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Population Pharmacokinetics of Emtricitabine in HIV-1-Infected Adult Patients

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The aims of this study were to describe emtricitabine concentration-time courses in a large population of HIV-1-infected adults, to evaluate the influence of renal function on emtricitabine disposition, and to assess current dosing adjustment recommendations. Emtricitabine blood plasma concentrations were determined from samples collected from 161 adult patients during therapeutic drug monitoring and measured by liquid chromatography coupled to tandem mass spectrometry. The data were analyzed by a population approach. Emtricitabine pharmacokinetics was best described by a two-compartment model in which the absorption and distribution rate constants were assumed to be equal. Typical population parameter estimates (interindividual variability) were apparent elimination and intercompartmental clearances of 15.1 liters/h (17.4%) and 5.75 liters/h, respectively, and apparent central and peripheral volumes of distribution of 42.3 liters and 55.4 liters, respectively. The apparent elimination clearance was significantly related to creatinine clearance (CL_{CR}), reflecting renal function. For 200 mg once a day (QD), the median area under the concentration-time curve over 24 h (AUC_{0-24}) was 12.5 mg · h/liter for patients with normal renal function (CL_{CR}, >80 ml/min), 14.7 mg · h/liter for patients with mild renal impairment (CL_{CR}, 79 to 50 ml/min), and 17.9 mg · h/liter for patients with moderate renal impairment (CL_{CR}, 49 to 30 ml/min). Simulations of the recommended dosing schemes for the oral solid form of emtricitabine (i.e., 200 mg per 48 h according to renal function) led to lower emtricitabine exposures for patients with moderate renal impairment (median AUC_{0-48}, 17.2 mg · h/liter) than for patients with normal renal function (median AUC_{0-48}, 25.6 mg · h/liter). Administering 18 ml of emtricitabine oral solution (10 mg/ml) QD to patients with moderate renal impairment should yield emtricitabine exposures similar to those in patients with normal renal function.

Emtricitabine (FTC) is a potent nucleoside reverse transcriptase inhibitor (NRTI) widely used as part of first-line regimens for the combined treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults (1). While the pharmacokinetics of other NRTI, such as tenofovir or lamivudine, has been well documented, the pharmacokinetics of FTC has been much less studied. The pharmacokinetics of a 200-mg FTC dose given once daily (QD) has been described by noncompartmental analysis in studies performed in 6, 17, or 21 healthy volunteers (2–4). It has also been described in two very small studies that included HIV-1 infected adults ($n = 20$) (5, 6).

FTC is mainly eliminated by renal excretion, with 86% of an oral dose recovered unchanged in urine (5). FTC renal elimination combines glomerular filtration and active tubular secretion. Following the administration of one 200-mg FTC capsule QD, a significant increase in FTC exposure (area under the concentration-time curve over 24 h [AUC_{0-24}]) has been shown in healthy volunteers with moderate renal impairment (creatinine clearance [CL_{CR}], 49 to 30 ml/min). Thus, a dosing interval adjustment of one 200-mg capsule every 48 h has been recommended in this subpopulation (5). However, this study has some limitations: the influence of renal function on FTC pharmacokinetics has not been determined in HIV-1 infected patients, a small number of healthy volunteers with moderate renal impairment ($n = 6$) have been included, and the safety and efficacy of the recommended dosing adjustment (200 mg every 48 h) have not been clinically evaluated (5).

The aims of this study were (i) to describe the pharmacokinetics of FTC in a large population of HIV-1-infected adults, (ii) to evaluate the influence of renal function on FTC pharmacokinetics, and (iii) to assess recommended dosing adjustments according to the degree of renal impairment.

MATERIALS AND METHODS

Patients and treatment. The study population included HIV-1-infected adult patients treated at Cochin Hospital, Paris, France, receiving an FTC dose of 200 mg QD. FTC was part of their antiretroviral regimen and was taken in oral solid forms (Emtriva, Truvada, or Atripla). FTC blood plasma concentrations at steady-state were measured at random times for therapeutic drug monitoring. For each patient of this retrospective study, the time elapsed between FTC intake and sampling times, gender, body weight (BW), age, serum creatinine (S_{CR}), and associated antiretroviral drugs were recorded. Creatinine clearance (CL_{CR}) was calculated for each occasion using the Cockroft-Gault formula (7).

