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Long-term Virological Outcomes of ART-experienced Patients Receiving Raltegravir in a Large European Cohort Study

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BACKGROUND

The use of integrase inhibitors such as Raltegravir (RAL) has recently increased in both ART-experienced and ART-naive individuals. Although data from clinical trials suggest good long-term response rates, evaluations of long-term outcomes using routinely collected data is important as it can provide a 'real-life' picture, often with greater generalisability.

AIM:

- Describe long-term virological outcomes of individuals receiving RAL

METHODS

We used data from the EuroSIDA cohort: a large cohort of almost 19,000 individuals from across Europe, Israel and Argentina. The study regularly collects both CD4 counts and viral loads, details on ART use including start and stop dates and resistance data. Individuals were included if they started RAL as ART-experienced for the first time after 1/1/2006, and had at least one month of follow-up and a baseline HIV-RNA measurement available. Virological failure was defined in different ways depending on the baseline level of viral suppression:

- ***If baseline VL ≤ 50:*** Confirmed VL≥200
- ***If baseline VL>50:*** Confirmed VL≥200 after 6 months of receiving RAL
- ***Irrespective of baseline VL:*** Discontinuation of RAL with the main reason for stopping given by the treating physician as being VF

Time to and risk factors for VF identified using Kaplan-Meier plots and Cox Regression models, and all analyses were conducted both as:

- ***On Treatment:*** Individuals' follow-up lasted until they failed RAL, stopped RAL or their last clinic visit, whichever came first.
- ***Intention to Treat:*** Individuals follow-up lasted until they failed RAL or their last available clinic visit, whichever came first.

All analyses were stratified according to baseline VL (>50 or ≤50), as we hypothesised that the probability of virological failure would be different among individuals who were switched in order to control viral replication, and individuals who were switched in order to simplify the regimen or to avoid certain side-effects.

RESULTS

1796 individuals could be included: the majority started RAL with a supressed viral load ***(Table 1).*** A large variety of drugs, over 693 combinations, were used with Raltegravir. The majority of people received at least 3 drugs, and the most common combinations can be seen in ***Table 1***. Baseline resistance profiles can be seen in ***Figure 1***; data on integrase resistance was not available.

In on treatment analysis 126 individuals experienced VF during their FU, which equals a cumulative probability of VF at 20% by 6 years (baseline VL>50) and 7% by 6 years (baseline VL ≤50; ***Figure 2a***). This was similar, but slightly higher in intention to treat analyses ***(Figure 2b)***: 24% by 6 years (baseline VL>50) and 11% by 6 years (baseline VL ≤50. Risk factors for VF can be seen in ***Figure 3***.

LIMITATIONS

The study has some limitations. Firstly, the fact that we do not collect a fully validated measure of adherence in EuroSIDA means that we cannot capture or assess the influence of poor adherence on our results. Secondly, these failure probabilities may be difficult to put into context, as there is no clear control group that we can use as a comparison arm. And finally, we were only able to describe risk factors for VF among individuals starting RAL with a raised VL, as the number of events in those starting with a supressed viral load was low.

CONCLUSIONS:

- Up to 11% of ART experienced individuals starting Raltegravir with a supressed VL experienced VF by 6 years.
- Among those who started with a raised VL, up to 24% experienced virological failure by 6 years
- In this latter group, the determinants of virological failure we could identify were baseline CD4, geographical region and calendar year.

FUTURE WORK

We are currently genotyping individuals who experienced VF to describe integrase resistance patterns following VF.

