

BACKGROUND

Viral load (VL) was found to be associated with a worse prognosis in a previous multi-cohort study [1] on HIV-1 infected subjects who started antiretroviral triple therapy (ART) before 1998 [the median calendar month of ART start was December 1997 (IQR: June 1997 – July 1998)]. In a population-based analysis [2], pre-ART HIV-RNA >100 000 copies/mL showed a marginally significant risk of death. Thus, the aim of this study was to evaluate whether, in recent years, pre-ART VL is still predictive of all-cause mortality, AIDS- or non-AIDS-related mortality, in a large population of HIV-1-infected treatment-naïve patients who started ART.

METHODS

We included HIV-1-infected treatment-naïve patients, from San Raffaele Hospital and ICONA Cohort, who started ART (≥ 3 drugs) >1998 and with available pre-ART VL and CD4+ cell count (the nearest values before ART start).

Pre-ART VL values (cross-sectional, single time-point) were categorized as $\leq 100K$, >100-500K, >500-1000K, >1000K copies/mL.

Kaplan-Meier curves and Cox regression analyses were used to evaluate the association between pre-ART VL and the risk of all-cause, AIDS- or non-AIDS-related mortality.

RESULTS

Overall, 11877 patients included: 7313, 3334, 652, 578 patients with pre-ART VL $\leq 100K$, >100-500K, >500-1000K, >1000K copies/mL, respectively.

The median (IQR) calendar year of ART initiation was 2011 (2005-2014); other patients' characteristics are shown in **Table 1**.

During a median follow-up of 3.8 years (IQR: 1.6-7.2) after ART start, a total of 494 patients died, including 171 AIDS-related deaths (35%), 272 non-AIDS-related deaths (55%) and 51 of unknown cause (10%). Incidence rates of death according to pre-ART VL are shown in **Table 2**.

Pre-ART VL predicted all-cause, AIDS- or non-AIDS-related mortality in a single-factor analysis (**Figure 1**, **Figure 2**) and remained strongly predictive of all-cause mortality after adjusting for the other factors (**Table 3**); people with pre-ART VL in the >500-1000K range, >1000K range had adjusted HRs (AHR) of 1.48, and 2.23, respectively, relative to those with $\leq 100K$.

Separating out causes of death, the associations with AIDS-related mortality were confirmed in the >500-1000K range (AHR=1.98) and in the >1000K range (AHR=2.16); pre-ART VL was also associated with non-AIDS-related mortality; a significant higher risk was evident for subjects with a >1000K (AHR=2.62).

CONCLUSIONS

In recent years, pre-ART VL predicted all-cause and AIDS-related mortality. The risk of AIDS-related death increased for ascending pre-ART VL ranges and was more than double for subjects with pre-ART VL >1000K as compared to those with pre-ART VL $\leq 100K$. The effect of pre-ART VL on the risk of non-AIDS-related death seems to be less potent and needs further investigations. These findings suggest that viral-induced damage does not completely regress even with modern antiretroviral therapies; therefore, patients with high pre-ART VL may have a worse prognosis regardless the efficacy of ART.

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Table 1 – Characteristics at ART initiation of the 11877 HIV-1 infected subjects included in the study according to pre-ART viral load (VL)

