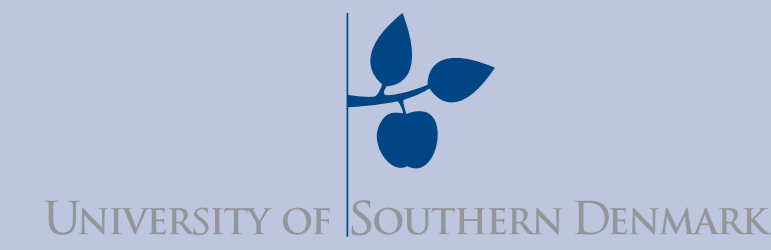


# Virological Control during the First 6-18 Months after Initiating HAART as a Predictor for Mortality, CD4+ Cell Increase, and Viral Suppression

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## Introduction

- After 6 months on highly active antiretroviral therapy (HAART), VL should stay undetectable, and the acute toxicities have passed or the drugs have been changed. Even though long term toxicities have not emerged yet, the patients have probably entered a period which is representative for the remaining lifelong treatment period.
- Our aim was to examine if virological control during the first year of this period (6-18 months after HAART initiation) is a predictor for viral suppression, CD4+ cell increase, and mortality in HIV-infected patients 18-90 months after HAART.

## Subjects and methods

- The Danish HIV Cohort Study is a prospective, nation-wide, population-based cohort study of all HIV-infected individuals treated in Danish HIV clinics since 1 January 1995. Eligible for the study were patients who initiated HAART before 1 January 2002, who had at least one VL measurement within 6 months following HAART initiation, and who were alive at 18 months after HAART initiation.
- For each patient we calculated the proportion of time with detectable VL (>400 copies/ml) during the one-year period extending from 6 to 18 months following HAART initiation. Based on this proportion patients were divided into three subgroups: 0% detectable (Group 1), 1-99% detectable (Group 2), and 100% detectable (Group 3).
- The prevalence of patients with undetectable VL was calculated at baseline (18 months following HAART initiation) and every 18 months thereafter, and ratios between groups at 72 months were examined using a logistic regression model.
- CD4+ cell count increases were computed for each of four consecutive 18-month periods after baseline, and for the whole 72-month period. Individual increases were calculated for all patients observed throughout each period. Differences in mean CD4+ cell increases between groups were examined using a linear regression model.
- We computed time from baseline to death or end of follow-up and constructed cumulative mortality curves, and Cox's proportional hazards regression analyses were performed to estimate mortality rate ratios.
- Using the patient group as the predictor variable, all other variables (Table 1) causing a 10% change in the risk estimates were entered into the regression models one by one.

## Results

- 2,046 patients (1,173 in Group 1, 546 in Group 2, and 327 in Group 3) met the inclusion criteria at 18 months (baseline), and were observed for a total of 8,898 years after baseline. (Table 2). 67 (3.2%) were lost to follow-up.
- At 72 months after baseline, 96% of patients in Group 1 (95% CI: 93-98), 83% in Group 2 (95% CI: 78-89), and 57% in Group 3 (95% CI: 47-66) had undetectable VL (P<0.01 for individual group comparisons) (Figure 1).
- The CD4+ cell count increased significantly for four consecutive 18-month periods in all groups (Figure 1). The crude mean CD4+ cell count increase in the 72-month period after baseline was 3.3 x10<sup>6</sup> cells/l per month (95% CI: 2.9-3.7) for Group 1, 2.9 x10<sup>6</sup> cells/l per month (95% CI: 2.5-3.3) for Group 2, and 2.6 x10<sup>6</sup> cells/l per month (95% CI: 2.0-3.3) for Group 3. The difference between groups in this 72-month period was significant in the adjusted model (P<0.01 for individual group comparisons).
- The cumulative 72-month survival from baseline was 87.7% (95% CI: 85.9-89.3) for all patients; and 92.7% (95% CI: 90.5-94.4), 85.6% (95% CI: 82.1-88.5), and 76.1% (95% CI: 70.6-80.7) for Groups 1, 2, and 3, respectively (Figure 2). The crude MRRs with Group 1 as the reference group were: Group 2, 2.38 (95% confidence intervals [CI]: 1.68-3.36); Group 3, 3.96 (95% CI: 2.81-5.60). The adjusted MRRs were: Group 2, 2.63 (95% CI: 1.86-3.72); Group 3, 4.53 (95% CI: 3.20-6.42).
- The Group 2 subgroup which experienced treatment interruption (TI) for any reason during the first 18 months of HAART (N=92) had a mortality rate of 6.87 per 100 person-years at risk (95% CI: 4.57-10.34). The most common reasons for TI were compliance problems (30%), patient's wish (25%), and drug intolerance (27%). "Doctor's decision" was noted as a reason in only 6% of patients.
- The causes of death were categorized as either HIV-related (AIDS-defining conditions and bacterial infections), non-HIV related, or unknown. These were in Group 1: 18%, 58%, and 24%, in Group 2: 35%, 47%, and 18%, in Group 3: 43%, 40%, and 17%, in Group 2 without TI: 31%, 53%, and 16%, and in Group 2 with TI: 43%, 35%, and 22%.

