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What frequency of monitoring is needed for health-care in an HIV-infected person?

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INTRODUCTION

Current guidelines recommend that patients on combination antiretroviral therapy (cART) visit clinics on a three monthly basis, for monitoring treatment together with testing of viral load, CD_4 cell count, liver and renal function tests, lipid profiles and glucose levels. Previous studies have shown that the greatest risk of treatment failure is in the first few months after starting treatment and that the risk of clinical disease progression (new AIDS/death) is significantly higher in patients with low CD_4 counts and those who can not maintain an undetectable viral load. It might be possible to monitor patients who are stable on their current cART regimen less frequently, which would be advantageous for both patient and clinic.

AIMS

- Assess whether patients on a stable and fully suppressed cART regimen regimen could be monitored less frequently
- Determine the increased risk of cART treatment failure with less frequent monitoring

METHODS

Patients

2082 patients on a stable and fully suppressed cART regimen for a period of one year within EuroSIDA. cART was defined as a regimen of at least 3 drugs, of which at least 2 were nucleosides/nucleotides (NRTI) and one was a non-nucleoside (NNRTI) or a protease inhibitor (PI).
A stable and fully suppressed regimen was defined as a period of ≥ 1 year with

- Maximal viral suppression (all HIV-RNA in 12 month period < 500 copies/ml; ≥ 2 measurements required)
- All measured CD_4 counts >200/mm^3 (≥ 2 measurements required)
- A minimum CD_4 count increase after starting cART of 100/mm^3
- No changes to cART regimen in the previous 12 months
- No AIDS defining illnesses or non AIDS defining malignacies in 12 month period
- No other serious morbidity (CVD, diabetes, hypertension, grade III/IV liver failure) diagnosed in 12 month period

Statistical Methods

Baseline was defined as the end of the 12 month period after satisfying the inclusion criteria above. Kaplan Meier estimation was used to find the probabilty of failure in the 3, 6 or 12 months after baseline. Failure was defined as:

- 2 consecutive CD_4 <200/mm^3 or < pre-cART levels
- 2 consecutive viral load measurements above 500 copies/ml
- Development of any new AIDS defining illness, non-AIDS defining malignancy, other serious opportunistic infection (OI), cardiovascular disease (CVD), diabetes, hypertension or grade III/IV liver failure or death
- Any of the above

Univariate and Multivariate Cox proportional hazards models, stratified by centre, were used to determine which factors were related to failure.

Table 1

Patient characteristics at baseline

		N	%
All patients		2082	100
Gender	Male	1602	77.0
Race	White	1788	85.9
Exposure group	Homosexual	1043	50.1
	IDU	340	16.3
	Heterosexual	565	27.1
	Other	134	6.4
Treatment at baseline	PI	756	36.3
	PI boosted	566	26.9
	NNRTI	766	36.8
		Median	IQR
Age	Years	40	35-47
Baseline CD_4 count	mm^3	520	394-691
Time since started cART	Years	2.8	1.9-4.3
% time on cART with RNA <500 from 4 months	%	95.2	83.9-100.0

Figure 1

Percentage of patients failing in each category in the 12 months after baseline

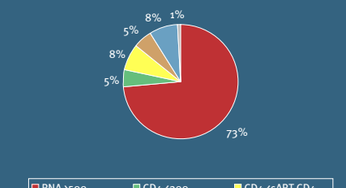
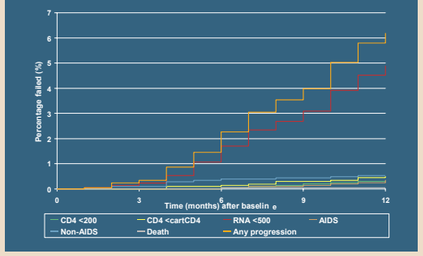


Figure 2

Kaplan Meier
Time to treatment failure after maintaining a stable regimen for > 12 months



RESULTS

Baseline characteristics are described in **table 1**. 1054 patients (50.6%) were ARV-naïve at starting cART and 515 (24.7%) had a prior diagnosis of AIDS. Median CD_4 nadir was 158/mm^3 IQR (67, 253), median CD_4 at starting cART 220/mm^3 IQR (110, 330), median viral load at starting cART 4.63 $\log_{10}$ copies/ml IQR (3.79, 5.23), and median peak viral load 4.94 $\log_{10}$copies/ml, IQR (4.53, 5.42).

