Use of Pentamidine as Secondary Prophylaxis to Prevent Visceral Leishmaniasis Relapse in HIV Infected Patients

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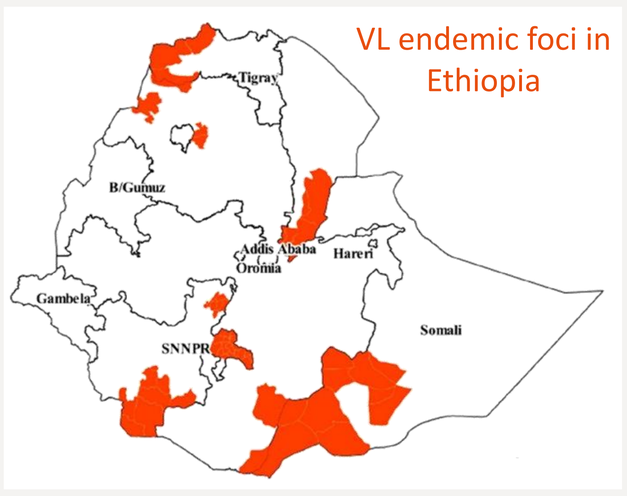
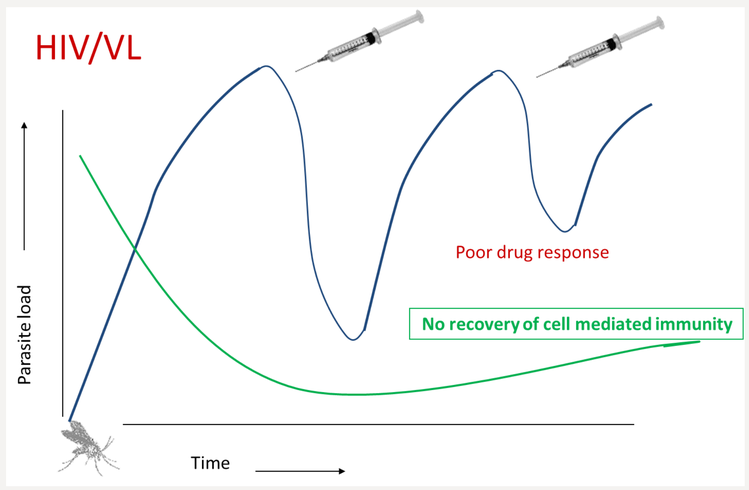
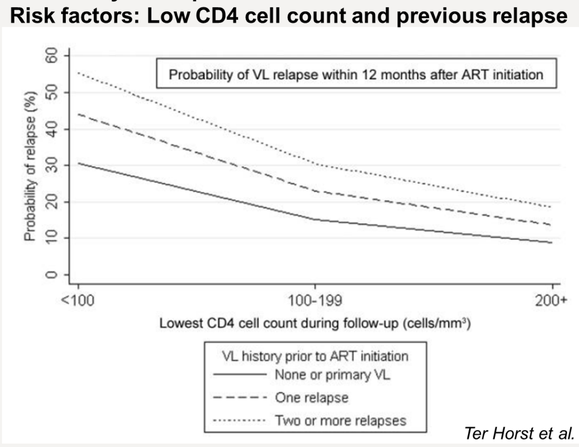
There are approximately 4,000 visceral leishmaniasis (VL) cases in Ethiopia per year, 60% of which occur in the northwest region. In addition, approximately 1.5% of the country's population is infected with HIV, with most of these also occurring in northwest Ethiopia (2.8-2.9%), where approximately 20-40% of patients are coinfected with HIV/VL. Co-infection leads to profound immunosuppression and an annual VL relapse in 67% of the patients.

This study assessed the effectiveness, safety and feasibility of monthly pentamidine infusions to prevent recurrence of VL in HIV co-infected patients. Pentamidine was chosen for secondary prophylaxis as it has a good safety profile at a low dose, even though it is no longer used as a treatment due to its toxicity. In addition to which, it is important to spare the first line drugs in this anthroponotic transmission region.





