Combination Treatment for Visceral Leishmaniasis Patients Coinfected with Human Immunodeficiency Virus in India

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Background. There are considerable numbers of patients coinfected with human immunodeficiency virus (HIV) and visceral leishmaniasis (VL) in the VL-endemic areas of Bihar, India. These patients are at higher risk of relapse and death, but there are still no evidence-based guidelines on how to treat them. In this study, we report on treatment outcomes of coinfected patients up to 18 months following treatment with a combination regimen.

Methods. This retrospective analysis included all patients with confirmed HIV-VL coinfection receiving combination treatment for VL at a Médecins Sans Frontières treatment center between July 2012 and September 2014. Patients were treated with 30 mg/kg body weight intravenous liposomal amphotericin B (AmBisome) divided as 6 equal dose infusions combined with 14 days of 100 mg/day oral miltefosine (Impavido). All patients were encouraged to start or continue on antiretroviral therapy (ART).

Results. 102 patients (76% males, 57% with known HIV infection, 54% with a prior episode of VL) were followed-up for a median of 11 months (interquartile range: 4–18). Cumulative incidence of all-cause mortality and VL relapse at 6, 12, and 18 months was 11.7%, 14.5%, 16.6% and 2.5%, 6.0%,13.9%, respectively. Cumulative incidence of poor outcome at 6, 12, and 18 months was 13.9%, 18.4%, and 27.2%, respectively. Not initiating ART and concurrent tuberculosis were independent risk factors for mortality, whereas no factors were associated with relapse.

Conclusions. In this Bihar-based study, combination therapy appeared to be well tolerated, safe, and effective and may be considered as an option for treatment of VL in HIV coinfected patients.

Keywords. visceral leishmaniasis; HIV; AmBisome; miltefosine; combination treatment.

Visceral leishmaniasis (VL; Kala-azar) is a vector-borne disease caused by *Leishmania donovani* parasites. VL is endemic in the Indian state of Bihar, which accounts for 40% of the worldwide burden of VL [1]. Although the prevalence of human immunodeficiency virus (HIV) in Bihar is considered low (0.2%–0.3%), it is one of the few states where prevalence is increasing [2]. A recent study from India has suggested that 2.4% of all patients ≥14 years of age presenting with VL were unknowingly coinfected with HIV [3].

HIV-infected patients are more likely to develop symptomatic VL due to reactivation of dormant *Leishmania* infection acquired prior to being infected with HIV or due to a much higher rate of clinical manifestation following primary *Leishmania* infection after acquiring HIV. Therefore, VL is generally considered an opportunistic infection in patients with HIV and often presents with atypical clinical features [4].

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Coinfected patients are at higher risk of relapse and death, and this risk appears inversely correlated with CD4 counts. Furthermore, VL adversely affects the response to antiretroviral treatment [4, 5]. Worse outcomes and the treatment challenges faced by coinfected patients as compared to immunocompetent patients are well documented in the literature [6].

There are currently no evidence-based treatment recommendations for coinfected patients in Asia. Moreover, observational studies by Médecins Sans Frontières (MSF) in India have shown that outcomes for HIV coinfected patients receiving 20 mg/kg AmBisome (Gilead Pharmaceuticals, Foster City, California) were substantially worse than in VL patients not known to be HIV coinfected [7–9], whereas a recent study in Ethiopia showed that 32% of coinfected patients demonstrated parasitological failure following treatment with 30 mg/kg AmBisome despite clinical improvement [10]. Therefore, the MSF VL treatment program in Bihar, in collaboration with the Rajendra Memorial Research Institute (RMRI), chose to treat HIV-VL coinfected patients on a compassionate basis using a combination of 30 mg/kg AmBisome and 14 days of miltefosine (Impavido, Paladin, Canada). This combination was adopted after consultation of experts, taking into account the synergistic properties of AmBisome and miltefosine [6, 11] and has been used in another center with promising results [12]. Additionally, the compassionate use of miltefosine in combination with liposomal amphotericin B (at 30 mg/kg total dose) in 111 HIV coinfected VL patients in east Africa seems to suggest substantially higher cure rates and lower failure rates both in primary VL and VL relapse than high-dose AmBisome monotherapy[12]. In this report, we describe the outcomes up to 18 months following treatment with this combination therapy under routine program conditions in Bihar, India.

