

# A Pharmacokinetic-Pharmacodynamic Model to Optimize the Phase IIa Development Program of Maraviroc

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**Objectives:** To use a viral dynamics model to compare the effectiveness of in vivo viral inhibition of several doses of maraviroc (MVC;UK-427,857) and to use a modeling approach to support design decisions for a monotherapy study using various dosing regimens of maraviroc given with and without food.

**Design:** The pharmacokinetic-pharmacodynamic model was developed using clinical data from a first monotherapy study (study A4001007). This was a randomized, double-blind, placebo-controlled, multicenter study of maraviroc in 44 asymptomatic HIV-1-infected patients. Patients received maraviroc under food restrictions at 25 mg once daily or 50, 100, or 300 mg twice daily, or placebo for 10 days.

**Methods:** Antiviral responses were assessed by measuring plasma HIV-1 RNA levels during screening, during randomization, at baseline, and daily during the 10 days of treatment and at days 11 to 15, 19, 22, 25, and 40. An integrated pharmacokinetic-pharmacodynamic model was developed using the mixed effects modeling approach with patients' pharmacokinetic profiles on the last day of treatment, HIV-1 RNA levels over time, and the individual viral susceptibility. The parameters derived from the viral dynamic model were used to calculate average viral inhibition fraction, decay rate of actively infected cells, and basic reproductive ratio for each treatment group. Monte Carlo simulation was then used to determine the distribution of viral load change across simulated patients over time for each regimen to be studied in another monotherapy study, A4001015.

**Results:** The decline rate in the 300 mg twice daily group was comparable to that induced by potent protease inhibitor monotherapy, but was significantly slower than that in patients receiving combination therapy including both protease inhibitor and reverse transcriptase inhibitors. The efficacy of inhibition in vivo was estimated to range from 0.15 to 0.38 for the 25 mg once daily dose group and from 0.88 to 0.96 for the 300 mg twice daily dose group.

**Conclusions:** The model has aided the analysis and interpretation of the clinical data. The use of a model-based approach for selecting doses can accelerate drug development by replacing some arms or trials with simulations.

**Key Words:** viral dynamics model, UK-427,857, modeling, simulations, CCR5 antagonists, maraviroc, MVC

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Maraviroc (MVC;UK-427,857) is a novel CCR5 antagonist in development for the treatment of HIV. The mechanism of action is blocking of the CCR5 receptor, which is used by HIV to enter CD4<sup>+</sup> cells. Pharmacokinetic/pharmacodynamic models are ideally developed during the learning phase and then utilized in the design of the confirming phase of drug development. It is important that the models allow both interpolation and extrapolation beyond the conditions in which they were developed. Logically, models formulated on a mechanistic basis (ie, models that incorporate biological knowledge) are more likely to possess the required qualities compared with empirical models. However, mechanistic models take time to develop.

Mathematical models have been widely used in HIV research and have contributed a great deal to our understanding of virus and cell dynamics.<sup>1,2</sup> However, the value of these models is limited by lack of integration of pharmacokinetic and viral inhibition data. Models that integrate all relevant information generated during drug development, especially pharmacokinetic data, have much greater potential predictive power. To realistically simulate patient data in clinical trials, it is necessary to integrate continuous-time models of pharmacokinetics (PK), pharmacodynamics (PD), and disease. Recently, there have been a few reports of examples of integrated PK-PD-Disease models in the HIV area. Hsu et al<sup>3</sup> used the PK-PD-Disease model approach to predict the long-term success rate of lopinavir/ritonavir in naive patients. A more complex PK-PD-Disease model was developed by Hurwitz et al. This model predicted short-term monotherapy outcomes, but it failed to predict long-term efficacy.<sup>4</sup> A combined PK-PD-Disease model, also called a drug-disease model, has also been applied to drug development decisions.<sup>5</sup> Some authors have also used empirical models in the confirming phases of drug development.<sup>6,7</sup>

