The impact of integrase strand inhibitors on creatine kinase levels in antiretroviral naïve people living with HIV

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Background

- Integrase Inhibitor (II) based regimens are first line treatments for antiretroviral therapy (ART) naïve people living with HIV (PLHIV).
- Raltegravir (RAL), first approved in Canada in 2007, has been associated with marked creatine kinase (CK) elevations and rare muscle toxicity in clinical practice.[1,2]
- Whether dolutegravir (DTG) and elvitegravir (EVG) are associated with CK elevation is unknown.
- This study aims to compare changes in CK levels between ART naïve PLHIV initiating treatment with DTG or EVG relative to RAL among participants in the Canadian Observational Cohort (CANOC).

Methods

Design: Observational cohort

Participants: ART naïve PLHIV initiating a regimen containing RAL, DTG or EVG between January 2000 - December 2016 from CANOC who had a baseline CK and follow-up CK measurement. Participants were truncated at the time of treatment switch if it occurred.

Analysis: Cox proportional hazard models were used to compare the risk of grade 2 or higher CK elevations (defined as ≥1.6 x upper limit of normal [ULN], ULN=170 U/L) between those initiating DTG, EVG and RAL. Models were adjusted for age, gender, race, risk category, province and year of ART initiation.

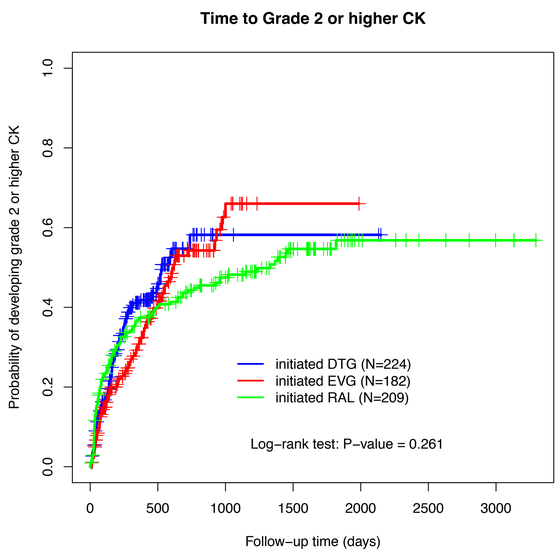
Results

Table 1. Characteristics of study participants at baseline

Characteristics	Initiated DTG	Initiated EVG	Initiated RAL
n	224	182	209
Age (median, Q_1-Q_3)	37, 29-48	38, 29-45	41, 32-48
Gender-Male	90.2%	92.3%	91.4%
Race			
Other	29.9%	28.6%	21.5%
Caucasian	50.0%	42.3%	49.3%
Risk Category			
MSM	**69.2%**	**65.4%**	**61.7%**
IDU	**6.7%**	**6.0%**	**2.4%**
MSM +IDU	**2.7%**	**2.2%**	**2.9%**
Other	**13.8%**	**15.4%**	**8.1%**
Province			
BC	16.5%	7.7%	14.8%
NL	3.6%	1.1%	1.0%
ON	23.7%	40.7%	46.9%
QC	50.5%	42.9%	37.3%
SK	5.8%	7.7%	0%
Year of ART Initiation >2014	**75.0%**	**44.0%**	**5.7%**

Values in bold have a p-value <0.05.

Figure 1. Kaplan Meier curve for probability of developing grade 2 or higher CK levels among PLHIV who initiated a regimen containing DTG, EVG or RAL



- Grade 2 or higher CK elevations were achieved by 15.8% of those who initiated DTG, 12.7% of those who initiated EVG and 16.4% of those who initiated RAL.

Results

Table 2. Unadjusted and Adjusted Hazard Ratios (HR) for time to developing a grade 2 or higher CK levels for PLHIV who initiated a regimen containing EVG, DTG or RAL

	Unadjusted HR (with 95% CI)	Adjusted HR (with 95% CI)
Variable of Interest		
Initiating drug		
initiated RAL	1.00 (-)	1.00(-)
initiated DTG	1.28 (0.95-1.71)	1.18 (0.83-1.69)
initiated EVG	1.12 (0.82-1.51)	0.98 (0.71-1.35)
Confounders		
Age (at ART initiation, per 10 year increment)	**0.79 (0.71-0.88)**	**0.78 (0.70-0.88)**
Gender		
Female	1.00 (-)	1.00 (-)
Male	**2.38 (1.37-4.16)**	**3.47 (1.83-6.57)**
Race		
Other	1.00(-)	1.00 (-)
Caucasian	**0.69 (0.52-0.91)**	**0.67 (0.50-0.90)**
Risk Category		
MSM	1.00(-)	1.00 (-)
IDU	0.59 (0.30-1.15)	0.82 (0.39-1.74)
MSM+IDU	0.65 (0.27-1.57)	0.77 (0.31-1.90)
Other	0.81 (0.55-1.18)	1.36 (0.87-2.13)
Province		
BC	1.00(-)	1.00 (-)
NL	0.76 (0.27-2.15)	0.91 (0.32-2.59)
ON	1.02 (0.69-1.50)	0.85 (0.56-1.30)
QC	1.20 (0.82-1.75)	1.05 (0.70-1.57)
SK	0.72 (0.32-1.62)	0.76 (0.32-1.82)
Year of ART initiation		
≤ 2014	1.00(-)	1.00 (-)
> 2014	0.99 (0.77-1.29)	0.95 (0.69-1.32)

Table 3. Cumulative Incidence of grade 2 or higher CK levels for PLHIV who initiated a regimen containing EVG, DTG or RAL

Initiating Drug	30 days	90 days	180 days
DTG	0.054	0.163	0.274
EVG	0.044	0.143	0.200
RAL	0.087	0.219	0.290

Discussion

- There was no evidence of a difference in time to developing elevated CK levels among ART naïve PLHIV initiating a DTG, EVG or RAL based regimen.
- We did not have information on other medications or variables (e.g. intensity of exercise) that could affect CK levels.

References

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