METHODS

We did a retrospective analysis of a clinical cohort of coinfected patients using data collected routinely during MSF's VL care programme activities in Bihar. In August 2013, MSF participated in a pilot study to produce evidence on the field safety and effectiveness of new lower dose treatment modalities recommended by the World Health Organization (WHO) [9] to treat VL in Bihar (CTRI/2012/08/002891). Patients with HIV/VL coinfection were excluded from the study as these treatments are not recommended for this group [5]; however, their data were recorded in the trial surveillance register and as suggested in the pilot study protocol were treated on a compassionate basis with a combination regimen of AmBisome and miltefosine (Figure 1).

Visceral Leishmaniasis and HIV Diagnosis

Diagnosis of VL involved a clinical case definition (fever >2 weeks and splenomegaly), which was confirmed using the rK39 rapid diagnostic test (DiaMed-IT-Leish). For immunocompetent patients in India it is 98.8% and 97.6% sensitive and specific respectively [13]; its accuracy in immunocompromised patients had not yet been fully established although is likely to be lower. In cases of suspected relapse, or where there was high suspicion despite negative antibody detection tests, confirmation by splenic or bone marrow aspiration was performed.

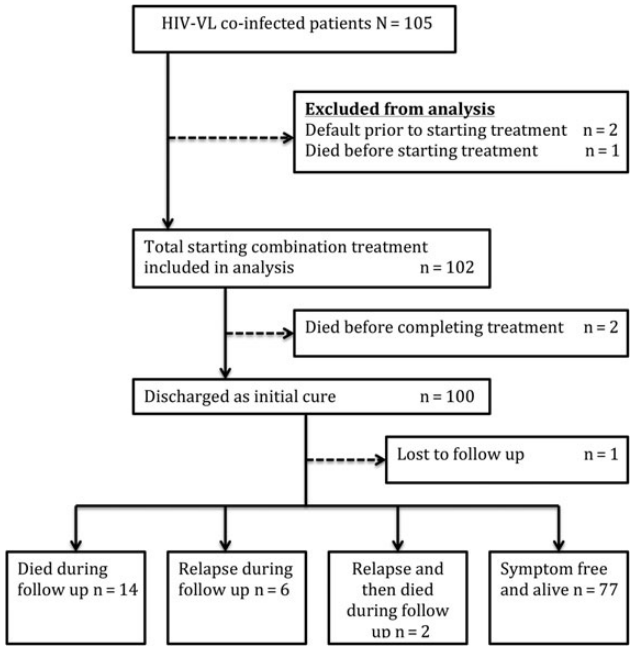

Figure 1. Flow chart of analysis of 102 human immunodeficiency virus visceral leishmaniasis (HIV-VL) coinfected patients, Bihar India.

All patients diagnosed with VL (both primary and relapses) were offered patient initiated counselling and testing (PICT) for HIV regardless of known HIV status. HIV testing was performed using the Determine-HIV 1/2 rapid diagnostic test, and positive patients were referred to the Ministry of Health HIV testing facility within the same hospital for confirmation using two to three further testing kits as per National AIDS Control Organization (NACO) guidelines [14]. Any discordant tests were confirmed using Western Blot.

Visceral Leishmaniasis Treatment Protocol

Patients with HIV-VL coinfection were treated as in-patients using a combination of 30 mg/kg body weight AmBisome divided in 6 equal dose infusions given on alternate days, concurrently with 14 days of oral miltefosine. The dose of miltefosine was calculated according to patient weight (≥25 kg 50 mg twice daily; Weight 12–<25 kg, 50 mg once daily). Test of cure was not routinely performed, with patients discharged as "initial cures" once they completed a full course of VL treatment and showed clinical improvement, cessation of fever, reduction of

spleen size, and return of appetite at the time of discharge as per WHO descriptions of treatment response [15].