A PK-PD-Disease model was developed for maraviroc before any clinical data were available. This model was used to help in selecting the range of doses to be studied in a proof-of-principle study (study A4001007) to characterize the dose-response relationship of viral load decline.<sup>8,9</sup> A viral dynamics model reported in the literature for protease inhibitors and nonnucleoside reverse transcriptase inhibitors was adapted for a CCR5 receptor antagonist<sup>10,11</sup> and

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extended to include PK and PD information. This PK-PD-Disease model integrated information from different sources: concentration-time profiles from healthy volunteers, HIV-1 RNA plasma levels from another investigational compound with a different mechanism of action, and maraviroc in vitro viral inhibition ( $IC_{50}$ ). Technical details regarding the PK-PD-Disease model are given elsewhere.<sup>8,9</sup> Later, when clinical data from study A4001007 became available, the PK-PD-Disease model was updated and used to simulate several design options for a second monotherapy study, A4001015. Clinical trials are required to demonstrate the efficacy of new drugs and regimens. However, these studies are often expensive and time consuming. In silico simulation as predictive tools are becoming increasingly popular methods for improving the design of clinical trials.<sup>9,12</sup> This article describes modeling and simulation activities undertaken to predict the impact of food and dosing regimens (twice daily vs. once daily) to assist the clinical development team for maraviroc in designing study A4001015. The aims of this study were to assess the impact of once-daily dosing and food intake on viral load reduction in antiretroviral-naïve patients treated for 10 days with maraviroc as monotherapy. In addition, the impact of different doses on population cell dynamics was evaluated.

## METHODS

### The Data

Study A4001007 was a multicenter, placebo-controlled, double-blind study of 44 asymptomatic HIV-1-infected patients to investigate the PK and PD of maraviroc after the administration of 25 mg once daily, 50 mg twice daily, 100 mg twice daily, 300 mg twice daily, or placebo for 10 days under food-restricted conditions. Patients were either antiretroviral drug-naïve or off antiretroviral treatment for a minimum of 8 weeks before enrolling in the study. Patients had plasma HIV-1 RNA  $\geq 5000$  copies/mL and CD4 cell count  $>250$  cells/ $\mu$ L. Patients had only CCR5-tropic virus as determined by the Monogram Biosciences PhenoSense Entry (South San Francisco, CA, USA) recombinant virus entry assay. Plasma HIV-1 RNA levels were evaluated using the Roche Amplicor v1.5 reverse transcriptase-polymerase chain reaction assay at 3 prestudy visits (screening, randomization, and at baseline), from day 2 through to day 13, and on days 15, 19, 22, 25, and 40. On day 1, plasma samples were taken at 0, 1, 2, 4, 6, 8, and 12 hours, and on day 10 (the last day of treatment), plasma samples were taken at 0, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, and 120 hours postdose for PK measurements. Plasma concentrations were analyzed by a centralized laboratory (Maxxam Analytics, Inc, Mississauga, ON, Canada) using high-performance liquid chromatography-tandem mass spectrometry. Susceptibility of each individual's virus to maraviroc was determined on days 1, 11, and 40 by calculating an  $IC_{50}$  and  $IC_{90}$  using a recombinant assay (Monogram Biosciences PhenoSense entry assay).<sup>13</sup> Patients participating in this study were advised to be under fasting conditions for the morning dose of maraviroc on days 1 and 10 to at least 4 hours postdose. A light snack was permitted 1 hour after the evening dose of maraviroc or placebo. For

days 2 to 9, patients were advised not to eat or drink before and for 1 hour after the morning dose of maraviroc and not to eat a large meal less than 2 hours before the evening dose or within 1 hour after it.

Local independent ethics committees approved the study protocol, and all subjects voluntarily provided informed consent according to the Declaration of Helsinki, 1989 (Revised Edinburgh, October 2000). Further details of this study are given elsewhere.<sup>14</sup>

### The PK-PD-Disease Model

#### Pharmacodynamic Model

This model characterizes the viral inhibition fraction as a function of time. This fraction ranges from 0, for no inhibition, to 1, for complete inhibition. An  $E_{max}$  model was used to describe the inhibition fraction, with the Hill coefficient fixed at 1.