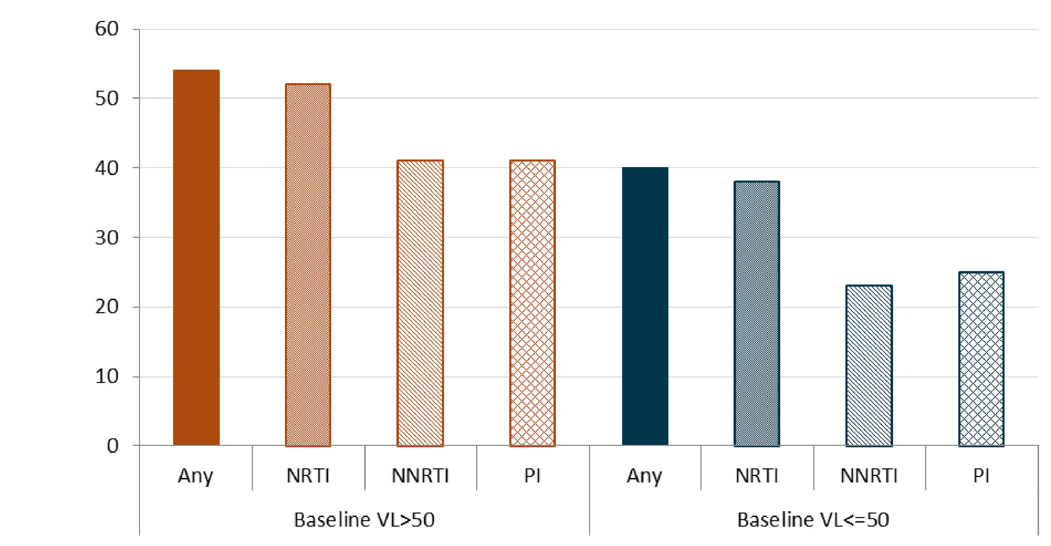
Table 1

Baseline characteristics of the study population, stratified by baseline VL

		Baseline VL > 50	Baseline VL ≤ 50
		N (%)	*N%*
Total	1796	716 (40)	1080 (60)
Gender	Male	522 (72.9)	853 (79.0)
Region	Central West	217 (30.3)	425 (39.4)
	North	142 (19.8)	246 (22.8)
	East	87 (12.2)	86 (8.0)
Risk Group	MSM	293 (41.3)	518 (48.3)
	PWID	128 (18.0)	178 (16.6)
	Heterosexual	239 (33.7)	294 (27.4)
		Median (IQR)	*Median (IQR)*
Age	Years	47 (42 - 54)	50 (45 - 57)
CD4	Cells/mm^3	325 (192 - 498)	536 (365 - 731)
Treatment Regimens	Number of drugs	4 (3-6)	4 (4-5)
	Less than 3 drugs	45 (6%)	43 (4%)
	Most common:		
	1) RAL +	TDF/FTC (5%)	TDF/FTC + DRV/r (4%)
	2) RAL +	TDF/FTC +DRV/r (4%)	TDF/FTC (4%)
	3) RAL +	ETR + DRV/r (4%)	EFV + FTC + DRV/r (4%)

Figure 1

Baseline Cumulative Resistance[1] Prevalence



1. Resistance associated mutations were identified using the IAS-2014 list in a cumulative manner, that is, all resistance detected before baseline contributed to the prevalence estimates The denominator is everyone in the relevant subgroup, irrespective of whether they had a resistance test.