All newly diagnosed HIV patients were advised and counselled to start ART at the nearest government ART centre as per NACO guidelines [14]. Of note, unlike in the African subcontinent, typical VL in India is not yet considered a stage IV AIDS-defining opportunistic infection; hence ART initiation is not typically offered to all HIV patients with VL regardless of CD4-count [16].

Patient Follow-up

At the time of discharge, all patients were instructed to return to the treatment centre if experiencing symptoms of relapse. Routine follow-up visits for all patients were scheduled every month to coincide with collection of ART from the ART centre. Follow-up absentees were actively traced. During each follow-up, patients were clinically screened by a physician for signs of relapse, and parasitological confirmation performed in case of suspicion. CD4 counts and ART adherence information were collected, and communication with ART providers maintained to allow integrated longer-term management of patients.

Data Collection and Analysis

As with all patients treated in the MSF program, sociodemographic characteristics, clinical, anthropometric, laboratory data, and data on adverse events were routinely recorded on patient treatment cards and entered in an electronic database by trained data entry encoders. In the case of co-infected patients, CD4 counts and ART status were also routinely recorded, and the program epidemiologist performed double data entry prior to the retrospective analysis. The primary endpoint for analysis was relapse-free survival during follow-up after the start of treatment. For each patient, person-time at risk was calculated from the date of treatment initiation to the date of the "death," "first relapse," "poor outcome" (defined as either relapse or death), "lost to follow-up" (defined as not attending follow-up visit after discharge), or the date of last visit. All data were censored on 31 November 2014. Cumulative incidence of outcome was then estimated using the Kaplan–Meier method. Comparisons between groups were performed using the log-rank test. For risk factor analysis multivariable Cox proportional hazards modeling was performed. All variables associated with the outcome at the $P < .05$ significance level in bivariate analysis were considered in a forward step-wise multivariable model, with a significance level of $P < .05$ used to retain variables in the final model. All data analyses were conducted using SPSS version 21 statistical software (IBM Chicago, Illinois).

Ethics Consideration

This retrospective analysis of clinical cohort data was approved by the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease and met the criteria of MSF's International Ethics Review Committee for a study involving the analysis of routinely collected program data. The compassionate use of the combination regimen for coinfected patients was approved ex-ante (on the basis of protocol CTRI/2012/08/002891) by the MSF International Ethics Review Committee and the Institutional Ethics Review Board of RMRI, Patna. All patients were invited to give informed consent prior to HIV testing, and all electronic data were analysed anonymously.

RESULTS

Baseline and Clinical Characteristics

A total of 102 HIV-VL coinfected patients initiated treatment with AmBisome and miltefosine combination therapy during the study period. The median length of follow-up was 11 (interquartile range [IQR]: 4–18) months following VL treatment initiation. The majority (76%) was male. Over half (57%) of patients reported being aware they were HIV positive at the time of VL diagnosis; the remainder were diagnosed with HIV at the same time as VL diagnosis. A total of 39 (38%) cases were diagnosed with VL on the basis of clinical criteria and rk39 rapid diagnostic test alone, whereas 63 (61.8%) patients had either splenic or bone marrow biopsy for additional parasitological confirmation. Baseline CD4-counts were available for 73 patients with a median CD4 count of 169 (IQR: 88–230) cells/μL. Of these, 67% had CD4-count <200 cells/μL. All but 8 of the cohort received ART treatment; of those who did not, half died within 4 months of completing treatment for VL. Of those receiving ART, 52 (51%) were already established on ART at the time of initiating VL treatment; the remainder started after completion of VL treatment. Baseline and clinical characteristics of patients are summarized in Table 1 and laboratory parameters are shown in Table 2.

