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Elderly Patients on Antiretroviral Therapy with Dolutegravir are at Increased Risk for ALT Elevation

HIVCENTER
HIV-SCHWERPUNKT IM KLINIKUM DER JOHANN WOLFGANG GOETHE-UNIVERSITÄT FRANKFURT AM MAIN

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Background

Liver toxicity is an important adverse event in patients on ART. Even though newer antiretroviral drugs like integrase inhibitors are generally well tolerated, ageing patients might be at higher risk for elevation of liver enzymes most possibly due to comorbidity and/or comedication.

Methods

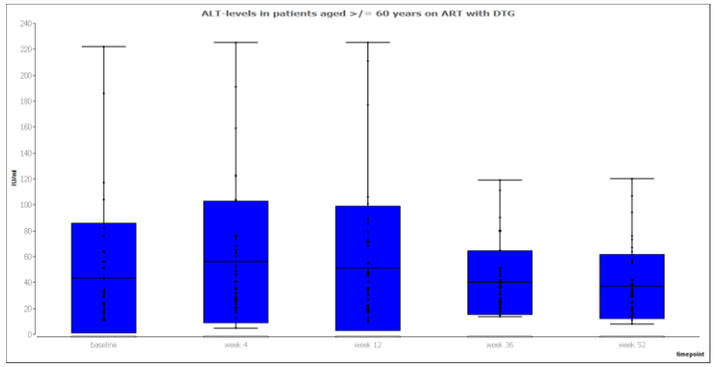
Pooled data from the HIV clinical cohorts at Frankfurt HIV-CENTER and the Center for Infectious Diseases Berlin were analyzed retrospectively for liver enzyme elevations in patients, who initiated dolutegravir (DTG), elvitegravir (EVG) or raltegravir (RAL)-containing ART prior to November, 1st 2017 (Table 1).

Data were analyzed at baseline, week 4, 12, 36 and 52.

Statistics were performed with non-parametrical tests (Wilcoxon-matched-pairs-test,Mann-Whitney-test,Friedman-test,Van-Elteren-test). P-values < 0.05 were considered as significant.

Results

We included 486 patients (male 408, female 78) in our analysis; 333 on DTG, 48 on EVG and 105 on RAL. Median baseline ALT levels were 28 IU/ml (range (r): 8-325) in the DTG group, 26 IU/ml (r:12-134) in the EVG group and 28 IU/ml (r:8-210) in the RAL group (p>0.1) *(Table 1).*

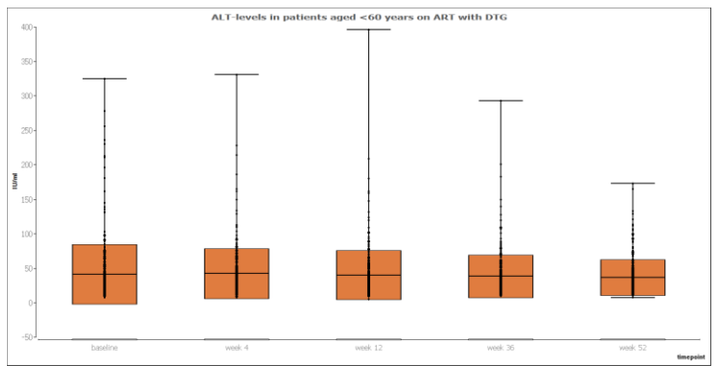


Graph 1

We observed a highly significant increase in ALT-levels in the DTG-group in patients aged >/= 60 years (median change 10.0 IU/ml (r:5-225), p<0.003) between baseline and week 4. ALT-levels then declined significantly (p<0.0001) consecutively and there was no difference between baseline levels and levels in week 52 (median 30.0 (8-120), p>0.1) *(Graph 1)*. The elevation was not associated with any liver comorbidity or intake of concomitant medication (p>0.1).

No significant change in ALT values was observed of patients aged >/= 60 in the RAL- or EVG-group (p>0.1) during all study timepoints up to week 52.

In patients aged < 60 years we did not observe any significant change in ALT-levels in the DTG, RAL or EVG arm (p>0.1) *(Graph 2).* Furthermore, there was no significant difference in liver enzymes in HIV/HCV-coinfected patients compared to HIV-monoinfected patients (p>0.1) in any of the three treatment groups during 52 weeks of therapy.



Graph 2

Table 1. Demographics and Baseline Characteristics

	<60 years	≥60 years		<60 years	≥60 years
Mean age (range) – years	48 (23-59)	68 (60-82)	Liver disease – no. (%)		
Sex – no. (%)			Hepatitis C-Infection	43 (11)	8 (8)
Male	320 (82)	88 (92)	NASH	18 (5)	7 (7)
Female	70 (18)	8 (8)	Liver fibrosis	4 (1)	6 (6)
Race – no. (%)			Liver cirrhosis	4 (1)	2 (2)
Caucasian	287 (74)	94 (98)	INI use at baseline		
Black	35 (9)	1 (1)	DTG	279 (72)	54 (56)
Asian	10 (3)	0 (0)	EVG/COBI	44 (11)	4 (4)
Latin	6 (1)	1 (1)	RAL	67 (17)	38 (40)
Other	52 (13)	0 (0)	NRTI backbone – no. (%)		
Missing data	0 (0)	0 (0)	TDF/FTC	152 (39)	20 (21)
Mean CD4 count, cells/µl (range; IQR)	621 (10-1976; 408-800)	513 (28-1166; 335-702)	TAF/FTC	4 (1)	1 (1)
CDC stage			ABC/3TC	124 (32)	32 (33)
A	108 (28)	23 (24)	3TC/AZT	3 (0.8)	1 (1)
B	198 (50)	44 (46)	ART use at baseline		
C	84 (22)	29 (30)	PI (ATV, DRV, LPV, SQV or TPV)	50 (13)	19 (20)
Liver disease – no. (%)			NNRTI (RPV, NVP, EFV or ETV)	14 (4)	4 (4)
Hepatitis B-Infection	8 (2)	1 (1)	Entry-Inhibitor (T20 or MVC)	12 (3)	7 (7)

3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; COBI, cobicistat; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; ETV, etravirine; EVG, elvitegravir; LPV, lopinavir; MVC, maraviroc; NASH, non-alcoholic steatohepatitis; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RAL, raltegravir; RPV, rilpivirine; SQV, saquinavir; T20, enfurvitide; TPV, tripanavir.

Conclusion

In our analysis integrase inhibitors did not cause clinically significant elevation of liver enzymes. However in elderly patients aged >/= 60 years dolutegravir caused significantly more ALT-elevations at week 4 compared to elvitegravir or raltegravir. ALT normalized up to week 52 and none of the patients had to stop treatment due to liver toxicity. Clinicians should be aware of this ALT-peak when they initiate ART with dolutegravir in elderly patients.