TOTAL DOLUTEGRAVIR LEVELS DECREASED BUT FREE FRACTION INCREASED BY VALPROIC ACID

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Henrieke Prins[1], Pauline Bollen[2], Kirsten Velthoven[2], Bart Rijnders[1], Theodora de Vries-Sluijs[1], Els van Nood[1], Jan Nouwen[1], Hannelore Bax[1], Mariana de Mendonca Melo[1], Annelies Verbon[1], David Burger[2], Casper Rokx[1]*

[1]Department of Internal Medicine and Infectious Diseases, Erasmus MC University Medical Center, Rotterdam, Netherlands

[2]Department of Pharmacy, Radboud University Medical Centre and Radboud Institute for Health Sciences (RIHS) , Nijmegen, The Netherlands

**Corresponding author: h.prins@erasmusmc.nl*

BACKGROUND

Previous literature suggests that there is a drug-drug interaction (DDI) between dolutegravir (DTG) and valproic acid (VPA) that leads to >80% decreased DTG plasma concentrations. Possible explanations include induction of DTG's metabolizing enzymes by VPA, impaired DTG absorption due to complexation of DTG by excipients in VPA, or competition for binding sites on plasma proteins. In this pharmacokinetic (PK) sub study, we evaluated DTG-PK in HIV-infected individuals on DTG-containing regimens participating in the "LRAs United as a Novel Anti-HIV strategy" (LUNA) study (clinicaltrials.gov NCT: 03525730).

METHODS

Intrasubject comparisons were made for DTG PK (50mg QD) with and without co-administration of VPA (15 mg/kg BID for 14 days). Total DTG, unbound DTG, and DTG-glucuronide trough plasma concentrations were measured on day 0 (pre-dose and 6 hours post-dose VPA and DTG), and on day 1, 7, 14, and 42 (table 1). Participants in study arms without VPA served as controls.

RESULTS

Preliminary results of nine participants (six on VPA) showed total DTG trough levels (geometric mean (GM)) prior and after VPA of 1.35 mg/L on Day 0 and 1.11 mg/L on Day 42. During VPA administration total GM DTG levels decreased sharply to 0.85, 0.31 and 0.14 mg/L on Day 1, 7 and 14, respectively (figure A). We observed a parallel increase in the unbound fraction of DTG and ratio DTG-glucuronide/DTG: 0.46-0.58% and 0.05-0.18 during VPA administration vs 0.23-0.32% and 0.06-0.07 without VPA administration (figure B and C). Of the unbound DTG concentrations >90% was above the proposed in vitro EC90 value for unbound DTG of 0.9 µg/L (figure D). None of the total VPA trough levels at the matching time points were below the therapeutic range of 50-100 mg/L (data not shown).

Table 1: DTG sampling schedule

	Day 0	Day 1	Day 7	Day 14	Day 42
Valproic acid administration	Yes	Yes	Yes	No	No
Dolutegravir trough sample	Yes (pre dose)	Yes	Yes	Yes	Yes
6-hour sample	Yes (post dose)				

