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Research Article

A Retrospective Analysis Comparing Treatment Response for Visceral *Leishmaniasis*-HIV Co-Infected Patients from the New World

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Abstract

Background: Visceral Leishmaniasis and Human Immunodeficiency Virus co-infection (VL-HIV) occurs mainly in risk groups for HIV/AIDS (youth adult males). These co-infected individuals have greater mortality and relapses rates compared to VL as they share similar immune pathogenic mechanisms. Interest in co-infection VL/HIV and the lack of data in the literature led the authors to a survey on the subject comparing outcomes in VL-HIV co-infected treated with different drugs anti-Leishmania used in Brazil, such that Pentavalent Antimoniate (MA), Amphotericin B deoxicolate (AmBd), and liposomal Amphotericin B (LAmB).

Methods: A retrospective descriptive study using routine program data was performed comparing drugs used for treatment of co-infected patients in Sao Paulo state, Brazil, among 1999-2010, observing their outcomes (cure, failure, relapse or death), and analyzing them by each drug used.

Results: In the period of twelve years were reported 1,614 VL cases in Sao Paulo state from whom 1 070 (66.30%) were HIV-negative, 117 (7.25%) were HIV-positive and in 427 patients (26.45%) HIV status was unknown. To compare treatment response according to drugs used, we included only the 117 VL/HIV co-infected patients. Related to demographic data we found 72.65% (85/117) of males and 80.34% (94/117) of young adults (21-50 years old). From 117 co-infected patients, 95 had complete data of the treatment performed and these were included in the analysis. The lethality of VL-HIV co-infected patients was 24.2% (23/95) and general relapse rate was 10.5% (10/95). Deaths in co-infected were more prevalent among 31-50 years. According to drug used, 35.64% (36/101) were treated with pentavalent antimoniate (20 mg/kg/day per 28 days), 12 (11%) received Amphotericin B deoxicolate (AmBd) (total dose: 20 to 24 mg/kg) and 47 were treated with Liposomal amphotericin B (LAmB) (total dose: 20 to 24 mg/kg). Patients treated with PA presented similar cure rates compared to LAmB. Patients treated with AmBd had higher lethality and patients treated with LAmB had no failures.

Conclusion: High lethality and relapses rates occur in VL-HIV co-infected patients. Poor outcome leading to death was observed in AmBd group. There is an urgent necessity to perform prospective clinical trials to evaluate the safety and efficacy of different schemes for treatment of co-infected patients, especially in New World.

Introduction

Visceral Leishmaniasis and Human Immunodeficiency Virus co-infection (VL-HIV) has emerged as an important public health problem worldwide. However it was observed a decreasing in the number of co-infected patients in Mediterranean area [1,2]. VL-HIV has increased in East Africa and Latina America [3,4] and the prevalence of VL-HIV is still low in Indian subcontinent which estimates ranges from 2-5.6% [5]. The impact of VL-HIV co-infection is directly related to unusual clinical manifestation, poor outcome and worst treatment response for VL. Remarkably, HIV increases the risk of *Leishmania* infection to disease progression to VL and *Leishmania* enhance HIV replication, depleting more $CD4^+$ T Lymphocytes, leading the patient to AIDS more rapidly. As they share similar immune pathogenic mechanisms by attacking the same cellular immune compartment, there is an impairing in the immune response to opportunistic infections consequently [6,7]. By this way, atypical manifestation, high relapse and high lethality rates have been observed [3].

Reports evaluating drug response of VL in HIV co-infected patient are scarce [8]. Treatment failure has been observed in VL-HIV co-infected patients treated with Liposomal Amphotericin B (LAmB), pentavalent antimoniate (Sb^{V+}) or drug associations [9-14]. In Ethiopia, the reported risk of relapse at six months varied between 25.4% and 11.4%, as the drug used for treatment of co-infected were miltefosine or sodium stibogluconate, respectively [9]. After one-year of follow up,

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the relapse risk is close to 20% for individuals with primary VL and having a $CD4^+$ T cell counts of around 200 cells/mL and for those with multiple previous VL episodes and $CD4^+$ T cell counts below 100 cells/mL is around 60% [10]. In Europe (Mediterranean area specifically), pentavalent antimonials have been compared with Amphotericin B deoxicolate (AmBd) and Amphotericin B Lipid Complex (AmBLC) showing similar cure rates, but with more severe toxicity [15-17]. In Brazil, some reports have valuated the overall therapy response in co-infected patients showing relapses rates of 56.5% and 52.9% [18-19], and an increasing lethality ranging from 4.8 to 22.0%, depending on the drug used for VL treatment [9-14,20]. Indeed, these reports do not compare relapse and lethality rates among anti-*Leishmania* drugs used. Here we show the lethality and relapse rates in a cohort of VL-HIV co-infected patients from Sao Paulo state, Brazil, comparing the drugs response used to treat VL.