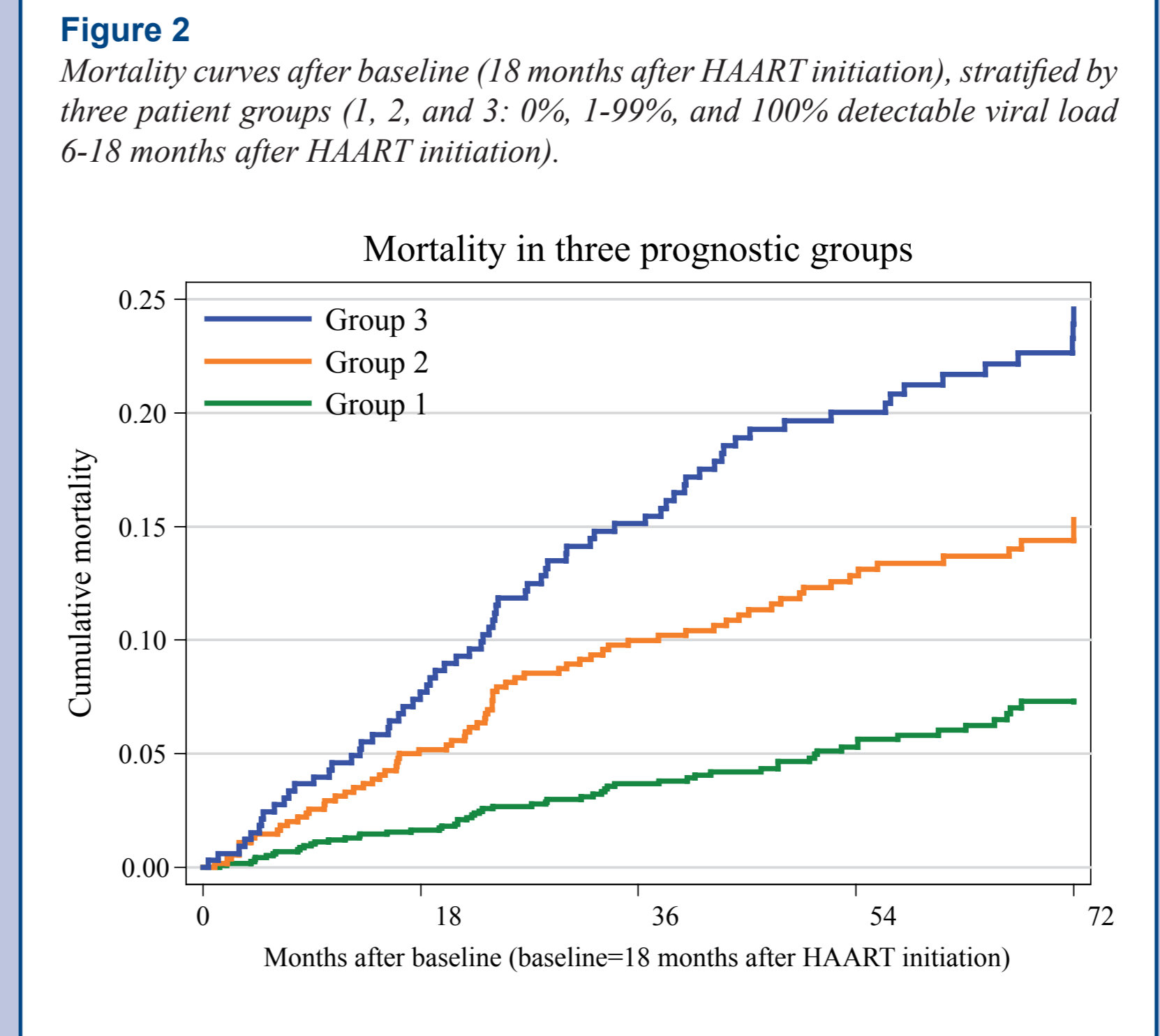
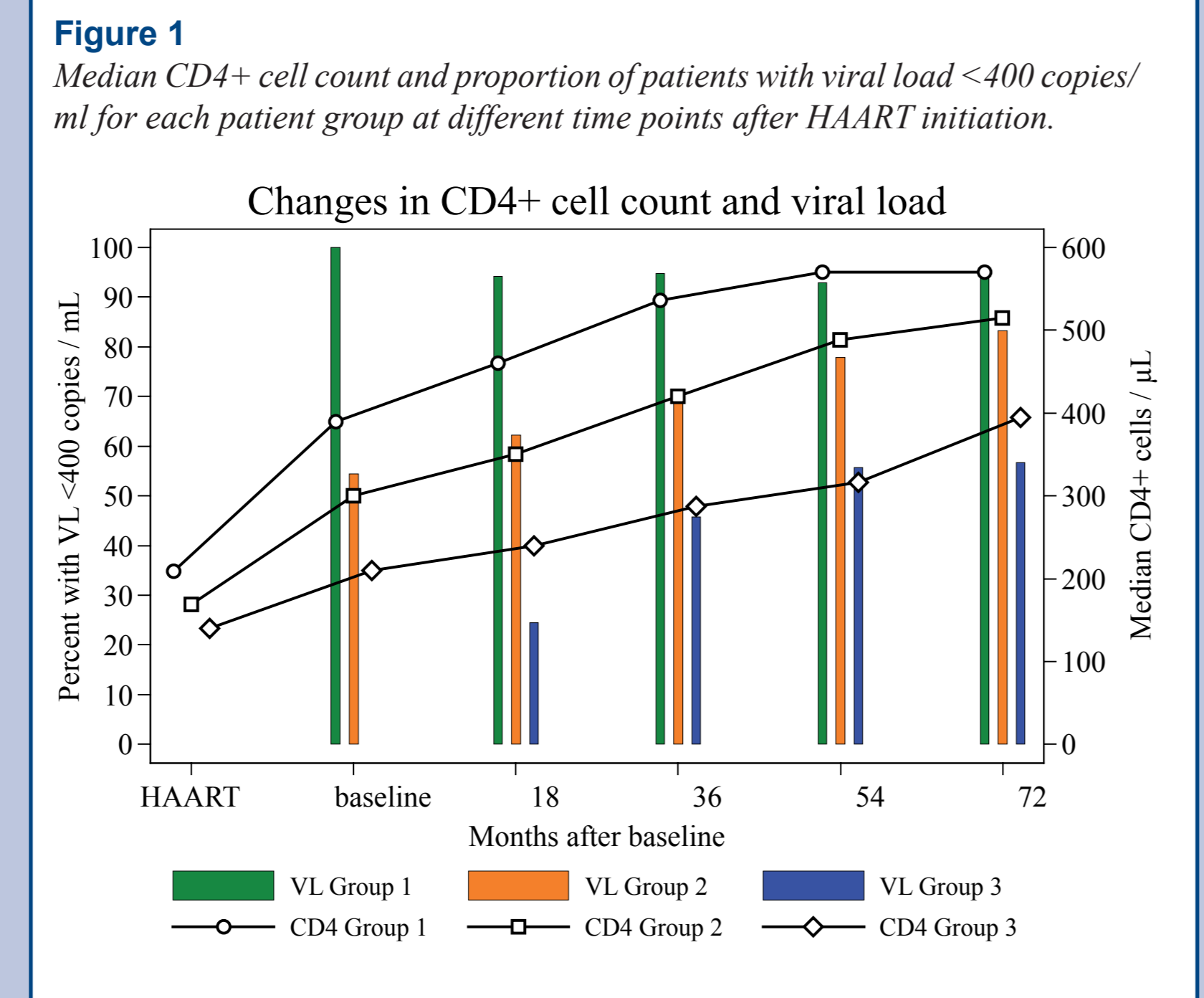
## Conclusion and Interpretation