Characteristic	Overall (n=11877)	VL $\leq 100K$ (n=7313)	VL 100-500K (n=3334)	VL 500-1000K (n=652)	VL >1000K (n=578)	p-value [§]
Age (years)	38 (32-46)	38 (32-45)	39 (33-47)	39 (33-48)	41 (34-49)*	<.0001
Male gender	9312 (78.4%)	5613 (76.8%)	2744 (82.3%)	509 (78.1%)	446 (77.2%)*	<.0001
Italian	9713 (81.8%)	5952 (81.4%)	2790 (83.7%)	513 (78.7%)	458 (79.2%)*	0.001
Mode of HIV transmission						<.0001
Heterosexual	4328 (35.5%)	2576 (35.2%)	1204 (36.1%)	275 (42.2%)	273 (47.2%)	
IDU	1544 (13.0%)	1020 (14.0%)	414 (12.4%)	69 (10.6%)	41 (7.1%)	
MSM	4837 (40.7%)	3037 (41.5%)	1359 (40.8%)	237 (36.3%)	204 (35.3%)	
Other/unknown	1166 (9.8%)	680 (9.3%)	355 (10.7%)	71 (10.9%)	60 (10.4%)	
Positive antibody anti-HCV	2147 (18.1%)	1389 (19.0%)	596 (17.9%)	94 (14.4%)	68 (11.8%)*	0.0001
Positive HbsAg	648 (6.1%)	419 (6.5%)	160 (5.4%)	39 (6.6%)	30 (5.8%)*	0.174
Calendar year of first HIV positive test	2009 (2000-2013)	2008 (2000-2013)	2009 (2001-2013)	2011 (2002-2014)	2012 (2008-2014)	<.0001
Calendar year of ART start	2011 (2005-2014)	2011 (2005-2014)	2011 (2004-2014)	2012 (2004-2014)	2012 (2009-2014)	<.0001
Time to ART start since HIV infection (months)	7.1 (1.3-47.3)	14.8 (2.1-57.8)	3.2 (1.0-35.5)	1.3 (0.6-5.9)	0.82 (0.39-2.1)	<.0001
ART start ≤ 6 months from diagnosis of HIV infection	5790 (48.8%)	2912 (39.8%)	1892 (56.8%)	492 (75.5%)	492 (85.5%)	<.0001
AIDS diagnosis before ART start	1279 (10.8%)	449 (6.1%)	538 (16.1%)	154 (23.2%)	141 (24.4%)	<.0001
CD4+ (cells/ μ l)	309 (163-449)	348 (241-481)	245 (94-389)	121 (40-293)	131 (44-331)*	<.0001
CD4%	18.4 (12.0-25.0)	20.8 (15.0-26.8)	15.1 (9.0-22.0)	10.0 (5.1-17.9)	10.8 (5.5-18.0)*	<.0001
CD8+ (cells/ μ l)	895 (612-1274)	910 (647-1264)	895 (586-1317)	727 (408-1240)	752 (396-1245)*	<.0001
CD8%	56.1 (47.9-65.0)	54.6 (46.1-63.0)	59.0 (51.0-67.0)	61.7 (53.0-70.0)	61.2 (50.0-71.0)*	<.0001
CD4/CD8 ratio	0.33 (0.19-0.51)	0.38 (0.25-0.56)	0.26 (0.14-0.40)	0.16 (0.08-0.31)	0.18 (0.09-0.35)*	<.0001
Viral load (copies/mL)	62228 (17167 - 190000)	24311 (8050 - 51940)	196929 (137992 - 304819)	680000 (570000 - 815500)	1766653 (1281061 - 3100000)	<.0001
Time window between pre-ART VL / CD4+ values and ART start (days)	16 (4-35)	19 (6-42)	14 (3-29)	10 (2-22)	8 (2-19)*	<.0001

Results as median (IQR) or frequency (%). *Not significantly different from 500-1000K; § by Wilcoxon rank-sum test or chi-square test.

Figure 1 – Estimated probabilities of all-cause, AIDS- and non-AIDS-related mortality according to pre-ART viral load

