Didanosine Population Pharmacokinetics in West African Human Immunodeficiency Virus-Infected Children Administered Once-Daily Tablets in Relation to Efficacy after One Year of Treatment

Déborah Hirt, Christophe Bardin, Serge Diagbouga, Boubaçar Nacro, Hervé Hien, Emmanuelle Zoure, François Rouet, Adama Ouimenga, Saïk Urien, Vincent Fouloungne, Philippe Van De Perre, Jean-Marc Tréluyer, and Philippe Mselati

EA3620 and Service de Pharmacologie Clinique, AP-HP, Hôpital Cochin-Saint-Vincent-de-Paul, Université Paris–Descartes, Unité de Recherche Clinique, AP-HP, Hôpital Tarnier, and Service de Pharmacie-Pharmacologie-Toxicologie, AP-HP, Hôtel-Dieu, Université Montpellier, Laboratoire de Bactériologie-Virologie, Montpellier, and UMR 145, IRD, Université de Montpellier 1, Centre de Recherche Cultures Santé Sociétés/IFEHA, Université Paul Cézanne, Aix en Provence, France, and Centre Muraz and Service de Pédiatrie, CHU Sourou Sanou, Bobo Dioulasso, Burkina Faso

Our objective was to study didanosine pharmacokinetics in children after the administration of tablets, the only formulation available in Burkina Faso for which data are missing, and to establish relationships between doses, plasma drug concentrations, and treatment effects (efficacy/toxicity). Didanosine concentrations were measured for 40 children after 2 weeks and for 9 children after 2 to 5 months of treatment with a didanosine-lamivudine-efavirenz combination. A population pharmacokinetic model was developed with NONMEM. The link between the maximal concentration of the drug in plasma (C_{max}), the area under the concentration-time curve (AUC), and the decrease in human immunodeficiency virus (HIV) type 1 RNA levels after 12 months of treatment was evaluated. The threshold AUC that improved efficacy was determined by the use of a Wilcoxon test for HIV RNA, and an optimized dosing schedule was simulated. Didanosine pharmacokinetics was best described by a one-compartment model with first-order absorption and elimination. The apparent clearance and volume of distribution were higher for tablets, probably due to a lower bioavailability with tablets than with pediatric powder. The decrease in the viral load after 12 months of treatment was significantly correlated with the didanosine AUC and C_{max} (P ≤ 0.02) during the first weeks of treatment. An AUC of >0.60 mg/liter · h was significantly linked to a greater decrease in the viral load (a decrease of 3 log_{10} versus 2.4 log_{10} copies/ml; P = 0.03) than that with a lower AUC. A didanosine dose of 360 mg/m² administered as tablets should be a more appropriate dose than 240 mg/m² to improve efficacy for these children. However, data on adverse events with this dosage are missing.

According to the latest UNAIDS estimates, 2.5 million children around the world were living with human immunodeficiency virus (HIV) in 2007. Nearly 90% of them were living in sub-Saharan Africa (33). Highly active antiretroviral therapy (HAART) has been shown to be effective for children from industrialized countries (34) and is feasible in developing countries (10, 13). Since compliance is essential for individual efficacy (36), once-daily administration of HAART could decrease treatment failure, especially for children from developing countries. The once-a-day combination of didanosine (ddI), lamivudine (3TC), and efavirenz (EFV) has been successfully used for adults (11, 12, 25, 26). It improves compliance, antiretroviral efficacy (25), and long-term tolerance (11, 12, 26). For children, the once-daily administration of HAART is recommended in the United States and possibly in Europe, but the efficacy and tolerance of this ddI-3TC-EFV combination remain to be shown.
ddf is susceptible to acid hydrolysis when administered orally; an estimated 10% of ddI is degraded every 2 min at pH 3.0 or below (22). Another limitation of ddI is its poor solubility at low pH values (pK_{a} = 9.1). As a result, one oral dosage formulation contains buffers to prevent the degradation of the drug in the gastrointestinal tract and to improve its solubility. The available formulation of ddI is a chewable, dispersible tablet containing calcium carbonate and magnesium hydroxide buffers. After administration of these 200- or 400-mg tablets, the maximum gastric pH reached 8.7 or 8.6, and the area under the gastric pH-versus-time curve for pHs greater than 3.0 was 2.4 pH · min^{-1} or 2.8 pH · min^{-1}, respectively. The mean times for which the gastric pH exceeded 3.0 were 22.7 and 27.2 min for the 200- and 400-mg ddI doses, respectively, and demonstrated a wide range of variability, from 15 to 55 min. This short duration of elevated gastric pH may help explain the wide variability in ddI bioavailability observed clinically (9). It has been shown that ddI bioavailability was lower...
for buffered tablets (25%) than for the oral solution (or reconstituted powder) with antacid (41%) or the enteric coated form (36%) (16).