Treatment Outcomes

The combination treatment was well tolerated by the majority of patients with minor adverse events recorded among 7 patients; 5 patients reported nausea and vomiting, 1 patient developed back pain, and 1 patient had rigors. Two patients died after being referred to nearby specialist centers for complications related to HIV before completion of treatment; 1 died from sepsis secondary to a large scrotal abscess whereas the other died from bacterial meningitis. Completion of treatment was associated with a significant decrease in spleen and liver size at time of discharge from the hospital; however, no significant changes in haemoglobin level or body weight were observed by completion of treatment. Kidney and liver function tests were performed after treatment completion on a limited number of patients suspected to have complications; changes in mean values of these tests are shown in Table 3.

Table 1. Baseline Characteristics of Patients With Visceral Leishmaniasis and Human Immunodeficiency Virus Coinfection

Variable	N	%	Median (IQR)
Sex			
Male	77	75.5	
Female	25	24.5	
Age group (years)			36 (30,45)
<15	2	2.0	
15–29	13	12.7	
30–44	58	56.9	
45–59	23	22.5	
≥60	6	5.9	
Time from symptoms onset to diagnosis			8 (4,12)
>4 wk	64	62.7	
≤4 wk	38	37.3	
History of previous treatment for VL			1 (0,1)
Second or more relapse	13	12.7	
First relapse	42	41.2	
Primary episode	47	46.1	
VL drug used previously			
None	47	46.1	
AmBisome (20 mg/kg body weight)	18	17.6	
Miltefosine	12	11.8	
Amphotericin B	11	10.8	
Sodium stibogluconate (SSG)	8	7.8	
Fungisome	2	2.0	
AmBisome (5 mg/kg body weight) and Miltefosine combination	1	1.0	
Drug unknown	3	2.9	
Spleen size, (in cm)			8 (6,10)
>6	60	58.8	
3–6	36	35.3	
<3	6	5.9	
Liver size, (in cm)			2 (0,4)
>3	30	29.4	
1-3	33	32.4	
0	39	38.2	
Body mass index (kg/m^2)			17.4 (15.8,18.7)
<16	29	28.4	
≥16	73	71.6	
Concurrent tuberculosis diagnosis			
Positive	9	8.8	
Negative	93	91.2	
HIV status at time of treatment for VL			
Previously diagnosed as HIV positive	58	56.9	
Diagnose HIV positive at time of VL treatment	44	43.1	

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; VL, visceral leishmaniasis.

Table 2. Baseline Laboratory Parameters of Patients With Visceral Leishmaniasis and Human Immunodeficiency Virus Coinfection

Variable	N	%	Median (IQR)
Hemoglobin (g/dL) (n = 102)			8.2 (6.4,9.7)
<6	16	15.7	
6–7	32	31.4	
≥8	54	52.9	
Potassium (mEq/L) (n = 65)			3.9 (3.5,4.2)
2.5 to <3	1	1.5	
3 to <3.5	15	23.1	
≥3.5	49	75.4	
Creatinine mg/dL (n = 97)			
<1.2	81	83.5	
1.2–2	11	11.3	
>2	5	5.2	
SGPT U/L (n = 92)			26.3 (17.1,39.3)
<48	77	41.3	
>48–200	14	56.5	
>200	1	2.2	
SGOT U/L (n-92)			51 (35.3,66.7)
<46	38	41.3	
>46–200	52	56.5	
>200	2	2.2	
Bilirubin (mg/dL) (n = 68)			
≥1.9	1	1.5	
0.5–1.9	28	41.2	
<0.5	39	57.4	
Platelets count cells/μL (n = 89)			146 000 (109 500, 202 500)
<150 000	46	51.7	
≥150 000	43	48.3	
Baseline CD4 count, cells/μL (n = 73)[a]			169 (88.5,230.5)
<100	22	30.1	
100 to <200	27	37.0	
200 to <350	16	21.9	
≥350	8	11.0	

Abbreviations: IQR, interquartile range; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamate-pyruvate transaminase; VL, visceral leishmaniasis.