Analytical method. The FTC assay was performed according to a previously published method of liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) (8). The limit of quantification (LOQ) was 0.01 mg/liter, intra-assay precision was 3.6%, and interassay precision was 7.9%.

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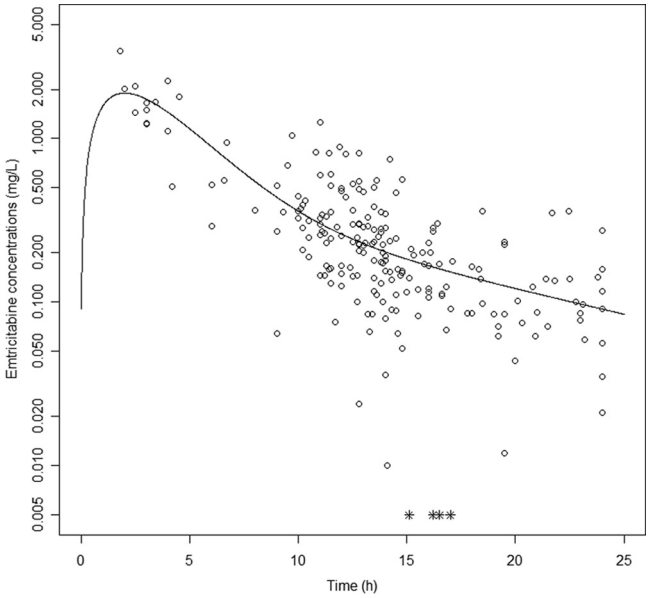

FIG 1 Observed (circles) and population-predicted (line) FTC concentrations versus time. Asterisks represent FTC concentrations below the LOQ.

Population pharmacokinetic modeling strategy. The data were analyzed with a nonlinear mixed-effect modeling approach using the Monolix software program version 4.1.3 (available at www.lixoft.eu) (9). The parameters were estimated by computing the maximum likelihood estimator of the parameters without any linearization of the model, using the stochastic approximation expectation maximization (SAEM) algorithm combined with a Markov chain Monte Carlo (MCMC) procedure. The number of MCMC chains was fixed at 5 for all estimations.

Several structural pharmacokinetic models were investigated using one or two compartments with linear absorption and elimination. Since very few samples were recorded in the absorption phase (Fig. 1), we could not estimate the absorption rate constant (k_a). Models with fixed k_a values (10, 11) were tested. However, these k_a values have only been estimated in pregnant women. Thus, as the effects of pregnancy on absorption are not well understood and pregnancy might alter drug absorption (12), we also considered a model with an absorption rate constant (k_a) equal to the distribution rate constant (α). This model was tested according to the following equation (13):

$$C_{SS}(t) = \frac{\alpha \cdot F \cdot \text{dose} \cdot (k_{21} - \beta)}{V_c \cdot (\alpha - \beta)^2} \cdot \left(\frac{e^{-\beta \cdot t}}{1 - e^{-\beta \cdot \tau}} - \frac{e^{-\alpha \cdot t}}{1 - e^{-\alpha \cdot \tau}} \right) + \frac{\alpha \cdot F \cdot \text{dose} \cdot (\alpha - k_{21})}{V_c \cdot (\alpha - \beta)} \cdot \frac{e^{-\alpha \cdot t}}{1 - e^{-\alpha \cdot \tau}} \cdot \left(t + \frac{\tau \cdot e^{-\alpha \cdot \tau}}{1 - e^{-\alpha \cdot \tau}} \right)$$

where α is the distribution rate constant, k_{21} is the constant of transfer from the peripheral to the central compartment, β is the elimination rate constant, V_c is the central volume of distribution, F is the bioavailability, and τ is the dosing interval.

Several error models (proportional, additive, and mixed) were investigated to describe the residual variability (ϵ). Interindividual variabilities (IIV or η) were tested using an exponential model. The influence of continuous covariates (CO) on pharmacokinetic parameters was tested according to the following equation, using apparent elimination clearance (CL/F), for example: $\text{CL}/F = \theta_{\text{CL}/F} \cdot (\text{CO}/[\text{median (CO)}])^{\theta\text{CO}}$, where $\theta_{\text{CL}/F}$ is the typical value of apparent elimination clearance for a subject with the median covariate value, and θ_{CO} is the estimated influential factor for the continuous covariate. The main continuous covariates were BW, age, S_{CR}, BW/S_{CR}, and CL_{CR}. The influence of categorical covariates (CA) was tested according to the equation $\text{CL}/F = \theta_{\text{CL}/F} \cdot \theta_{\text{CA}}{}^{\text{CA}}$, where CA is 0 for the reference value of CL/F, CA is 1 for the value of CL/F with the covariate, and θ_{CA} is the estimated influential factor of the CA. The main CA were gender and associated antiretroviral treatments.