The equation describing the inhibition as a function of time is:

$$INH_{(t)} = \frac{C_{(t)}}{C_{(t)} + IC_{50}} \quad (1)$$

The  $IC_{50}$  is the concentration where inhibition is 50%, and  $C_{(t)}$  is the maraviroc plasma concentration as a function of time.

#### Disease Model

This model characterizes viral dynamics as a function of time, and describes changes in the amounts of virus and host immune cells during treatment.<sup>10,11</sup> To compare the effectiveness of maraviroc in blocking viral replication, parameters of a set of differential equations for viral and host immune cell dynamics were fitted to the measured viral load data from all treatment arms as described before. The rate of viral replication within a patient at a given time can be summarized by the basic reproductive ratio ( $R_0$ ).<sup>1</sup>  $R_0$  is defined as the number of newly infected cells that arise from any one infected cell (when almost all cells are uninfected). Each type of infected cell contributes to the basic reproductive ratio  $R_0$ , which determines whether the virus will proliferate or die out. In our model, it can be represented as:

$$R_0 = \frac{b_i}{d_1 c} \left( \frac{f_1 p}{d_2} + \frac{f_2 p a}{d_2(d_3 + a)} \right) \quad (2)$$

Note that the numerators contain birth/activation rate constants and the denominators contain death/clearance rate constants of cells and virus. The first and second terms from Eq. (2) represent the contributions from actively and latently infected cells, respectively;  $R_0$  is mainly determined by the first term of Eq. (2), because  $f_1$  is close to 1. The virus will die out if  $R_0 < 1$  and otherwise will grow to an equilibrium level  $(d_1/i)(R_0 - 1)$ . During treatment,  $R_0$  is multiplied by the time-varying inhibition expression  $(1 - INH)$ . The reduction in  $R_0$  during treatment is a measure of the effectiveness of treatment at blocking viral replication. The further  $R_0$  is above 1, the faster the number of infected cell increase, and therefore, the faster the treatment will fail. If  $R_0$  is driven below 1, the viral load will decrease

approximately exponentially, but if  $R_0$  is slightly above 1, initial suppression will slowly turn into treatment failure.

The infection rate is assumed to be proportional to the product of the number of uninfected cells and infectious virus. It is assumed that maraviroc acts by reducing the viral infectivity rate constant  $i$  by a factor. This factor is 1 minus the inhibition fraction, INH (Eq. (1)). A schematic representation of the viral dynamics model is given in Figure 1. Assuming that the life span of the virus is much shorter than that of infected cells, the observed decay of free virus can be used to estimate  $d_2$  and hence the life span of infected cells. To estimate the turnover rate of the actively infected cell population, we assumed that the free virus is produced by 2 distinct populations of cells: actively infected with rapid decay, and long-lived infected, with slow decay. The decay rate of these two populations is reflected in the 2-phase kinetics of plasma HIV-1 decline after treatment initiation. Because not all parameters of this model are identifiable, some of the parameters were fixed to values reported in the literature.<sup>10,11</sup> Viral dynamics parameters estimated in the analysis presented here were  $b$ ,  $d_2$ ,  $R_0$ , and scaling factor of  $IC_{50}$ .

**Pharmacokinetic Model**

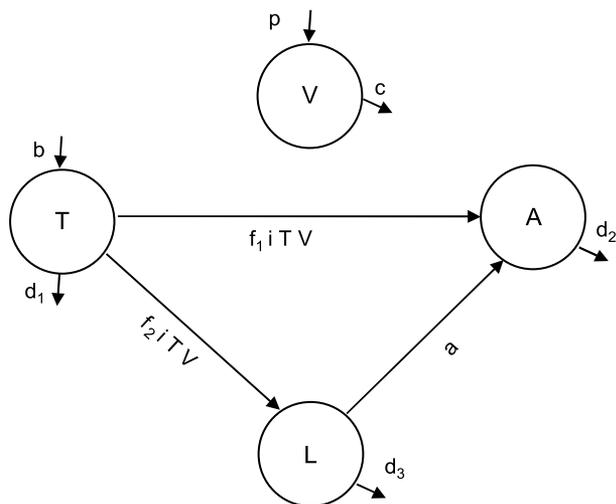
At the time of this analysis, no pharmacokinetic (PK) data were available from patients under the fed condition, and the only once-daily regimen patient data available were for the lowest dose, which showed limited efficacy. Healthy volunteers' PK information from the first-in-human study was used to calculate the impact of food and dosing interval on the average inhibition fraction over a dosing interval. A sensitivity analysis performed on the average inhibition

