

## Pharmacokinetics of Lamivudine in Human Immunodeficiency Virus-Infected Patients with Renal Dysfunction

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The purpose of this study was to determine the safety and pharmacokinetics of lamivudine (3TC), a nucleoside analog that has shown potent *in vitro* and recent *in vivo* activity against human immunodeficiency virus. Sixteen human immunodeficiency virus-infected patients, six with normal renal function (creatinine clearance [ $CL_{CR}$ ],  $\geq 60$  ml/min), four with moderate renal impairment ( $CL_{CR}$ , 10 to 40 ml/min), and six with severe renal impairment ( $CL_{CR}$ ,  $< 10$  ml/min), were enrolled in the study. After an overnight fast, patients were administered 300 mg of 3TC orally. Blood was obtained before 3TC administration and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 32, 40, and 48 h afterward. Timed urine collections were performed for patients able to produce urine. Serum and urine were assayed for 3TC by reverse-phase high-performance liquid chromatography with UV detection. Pharmacokinetic parameters were calculated by using standard noncompartmental techniques. The peak concentration of 3TC increased with decreasing renal function; geometric means were 2,524, 3,538, and 5,684 ng/ml for patients with normal renal function, moderate renal impairment, and severe renal impairment, respectively. The terminal half-life also increased with decreasing renal function; geometric means were 11.5, 14.1, and 20.7 h for patients with normal renal function, moderate renal impairment, and severe renal impairment, respectively. Both oral and renal clearances were linearly correlated with  $CL_{CR}$ . A 300-mg dose of 3TC was well tolerated by all three patient groups. The pharmacokinetics of 3TC is profoundly affected by impaired renal function. Dosage adjustment, by either dose reduction or lengthening of the dosing interval, is warranted.

Lamivudine (3TC) is a cytosine dideoxynucleoside analog that has shown potent *in vitro* activity against human immunodeficiency virus (HIV) by inhibiting reverse transcriptase (3, 18, 19). The mechanism of action is similar to that of other proven reverse transcriptase inhibitors, such as zidovudine, didanosine, and zalcitabine, but there is little inhibition of mammalian DNA polymerases, and therefore treatment with 3TC may not result in the peripheral neuropathy associated with didanosine and zalcitabine (8). Phase I-II trials of 3TC monotherapy have demonstrated antiretroviral activity and an excellent safety profile (14, 21). Preliminary results of phase III trials (1, 5, 11, 20) have shown that 3TC in combination with zidovudine effectively decreases the viral burden as measured by HIV RNA PCR and increases CD4<sup>+</sup> lymphocyte counts.

The bioavailability and pharmacokinetics of 3TC have been determined over the dose range of 0.25 to 20 mg/kg in HIV-infected, asymptomatic patients with normal renal function (22). Single doses (0.25, 1.0, 2.0, 4.0, and 8.0 mg/kg) were administered as an intravenous infusion (over 1 h) followed 2 to 3 days later by administration orally as a capsule formulation to four patients at each dose level. Following oral administration, 3TC was rapidly absorbed, with a mean time to maximum serum concentration of 1 h. The mean absolute bioavailability was 82%. Approximately 70% of the oral dose was excreted as the unchanged drug in the urine. The disposition of 3TC is therefore expected to be altered in patients with renal insufficiency, resulting in systemic concentrations higher than those in patients with normal renal function.

Renal insufficiency is becoming increasingly common in HIV-infected patients (2, 16). The etiology of renal insufficiency is diverse. HIV-associated nephropathy can cause heavy proteinuria, nephrotic syndrome, and rapidly progressive renal failure in some patients (10, 17). Acute renal failure can result from nephrotoxic drugs, sepsis, dehydration, and systemic infection. Renal insufficiency can also result from concomitant systemic medical diseases such as hypertension and diabetes, as well as a heterogeneous collection of glomerular, tubulointerstitial, and vascular diseases from other, incidental processes (6). Given the increasing numbers of HIV-infected patients with renal insufficiency, the pharmacokinetics and safety profiles of renally excreted medications are of utmost importance in this patient population to guide dosing recommendations.

