

Figure 1 Observed vs. simulated C_{max} plot of oral TAF at various doses. The orange markers indicate 5 mg, black - 8 mg, blue - 10 mg and green - 25 mg. The triangles indicate tenofovir, diamonds – TFV-DP and circles – TAF plasma C_{max} . Solid fill indicates single dose and dotted fill – multiple dose (day 8 or 10). The grey lines represent 0.8 and 1.25-fold range from the mean and the outer black lines represent 0.5 and 2-fold range

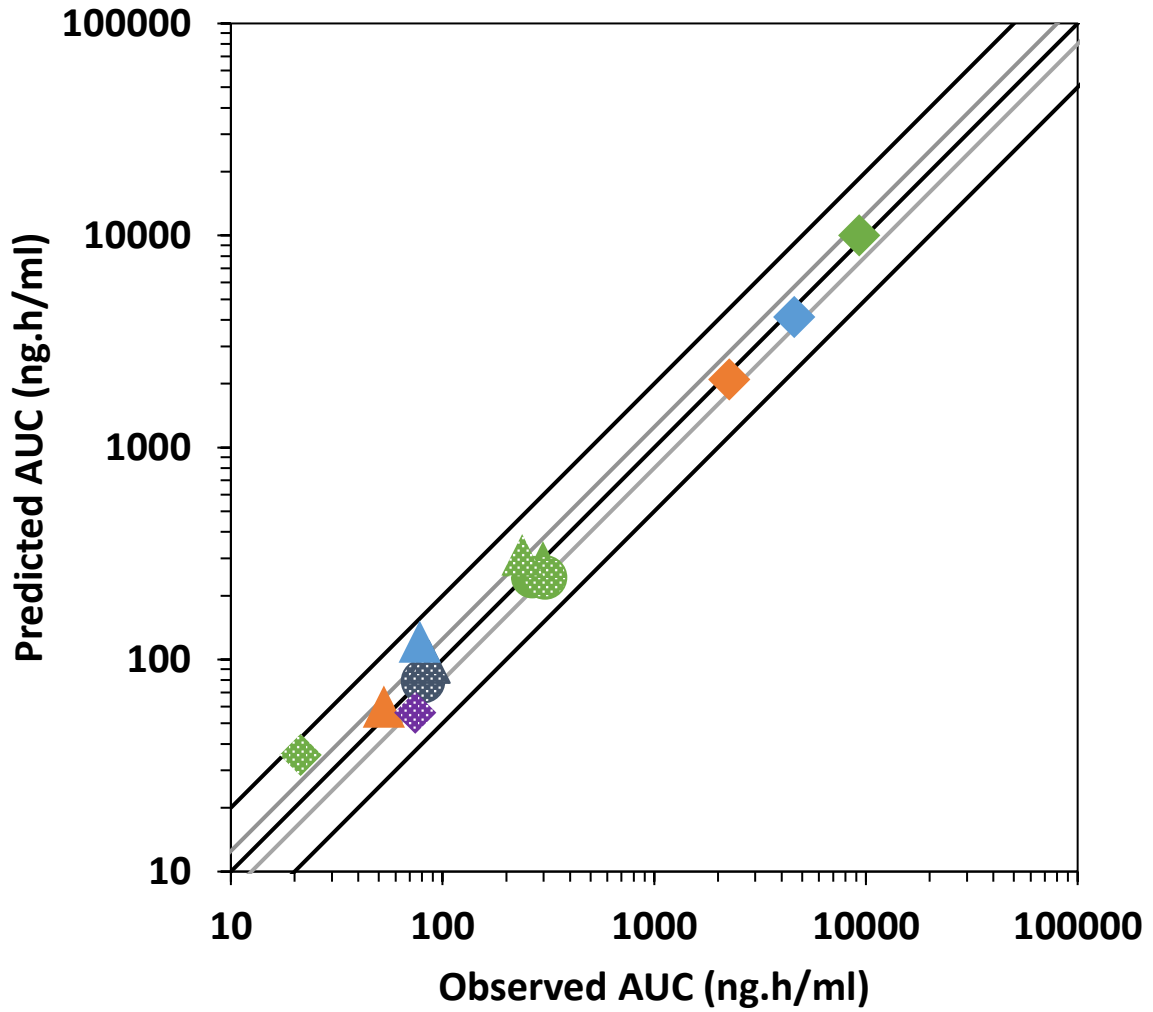


Figure 2 Observed vs. simulated AUC plot of oral TAF at various doses. The orange markers indicate 5 mg, black - 8 mg, blue - 10 mg, green - 25 mg and violet – 40 mg. The triangles indicate tenofovir, diamonds – TFV-DP and circles – TAF plasma AUC. Solid fill indicates single dose and dotted fill – multiple dose (day 8 or 10). The grey lines represent 0.8 and 1.25-fold range from the mean and the outer black lines represent 0.5 and 2-fold range

Table 1 PBPK qualification of TFV and TFV-DP at a single dose of 5 mg TAF [1]

| Study | Clinical | | Simulated | | % difference | | |
|----------------|----------------------------|------------------|---------------------|------------------|---------------------|------------------|--------|
| | AUC _{last} | C _{max} | AUC _{last} | C _{max} | AUC _{last} | C _{max} | |
| TAF 5 mg day 1 | ² TFV, plasma | 52.8 (49.5-59.6) | 0.8 (0.6-1) | 59.8 (31-120) | 1.55 (0.6-2.99) | 13.3% | 93.8% |
| | ² TFV-DP, PBMC* | 2268 (1519-4090) | 33.7 (26.4-50.6) | 2092 (1303-3981) | 22.3 (14.2-42.6) | -7.8% | -33.8% |

