TIME TO UNDETECTABLE VIRAL LOAD ACHIEVEMENT AFTER ART START AND RISK OF MORTALITY

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BACKGROUND AND AIMS

The goal of ART for people living with HIV (PLWH) is to achieve and maintain virological suppression to allow immune reconstitution, minimise the risk of resistance emergence [1,2], prevent HIV-related mortality, and to prevent transmission [1-3].

However, no data on the association between the time to first undetectable viral load (FUVL) achievement, after antiretroviral therapy initiation, and mortality are available.

In this study we evaluated whether time to FUVL after ART start is predictive of all-cause mortality in a large population of PLWH.

STUDY DESIGN AND METHODS

Retrospective, longitudinal, cohort study, on HIV-1-infected treatment-naïve patients (pts), from the ICONA Cohort, who started ART (≥3 drugs) >1998, with ≥1 viral load (VL) and CD4+ values before and after ART start, who achieved undetectable VL (defined by a single HIV-RNA <50 copies/mL) after ART start.

Results were described as median (IQR) or frequency (%).

Cumulative all-cause mortality probabilities were estimated by use of Kaplan-Meier curves that were compared by log-rank test; follow-up for these analyses started from the date of FUVL achievement until patient's death, loss to-follow-up or last visit. Factors associated with the risk of all-cause mortality were identified using multivariable Cox proportional hazards regression models.

RESULTS

Overall, 10,000 patients (pts) achieved undetectable VL after ART start and were included in the analyses. At ART start, age was 38 (32-46) years, 7805 (78%) males, 1701 (17%) HCV-coinfected, 1028 (10.3%) had a previous AIDS diagnosis, CD4+ 319 (172-464) cells/μL, CD4+/CD8+ ratio was 0.35 (0.20-0.53), HIV-RNA 4.77 (4.20-5.26) $\log_{10}$cps/mL; calendar year of ART start was 2012 (2007-2015), 153 (1.5%) started a NRTI-, 3540 (35.4%) a NNRTI- , 4074 (40.7%) a PI- and 1956 (10.6%) an INSTI-based ART, 277 (2.8%) started more complex regimens.

After ART start, 3161 (31.6%), 3399 (34%) and 3440 (34.4%) pts achieved the FUVL ≤3 months (M), 3-6M and >6M, respectively. Patients' characteristics according to time of achievement of FUVL are shown in **Table 1**. Overall, 7841 pts had ≥1 VL determination ≤3M, 6944 pts in the interval 3-6M and 9427 in the interval >6M from ART start; 5343 pts had ≥1 VL determination in all the three FUVL time intervals and 7451 pts had ≥1 VL determination in ≥1 time interval preceding that of FUVL classification.

During 47019 person-years of follow-up [median follow-up of 3.4 years (1.5-6.5)], 300 deaths for any-cause occurred: 90 among pts with FUVL ≤3M, 86 with FUVL 3-6M, 124 with FUVL >6M.

Kaplan-Meier cumulative mortality estimates at 1, 3 and 5 years (**Figure 1**) were higher (log-rank test: p=0.001) in subjects who achieved FUVL >6M [0.8% (95% CI 0.5-1.2), 2.4% (1.9-3.0) and 4.0% (3.2-4.9)] as compared to those who achieved FUVL ≤6M [0.6% (95% CI 0.4-0.8), 1.6% (1.2-1.9) and 2.3% (1.9-2.8)].

The achievement of FUVL ≤6M as compared to >6M was associated with a lower risk of all-cause mortality in a single-factor analysis [HR(≤6M vs >6M)=0.69 (95%CI: 0.55-0.87); HR(≤3M vs >6M)=0.74 (95%CI: 0.57-0.98); HR(3-6M vs >6M)=0.64 (95%CI: 0.48-0.84)] and remained predictive after adjusting for other factors (**Table 2**) with AHRs ranging from 0.65 to 0.77 depending on the considered model.

Multivariable sensitivity analyses were performed in different patients' subsets in order to exclude that the observed findings might be associated with a potential misclassification of time to FUVL due to the lack of VL determinations in time intervals preceding that of FUVL classification (**Table 3**).

