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Rate of Accumulation of Drug Resistance Mutations during Virological Failure According to Different Measures of Viral Load Exposure

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Background

- Development of HIV drug resistance is a major concern for determining when to switch therapy in resource limited settings (RLS), as individuals who are kept on a failing regimen can accumulate drug resistance mutations (DRM) that compromises later treatment options.
- The level of viral replication can affect the speed at which resistance develops.

Aims

- To estimate the rate of resistance accumulation and genotypic sensitivity score (GSS) reduction according to a number of measures of viral load (VL) exposure over periods of virological failure (VF)
- To identify predictors of resistance accumulation and GSS reduction

Methods

Inclusion Criteria

Individuals from the EuroSIDA cohort were included if they:

- Were on cART: at least 3 drugs of any class
- Experienced an episode of VF: VL>50 while on cART after at least 6 months of cumulative exposure to any cART regimen
- Had a resistance test (T1) available during this VF episode
- Either experienced their first VF from ART-naive or had a resistance test available no more than 3 months before the first date of failure

- Baseline was defined as the first date of included VF.
- Individuals were required to be on the same cART regimen from baseline until T1 and could contribute multiple episodes.

Exposure and Outcome

- DRM were identified using the 2013 IAS[1] list and excluded minor PI mutations.
- GSS reduction of 1 or more (the equivalent of losing 1 or more drugs as a treatment option) was used as a secondary end-point; GSS was calculated using the ANRS interpretation rules version 23.
- VL exposure was defined by:

1) **Baseline VL**: VL at the beginning of a VF episode
2) **Peak VL:** Highest VL experienced during the VF episode
3) **Viraemia Copy-Years (VCY)[2]:** A measure of cumulative VL exposure over time of VF

Statistical Methods

Rate of resistance accumulation was calculated as the number of new DRM to the failing regimen detected at T1 divided by the time between baseline and T1 (PYFU). Multivariable Poisson models with generalised estimating equations were used to model the rate of resistance accumulation.

Results

Baseline Characteristics

A total of 516 individuals contributing 653 VF episodes (79, 15 and 6% with 1, 2 and >2 episodes respectively) were included; characteristics can be seen in Table 1.

Table 1. Characteristics of the study population

At baseline:		N (%)
Gender	Female	102 (19.8)
Age	Years [Median, IQR]	40 [34, 46]
Risk Group	MSM	257 (50.3)
	PWID	83 (16.2)
	Heterosexual	137 (26.8)
	Other	34 (6.7)
HIV subtype	B	393 (85.4)
At the beginning of each failure episode:		N (%)
Calendar Year of Inclusion	Year [Median, IQR]	12/00 [11/98-08/03]
Laboratory	RNA, cp/ml [Median, Range]	21100 [53, 5E6]
	CD4, cells/mm3 [Median, Range]	220 [0, 1445]
cART	Cumulative exposure, months [Median, IQR]	29 [8, 55]
	NNRTI cART	88 (13.5)
	of NNRTI, on TDF	5 (5.7)
	Number of drugs (Median, IQR)	3 [3, 7]
Naïve	Yes	144 (22.1)
Time: baseline to T1	Months [Median, IQR]	9 [1, 81]

DRM accumulation

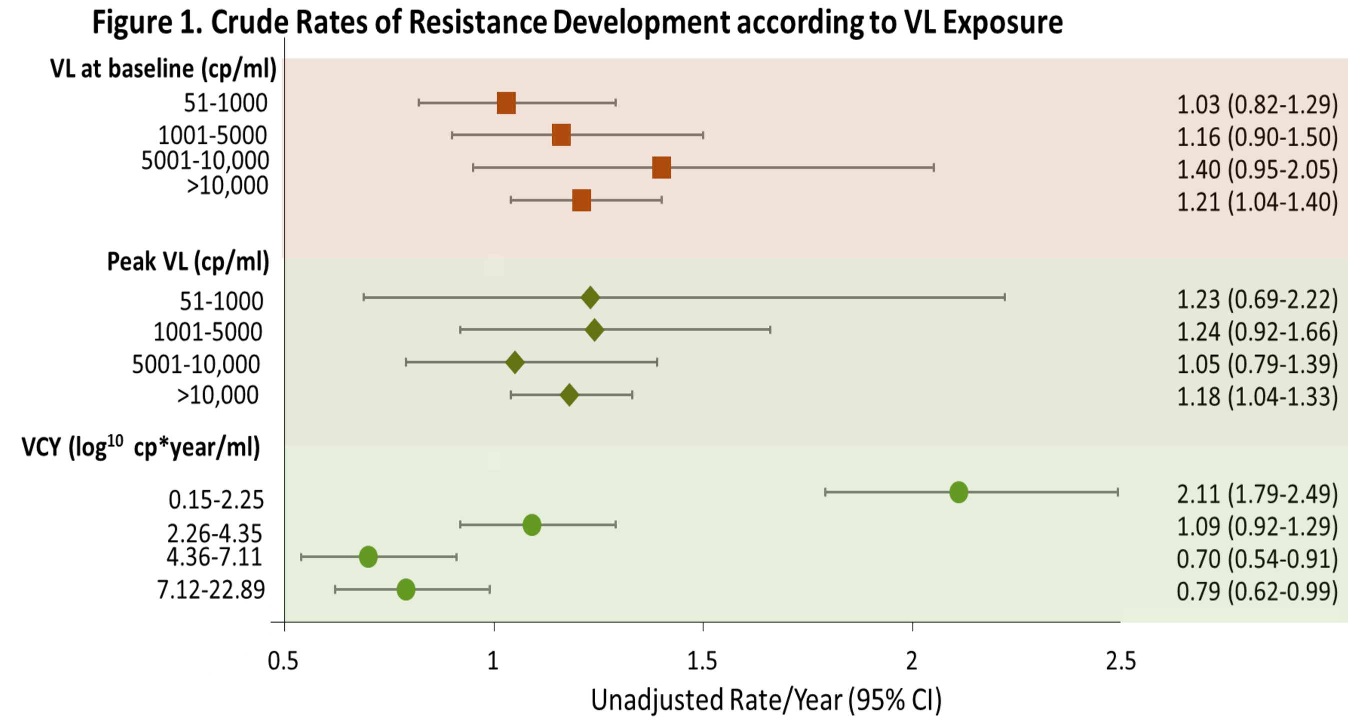
Overall, 672 new DRM accumulated during 573 person-years of PYFU, giving an overall rate of 1.17 (95%CI=1.05-1.31) DRM/year. This rate was similar when restricting to individuals who experienced their first failure from ART-naïve and who were infected with a subtype non-B virus (**Table 2**). The rate of GSS reduction was 0.44 (0.40-0.49) per year longer on failing cART.

