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Long-term Clinical Outcomes in Visceral Leishmaniasis/Human Immunodeficiency Virus–Coinfected Patients During and After Pentamidine Secondary Prophylaxis in Ethiopia: A Single-Arm Clinical Trial

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Background. We have conducted a single-arm trial evaluating monthly pentamidine secondary prophylaxis (PSP) to prevent visceral leishmaniasis (VL) relapse in Ethiopian human immunodeficiency virus–infected patients. Outcomes at 12 months of PSP have been previously reported, supporting PSP effectiveness and safety. However, remaining relapse-free after PSP discontinuation is vital. We now report outcomes and associated factors for a period of up to 2.5 years after initiating PSP, including 1-year follow-up after PSP discontinuation.

Methods. The trial had 3 phases: (1) 12 months of PSP; (2) a 6-month PSP extension period if CD4 count was ≤200 cells/μL at month 12; and (3) 12-month follow-up after stopping PSP. The probability of relapse and risk factors were calculated using Kaplan-Meier methods and Cox regression analysis.

Results. For the 74 patients included, final study outcomes were as follows: 39 (53%) relapse-free, 20 (27%) relapsed, 5 (7%) deaths, 10 (14%) lost to follow-up. The 2-year risk of relapse was 36.9% (95% confidence interval, 23.4%–55.0%) and was highest for those with a history of VL relapse and low baseline CD4 count. Forty-five patients were relapse-free and in follow-up at month 12 of PSP. This included 28 patients with month 12 CD4 counts >200 cells/μL, remaining relapse-free after PSP discontinuation. Among the 17 with month 12 CD4 count <200 cells/μL, 1 relapsed and 3 were lost during the PSP extension period. During 1-year post-PSP follow-up, 2 patients relapsed and 1 was lost to follow-up. No PSP-related serious adverse events were reported during the PSP-extension/post-PSP follow-up period.

Conclusions. It seems safe to discontinue PSP at month 12 CD4 counts of >200 cells/μL. The management of those failing to reach this level remains to be defined.

Clinical Trials Registration. NCT01360762.

Keywords. visceral leishmaniasis; HIV; pentamidine; secondary prophylaxis; Ethiopia.

Visceral leishmaniasis (VL) is a systemic infection caused by the *Leishmania donovani* complex that mainly affects the reticuloendothelial organs [1]. It is fatal without treatment. The disease is found in about 70 countries, with 6 of them (India, Bangladesh, Brazil, Sudan, South Sudan, and Ethiopia) contributing to 90% of the global case load [2]. In the Mediterranean region and Latin America, where *Leishmania infantum* is prevalent, transmission is zoonotic (ie, infection is maintained in an animal reservoir). In the Indian subcontinent and East Africa, VL is caused by *L. donovani,* and transmission is predominantly anthroponotic (from human to human) [1].

In the era of human immunodeficiency virus (HIV)/AIDS, VL has emerged as an important opportunistic infection in endemic regions, occurring in 35 countries [3]. The northwestern region of Ethiopia has a very high prevalence of HIV coinfection among VL patients, in the range of 10%–20% [4].

As both infections have a clear immunosuppressive nature and reside within similar host cells (eg, macrophages), marked synergistic effects have been observed. VL/HIV-coinfected patients have a high rate of death and VL treatment failure [3, 4]. There is also a very pronounced risk of VL relapse after achieving apparent cure with VL treatment, estimated at 60%–70% in a recent systematic review [5], highest in patients with low CD4 cell count or a history of (multiple) relapses [5].

For zoonotic VL, the use of secondary prophylaxis to prevent relapse of disease is recommended [3]. Current first-line drugs

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(sodium stibogluconate, liposomal amphotericin B, paromomycin, miltefosine) have been used for secondary prophylaxis. For areas with anthroponotic transmission, the World Health Organization (WHO) guidelines argue against using prophylaxis with these drugs, as the emergence and spread of resistant parasites could compromise their efficacy [3, 6].

For this reason, we conducted a single-arm clinical trial using pentamidine, a drug that is currently not in use for VL treatment in East Africa because of drug toxicity but was found safe at prophylactic dosage [7, 8]. Previously, we reported the outcomes at 12 months of pentamidine use, and our data were supporting the effectiveness, safety, and feasibility of this intervention [9].

