Relative bioavailability of dolutegravir (DTG) and emtricitabine/tenofovir alafenamide fumarate (F/TAF) administered as paediatric tablet formulations in healthy volunteers

Bevers L.A.H. [1], Kamphuis A.E.M. [1], van der Wekken-Pas L.C. [1], Leisegang R. [2], Lewis L. [3], Burger D.M. [1], Colbers A. [1]

[1]Department of Pharmacy, Radboud Institute for Medical Innovations (RIMI), Radboud University Medical Center, Nijmegen, the Netherlands
[2]Clinical Pharmacology, Paediatric Centre of Excellence, Gilead Sciences, Dublin, Ireland
[3]Clinical and Regulatory Affairs, Product Development and Regulatory Affairs team, Clinton Health Access Initiative (CHAI)

Introduction

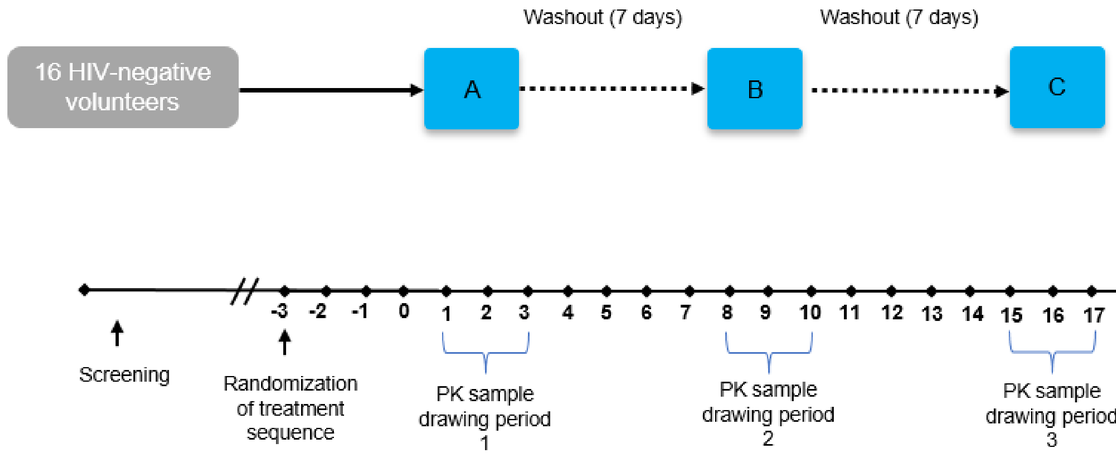
- In the EDCTP2-funded UNIVERSAL project (RIA2019PD-2882) a paediatric fixed dose combination (FDC) product containing dolutegravir/emtricitabine/tenofovir alafenamide (DTG/FTC/TAF) will be developed.

- The pharmacokinetic data on the combination of DTG dispersible tablets (DT) and F/TAF for oral suspension (TOS) are currently lacking.

We undertook a relative bioavailability (RBA) study in HIV-negative volunteers to investigate a potential pharmacokinetic effect when paediatric DTG DT (30 mg dose) and F/TAF TOS (180/22.5 mg dose) are taken together.

Material and Methods

- An open label, single-center, single-dose, 3-period, randomized, cross-over trial in 16 HIV-negative volunteers.



  - **Reference A**: Single dose of 3 X 60/7.5 mg (180/22.5 mg) F/TAF TOS.
  - **Reference B:** Single dose of 6 X 5 mg (30 mg) DTG DT.
  - **Test C**: Single dose of 180/22.5 mg F/TAF TOS plus 30 mg DTG DT.

- Randomized treatment sequences: ABC; ACB; BCA; BAC; CAB; CBA.

- Blood samples were collected at time = 0, 0.17, 0.33, 0.5, 0.75, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24 and 48 hours post-dose.

- Pharmacokinetic parameters were determined using a non-compartmental analysis in Phoenix/WinNonlin version 8.4.

- We applied the statistical method used in bioequivalence studies (ANOVA on log-transformed PK parameters with fixed effects: treatment, period, sequence and subject within sequence) to investigate the presence of a relevant pharmacokinetic interaction between two treatments.

- **Pre-defined criteria:** if after a single dose the 90% CIs of the GLSM ratios (Test/Reference) of AUC and C_{max} of each compound is within 0.70 and 1.43, there is no clinically relevant pharmacokinetic interaction.

