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Adequate plasma levels of dolutegravir in combination with ritonavir-boosted darunavir: a pharmacokinetic subgroup analysis of the DUALIS study

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Sir,

Successful combination ART (cART) has substantially increased the life expectancy of patients infected with HIV.[1] Although triple therapy has been the standard of care since 1996, recent studies have demonstrated the non-inferiority of a number of dual ARTs.[2,3] Although dolutegravir in combination with the NRTI lamivudine has demonstrated safety and efficacy for therapy-naive patients and after switch of therapy in patients with HIV,[3,4] only limited evidence exists for the combination of dolutegravir and the ritonavir-boosted PI, darunavir.[5,6] This gap was addressed by the DUALIS study, a large prospective, interventional, multicentre, randomized controlled trial (DUALIS, Eudra-CT: 2015-000360-34), which demonstrated the safety and efficacy of a switch to once-daily dolutegravir (50 mg) and darunavir boosted with ritonavir (800/100 mg) in virally suppressed participants. Data of intensive pharmacokinetic (PK) sampling from a substudy of 10 subjects were published in this journal; some subjects were included in both the PK I and PK II substudies.[7] The additional substudy presented here, PK II, aims to describe untimed dolutegravir and darunavir plasma concentrations and changes in safety parameters in a larger subgroup of subjects from the DUALIS study. Approval was obtained from the ethics committee of the University Hospital rechts der Isar, Munich, Germany (approval number 162/15AF) and the study was carried out in accordance with the Declaration of Helsinki. After obtaining written informed consent from all subjects, their medications were switched to dolutegravir (50 mg) and darunavir boosted with ritonavir (800/100 mg) once daily. Study medication was recommended to be taken with a fatty meal. For the PK II substudy, serum blood was collected on scheduled visits but not at a set time after last pill intake at Week 4, 12 and 24. Blood samples were centrifuged at 4500 rpm for 10 min and plasma samples were stored at −80°C; drug concentrations were measured using modified liquid chromatography.[7] Carbamazepine and quinoxaline were employed as internal standards for dolutegravir and darunavir, respectively. Lower limits of quantification were 150 ng/mL for dolutegravir and 125 ng/mL for darunavir (limits of detection were 2.0 and 1.8 ng/mL for dolutegravir and darunavir, respectively). All data are presented as median (IQR) unless stated otherwise. To evaluate the significance of changes from baseline in safety laboratory parameters, two-sided Wilcoxon signed-rank test for paired samples was used. For PK analysis, 57 subjects (50 male and 7 female) with a median (IQR) age of 45 (37–51) years and a median BMI of 24.3 (22.6–26.2) kg/m^2 were included in the substudy at the first PK measurement at Week 4. HIV RNA was <50 copies/mL in 98.1%, 96.3% and 96.3% of subjects at Week 4, 12 and 24, respectively. Median CD4 cell count remained at 638.0, 602.5 and 637.0 cells/mm^3 at Week 4, 12 and 24, respectively. Adherence of the subjects to study medication measured by pill count was 78.9%, 87.5% and 89.3% for dolutegravir and 75.4%, 87.5% and 89.3% for darunavir at Week 4, 12 and 24, respectively. The median (IQR) time difference between the last reported intake of dolutegravir and darunavir boosted with ritonavir and blood sampling for PK analysis at Week 4, 12 and 24 was 20.6 (8.1–24.0), 18.3 (5.8–23.5) and 18.3 (8.9–23.0) h, respectively. Median (IQR) plasma levels at Week 4, 12 and 24 were 1258 (662–2556), 1345 (870–3021) and 1494 (816–2274) ng/mL for dolutegravir and 1543 (1123–2832), 1961 (1111–3279) and 1751 (1314–3008) ng/mL for darunavir, respectively, (Figure 1a–c). Median plasma concentrations were 0–82-fold (Week 4), 3–79-fold (Week 12) and 4–98-fold (Week 24) above the protein-adjusted IC_{90} (64 ng/mL, calculated for WT virus) for dolutegravir[8] and 0–45-fold (Week 4), 2–33-fold (Week 12) and 1–42-fold (Week 24) above the protein-adjusted EC_{90} (200 ng/mL, calculated for WT virus) for darunavir.[9] Liver and kidney functions remained normal during the investigation period [ALT level was 20.0 (18.0–25.0), 21.0 (16.0–28.0) and 22.0 (17.0–24.0) U/L at Week 4, 12 and 24, respectively; AST level was 22.0 (19.0–26.0), 23.0 (20.0–26.0) and 23.5 (20.0–28.0) U/L at Week 4, 12 and 24,