However, from the patient perspective, what really matters is remaining relapse-free after discontinuing prophylaxis, and evidence is lacking on the duration of secondary prophylaxis and on CD4 cell count indicating when prophylaxis can be safely discontinued. If the reduction in relapse with pentamidine secondary prophylaxis (PSP) is negated by a subsequent increase in events after PSP discontinuation, the ultimate clinical effect might be minimal. On the other hand, continuing prophylaxis for too long carries the risk of additional drug-related adverse events and might compromise adherence. As VL/HIV coinfection is a chronic condition, long-term follow-up of these patients is required, but such studies are currently lacking at the global level.

In the present article, we report on the long-term clinical outcomes (relapse and relapse-free survival) and associated risk factors in VL/HIV-coinfected patients observed for a period of up to 2.5 years after initiating PSP, including a 1-year period after PSP discontinuation. To the best of our knowledge, this report provides the longest and most complete follow-up data of VL/HIV-coinfected patients ever reported and is the first to report on the risk of relapse after discontinuing VL secondary prophylaxis.

METHODS

Ethics Statement

The trial protocol was approved by the Ethiopian regulatory authority, the National Research Ethics Review Committee, the University of Gondar Institutional Review Board (IRB), the Ethics Review Board of Médecins sans Frontières, the IRB of the Institute of Tropical Medicine, Antwerp, and the Ethics Committee of Antwerp University Hospital. Written informed consent was obtained from all participants. The protocol was registered at ClinicalTrials.gov (NCT01360762).

Study Design

This was an open-label, single-arm trial evaluating the effectiveness, safety, and feasibility of monthly pentamidine prophylaxis to prevent VL relapse in patients with HIV. The study had 3 phases: an initial 12 months of monthly pentamidine prophylaxis (main study period); a 6-month treatment extension period (with monthly pentamidine) for those who remained at a CD4 count ≤200 cells/μL at 12 months of PSP; and a subsequent 12-month follow-up after discontinuing PSP to assess the long-term outcomes (Figure 1). The findings of the first 12-month PSP period have been published previously [9].

Study Setting

The study was conducted at the 2 main leishmaniasis treatment centers in Northwest Ethiopia: the Leishmaniasis Research and Treatment Center at the University of Gondar (established by the Drugs for Neglected Diseases initiative), and the Abdurafi Health Center (supported by Médecins sans Frontières). For details of the HIV and VL diagnostic and treatment practices and study procedures, we refer to the article reporting on the 12-month outcomes [9].

Recruitment and Follow-up

As reported before [9], there were 3 types of study participants considered at increased risk of relapse and included in the trial. Patients presenting with active VL disease during the recruitment period ("current VL") were classified into 2 groups. Current primary cases were those presenting with VL disease for the first time (first VL episode ever) before starting PSP, and current relapse cases were patients presenting with a previous history of VL (having had at least 2 VL episodes prior to starting PSP). The drugs used to treat VL were sodium stibogluconate alone or in combination with paromomycin and liposomal amphotericin B alone or in combination with miltefosine. The current primary VL cases were included in the study after VL cure if they had a CD4 count ≤200 cells/μL or had a WHO HIV/AIDS clinical stage 4 condition (other than VL), whereas the current relapse cases were included in the study regardless of the CD4 cell count and WHO stage. A third group of enrolled patients were those who were treated for VL before the start of the study recruitment but in HIV follow-up, who were defined as past VL cases and were included if their CD4 cell count was ≤200 cells/μL at the time of screening for the study or if they were in HIV/AIDS clinical stage 4 on presentation. All cases were included after ascertaining parasitological cure (no parasites on tissue aspirate microscopy). Renal dysfunction, diabetes, pregnancy and lactation, and chronic medical conditions were exclusion criteria [9].

As reported before [9], 4 mg/kg of pentamidine isethionate (provided by Sanofi-Aventis) was given intravenously every month for a minimum period of 1 year, which was extended to 18 months for patients who had CD4 count ≤200 cells/μL at the 12-month visit. In addition, a clinical and laboratory evaluation was performed monthly [9]. Once 12–18 months of PSP prophylaxis was completed, patients were followed every 3 months for 1 year (total maximum follow-up period of 24–30 months). During follow-up, clinical evaluation for VL relapse, adherence monitoring of antiretroviral therapy (ART), and blood sugar and renal function assessments were conducted at every scheduled study visit. Patients were encouraged to visit the research site in between their scheduled appointments if they developed