Methods

Study design

A retrospective descriptive study was performed to analyze the outcome (cure, failure, relapse or death) according to the drug used for treatment of VL, in HIV-coinfected patients.

Studied area and population

In this study, we included only patients whom presented VL confirmed by parasitological method and a positive result to anti-HIV serology from Sao Paulo state.

Diagnostic of VL and HIV

VL diagnostic: Patients presenting clinical signals suggestive of VL (fever, splenomegaly or hepatomegaly) from VL endemic area were submitted to bone marrow aspirate to detect *Leishmania* amastigotes by direct search, according to laboratorial routine (Guideline to Treatment and Diagnostic of Visceral Leishmaniasis from Health Ministry from Brazil).

HIV infection: All patients included in this study were submitted to serology from HIV, using ELISA method, according to laboratorial routine (Guideline to Treatment and Diagnostic of HIV/AIDS from Ministry of Health from Brazil).

Data source of VL and HIV/AIDS patients

VL data (clinical features, epidemiology and treatment) was carried out by searching databases from the Epidemiological Surveillance Center "Prof. Alexandre Vranjac" from São Paulo Health Department (CVE-SES-SP) and database from SINAN (National System from Ministry of Health of Brazil). Notification forms provided all information and it was not necessary to do a search in the medical records.

Regarding to data on HIV infection ($CD4^+$ and $CD8^+$ T cells count and viral load of HIV from HIV/AIDS patients), they were collected by active search in the database of STD/AIDS from Sao Paulo state in addition to the databases of CVE-SES-SP and SINAN.

Diagnostic criteria

VL cases: VL cases included were those with parasitological confirmation, i.e., presence of *Leishmania spp* in aspirate of bone marrow by direct search or culture.

HIV/AIDS cases: Patients considered to be HIV-positive were those with laboratory confirmation according to the Brazilian Ministry of Health, i.e., two screening tests (ELISA or immunocromatography) and a confirmatory test (Western blot, immunoblot, IFI) or by the presence of HIV viral load.

Outcome definitions

Cure: Absence of fever, reduced viscera (liver and/or spleen), weight gain and return of appetite, and the patient remained without symptoms and active signal of VL for twelve months at the end of treatment.

Failure: Regular treatment that does not meet criteria for clinical cure after a series of treatment.

Relapse: Recrudescence of symptoms within twelve months after the end of treatment.

Death: Information about death by VL or other causes (when not specified) until the closing of the case.

Data collection and statistical analysis

The Microsoft Excel 2007 program was used to produce comparative tables for analysis of the results and interpretation, after crossing information of data obtained from the CVE-SES-SP, SINAN and STD/AIDS databases, one complementing another. Individuals who were notified between 30 days after the start of treatment until one year of that were considered recurrence. Those with the same date of notification were considered duplicates and were excluded. Using the GraphPad Prism 3.0 (Chi-square and Fisher's exact test for categorical variables and Kruskal-Wallis One Way Analysis of Variance on Ranks for continuous variables) it was performed statistical analysis of demographic data. P values <0.05 were considered significant in this study. After performing the descriptive analysis and pointing out the frequencies of the independent variables studied they were characterized in two distinct groups: cure and death. Thus, a bivariate analysis of treatment and death was developed using the EpiInfo 3.5.4 program whose basic database was developed in Microsoft Excel 2007. It was performed chi-square test or Fisher's exact test for qualitative variables, which those with $p < 0.05$ were considered to make the completion of the multivariate logistic regression model, using the "stepwise forward", from the lower value of p to the largest. The existence of an association between death by VL and drugs used for treatment was investigated by unadjusted and adjusted estimates of Odds Ratios (OR) with confidence intervals of 95%, using unconditional logistic regression. The statistical significance of the variables in the models was assessed by likelihood ratio test.

Ethics

The data included in this retrospective analysis were constituted from routine data and was approved by the Ethical Committee of Department of Health of Sao Paulo state, respecting the National Counseling of Health for Scientific Research in Human Beings from Brazilian Ministry of Health.