In all previous studies performed with children (1, 4, 7, 14, 20, 21, 32), ddI was administered as an enteric coated bead formulation or, more often, as a pediatric powder for oral solution (after reconstitution, the oral solution was prepared by mixing the appropriate volume of ddl solution with a volume of antacid), as recommended by the National Institutes of Health (37). However, these formulations are not available at the governmental Centrale d’Achat des Médicaments Essentiels et Génériques (CAMEG) in Burkina Faso, where only chewable/dispersible tablets can be found. These chewable tablets are not specific to this study and will continue to be at the CAMEG after this trial. No study reports ddI pharmacokinetics for children after once-daily administration of ddI tablets (Videx).

The three drugs administered have different major routes of elimination. Available data indicate that ddI is renally excreted and can also be broken down to hypoxanthine, which can either enter the purine metabolic pool or be degraded further to uric acid. ddI can also be used to form 2',3'-ddATP, which is the putative species against reverse transcriptase (3, 15). EFV is metabolized exclusively via CYP2B6 (cytochrome P450 isoenzyme) in the liver (35). Finally, the majority of 3TC (approximately 70%) is eliminated unchanged in the urine over 24 h (17). While one would expect that renal function is essentially mature in 15-month-old children, little is known about the ontogenesis of ddI metabolism.

The aims of the BURKINAM-ANRS 12103 trial were to estimate the pharmacokinetics of ddI, 3TC, and EFV given once daily for children aged 30 months to 15 years and to evaluate the efficacy and tolerance of this drug combination. In the present study, ddI population pharmacokinetics in children was investigated in order to describe the concentration-time courses, to study the influence of covariates (such as body weight, age, and body surface area) on pharmacokinetics, and to investigate relationships between drug concentrations and effects (efficacy and toxicity).

**MATERIALS AND METHODS**

**Patients.** The BURKINAM-ANRS 12103 study was an open phase II trial evaluating the pharmacokinetics, efficacy, and toxicity of the once-daily ddl-3TC-EFV combination for HIV-infected children in Bobo-Dioulasso, Burkina Faso. The study was approved by the National Ethics Committee on AIDS of Burkina Faso and was registered in the NIH international database of clinical trials with the number NCT00122538. The patients enrolled in this study included children 30 months to 15 years old, weighing at least 10 kg, infected with HIV type 1 (HIV-1), and naive to antiretroviral treatment (except for prophylaxis of mother-to-child transmission). They were eligible if their HIV disease was classified, according to the Centers for Disease Control and prevention (CDC), as either (i) clinical category C and/or ≤15% CD4 cells for children ≤5 years old or a CD4 cell count of ≤200 µl/mm³ for children >5 years old or (ii) clinical category B, A or N and a CD4 cell percentage of ≥15% and ≤20% for children ≤5 years old or a CD4 cell count of ≥200 and ≤350 µl/mm³ for children >5 years old and a viral load greater than 100,000 copies/ml.

The following baseline laboratory values were required: a hemoglobin concentration of 7 g/dl or greater, a platelet count of at least 50,000/µl, an amylase level less than 2.5 times the upper limit of normal, and aspartate aminotransferase and alanine aminotransferase levels less than 5 times the upper limit of normal. The mother or the legal guardian provided written informed consent. Clinical evaluations were carried out monthly during the follow-up period.

Children were also seen for any intercurrent diseases if necessary. Consultations, hospitalizations, treatments and tests were free of charge. Virological and biochemical measurements were performed, beyond baseline, 3, 6, 9, and 12 months after the beginning of the treatment. Plasma HIV-1 RNA levels were determined by means of a commercial real-time reverse transcriptase PCR assay (Generic HIV viral load assay; Biocentric, Bandol, France). The detection threshold of this assay is 300 copies/ml using 0.2 ml of plasma (31). Biochemistry analyses were conducted by using the Lisa 300 Plus machine (Hycel Diagnostics, Massy, France).