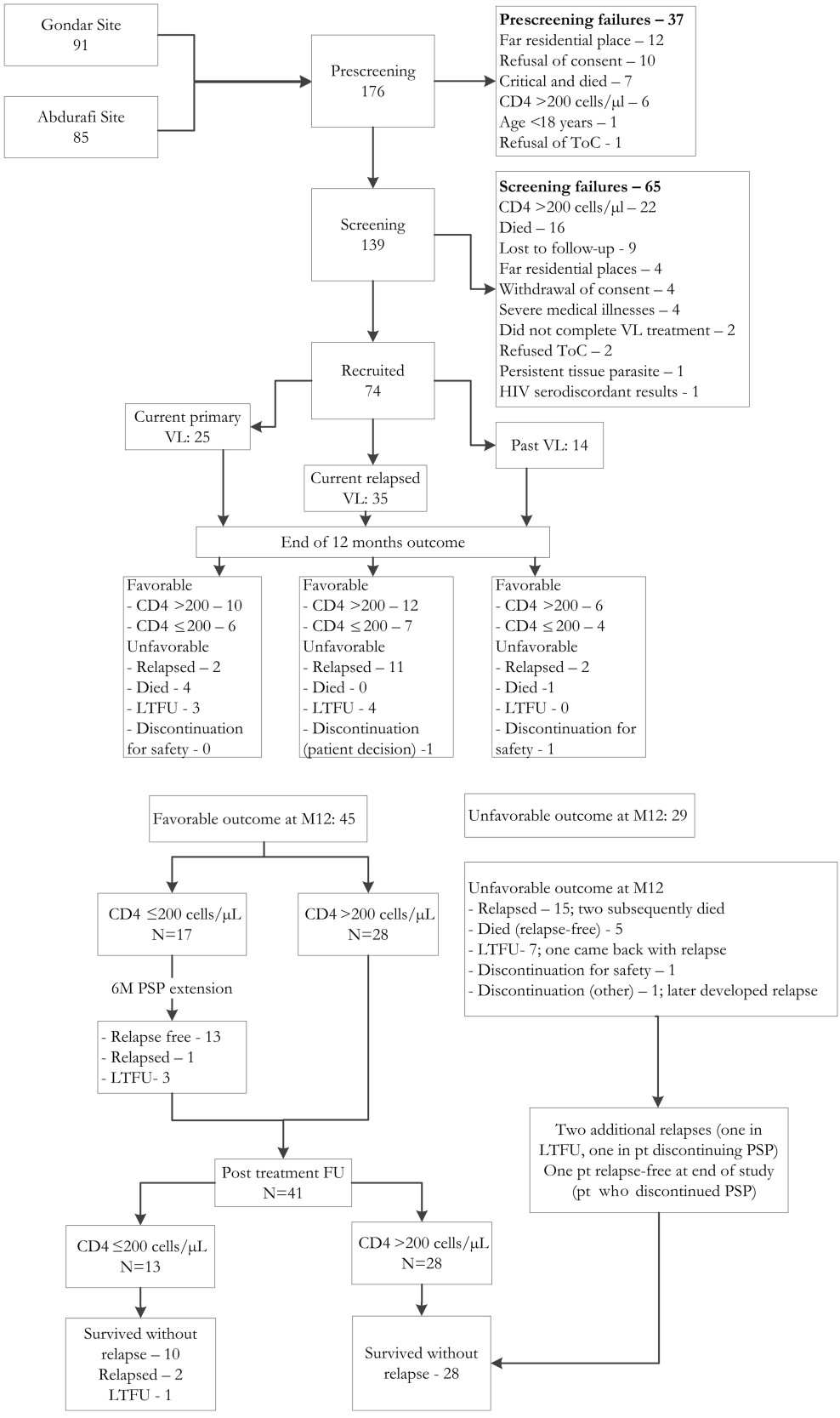

Figure 1. Flowchart showing the recruitment process and patient outcomes in the pentamidine secondary prophylaxis trial to prevent visceral leishmaniasis (VL) relapse in Ethiopian VL/human immunodeficiency virus–coinfected patients, 2011–2015 (N = 74). The trial had 3 periods: the main treatment period (12 months), a 6-month treatment extension period for those failing to achieve a CD4 count >200 cells/μL by 12 months, and a 1-year posttreatment period. Abbreviations: FU, follow-up; HIV, human immunodeficiency virus; LTFU, lost to follow-up; M, month; PSP, pentamidine secondary prophylaxis; pt, patient; ToC, test of cure; VL, visceral leishmaniasis.