### MATERIALS AND METHODS

**Patient population.** HIV-infected study subjects were recruited from the Raleigh-Durham area of North Carolina by contacting local HIV care providers. Most of our subjects were recruited from the Duke Infectious Diseases Clinic. Patients were stratified according to renal function by using the Cockcroft-Gault equation (4) to estimate creatinine clearance ( $CL_{CR}$ ). The normal renal function group consisted of six patients with a  $CL_{CR}$  of  $\geq 60$  ml/min, the moderate renal impairment group consisted of four patients with a  $CL_{CR}$  of 10 to 40 ml/min, and the severe renal impairment group consisted of six patients with a  $CL_{CR}$  of  $< 10$  ml/min on dialysis therapy. All patients had to have documented HIV infection, be  $\geq 18$  years old, have a minimum body weight (males,  $\geq 50$  kg; females,  $\geq 41$  kg), and be able to give written, informed consent. Patients with normal renal function were eligible for the study if they had  $\geq 200$  CD4<sup>+</sup> lymphocytes/mm<sup>3</sup>, were at Centers for Disease Control and Prevention clinical stage A or B, and were able to discontinue all medication 7 days prior to and during the study period. Other entry criteria for patients with normal renal function included a hemoglobin concentration of  $\geq 11.0$  mg%; an absolute neutrophil count of  $\geq 1,500$ /mm<sup>3</sup>; a platelet count of  $\geq 75,000$ /mm<sup>3</sup>; serum bilirubin, serum alanine aminotransferase, and serum aspartate aminotransferase levels of less than twice the upper limit of normal; and a normal serum lipase level.

Patients with moderate or severe renal impairment had no restrictions of

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TABLE 1. Patient characteristics

Parameter	Normal renal function <sup>a</sup>	Moderate renal impairment <sup>b</sup>	Severe renal impairment <sup>c</sup>
No. of subjects	6	4	6
Mean (range) age (yr)	33 (29–41)	50 (29–68)	41 (31–51)
Gender distribution			
No. of males	6	3	5
No. of females	0	1	1
Ethnic origin			
No. of African Americans	1	4	6
No. of Caucasians	4	0	0
No. of Asian-Caucasians	1	0	0
CDC <sup>d</sup> classification			
Stage A	4	1	3
Stage B	2	0	2
Stage C	0	3	1
Median (range) no. of CD4 <sup>+</sup> cells/mm <sup>3</sup>	402 (239–512)	46 (7–631)	134 (33–498)
Smoking status			
No. of smokers	3	1	4
No. of nonsmokers	3	3	2
Mean CL <sub>CR</sub> ± SD (ml/min) <sup>e</sup>	110.8 ± 13.6	27.5 ± 7.8	5.8 ± 2.1
Coefficient of variation	12.2	28.2	36.6

<sup>a</sup> CL<sub>CR</sub> ≥ 60 ml/min.

<sup>b</sup> CL<sub>CR</sub>, 10 to 40 ml/min.

<sup>c</sup> CL<sub>CR</sub> < 10 ml/min.

<sup>d</sup> CDC, Centers for Disease Control and Prevention.

<sup>e</sup> Estimated by the Cockcroft-Gault equation.

CD4<sup>+</sup> cell count or Centers for Disease Control and Prevention clinical stage but were required to discontinue trimethoprim-sulfamethoxazole and antiretroviral agents 7 days prior to the study period and other concomitant medications 48 h prior to dosing. Select medications were continued during the study period at the discretion of the study sponsor, provided there was no evidence of interference with the elimination of 3TC. Additional entry criteria for patients with moderate or severe renal impairment included a hemoglobin concentration of ≥ 7.0 mg%; an absolute neutrophil count of ≥ 750/mm<sup>3</sup>; a platelet count of ≥ 50,000/mm<sup>3</sup>; a serum bilirubin level of less than twice the upper limit of normal; serum alanine aminotransferase and serum aspartate aminotransferase levels of less than five times the upper limit of normal; and a normal serum lipase level. The characteristics of all of the study subjects are summarized in Table 1.