AUC is AUC_{0-14 days}. Values are represented as mean (CV). AUC is represented in ng.h/ml, C_{max} in ng/ml. *TFV-DP values are in fmol.h/10⁶ cells, C_{max} is in fmol/10⁶ cells and are represented as median (range).

Table 2 PBPK qualification of TAF and TFV on day 14 with once daily 8 mg TAF [2]

| Study | Clinical | | Simulated | | % difference | | |
|-----------------|---------------------------|------------------|----------------------|------------------|----------------------|------------------|--------|
| | AUC _{0-24h} | C _{max} | AUC _{0-24h} | C _{max} | AUC _{0-24h} | C _{max} | |
| TAF 8 mg day 14 | ³ TAF, plasma | 81.2 (43.9) | 71.0 (72.9) | 78.7 (19.3) | 43.0 (21.9) | -3.1% | -39.4% |
| | ³ TFV, plasma* | 86.1 (19.4) | 5.8 (19.5) | 97.6 (37.5) | 5.14 (32.9) | 13.4% | -11.4% |

*AUC is AUC_{0-24 h} on day 14. Values are represented as mean (CV). AUC is represented in ng.h/ml, C_{max} in ng/ml.

Table 3 PBPK qualification of TFV and TFV-DP at a single dose of 10 mg TAF [1]

| Study | Clinical | | Simulated | | % difference | | |
|-----------------|----------------------------|------------------|---------------------|------------------|---------------------|------------------|--------|
| | AUC _{last} | C _{max} | AUC _{last} | C _{max} | AUC _{last} | C _{max} | |
| TAF 10 mg day 1 | ² TFV, plasma | 78.1 (68.2-86.9) | 1.5(1.4-1.7) | 121 (61.5-239) | 3.1 (1.8-5.9) | 55.2% | 106.7% |
| | ² TFV-DP, PBMC* | 4584 (3113-5734) | 68 (56.9-88.8) | 4121 (2598-7961) | 44.4 (29.8-85.2) | -10.1% | -34.7% |

AUC is AUC_{0-14 days}. Values are represented as mean (CV). AUC is represented in ng.h/ml, C_{max} in ng/ml. *TFV-DP values are in fmol.h/10⁶ cells, C_{max} is in fmol/10⁶ cells and are represented as median (range).