The Akaike information criterion (AIC) and the Bayesian information criterion (BIC) were used to test hypotheses for nonembedded models. The objective function value (OFV) was used to test hypotheses regarding the structural model, structure of the variance-covariance matrix for IIV, and covariate effect(s) on pharmacokinetic parameters. A covariate was retained in the model if its effect was biologically plausible, if the OFV was decreased by at least 3.84, and if it produced a reduction in the variability of the pharmacokinetic parameter (IIV). Individual Bayesian estimates of the pharmacokinetic parameters were used to calculate the individual area under the concentration-time curve (AUC) and the minimal concentration (C_{min}) of FTC.

Model evaluation. Graphical evaluation of the goodness of fit was performed with graphs of observed concentrations versus population predictions (PRED) or individual predictions (IPRED), weighted residuals versus time, and weighted residuals versus PRED.

In order to evaluate the model, simulated FTC concentrations and observed data were compared by a prediction-corrected visual predictive check (PC-VPC) (14). The 5th, 50th, and 95th percentiles of the observed data were overlaid on the 90% confidence interval of the 5th, 50th, and 95th simulated percentiles, and a visual inspection was performed. The model was also evaluated by the normalized prediction distribution errors (NPDE) metrics (15). Diagnostic graphics and distribution statistics were performed using RfN (see http://wfn.sourceforge.net) of the R program (16).

Dosing adjustment simulations. Using the final model, the recommended dosing schemes for the oral solid form of FTC were simulated (1,000 Monte Carlo simulations), using 200 mg QD for patients with normal renal function or mild renal impairment (CL_{CR}, 79 to 50 ml/min) and 200 mg every 48 h for patients with moderate renal impairment (CL_{CR}, 49 to 30 ml/min). The $AUC_{0\text{-}48}$ values and minimal concentrations (C_{min}) obtained from the simulations were compared according to renal function. The percentage of patients with a daily AUC of $<$10 mg · h/liter was calculated. This value (10 mg · h/liter) was associated with maximal anti-HIV activity in a previous study (6). Simulations of other FTC dosing schemes were also performed for patients with moderate renal impairment, such as an oral solid dose of 200 mg QD or different doses of a 10-mg/ml oral solution QD. A relative bioavailability of 83% between the oral solution and the solid oral form was used (5). Similarly, the $AUC_{0\text{-}24}$ values and minimal concentrations (C_{min}) obtained from the simulations were compared according to renal function.

RESULTS

Demographic data. A total of 211 blood plasma concentrations, determined from samples collected from 161 adult patients (85 men, 76 women), were available for FTC pharmacokinetic evaluation. All patients received an FTC dose of 200 mg QD in capsule or tablet form. Table 1 summarizes the characteristics of the patients.

In this population, 78% of the FTC samples came from patients with normal renal function (median CL_{CR}, 110.9 ml/min; range, 80.3 to 246.1 ml/min), 19% came from patients with mild renal

TABLE 1 Patient characteristics (n = 161)

Characteristic	Median	Mean	Range
Age (yr)	41	41	18–72
BW (kg)	69	71	37–133
S_{CR} (μmol/liter)	76	79	32–242
BW/S_{CR}	0.897	0.972	0.421–2.250
CL_{CR} (ml/min)	104.5	109.9	34.1–246.1

TABLE 2 Population pharmacokinetic parameters of emtricitabine in 161 HIV-1-infected adult patients

Parameter[a]	Estimated value	RSE (%)[b]
Structural model		
CL/*F* (liters/h)	15.1	6
V_c/F (liters)	42.3	12
Q/*F* (liters/h)	5.75	38
V_p/F (liters)	55.4	28
Effect of creatinine clearance on CL/*F*	0.278	23
k_a (h^{-1})	0.53	
Statistical model		
$IIV_{CL/F}$	0.174	14
Proportional error	0.422	7

[a] CL/*F*, apparent elimination clearance; V_c/F, apparent central volume of distribution; Q/*F*, apparent intercompartmental clearance; V_p/F, apparent peripheral volume of distribution; k_a, absorption rate constant; $IIV_{CL/F}$, interindividual variability estimate.
[b] RSE, relative standard error (standard error of estimate/estimate × 100).

impairment (median CL_{CR}, 71.3 ml/min; range, 50.4 to 79.6 ml/min), and 3% came from patients with moderate renal impairment (median CL_{CR}, 40.6 ml/min; range, 34.1 to 44.9 ml/min). The mean number of samples per patient was 1.3 (range, 1 to 5). No differences in the sampling schemes between patients with normal renal function and moderate renal impairment were observed.