Figure B

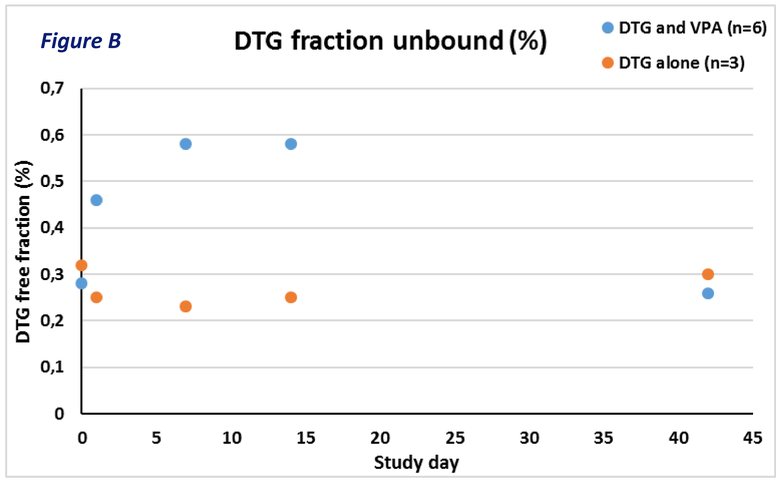


Figure C

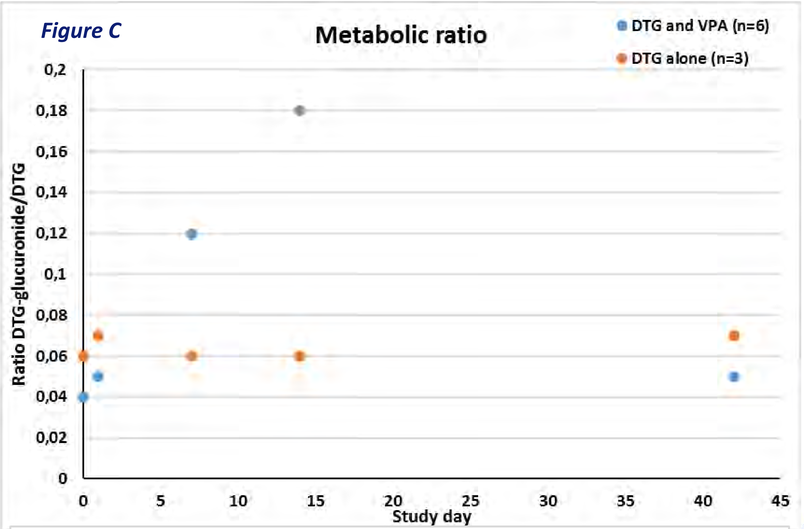
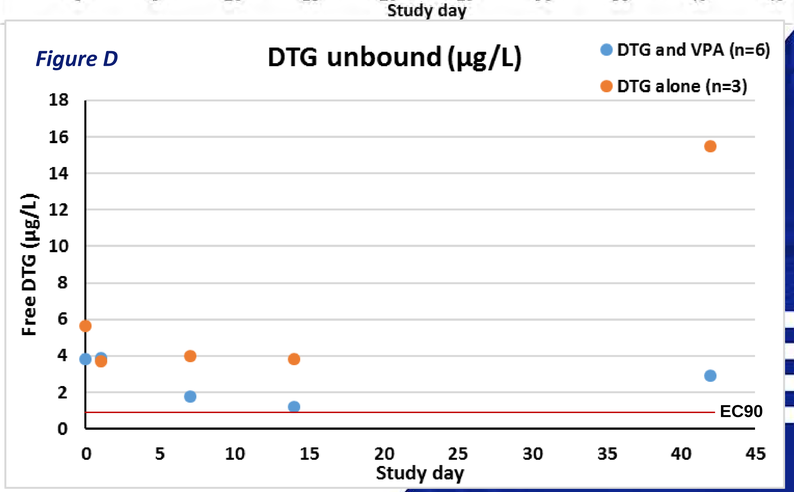


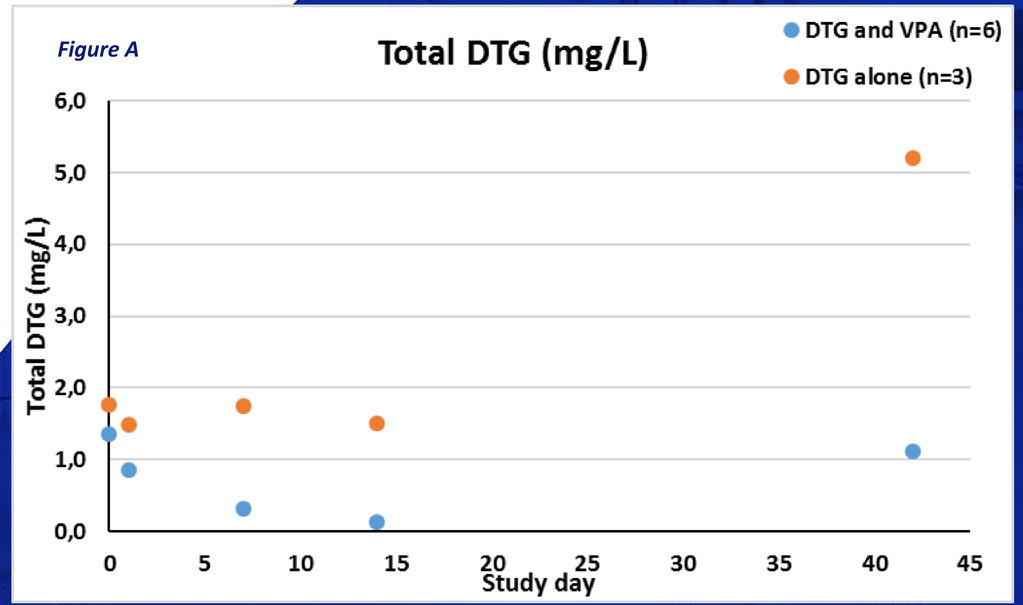
Figure D



CONCLUSION

The unbound fraction of DTG and ratio DTG-glucuronide/DTG both increase in patients while VPA is coadministrated, but this is driven by the decrease in total DTG concentration. The main explanation for the reported decrease in total DTG plasma concentrations after addition of VPA is the displacement of protein binding of DTG by VPA. This DDI is not clinically relevant.

Figure A



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