**Study design.** This was an open-label, parallel, single-center, single-dose study designed to study the pharmacokinetics and safety of 3TC in renally impaired, HIV-infected patients. After outpatient screening, subjects were admitted to the Clinical Research Unit of Duke University Medical Center for pharmacokinetic study. Subjects were administered a 300-mg tablet of 3TC orally with 200 ml of water after an overnight fast. The patient's usual diet was resumed 4 h after dosing, although foods and beverages containing xanthines (e.g., coffee, tea, cola, etc.) and alcoholic beverages were not allowed 10 h prior to dosing until 24 h postdosing. Patients were not allowed to smoke tobacco products from 4 h before dosing until 4 h postdosing. Patients with severe renal impairment on dialysis therapy were studied off dialysis. Patients on hemodialysis (*n* = 3) were dialyzed the day prior to dosing and immediately after the 48 h pharmacokinetic sampling period. Patients on peritoneal dialysis (*n* = 3) drained their peritoneal dialysate 2 h prior to dosing and reinstalled dialysate fluid immediately following the conclusion of pharmacokinetic sampling. The study protocol was approved by the Investigational Review Board of Duke University Medical Center.

Patients remained in the Clinical Research Unit until 48 h after dosing. Patients were questioned and examined daily for occurrence of adverse events. Vital signs were carefully monitored, and routine laboratory test results were obtained daily. Blood for pharmacokinetic study was obtained predosing and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 32, and 48 h after dosing. Timed urine collections were performed for patients able to produce urine 0 to 4, 4 to 8, 8 to 12, 12 to 16, 16 to 24, and 24 to 48 h after dosing. Blood was processed,

and the serum was frozen at -20°C until assay. Aliquots of urine were frozen at -20°C until assay. Serum and urine were assayed for 3TC by reverse-phase high-performance liquid chromatography with UV detection. The 3TC serum assay used was linear between 10 and 5,000 ng/ml. The lower limit of quantitation was 10 ng/ml. The interday coefficients of variation were 1.3% at 3,500 ng/ml and 10.8% at 25 ng/ml (7). The 3TC urine assay used was linear between 0.5 and 500 µg/ml. The lower limit of quantitation was 0.5 µg/ml. The interday coefficients of variation were 0.51% at 375 µg/ml and 7.7% at 1.5 µg/ml (13).

**Pharmacokinetic analysis.** The maximum drug concentration in serum (*C*<sub>max</sub>) and the time to *C*<sub>max</sub> were obtained directly from the concentration-time data. The terminal rate constant (*t*<sub>1/2</sub>) was estimated by linear regression of logarithmic transformed concentration-versus-time data. The area under the concentration-time curve (AUC<sub>∞</sub>) was calculated by conventional linear trapezoidal methods with log-linear extrapolation to infinity. Total recovery of the unchanged drug in urine up to 48 h (*Ae*<sub>48</sub>) was calculated from the urine volumes of the collection intervals up to time *t* and the associated drug concentrations in urine. Renal clearance (CL<sub>CR</sub>) was calculated as follows: CL<sub>CR</sub> = *Ae*<sub>48</sub>/AUC<sub>48</sub>. Oral serum clearance (CL<sub>O</sub>) was calculated as dose/AUC<sub>∞</sub>. The fraction of the dose excreted unchanged in the urine was calculated as *Ae*<sub>48</sub>/dose.

**Safety.** Safety was evaluated by monitoring adverse events and vital signs, by physical examinations, by clinical laboratory tests, and by electrocardiograms. Each patient was questioned periodically throughout the study regarding possible adverse effects. All adverse experiences that occurred from screening until completion of the study were recorded as adverse events, regardless of their potential relationship to receipt of the study drug. The date, time of onset after administration of the study drug, severity (mild, moderate, or severe), duration, and potential relationship to receipt of the study drug (unrelated or possibly, probably, or almost certainly related) of adverse events were recorded.

**Statistical considerations.** A group size of six would have a 75% power to detect a 50% difference between groups assuming a 30% coefficient of variation between patients. On the basis of expected changes in 3TC pharmacokinetics with renal dysfunction, a 50% difference in AUC<sub>∞</sub> (drug clearance) between patients with normal renal function and those with moderate impairment was expected. A larger difference between patients with normal renal function and those with severe impairment was expected.