FTC was combined with tenofovir disoproxil fumarate (TDF) in 99.5% of the samples. The combination of FTC and TDF was associated with only one protease inhibitor in 66.7% of the samples and with only one nonnucleoside reverse transcriptase inhibitor in 21.9% of the samples.

Population pharmacokinetics. Four concentrations were below the LOQ (1.9% of samples) and were set to half of the LOQ (17). The data did not allow us to estimate an absorption rate constant (Fig. 1). Thus, our study data were best described by a 2-compartment model in which the k_a and the slope of the distribution rate constant (α) were equal (13). The parameters of this model were apparent elimination clearance (CL/*F*), apparent intercompartmental clearance (Q/*F*), and apparent central (V_c/F) and peripheral (V_p/F) volumes of distribution, with *F* being the unknown bioavailability.

Residual variability was best described by a proportional error model. Interindividual variability was described by an exponential error model and was estimated only on CL/*F*. Gender and associated antiretroviral treatments had no effect on the objective function value (OFV). Age, BW, S_{CR}, CL_{CR}, and BW/S_{CR} decreased the OFV significantly. The most significant decrease in OFV was obtained with CL_{CR}, calculated by the Cockroft-Gault formula for each patient. After the inclusion of CL_{CR} in the model, the addition of other covariates did not further improve the model. Thereby, the final covariate model was $CL/F = \theta_{CL/F} \cdot (CL_{CR}/104.5)^{0.278}$, where $\theta_{CL/F}$ is the typical value of CL/*F* for an adult, with a CL_{CR} of 104.5 ml/min.

Table 2 summarizes the final population pharmacokinetic estimates. All the parameters were well estimated, with a relative standard error (RSE) of <40%.

Model evaluation. The prediction-corrected visual predictive check showed that the 5th, 50th, and 95th percentiles of the observed data are well included in the 90% confidence interval of the 5th, 50th, and 95th simulated percentiles (Fig. 2). The mean and variance of the normalized prediction distribution errors were not significantly different from 0 ($P = 0.75$, Wilcoxon signed rank test) and 1 ($P = 0.64$, Fisher variance test), respectively. Their distribution was not different from a normal one ($P = 0.23$, Shapiro-Wilk test of normality). The global adjusted *P* value was 0.69.

Individual exposure to FTC. Individual Bayesian clearances were used to calculate individual AUC_{0-24} values. FTC exposure after a standard dose of 200 mg QD increased when the CL_{CR} decreased: the median AUC_{0-24} (95% confidence interval) increased from 12.5 (12.3 to 12.8) mg · h/liter in patients with normal renal function (CL_{CR}, >80 ml/min) to 14.7 (13.9 to 15.5) mg · h/liter in patients with mild renal impairment (CL_{CR}, 79 to 50 ml/min), and to 17.9 (15.6 to 20.6) mg · h/liter in patients with moderate renal impairment (CL_{CR}, 49 to 30 ml/min).

Dosing adjustment simulations. Figure 3 displays FTC exposures derived from 1,000 simulations of the final model, according to the degree of renal impairment. Figure 3a shows that the recommended dosing schemes for the oral solid form of FTC (200 mg QD for patients with normal renal function and patients with a CL_{CR} of 79 to 50 ml/min; 200 mg every 48 h for patients with a CL_{CR} of 49 to 30 ml/min) led to lower AUC_{0-48} for patients, with a CL_{CR} of 49 to 30 ml/min (median AUC_{0-48}, 17.2 versus 25.6 mg · h/liter). Despite the median AUC_{0-24} being close (15.6 mg · h/liter in patients with moderate renal impairment versus 12.8 mg · h/liter in patients with normal renal function), 100% of the patients with moderate renal impairment had an AUC_{24-48} of <10 mg · h/liter (median AUC_{24-48}, 1.6 mg · h/liter). The same trend was observed for minimal concentrations, with a mean C_{min} of 0.032 mg/liter for patients with moderate renal impairment and 0.091 mg/liter for patients with normal renal function.

