# POPULATION PHARMACOKINETIC MODELLING TO CHARACTERIZE THE EFFECT OF CHRONIC KIDNEY DISEASE ON TENOFOVIR EXPOSURE AFTER TENOFOVIR ALAFENAMIDE ADMINISTRATION

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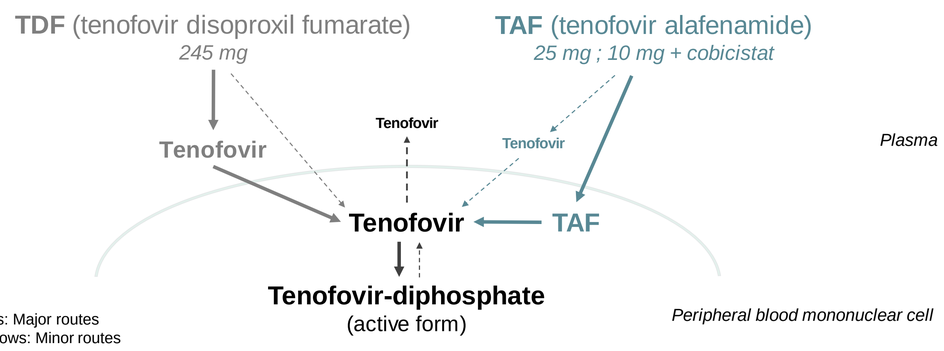
## Introduction

- Tenofovir is an **NRTI** active in preventing and treating HIV-1 infection, and treating HBV infection.
- Tenofovir plasma levels are associated with **kidney tubular damage** and, in the long term, **bone demineralization**.
- **Two prodrugs available** *(dosing 1x/day)*:



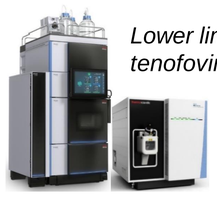

### Objectives

- To characterize the **concentration-time profile of tenofovir and its associated variability** in people living with HIV (PLWH) under TAF in a *real-life* setting.
- To assess the **impact of chronic kidney disease** (CKD) on tenofovir exposure.

## Methods

**569** PLWH
**877** Tenofovir concentrations
**100** TAF concentrations
**4** Detailed PK (44 samples)

**LC-MS/MS**[1]



*Lower limit of quantification for TAF and tenofovir of 1 ng/mL*

**Stepwise procedure***
**793** tenofovir concentrations
**100** TAF concentrations
Cobicistat effect on TAF bioavailability (F) directly integrated in the model.

**Covariate analysis**
Age, sex, ethnicity, bodyweight, height, BMI, creatinine clearance ($CL_{CR}$), estimated glomerular filtration rate, and comedications, and cobicistat "ceiling effect".

**Model evaluation**
Statistical and clinical significance assessment of covariates.
Bootstrap.
External validation (data-splitting) on **84** tenofovir concentrations (**83** PLWH).

**Model-based simulations**
Impact of CKD, and other significant covariates, on tenofovir exposure (PK profiles, area under the curve, trough concentration ($C_{min}$)).

**applied to find the models that best fit first TAF and tenofovir simultaneously (data not shown), and then exclusively tenofovir data.*

## Results

| Parameters | Final model | | | | Bootstrap (n = 2000 samples) | | | |
|---|---|---|---|---|---|---|---|---|
| | Estimate | RSE (%) | BSV (%) | RSE (%) | Median | $CI_{95\%}$ | BSV (%) | $CI_{95\%}$ |
| $k_a$ ($h^{-1}$) | 2 FIX | - | | | 2 FIX | - | | |
| $V_{TFV}$ (L) | 2390 | 9 | | | 2397 | 2037 - 2891 | | |
| $CL_{TFV}$ (L/h) | 42.2 | 2 | | | 42.3 | 40.1 - 44.3 | | |
| $\theta_{CLCR}$ | 0.707 | 10 | | | 0.703 | 0.549 - 0.837 | | |
| $\theta_{Age}$ | -0.244 | 30 | | | -0.242 | -0.398 to -0.099 | | |
| $\theta_{Black\ or\ Hispano\ American}$ | 0.119 | 23 | | | 0.120 | 0.068 - 0.175 | | |
| $\theta_{Potent\ P\text{-}gp\ inhibitors}$ | -0.121 | 39 | | | -0.119 | -0.202 to 0 | | |
| F (%) | 1 FIX | - | 21.1 | 6 | 1 FIX | - | 20.9 | 18.4 - 23.5 |
| $\theta_{Cobicistat}$ | 1.15 | 6 | | | 1.16 | 1.02 - 1.28 | | |
| $\sigma_{add}$ (nmol/mL) | 0.0099 | 5 | | | 0.0099 | 0.0088 - 0.0110 | | |

