not been established with precision. Kabylie, endemic area for visceral leishmaniasis, sees a number in co-infection in adults, progress. There is a complex management of HIV/visceral leishmaniasis co-infection. Diagnosis is difficult because clinical forms are atypical. The pathogenic effects of HIV infection and potentiate VL in patients co-infected with HIV/VL, the upper limit morbidity/mortality with a less effective first line of treatment and the risk of relapse, of "refuges" inaccessible treatment. Immune restoration with ARVs is essential but not sufficient for healing.

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