

A new model for the population pharmacokinetics of didanosine in healthy subjects

L.S. Velasque¹,
R.C.E. Estrela²,
G. Suarez-Kurtz²
and C.J. Struchiner¹

¹Programa de Computação Científica, Fundação Oswaldo Cruz,
²Coordenação de Pesquisa, Instituto Nacional de Câncer,
Rio de Janeiro, RJ, Brasil

Abstract

Didanosine (ddI) is a component of highly active antiretroviral therapy drug combinations, used especially in resource-limited settings and in zidovudine-resistant patients. The population pharmacokinetics of ddI was evaluated in 48 healthy volunteers enrolled in two bioequivalence studies. These data, along with a set of co-variables, were the subject of a nonlinear mixed-effect modeling analysis using the NONMEM program. A two-compartment model with first order absorption (ADVAN3 TRANS3) was fitted to the serum ddI concentration data. Final pharmacokinetic parameters, expressed as functions of the co-variables gender and creatinine clearance (CL_{CR}), were: oral clearance ($CL = 55.1 + 240 \times CL_{CR} + 16.6$ L/h for males and $CL = 55.1 + 240 \times CL_{CR}$ for females), central volume ($V_2 = 9.8$ L), intercompartmental clearance ($Q = 40.9$ L/h), peripheral volume ($V_3 = 62.7 + 22.9$ L for males and $V_3 = 62.7$ L for females), absorption rate constant ($K_a = 1.51$ /h), and dissolution time of the tablet ($D = 0.43$ h). The intraindividual (residual) variability expressed as coefficient of variation was 13.0%, whereas the interindividual variability of CL, Q, V_3 , K_a , and D was 20.1, 75.8, 20.6, 18.9, and 38.2%, respectively. The relatively high (>30%) interindividual variability for some of these parameters, observed under the controlled experimental settings of bioequivalence trials in healthy volunteers, may result from genetic variability of the processes involved in ddI absorption and disposition.

Key words

- Didanosine
- Pharmacokinetics
- NONMEM

Correspondence

L.S. Velasque
Programa de Computação Científica
Fundação Oswaldo Cruz
Av. Brasil, 4365
21045-900 Rio de Janeiro, RJ
Brasil
Fax: +55-21-2270-5141
E-mail: velasque@fiocruz.br

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Introduction

Didanosine (ddI) is a nucleoside analog of adenosine, which prevents replication of human immunodeficiency virus (HIV) by inhibiting HIV reverse transcriptase (1). ddI is a component of highly active antiretroviral therapy drug combinations, used especially in resource-limited settings and among

zidovudine-resistant patients (1,2). The pharmacodynamic and pharmacokinetic properties of ddI in HIV-infected individuals and in AIDS patients have been the subject of several reviews (3-6). Regarding the pharmacokinetics of ddI, which is the focus of the present study, important interindividual variability has been reported for several parameters (3-7). Uncontrolled experimental con-

ditions due to various factors, such as food intake, concomitant administration of other drugs, unbalanced data, etc., could partially explain the variability observed.

Knowledge of the sources and magnitude of this variability can help explain pharmacokinetic differences due to environmental, genetic, and pathophysiologic factors (8). In the present study, we used a broad range of serum ddI concentrations obtained from two bioequivalence trials to develop a new model for this antiretroviral drug in healthy volunteers. Bioequivalence trials are conducted in controlled settings and thus minimize various sources of variability, such as diet, timing of dosing, physical activity, etc. In addition, the pharmacokinetics of highly active antiretroviral therapy components among healthy volunteers may better describe the behavior of these drugs among infected individuals who start therapy early during the course of the infection.

Material and Methods

Clinical protocol and pharmacokinetic analysis

The concentrations of ddI in serum samples and the corresponding pharmacokinetic parameters were derived from two bioequivalence studies, in which 48 healthy adult volunteers were enrolled. The studies were conducted in accordance with the revised Decla-

ration of Helsinki and the rules of Good Clinical Practice (ICH-GCP), the clinical protocols were approved by the Ethics Committee of Instituto Nacional de Câncer, Rio de Janeiro, RJ, Brazil, and all participants provided written informed consent.

