



Meta-based External Validation Through Model Integration Incorporated Prior Information: Application of Tenofovir Alafenamide and Tenofovir

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BACKGROUND AND PURPOSE

- Tenofovir alafenamide (TAF), a novel prodrug of tenofovir approved by the FDA in 2016 for chronic hepatitis B treatment, demonstrates superior plasma stability and significantly reduced adverse events compared to tenofovir disoproxil fumarate (TDF), while maintaining the established therapeutic efficacy of tenofovir in managing chronic hepatitis B and HIV-1 infections.
- This study aims to collect and evaluate previously reported population pharmacokinetic (PopPK) models for TAF and TFV, and to propose a single integrated PopPK model that comprehensively represents study populations with diverse pharmacokinetic characteristics, utilizing prior information (prior subroutine).

METHODS

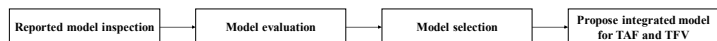


Figure 1. Workflow of meta-based external validation

PopPK model collection of TAF and TFV

- A comprehensive literature review was conducted to identify existing PopPK models for TAF and TFV. Subsequently, relevant literature was selected based on predefined criteria.

Model evaluation and selection

- Prediction-based evaluation:** Models underwent assessment using Visual Predictive Check (VPC) and various prediction error metrics (PE, MAE, MSE, MPE, MAPE, RMSE) derived from post-hoc estimation results.
- Simulation-based evaluation:** Model predictive performance was evaluated by calculating Normalized Prediction Distribution Errors (NPDEs) via 1000 model simulations.

Model selection

- The individual models that best described the pharmacokinetics of TAF and TFV were selected through a comprehensive evaluation.

Model integration

- A single, integrated PopPK model was derived by utilizing prior information from the selected TAF and TFV models, along with an external dataset, via NONMEM's SPRIOR (NWPRI) subroutine.
- Informative and non-informative priors were applied as needed to assess model adequacy. The final integrated model was selected based on criteria.
- Figure 2 provides a detailed description of the step-by-step evaluation criteria.

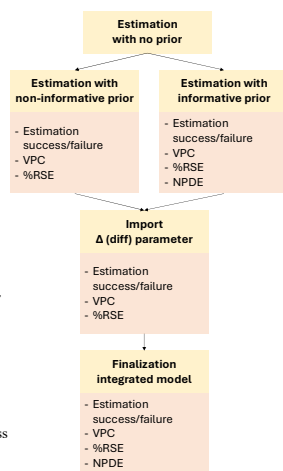


Figure 2. Schematic diagram of model integration with prior subroutine

RESULTS

Characteristics of the External dataset

- A single 25 mg oral dose of TAF (commercial tablet) was administered to 60 healthy Korean subjects in a fasted state. Plasma samples were collected for TAF quantification up to 3 hours post-dose and for TFV quantification up to 72 hours post-dose.

Characteristics	N (%) or Median [Range]
Male	46 (76.7%)
Age (year)	28.5 [21 – 50]
Weight (kg)	72.7 [54.6 – 96]
Height (cm)	172.85 [155.7 – 185.6]
BMI (kg/m ²)	24.9 [18.3 – 29.7]

Table 1. Demographic characteristics of external validation dataset

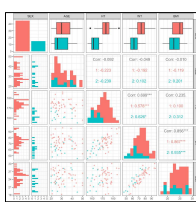


Figure 3. Correlation Matrix of Demographic Covariates

Inspection PopPK models for TAF and TFV

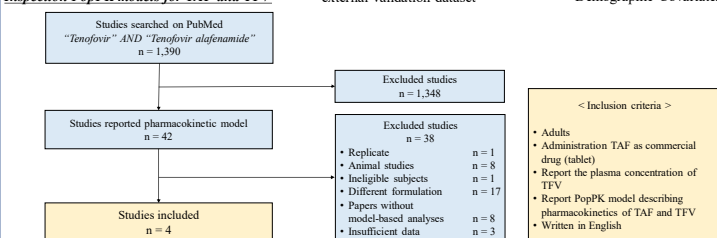


Figure 4. Diagram of literature inspection for external validation

Main Author (publication year)	Subjects	Dosing scenario	Covariate	Parameters	Absorption	Compartment	Method
Stephen A. Greene (2019)	HIV +/- male	10, 25 mg / MD	-	-	Depot-comp	1-comp for TAF 1-comp for TFV	Laplacean with interaction
Aida N. Kawuma (2023)	HIV positive South African adults	25 mg / MD	WT	Vd TFV CL _{TFV} Q _{TFV}	Depot-comp F, Lag time, transit comp	2-comp for TFV	FOCE with interaction
Paul Thoeuille (2023)	People living with HIV (PLWH)	25 mg / MD	Creatinine clearance Cobicistat	CL _{TFV} F _{TAF}	Depot-comp F (not bioavailability)	1-comp for TAF 1-comp for TFV	FOCE with interaction
Xingfang Ji (2024)	Healthy Chinese subjects	25 mg / SD	Meal state Sex Meal state	CL _{TAF} Vd TFV CL _{TFV} Q _{TFV}	Depot-comp Transit comp (MTT, NT)	1-comp for TAF 2-comp for TFV	FOCE with interaction

Table 2. Summary of collected PopPK models for TAF and TFV

RESULTS

Model evaluation and selection

- Red area, blue area represent 90% predicted interval, observed interval, respectively. The observed data are showed as points either.