**RSE:** Relative standard error **BSV:** Between-subject variability $CI_{95\%}$: 95% confidence interval

**Final model:** $\theta_X$ , effect of the X covariate on the typical value (TV) of $CL_{TFV}$

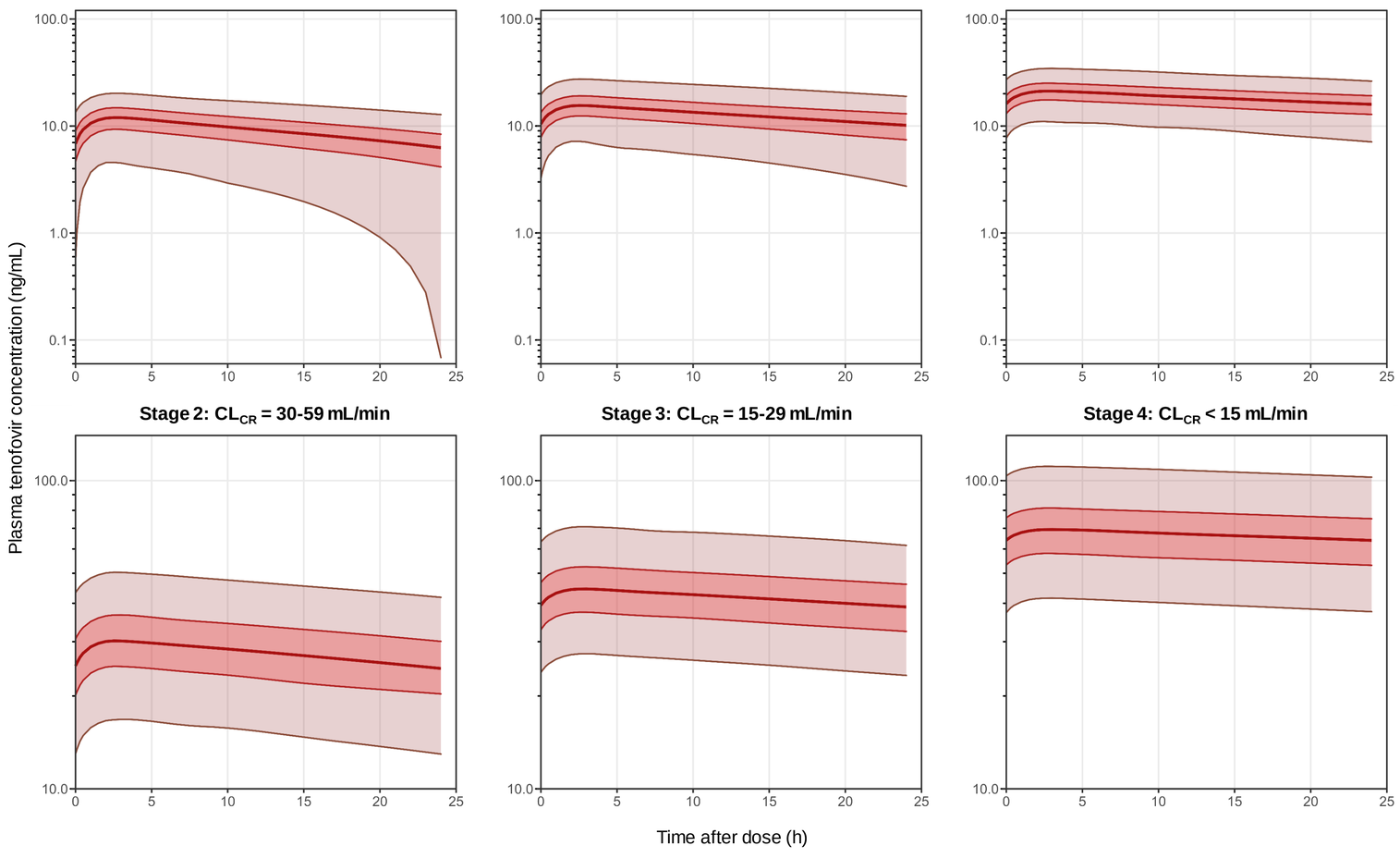
TAF 10 mg: $F = (1 + \theta_{cobicistat})$

$$TVCL_{TFV} = CL_{TFV} \times \left(1 + \frac{\theta_{CLCR} \times (CL_{CR} - CL_{CR-ref})}{CL_{CR-ref}}\right) \times \left(1 + \frac{\theta_{Age} \times (Age - Age_{median})}{Age_{median}}\right) \times (1 + \theta_{Black\ or\ Hispano\ American}) \times (1 + \theta_{Potent\ P-gp\ inhibitors})$$