Twenty-four volunteers (12 males) were selected for each study according to medical history, physical examination, electrocardiogram, and standard laboratory test results (blood cell count, biochemical profile and urinalysis). These volunteers, whose demographics are shown in Table 1, had not used any investigational drug during the preceding 6 months and prescription drugs other than oral contraceptives were not permitted during the study. In each study, a single-dose (200 mg), three-period, six-way, randomized, crossover protocol was used. A detailed description of this experimental design has been published (5). Briefly, in each study, the 24 enrolled volunteers received orally, at weekly intervals, two 100-mg tablets of three different didanosine formulations, one being the reference (Videx[®], Bristol-Myers-Squibb, Evansville, IN, USA) and the other two generic formulations manufactured in Brazil. The generic formulations used in study No. 1 were manufactured by Laboratório Farmacêutico do Estado de Pernambuco S.A. (LAFEPE, Recife, PE, Brazil) and Indústria Química do Estado de Goiás (IQUEGO, Goiânia, GO, Brazil) whereas in study No. 2 the manufacturers were Instituto Vital Brasil (IVB, Niterói, RJ, Brazil) and Fundação Ezequiel Dias (FUNED, Belo Horizonte, MG, Brazil). Thus, all 48 enrolled volunteers received the reference formulation, whereas each generic formulation was administered to two sets of 24 volunteers. The ddI tablets were administered with 200 mL water at 7:00 am after an overnight fast, and blood samples (8 mL) were collected immediately before and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 h post-dosing. The serum was separated within 30 min and stored at -20°C until the meas-

Table 1. Demographics of the study subjects.

Characteristic	Value	Range
Gender	24M/24F	
Age (years)	26	19-48
Weight (kg)	64	51.7-83
Height (cm)	166.5	149-187
Estimated creatinine clearance (mL/min)	0.14	0.10-0.19

Data are reported as median and range except for gender. Creatinine clearance was calculated by the Cockcroft-Gault equation (14).

urement of ddI concentration using online solid phase extraction coupled to liquid chromatography with positive ion electrospray ionization and tandem mass spectrometry detection (9).

Compartmental pharmacokinetic model

We used the computer program nonlinear mixed-effect model (NONMEM; double precision, version V, level 1.1), developed by Beal and Sheiner (10). Model fitting was done with NONMEM using the PHOSTOC method (11) and the serum ddI concentrations ($N = 624$ samples) measured after administration of the reference formulation to the 48 enrolled volunteers. Our choice of an appropriate statistical model was preceded by preliminary modeling exercises when we tried several compartmental models in combination with different types of additive and proportional intraindividual error structures (results not shown). We finally chose the proportional intraindividual error structure and a two-compartment pharmacokinetic model (ADVAN3 TRANS3) using absorption rate constant (K_a), clearance (CL), volume of the central compartment (V_2), intercompartmental clearance (Q), volume of the peripheral compartment (V_3), and duration time of the dose (D, used to model the dissolution time of the tablet: rate = -2). This latter model provided the best fit among the models tried.

We assumed that interindividual variability of the pharmacokinetic parameters is log-normally distributed, i.e., each parameter value for the i th individual is expressed as $P_i = \hat{P} + \exp(\eta_i)$, where \hat{P} is the typical value of the parameter in the population and η_i is the interindividual error with mean zero and variance Ω^2 . In addition, intraindividual proportional errors were expressed as $C_{ij} = \hat{C}_{ij}(1 + \varepsilon_{ij})$, where C_{ij} is the observed concentration in serum for the i th individual at time j , \hat{C}_{ij} is the concentration in serum for the i th individual at time j predicted by the

model, and ε_{ij} is the residual or intraindividual error with mean zero and variance σ^2 . Intraindividual and interindividual variabilities were expressed as coefficients of variation (CV). In the model there is only one intraindividual CV which is calculated as the square root of σ^2 . On the other hand, the number of interindividual CVs depends on the number of random effects included in the model and, therefore, is calculated as the square root of the elements of the matrix Ω^2 (11).

Model-building procedure

We compared an initial set of models that differed from each other by the random effects component associated with each parameter. The model containing random effects associated with all parameters, except V_2 , minimized the objective function ($-2 \log$ likelihood). Using this model as a starting point, we subsequently plotted the individual parameters against co-variables of interest (age, weight, creatinine clearance (CL_{CR}), and gender) to check for trends. The co-variables visually identified as possible factors affecting the pharmacokinetic parameters were formally tested using NONMEM. We retained in the model the set of co-variables that minimized the AIC statistics (Akaike information criterion = $-2 \log$ likelihood + $2 \times$ (number of parameters); 12).