- Virological suppression during the period 6 to 18 months following HAART initiation was associated with clinical outcome at 90 months.
- Patients experiencing one or more VL measurements above 400 copies/ml were at considerably higher risk of clinical progression than fully suppressed patients. This could be due to drug resistant virus emerging during the initial viremic period, it could be due to less strict virological targets in patients with competing co-morbidity, or most likely, viremia could be a marker of poor adherence and even a marker of non-HIV-related risk factors for death. Further studies are needed to explore the underlying causes of this treatment failure.
- A treatment interruption during the first 18 months of HAART was a strong predictor of death in patients with partial virological suppression. TI could be associated with other risk factors for death, such as end-stage AIDS, drug toxicities, or non-HIV associated conditions related to poor adherence. However, the excess mortality observed in patients who had an episode of TI before baseline remained constant throughout the 6-year period after baseline, making it unlikely that it could be explained by end-stage AIDS or drug toxicities at the time of treatment interruption. Furthermore, a smaller proportion died of non-HIV related causes of death in the subgroup with TI than in the subgroup without TI, suggesting that non-HIV associated conditions were not responsible for the excess mortality.
- Physicians should focus on improving adherence through intensive patient coaching, individualizing drug regimens, and treatment of underlying comorbidity in order to avoid virological failure and these interruptions.