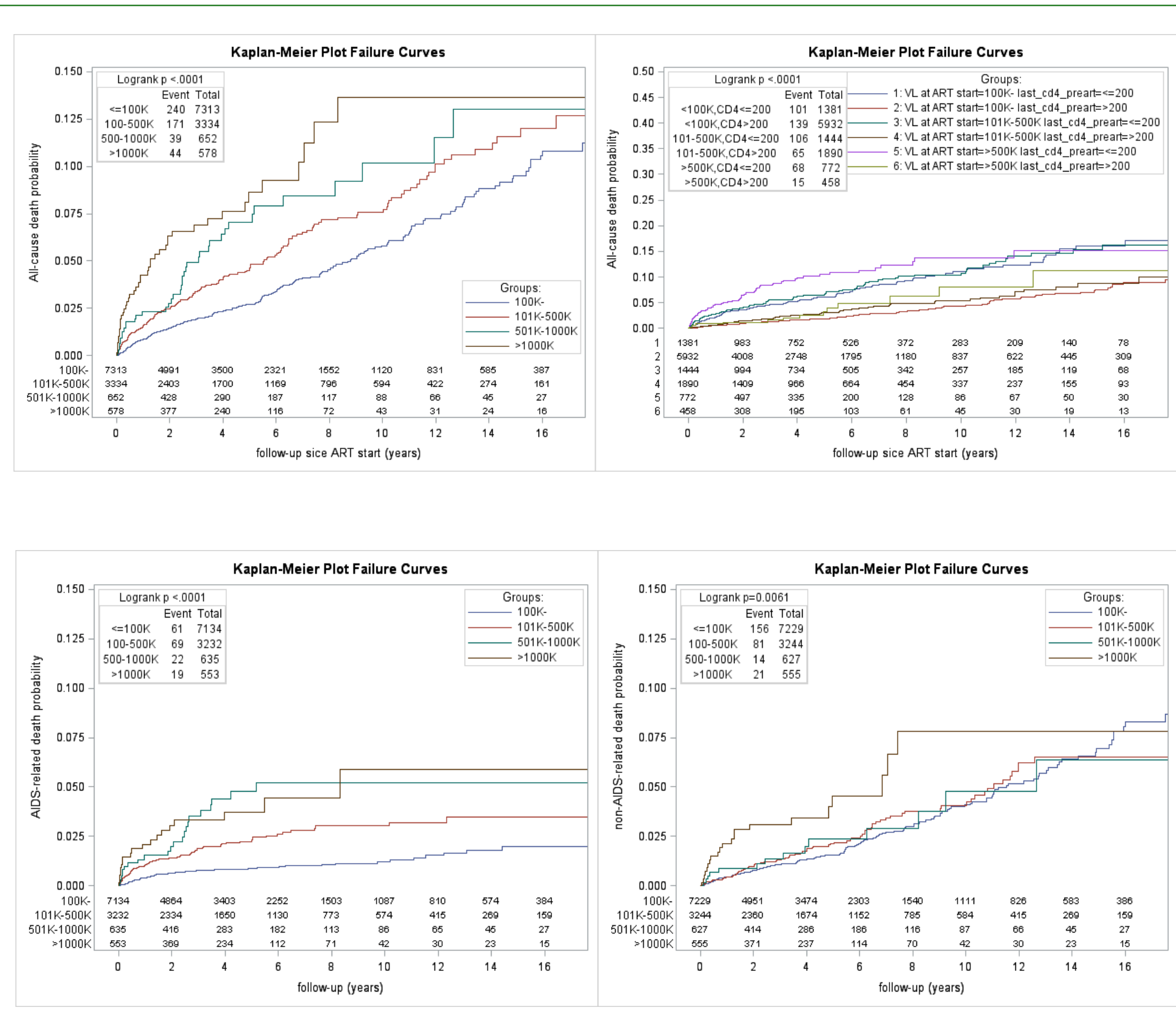


Table 2 – Incidence rates of death according to pre-ART VL

Pre-ART VL	Number of deaths from any cause	Person-years	Crude IR of all-cause mortality per 100-PYFU	LL95%CI	UL95%CI	P-value [§]
100K-	240	37702	0.637	0.556	0.717	Ref
101K-500K	171	18244	0.937	0.797	1.078	0.0007
501K-1000K	39	3084	1.265	0.868	1.661	0.0004
>1000K	44	2365	1.861	1.311	2.410	<.0001

Pre-ART VL	Number of AIDS-related deaths	Person-years	Crude IR of AIDS-related mortality per 100-PYFU	LL95%CI	UL95%CI	P-value [§]
100K-	61	37702	0.162	0.121	0.202	Ref
101K-500K	69	18244	0.378	0.289	0.467	<.0001
501K-1000K	22	3084	0.713	0.415	1.011	<.0001
>1000K	19	2365	0.804	0.442	1.165	<.0001

Pre-ART VL	Number of non-AIDS-related deaths	Person-years	Crude IR of non-AIDS-related mortality per 100-PYFU	LL95%CI	UL95%CI	P-value [§]
100K-	156	37406	0.417	0.352	0.483	Ref
101K-500K	81	17937	0.452	0.353	0.550	0.963
501K-1000K	14	3024	0.463	0.221	0.706	0.998
>1000K	21	2312	0.908	0.520	1.297	0.005

Abbreviations: IR = incidence rate; LL95%CI = lower limit 95%confidence interval; UL95%CI = upper limit 95%confidence interval; PYFU = person-years of follow-up; VL = viral load. § by univariate Poisson regression.