Model validation

The serum ddI concentrations ($N = 1248$ samples) measured after administration of the four test formulations to the volunteers were compared to the curve predicted by the final model.

Results

Pharmacokinetic data and bioequivalence assessment

All the volunteers completed the bioequiva-

lence trials, and none experienced clinically relevant adverse effects. Figure 1 shows the mean serum concentration-time curves for each ddI formulation, and the pharmacokinetic parameters derived from these curves are presented in Table 2. The values of C_{max} , $AUC_{0-\infty}$, T_{max} , $t_{1/2}$, or CL/F for the reference formulation did not differ significantly (Mann-Whitney rank sum test) between the two trials, and were in excellent agreement with previous

studies in which adult healthy volunteers or HIV-infected individuals were treated with 200 mg oral ddI (1,13). No significant differences in C_{max} , $AUC_{0-\infty}$, T_{max} , $t_{1/2}$, or CL/F were observed between the reference and the generic formulations tested in each bioequivalence trial. Bioequivalence assessment indicated that each of the four test formulations fulfilled the adopted bioequivalence criteria (Methods).

Figure 1. Didanosine (ddI) concentrations in the serum of healthy volunteers after single oral doses (200 mg) of the drug in two bioequivalence trials. In each trial (A, B) 24 volunteers were treated with the reference (Videx®) and two test (generic) ddI formulations (100-mg tablets) at weekly intervals. Data are reported as means \pm SD.

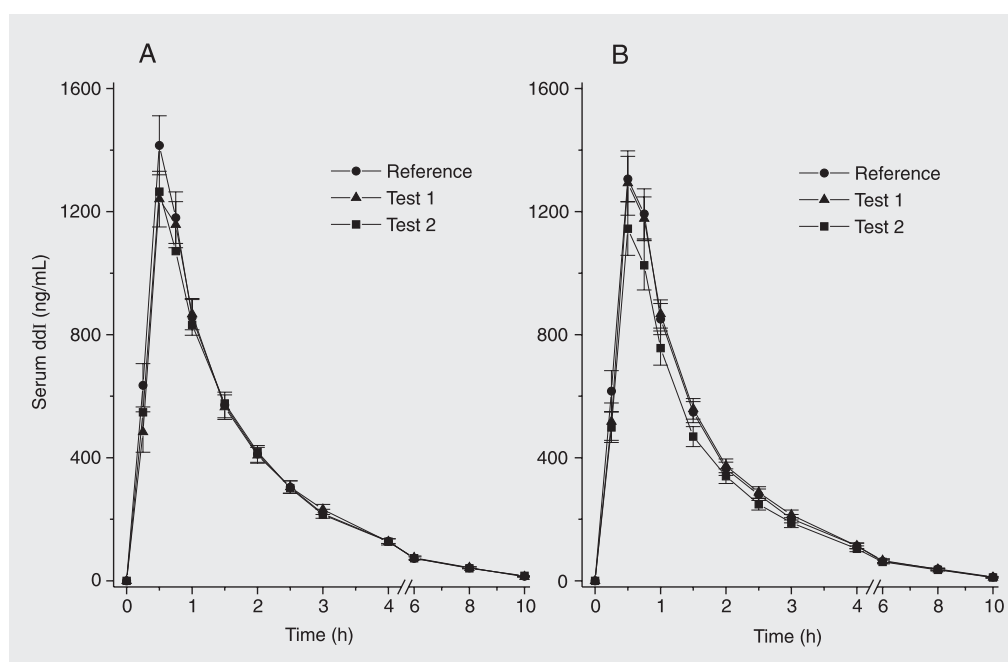


Table 2. Pharmacokinetic parameters of didanosine in healthy volunteers.

