



Population pharmacokinetic models for lamivudine and nevirapine for measuring adherence using therapeutic drug monitoring

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INTRODUCTION AND AIM

Adherence to combined antiretroviral (ARV) therapy (cART) is a predictor of suppression of HIV replication, drug resistance, disease progression and death.¹ Methods used to measure cART adherence include medication event monitoring systems, self report, clinical review, questionnaires, diaries, therapeutic drug monitoring (ARV TDM), pill count and pharmacy refill data.² ARV TDM may improve patient outcome due to the clinical consequences of therapeutic failure, marked interindividual variability in ARV plasma concentrations, and data supporting concentration/response relationships.³ Unlike non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), nucleoside reverse transcriptase inhibitors (NRTIs) are not considered suitable candidates for ARV TDM. The NRTI intracellular triphosphate analogue is the active moiety and is only weakly correlated with parent plasma concentrations.⁴ However, due to long half-lives of NNRTIs, it may be difficult to evaluate cART adherence using NNRTI steady-state concentrations (Fig. 1).

The NRTI lamivudine (3TC) has suitable pharmacokinetic (PK) properties ($T_{max} = 0.9$ h [SD 0.41h], half-life = 8.41h [SD 1.46])⁵ to assess dosing history up to 36 hours post-dose. Additionally, 3TC pharmacokinetics is unaltered by concomitant anti-tuberculosis treatment, a common opportunistic infection in our population.

Routine blood sampling at ARV-outpatient clinics is seldom pre-dose/trough concentrations and acceptable minimum single time-point concentration data during the whole 12-hour NVP and 3TC dosing intervals were unavailable. The aim of the analyses was to use a population modeling approach to obtain concentration "cut-off" values (e.g. the lower limit of the 95% prediction intervals) for NVP and 3TC concentrations to assess adherence to cART.

METHODS

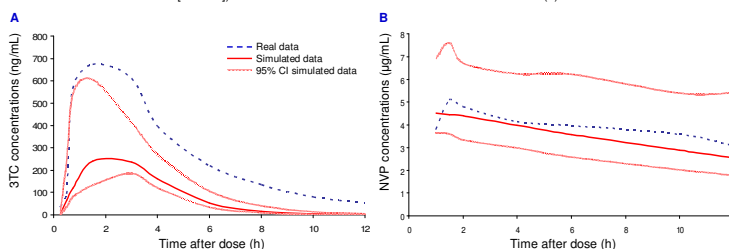
Population PK models for 3TC and NVP were developed using rich and sparse data obtained from three pharmacokinetic studies (Table 1). One compartment models with first-order absorption and elimination were fitted to log-transformed concentration-time data. Typical population values for PK parameters, and interindividual and residual variability were obtained using the FOCE INTER estimation method in NONMEM VI. Interindividual variability (IIV) was modeled as an exponential variance model and proportional or slope-intercept variance models were used to describe the residual variability. χ^2 pose 4 was used to visualize the data. Models were selected by comparing the NONMEM objective function value, goodness-of-fit plots and scientific plausibility. The non-parametric bootstrap and visual predictive check (VPC) functionalities of Perl-speaks-NONMEM (PsN) were used to evaluate the final models. Rich and sparse data were analyzed separately, simultaneously (combined) and using rich data as prior information for sparse data analysis (prior using the TNPRI functionality in NONMEM VI).

RESULTS

Mean (relative standard error [RSE]) population parameter estimates are provided in Table 2 (NVP) and Table 3 (3TC). NVP sparse patient data were inadequate to reliably estimate population parameters. However, there were no marked differences in parameters between rich and sparse patient data and a combined analysis of sparse and rich data (CL/F = 2.52 L/h [4.7% RSE]; V/F 115 L [14%]; k_a 3.21 /h [41%]) or an analysis of sparse data with prior from rich data (CL/F = 2.52 L/h [4.56% RSE]; V/F 104 L [8.8%]; k_a 2.69 /h [35%]) gave similar population parameter estimates. For 3TC, higher CL/F and k_a in HV than patients were indicated in both the combined analysis and when using the prior functionality. Once this was accounted for, the different analyses provided similar patient parameter estimates: combined analysis (CL/F = 14.6 L/h [3.6%]; V/F 86 L [2.4%]; k_a 1.52 /h [18.0%]), prior (CL/F = 14.3 L/h [2.5%]; V/F 86 L [2.5%]; k_a 1.80 /h [0.2%]).

The VPC lower limit of the 95% confidence interval (2.5th percentile real and simulated data with 95% confidence interval for the simulated data) for the final models are plotted in Fig. 2A (3TC) and 2B (NVP).