Table 2. Estimates of resistance accumulation stratified by different factors

	N (any)	Total FU	Crude Rate/Year (95%CI)
ART-history			
Failed from naïve only	226	182	1.24 (1.04 - 1.48)
Viral Subtype			
Non-B subtype only	70	78	0.90 (0.62 - 1.29)
Type of cART			
NNRTI cart only	161	97	1.65 (1.36 - 2.01)
Unboosted PI only	169	137	1.23 (1.00 - 1.52)
Boosted PI only	20	49	0.41 (0.23 - 0.73)

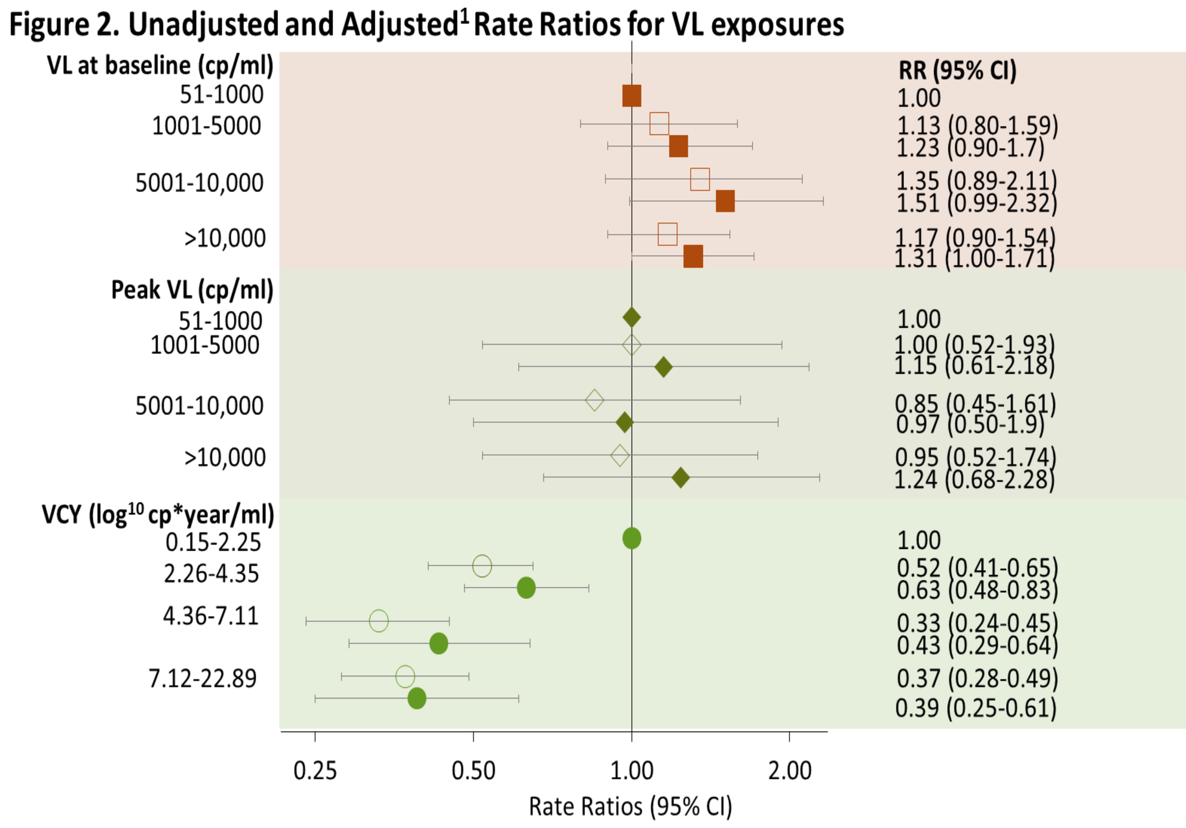
There was no evidence to suggest that the rate of DRM accumulation was associated with level of baseline VL or peak VL (p=0.55 and 0.86 respectively), however, the rate of resistance accumulation was lower with higher quartiles of VCY (p<.001; **Figure 1**).