VL-suggestive symptoms. In case of suspicion of VL relapse, microscopic evaluation of tissue aspirates was done. CD4 count was done every 6 months [3]. HIV type 1 viral load testing was done on indication.

Outcomes

For effectiveness, we report the risk of relapse, death, and loss to follow-up during the 6 month extension period and during the 12-month follow-up period after PSP discontinuation. Additionally, we report the overall patient outcomes across the entire study period, providing an assessment of their long-term outcomes. For safety, we report pentamidine-related serious adverse events (SAEs) or pentamidine-related adverse events (AEs) that led to the discontinuation of the drug during the 6-month extension period and during the 12-month follow-up period after PSP discontinuation. An AE was considered drug-related when the relationship was judged as possibly, probably, or definitely related according to the treating physician.

Statistical Methods

The analysis of the PSP extension and post-PSP follow-up period was mostly descriptive. Continuous variables were summarized as median and interquartile range (IQR) and categorical variables as count and percentage. Effectiveness was summarized as cumulative incidence with 95% confidence intervals (CIs) and as Kaplan-Meier survival curves. In the main effectiveness analysis, relapse was taken as the study outcome. In secondary analyses, the risk of relapse or death (relapse-free survival) and relapse with the competing risk of death were the outcomes. In worst-case scenario analyses, patients lost to follow-up were also considered as unfavorable outcomes combined with relapse only and with relapse-free survival.

Cox proportional hazard models were run to identify potential risk factors for the different outcomes. The corresponding hazard ratios (HRs) and 95% CIs are reported. Predictors with a significant effect on a 10% significant level in univariate analysis were used in the multivariate model, which was reduced by backward elimination to retain those factors with a P value < .05. The following predictors were assessed in univariate analysis: age, sex, baseline CD4 cell count, a history of previous VL relapse, duration of ART use, and use of antituberculosis drugs at enrollment. The cumulative incidence of relapse, with death as a competing risk was also calculated, as standard survival methods could lead to biased estimates [18, 19]. All statistical analyses were performed with Stata version 14 software.

RESULTS

A total of 74 patients were included in the trial, 60 with current VL (25 with a primary VL episode, 35 with a VL relapse episode, and 14 with past VL; Figure 1). At 12 months after PSP initiation, 45 patient were still receiving PSP: 28 with a CD4 count >200 cells/μL were relapse-free and discontinued PSP, whereas 17 had a CD4 count ≤200 cells/μL and continued PSP for another 6 months. The remaining cases relapsed (n = 15), died (n = 5), were lost to follow-up (n = 7), or discontinued PSP (n = 2) (Figure 1).

Patients with a CD4 count ≤200 cells/μL at month 12 tended to have a lower baseline CD4 count and a less pronounced increase in CD4 count over the 12 months of PSP and were more likely to have been enrolled after a VL relapse episode (Table 1).

Among the 17 patients needing prolonged PSP, 1 patient relapsed and 3 were lost to follow-up during the 6-month extension period.

The 41 patients who were relapse-free at the end of PSP administration (13 patients with a month 12 CD4 count ≤200 cells/μL and 28 with a month 12 CD4 count >200 cells/μL) were subsequently followed every 3 months for 12 months after PSP discontinuation. All those who had a CD4 count >200 cells/μL by month 12 of PSP survived without relapse. However, from the 13 patients with a CD4 count ≤200 cells/μL by month 12 of PSP (but were relapse-free at the end of the month 6 PSP extension), 10 survived without relapse, 2 relapsed, and 1 was lost to follow-up after PSP discontinuation. For the 2 relapse cases, the month 18 CD4 cell count (at PSP discontinuation) was 176 cells/μL for 1 case and missing for the other. For the 10 patients who remained relapse-free and in follow-up at month 30 (end of the study), 9 were >200 cells/μL, and 1 was ≤200 cells/μL.

There were no pentamidine-related SAEs or pentamidine-related AEs leading to PSP discontinuation of the drug during the 6-month extension period and during the 12-month follow-up period after PSP discontinuation. There were 5 pentamidine-related nonserious AEs during the 6-month extension period (nasal congestion, 4; pain at the injection site, 1).

Relating to the 29 patients who had unfavorable outcomes by month 12, 1 patient who was lost to follow-up came back with relapse, and 1 discontinuing PSP (not related to safety) relapsed.