Parameter	Trial No. 1				Trial No. 2			
	Reference	Test 1	Test 2	ANOVA P value	Reference	Test 1	Test 2	ANOVA P value
C_{max} ($\mu\text{g/L}$)	1.5 ± 0.4	1.3 ± 0.4	1.3 ± 0.5	0.60	1.4 ± 0.4	1.4 ± 0.4	1.2 ± 0.4	0.21
$AUC_{0-\infty}$ ($\mu\text{g h}^{-1} \text{L}^{-1}$)	2.2 ± 0.6	2.2 ± 0.5	2.2 ± 0.5	0.86	2.1 ± 0.5	2.1 ± 0.6	1.9 ± 0.6	0.23
T_{max} (h)	0.6 ± 0.1	0.6 ± 0.2	0.6 ± 0.2	0.99	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.1	0.90
$t_{1/2}$ (h)	1.3 ± 0.2	1.2 ± 0.2	1.3 ± 0.2	0.99	1.3 ± 0.3	1.3 ± 0.2	1.3 ± 0.3	0.71
CL/F (L)	184.5 ± 58.8	173.0 ± 37.8	190.5 ± 55.2	0.55	187.2 ± 56.3	183.5 ± 63.4	224.8 ± 93.4	0.10
k_{el} (h)	0.53 ± 0.09	0.57 ± 0.07	0.53 ± 0.06	0.35	0.55 ± 0.12	0.56 ± 0.09	0.55 ± 0.11	0.84

Data are reported as mean \pm SD. Trial No. 1: 24 healthy volunteers ingested 200 mg didanosine as reference (Videx®) and two test formulations (LAFEPE and IQUEGO) at 7-day intervals. Trial No. 2: 24 healthy volunteers ingested 200 mg didanosine as reference (Videx®) and two test formulations (IVB and FUNED) at 7-day intervals.

Model development

Parameter estimates for two representative models from the set of models fitted to the data are presented in Table 3. The initial model is best among models that differ only by the presence or absence of random effects associated with the various parameters. The final model is best among models that allow for random effects as well as co-variate effects, i.e., parameter dependence on co-variables. Its objective function is significantly smaller than that of the initial model ($\Delta AIC = 62.45$).

CL is the parameter in the final model most influenced by explanatory variables. Its value varied significantly from the initial to the final model (the 95% CI's did not overlap). The overlap indicates that the observed difference may not be statistically significant.

Interindividual variability (ω^2) for several parameters decreased from the starting value in the initial model to the estimated values in the final model. However, the changes were not significant (overlapping 95% CI's for ω^2). Interindividual variability estimates, expressed as CV for CL, Q, V_3 , K_a , and D, were 20.1, 75.8, 20.7, 18.9, and 38.2%, respectively. Gender had a high and significant (95% CI's did not include the null value) influence on the parameters CL (16.6 for male) and V_3 (22.9 for male). Body weight effects on the various parameters were not significant. The intraindividual variability estimate was 13% (CV).

Figure 2 shows a plot of the measured versus the model-predicted serum ddl concentrations for the reference formulation in the 48 volunteers studied. The data indicate excellent correlation ($r = 0.98$, P value < 0.001). Figure 3 shows typical curves predicted from the model (solid curve) versus the curves observed for healthy volunteers. Analysis of the graph displaying the weighted residuals versus the predicted serum ddl concentrations, for the same model, reveals that

Table 3. Estimates of model parameters for didanosine.

Parameter	Initial model		Final model	
	Estimate	95% CI	Estimate	95% CI
θ_{CL} (L/h)	97.80	91.12 - 104.48	55.10	22.5 - 87.7
θ_{V_2} (L/h)	11.00	5.58 - 16.42	9.82	3.96 - 15.68
θ_Q (L/h)	45.60	22.60 - 68.60	40.90	21.08 - 60.72
θ_{V_3} (L/h)	75.40	58.28 - 92.52	62.70	50.54 - 72.46
θ_{K_a} (L/h)	1.55	1.24 - 1.98	1.51	1.15 - 1.87
θ_D (h)	0.43	0.41 - 0.45	0.44	0.40 - 0.46
$\theta_{CL_{CR-CL}}$ (L/h)	-	-	240.00	10 - 470
θ_{Sex-V_3} (L)	-	-	22.90	15.76 - 30.04
θ_{Sex-CL} (L/h)	-	-	16.6	5.33 - 27.26
ω^2_{CL}	0.06	0.02 - 0.11	0.04	0.02 - 0.05
ω^2_Q	0.48	0.07 - 0.89	0.57	0.07 - 1.07
$\omega^2_{V_3}$	0.10	0.04 - 0.15	0.04	0.01 - 0.06
$\omega^2_{K_a}$	0.05	0.01 - 0.09	0.04	0.00 - 0.07
ω^2_D	0.15	0.09 - 0.21	0.15	0.09 - 0.20
σ^2	0.02	0.01 - 0.02	0.02	0.01 - 0.02
OF	5150.32	-	5081.87	-
AIC	5172.32	-	5109.87	-

95% CI = 95% confidence interval; CL = clearance; V_2 = central volume; Q = intercompartmental clearance; V_3 = peripheral volume; K_a = absorption rate constant; D = dissolution time of the tablet; CL_{CR} = creatinine clearance; OF = objective function; AIC (Akaike information criterion) = objective function + $2x(\text{number of parameters})$.