Table 4 PBPK qualification of TFV and TFV-DP at single and multiple doses of 25 mg TAF [1-3]

| Study | Clinical | | Simulated | | % difference | | |
|------------------|---------------------|----------------------|-----------------------|----------------------|-----------------------|------------------|-------|
| | AUC _{last} | C _{max} | AUC _{last} | C _{max} | AUC _{last} | C _{max} | |
| TAF 25 mg day 1 | TAF, plasma [3] | 266 (49.5) | 199 (62.1) | 244 (17.9) | 135 (21.5) | -8.3 | -32.2 |
| | TFV, plasma [3] | 298 (26.1) | 9.50 (36.5) | 287 (36.6) | 7.54 (30.1) | -3.7 | -20.6 |
| | TFV-DP, PBMC* [1] | 9306 (6891-10785) | 113.6 (80.9-150.2) | 9991 (6539-16590) | 107.0 (66.8-191.6) | 7.4 | -5.8 |
| TAF 25 mg day 14 | TAF, plasma [2] | 306 (18.4) | 238 (25.5) | 243 (19.7) | 137 (20.7) | -20.6 | -42.4 |
| | TFV plasma [2] | 238 (14.0) | 14.4 (12.9) | 310 (40.3) | 16.5 (36.4) | 30.3 | 14.6 |

Values are represented as mean (CV). AUC is represented in ng.h/ml, C_{max} in ng/ml. *AUC is AUC_{0-14 days} and are in fmol.h/10⁶ cells, C_{max} is in fmol/10⁶ cells. TFV-DP values are represented as median (range).

Table 5 Computation of TFV-DP cervical and rectal tissue ratios for TAF [1]

TAF single dose

| TFV-DP PBMCs | | 5 mg | 10 mg | 25 mg | | 5 mg | 10 mg | 25 mg |
|-------------------------------------|----------------------|-------------|--------------|--------------|---|-------------|--------------|--------------|
| C_{max} | fmol/ 10^6 cells | 33.7 | 68 | 113.6 | fmol/g | 1.11E+05 | 2.23E+05 | 3.73E+05 |
| $AUC_{0-24\text{ h}}$ | fmol.h/ 10^6 cells | 657 | 1086 | 2094 | fmol.h/g | 2.16E+06 | 3.56E+06 | 6.87E+06 |
| $AUC_{0-14\text{ days}}$ | fmol.h/ 10^6 cells | 2268 | 4584 | 9306 | fmol.h/g | 7.44E+06 | 1.50E+07 | 3.05E+07 |
| TFV-DP female genital tissue | | | | | TFV-DP female genital tissue/TFV-DP PBMC | | | |
| C_{max} | fmol/g | BLQ | 4499 | 9552 | | | 0.020 | 0.026 |
| $AUC_{0-24\text{ h}}$ | fmol.h/g | BLQ | 63703 | 104086 | Average – 0.031 | | 0.018 | 0.015 |
| $AUC_{0-14\text{ days}}$ | fmol.h/g | BLQ | 986421 | 1309305 | | | 0.066 | 0.043 |
| TFV-DP rectal tissue | | | | | TFV-DP rectal tissue/TFV-DP PBMC | | | |
| C_{max} | fmol/g | BLQ | 3456 | 11163 | | | 0.015 | 0.030 |
| $AUC_{0-24\text{ h}}$ | fmol.h/g | BLQ | 45103 | 39162 | Average – 0.02 | | 0.013 | 0.006 |
| $AUC_{0-14\text{ days}}$ | fmol.h/g | BLQ | 315145 | 1041352 | | | 0.021 | 0.034 |

Unit conversion from fmol/10⁶ cells to fmol/g

Volume of each PBMC = 282.9 fl [4]

Volume of each PBMC in litres = 2.829×10^{-13} L

Volume million PBMC in litres = 2.829×10^{-7} L

Volume million PBMC in ml = 2.829×10^{-4} mL

Density of PBMCs = 1.077 g/ml [5]

Weight of million PBMC in g = 3.05×10^{-4} g

References

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2. Begley, R., et al., *Pharmacokinetics of Tenofovir Alafenamide When Coadministered With Other HIV Antiretrovirals*. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 2018. **78**(4): p. 465-472.
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4. Simiele, M., et al., *Evaluation of the Mean Corpuscular Volume of Peripheral Blood Mononuclear Cells of HIV Patients by a Coulter Counter To Determine Intracellular Drug Concentrations*. *Antimicrobial Agents and Chemotherapy*, 2011. **55**(6): p. 2976-2978.
5. Norouzi, N., H.C. Bhakta, and W.H. Grover, *Sorting cells by their density*. *PLOS ONE*, 2017. **12**(7): p. e0180520.