**Table 1**  
Patient characteristics

	Group		
	1	2	3
Percent of time with VL ≥ 400 copies/ml during the period 6-18 months after HAART initiation	0%	1-99%	100%
N	1173	546	327
Gender			
male	76%	75%	75%
female	24%	25%	25%
Median age at HAART initiation (IQR)	39 (33-48)	37(32-45)	37(32-45)
Median CD4 at HAART initiation	209(97-304)	169(72-279)	140(60-270)
Median CD4 at baseline	390(242-530)	300(190-440)	210(120-340)
Median log(10) VL at HAART initiation	4.6(3.2-5.3)	4.6(3.4-5.2)	4.7(3.7-5.2)
Mode of infection			
Intravenous drug use	7%	11%	16%
Other	93%	89%	84%
Hepatitis C co-infection			
Yes	13%	19%	23%
No	85%	80%	75%
Unknown	2%	1%	2%
Previous antiretroviral exposure at HAART initiation			
yes	29%	52%	65%
no	71%	48%	35%
Race			
Caucasian	81%	81%	82%
Other	19%	19%	18%
AIDS at HAART initiation			
yes	20%	24%	31%
no	80%	76%	69%
Treatment interruption (minimum of two weeks) within first 18 months on HAART			
yes	1%	17%	17%
no	99%	83%	83%
Date of HAART initiation			
Before 1 Jan 1999	53%	73%	84%
After 1 Jan 1999	47%	27%	16%

VL: viral load Baseline: 18 months after HAART initiation



**Table 2**  
Number of patients under follow-up at different time periods after baseline

	Observation period (months after baseline)	Group 1	Group 2	Group 3	total
Number under observation at the beginning of the period	0-18	1173	546	327	2046
Number censored		61	19	10	90
Number dead	18-36	19	28	25	72
Number followed during the period		1093	499	292	1884
Number censored	36-54	275	56	16	347
Number dead		20	24	23	67
Number followed during the period	54-72	798	419	253	1470
Number censored		235	77	35	347
Number dead	Baseline: 18 months after HAART initiation	11	12	14	37
Number followed during the period		552	330	204	1086
Number censored		312	143	80	535
Number dead		9	5	8	22
Number followed during the period		231	182	116	529