By the end of the study, 39 (53%) patients were relapse-free and alive, 20 (27%) had relapsed (including 2 with subsequent death), 5 (7%) had died, and 10 (14%) were lost to follow-up. Compared to those remaining relapse-free, individuals with VL relapse during follow-up displayed a blunted CD4 cell count recovery (Figure 2). The cumulative incidence of "relapse" and "relapse or death" by 2 years of follow-up was 36.9% (95% CI, 23.4%–55.0%) and 41.7% (95% CI, 28.2%–58.4%), respectively (Table 2 and Figure 3). Independent risk factors for relapse during the entire study period (during PSP and during the 1-year post-PSP follow-up period) were a history of VL relapse before enrollment (HR, 5.7 [95% CI, 1.3–24.7]) and a CD4 count ≤100 cells/μL at enrollment (HR, 4.8 [95% CI, 1.9–12.1]) (Table 3 and Figures 4 and 5). The only statistically significant factor

Table 1. Baseline and Follow-up Characteristics of Visceral Leishmaniasis/Human Immunodeficiency Virus–Coinfected Patients With Favorable Outcomes by 12 Months of Pentamidine Secondary Prophylaxis in Ethiopia, 2011–2015 (N = 45)

Characteristics	Total (N = 45)	CD4 Count >200 Cells/μL by 12 mo (n = 28)	CD4 Count ≤200 Cells/μL by 12 mo (n = 17)
Baseline (month 0)			
Age, y, median (IQR)	31 (27–36)	31 (27–37)	32 (27–35)
Male sex	43 (96)	26 (93)	17 (100)
VL relapse prior to enrollment	23 (51)	13 (46)	10 (59)
Baseline CD4 count, cells/μL, median (IQR)[a]	146 (112–197)	170 (131–206)	114 (85–181)
Time on ART at PSP start			
≤6 mo	39 (87)	24 (86)	15 (88)
>6 mo	6 (13)	4 (14)	2 (12)
BMI <16 kg/m^2, median (IQR)[b]	12 (27)	6 (21)	10 (59)
Spleen size			
Nonpalpable	17 (39)	11 (41)	6 (35)
<5 cm	9 (20)	5 (18)	4 (23)
≥5 cm	18 (41)	11 (41)	7 (41)
Parasite grading at latest VL episode before PSP of 6+[c]	11 (32)	6 (27)	5 (42)
Month 12 of PSP			
BMI[b] <18.5 kg/m^2	19 (42)	11 (39)	8 (47)
Spleen size			
Nonpalpable	24 (53)	17 (61)	7 (41)
<5 cm	18 (40)	9 (32)	9 (53)
≥5 cm	3 (7)	2 (7)	1 (6)
CD4 cell count, cells/μL, median (IQR)	264 (173–331)	323 (265–413)	159 (110–184)
Change in CD4 count from baseline, median (IQR)	84 (–5 to 176)	136.5 (84–197)	0 (–24 to –80)
≤10 PSP doses taken	8 (18)	1 (4)	7 (41)
End of PSP extension period relapse-free group (month 18)			n = 13
≤200 cells/μL		NA	5 (38)
>200 cells/μL		NA	4 (31)
Missing		NA	4 (31)
End of posttreatment follow-up period relapse-free group		(n = 28)	(n = 10)
≤200 cells/μL		1 (4)	1 (10)
>200 cells/μL		27 (96)	9 (90)
Missing		0	0

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; IQR, interquartile range; NA, non-applicable; PSP, pentamidine secondary prophylaxis; VL, visceral leishmaniasis.

[a]At PSP start (n = 43).

[b]Month 30 for those with 6-month PSP extension, month 24 for those with CD4 count >200 cells/μL at month 12 PSP.

[c]Only for current VL cases.

associated with unfavorable outcomes (relapse or death) was a CD4 count ≤100 cells/μL at enrollment (HR, 4.8 [95% CI, 2.1–10.9]).

DISCUSSION

The ultimate goal of secondary prophylaxis in VL/HIV-coinfected patients is not only to prevent relapse while on the regimen, but also for patients to remain relapse-free after stopping prophylactic treatment. Consequently, long-term follow-up data are required. We reported before that with the use of a monthly pentamidine infusion of 4 mg/kg in patients at high risk of relapse and death, 71% were relapse-free and alive by 12 months [9].