Of the 2082 patients in this study, 126 patients (6%) failed for any reason in the first year after baseline.

- **Figure 1** shows the percentage of a patients failing each of the failure categories
- **Figure 2** shows the Kaplan Meier plot of the risk of failure in the first 12 months after baseline

There was an estimated 0.3%, (95% CI 0.1,0.5), n=7, probability of cumulative failure within 3 months, increasing to 2.2% (1.6,2.8), n=47, and 6.2% (5.2,7.2), n= 126, after 6 and 12 months respectively.

The main reason for failure was viral rebound, with an estimated 4.9% of patients (4.0,5.8) with viral rebound after 12 months. The individual risk of deterioration of immune function, new morbidity (AIDS or non-AIDS) or death, were all less than 1% over 12 months.
The results of the multivariate model are shown in **table 2:**

- Increased risk of failure in female patients, decreased risk of failure if patients were on a NNRTI regimen compared to a single-PI regimen, however these were only marginally significant
- Increased risk of failure in patients with more time spent with unsuppresses viremia prior to baseline
- A patient was 7 times more likely to fail if they stopped or decreased the number of ARV's they were taking

Figure 3 shows the reduced risk of treatment failure in patients who have spent less than 6 months with uncontrolled viremia and on an NNRTI based cART, with patients censored if they reduce or stopped taking ARV's. Of the 2082 patients, 941(45.2%) fitted this criteria and after 12 months of follow-up 33 patients had failed (3.5%) and 820 were still under follow up. In this subgroup of patients, the proportion of patients estimated to have failed at 6 months was 1.3% (95%CI 0.6,2.0) and 3.6% (95%CI 2.4,4.8) after 12 months.

CONCLUSIONS

Patients who have responded well to cART and are on a well tolerated and fully suppressive cART regimen, provided they have experienced extended periods, of at least a year, with complete viral suppression and if the regimen contains a NNRTI, have a low chance of failure of cART for the next 3-6 months. Therefore in this subgroup of otherwise healthy patients it may be reasonable to extend visit intervals to 6 months, with cost and time savings to both the treating clinics and the patients.

Table 2

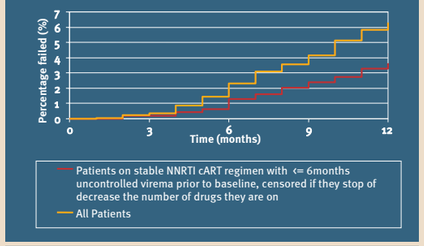
Multivariate Cox proportional hazards model predictors of failure in 12 months after baseline

Predictors of cumulative failure		Multivariate Hazard Ratio	95% Confidence interval	P-value
Gender	Male	1.00	-	-
	Female	1.46	(0.97,2.21)	0.07
Treatment regimen	PI	1.00	-	-
	Boosted PI	0.90	(0.56,1.42)	0.64
	NNRTI	0.69	(0.44,1.07)	0.10
% time on cART with RNA < 500 from 4 months	Per 10%	0.82	(0.75,0.91)	<.0001
Decreasing or stopping the treatment	Time updated	6.64	(2.69,16.40)	<.0001

PI - Protease inhibitor, NNRTI – non-nucleoside reverse transcript inhibitor

Figure 3

Kaplan Meier
Time to treament failure after maintaining a stable treatment regimen for 12 months



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