Probability of relapse ~ 60%
Risk factors: Low CD4 cell count and previous relapse



Ter Horst et al. Clin Inf Dis, 2008

Methods

A single arm, open-label trial was carried out at two sites in northwest Ethiopia - Gondar, Abdurafi. Pentamidine started one month after the index leishmania was treated and parasitologicaly cured, and antiretroviral therapy started or continued:

Pentamidine 4mg/Kg IV every month, for 12 months

Recruitment: Nov 2011 – Sept 2013

Monthly clinical and laboratory assessments and monitoring of adverse events. CD4 and viral load assessed at 6, 12 and 18 months.

Primary endpoints:

Effectiveness - Time to relapse or death

Safety - Drug related serious adverse events

- Adverse events that led to the discontinuation of pentamidine

Feasibility - Number of patient who took 11 of the planned 12 doses without experiencing relapse or drug related SAE

Results

74 patients were included:
71 (96%) were male
median age 32 (28-37) years
Sites: Gondar – 36 (49%), Abdurafi – 38 (51%)

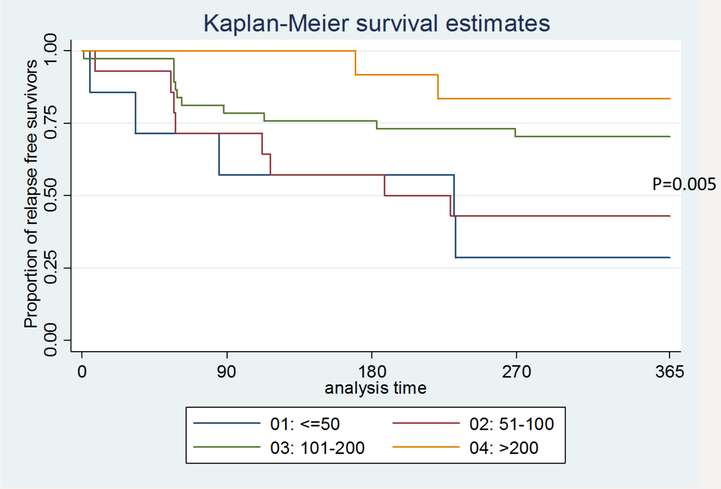
Baseline findings

Body mass Index:
<18.5kg/m^2 – 56 (76%)
>18.5kg/m^2 – 18 (24%)
VL status:
Primary – 31 (42%)
Relapse – 43 (58%)
CD4 count, median – 127 cells/µl

Effectiveness

Results after 6 and 12 months follow up

	Month 6		Month 12	
	n failed / n censored	Probability Relapse Free (95% CI)	n failed/ n censored	Probability Relapse Free (95% CI)
Primary Analysis				
All Patients	15/74	**0.79** (0.67-0.87)	20 / 74	**0.71** (0.59-0.80)



Low CD4 count predicts relapse

Safety analysis

Safety outcomes	All (N=74) n (%; 95% CI)
- drug-related SAE or AE leading to study drug discontinuation	3
- renal failure	2
- hyperglycemia	1
- any SAE (other severe infections)	17 (23; 14.9 -33.7)

Feasibility

Reasons for discontinuation	Number of patients (%)
Those who permanently discontinued	**29 (39.2)**
- Relapse of VL	15 (20.3)
- Lost to follow up	7 (9.5)
- Death	5 (6.8)
- Discontinuation due to safety	1 (1.4)
- Withdrawal of consent	1 (1.4)
Interruption (missed >1 dose)	**4 (5.4)**

41/74 (55%) of patients completed the treatment, fulfilling the feasibility criterion

Conclusions

Secondary prophylaxis increases relapse-free survival rates, although it does not totally prevent recurrence. However patients with low CD4+ cell counts are at increased risk of relapse despite effective initial VL treatment, ART and secondary prophylaxis. The study was limited by a lack of systematic viral load testing, pharmacokinetics, and testing for drug resistance. The study was not randomized with an untreated control arm, as this was considered unethical.

VL should be detected and treated early enough in patients with HIV infection before profound immune deficiency becomes established.

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