Results

Demographic data

Table 1: Lethality and relapses in VL and VL-HIV co-infected in Sao Paulo State, Brazil, in the period from 1999 to 2010.

OUTCOME	VL	VL-HIV	*p* value*
Deaths % (No)	8.2(88/1078)	24.2(23/95)	0
Relapses % (No)	1.8(19/1078)	10.5(10/95)	0

*Chi-square (Fisher Exact Test).

From 1999 to 2010 it was reported 1,614 VL cases in Sao Paulo state from whom 1070 (66.30%) were HIV-negative and 117 (7.25%) were HIV-positive and 427 patients (26.45%) were excluded due to HIV status unknown. Only VL/HIV coinfected patients were included in the drug response analyze. We found 117 those VL/HIV coinfected patients (9.5%), being 72.65% (85/117) male and 80.34% (94/117) young adults (21-50 years old).

Overall treatment

From 117 co-infected patients, 95 had complete data of the treatment performed and these were included in the analysis. The lethality of VL-HIV coinfected patients was 24.2% (23/95). The general relapse rate was 10.5% (10/95). Deaths in co-infected were more prevalent among 31-50 years (Table 1).

Anti-Leishmania treatment

Regarding the drugs for VL-HIV co-infected treatment, 35.64% (36/101) were treated with pentavalent antimoniate (20 mg/kg/day per 28 days), 12 (11%) received amphotericin B deoxicolate (total dose: 20 to 24 mg/kg) and 47 were treated with liposomal amphotericin B (total dose: 20 to 24 mg/kg) (Table 2).

Pentavalent Antimoniate group (PAg): From those treated with PA, 80.80% (29/36) were young adults (21 to 50 years old) and 69.44% (25/36) were male. Cure was observed in 69.44% (25/36), whereas failures during treatment occurred in 11.11% (4/36) and relapses were observed in 2.77% (1/36). Lethality was 16.66% (6/36).

Amphotericin B deoxicolate group (AmBdg): From those treated with AmBd, 75.00% (9/12) were young adults (21 to 50 years old) and 83.33% (10/12) were male. Cure was observed in 41.66% (5/12), failures were 16.66% (2/12) and no relapses were observed. Lethality was 41.66% (5/12).

Liposomal Amphotericin B group (LAmBg): From those that used LAmB for treatment, 72.20% (34/47) were young adults (21 to 50 years old) and 68.08% (32/47) were male. Cures were observed in 63.82% (30/47), and no failures (0/47) were detected, whereas relapses were observed in 14.89% (7/47). Lethality was 21.27% (10/47).

Table 2: Response to treatment from anti-*Leishmania* drugs in VL-HIV co-infected patients in São Paulo State, Brazil (1999--2010).

OUTCOME	PA	AmBd	LAmB	*p* value*
Cure % (No)	69.44 (25)	41.66 (5)	63.82 (30)	0.223
Failures% (No)	11.11 (4)	16.66 (2)	00.00 (0)	0.034
Deaths% (No)	16.66 (6)	41.66 (5)	21.27 (10)	0.192
Relapses% (No)	2.77 (1)	0.00 (0)	14.89 (7)	0.076
TOTAL % (No)	100% (36)	100% (12)	100% (47)	

*Kruskal-Wallis One Way Analysis of Variance on Ranks ($p < 0.05$).
PA= Pentavalent Antimoniate, AmBd = Amphotericin B deoxicolate, LAmB = Lipossomal Amphotericin B.

Table 3: Anti-*Leishmania* treatment from VL-HIV co-infected patients in São Paulo State, from 1999 to 2010, according to positive and negative outcomes.

OUTCOME	No	%
Positive	60	63.16
Negative	35	36.84
TOTAL	**95**	**100**

Fisher ExactTest ($p = 0.0005$).
Positive outcomes = Cure; Negative outcomes = Death, Failure and Relapse.

Demographic and clinical characteristics of co-infected patients according to the drugs used were similar. When comparing positive outcomes (cure) with negative outcomes (failures, relapses and deaths) and regardless of drug used, there was a significant difference between them favoring positive outcomes ($p = 0.0005$ - Fisher Exact Test) (Table 3).