The second part of the study, reported here, focused on the risk of relapse after PSP discontinuation and the long-term clinical outcomes. The sample size was calculated based on the assumption of preventing VL relapse in the first 12 months (main analysis). Due to deaths, losses to follow-up, and relapse in the initial follow-up period, the sample size was reduced for this second part of the analysis. Despite the smaller sample size, a clear trend in the outcomes of patients with a CD4 count >200 and ≤200 cells/μL was observed. As there were no relapses in those discontinuing PSP at month 12 with a CD4 count >200 cells/μL, a threshold value of 200 cells/μL could be used as a marker for discontinuing secondary prophylaxis. This is in line with international VL guidelines and also correlates with the recommendations for other opportunistic infections [10, 11].

Those failing to achieve a CD4 count >200 cells/μL at month 12 remained vulnerable, with 7 of 17 patients relapsing or lost to follow-up. While 3 patients were lost during the PSP extension period, all others remained adherent to the monthly administration, and no (cumulative) toxicity was seen, supporting the feasibility and acceptability of prolonged PSP. As there was no control group, we cannot draw firm conclusions on the potential clinical benefit of PSP prolongation, although the fact that several patients achieved a CD4 count >200 cells/μL after PSP prolongation and remained relapse-free afterward would suggest that extending secondary prophylaxis to allow further immune recovery might be clinically relevant. Two patients relapsed after PSP discontinuation (the single available CD4 count <200 cells/μL), suggesting that for vulnerable patients failing to achieve good immune recovery, further PSP extension could be considered on a case-by-case basis, if considered feasible, with close observation for side effects.

The present data also provide a view on what can be expected with the current standard of care, which aims at achieving a parasitological cure after the VL episode, early initiation of effective ART, and provision of secondary prophylaxis. While the relapse rate was reduced compared to historical data [5, 12], the overall long-term patient outcomes remain far from satisfactory. In a worst-case scenario (loss to follow-up equals failure), relapse-free survival at 2 years would only be 48.4%. Factors contributing to the loss to follow-up include the high mobility of the study population, mainly consisting of migrant workers. We also selectively enrolled patients at high risk of relapse, which of course biases the results to higher failure rates.

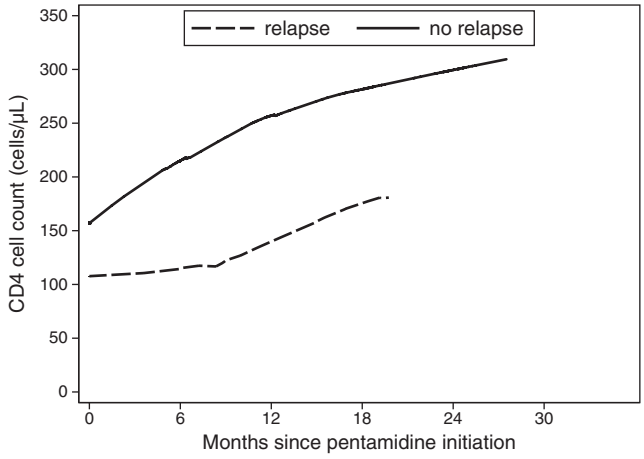

Figure 2. CD4 evolution after starting pentamidine secondary prophylaxis for Ethiopian visceral leishmaniasis/human immunodeficiency virus–coinfected patients who relapsed or remained relapse-free, 2011–2015 (N = 74). The evolution of CD4 counts over time was displayed using the nonparametric LOWESS smoothing method (lowess command in Stata).

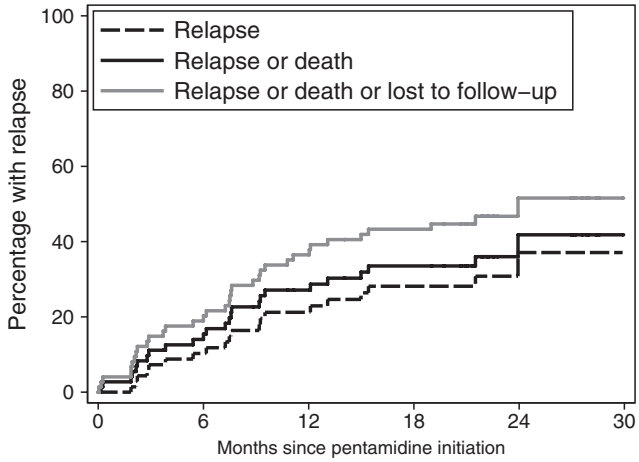

Figure 3. Probability of relapse during and after pentamidine secondary prophylaxis in Ethiopian visceral leishmaniasis/human immunodeficiency virus–coinfected patients, 2011–2015 (N = 74).