**Treatments.** Children received 240 mg of ddI/m² of body surface area once daily as 25-, 50-, 100-, or 200-mg tablets of Videx. The ddl dose was rounded as a function of the available galenic forms, and the actual dose administered was recorded for each patient. Water was given just to dissolve the tablets (less than half a glass). The formulation did not contain an antacid; aluminum hydroxide (Maalox) was added as an antacid when the prescription of ddl was below two pills. Children were supposed not to have eaten for at least 2 h before taking the tablet and to wait at least 1 h after drug intake before eating. All parents were instructed to administer all of the treatment every day at 06:00 h. Children also received a once-daily dose of 3TC at 8 mg/kg of body weight and the recommended body weight-dependent dose of EFV (200 mg of EFV from 13 to ≤15 kg of body weight, 250 mg from 15 to ≤20 kg, 300 mg from 20 to <25 kg, 350 mg from 25 to ≤32.5 kg, 400 mg from 32.5 to ≤40 kg, and 600 mg above 40 kg).

**Sampling.** The pharmacokinetic study was performed after 15 days of treatment for 40 children and between 2 and 5 months of treatment for 9 children. Children underwent blood sampling both before and 1, 2, 3, 6, 12, and 24 h after ddl administration (for 10 children) or before and 1 and 3 h after ddl intake (for 39 children). For sampling, children had to be present at the hospital for a short time. Children’s beds, which were prepared for 24 h, and children had to be in relatively good health, so the full pharmacokinetic schedule of seven samples, initially proposed in order to determine the area under the concentration-time curve (AUC), could not be performed for all children. The time that had elapsed between drug administration and sampling, age, body weight, and height were carefully recorded. Blood samples were centrifuged at 3,000 × g for 10 min. Plasma samples were aliquoted and stored at −70°C until they were assayed for drug concentrations.

**Analytical method.** Concentrations of ddI in plasma were determined using a modified version of a validated reverse-phase high-pressure liquid chromatography assay, with detection by UV absorbance, initially described by Knupp et al. (24). ddI and the internal standard (famotidine) were purchased from Sigma (St. Louis, MO). A solid-phase extraction procedure (C18 SPE columns, 500 mg, from Varian) was used to extract plasma, standards, quality controls, and unknown samples. SPE columns were activated with methanol, followed by 2 ml of water. Plasma (500 μl) was mixed with 50 μl of the internal-standard solution and placed on the cartridge. Samples were aspirated slowly, and columns were washed with 6 ml of water, dried, and then eluted using 2 ml of methanol. Plasma eluates were evaporated under a stream of nitrogen at 40°C, followed by reconstitution of 0.1 ml of the mobile phase. A 50-μl aliquot of the reconstituted extract was injected onto a Thermo Hypersil BDS C18 column (height, 250 mm; inner diameter, 4.6 mm; particle diameter, 5 μm). The mobile phase consisted of a tetrahydrofuran-acetonitrile-potassium phosphate buffer (1:1:98, vol/vol/vol; 30 mM; adjusted to pH 4.6). The flow rate was set at 1 ml/min on an Ultimate 3000 Dionex pump with the temperature maintained at 20°C. Compounds were detected at 250 nm on a Dionex Ultimate 3000 variable-wavelength UV detector. The retention times for ddI and the internal standard, famotidine, were approximately 8.2 and 14.6 min, respectively. There was no evidence of any endogenous substances causing interference at the retention times of ddI and the internal standard. 3TC and EFV were evaluated for interference in the quantification of the compounds, and no such interference was observed. An 8-point standard curve was constructed over the range of 0.01 mg/liter to 5 mg/liter. The lower limit of quantification was 0.01 mg/liter. The mean recovery from extracted plasma samples was found to be 85% ± 5% for ddI. Two quality control samples for ddI, prepared in human plasma at concentrations of 0.04 mg/liter and 3.75 mg/liter, were included with each study run to monitor assay performance. The intraday coefficient of variation (used as an indicator of precision) and mean deviation (used as an indicator of accuracy) of the assay were less than 10% and 4%, respectively. The interday coefficient of variation and mean deviation were less than 12% and 5%, respectively.

**Modeling strategy and population pharmacokinetic model.** Data were analyzed using the nonlinear mixed-effect modeling software program NONMEM (version VI, level 1.0; Icon Development Solutions, Ellicott City, MD) with the Digital Fortran Compiler (6). First-order conditional estimation was used. M2 and M3 approaches were used to account for the pharmacokinetic data below the lower limit of quantification (5). ddI data were analyzed according to one-
compartment and two-compartment models. Because no pharmacokinetic samples were obtained during the absorption phase in our study, first-order absorption was not estimated, as previously described (14). The absorption rate constant ($k_a$) was not fixed to a value from the literature but was chosen (among values of 1, 2, 3, 4, and 5 $h^{-1}$) so as to have a time of maximal concentration around 0.5 $h$, as previously reported (1, 14, 18, 26, 32). Different error models were investigated (i.e., multiplicative and additive error models) to describe residual variability. An exponential model was used for intersubject variability (ISV). Only significant ISVs in pharmacokinetics were kept, i.e., those producing a minimum decrease of 6.63 units (by a $Z$-test; $n=0.01$) using a likelihood ratio test in a backward elimination procedure. The effect of each patient covariate was systematically tested via generalized additive modeling on the basic model; as an example, for clearance (CL), the equation $CL = \theta_C \times [CO\text{median(CO)}]^\beta$ was used, where $\theta_C$ is the typical value of CL for a patient with the median covariate value and $\beta$ is the estimated influential factor for the continuous covariate (CO).