**Augmented kidney function: $CL_{CR}$ > 149 mL/min** **Normal kidney function: $CL_{CR}$ = 90-149 mL/min** **Stage 1: $CL_{CR}$ = 60-89 mL/min**

### Covariates effect

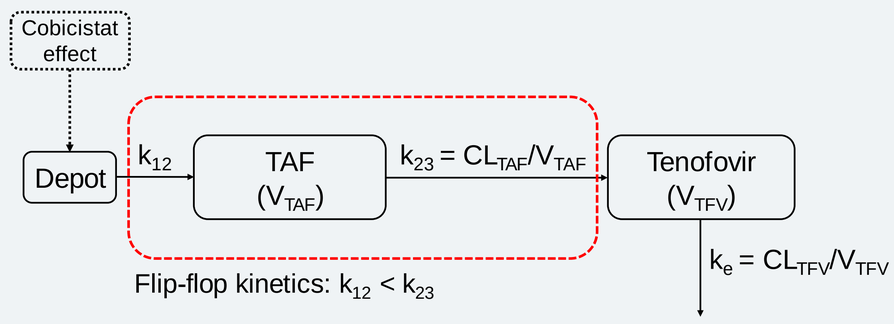
- A full model incorporating all covariates explained 59% of the BSV on F.
- A reduced model with $CL_{CR}$ alone as covariate explained 53% of the BSV on F.
- **Only the effect of $CL_{CR}$ on $CL_{TFV}$ was considered clinically relevant for simulations of PK profiles as a function of different CKD stages.**



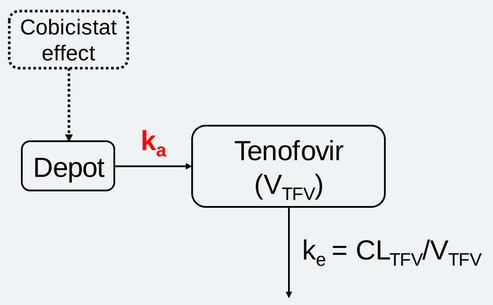

Simulated PK profiles for tenofovir after 25 mg TAF administration in individuals with different CKD stages, with the 2.5%, 25%, 50% (median), 75% and 97.5% percentiles (red solid lines), $PI_{50\%}$ and $PI_{95\%}$ (shaded areas).

## Schematic representation of the PK models

### Model with TAF and tenofovir




### Model with tenofovir only




$k_{12}$: absorption rate constant from depot to the TAF compartment; $k_a$: first-order absorption rate constant of tenofovir; $k_{23}$: rate constant from TAF compartment to the tenofovir compartment; $CL_{TAF}$: apparent clearance of TAF; $V_{TAF}$: apparent volume of distribution of TAF; $CL_{TFV}$: apparent clearance of tenofovir; $V_{TFV}$: apparent volume of distribution of tenofovir; $k_e$: tenofovir elimination rate constant.

## Conclusions

- PLWH with stage 3 and stage 4 CKD under TAF achieve similar tenofovir exposure to those with normal kidney function receiving TDF.
- Evidence[2-6] suggests that TAF is more permissive than TDF with respect to missed doses or longer dosing intervals, and that **PLWH with stage 3 or 4 CKD could potentially receive TAF once every 2 days or 3 days**, respectively, in order to maintain adequate circulating levels of tenofovir while preserving sufficient tenofovir-diphosphate exposure.

**References**

[1] Courlet P, et al. Clinical Mass Spectrometry. 2018
[2] Thurman AR, et al. eClinicalMedicine. 2021
[3] Podany AT, et al. AIDS. 2018
[4] Yager JL, et al. AIDS. 2021
[5] Brooks KM, et al. The Journal of Antimicrobial Chemotherapy. 2020
[6] Dumond JB, et al. Antiviral Therapy. 2019

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