[a] Window of 3 months prior to VL treatment until 3 months after.

Sixteen (15.7%) deaths were identified during the follow-up period. Two patients died before completion of treatment, whereas 4 others died within 2 months following treatment completion. Median time to death was 3.3 months (IQR: 1.3–6.5). Cumulative incidence of mortality at 6, 12, and 18 months was 11.7%, 14.5%, and 16.6%, respectively (Supplementary Figure 1). Among the patients discharged as initial cure, eight cases of VL relapse were identified during follow-up with a median time to relapse of 11 (IQR: 4–15) months. The estimated risk of relapse was 2.5%, 6.0% and 13.9% at 6, 12 and 18 months respectively. In terms of overall VL treatment response, the estimated cumulative incidence of poor outcomes by 6, 12, and 18 months were 13.9%, 18.4%, and 27.2%, respectively. One patient

Table 3. Clinical and Laboratory Parameters Before and After Treatment (Assessed ≥day 14) With Combination Therapy

Variable	Before Treatment Mean (SD)	End of Treatment Mean (SD)	Within Patient Difference	*P* Value
Weight, kg (n = 100)	44.3 (8.8)	44.6 (8.7)	0.3 (−0.1, 0.6)	.15
Spleen size, cm (n = 101)	8.2 (4.1)	4.1 (3.9)	−4.1 (−4.7, −3.6)	<.001
Liver size, cm (n = 101)	2.2 (2.3)	0.8 (1.4)	−1.4 (−1.9,−0.9)	<.001
Hemoglobin, g/dL (n = 93)	8.2 (2.1)	8.1 (1.8)	−0.2 (−0.4,0.1)	.27
Potassium (n = 17)	3.7 (0.6)	4.3 (0.7)	0.5 (0.2, 0.9)	.003
SGPT, U/L (n = 18)	37.8 (33.0)	29.2 (17.2)	−8.6 (−26.1,8.9)	.31
SGOT, U/L (n = 17)	61.9 (56.3)	52.8 (43.9)	−9.1 (−46.1,27.9)	.61
Platelets cells/L (n = 12)	156 667 (77 713)	222 250 (115 180)	65 583 (30 868 100 299)	.002

Abbreviations: SD, standard deviation; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamate-pyruvate transaminase.

was diagnosed with macular lesions suggestive of PKDL 13 months after completing VL treatment.

Predictors for Death, Relapse and Poor Outcome

No demographic or clinical characteristics were significantly associated with relapse in bivariate analysis, even though a diagnosis with tuberculosis (Supplementary Table 1) showed a strong association (hazard ratio [HR]: 9.5; 95% confidence interval [CI], .9–97.9; $P = .06$). Concurrent tuberculosis, haemoglobin ≤6 g/dL, baseline CD4-count <100 cell/μL, and lack of ART initiation were identified as risk factors for mortality in bivariate analysis. However, only infection with tuberculosis (adjacent HR [aHR]: 5.3; 95% CI, 1.6–17.8; $P < .01$) and ART initiation status maintained statistical significance through the forward step-wise approach and were therefore retained in the final multivariable model for mortality (Table 4). Of the 102 patients presenting, 73 had documented CD4 counts at the time of treatment; for the purposes of multivariable modeling multiple imputation was used to complete the data set; however, this had minimal impact on the model output [17].

In the final multivariable model, failure to start ART was an independent risk factor for mortality compared to those who started ART prior to VL treatment (aHR: 8.0; 95% CI, 2.0–32.5; $P < .01$). ART initiation following VL treatment was similarly associated with higher mortality than those already established on ART, but did not reach statistical significance (aHR: 2.8; 95% CI, .8–9.5; $P = .101$).

In terms of overall poor outcome, only concurrent tuberculosis (aHR: 7.5; 95% CI, 2.5–22.1; $P < .01$) was retained as an independent risk factor (Supplementary Table 2).