The means and standard deviations of *C*<sub>max</sub>, the time to *C*<sub>max</sub>, and AUC<sub>∞</sub> were determined for the three patient groups. Comparison between groups was performed by using the two-sample *t* test. Because the hypothesis of homogeneous variances was not rejected, data from all three groups were pooled and analysis of variance was used for comparisons between groups.

## RESULTS

**Pharmacokinetic analysis.** As shown in Fig. 1, median serum concentration-time profiles were distinct in the three groups of patients. In patients with normal renal function, 3TC concentrations rose quickly, reached a maximum (geometric mean, 2,524 ng/ml) at approximately 1 h, and decayed in a biexponential fashion. In patients with moderately impaired renal function, 3TC concentrations also rose quickly, reaching a higher *C*<sub>max</sub> (3,538 ng/ml) at approximately 1 h. The decay of 3TC concentrations was slower in moderately impaired patients than in patients with normal renal function and occurred in a monoexponential fashion. In patients with severe renal

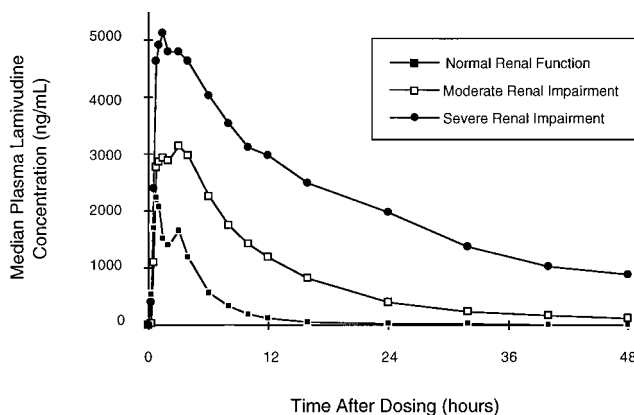


FIG. 1. Median 3TC concentration-time curves for patients with normal renal function, moderate renal impairment, and severe renal impairment.

TABLE 2. Pharmacokinetic data

Parameter	Normal renal function <sup>a</sup>	Moderate renal impairment <sup>b</sup>	Severe renal impairment <sup>c</sup>
AUC <sub>∞</sub> (ng · h/ml)			
Median (range)	11,249 (8,905–13,194)	40,126 (36,014–75,670)	129,109 (105,061–305,536)
Geometric mean (95% CI)	10,891 (8,327–14,244)	45,655 (32,864–63,425)	146,482 (111,999–191,581)
C <sub>max</sub> (ng/ml)			
Median (range)	2,355 (2,200–3,340)	3,295 (3,050–4,730)	5,335 (4,800–7,760)
Geometric mean (95% CI)	2,524 (2,144–2,971)	3,538 (2,896–4,321)	5,684 (4,828–6,692)
t <sub>1/2</sub> (h)			
Median (range)	11.2 (8.0–17.6)	13.6 (11.5–18.6)	19.4 (15.0–34.6)
Geometric mean (95% CI)	11.5 (9.0–14.6)	14.1 (10.5–19.0)	20.7 (16.3–26.4)
CL <sub>O</sub> (ml/min)			
Median (range)	446 (379–562)	126 (66–139)	39 (16–48)
Geometric mean (95% CI)	459 (349–603)	109 (78–153)	34 (26–45)
CL <sub>R</sub> (ml/min)			
Median (range)	364 (264–388)	48 (25–70)	1.8
Geometric mean (95% CI)	339 (244–469)	43 (29–64)	1.8
Volume of distribution (liters)			
Median (range)	145 (121–279)	109 (64–128)	63 (46–74)
Geometric mean (range)	164 (126–215)	99 (74–134)	61 (54–70)
Ae <sub>48</sub> <sup>d</sup> (%)			
Median (range)	72 (65–82)	40 (25–49)	Not done
Geometric mean (range)	73 (67–79)	37 (28–50)	Not done

<sup>a</sup> CL<sub>CR</sub>, ≥60 ml/min.<sup>b</sup> CL<sub>CR</sub>, 10 to 40 ml/min.<sup>c</sup> CL<sub>CR</sub>, <10 ml/min.<sup>d</sup> Ae<sub>48</sub>, total recovery of drug in urine up to 48 h.