Linear (per square meter or per kilogram of body weight) and allometric (for body weight and body surface area) models were also tested. All the covariates were tested via upward model building. The effect of the duration of treatment on CL was calculated by the equation $CL = \theta_C \times [P\text{median(P)}]^\beta$, where $\beta$ is the estimated influential factor for the duration of treatment and $DUR$ is equal to zero for samples taken after 2 weeks of treatment and to 1 for samples taken after at least 2 months of treatment. A covariate was selected if (i) its effect was biologically plausible, (ii) it produced a minimum decrease of 6.63 units ($P < 0.01$) in the objective function value, and (iii) it produced a reduction in the variability of the pharmacokinetic parameter, assessed by the associated ISV. Among the covariates tested on the base model, the most significant was added in an intermediate model. Then the other covariates were tested on this intermediate model, and the most significant covariate was added. This process was repeated until no more covariates were significant (i.e., $P > 0.01$). For evaluation of the goodness of fit, the following graphs were plotted for the final model: observed and predicted concentrations versus time, observed concentrations versus population predictions, weighted residuals versus time, and weighted residuals versus predictions. Similar graphs using individual predictive post hoc estimation were displayed. Diagnostic graphics were obtained using Rfn (http://rfn.sourceforge.net/) with the R program (R Foundation and University of Vienna, Vienna, Austria) (19).

Evaluation and validation. (i) Bootstrap evaluation. The precision and robustness of the final population model were assessed using a nonparametric bootstrap evaluation with 1,000 replicates (without stratification by patient group), as described in detail previously (29).

(ii) Visual predictive check validation. ddI concentration profiles were simulated and compared with the observed data to evaluate the predictive performance of the model. More precisely, the vector of pharmacokinetic parameters from 1,000 patients was simulated using the final model. Each vector parameter was drawn in a log-normal distribution with a variance corresponding to the ISV previously estimated. A simulated residual error was added to each simulated concentration. The simulations were performed using NONMEM. All observed and simulated concentrations were standardized for a 150-mg ddI dose, since dose proportionality of ddI pharmacokinetics has been demonstrated previously (4, 23). The 5th, 50th, and 95th percentiles of the observed and simulated concentrations at each time were then overlaid on the observed concentration data using the R program, and visual inspection was performed. The model adequately predicts the central tendency and variability of plasma concentrations if the median and respective percentiles of the observations and model predictions fall on top of each other. To account for differences in administered doses, a dose adjustment was performed for this visual predictive check which assumes linear pharmacokinetics for ddI.

Drug concentrations in children and link with effects. For each patient, the maximal concentration ($C_{max}$) of ddI and the AUC were derived from the estimated individual pharmacokinetic parameters. Median values and ranges were calculated and compared to data reported in the literature for children with different administration schemes and ddI formulations. Efficacy was studied by monitoring the difference in the log viral load after 12 months of treatment. The significance of the viral load decrease was first tested using a nonparametric Wilcoxon paired test. A viral load of $\leq 300$ copies/ml was considered undetectable, so undetectable loads on a log scale were treated as $\log_{10}(300)$ equal to 2.48 $\log_{10}$ copies/ml. With respect to efficacy, the links among $C_{max}$, AUC, and the difference in HIV-1 RNA levels between the time of inclusion and month 12 of treatment were evaluated using Spearman correlation tests. The threshold AUC and $C_{max}$ that would significantly improve the viral load decrease after 1 year of treatment were determined by a Wilcoxon test. Then different doses were simulated for each patient with individual parameters in order to achieve the threshold AUC. The proposed dose adjustment was then evaluated by calculating the probability of reaching the target AUC in 49,000 children, obtained from 1,000 simulations of the 49 children in the database. For toxicity during the first year of treatment, adverse experiences that could be considered possibly related to a drug effect were recorded.