Simulations of the 200-mg oral solid form dose QD in patients with a CL_{CR} of 49 to 30 ml/min resulted in a slightly higher AUC_{0-24} than in patients with mild renal impairment (Fig. 3b). With this dosing scheme, only 0.1% of the patients with moderate renal impairment had a daily AUC of <10 mg · h/liter.

Figure 3c shows that similar FTC exposures were obtained in patients with moderate renal impairment receiving 18 ml of FTC oral solution QD and patients with normal renal function receiving 200 mg of the oral solid form QD (median AUC_{0-24}, 12.9 versus 12.8 mg · h/liter). The 18 ml of FTC oral solution was considered equivalent to 150 mg of FTC in oral solid form, taking into account a relative bioavailability of 83% (5). The percentage of patients with moderate renal impairment having an AUC_{0-24} of <10 mg · h/liter was also close (9.6% for the oral solid form versus 7.2% for the oral solution).

DISCUSSION

This article describes the emtricitabine pharmacokinetics in 161 HIV-1-infected adults. FTC blood plasma concentrations were satisfactorily described by a two-compartment model. As the data did not allow us to estimate an absorption rate constant, a model with a k_a equal to the slope of the distribution phase or models with fixed k_a values were tested. The k_a value estimated in our population (0.53 h^{-1}) thanks to the model developed (i.e., with $k_a = \alpha$) was close to previously published values for pregnant women (0.54 h^{-1} and 0.709 h^{-1}) (10, 11). However, even by fixing k_a to these values, the best fit was obtained for the model with a common value estimated for k_a and α.

Our typical CL/*F* estimate (15.1 liters/h) was slightly lower than the calculated values (dose-to-AUC ratios) in healthy volun-