DISCUSSION

This is the first report to our knowledge on HIV-VL coinfected patients receiving treatment with a combination of AmBisome and miltefosine therapy in the Indian subcontinent. Our data suggest that combination therapy is a well-tolerated and effective treatment regimen for an episode of VL in HIV-VL coinfection within the Indian setting. The choice of 14 days of concurrent oral treatment had the added benefit of ensuring compliance as both treatments can be administered during the inpatient stay. However, a high risk of relapse and early death, similar to earlier studies on short- and long-term outcomes of coinfected patients is described in this cohort, particularly among tuberculosis patients and those not initiated on antiretroviral treatment. When compared to patients with VL not known to be HIV-infected treated with a lower dose monotherapy of 20 mg/kg AmBisome in the same setting [7], the outcome among coinfected patients observed in our study was considerably worse—mortality and relapse rates at 12 months for patients were 0.9% and 3.7% compared to 14.5% and 6.0%, respectively, for the coinfected patients described here.

In HIV-VL coinfected patients already taking or initiated on ART, this study demonstrated slightly higher overall mortality but substantially reduced relapse rates compared to coinfected patients treated with a lower dose 20–25 mg/kg AmBisome monotherapy, with mortality and relapse rates at 12 months of 11.2% and 6.4% compared to 8.7% and 16.2%, respectively [8]. Concurrent tuberculosis was found to be an independent risk factor for overall poor outcome in our multivariable model, similar to other studies [8, 9]. No other sociodemographic or clinical factors were found to be associated with poor outcomes.

Baseline CD4 counts at the time of VL diagnosis were low in our cohort, with counts <100 cells/μL at baseline being a significant risk factor for mortality in bivariate analysis, consistent with reports from an Ethiopian coinfected cohort [18]. Patients receiving ART had substantially lower mortality than those who did not, confirming results of earlier studies on coinfected patients in the same programme [8, 9] and reinforcing the need for the central place of ART in the management of this group of patients.

Considering relapse, no associations with demographic characteristics were found, which is in keeping with a systematic review describing predictors of VL relapse in HIV-infected patients [19]. However, unlike this review, our study failed to

Table 4. Risk Factors Analysis for Mortality in Patients With Visceral Leishmaniasis-Human Immunodeficiency Virus Coinfection

Variable	Death N (%)	Survived N (%)	Crude HR (95% CI)	Crude *P* Value	Adjusted HR (95% CI)	Adjusted *P* Value
Sex						
Female	6 (24.0)	19 (76.0)	1.7 (.6,4.8)	.28		
Male	10 (13.0)	67 (87.0)				
Age (years)						
>40	7 (17.1)	34 (82.9)	1.2 (.4,3.2)	.74		
≤40	9 (14.8)	52 (85.2)				
Tuberculosis diagnosis						
Positive	4 (44.4)	5 (55.6)	6.6 (2.0,22.0)	.002	5.3 (1.6, 17.8)	.008
Negative	12 (12.9)	81 (86.0)				
History of previous VL treatment						
Yes	7 (12.7)	48 (87.3)	0.6 (.2,1.6)	.32		
No	9 (19.1)	38 (87.1)				
Spleen size (cm)						
>8	6 (14.3)	36 (85.7)	0.8 (.3,2.2)	.67		
≤8	10 (16.7)	50 (83.3)				
BMI (kg/m^2)						
<16	7 (24.1)	22 (75.9)	2.1 (.8,5.8)	.13		
≥16	9 (12.3)	64 (87.7)				
Hemoglobin (g/dL)						
≤ 6	6 (30.0)	14 (70)	2.9 (1.03,7.9)	.04		
>6	10 (12.2)	72 (87.8)				
Baseline CD4 count (cells/μL)[a]						
<100	8 (25)	23 (75)	2.0 (1.1,30.8)	.04		
≥100	8 (11.7)	62 (88.3)				
ART initiation						
Never started	4 (50.0)	4 (50.0)	9.1 (2.3,36.5)	.002	8.0 (2.0,32.5)	.004
After VL diagnosis	8 (19.0)	34 (81.0)	3.2 (0.95,10.7)	.06	2.8 (.8,9.5)	.101
Before VL diagnosis	4 (7.7)	48 (92.3)				

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; HR, hazard ratio; VL, visceral leishmaniasis.