Nevertheless, additional interventions should be explored. As to relapse, most cases occurred within the first 9 months. Ways to increase PSP efficacy should be explored, including starting PSP earlier after cure (instead of delaying for 1 month), higher doses and/or more frequent administration, or combination with an oral antileishmanial drug with moderate efficacy (eg, azole drugs) [13]. Those patients with very low CD4 counts at the time of diagnosis had a higher risk of death and relapse, and even without relapse, several failed to achieve good CD4 recovery by 12 months. Thus, early HIV case detection and treatment before profound immunosuppression should be aimed for, as is currently considered within the HIV test-and-treat strategy.

We acknowledge several study limitations. We did not include a control arm as it was considered that all patients should benefit from secondary prophylaxis, in line with international guidelines [10] and because only 1 drug (pentamidine) that was not used for VL treatment was available in Ethiopia. Similarly, relating to discontinuing PSP, randomization to intervention or control would have been preferred, but the sample size for the second part of the analysis was relatively limited, and the high mobility of the study population resulted in some loss to follow-up. The study also has several strengths. Despite working in difficult and remote conditions with mobile populations, high-quality data could be obtained within a clinical trial setting as described previously [9]. This article provides the most complete long-term follow-up information of VL/HIV-coinfected patients ever reported. Additionally, it is the first to report on the risk of relapse after discontinuing VL secondary prophylaxis.

In conclusion, after 12 months, PSP can be safely discontinued in patients with a CD4 count >200 cells/μL. For those failing to achieve this level, a 6-month treatment extension was found to be safe and feasible, although several patients were lost to follow-up and 1 relapse was seen during the PSP extension and 2 after PSP discontinuation in this patient group. The risk of relapse was 36.9% at 2 years after PSP initiation. While clinical outcomes are better than in studies without prophylaxis, additional strategies to further improve long-term outcomes remain to be explored. Meanwhile, PSP should be considered for VL/HIV-coinfected patients in areas with anthroponotic transmission.

Table 2. Probabilities of Unfavorable Outcomes at Different Months After Starting Pentamidine Secondary Prophylaxis in Visceral Leishmaniasis/Human Immunodeficiency Virus–Coinfected Patients, Ethiopia, 2011–2015 (N = 74)

Months After Starting PSP	Outcome				
	Relapse (CI)	Relapse (CR)	Relapse or LTFU	Relapse or Death	Relapse, Death, or LTFU
3	7.3 (3.1–16.6)	7.0 (2.6–14.5)	11.1 (5.7–21.1)	11.1 (5.7–21.0)	14.9 (8.5–25.2)
6	11.8 (6.1–22.2)	11.3 (5.3–19.9)	16.8 (9.9–27.7)	15.4 (8.9–26,2)	20.3 (12.7–31.3)
12	22.7 (14.3–34.9)	21.5 (12.8–31.8)	32.8 (23.1–45.1)	28.6 (19.4–40.7)	37.8 (27.9–31.3)
24	36.9 (23.4–55.0)	34.7 (20.3–49.4)	47.6 (34.3–63.0)	41.7 (28.2–58.4)	51.6 (38.6–66.0)

Data are presented as cumulative incidence (95% confidence interval).

Abbreviations: CR, competing risks analysis; LTFU, loss to follow-up; PSP, pentamidine secondary prophylaxis.

Table 3. Risk Factors for Relapse and Relapse or Death for the Entire Study Period in Visceral Leishmaniasis/Human Immunodeficiency Virus–Coinfected Patients, Ethiopia, 2011–2015 (N = 74)