Table 1 – Baseline characteristics of patients who achieved undetectable viral load after ART start

CHARACTERISTIC	OVERALL (n=10,000)	Months to FUVL from ART start ≤ 3M (n=3161)	Months to FUVL from ART start 3-6M (n=3399)	Months from ART start to FUVL >6M (n=3440)	p-value§
Age at ART start (years)	38 (32-46)	38 (31-46)	39 (32-46)	39 (32-47)	0.020
Italian nationality	8265 (83%)	2611 (83%)	2806 (83%)	2848 (83%)	0.963
Male gender	7805 (78%)	2410 (76.2%)	2667 (78.5%)	2728 (81.7%)	0.009
Antibody anti-HCV					0.371
Negative	7609 (76%)	2408 (76%)	2599 (76%)	2602 (76%)	
Positive	1701 (17%)	524 (17%)	561 (17%)	616 (18%)	
Unknown	690 (7%)	229 (7%)	239 (7%)	222 (6%)	
HbSAg					0.026
Negative	8367 (84%)	2610 (83%)	2845 (84%)	2912 (85%)	
Positive	627 (6%)	198 (6%)	204 (6%)	225 (7%)	
Unknown	1006 (10%)	353 (11%)	350 (10%)	303 (9%)	
Mode of HIV transmission					0.006
Heterosex	3922 (39%)	1205 (38%)	1348 (40%)	1369 (40%)	
PWID	1249 (13%)	374 (12%)	395 (12%)	480 (14%)	
MSM	4196 (42%)	1371 (43%)	1456 (43%)	1369 (40%)	
Other/unknown	633 (6%)	211 (7%)	200 (6%)	222 (6%)	
AIDS diagnosis before ART start	1028 (10%)	277 (9%)	337 (10%)	414 (12%)	<.0001
Calendar year of ART start	2012 (2007-2015)	2013 (2008-2016)	2012 (2008-2015)	2012 (2006-2014)	<.0001
Time to ART start since HIV diagnosis (months)	4.6 (1.1-40.8)	6.5 (1.2-46.4)	4.5 (1.1-38.6)	3.8 (1.0-39.0)	<.0001
Type of first-line ART					<.0001
NRTI-based	153 (1.5%)	52 (2%)	44 (1%)	57 (2%)	
NNRTI-based	3540 (35%)	1133 (36%)	1328 (39%)	1079 (31%)	
PI-based	4074 (41%)	897 (28%)	1385 (41%)	1792 (52%)	
INSTI-based	1956 (20%)	1075 (34%)	630 (19%)	404 (12%)	
> 3-drug regimens	277 (3%)	4 (0.1%)	12 (0.4%)	108 (3%)	
CD4+ at ART start (cells/μl)	319 (172-464)	359 (230-505)	311 (178-451)	282 (131-434)	<.0001
CD4% at ART start	19.1 (12.6-26.0)	21.0 (14.9-28.0)	19.0 (12.7-25.4)	17.9 (10.9-24.1)	<.0001
CD4/CD8 ratio at ART start	0.35 (0.20-0.53)	0.39 (0.24-0.60)	0.34 (0.20-0.52)	0.31 (0.17-0.49)	<.0001
Viral load at ART start ($\log_{10}$copies/mL)	4.77 (4.20-5.26)	4.44 (3.86-4.93)	4.80 (4.32-5.25)	5.02 (4.48-5.52)	<.0001
CD4+ at FUVL (cells/μl)	468 (301-645)	464 (303-636)	466 (296-638)	477 (306-660)	0.003
CD4/CD8 ratio at FUVL	0.51 (0.31-0.76)	0.50 (0.30-0.73)	0.51 (0.31-0.75)	0.53 (0.32-0.81)	<.0001

Abbreviation: FUVL, first undetectable viral load after ART start (<50 copies/mL);
§ by Kruskal-Wallis test or chi-square test among 4 categories of time to the first undetectable viral load from ART start

Table 2 – Multivariable Cox proportional hazard models on the risk of all-cause mortality

	Model (1) on all subjects		Model (2) excluding subjects treated with NRTI-based regimens		Model (3) on all subjects		Model (4) excluding subjects treated with NRTI-based regimens	
Months to FUVL from ART start	AHR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value
≤6M	0.69 (0.54-0.88)	0.003	0.74 (0.57-0.96)	0.023	0.72 (0.56-0.92)	0.009	0.77 (0.60-0.99)	0.048
>6M	1.00	-	1.00	-	1.00	-	1.00	-
≤3M	0.74 (0.55-1.00)	0.050	0.81 (0.59-1.10)	0.176	0.78 (0.58-1.05)	0.103	0.85 (0.62-1.15)	0.288
3-6M	0.65 (0.48-0.86)	0.003	0.69 (0.51-0.93)	0.015	0.67 (0.50-0.89)	0.007	0.72 (0.53-0.97)	0.029
>6M	1.00	-	1.00	-	1.00	-	1.00	-
Per month longer	1.017 (1.01- 1.023)	<.0001	1.015 (1.007- 1.022)	<.0001	1.014 (1.007- 1.021)	<.0001	1.012 (1.004-1.019)	0.002