impairment, 3TC concentrations rose to a much higher C<sub>max</sub> (5,684 ng/ml) at approximately 2 h and decayed at a slower rate with apparent monoexponential kinetics. The geometric mean of C<sub>max</sub> for patients with moderate renal impairment was significantly higher than that for patients with normal renal function (ratio, 1.4; 95% confidence interval [CI], 1.13 to 1.73; *P* = 0.014). The geometric mean of C<sub>max</sub> for patients with severe renal impairment was also significantly higher than that for those with normal renal function (ratio, 2.25; 90% CI, 1.86 to 2.72; *P* < 0.0001).

Renal excretion of 3TC was measured in patients capable of producing urine. In patients with normal renal function, at least half of the 3TC was excreted in the urine during the first 4 h, whereas 3TC excretion in patients with moderately impaired renal function was slower. Of the patients with severe renal impairment, only one produced sufficient urine for analysis of 3TC concentrations.

Pharmacokinetic parameters are listed in Table 2. Geometric mean AUC<sub>∞</sub> values (and 95% CIs) were 10,891 (8,327 to 14,244) ng · h/ml for patients with normal renal function, 45,655 (32,864 to 63,425) ng · h/ml for moderately impaired patients, and 146,482 (111,999 to 191,581) ng · h/ml for patients with severe renal impairment. Geometric t<sub>1/2</sub> values (and 95% CIs) were 11.5 (9.0 to 14.6) h for patients with normal renal function, 14.1 (10.5 to 19.0) h for moderately renally impaired patients, and 20.7 (16.3 to 26.4) h for patients with severe renal impairment. Geometric mean CL<sub>O</sub> values (and 95% CIs) were 459 (349 to 603) ml/min for patients with normal renal function, 109 (78 to 153) ml/min for moderately impaired patients, and 34 (26 to 45) ml/min for patients for severe renal impairment. CL<sub>R</sub> was calculated for patients producing urine. Geometric mean CL<sub>R</sub> values (and 95% CIs) were

339 (244 to 469) ml/min for patients with normal renal function and 43 (29 to 64) ml/min for patients with moderate renal impairment. Statistical analysis of pharmacokinetic parameters is summarized in Table 3. All pharmacokinetic parameters were statistically significantly different when patients with se-

TABLE 3. Statistical analysis of log-transformed pharmacokinetic parameters

Parameter and severity ratio estimated	Estimate <sup>a</sup>	90% CI	<i>P</i> value
AUC <sub>∞</sub>			
Moderate/normal	4.19	2.96–5.94	<0.0001
Severe/normal	13.45	9.85–18.36	<0.0001
C <sub>max</sub>			
Moderate/normal	1.40	1.13–1.73	0.014
Severe/normal	2.25	1.86–2.72	<0.0001
t <sub>1/2</sub>			
Moderate/normal	1.23	0.90–1.68	0.27
Severe/normal	1.80	1.36–2.39	0.0026
CL <sub>O</sub>			
Moderate/normal	0.24	0.17–0.34	<0.0001
Severe/normal	0.07	0.05–0.10	<0.0001
CL <sub>R</sub>			
Moderate/normal	0.13	0.08–0.19	<0.0001
Severe/normal	0.01	0.003–0.01	<0.0001

<sup>a</sup> Estimates are ratios based on geometric least-square means.

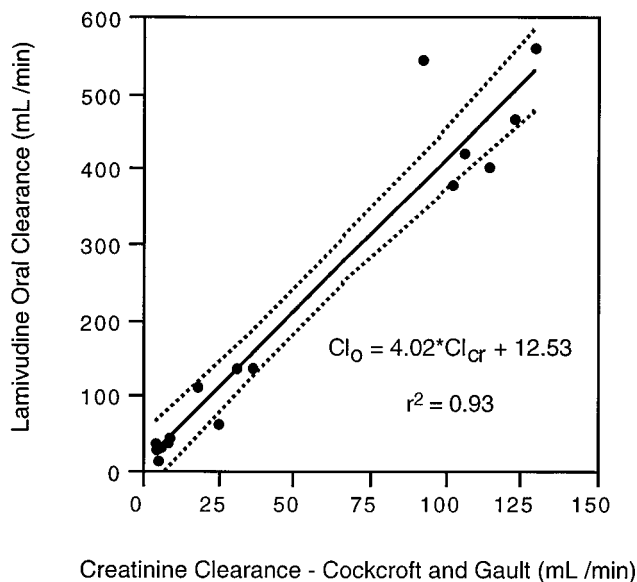


FIG. 2.  $Cl_O$  versus  $Cl_{CR}$  for 3TC determined with the Cockcroft-Gault equation.