RESULTS

Demographic data. Forty-nine children were available for pharmacokinetic evaluation. A total of 183 plasma samples were available for ddI measurements. Table 1 summarizes patient characteristics. The median ddI dose administered was 213 mg/m² (range, 164 to 313 mg/m²).

Clinical, immunological, and virological data. Of the 49 children included in this trial, 19 were girls and 30 were boys. The mean Z-score weight for age was $-1.91$, and the mean Z-score height for age was $-1.99$.

Clinically, 18 children were at stage A, 25 at stage B, 5 at stage C, and 1 at stage N of HIV infection, according to CDC clinical categories (8). Before treatment, the mean percentage of CD4 cells was 8.62% (median, 8%; range, 0.4 to >26%) and the average number of CD4 lymphocytes was 336/mm² (median, 260; range, 2 to 1,510). The median viral load was 5.5 $log_{10}$ copies/ml (range, 4.6 to 6.7 $log_{10}$ copies/ml). Patients with this degree of severity of infection were included in this trial because these are the criteria for receiving HAART in Burkina Faso; not every HIV-infected patient is eligible for HAART.

Population pharmacokinetics. A one-compartment model was chosen to describe the data, because objective functions were not significantly different between one- and two-compartment models, and diagnostic graphics were improved with the one-compartment model. The NONMEM subroutine ADVAN2 TRANS2 was used. The parameters of the model were the apparent clearance ($CL/F$), the apparent volume of distribution ($V/F$), and the $k_{e}$; $F$ is the unknown bioavailability. Intersubject and residual variabilities were best described by an exponential and an additive error model, respectively. The effects of body weight, postnatal age, body surface area, biomolecular parameters (basal creatinine, amylase, alanine aminotransferase, aspartate aminotransferase, and total bilirubin levels), and time from the beginning of treatment (2 weeks versus 2 to 5 months) on $CL/F$ and $V/F$ were tested. None of the covariates added to $CL/F$ or to $V/F$ was significant. Seventy-seven concentrations were below the limit of quantification. The Beal M3 method and the built-in Beal M2 method led to very similar pharmacokinetic parameter estimates, but diagnostic graphics were better with the first approach. The M3 method was finally used, and the NONMEM code was repro-

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Median (minimum–maximum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>6.5 (2.5–14)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>17 (11–37)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>0.69 (0.50–1.22)</td>
</tr>
<tr>
<td>Serum creatinine concn (µmol/liter)</td>
<td>63 (6.6–126.4)</td>
</tr>
<tr>
<td>Alanine aminotransferase concn (U/liter)</td>
<td>79 (6–409)</td>
</tr>
<tr>
<td>Aspartate aminotransferase concn (U/liter)</td>
<td>26 (7–92)</td>
</tr>
<tr>
<td>Total bilirubin concn (µmol/liter)</td>
<td>6.5 (0.9–42.8)</td>
</tr>
</tbody>
</table>

TABLE 1. Characteristics of the HIV-1-infected children ($n = 49$) enrolled in the pharmacokinetic study of the BURKINAM-ANRS 12103 trial
TABLE 2. Population pharmacokinetic parameters for ddI from the final model and bootstrap evaluation for HIV-1-infected children (n = 49) enrolled in the BURKINAM-ANRS 12103 study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value by:</th>
<th>Base model (mean [RSE])</th>
<th>Bootstrap evaluation (median [90% confidence interval])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL/F (liters/h)</td>
<td></td>
<td>208 (20)</td>
<td>192 (104–290)</td>
</tr>
<tr>
<td>V/F (liters)</td>
<td></td>
<td>278 (15)</td>
<td>266 (145–471)</td>
</tr>
<tr>
<td>kₑ (h⁻¹), fixed</td>
<td></td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Statistical model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>σ (mg/liter)</td>
<td></td>
<td>0.077 (7)</td>
<td>0.078 (0.049–0.130)</td>
</tr>
<tr>
<td>ωCLUF (%)</td>
<td></td>
<td>127 (29)</td>
<td>115 (86–178)</td>
</tr>
<tr>
<td>ωV/F (%)</td>
<td></td>
<td>83 (44)</td>
<td>86 (48–116)</td>
</tr>
<tr>
<td>τ₀ EUF-μyr</td>
<td></td>
<td>0.557 (49)</td>
<td>0.497 (−0.342–0.999)</td>
</tr>
</tbody>
</table>

a From the original data set. RSE, relative standard error, expressed as a percentage and calculated as (standard error of the estimate/estimate) × 100.

b Statistics from 1,000 bootstrap analyses.

c σ, additive residual variability estimate; ω, interindividual variability estimate.