Figure 2 – Percent of death from any cause or AIDS-related death according to pre-ART viral load and calendar year of ART start

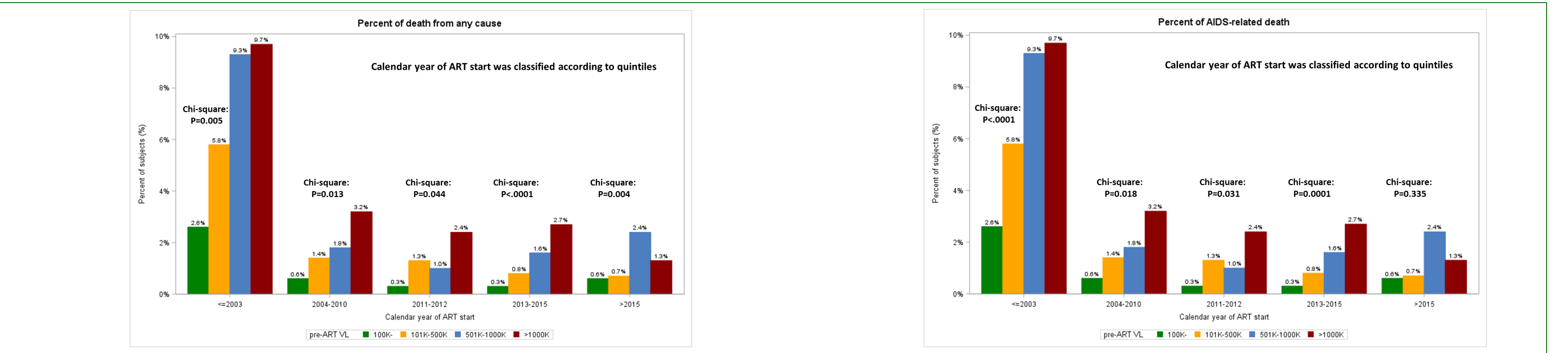


Table 3 – Multivariate Cox proportional hazard models on the risk of death from any cause or from AIDS-related cause

Characteristic	Risk of Death from any cause (427 deaths, n= 9905)		Risk of AIDS-related death (148 deaths, n= 9626)		Risk of non-AIDS-related death (239 deaths, n= 9717)	
	AHR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value
Age (per 5-years older)	1.194 (1.136-1.254)	<.0001	1.070 (0.983-1.163)	0.117	1.290 (1.206-1.379)	<.0001
Gender						
Female vs Male	1.035 (0.824-1.301)	0.765	1.209 (0.826-1.770)	0.329	0.917 (0.670-1.256)	0.384
HIV transmission risk						
IDU vs Heterosexual	1.607 (1.140-2.264)	0.007	1.223 (0.666-2.247)	0.516	1.700 (1.081-2.673)	0.022
MSM vs Heterosexual	0.524 (0.384-0.717)	<.0001	0.637 (0.394-1.030)	0.066	0.476 (0.305-0.742)	0.001
Other vs Heterosexual	0.882 (0.622-1.251)	0.483	0.524 (0.260-1.057)	0.071	1.027 (0.648-1.628)	0.911
HCV						
Positive vs Negative	1.494 (1.100-2.028)	0.010	0.981 (0.567-1.698)	0.947	2.294 (1.534-3.431)	<.0001
Unknown vs Negative	2.553 (1.719-3.790)	<.0001	3.175 (1.811-5.567)	<.0001	2.009 (1.068-3.778)	0.030
Diagnosis of AIDS						
Yes vs No	2.562 (2.028-3.237)	<.0001	5.111 (3.489-7.487)	<.0001	1.656 (1.168-2.348)	0.005
Calendar year of first HIV positive test (per more recent year)	0.975 (0.960-0.991)	0.003	0.949 (0.924-0.975)	0.0001	0.992 (0.970-1.013)	0.442
ART start ≤ 6 -month HIV diagnosis (Yes vs No)	1.052 (0.806-1.375)	0.708	1.152 (0.728-1.825)	0.946	0.871 (0.606-1.253)	0.458
Pre-ART CD4+ (per 50-cells/mm ³ higher)	0.947 (0.917-0.978)	0.001	0.886 (0.832-0.944)	0.0002	0.962 (0.925-1.001)	0.055
Pre-ART CD4+/CD8+ ratio (per 0.2 point higher)	0.994 (0.936-1.055)	0.831	0.998 (0.964-1.034)	0.915	0.995 (0.940-1.053)	0.865
Pre-ART HIV-RNA (copies/mL)						
$\leq 100K$	Ref	-	Ref	-	Ref	-
>100-500K	1.220 (0.979-1.520)	0.076	1.455 (0.990-2.140)	0.057	0.996 (0.739-1.342)	0.980
>500-1000K	1.477 (1.003-2.174)	0.048	1.979 (1.129-3.469)	0.017	0.990 (0.527-1.860)	0.976
>1000K	2.229 (1.530-3.249)	<.0001	2.156 (1.178-3.944)	0.013	2.619 (1.564-4.386)	0.0003

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