Abbreviations: FUVL, first undetectable viral load; M, months; AHR, adjusted hazard ratio; 95%CI, 95% confidence interval.
Model 1 and 2 were adjusted for age, gender, HIV risk factor, HCV co-infection, pre-ART viral load, pre-ART CD4+, pre ART AIDS diagnosis, time to ART start, type of first-line regimen, CD4 at FUVL and CD4/CD8 ratio at FUVL.
Model 3 and 4 were adjusted for age, gender, HIV risk factor, HCV co-infection, pre-ART viral load, pre-ART CD4+, pre ART AIDS diagnosis, time to ART start, calendar year of ART start, CD4 at FUVL and CD4/CD8 ratio at FUVL.

Figure 1 – Estimated probabilities of all-cause mortality according to time of achievement of FUVL from ART start

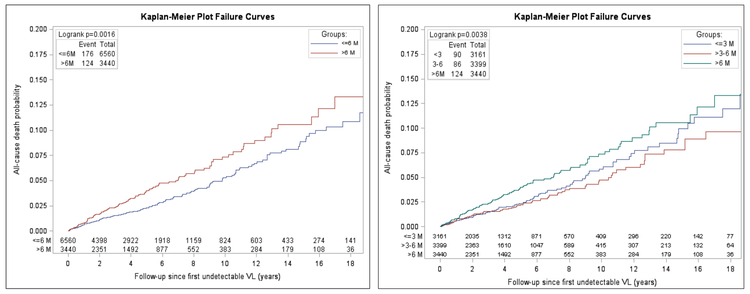

Table 3 – Sensitivity analyses (multivariable Cox proportional hazard models) on the risk of all-cause mortality

	Model (1)§		Model (2)§§		Model (3)§§		Model (4)§	
Months to FUVL after ART start	AHR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value
≤6M	0.65 (0.48-0.86)	0.003	0.61 (0.45-0.81)	0.001	0.64 (0.43-0.93)	0.020	0.65 (0.45-0.95)	0.027
>6M	1.00	-	1.00	-	1.00	-	1.00	-
≤3M	0.71 (0.51-0.99)	0.040	0.67 (0.48-0.93)	0.016	0.69 (0.44-1.08)	0.103	0.70 (0.45-1.08)	0.107
3-6M	0.58 (0.41-0.82)	0.002	0.55 (0.39-0.76)	0.001	0.60 (0.40-0.91)	0.017	0.62 (0.41-0.94)	0.025
>6M	1.00	-	1.00	-	1.00	-	1.00	-
Per month longer	1.014 (1.007- 1.021)	0.0001	1.014 (1.007- 1.021)	<.0001	1.020 (1.010- 1.031)	0.0001	1.018 (1.008-1.029)	0.0003

Abbreviations: FUVL, first undetectable viral load; M, months; AHR, adjusted hazard ratio; 95%CI, 95% confidence interval
Model 1 and 2 were calculated on the 7451 patients with ≥1 VL determination in ≥1 time interval preceding FUVL classification.
Model 3 and 4 were calculated on the 5343 patients with ≥1 VL determination in all the three time intervals.
§ adjusted for age, gender, HIV risk factor, HCV co-infection, pre-ART viral load, pre-ART CD4+, pre ART AIDS diagnosis, time to ART start, calendar year of ART start, CD4 at FUVL and CD4/CD8 ratio at FUVL.
§§ adjusted for age, gender, HIV risk factor, HCV co-infection, pre-ART viral load, pre-ART CD4+, pre ART AIDS diagnosis, time to ART start, type of first-line regimen, CD4 at FUVL and CD4/CD8 ratio at FUVL.

CONCLUSIONS

- In a large cohort of naïve HIV-1 infected subjects (n=10,000), who achieved an undetectable viral load after ART start, we observed 3% of mortality during a median follow-up of 3.4 years.
- The achievement of undetectable viral load within 6 months from ART start was associated with a lower risk of all-cause mortality.

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