Analytic study of treatment

It was observed that those patients treated with AmBd had higher mortality compared to the others, with a significant difference ($p = 0.03$) (Table 4). Note the increase in absolute numbers of cures (60 to 72) and death (21 to 23) in order that these 14 "extra" cases refer to more failures (6 cures) and failures (2 deaths and cures 6) previously analyzed separately. It was not possible to get other variables already associated with risk of death from VL, such as jaundice, bleeding or presence of co-morbidities, due to limitations of the databases searched, since there was change in the information system during the study period after 2007.

HIV/AIDS data

In all databases analyzed, regarding to $CD4^+$ and $CD8^+$ T Lymphocytes count and HIV viral load, data was available from only 32 of the 95patients whose treatments were reported. Analyzed by outcome, we observed that the median $CD4^+$ [range] and $CD8^+$ [range] T lymphocytes counts were 135 [13-684] and 550 [165-1652] for cures and 28.5 [4-967] and 244.5 [81-1049] for deaths, respectively. Only from one in eight who relapsed it was possible to obtain $CD4^+$ and $CD8^+$ T cells count (37 and 346, respectively). HIV viral load was rescued from four patients among relapses. The median HIV viral load was 27,197 [50-1000000], 50 [50-1000000] and 3,133 [2972-56164] for cures, relapses and deaths, respectively. Note that there was no significant difference between the outcomes (cure, death or relapse), when analyzed $CD4^+$ and $CD8^+$ T cells, and HIV viral load.

Table 4: Bivariate analysis of VL-HIV co-infected in São Paulo state (1999-2010), regarding to outcome (cure, death).

CARACTERISTICS	Cures % (No) (N=72)	Deaths % (No) (N=23)	CI 95%	*p* value
DRUGS				0,08[a]
PA	40,3 (29)	30,4(7)	0,52-4,99	0,40[b]
AmBd	8,3 (6)	26,1 (6)	0,06-1,11	**0,03[b]**
AmBL	51,4 (37)	43,5 (10)	0,48-3,99	0,51[b]

NOTE: Percentages were calculated in relation to cures column (n = 72 = 100%) and deaths (n = 23 = 100%). PA = Pentavalent Antimoniate, AmBd = Amphotericin B deoxicolate, LAmB = Lipossomal Amphotericin B.
[a]Chi-square; [b]Comparing each one to others.

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Discussion

VL-HIV co-infection has impacted directly in the epidemiology and clinical outcome of VL, mainly in relapse and lethality rates. Furthermore, HIV has contributed to the re-emergence of VL in some Mediterranean areas [3] and others regions as Ethiopia, where an increasing prevalence from 13.3% to 38.2% has been observed [11-21]. In Brazil VL/HIV prevalence is at about 8.5%, and the number of VL affected individuals and the number of co-infected patients is increasing yearly nationwide [2]. Data from treatment of co-infected patients have been shown an increasing in lethality and relapse rates, although the introduction of Antiretroviral Therapy (ART) promoted a decreasing in the incidence of VL in HIV-infected, as occurred in patients in Mediterranean area [3,4,22]. In our study we also observed that co-infected patients had higher lethality than VL alone (almost three-fold), and relapses rates of co-infected was fivefold higher compared to VL alone, independent on the drug used. Regarding to lethality, our data are similar to others presented by others authors [3,18,19,23,24]. A possible risk factor related with high lethality of co-infected patients is the low $CD4^+$ T cell count since Cota et al. (2011) observed in a systematic review that $CD4^+$ T count less than 100 cells/mm3is an important factor related to relapse in VL-HIV co-infected patients [25]. Also, HIV infection further suppresses $CD4^+$ T cell levels by direct attack. Therefore, HIV and VL reinforce each other, allowing the development of the latter (100-2320-fold higher risk), contributing to an increased spread of the *Leishmania* infection, and causing a negative response to ART [3,26]. On the other hand, infection by *Leishmania* increases the replication of HIV due to chronic activation of the immune system, favoring the entry of HIV into the reticuloendothelial system cells, integration and release of new viruses [3,22,27-29].