Figure 2a-2b

Cumulative Probability of Virological Failure

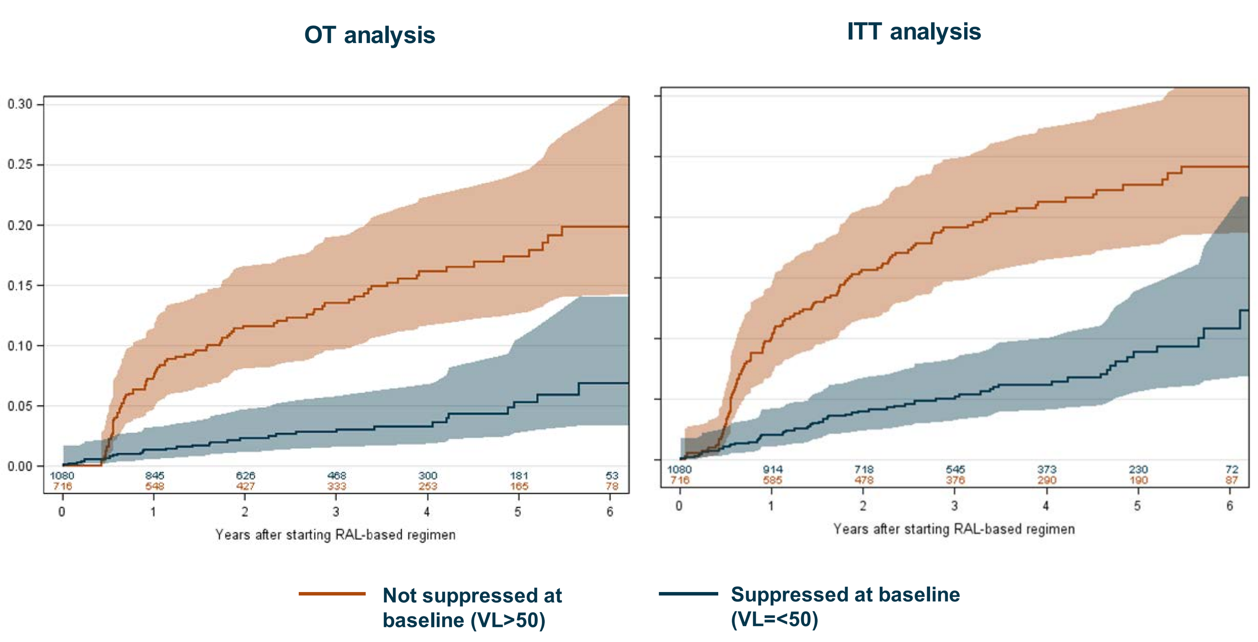
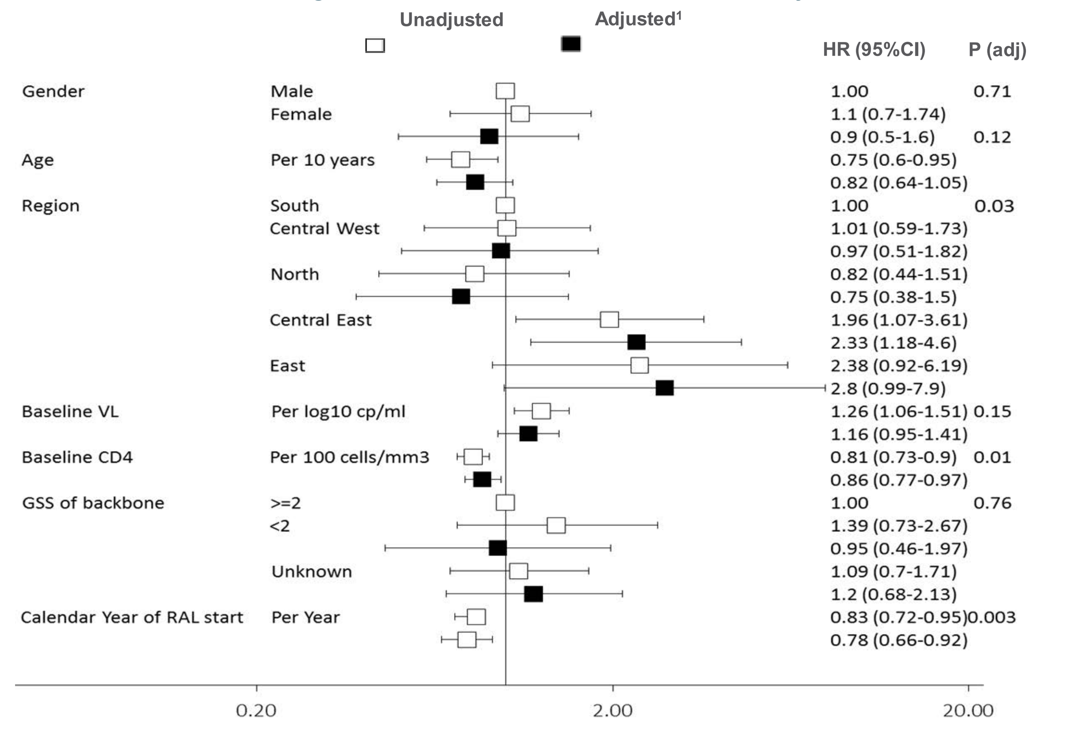


Figure 3

Hazard Ratios of Factors associated with VF
Among individuals with baseline VL>50: OT analysis



1. Additionally adjusted for ethnicity, risk group, viral subtype, hepatitis B status and hepatitis C status

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