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Viremia copy years and its impact on risk of clinical progression according to shape

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Background

- Viremia copy-years (VCY), a measure of cumulative HIV burden approximated by the area under a patient's viral load (VL) curve (AUVLC), was shown to predict mortality independently of VL and current CD4 count in antiretroviral treatment (ART)-experienced patients.
- For a given AUVLC , its shape (e.g. the rectangular with height a VL of 10,000 copies/mL and base 1 year as opposed to, say, that of a VL of 1,000 copies/mL maintained for 10 years) may provide different indications in terms of patients' future prognosis.

Aims

- To quantify the possible bias associated with estimating the association between current VCY and the risk of morbidity/mortality using standard regression techniques as opposed to a marginal structural (MSM) model with inverse probability weighting (IPW)
- To evaluate whether the association between VCY and the risk of morbidity/mortality may vary according to the shape of the AUVLC

Methods

Inclusion Criteria

Individuals in the Icona Foundation Study were included if they started combined ART (cART - defintion: ≥3 drugs of any class) after January 1, 2000 when they were ART-naïve

Exposure

VCY (log_{10} scale) was calculated using the trapezoidal rule on the VL log_{10} scale using the last VL value carried forward (Figure 1).

Participants were classified according to the proportion of AUVLC over the maximum rectangular with base the length of VL follow-up and height the person's ever observed VL peak under cART. Roughly, a proportion of 100% identifies patients with stable VL trajectory at peak level while low percentages people with dips and spikes in VL. The quartiles of this percentage distribution were used to create four distinct exposure groups (A, B, C, D; Figure 2). The association with pre-cART and the 24-week VL value was also evaluated.

Outcomes

i) AIDS or death due to any cause
ii) Severe non- AIDS (SNAE) or death due to any cause

Figure 1. Use of trapezoidal rule to calculate the AUVLC

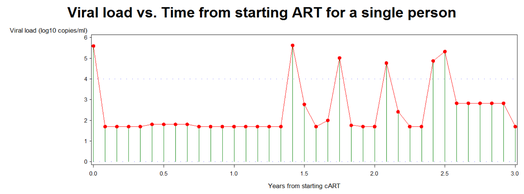
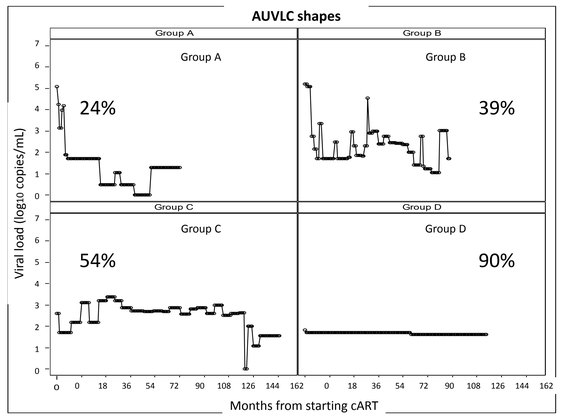


Figure 2. AUVLC shapes over the first 3 years of cART according to quartile of percentage distribution (one representative person per group)



Statistical analysis

Cox proportional hazards regression model was used to estimate the relationship between VCY and the two endpoints with patients' follow-up accruing from ART initiation.

Multivariable models were constructed both controlling for CD4 count as time-updated covariate and using a MSM with IPW

Results

Baseline Characteristics

We included 5,512 persons in Icona with the following characteristics: 36% MSM, 84% of Italian nationality with median (range) age of 37 (18-78) years, who started cART on average in 2010, 55% started PI/r-based cART. By the end of follow-up median (IQR) of VCY was 5.27 (2.69-11.19 log_{10} copies/mL). Table 1 shows other main characteristics of the population stratified by the type of regimen started.

Exposure Groups

The quartiles of the VCY distribution identified the following groups: A: 0-35%, B: 36-40% C: 41-55% and D: 56+% of maximum rectangular. We observed 175 AIDS, 187 SNAE and 69 deaths.