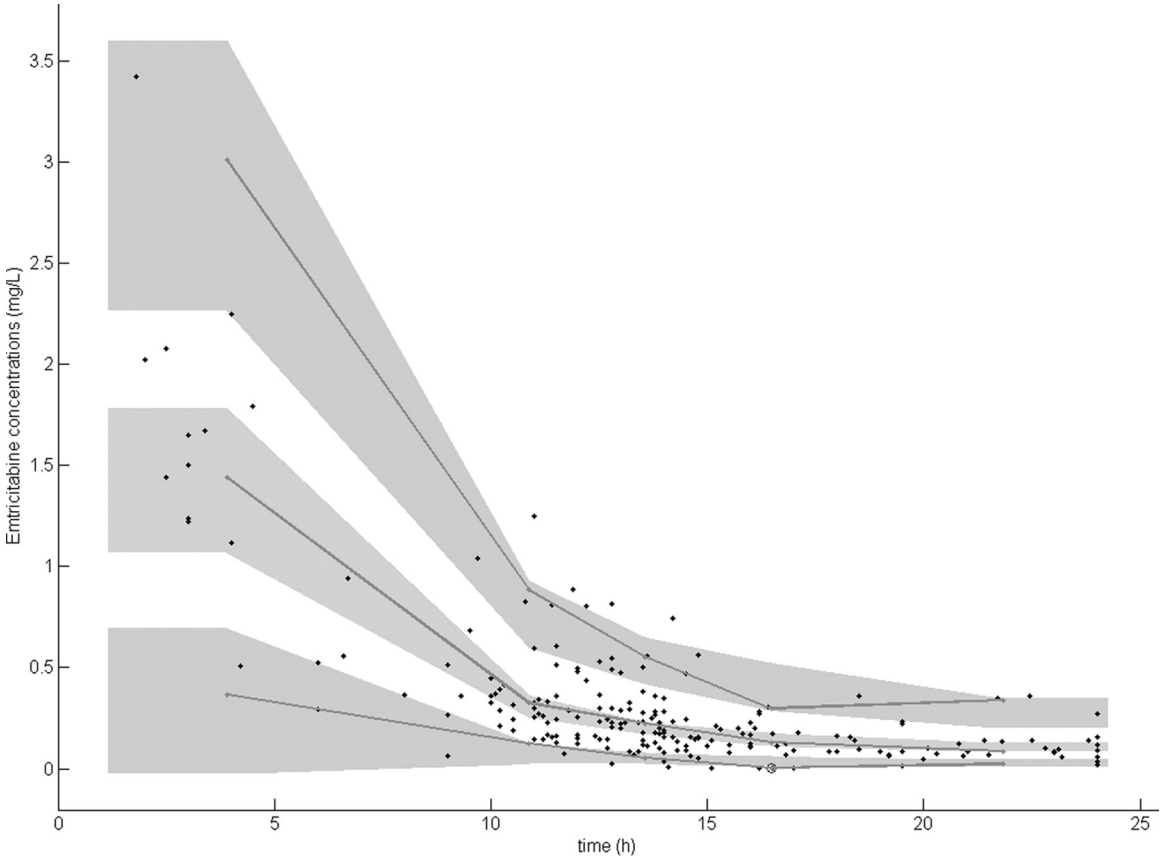

FIG 2 Prediction-corrected visual predictive check. The lines represent the 5th, 50th, and 95th percentiles of observed data. The shaded areas represent the 90% confidence intervals of the simulated percentiles.

teers (2–4) and HIV-1-infected patients (5, 6). However, most of these studies were performed in adults with normal renal function only. The mean half-life was 9.9 h and was in agreement with previously published values of 9.44 h (2) and 10.7 h (3). The mean C_{min} was 0.094 mg/liter, which was close to reported C_{min} values of 0.09 mg/liter in HIV-infected adults (5) and 0.075 mg/liter in healthy volunteers (3).

The population model was used to investigate whether demographic and biological characteristics could influence FTC pharmacokinetics. Our results confirmed that renal function was the most important factor influencing FTC pharmacokinetics. The BW/S_{CR} ratio has been suggested to be a surrogate marker of renal function (18). However, in our study, the effect of BW/S_{CR} on FTC CL/F was less pronounced than the effect of CL_{CR}. As ethnicity data were not available, we could not evaluate renal function by the modification of diet in renal disease (MDRD) or chronic kidney disease epidemiology collaboration (CKD-EPI) formulas, so we used the Cockroft-Gault formula, despite its limitations. Thus, the only and most significant influential factor for CL/F was CL_{CR}.

In our population, FTC exposure (AUC_{0-24}) after a dose of 200 mg QD increased, while CL_{CR} decreased. The FTC exposure increasing in accordance with the degree of renal impairment is in agreement with the FTC-107 study results (5). However, the increase in FTC exposure was more pronounced in the FTC-107 study (11.8 ± 2.9 mg · h/liter to 19.9 ± 1.2 mg · h/liter to 25.1 ± 5.7 mg · h/liter) compared to that in our study.

The current dosing recommendations for FTC in oral solid form are 200 mg QD for patients with normal renal function and patients with mild renal impairment and 200 mg every 48 h for patients with moderate renal impairment. However, for patients with moderate renal impairment, this dosing interval adjustment has never been evaluated. Thus, our population model was used to simulate this dosing adjustment recommendation. For patients with moderate renal impairment, the median AUC_{0-48} was 17.2 mg · h/liter. This median exposure was 33% lower than the one in patients with normal renal function receiving 200 mg QD (25.6 mg · h/liter). Even if FTC 5′-triphosphate is the active moiety of emtricitabine, a plasma FTC concentration-response relationship was previously demonstrated. A relationship between anti-HIV activity and plasma FTC AUC_{0-24} has been shown, with a plateau in the anti-HIV activity, for a daily AUC value of ≈10 mg · h/liter (6). Thus, as 100% of the simulated patients with moderate renal impairment receiving 200 mg every 48 h had an AUC_{24-48} of <10 mg · h/liter, we expected reduced anti-HIV activities for these patients.

Therefore, in order to guarantee the anti-HIV activity of FTC, we used our population model to simulate other dosing schemes for patients with moderate renal impairment to obtain exposures similar to what is found in patients with normal renal function receiving 200 mg FTC oral solid form QD. Simulated patients with moderate renal impairment receiving a 200-mg oral solid dose QD had a higher AUC_{0-24} than patients with normal renal func-

