Supplementary Note 1: Pharmacokinetics (module I)

In this note the utilized pharmacokinetic models and their parameterizations are outlined. At the end, we derive concentration time profiles for the intracellularly active NRTI-TP moieties, which can serve as an input for the molecular mechanisms of action model (module II, **Supplementary Note 2**). Note that we modelled *typical* patient profiles, but extensions to virtual patient populations derived from POP-PK models are straight forward.

SN1 Pharmacokinetics of TDF, FTC and 3TC and their active anabolites

The pharmacokinetics of TDF, FTC and 3TC can be modelled by the following set of ODEs [1,2]:

$$\frac{dC_1(t)}{dt} = \frac{F_{\text{bio}} \cdot k_a \cdot D(t)}{V_1} - C_1(t) \cdot k_e - k_{12} \cdot C_1(t) + k_{21} \cdot C_2(t) \quad \text{(SN1.1)}$$

$$\frac{dC_2(t)}{dt} = k_{12} \cdot C_1(t) - k_{21} \cdot C_2(t) \quad \text{(SN1.2)}$$

$$\frac{dC_{\text{cell}}(t)}{dt} = \frac{V_{\max} \cdot C_1(t)}{K_{\text{M}} + C_1(t)} - k_{\text{out}} \cdot C_{\text{cell}}(t) \quad \text{(SN1.3)}$$

where C_1 and C_2 represent the concentration of the circulating form of the respective NRTI (TFV, 3TC or FTC) in the central compartment (= blood plasma) and in the peripheral compartment in units μM. F_{bio} and V_1 represent the respective oral bio-availability and the volume of the central compartment in liters. The terms k_a and k_e denote the absorption and elimination rate constant for the central compartment in units 1/h. Similarly, k_{12} and k_{21} are the influx and the apparent outflux rate constants to/from the peripheral compartment respectively (in 1/h). The term C_{cell} denotes the intracellular concentration of the active agent of NRTI within the target cell. The term $V_{\max}$ is the maximum velocity (μM/h) and K_{M} (μM) the Michaelis-Menten constant for uptake and intracellular anabolism. All parameters are taken from [2], where an extensive derivation and validation is provided. The parameters are summarized in Table SN1.1.

The amount of drug (in μmol) in the dosing compartment $D(t)$ is modeled according to

$$D(t) = D(\tau_{i-1}) \cdot e^{-ka \cdot t} + I(t) \cdot \text{dose}(\tau_i), \quad \text{(SN1.4)}$$

where $D(\tau_{i-1})$ denotes the amount of the NRTI prodrug in the dosing compartment at the last dosing event τ_{i-1}. The term $I(t)$ denotes a delta dirac or impulse function, which takes the value 1 at the discrete dosing event $t = \tau_i$ and is otherwise zero.

Param.	3TC	FTC	TDF	Unit
F_{bio}	$0.86^{\dagger}$	$0.93^{\#}$	0.32^{*}	-
k_a	$0.945^{\S}$	0.542	$1^{\ddagger}$	1/h
V_1	61.252	43.823	110.31^{+}	L
k_e	0.3347	0.409	0.1234^{+}	1/h
k_{12}	0.0605	0.113	0.2926^{+}	1/h
k_{21}	0.0594	0.082	0.1537^{+}	1/h
$V_{\max}$	0.5819	0.6191	0.0032^{+}	μM· 1/h
K_{M}	3.3977	0.9464	0.1020^{+}	μM
k_{out}	0.0315	0.0176	0.006^{+}	1/h

Table SN1.1: **Pharmacokinetic (population) parameters.** Excerpt from [2]. †fixed value taken from [3]. The $^{\#}$fixed value taken from [4]. *fixed value from [5]. §fixed value taken from [6]. ‡fixed value from [7]. $^{+}$The plasma and intracellular pharmacokinetics parameters for TDF are derived from the previous work [1].

References

[1] Sulav Duwal, Christof Schütte, and Max von Kleist. Pharmacokinetics and pharmacodynamics of the reverse transcriptase inhibitor tenofovir and prophylactic efficacy against HIV-1 infection. *PLoS One*, 7(7):e40382, 2012.

[2] Sulav Duwal and Max von Kleist. Top-down and bottom-up modeling in system pharmacology to understand clinical efficacy: An example with NRTIs of HIV-1. *European Journal of Pharmaceutical Sciences*, Jan 2016.

[3] G. J. Yuen, D. M. Morris, P. K. Mydlow, et al. Pharmacokinetics, absolute bioavailability, and absorption characteristics of lamivudine. *J Clin Pharmacol*, 35(12):1174–1180, Dec 1995.

[4] Krysten A. Modrzejewski and Ronald A. Herman. Emtricitabine: a once-daily nucleoside reverse transcriptase inhibitor. *Ann Pharmacother*, 38(6):1006–1014, Jun 2004.

[5] P. Barditch-Crovo, S. G. Deeks, A. Collier, et al. Phase I/II trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother*, 45(10):2733–2739, Oct 2001.

[6] Johanna Linnankoski, Johanna M. Mäkelä, Veli-Pekka Ranta, Arto Urtti, and Marjo Yliperttula. Computational prediction of oral drug absorption based on absorption rate constants in humans. *J Med Chem*, 49(12):3674–3681, Jun 2006.

[7] Marie-Claude Gagnieu, Mirna El Barkil, Jean-Michel Livrozet, et al. Population pharmacokinetics of tenofovir in AIDS patients. *J Clin Pharmacol*, 48(11):1282–1288, Nov 2008.