Table 1. Characteristics of study population at starting cART by type of regimen

Characteristics at starting cART	Regimen started: NNRTI/INSTI	PI	p-value*	Total
	N= 2516	N= 2996		N= 5512
Gender, n(%)			0.018	
Female	567 (22.5%)	757 (25.3%)		1324 (24.0%)
AIDS diagnosis, n(%)			<.001	
Yes	114 (4.5%)	244 (8.1%)		358 (6.5%)
CVD diagnosis, n(%)			0.889	
Yes	15 (0.6%)	17 (0.6%)		32 (0.6%)
Hepatitis co-infection, n(%)			<.001	
No	2157 (85.7%)	2703 (90.2%)		4860 (88.2%)
Yes	359 (14.3%)	293 (9.8%)		652 (11.8%)
Not tested	1016 (40.4%)	1601 (53.4%)		2617 (47.5%)
CD4 count, cells/mmc			<.001	
Median (IQR)	318 (223, 416)	254 (117, 376)		288 (162, 396)
Viral load, log10 copies/mL				
Median (IQR)	4.66 (4.04, 5.10)	4.87 (4.17, 5.40)		4.76 (4.10, 5.24)
Diabetes, n(%)			0.652	
Yes	46 (1.8%)	50 (1.7%)		96 (1.7%)
Antivirals started, n(%)				
Zidovudine	626 (24.9%)	600 (20.0%)		1226 (22.2%)
Lamivudine	966 (38.4%)	1028 (34.3%)		1994 (36.2%)
Abacavir	306 (12.2%)	285 (9.5%)		591 (10.7%)
Tenofovir	1611 (64.0%)	1868 (62.3%)		3479 (63.1%)
Emtricitabine	1474 (58.6%)	1805 (60.2%)		3279 (59.5%)
Efavirenz	1722 (68.4%)	13 (0.4%)		1735 (31.5%)
Nevirapine	300 (11.9%)	5 (0.2%)		305 (5.5%)
Rilpivirine	210 (8.3%)	0 (0.0%)		210 (3.8%)
Liponavir/r	0 (0.0%)	852 (28.4%)		852 (15.5%)
Atazanavir/r	0 (0.0%)	879 (29.3%)		879 (15.9%)
Darunavir/r	0 (0.0%)	797 (26.6%)		797 (14.5%)
Raltegravir	116 (4.6%)	157 (5.2%)		273 (5.0%)

*Chi-square or Kruskal-Wallis test as appropriate

Bias from fitting standard regression analysis (AIDS/death endpoint)

The magnitude of risk associated with 1 log_{10} higher VCY was under-estimated when controlling for CD4 as time-updated covariate vs. using IPW (e.g. for AIDS/death HR=1.08 vs. HR=1.16, Table 2).

Table 2. HR from fitting standard Cox regression vs. a MSM with IPW

Hazard Ratios (95% CI) of severe non-AIDS/death from fitting a Cox regression analysis			
	Unadjusted	Adjusted[1]	Adjusted[2]
Viral load exposure per log_{10} copies/mL higher			
Pre-cART value	1.52 (1.31, 1.77)		
	<.001		
24-week value	1.54 (1.43, 1.65)		
	<.001		
Most recent value	1.59 (1.47, 1.72)	1.26 (1.15, 1.37)	1.49 (1.36, 1.63)
	<.001	<.001	<.001
Most recent VCY	1.17 (1.12, 1.21)	1.08 (1.05, 1.13)	1.16 (1.12, 1.21)
	<.001	<.001	<.001

**(1)Adjusted for age, mode of HIV transmission, nationality,calendar year of starting cART and current CD4 count as time dependent variable

**(2)Adjusted for age, mode of HIV transmission, nationality, calendar year of starting cART and current CD4 count using inverse probability weighting

Risk of AIDS/SNAE/death according to AUVLC shape

When evaluating the association between VCY and the risk of SNAE/death it was apparent that the significance and the magnitude of the effect varied according to the shape of the AUVLC (interaction p=0.013, Table 3, top panel).

In particular, in people showing stable VL trajectories rather than periods of VL dips and spikes, VCY appear to better discriminate the risk (10% increase in risk per log_{10} higher VCY). Results were even more extreme for the endpoint of AIDS/death (interaction p<0.001, Table 3, bottom panel).

Table 3. HR associated with VCY stratified by AUVLC shape

	Unadjusted	Adjusted*	p-value#
VCY (per log_{10} copies/mL higher)			.013
	Hazard Ratio of SNAE/death (95% CI)		
Shape A[1]	0.74 (0.58, 0.93)	0.75 (0.60, 0.94)	
Shape B[2]	0.92 (0.83, 1.02)	0.91 (0.82, 1.01)	
Shape C[3]	0.92 (0.83, 1.03)	0.91 (0.81, 1.02)	
Shape D[4]	1.12 (1.06, 1.19)	1.10 (1.04, 1.16)	
	Hazard Ratio of AIDS/death (95% CI)		
Shape A[1]	0.79 (0.61, 1.02)	0.77 (0.60, 0.98)	<0.001
Shape B[2]	0.95 (0.82, 1.09)	0.94 (0.82, 1.09)	
Shape C[3]	0.96 (0.86, 1.07)	0.92 (0.81, 1.04)	
Shape D[4]	1.20 (1.14, 1.27)	1.20 (1.13, 1.27)	

*Adjusted for age, mode of HIV transmission, nationality, calendar year of starting ART and time-updated CD4 count using IPW
#Type 3 interaction p-value
[1]AUC 0-35% of the maximum rectangular (dips and spikes in VL)
[2]AUC 36-40% of the maximum rectangular
[3]AUC 41-55% of the maximum rectangular
[4]AUC 56-100% of the maximum rectangular (stable VL trajectories)

Limitations

- The potential impact of using the last VL carried forward to estimate individuals' AUVLC is unknown
- It might be argued that VCY is not a well-defined 'intervention' and therefore a causal link cannot be established
- The use of MSM with IPW does not remove the issue of bias due to unmeasured confounding

Conclusions

- In people receiving cART, VCY appears to be a significant predictor of future clinical progression particularly in people showing fairly stable VL trajectories
- **Strategies to maximize the chance of viral suppression should be considered for patients with suboptimal viral response even in people with stable low-level detectable viraemia**

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