

## Abstract

**Background.** Viral load is not available for treatment monitoring in most ART programs in Sub-Saharan Africa. We aimed at investigating the prognostic role of virological response to ART in patients from 5 Dream-supported sites in 3 countries undergoing comprehensive treatment monitoring.

**Methods.** Naïve patients from sites in Mozambique, Malawi and Guinea Konakry starting ART with available viral load (VL, bDNA, lower limit 50 cp/mL) at around 6 months (12-36 weeks) after treatment initiation and subsequent follow-up (FU) were investigated. Baseline and 6-month CD4 and VL, baseline WHO stage, hemoglobin (Hb), body mass index (BMI) and proportion of missed (>7 days delay) pharmacy appointments during FU were also retrieved for analysis. Predictors of time from the 6-month VL to death were analyzed by Cox regression models. FU was right-censored at last clinical visit.

**Results.** 1,899 patients were analyzed: females 62%, at baseline median age was 35y, 28% were on WHO stage III/IV, median CD4 208 cells/mL, VL 4.6 log<sub>10</sub> cp/mL, Hb 10.8 g/dL, BMI 20.6 kg/m<sup>2</sup>. Most frequently employed regimens were d4T or ZDV+3TC+NVP (97%); 18% missed >5% drug pick-up appointments. At 6 months, 84.8% had VL<50 cp/mL and median CD4 change was +118 cells/mL. After month 6 VL, during a cumulative fu of 2,356 person-years, 74 patients died, 46 were lost to FU. Predictors of time-to-death are summarized in the table.

In a sensitivity analysis, when the multivariable model was additionally predictive of WHO stage, HIV RNA >10,000 cp/mL remained independently predictive of death (vs <50 cp/mL, HR 3.97, 1.75-8.00, p=0.001). Conclusions: in a Sub-Saharan African setting, achieving an HIV RNA <10,000 cp/mL at 6 months (12-36 weeks) after ART initiation is a strong, independent predictor of subsequent survival. Other independent predictors are higher CD4 at 6 months, baseline Hb, female sex and adherence to pharmacy appointments.

## BACKGROUND AND OBJECTIVES

Most ART programs in resource-limited settings monitor treatment efficacy using clinical criteria and, in part, CD4; viral load monitoring is not considered cost-effective.

In the DREAM program, ART patients are monitored using a comprehensive approach by means of clinical, laboratory (including 3-monthly CD4 and 6-monthly HIV RNA) and adherence measures (by recording proportion of missed visits and drug pick-up appointments).

Objectives of the present study were:

- to analyze the patients survival and the drop-out rates after the viral load monitoring at 6 months;
- to investigate the association of the 6-month viral load and of other co-variables with death and drop-out.

## PATIENTS AND METHODS

Patients were selected from the database of DREAM using following criteria:

Adult (≥15 y), non-pregnant, treatment-naïve pts initiating a standard 1st-line regimen at 5 public sector sites partner of DREAM in Mozambique

(Machava, Manga Chingoussura); Malawi (Blantyre, Lilongwe) and Guinea (Conakry)

Patients were selected with an HIV RNA quantified 6 months after ART

initiation (allowing for a 12-36 weeks range and including the value closest to 6 months) and subsequent clinical follow up

Patients adherence was estimated according to proportion of missed clinical visits and missed pharmacy drug pick-up appointments (allowing for 7 days delay) by dichotomizing the values at thresholds of 95%.

Kaplan Meier estimates and Cox regression models were employed to

analyze estimated probabilities and predictors of the following outcomes:

- death
- Loss to follow-up (lost for >3 months unless returned later)

**Tab 1. Patients characteristics at ART initiation and type of ART regimen employed**

Variable	n%/median
Number of patients	1,898
Age, years (IQR)	35 (28-42)
Sex (male/female)	38.5%/61.5%
WHO class III/IV	28%
CD4, cells/mm <sup>3</sup> (IQR)	208 (105-326)
HIV RNA, log <sub>10</sub> cp/ml (IQR)	4.62 (3.85-5.09)
Hb, g/dL (IQR)	10.8 (9.2-12.4)
Body mass index, kg/m <sup>2</sup> (IQR)	20.6 (18.7-23.0)
ZDV+3TC+NVP	37.6%
d4T+3TC+NVP	59.0%
ZDV+3TC+EFV	1.1%
d4T+3TC+EFV	0.4%
other	1.8%

**Tab 2. Adherence, CD4 and HIV RNA responses**

Variable	% or median
On time attended visits ≥95%	71.9%
On time drug pick-up attendance ≥95%	81.5%
6-month HIV RNA change from baseline (log <sub>10</sub> cp/mL)(IQR)	-2.61 (-3.22,-0.79)
6-month HIV RNA (copies/mL)	<50 60.6%
	50-1,000 24.6%
	1,001-10,000 7.0%
	>10,000 7.8%
6-month change from baseline CD4 (cells/μL) (IQR)	+112 (-38,+191)
6-month abs. CD4 counts (cells/μL)	≤50 1.6%
	51-200 21.1%
	201-350 32.5%
	351-500 24.4%
	>500 20.5%

