

Immuno-virological and toxicity outcomes of HIV-infected patients after 48 months of ART in Phnom Penh, Cambodia

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Rationale

Data on long-term immuno-virological outcomes, HIV resistance patterns and drug toxicity in patients treated with antiretroviral therapy (ART) in resource-limited settings are scarce.

Since 2001, MSF in collaboration with the Ministry of Health (MoH) has provided ART to HIV-infected patients in the infectious disease department of the AKS hospital of Phnom Penh, Cambodia. Generic and fixed-dose combinations of antiretroviral drugs (ARV) are provided free of charge and started according to WHO guidelines. No viral monitoring is performed.

Objectives

- To determine the clinical and immuno-virological outcomes of adults on ART for 48 months
- To describe ARV resistance patterns in patients with detectable HIV RNA
- To describe ARV-related toxicity
- To assess patients' ART adherence

Methods

Population: Adults aged ≥ 15 years and started on a 2NRTI + 1NNRTI-based regimen in the MSF/MoH HIV program of Phnom Penh between October 2002 and June 2003.

Kaplan-Meier methods: To determine the probabilities of death or loss to follow-up.

Cross-sectional survey: All patients alive and on ART and not pregnant at the time of the study were eligible.

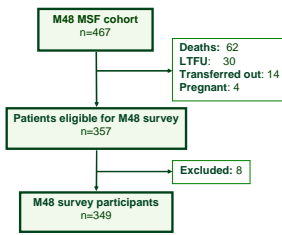
• **ARV toxicity** was assessed by clinicians and through laboratory testing (WHO toxicity grading 2003 and 2006)

• **Adherence** was assessed through pill counting and through patients' self-report of the last month observation using a 10-point visual analog scale (VAS)

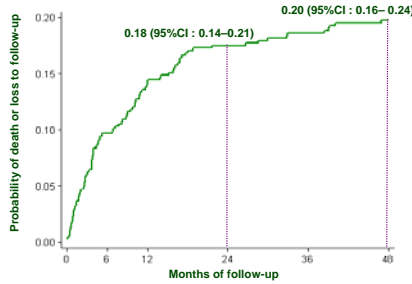
• **ARV mutations and resistance patterns** (www.hivfrenchresistance.org and www.lasusa.org algorithms) were determined in patients with HIV RNA >250 copies/ml (RT quantitative PCR)

Results I : Eligibility, study participation and characteristics of patients included in the survey

1. Study profile



2. Probabilities of death or loss to follow-up



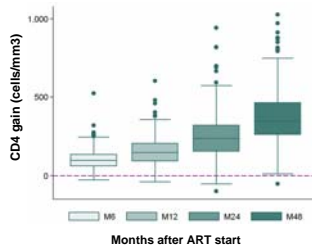
3. Patient characteristics at ART start

Characteristics	M48 participants (N=349)
Males (%)	137 (60.5)
Median age, yr [IQR]	34 [31-39]
ARV naïve (%)	328 (94.0)
WHO clinical stage (%)	
Stage 3	117 (33.5)
Stage 4	207 (59.3)
BMI <18.5 kg/m² (%)	143 (43.9)
3TC-D4T-EFV regimen (%)	287 (82.7)
Median CD4, cells/mm³ [IQR]	16 [4-71]; n=324

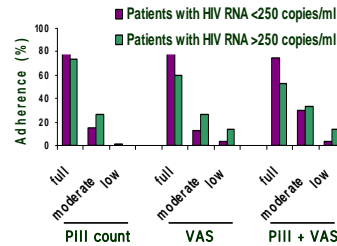
Results II : Clinico-immunological study outcomes at 48 months of ART

4. Patient characteristics and CD4 evolution

Characteristics	M48 cohort (N=349)
Non-cumulative clinical stage (%)	
Asymptomatic	326 (93.4)
WHO stage 3 or 4	8 (2.2)
Second-line LPV-based therapy (%)	36 (10.3)
Median BMI, kg/m² [IQR]	20 [19-23]
Median CD4, cells/mm³ [IQR]	410 [290-511]
Median CD4 gain, cells/mm³ [IQR]	+354 [262-474]



5. Patient adherence to ART* by HIV RNA status



Eighty-three percent of participants reported full adherence to ART (VAS). The use of VAS identified greater differences in adherence levels between patients with or without detectable HIV RNA. Nevertheless, 60% of those with detectable HIV RNA reported fully adherence to ART at the time of the survey. Because patients treated with ART for 48 months might have developed mutations in the past despite optimal adherence to therapy, we cannot assume that such reports do not reflect actual patient behavior at the time of the survey.