Results

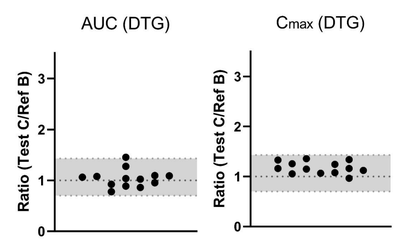
- In total, **15 participants were included**. The median age of these included subjects (6 female / 9 male) was 27.0 (IQR 21.0-31.0) years with a median BMI of 25.1 (IQR 21.6-26.0) kg/m^2.

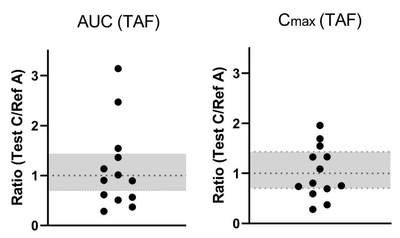
DTG (n=15)			
PK parameter	**DTG + F/TAF (Test C)**	**DTG (Reference B)**	**GLSM Ratio (90% CI)**
$AUC_{0-\infty}$ (h*mg/L)	40.71 (30)	40.18 (27)	1.02 (**0.94-1.10**)
C_{max} (mg/L)	2.69 (22)	2.35 (24)	1.16 (**1.10-1.23**)
T_{max} (h)	0.75 (0.5-1.0)	1.0 (1.0-2.0)	
$T_{1/2}$ (h)	12.97 (17)	13.38 (15)	

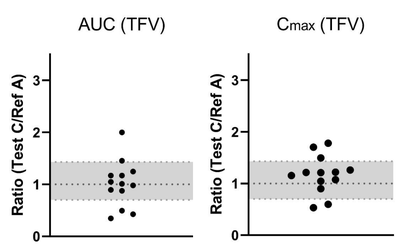
TAF (n=13)			
PK parameter	**DTG + F/TAF (Test C)**	**F/TAF (Reference A)**	**GLSM Ratio (90% CI)**
$AUC_{0-\infty}$ (h*ng/L)	104.87 (57)	115.75 (42)	0.83 (**0.62-1.11**)
C_{max} (ng/L)	180.14 (44)	204.95 (37)	0.81 (**0.65-1.01**)
T_{max} (h)	0.3 (0.3-0.3)	0.3 (0.2-0.3)	
$T_{1/2}$ (h)	0.35 (21)	0.33 (24)	

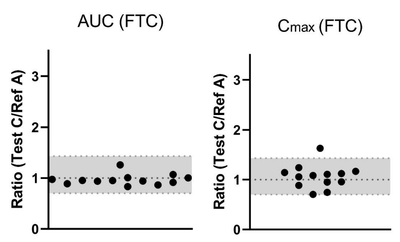
TFV (n=13)			
PK parameter	**DTG + F/TAF (Test C)**	**F/TAF (Reference A)**	**GLSM Ratio (90% CI)**
$AUC_{0\text{-}last}$ (h*ng/L)	89.19 (54)	98.04 (32)	0.84 (**0.70-1.01**)
C_{max} (ng/L)	180.14 (44)	204.95 (37)	1.06 (**0.92-1.23**)
T_{max} (h)	0.8 (0.3-0.9)	0.8 (0.6-1.0)	
$T_{1/2}$ (h)	32.44 (36)	36.73 (33)	

FTC (n=13)			
PK parameter	**DTG + F/TAF (Test C)**	**F/TAF (Reference A)**	**GLSM Ratio (90% CI)**
$AUC_{0-\infty}$ (h*mg/L)	7.52 (15)	7.80 (20)	0.97 (**0.92-1.02**)
C_{max} (mg/L)	1.49 (20)	1.44 (25)	1.05 (**0.94-1.17**)
T_{max} (h)	0.8 (0.5-1.0)	0.8 (0.8-1.5)	
$T_{1/2}$ (h)	7.41 (22)	8.14 (34)	









Discussion and Conclusion

- We observed no relevant pharmacokinetic interaction for **DTG** in this study, however individual ratios for C_{max} showed a trend above 1. There might be a small increase in the absorption of DTG when combined with FTC/TAF TOS.

- For **TAF** the GLSM ratio was outside the pre-defined criteria, but with half of the individual ratios above and half below 1, we don't see a trend. Moreover, we rely on TFV exposure over TAF because of TAF being a pro-drug and no relevant interaction was found for **TFV**.

- We found no relevant pharmacokinetic interaction for **FTC**.

These data will inform on the dose ratio and dose selection for a paediatric DTG/FTC/TAF FDC to be developed in the UNIVERSAL project.

Conflicts of Interest and Source of Funding:
Trial medication (F/TAF TOS) was provided and trial was funded by Gilead Sciences, Inc. This study was conducted as an addendum to the EDCTP2-funded UNIVERSAL project (RIA2019PD-2882)