The data presented in Fig. 2 (ii) Visual predictive check. The data presented in Fig. 2 confirm that the average prediction matches the observed concentration-time courses and that the variability is reasonably estimated. Thus, 169 of 183 observed points (92.3%) fell within the 90% prediction interval. However, ISV seems to be overpredicted at 6 and 12 h; this could be due to a patient who had very low CL, for whom concentrations just before drug intake were very high (0.79 mg/liter).

Drug concentrations in children and link with effects. Table 3 shows the $C_{\text{max}}$ of ddI for the children, the time to reach $C_{\text{max}}$ ($T_{\text{max}}$), the AUC, and the elimination half life ($t_{1/2}$) (median values derived from estimated individual pharmacokinetic parameters) compared with corresponding data from previous studies. For the present study, medians and interquartile ranges were chosen to describe the parameters because one patient had an extremely low CL, greatly influencing the means of CL, AUC, and $t_{1/2}$.

The treatment of two patients was changed before the end of the year of treatment, so they were excluded from the concentration-efficacy analysis. Both the viral load at baseline and that after 12 months of treatment were available for 44 of the 47 children. The viral load decreased significantly after 12 months of treatment from a median (minimum to maximum) value of 5.5 (4.6 to 6.7) log₁₀ copies/ml to 2.5 (2.5 to 5.7) log₁₀ copies/ml ($P < 10^{−4}$). This significant decrease in the HIV-1 RNA level was significantly correlated with the ddI AUC ($P = 0.004$) and with the ddI $C_{\text{max}}$ ($P = 0.02$) (Fig. 3). These relationships were obtained using the maximal viral load for undetectability (i.e., 2.48 log₁₀ copies/ml after 1 year of treatment), so if the real viral load of the patient had been used, the relationship would have been even more significant. As shown in Fig. 3, a $C_{\text{max}}$ of 0.45 mg/liter and an AUC of 0.60 mg/liter · h were the most discriminative pharmacokinetic parameters that significantly improved viral load. Thus, the difference in viral load was 3.0 log₁₀ copies/ml for children with values over these targets compared to 2.4 log₁₀ copies/ml for those below these targets ($P = 0.01$ for $C_{\text{max}}$; $P = 0.03$ for AUC). Doses were simulated for each of the 49 children of the database with individual parameters. The threshold AUC was reached for 55% of the children with the study’s ddI doses (164 to 313 mg/m²), for 65% with a 240-mg/m² dose, and for 74% with a 360-mg/m² dose. The dose of 360 mg/m² administered once daily as tablets seems to be the most appropriate dosage for efficacy. This proposed dose adjustment was evaluated by calculating the probability of reaching the AUC of 0.60 mg/liter · h for 49,000 children (1,000 simulations of our 49 children) with different doses. This
probability was 59% with a 240-mg/m² dose and 71% with a 360-mg/m² dose of ddI. Administering a ddI dose higher than 360 mg/m² would not increase this percentage very much (Fig. 4). Finally, among the 44 children studied in the pharmacodynamic analysis, 4 developed viral resistance to ddI, and their drugs were changed after the first year of treatment; all of these children had AUCs of <0.60 mg/liter·h and $C_{\text{max}}$s of <0.45 mg/liter at week 2. During the first year of follow-up of this trial, there were only four adverse experiences that have been considered possibly related to drug effects: one incident of pruritis, one increase in pancreatic enzyme levels, and two increases in liver enzyme levels. These four effects were of short duration and transitory, and the children again underwent the same treatment after the resolution of the adverse experiences. No child experienced pancreatitis.

**DISCUSSION**

This paper describes the pharmacokinetics of ddI in association with EFV and 3TC. No pharmacokinetic interaction between these drugs has previously been shown in the literature (27). ddI concentrations were satisfactorily described by a one-compartment model with first-order elimination. This model has already been used for children (1, 14, 32) to describe the concentration-time course of ddI. Since no pharmacokinetic sample was obtained during the absorption phase, first-order absorption was fixed to different values, as previously published (14). When the $k_a$ was successively fixed to 1, 2, 3, 4, and 5 h⁻¹, ddI CL did not change and the mean population predicted $C_{\text{max}}$ was quite constant; only $V$ varied, modifying the $T_{\text{max}}$. To obtain a $T_{\text{max}}$ close to 0.5 h, as previously reported (1, 4, 14, 32), $k_a$ was fixed to 4 h⁻¹.