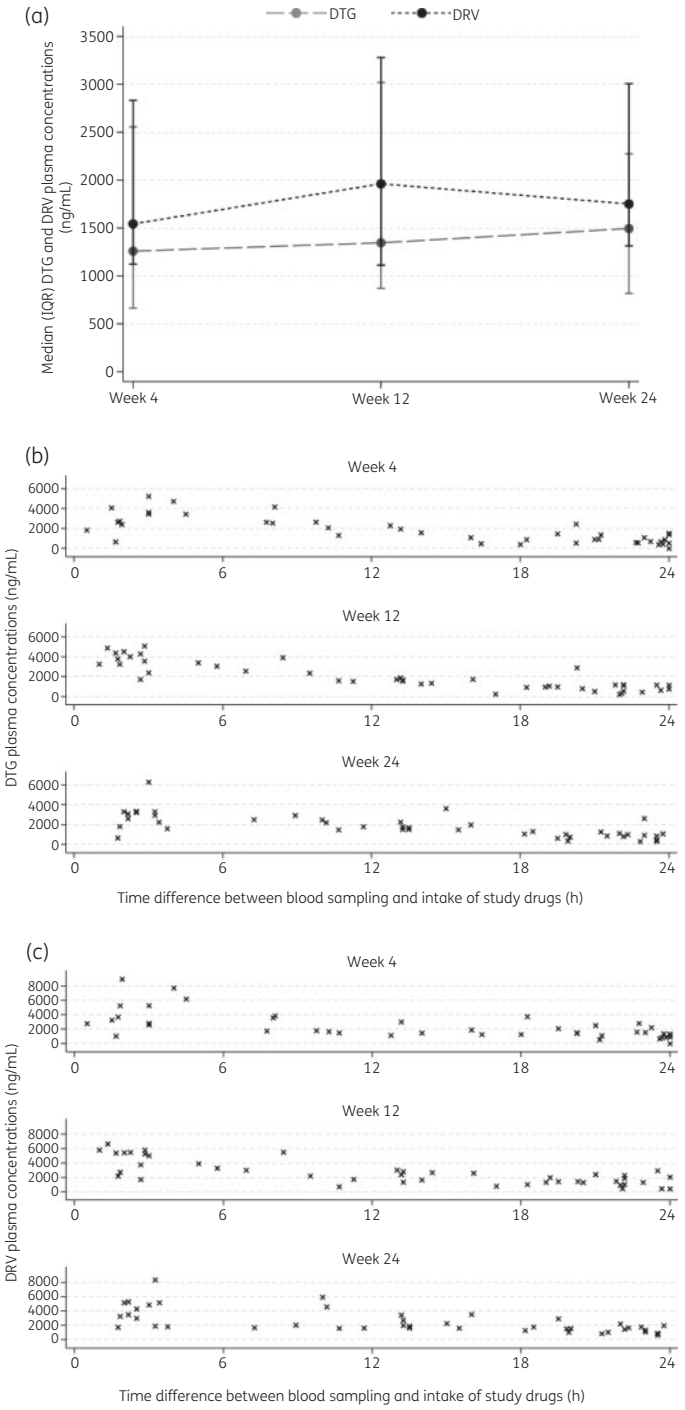

Figure 1. (a) Median (IQR) plasma concentrations for dolutegravir (DTG) and darunavir (DRV) after Week 4, 12 and 24 in a subset of 57 subjects within substudy PK II of the DUALIS study. Distribution of plasma levels of (b) dolutegravir and (c) darunavir in hours after last reported intake at Week 4, 12 and 24. Each cross represents one subject.

respectively; and serum creatinine was 1.0 (0.9–1.1), 1.1 (1.0–1.1) and 1.1 (0.9–1.1) mg/dL at Week 4, 12 and 24, respectively].

In the PK II study, adequate and well-distributed plasma dolutegravir and darunavir levels were observed in randomly collected blood samples from subjects. PK safety of coadministration of dolutegravir and darunavir boosted with ritonavir has been discussed in the PK I substudy.[7] Notably, one subject had inadequate dolutegravir and darunavir plasma concentrations at Week 4 (25 h after the last dose) and reported an issue with adherence. However, during follow-up, drug levels at Week 12 and 24 were adequate in this subject. In two other subjects, each darunavir level (155 and 172 ng/mL) was slightly below the protein-adjusted EC_{90} at 25 h after the last dose, although drug levels at all other times were adequate. According to the protocol, neither of these subjects had complete adherence to study medication by the pill count. For all other subjects, dolutegravir and darunavir concentrations were above the respective protein-adjusted IC_{90} and EC_{90}. Liver, renal and haematological function remained unchanged during the 24 week period. Since blood samples were not taken at a fixed timepoint, a limitation of the study could be that short-time concentrations of dolutegravir and darunavir below the therapeutic target might be missed in some subjects. However, the data obtained from the PK II substudy support the safe PK combination of once-daily dolutegravir and darunavir boosted with ritonavir.

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Author contributions

S.W. has drafted the manuscript. C.B., J.S., A.Z. and H.H.F.K. have supervised patient care and assisted data interpretation and editing of the manuscript. A.B. and E.W. have performed statistical analysis and data interpretation and assisted editing of the manuscript. H.B. has been involved in supervision and management of the study as well as data handling. C.D.S. has coordinated the entire study as well as supervising patient care and editing of the manuscript.

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Stopping lopinavir/ritonavir in COVID-19 patients: duration of the drug interacting effect

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Sir,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is highly infectious, causing coronavirus infectious disease 2019 (COVID-19) worldwide.[1] One of the experimental treatments includes the HIV drug lopinavir boosted with ritonavir. Both PIs