**Population Pharmacokinetics (PK) of Dolutegravir (DTG) Alone and Following Treatment Switch**

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**Background:** The integrase inhibitor DTG is a preferred antiretroviral in many treatment guidelines. Efavirenz (EFV) induces DTG UGT1A1 and CYP3A4-dependent metabolism but dose adjustments are not recommended following treatment switch with steady-state DTG reached WK4 post-switch.1,2 Population PK analysis was performed to describe DTG PK and investigate changes in DTG after switching from an EFV-based regimen.

**Materials & Methods:** Model development (NONMEM v 7.3) combined DTG concentration-time data (50mg once daily) from 2 studies. Study 1 was in healthy volunteers administered DTG for 10 days with serial blood sampling performed for 216h following the final dose.3 Study 2 was in HIV-infected, virologically suppressed patients switched from EFV to DTG with random single samples drawn at WK1, 2, 3 and 4 post-switch (samples between 1-25.75h post-dose). The impact of residual EFV on DTG apparent oral clearance (CL/F) after switching compared to DTG alone was determined. Covariates including weight, age, BMI, sex, ethnicity, HIV status and food consumption within 3h of drug intake were also assessed and the model evaluated by simulation and visual predictive check.

**Results:** Fifty-six individuals were included (n=14 female, n=35 Caucasian; n=17 healthy, n=39 HIV). DTG up to 216h was described by a 2-compartment model parameterised by CL/F [estimate (RSE%): 0.85L/h (5%)], central volume of distribution [Vc/F: 17L (7%)], intercompartmental clearance [Q/F: 0.0082L/h (20%)] and peripheral volume of distribution [Vp/F: 0.73L (8%)] with absorption rate constant fixed to 2.24h-1.4 Interindivdual variability was 17% (41%) and 16% (39%) for CL/F and Vc/F, respectively. Following multivariate analysis weight was the only significant covariate to remain in the model. DTG CL/F was increased by 34%, 60%, 13% and 11% at WK1, 2, 3 and 4 following switch, respectively compared to DTG alone. Based on 100 simulations DTG AUC0-24, Cmax and trough (C24) at WK1, 2, 3, 4 post-switch were significantly lower than DTG alone (Table 1), however all simulated C24 were above the protein-adjusted IC90 of 0.064mg/L post-switch [median (range) 0.81mg/L (0.25-1.75)].

**Table 1** Changes in DTG PK parameters following switch from an EFV-based regimen expressed as geometric mean ratio (GMR; 90% CI) determined from simulations using the final model parameters (n=100).

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| --- | --- | --- | --- | --- |
| **Parameter** | **GMR (90% CI)\*** | | | |
|  | **WK1** | **WK2** | **WK3** | **WK4** |
| AUC0-24 (mg.h/L) | 0.73 (0.69-0.76) | 0.61 (0.58-0.64) | 0.87 (0.83-0.91) | 0.88 (0.84-0.92) |
| Cmax (mg/L) | 0.84 (0.80-0.88) | 0.78 (0.74-0.82) | 0.92 (0.88-0.96) | 0.92 (0.88-0.97) |
| C24 (mg/L) | 0.57 (0.53-0.61) | 0.40 (0.37-0.42) | 0.79 (0.74-0.84) | 0.81 (0.76-0.86) |

\* DTG alone as reference

**Conclusions:** Population PK parameters were comparable to previous reports4 with between-study differences attributable to EFV. Simulated DTG PK parameters were reduced following switch even at WK3/WK4 (~20% for C24), potentially highlighting important PK differences between healthy & HIV-infected individuals. However, consistent with recent data1 concentrations remained above the protein-adjusted IC90 post-switch, supporting findings that dose adjustments may not be required in the described patient population.

**Words 385 (max. 400)**

**References**

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