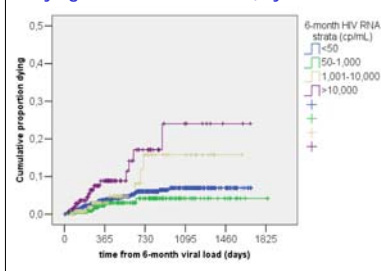
**Tab 3. Predictors of time-to-death after month-6 VL (n=74 deaths)**

Variable	Crude		Adjusted (forward conditional method)	
	HR for death (95% CI)	p	HR for death (95% CI)	P
Sex (female vs male)	0.65 (0.41-1.02)	0.065	0.55 (0.34-0.29)	0.017
Baseline CD4 (+100 cells/μL)	0.79 (0.68-0.92)	0.002	n.e.	
Baseline VL (+log <sub>10</sub> cp/mL)	1.12 (0.91-1.37)	0.281	n.e.	
WHO stage III/IV vs I/II (n=1,172)	2.01 (1.03-3.92)	0.041	n.c.	
Baseline Hemoglobin (+1 g/dL)	0.88 (0.79-0.97)	0.012	0.86 (0.77-0.95)	0.004
>95% drug pick-ups on time	0.47 (0.29-0.76)	0.002	0.51 (0.31-0.85)	0.009
6-month HIV RNA (cp/mL)	<50 (ref) 1.00		1.00	
	50-1,000 0.60 (0.29-1.23)	0.166	0.56 (0.27-1.14)	0.110
	1,001-10,000 1.51 (0.68-3.35)	0.314	1.26 (0.56-2.85)	0.583
	>10,000 2.78 (1.52-5.09)	0.001	2.15 (1.14-4.53)	0.017
6-month CD4 (ref) (cells/μL)	≤50 1.00		1.00	
	51-200 0.44 (0.18-1.08)	0.072	0.38 (0.16-0.94)	0.036
	201-350 0.23 (0.09-0.58)	0.002	0.22 (0.09-0.56)	0.001
	351-500 0.15 (0.06-0.43)	<0.001	0.15 (0.05-0.42)	<0.001
	>500 0.18 (0.07-0.48)	0.001	0.18 (0.07-0.51)	0.001

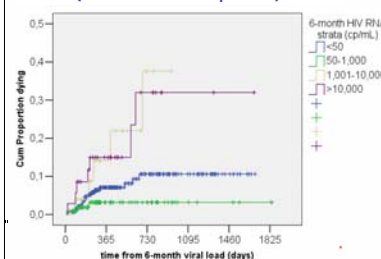
n.e., not entered in the model; n.c. variable not computed

In a model adjusting for baseline WHO stage the only independent predictors were: 6-month VL>10,000 cp/mL, (vs <50 cp/mL, HR 3.97, 1.75-8.00) and WHO stage III/IV (HR 0.44, 0.22-0.86)

**Fig 1. Estimated cumulative proportion dying after the 6-month VL, by VL stratum**



**Fig 2. Estimated cumulative proportion dying after month-6 VL, by VL stratum in the subset with 6-month CD4<200 (n=32 deaths in 421 patients)**

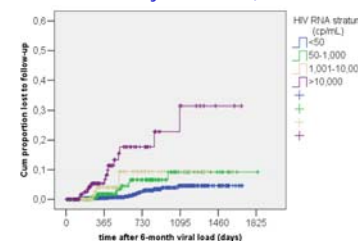


**Tab 4. Predictors of the time-to-death in the subgroup with 6-month CD4<200 multivariable Cox regression (stepwise fwd)**

Variable	HR (95% CI)	P-value
6-month HIV RNA (cp/mL)	<50 1.00	
	50-1,000 0.43 (0.12-1.46)	0.175
	1,001-10,000 2.87 (1.06-7.78)	0.039
	>10,000 2.80 (1.16-6.75)	0.022

Other variables tested in the model: baseline and 6-month CD4, sex, Baseline Hb and VL

**Fig 3. Estimated cumulative proportion lost to follow-up after 6-month VL, by VL stratum,**



**Tab 5. Predictors of time-to-drop-out (n=46) after month-6 VL multivariable Cox regression (stepwise fwd)**

Variable	HR (95% CI)	P-value
6-month HIV RNA (cp/mL)	<50 1.00	
	50-1,000 1.59 (0.72-3.52)	0.249
	1,001-10,000 1.19 (0.43-3.29)	0.733
	>10,000 3.38 (1.65-6.93)	0.001
On time drug pick-up attendance ≥95%	0.05 (0.01-0.16)	<0.001
Attended visits ≥95%	0.29 (0.10-0.85)	0.023
Age (+1 year)	0.94 (0.90-0.98)	0.002

Additional variables not related to this outcomes: baseline CD4, VL, WHO stage, Hb, calendar year, 6-month CD4

## CONCLUSIONS

- In patients starting a standard WHO 1st-line ART regimen mortality after month 6 was low. In this program patients retention was also very high
- 6-month HIV RNA>10,000 cp/mL independently predicted subsequent mortality and loss to follow-up
- In patients with 6-month CD4 counts <200 cells/μL, a 6-month HIV RNA>1,000 cp/mL was already associated with increased risk of death
- For patients undergoing first-line ART in Sub-Saharan Africa, 6-month VL represents a significant prognostic marker