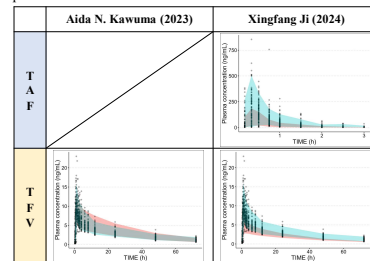


Figure 5. VPC for the selected model

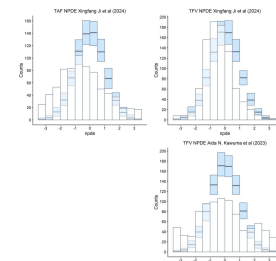


Figure 6. NPDE histogram for the selected model

PopPK model integration

- The healthy Asian model for TAF and TFV was developed using informative priors from the healthy Chinese model and an external dataset.

	Reference	Healthy Asian
Fixed effect (%RSE)		
MTT (hour)	0.569 (11.7)	0.525 (3)
NT	4.05 (16.6)	5.69 (3)
CL/F (L/h)	140 (9.6)	282 (4)
V/F (L)	62.6 (7.2)	62.7 (0)
CL _M /F (L/h)	52.9 (5.4)	64.5 (3)
Q _M /F (L/h)	307 (15.1)	425 (6)
V _M /F (L)	1360 (4.6)	1530 (3)
V _{ss} /F (L)	1030 (5.3)	1600 (3)

Table 3. Estimated model parameters of reference model and healthy Asian model

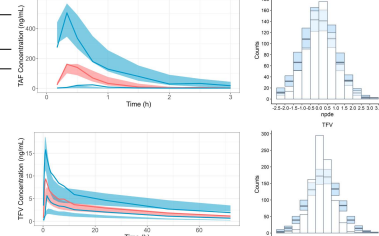


Figure 7. VPC as NPDE histogram for healthy Asian model

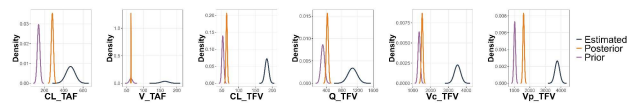


Figure 8. Parameter density plots for healthy Asian model

- The integrated PopPK model was developed by combining external data with informative priors from a healthy Chinese TAF model (for TAF parameters) and weakly informative (90% RSE) priors from an HIV-positive South African TFV model (for TFV parameters).

Final model	
Fixed effect (%RSE)	
TAF	Fixed
CL _M /F (L/h)	155 (2.8)
Q _M /F (L/h)	929 (3.3)
V _c /F (L)	2920 (3.4)
V _p /F (L)	3570 (1.8)

Table 3. Estimated model parameters of integrated model

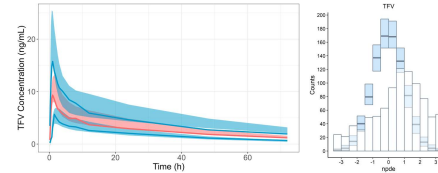


Figure 9. VPC as NPDE histogram for integrated healthy Asian and HIV-positive South African model

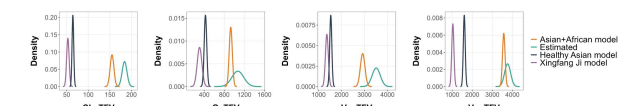


Figure 10. Parameter density plots for integrated healthy Asian and HIV-positive South African model

CONCLUSION & DISCUSSION

- Comparison of four previously reported pharmacokinetic models against an external dataset revealed that models developed in healthy Chinese and HIV-positive South African populations exhibited the lowest residuals. These models were subsequently utilized as prior information in a sequential integration process to develop the final population pharmacokinetic model.
- This integrated model development presents a scientific approach to generalize and explain pharmacokinetic characteristics observed across diverse populations, which exhibit substantial variability due to intrinsic factors such as body weight, as well as extrinsic factors like co-medication and diet.

ACKNOWLEDGEMENT

This study was supported by Chungnam National University, Institute of Information & Communications Technology Planning Evaluation (IITP) grant funded by the Korea government (MSIT) (No.RS-2022-00155857, Artificial Intelligence Convergence Innovation Human Resources Development (Chungnam National University)), National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT; No. RS-2023-00278597, RS-2022-NR070856, Senior Health Convergence Research Center based on Life Cycle (Chungnam National University)), Korea Environmental Industry & Technology Institute (KETI) through Core Technology Development Project for Environmental Diseases Prevention and Management (RS-2021-KETD01333), funded by the Korea Ministry of Environment (MOE), a grant of the Korea Machine Learning Ledger Orchestration for Drug Discovery Project (K-MELLODDY), funded by the Ministry of Health & Welfare and Ministry of Science and ICT, Republic of Korea (grant number - RS-2024-00460904), the Korea Institute of Toxicology (KIT) Research Program (No. 2710008763, KK-2401-01), Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) grant funded by the Ministry of Health & Welfare, Republic of Korea (grant number - RS-2024-00336984), supported by the Ministry of Trade, Industry, and Energy (MOTIE), Korea, under the "Infrastructure program for industrial innovation" supervised by the Korea Institute for Advancement of Technology (KIAT/RS-2024-00434342).