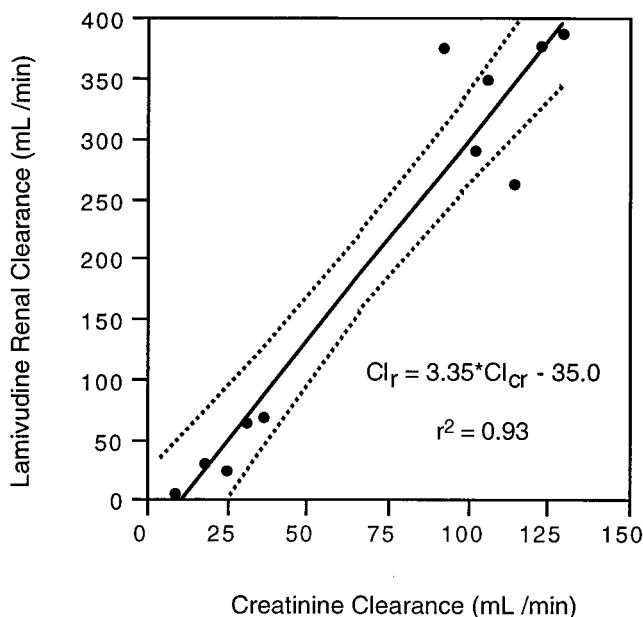


FIG. 4.  $Cl_R$  versus  $Cl_{CR}$  for 3TC.

vere renal impairment were compared with patients with normal renal function. With the exception of  $t_{1/2}$ , all pharmacokinetic parameters were statistically significantly different when patients with moderate renal impairment were compared with patients with normal renal function.

The relationship between  $Cl_O$  and renal function as determined by  $Cl_{CR}$  by using the Cockcroft-Gault equation is illustrated in Fig. 2. A linear relationship between  $Cl_O$  and  $Cl_{CR}$  can be described by the equation  $Cl_O$  (in milliliters per minute) =  $4.02 \cdot Cl_{CR} + 12.5$  ( $r^2 = 0.93$ ). In patients whose  $Cl_{CR}$  had been measured by urine collection, the following relationship was determined between  $Cl_O$  and  $Cl_{CR}$ :  $Cl_O$  (in milliliter per minute) =  $3.5 \cdot Cl_{CR} + 26.4$  ( $r^2 = 0.95$ ). The results are illustrated in Fig. 3. Only clinically nonsignificant

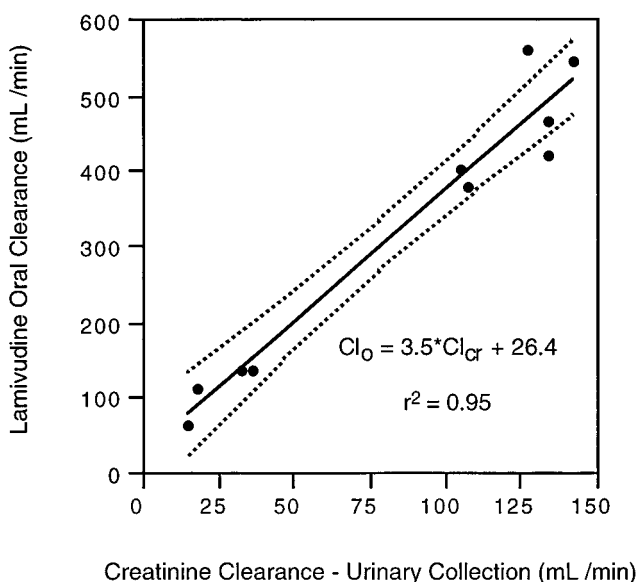


FIG. 3.  $Cl_O$  versus  $Cl_{CR}$  for 3TC on the basis of measured creatinine in collected urine.

differences were observed between the relationships derived from the estimated  $Cl_{CR}$  (from the Cockcroft-Gault equation) and the measured  $Cl_{CR}$ .