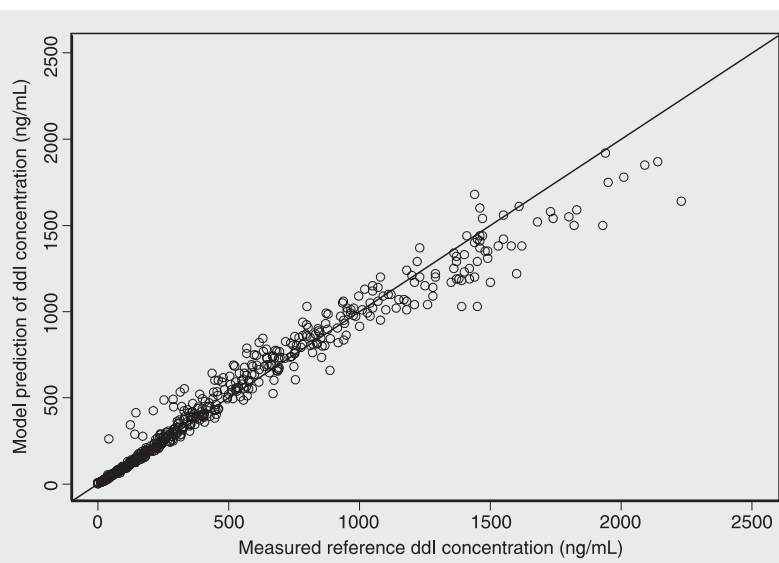


Figure 2. Scatter plot showing the relationship between the serum didanosine (ddl) concentrations measured in 48 healthy volunteers treated with 200 mg of the reference (Videx®) ddl formulation (abscissa) and the corresponding concentrations predicted by the final model developed in the present study (ordinate). The continuous line is the identity line.

the residuals are distributed randomly and concentrate within the ± 2 standard deviation limits (Figure 4).

The final model describing the population pharmacokinetics of ddI is as follows:

Population mean. The set of equations specific for males was $CL (L/h) = 55.1 + 240$

$\times CL_{CR} + 16.6$, $V_3 (L) = 62.7 + 22.9$. Females followed the equations $CL (L/h) = 55.1 + 240 \times CL_{CR}$ and $V_3 (L) = 62.7$.

In addition, the following equations were gender independent: $V_2 (L) = 9.82$, $Q (L/h) = 40.9$, $K_a (h) = 1.51$, $D (h) = 0.43$.

Interindividual variability (CV%). $\omega^2_{CL} = 20.10\%$, $\omega^2_Q = 75.83\%$, $\omega^2_{V_3} = 20.66\%$, $\omega^2_{K_a} = 18.95\%$, $\omega^2_D = 38.21\%$.

Intraindividual variability (CV%). $\sigma^2 = 12.96\%$.

Model validation

The serum ddI concentrations measured after administration of the test formulations to the 48 volunteers were used for validation of the final model. The plot in Figure 5 shows the population curve predicted from the model for both gender (solid curve A and B) versus the curves observed for healthy volunteers who took the test drug.

Discussion

This is the first study of the population pharmacokinetics of ddI in healthy adults. The software NONMEN and a large number of serum ddI concentrations ($N = 1872$) from 48 subjects studied under the controlled conditions prevalent in bioequivalence trials were used for model development and validation. Model development was based on data obtained with the reference formulation. The values of the pharmacokinetic parameters C_{max} , $AUC_{0-\infty}$, T_{max} , $t_{1/2}$, or CL/F for this formulation were in excellent agreement with previous results for healthy adult volunteers or HIV-infected individuals treated with 200 mg oral ddI (1,13). The consistency of these pharmacokinetic data suggests the broader applicability of the population model developed in the present study.