FIGURE 2
Lower limit of the 95% confidence interval (2.5th percentile real data [---], simulated data [—] and 95% confidence interval for the simulated data [---]) for 3TC and NVP concentrations versus time after dose (h).



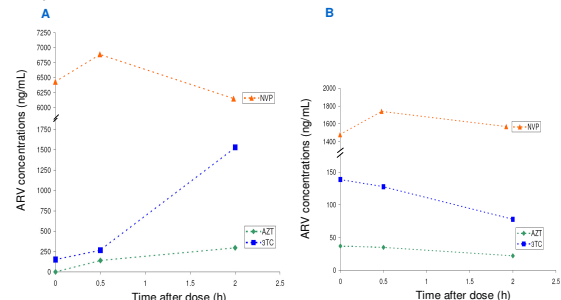
CONCLUSION

Population pharmacokinetic models for 3TC and NVP were developed from rich and sparse data. Combined analyses and sequential rich-sparse analyses using the prior functionality led to the same model decisions and very similar parameter estimates. The minimum "cut-off" values to assess adherence will be evaluated in ongoing cART adherence studies.

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FIGURE 1
NVP, AZT and 3TC concentrations (ng/mL) vs. time after dose (h) in two subjects with uncertain adherence.



- A** Increasing concentrations of AZT and 3TC (absorption phase) compatible with a history that previous ARV dose was taken.
B Decreasing 3TC and AZT concentrations (elimination phase) compatible with a history that the previous ARV dose was not taken.

TABLE 1. Summary of pharmacokinetic studies

Study design	Analytes	Subjects	Sampling (h)	Comments
A Bioequivalence study	3TC [AZT]	Male healthy volunteers N = 25	0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36	Fasted. Data for reference product (Combivir®) available for analysis..
B NVP-rifampicin drug-interaction study [PK profiles during and after TB-treatment]	NVP, 3TC [AZT, d4T]	Male and female HIV-infected patients N = 25	0, 0.5, 1, 1.5, 2, 4, 6, 12, 12.25, 12.75, 14, 16, 24	Fasted. Only data from morning dose analyzed..
C Cross-sectional study investigating the metabolic complications of cART	NVP, [EFV] 3TC, [d4T, AZT, LPV/r]	Male and female HIV-infected patients N = 128	Various [1 to 3 samples per subject]	Samples collected during oral glucose tolerance tests (0, 0.5 and 2h) at varied times since the ARV dose.

TABLE 2. Mean (RSE) population parameters estimates for NVP.

Parameters	Rich data (N = 25)	Sparse data (N = 48)	With prior (N = 48)	Combined data (N = 73)
CL/F (L/h)	2.97 (7.1)	2.05 (10.1)	2.52 (4.6)	2.52 (4.7)
V/F (L)	87.1 (8.9)	11 (75.6)	104 (8.8)	115 (13.8)
K _a (/h)	3.19 (21.3)	0.13 (61.1)	2.69 (35.1)	3.21 (40.5)
Residual error				
σ_{prop}	0.104 (5.8)	0.159 (32.5)	0.103 (6.1)	0.155 (11.4)
σ_{add}	-	0.32 (31.6)	-	0.118 (43.1)
IIV (CV%)				
CL/F	34% (29.2)	36% (28.3)	19% (29.3)	40% (20.1)
V/F	31% (49.8)	-	32% (48.2)	35% (220.0)
K _a	33% (120.0)	-	43% (88.7)	-

TABLE 3. Mean (RSE) population parameter estimates for 3TC.

Parameters	Rich HV data (N = 25)	Rich patient data (N = 25)	Combined rich data (N = 50)	Sparse data (N = 128)	With prior (N=128)	Combined data (N=178)
CL/F (L/h)	24 (3.0)	20 (6.1)	23.5 (4.5)	13.9 (4.4)	14.3 (2.5)	14.6 (3.6)
V/F (L)	89.4 (3.5)	83.3 (4.6)	90.4 (2.7)	86.8 (3.0)	85.7 (2.5)	87.9 (2.4)
K _a (/h)	3.04 (21.9)	2.07 (23.0)	3.04 (19.9)	2.43 (37.6)	1.80 (0.2)	1.52 (18.0)
Residual error						
σ_{prop}	1.97 (15.0)	0.301 (5.9)	2.06 (16.7)	0.337 (5.4)	1.49 (7.1)	1.19 (18.6)
σ_{add}	0.184 (42.3)	-	0.189 (48.5)	-	0.305 (9.9)	0.317 (7.4)
IIV (CV%)						
CL/F	9% (45.4)	28% (33.3)	19% (25.3)	34% (19.4)	22% (18.7)	26% (17.6)
K _a	95% (34.0)	85% (33.9)	43% (25.0)	144% (40.7)	135% (20.9)	109% (20.7)