The $t_{1/2}$ (0.84 h) was consistent with values reported previously for children and adults (0.5 to 1.9 h) (1, 4, 14, 18, 28, 32). The CL/F and $V/F$ of ddI were both higher in our study than in previous studies performed with children: 300.4 liters/h/m² and 393.8 liters/m² respectively, in our study compared with 110.6 liters/h/m² and 213.7 liters/m² in the study of King et al. (20) and 152.5 liters/h/m² and 181.5 liters/m² ($V/F = t_{1/2} \times CL/F/\ln 2$) in the study of Stevens et al. (32). In these three studies, median ages were similar but drug formulations differed. The bioavailability ($F$) could be higher for enteric coated ddI and reconstituted ddI powder taken with an antacid than for ddI tablets, leading to lower CL/F and $V/F$ values. This is in agreement with the study of Hartman et al. (16), reporting a bioavailability around 41% (±7%) when ddI was given to fasting patients as an oral solution (or reconstituted powder) with an antacid, 36% (±5%) for enteric coated ddI, and only 25% (±5%) for buffered tablets. An estimated 10% of ddI administered orally is degraded every 2 min in the stomach (for pH ≤3.0). Since the transit time through the stomach should be shorter for the powder formulation than for the tablet, the bioavailability of the tablet could be lower than that of the powder. In our study, the increase in CL/F and $V/F$ led to lower $C_{\text{max}}$s and AUCs than in previous studies: $C_{\text{max}}$ was 0.35 mg/liter in our study compared to 0.75 mg/liter (20) and 0.80 mg/liter (32), and AUC was 0.61 mg/liter·h in our study compared to 2.10 mg/liter·h (20) and 1.49 mg/liter·h (32). In addition to the formulation, the variability of bioavailability within and between patients should be considered. No data were found for within-patient variability. However, for 31 children who were administered ddI powder, Balis et al. (4) found that the fraction of the oral dose absorbed was 19% ± 17% (mean ± standard deviation), with a considerable range from 2% to 89%. We did not find data on tablets, but we can suppose even less reliable absorption for the tablets than for powder. In most studies performed with children, ddI was administered as a pediatric powder for oral solution or as an enteric coated formulation, but these formulations were not available at the CAMEG; only chewable/dispersible tablets
were available. This is the first study reporting ddI pharmacokinetics in children after once-daily administration of Videx tablets.

The population model was also used to separate out the effect of growth (body surface area or body weight) and maturation (age) on pharmacokinetic parameters. No effect of body surface area, body weight, or age could be demonstrated here. This may be due to ages of the children (none under the age of 2.5 years) and to the moderate-size data set, which may not allow significance testing of covariates (30). Since no effect of the duration of treatment on clearance could be demonstrated in our model and since we could not find any data in the literature suggesting it, we assumed that clearance of ddI does not change systematically or notably over 12 months in the pediatric patient group.

Since the $t_{1/2}$ of ddI was short (0.84 h), in agreement with values previously reported for children and adults (0.5 to 1.9 h) (1, 4, 14, 18, 28, 32), and no interaction between ddI, EFV, and 3TC was evidenced (27), we considered that the pharmacokinetics of ddI in this drug combination has essentially achieved steady state after 2 weeks of treatment. For the 44 children of the BURKINAM-ANRS 12103 study, the decrease in viral load after 12 months of treatment was significantly correlated with the AUC ($P = 0.004$) and $C_{\text{max}}$ ($P = 0.02$) of ddI. A link between concentrations and efficacy after 6 months of treatment has been already reported in two previous studies. Balis et al. and Butler et al. reported that, among 26 patients with baseline p24 antigen levels of $>$100 pg/ml, the 11 children with undetectable p24 levels at 20 to 24 weeks of therapy had significantly higher ddI AUCs than the 15 children with detectable p24 levels (4, 7). Fletcher et al. reported for nine children that the $\log_{10}$ change in plasma HIV-1 RNA levels from baseline to week 24 of therapy was inversely related to the AUC of ddI and that the seven (out of nine) children with AUCs from 0 to 12 h of $>0.6$ mg/liter had $\geq 1 \log_{10}$ drop in their HIV-1 RNA levels (14). No pharmacokinetic-pharmacodynamic model could be found for ddI.

Since the $t_{1/2}$ of ddI is very short (0.84 h), only 5 out of 67 concentrations measured at 12 or 24 h were greater than the limit of quantification. Among these five concentrations, one was very high at 24 h (0.79 mg/liter), the 11 children with undetectable p24 levels at 20 to 24 weeks of therapy had significantly higher ddI AUCs than the 15 children with detectable p24 levels (4, 7). Fletcher et al. reported for nine children that the $\log_{10}$ change in plasma HIV-1 RNA levels from baseline to week 24 of therapy was inversely related to the AUC of ddI and that the seven (out of nine) children with AUCs from 0 to 12 h of $>0.6$ mg/liter had $\geq 1 \log_{10}$ drop in their HIV-1 RNA levels (14). No pharmacokinetic-pharmacodynamic model could be found for ddI.