Model diagnostics did not show any deviant pattern. Excellent correlation was observed between the measured and the mo-

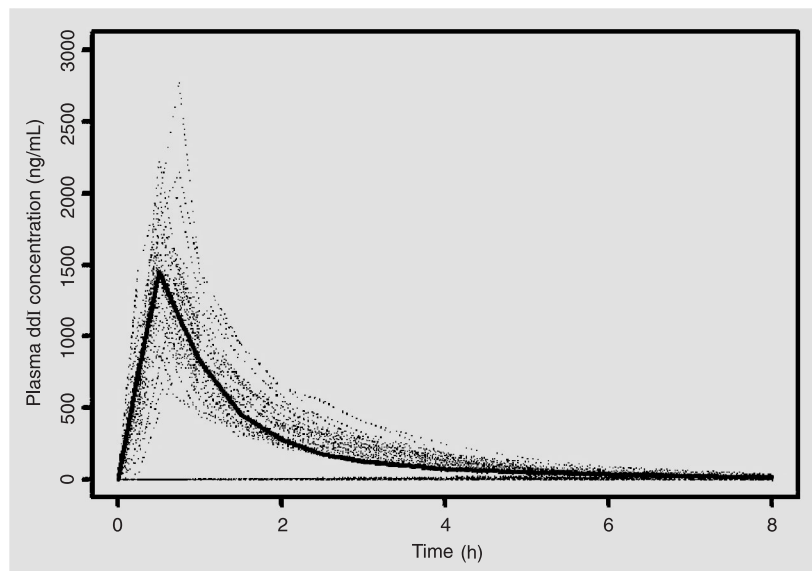


Figure 3. The solid curve is the typical didanosine (ddI) curve predicted by the population model versus time. The dotted lines are plasma ddI concentrations measured in 48 healthy volunteers treated with 200 mg of the reference (Videx®) ddI formulation.

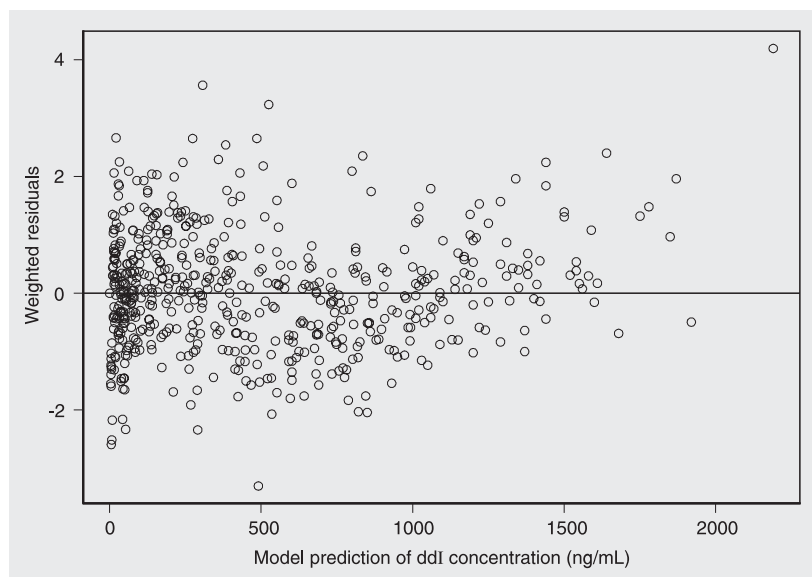


Figure 4. Scatter plot of weighted residual didanosine (ddI) concentration versus the concentration predicted by the final model developed in the present study for reference (Videx®) formulation.

del-predicted serum ddI concentrations for the reference formulation (Figure 2). A distinct feature of our final model was the reduction of the intraindividual (residual) variability to 13%, which implies improved inference properties when compared to previously described models in which the intraindividual variability ranged from 50.2 (6) to 53.9% (7). The relatively small intraindividual variability in our model can be attributed, at least in part, to the control of potential sources of pharmacokinetic variation in the setting of bioequivalence trials.

The final model included gender as an explanatory variable for CL and V_3 . This contrasts with previous studies which excluded effects of gender on the model descriptive parameters for ddI (6,7). One of these studies, however, reported that gender affects the CL of nevirapine (7). Our model identified CL_{CR} as another explanatory variable for the CL of ddI, which again contrasts with previous models. At present, we have no explanation for these discrepancies.