The relationship between  $Cl_R$  and renal function as determined by  $Cl_{CR}$  estimation with the Cockcroft-Gault equation is illustrated in Fig. 4. A linear relationship between  $Cl_R$  and  $Cl_{CR}$  can be described by the equation  $Cl_R$  (in milliliters per minute) =  $3.35 \cdot Cl_{CR} - 35.0$  ( $r^2 = 0.93$ ). The linear model used to describe the relationship between  $Cl_R$  of 3TC and  $Cl_{CR}$  demonstrates some model misspecification with a negative intercept of  $-35$ . However, because of the practical constraints in assessing  $Cl_R$  in end stage renal dysfunction patients who produce little or no measurable urine, further refinement in the relationship to more complex mathematical models is not practical.

**Safety profile.** A single 300-mg dose of 3TC was well tolerated by renally impaired patients, similar to patients with normal renal function. No serious adverse events, deaths, or withdrawals of patients due to adverse events occurred. No drug-related adverse events occurred during the study.

## DISCUSSION

3TC is a promising antiretroviral agent (1, 5, 11, 20). The pharmacokinetics of 3TC in HIV-infected patients with normal renal function has been previously described (9, 12, 14, 15, 22, 23). Approximately 70% of the administered dose is excreted unchanged in the urine in a 24-h period (22). As renal insufficiency is an increasingly common problem in HIV-infected patients (2, 16), investigation of pharmacokinetics in patients with renal insufficiency is warranted. The results of the current study characterize the pharmacokinetic changes of 3TC observed in patients with various degrees of renal dysfunction.

The results of the pharmacokinetic analysis of patients with normal renal function are similar to those observed in previous studies (9, 12, 14, 15, 22, 23), with the exception of  $t_{1/2}$ . The  $t_{1/2}$  in patients with normal renal function ( $Cl_{CR} > 60$  ml/min) ranged from 8 to 17.6 h. Previous studies have noted  $t_{1/2}$  estimates ranging from 2 to 7 h (9, 12, 14, 15, 22, 23). The longer

$t_{1/2}$  estimates observed in the current study are likely due to differences in blood sampling. Shorter  $t_{1/2}$  estimates of 2 to 4 h have been observed in very early studies (22, 23) of 3TC and in studies with blood sampling only up to 12 h (14). More typically,  $t_{1/2}$  estimates in the range of 5 to 7 h are observed in studies with blood sampling up to 24 h (9, 12, 15, 23). These values are clinically relevant estimates, as they predict observed drug accumulation upon multiple dosing. The longer  $t_{1/2}$  estimates (geometric mean, 11.5 h with normal renal function) obtained in the current study reflect the longer blood sampling time of up to 48 h. These longer  $t_{1/2}$  estimates likely describe elimination from a slowly equilibrating compartment. Only a small portion of the AUC is described by this  $t_{1/2}$ . Thus, it is unlikely to be significant in describing the efficacy or toxicity of 3TC.

Renal dysfunction appears to have significant effect on the pharmacokinetics of 3TC, resulting in large increases in  $AUC_{\infty}$  of 419% in patients with moderate renal impairment ( $CL_{CR}$ , 10 to 40 ml/min) and 1,344% in patients with severe renal impairment ( $CL_{CR}$ , <10 ml/min). A linear relationship between both  $CL_O$  and  $CL_R$  and  $CL_{CR}$  as a measure of glomerular filtration has been observed (Fig. 2 and 4):  $CL_O$  (in milliliters per minute) =  $4.02 \cdot CL_{CR} + 12.5$  ( $r^2 = 0.93$ ) and  $CL_R$  (in milliliters per minute) =  $3.35 \cdot CL_{CR} - 35.0$  ( $r^2 = 0.93$ ). Thus,  $CL_{CR}$  accounts for ~93% of the variability in both  $CL_O$  and  $CL_R$  3TC. These relationships are then useful for prediction of 3TC clearance and dosage adjustments in patients who have renal dysfunction. Consistent with the change in clearance are  $t_{1/2}$  values increased by 123 and 180% in patients with moderate and severe renal impairment, respectively.