Figure 1. Crude Rates of Resistance Development according to VL Exposure



These findings persisted after adjusting for a range of confounders (**Figure 2**), including time between baseline and T1. The associations with VL exposures were similar when using GSS-reduction as the outcome.

Figure 2. Unadjusted and Adjusted[1] Rate Ratios for VL exposures

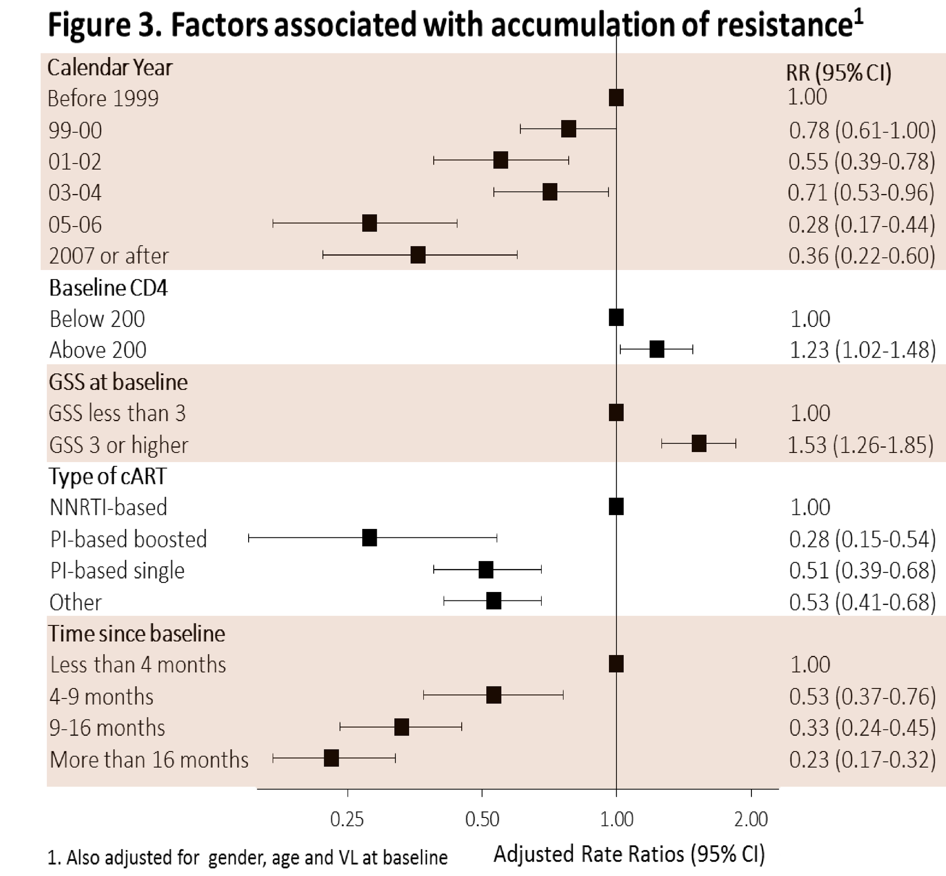


1. Adjusted for gender, age, calendar year, type of cART, time since baseline, CD4 count and GSS.

Predictors of DRM accumulation

Factors independently associated with the rate of DRM accumulation can be seen in **Figure 3**; results were similar when modelling all different VL exposures and using GSS-reduction as the outcome.

Figure 3. Factors associated with accumulation of resistance[1]



1. Also adjusted for gender, age and VL at baseline

Limitations

- **Limitations of available resistance data:** We are restricted to calculating the rate of DRM accumulation among those who had at least two resistance tests
- **Generalizability to RLS:** EuroSIDA is a European cohort, and our results may not be generalizable to some RLS with different demographics
- **Influence of different regimens:** The overall estimate of resistance accumulation is an average, and the agents used and their genetic barrier will also impact the speed of accumulation.

Interpretation and Conclusions

- We estimated that per every 10.3 months of patients being kept on a failing regimen, 1 new IAS mutation accumulated. As a consequence patients lost 1 drug option per every 27.3 months of being kept on a failing regimen.
- Low VCY, which depends both on the level and duration of viraemia during an episode, was a strong predictor of the accumulation of resistance, which could indicate that high VCY is a marker of low selective pressure as a result of poor adherence.
- This would be consistent with the associations found with high CD4 and GSS, but factors such as the effect of certain mutations on viral fitness could also play a role.

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