The interindividual variability associated with Q in the final model was highest in the parameter set (CV = 75.8%), which points to the intercompartmental clearance of ddI as

the pharmacokinetic process exhibiting the largest heterogeneity among the subjects in the study. Of the other parameters in our final population model, the dissolution time of the tablet - D - was the only one to show substantial (CV = 38.2%) interindividual variability. This can be tentatively explained by the different rates of disintegration and dissolution of the ddI tablets in the gastrointestinal tract, despite the pH buffering included in the formulations. The intraindividual variability of V_3 , CL and K_a was relatively minor (CV ~20%), but nevertheless removal of each of these terms from the model resulted in significant increases in the objective function and therefore they were retained in the final model.

The final model was validated against the concentration-time observations obtained after administration of the test ddI formulations to the same individuals used for model development. Although distinct formulations were used for model development and validation, we recognize that enrolling different individuals would provide a more stringent validation test, especially in view of the bioequivalence between the reference and each of the test ddI formulations examined.

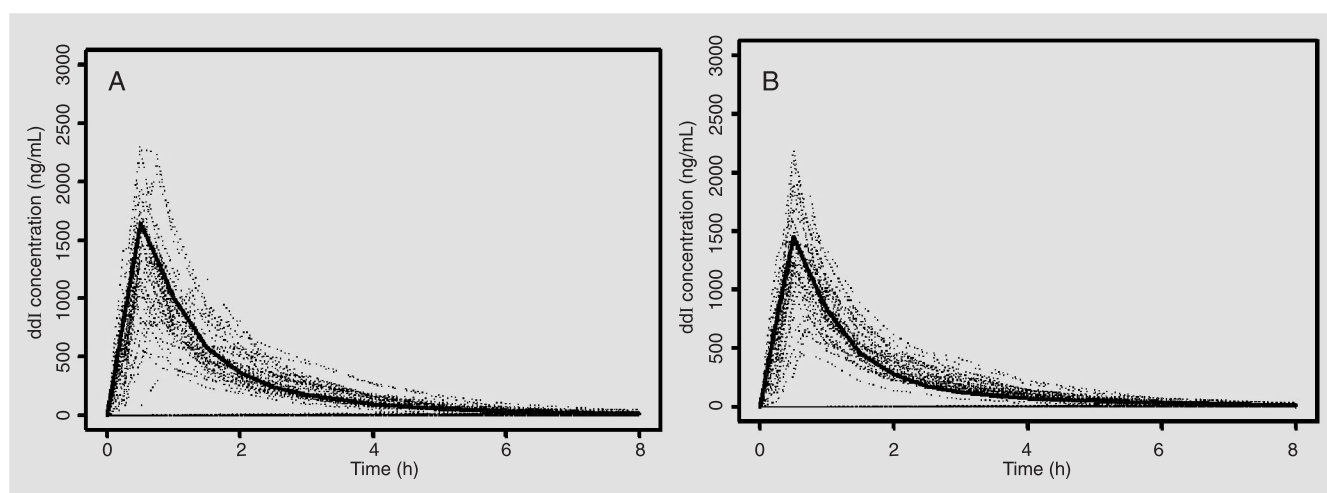


Figure 5. The solid curve is the typical didanosine (ddI) curve predicted by the population model versus time for men and women (A and B, respectively). The dotted lines are the concentrations observed in volunteers who took the test drug. A, Model for men: CL (L/h) = $55.1 + 240 \times CL_{CR} + 16.6$; V_3 (L) = $62.7 + 22.9$; V_2 (L) = 9.82; Q (L/h) = 40.9; K_a (h) = 1.51; D (h) = 0.43. B, Model for women: CL (L/h) = $55.1 + 240 \times CL_{CR}$; V_3 (L) = 62.7; V_2 (L) = 9.82; Q (L/h) = 40.9; K_a (h) = 1.51; D (h) = 0.43.

We report the development and validation of a population pharmacokinetic model for the antiretroviral drug, ddI, using data from two bioequivalence studies in which generic formulations manufactured in Brazil proved to be bioequivalent with the reference ddI tablet formulation available internationally. The final model achieved lower intraindividual (residual) variability than previous models reported in the literature, which were developed using data from HIV-infected individuals (6,7). Because our model was based on ddI data from healthy volunteers, it might be more relevant to the

pharmacokinetics of ddI administered to HIV-infected patients early in the course of the infection. We observed that the interindividual variability in the model descriptive parameters remained important even in the controlled setting of bioequivalence trials. Our observation that the interindividual variability in the model descriptive parameters remained important even in the controlled setting of bioequivalence trials may suggest that pharmacogenomic factors play a relevant role in the disposition of ddI in humans.

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