Surprisingly,  $C_{max}$  values were also increased by renal dysfunction.  $C_{max}$  values were increased 140% in patients with moderate renal impairment and 225% in patients with severe renal impairment. The mechanism for the increase in  $C_{max}$  values is unclear. Previous studies have demonstrated an absolute bioavailability of approximately 85% (22, 23). Thus, it is unlikely that increased absorption could account for the increase in  $C_{max}$  observed. Likewise, protein binding is not a factor, as 3TC is bound <36% to plasma proteins (Epivir package insert). 3TC is highly soluble and is highly distributed throughout the body. It is likely that alteration in fluid balance in patients with moderate and severe renal impairment could decrease the apparent volume of distribution of 3TC, resulting in the observed  $C_{max}$  estimates.

A single 300-mg dose of 3TC was well tolerated by both renally impaired patients and patients with normal renal function. No serious adverse events, deaths, or withdrawals of patients due to adverse events occurred in the study. Although no formal statistical comparisons were performed because of the small number of patients, there appeared to be no difference in the safety profiles of 3TC in renally impaired patients and patients with normal renal function. However, the long-term safety profile of 3TC in renally impaired patients remains to be defined.

3TC exhibits linear pharmacokinetics, allowing extrapolation from single-dose to multiple-dose situations. On the basis of single-dose pharmacokinetic data obtained in this study and safety data, dosing recommendations for patients with renal impairment have been formulated (Table 4). Dosage reduction for renal insufficiency could be accomplished by altering either the dose size or dosing intervals. Dosage recommendations were based on the provision of no more than a doubling of the AUC over normal values. For simplicity of administration, daily doses of 3TC for patients with renal impairment were calculated. For patients with renal impairment or those with swallowing difficulties, an oral solution of 10 mg/ml will be

TABLE 4. 3TC dosing recommendations for patients with renal impairment<sup>a</sup>

Renal function ( $CL_{CR}$ , ml/min)	First dose (mg)	Maintenance dose (mg)	Interval <sup>b</sup>	Tablet wt (mg)	Solution vol (ml)
≥50	150	150	BID	150	15.0
30–49	150	150	QD	150	15.0
15–29	150	100	QD		10.0
5–14	150	50	QD		5.0
<5	50	25	QD		2.5

<sup>a</sup> Based on dosage recommended for combination therapy.

<sup>b</sup> BID, twice daily, QD once daily.

available. The standard dose of 3TC for patients with normal renal function on combination therapy is 150 mg twice daily. For patients with a  $CL_{CR}$  of 30 to 49 ml/min, this dose should be decreased to 150 mg daily. For patients with a  $CL_{CR}$  of 15 to 29 ml/min, the recommended regimen is a 150-mg loading dose followed by 100 mg daily. For patients with a  $CL_{CR}$  of 5 to 14 ml/min, the recommended regimen is a 150-mg loading dose followed by 50 mg daily. For patients with a  $CL_{CR}$  of <5 ml/min, the recommended regimen is a 50-mg loading dose followed by 25 mg daily.

In conclusion, the observed changes in 3TC pharmacokinetics in patients with renal dysfunction with decreasing  $CL_O$  and  $CL_R$  estimates, increasing  $AUC_{\infty}$ , and increasing  $C_{max}$  indicate that dosage adjustment is required for these patients. Since  $CL_{CR}$  accounts for a significant portion (93%) of the observed variability in 3TC clearance, the above-described linear relationship can be used to estimate individual 3TC clearance. Dosage adjustment could be accomplished by either dose reduction or lengthening of the dosing interval. Our recommendations for dosage adjustment are based primarily on adjustment of serum exposure of 3TC. The relationship of intracellular 3TC triphosphate, the presumed active moiety, and concentrations in serum remains to be defined in vivo. When such information is available, a modification of dosing recommendations may be necessary. As the number of renally impaired, HIV-infected patients increases, this information will be increasingly helpful in guiding 3TC therapy.

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