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

P. de Leuw1*, K. Wiedmann1, N. Filmann2, I. Krzmaric3, P. Ingiliz4, A. Haberti4, G. Kann4, G. Schüttfeld1, J. Severain5, T. Wolf4, C. Stephan1
1HIV-Center, University Hospital, Department of Infectious Diseases, Frankfurt am Main, Germany; 2Institute of Biostatistics and Mathematical Modeling, Department of Medicine, Goethe University, Frankfurt am Main, Germany; 3Center for Infectious Diseases Berlin, Berlin, Germany;
* Correspondence: philipp.deleuw@kgu.de

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 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.

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.