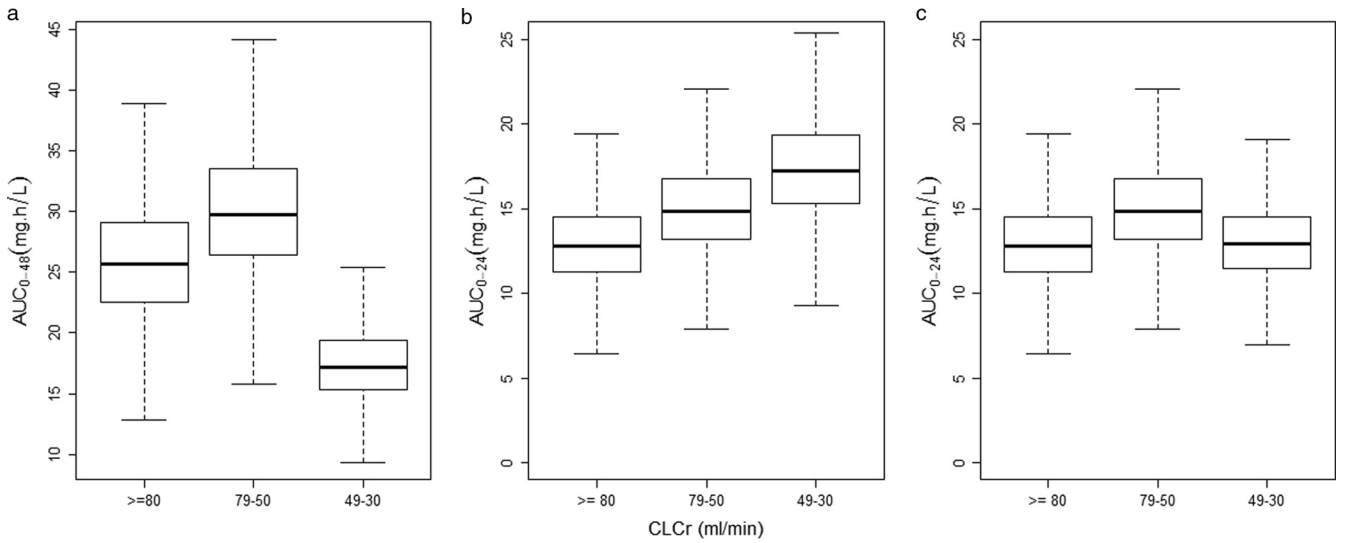

FIG 3 Simulated FTC exposures (AUC_{0-48} or AUC_{0-24}) versus degree of renal impairment (CL_{CR}). (a) AUC_{0-48} for oral solid form recommended dosing schemes: 200 mg QD in patients with normal renal function or mild renal impairment, 200 mg every 48 h in patients with moderate renal impairment. (b and c) AUC_{0-24} for 200 mg oral solid form QD in patients with moderate renal impairment (b) and for 18 ml of FTC oral solution (10 mg/ml) QD in patients with moderate renal impairment (c). Boxes represent the median and interquartile range, and whisker plots represent values within 1.5 times the interquartile range.

tion (17.2 versus 12.8 mg · h/liter). However, only 0.1% of patients with moderate renal impairment had a daily AUC lower than the threshold of maximal anti-HIV activity (10 mg · h/liter). As FTC is a well-tolerated drug, even at higher dosing levels (300 mg QD [19] or 200 mg twice a day (BID) [20]), an increase in FTC exposure for patients with moderate renal impairment receiving 200 mg QD is not expected to have major effects on the safety profile of FTC.

Simulated patients with moderate renal impairment receiving 18 ml of a 10 mg/ml oral solution of emtricitabine QD had a median AUC_{0-24} similar to that of patients with normal renal function receiving 200 mg QD in oral solid form (12.9 mg · h/liter versus 12.8 mg · h/liter L). Only 7.2% of patients with moderate renal impairment had an FTC AUC_{0-24} of $<$10 mg · h/liter. However, one limitation of this dosing recommendation may be the practicality of administering an oral solution, which is less convenient than an oral solid form.

These simulations may be regarded with caution since the number of HIV-1-infected patients with moderate renal impairment in our study was low. However, the current dosing recommendations derived from a study (FTC-107) that included only 6 healthy volunteers with moderate renal impairment.

In conclusion, this study reports FTC pharmacokinetics in a large population of HIV-1-infected patients with various degrees of renal impairment. FTC clearance was related to CL_{CR}. In our study, the current dosing recommendations led to lower FTC exposures for patients with moderate renal impairment. In order to reach exposures similar to those obtained in HIV-1-positive patients with normal renal function, patients with moderate renal impairment should receive 18 ml of a 10 mg/ml FTC oral solution QD. If the switch from an oral solid form to an oral solution is not possible for practical reasons, we propose to give 200 mg oral solid form QD rather than every 48 h, as long as FTC is well tolerated. These proposed recommendations should be prospectively confirmed.

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