*Full adherence = VAS of 10 and/or 100% pill count; poor adherence = pill count <95% or VAS<9.

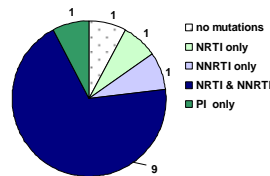
6. Prevalence of reported ARV-related toxicity

Reported severe toxicity	Grade 3	Grade 4
Digestive disorders	1 (0.3)	-
Peripheral neuropathy	1 (0.3)	-
Dermatological disorders	1 (0.3)	-
Morphological disorders	25 (7.2)	-
Myalgia	1 (0.3)	-
Laboratory severe toxicity	Grade 3	Grade 4
Hematological disorders	2 (0.6)	1 (0.36)
High SGOT or SGPT	4 (1.2)	-
Hypertriglyceridemia	14 (4.0)	10 (2.9)
High total cholesterol	2 (0.6)	-
Peripheral hyperlactemia	5 (1.4)	1 (0.3)

Grade 4 toxicity was found in 4% of patients but nearly 20% had 3 or 4 grade toxicity. Minor digestive disorders such as nausea were frequently reported (21%). All-grade lipodystrophy was reported by 63% and peripheral neuropathy by 25% of patients. Those with grade 3 lipodystrophy had used d4T for a median of 29 months, and 6 patients were still taking d4T at the time of the survey. All-grade hypertriglyceridemia was observed in 41% of patients.

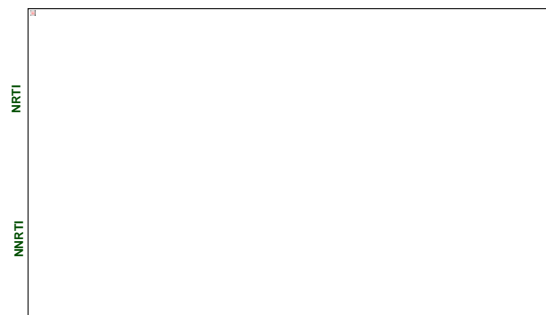
Results III : Viral detection and resistance patterns at 48 months of ART

7. Prevalence of mutations by class of ARV in 13 patients



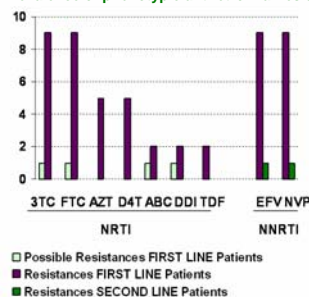
HIV RNA detection: 15 patients (4.3%) had HIV RNA >250 copies/ml. Their median viral load was 84,879 copies/ml [IQR: 5,542-184,081]. Twelve patients were on first-line ART and 3 had started second-line ART a median of 5.7 months before.

8. Prevalence of NRTI and NNRTI associated mutations: results of HIV RT genotyping



Mutations and resistances: Of the 13 patients with available sequencing (reaction failed for 2 patients), 12 had mutations, 9 had both NRTI and NNRTI mutations and 5 had thymidine analog mutations (TAMs). Eleven patients had resistance to ARV drugs: 9 to 3TC and FTC; 5 to AZT and D4T; and 10 to EFV and NVP. One patient on second-line therapy had 3 associated PI mutations but not resistance.

9. Prevalence of phenotypic antiretroviral resistance in 13 patients



□ Possible Resistances FIRST LINE Patients
■ Resistances FIRST LINE Patients
■ Resistances SECOND LINE Patients

Conclusion

Despite severe immunocompromised status at ART start, 77% of patients were alive and in care after 48 months of treatment, and 90% of these remained on first-line therapy. Overall, since the start of ART, 8% of the patients had been switched to second-line therapy before the study and, at M48, nine additional patients on first-line treatment had resistance mutations against ARV drugs. This gives an overall estimated therapeutic failure rate for the cohort of 9.7% (or 19.6% if we consider that half of the deaths and LTFU were also therapeutic failures).

Severe ARV toxicity was reported for one-fifth of patients. Mild and moderate lipodystrophy and peripheral neuropathy and minor digestive disorders were also common. Given that such side effects, even if of minor severity, might lead to poor patient adherence to treatment, they should be considered seriously and addressed by the health care providers.

Acknowledgements

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