[a] 73/102 baseline CD4 counts were available; the remainder were completed through multiple imputation.

establish low CD4 count and previous history of VL treatment as risk factors for relapse, possibly for lack of power.

This study has several limitations. Being a retrospective analysis of program data, and despite demographic and clinical data related to VL treatment being complete, some important HIV-related data were missing, particularly timely CD4 counts following diagnosis. Second, all-cause mortality was used in the analysis, and as such we were not able to ascertain documented causes of deaths discovered during follow-up. However, all but 2 patients were discharged in good clinical condition following treatment completion, and the 2 deaths occurring before completion of treatment were not considered related to the therapy. Therefore, we believe it is unlikely that any of the 16 deaths recorded in the cohort was a treatment related serious adverse event. The 2 patients who died after relapsing did so after retreatment was completed and were discharged with improved clinical condition. Finally, test of cure was not routinely performed on patients unless there was suggestion of treatment failure clinically, of which there were none; therefore the study may have underdiagnosed initial treatment failures.

Presently, the WHO recommends monotherapy with AmBisome up to a total of 40 mg/kg in divided doses for over a month in HIV-VL coinfected patients worldwide; however, this recommendation is made on the basis of patient case series involving *L. infantum* in Europe alone [4]. To our knowledge, no case of *L. donovani* infection in a patient with HIV treated with this regimen has been documented in the Indian subcontinent, whereas high dose monotherapy with AmBisome already appears to be ineffective in African *L. donovani* infection [10], where studies evaluating the combination of AmBisome and miltefosine in coinfected patients have already begun [20]. We therefore suggest that the use of this WHO-recommended regimen and the combination described in this study need to be investigated in further studies in order to help establish optimal dosing and safety profiles to help determine the best management of this challenging group of patients.

Considering the high probability of relapse in coinfected patients, there is a need to provide a safe and effective treatment while protecting the limited drugs available from the development of resistance. This is more pertinent because resistance mechanisms to amphotericin B have recently been described [21], and evidence from Ethiopia that high-dose AmBisome monotherapy was much less effective in HIV-positive VL relapse patients who had received previous treatment with AmBisome or amphotericin B compared with those who had not [10].

Our findings have a number of implications for policy and practice in India. Current WHO and NACO guidelines describe "atypical disseminated VL" as a stage IV-defining opportunistic infection, rather than simply "visceral leishmaniasis" and therefore do not recommend initiation of ART in all HIV patients with typical VL irrespective of CD4 count. This contrasts with WHO expert committee on VL recommendations delivered in 2010, where typical VL infection in HIV-infected patients is clearly identified as an AIDS-defining illness. These inconsistencies cause confusion in the field when making decisions to start ART in coinfected patients [16]. The outcomes of the recent expert meeting between NACO and the NVBDCP in India to develop guidelines for the management of HIV-VL coinfection [22] is a strong first step in developing clearer recommendations and convergence between WHO ART guidelines and VL guidelines. In turn, these study results strengthen emerging evidence that typical VL should be considered as a clear entry criterion in the stage IV definition of HIV, support the need to offer PICT to all patients diagnosed with VL and crucially that extended follow-up of coinfected patients is required to ensure relapses are detected early and treated appropriately. This needs to be done using a coordinated multidisciplinary approach between VL and HIV/AIDS programs.

In conclusion, the administration of a combination therapy of AmBisome and miltefosine appears safe and effective among HIV-VL coinfected patients under programme conditions in India. Early diagnosis of the coinfection, prompt initiation of ART, and anti-leishmania therapy, screening and treatment for tuberculosis and extended follow-up may lead to more favorable treatment outcomes.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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