Analyzing drugs used for the treatment of VL in co-infected patients and their outcomes, it was observed that: (1) patients treated with PA had similar cure rates compared to those who received LAmB; (2) there were no failures when co-infected were treated with LAmB; (3) lethality was higher when AmBd was used comparing to other ones; and (4) higher relapse rates was detected when LAmB were used comparing to PA and AmBd. In exception to failures, all results did not show significant difference. Possibly, there were selection biases when more severe cases were preferably treated with LAmB. As data about secondary prophylaxis was not available, we could not conclude that these co-infected patients had not received that, which would imply in a higher chance of relapse. As we use secondary data (retrospective study) some limitations of the study hinder a more accurate interpretation of the data obtained, since the lack of some information on the CD4 + lymphocyte count does not allow us to define which group is most vulnerable to therapeutic failure or to have an unfavorable outcome. Other factor to take into account is that a total dosage of 20mg/Kg of LAmB (as recommended by Ministry of Health of Brazil by 2000´s) might be insufficient for treatment of *L. infantum* in the New World as described for *L. donovani* in Ethiopia [14]. Furthermore, this same study in Ethiopia presents disappointing efficacy of LAmB monotherapy because high lethality and high relapse rate were observed in co-infected patients when compared to VL cases in HIV-negative ones (lethality 6.7% x 6.4% respectively), suggesting a reduced sensitivity of *L. donovani* in East Africa for LAmB [14]. Comparing the three drugs used in the treatment of VL-HIV co-infected in Sao Paulo, AmBd has presented worst outcomes than the two others drugs. As a greater number of negative outcomes in co-infected patients treated with AmBd compared to PA and LAmB was observed, it is assumed that treatment interruptions due to renal failure (high nephrotoxicity of AmBd) could had been responsible for the high rate of deaths and failures, given that this formulation was potentially causing serious side effects and require hospitalization for about 30 days [3]. However, this hypothesis could not be confirmed because it was not possible to obtain further information on the treatment due to the limitations of this study. The initial cure was achieved in 69.44% of co-infected patients treated with PA and some treatments have failed (11.11%) which required change in therapy for retreatment. Clinical improvement after treatment with PA in co-infected patients does not mean parasite cure and recurrence rate in 12 months is estimated to be approximately 70% in the absence of secondary prophylaxis [16]. Because PA is a drug known by presenting lower efficacy and by being more toxic to co-infected patients (in a dose-dependent manner), cardio, renal and pancreatic toxicity are responsible for the interruption of 11 to 28% of treatments [12,18,22,26,30,31]. As described elsewhere antimonials have a reasonable cure rate (85-95%) in HIV-negative patients, except in Bihar, India, where there are reports of resistance of *L. donovani*, in about 60% of cases [26,32,33]. The efficacy of PA depends on various factors (eg: the stage of the disease, pregnancy, poor nutrition, immunosuppression, drug toxicity). In a study in Ethiopia, between 92.9 to 100% of HIV-negative patients were cured when treated with pentavalent antimoniate, whereas among VL-HIV co-infected treated with the same drug, only 58.3% were cured at the end treatment and only 33.3% remained cured at six months follow-up after treatment [12]. A systematic review, which compared the use of pentavalent antimoniate against amphotericin B (deoxycholate or lipid formulation) in 920 episodes of VL-HIV co-infected patients showed superiority favorable to those treated with amphotericin B in relation to lethality, clinical improvement and presence of lower amount of adverse events, suggesting to be due to the lower toxicity of amphotericin B than pentavalent antimoniate, with greater effectiveness of lipid formulations of amphotericin B [30].

Regarding antiretroviral therapy, most of the patients had no data available, perhaps due to no tests have been ordered or to system failure. ART was not in use when VL was diagnosed in some patients. Of the 21 deaths and 68 cures observed, approximately 25% (both death and cure) had their data recorded regarding to ART. Concerning relapses, data from only one patient were available that included $CD4^+/CD8^+$ T cells count. This attracts attention to the necessity of training programs directed to physicians that focus on VL-HIV co-infection and emphasize the necessity of HIV testing for patients with a recent VL diagnosis, with respect to the difficulty that *Leishmania*-HIV co-infection brings to treatment, besides the overlap of epidemiological areas between these infections worldwide. In our study we noted that there was no significant difference between the outcomes (cure, death or relapse), when analyzing $CD4^+$ and $CD8^+$ T cells count and HIV viral load, mainly because of limitations imposed by few data available.

Some limitations of the study do not allow us to have more robust conclusions, mainly because we did not have data related to the adverse effects during the treatment, as well as we did not obtain data of $CD4^+$ and $TCD8^+$ lymphocyte counts, viral load and ART use of all patients involved.

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In conclusion, our study confirms high lethality and relapse in VL-HIV co-infected patients, independent of the drugs used to treat VL. The lack of well-designed clinical trials leaves an important gap in the knowledge of therapeutic response in this population, since this co-morbidity is increasing in many regions worldwide, with direct impact on the clinical course of both diseases.

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