Since the $t_{1/2}$ of ddI is very short (0.84 h), only 5 out of 67 concentrations measured at 12 or 24 h were greater than the limit of quantification. Among these five concentrations, one was very high at 24 h (0.79 mg/liter). The misfits at low ddI concentrations, observed in Fig. 1, come from the biased estimation of the concentrations measured 12 or 24 h after drug intake. VPC (visual predictive check) curves (Fig. 2) confirm the overprediction of the concentrations during the terminal elimination phase. Our model should be used very cautiously to predict trough concentrations and times above the 50% effective concentration; thus, no conclusion was drawn with regard to minimal concentrations. In our study, an AUC of $>0.60$ mg/liter $\cdot$ h (and a $C_{\text{max}}$ of $>0.45$ mg/liter) at week 2 (or month 2 to 5) of treatment was also significantly associated with a viral load decrease after 1 year of treatment: decreases in viral loads were around $3 \log_{10}$ copies/ml for children above these target values compared to $2.4 \log_{10}$ copies/ml for those below. Moreover, the four children who developed viral resistance to ddI had AUCs of $<0.60$ mg/liter $\cdot$ h and $C_{\text{max}}$ of $<0.45$ mg/liter at week 2. These relationships indicate that low ddI concentrations at the beginning of treatment may lead to a decrease in efficacy after 1 year of treatment and to the selection of resistant viral populations. A first approach could be to...
adapt the children’s ddI dose after 2 weeks of treatment in order to obtain a ddI concentration higher than 0.45 mg/liter 30 min after drug intake. Another approach is to increase doses so that a higher percentage of children would reach an AUC of $0.60 \text{ mg/liter} \cdot \text{h}$. However, since the study included almost no observations during the rapid absorption phase, the $C_{\text{max}}$ estimates are likely less precise than the AUC estimates. This is a limitation of the statistical conclusions and $P$ values for $C_{\text{max}}$; dose simulations were thus based only on AUCs. Using individual pharmacokinetic parameters, among the 49 children in the database, 65% of those receiving a 240-mg/m² ddI dose and 74% of those receiving 360 mg/m² ddI would reach the target AUC of $0.60 \text{ mg/liter} \cdot \text{h}$. When the proposed ddI dose of 360 mg/m² was evaluated (by 1,000 simulations of our 49 children), 71% of the 49,000 children in the simulation reached the target AUC. Assuming that the bioavailability fraction will be constant after the administration of 240 or 360 mg/m² of ddI, 360 mg/m² should be a more appropriate dose to improve efficacy than 240 mg/m². This assumption should be discussed, because a higher drug dose could lead to a greater extent of degradation prior to absorption. In the literature, we could not find data on this dose level. For lower doses, Abreu et al. compared the bioavailability of ddI at 180 mg/m² and 90 mg/m² in 24 children with advanced HIV infection and found a relative bioavailability of $0.95 \pm 0.49$ between these two doses (1). Balis et al. found that the fraction of the ddI dose absorbed was nonsignificantly lower at the higher dose (27% at 20 to 60 mg/m² versus 15% at 90 to 120 mg/m²) (4). Since no child had adverse events linked to ddI in this study, we cannot predict whether the dose of 360 mg/m² would increase the incidence of such events.

In conclusion, this is the first study reporting ddI pharmacokinetics in children after once-daily administration of Videx tablets. The $t_{1/2}$ (0.84 h) was consistent with previously reported values. However, the $V/F$ and $CL/F$ were increased. This may be attributed to a lower bioavailability with tablets than with other formulations. A ddI AUC of $>0.60 \text{ mg/liter} \cdot \text{h}$ (and a $C_{\text{max}}$ of $>0.45 \text{ mg/liter}$) at week 2 of treatment was significantly associated with a decrease in the viral load after 1 year of treatment.

ACKNOWLEDGMENTS

We acknowledge the French “Agence Nationale de Recherche contre le VIH/SIDA et les hépatites virales” (ANRS) for sponsoring the trial.

We also thank the children of the study and their parents.

REFERENCES

based approaches to handling data below the quantification limit using NONMEM VI. J. Pharmacokinet. Pharmacodyn. 35:401–421.