	Death or Relapse		Relapse	
Predictor	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Sex				
Female	1		1	
Male	0.9 (.1–6.7)		0.7 (.1–5.3)	
Age, y				
<35	1		1	
≥35	1.0 (.1–2.1)		1.2 (.5–2.9)	
Body mass index at enrollment				
≥18.5 kg/m^2	1		1	
>18.5 kg/m^2	1.1 (.4–2.7)		0.8 (.3–2.5)	
Spleen size, cm				
Nonpalpable	1		1	
<5	0.6 (.2–1.8)		0.6 (.2–1.9)	
≥5	0.8 (.3–1.8)		0.5 (.2–1.3)	
VL status at enrollment				
Primary VL	1		1	1
VL relapse	2.2 (.9–5.5)		6.3 (1.5–27.1)	5.7 (1.3–24.7)
ART duration at enrollment (n = 73)				
≤6 mo	1		1	
>6 mo	1.9 (.8–4.5)		5.2 (1.5–17.8)	
CD4 count at baseline (n = 71)				
>100 cells/μL	1	1	1	1
≤100 cells/μL	4.8 (2.1–10.9)	4.8 (2.1–10.9)	5.0 (2.0–12.5)	4.8 (1.9–12.1)
Antituberculosis treatment				
No	1		1	
Yes	1.5 (.4–5.0)		1.9 (.6–6.6)	

Abbreviations: ART, antiretroviral treatment; CI, confidence interval; HR, hazard ratio; VL, visceral leishmaniasis.

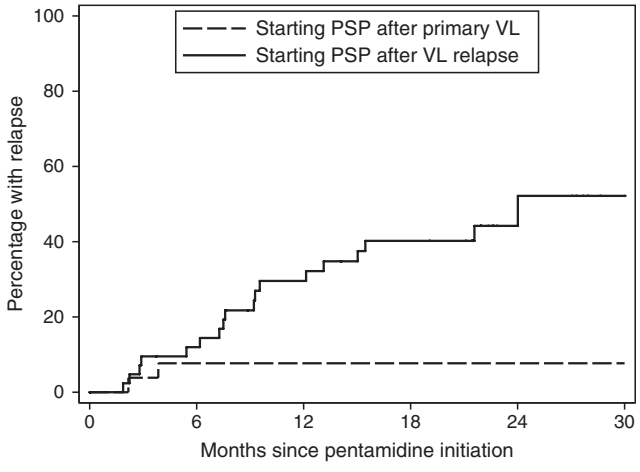

Figure 4. Probability of relapse by history of visceral leishmaniasis (VL) during and after pentamidine secondary prophylaxis (PSP) for patients in Ethiopian VL/human immunodeficiency virus–coinfected patients, 2011–2015 (N = 74). Starting PSP after primary VL refers to "current" or "past" cases of VL starting prophylaxis after having suffered a first episode of VL. Those with a history of VL relapse when starting PSP were patients who had experienced at least 2 episodes of VL before starting prophylaxis.

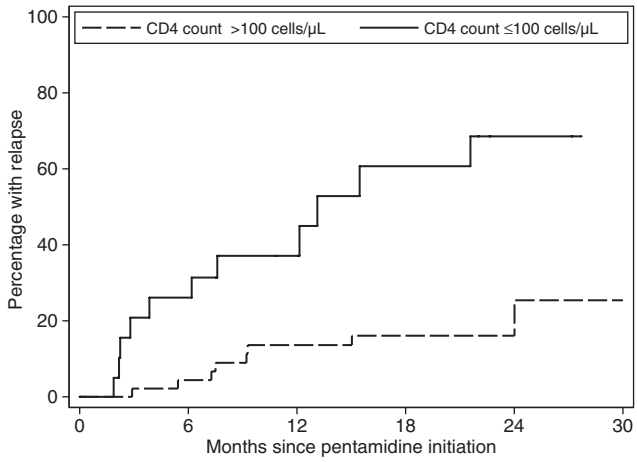

Figure 5. Probability of relapse by baseline CD4 count during and after pentamidine secondary prophylaxis for patients in Ethiopian visceral leishmaniasis/human immunodeficiency virus–coinfected patients, 2011–2015 (N = 74).

Notes

Author contributions. Conceived and designed the experiments: E. D., K. R., M. B., R. R., M. D. C., H. v. L., A. T., A. H., J. v. G. Performed the experiments: E. D., K. R., M. B., F. A., R. M., C. Ab., R. R., M. D. C., H. F., C. Ad., H. v. L., A. H., J. v. G. Analyzed the data: E. D., M. B., H. v. L., A. T., J. v. G. Contributed reagents, materials, and/or analysis tools: E. D., K. R., M. B., F. A., W. A., A. H., J. v. G. Wrote the manuscript: E. D., K. R., M. B., F. A., W. A., R. M., C. Ab., R. R., M. D. C., H. F., C. Ad., H. v. L., A. H., J. v. G.

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