fraction revealed that it was an accurate substitute for the time-varying inhibition fraction of Eq. (1). A 2-compartment pharmacokinetic model was developed using maraviroc plasma concentration-time profiles from a single-dose study in healthy volunteers. The doses ranged from 1 to 1200 mg given in the fasted state. In addition, a dose of 100 mg was given with a high fat meal. This model was used to simulate plasma concentration-time profiles for 100 subjects at 50, 100, 300, and 600 mg twice daily and 200 mg once daily. The individual concentrations over a 12-hour period for twice-daily a regimens and a 24-hour period for once-daily regimens were calculated and used to derive the individual average inhibition using Eq. (1). Each average inhibition was converted back to a concentration for ease of interpretation (the Equivalent Constant Concentration or ECC). This ECC was derived using the solution to Eq. (1) for  $C_{(t)}$  with INH replaced by  $INH_{avg}$ :

$$ECC = \frac{IC_{50} * INH_{avg}}{1 - INH_{avg}} \tag{3}$$

It was assumed that interpatient variability in ECC followed a lognormal distribution.

In vivo  $IC_{50}$  appropriate for a viral dynamics model may differ from that obtained in vitro, for complicated and poorly understood reasons (such as possibly receptor up-regulation or down-regulation). Therefore, the study A4001007 data were used to estimate the population  $IC_{50}$  of maraviroc, with a coefficient of variation fixed at 56% (*in-house* data). As the Equivalent Constant Concentration depends (weakly) on the  $IC_{50}$  that it was used to estimate, the estimated  $IC_{50}$  from successive NONMEM runs were fed back into the ECC calculations, and NONMEM was rerun iteratively until results stabilized. Together with viral dynamics parameters, a single maximum-likelihood  $IC_{50}$  for all patients was estimated: about 8 ng/mL. The in vivo  $IC_{50}$  distribution was then modeled as lognormal with median 8 ng/mL and a coefficient of variation of 56%.



**FIGURE 1.** The viral dynamics model includes actively infected cells, which generate virus and latently infected cells used for short-term simulations. T, target CD4<sup>+</sup> cells; A, actively infected CD4<sup>+</sup> cells; L, latently infected cells; V, infectious virus. b and p are activation rate constants of T cells and virus, respectively;  $d_1$ ,  $d_2$ , and  $d_3$  are death rate constants of target, actively infected, and latently infected CD4<sup>+</sup> cells;  $f_1$  and  $f_2$  are the fractions of infected CD4<sup>+</sup> cells that become actively or latently infected, respectively.<sup>1</sup>

**Model Assumptions**

To implement the model in the maraviroc program, several assumptions were made:

1. The viral dynamics are described adequately by interaction of the virus with uninfected and 3 classes of infected CD4<sup>+</sup> cells (including long-lived infected cells added to the model for long-term simulations).
2. Maraviroc reduces the infectivity rate constant in this model in proportion to the calculated fractional inhibitory efficacy.
3. Variability in viral load measurement is described adequately by an SD (estimated with trial data) around the log viral load (ie, a lognormal distribution around viral load with the maximum effect reached at the highest dose tested).
4. An  $E_{max}$  model adequately describes viral inhibition by maraviroc, 100% inhibition would cause viral load to decline toward 0 asymptotically. This equation also implies that the  $IC_{90}$  for each patient is 9 times  $IC_{50}$ .
5. The inhibition of the infection rate constant is equal to the functional receptor occupancy by the antagonist.

6. The pharmacologic action is described by a “noncompetitive” antagonism where the amount of virus does not play a significant role, as suggested from preclinical data.<sup>15</sup>
7. No escape routes from the antagonism of the CCR5 receptor will occur in the first 11 days of treatment.
8. There would be no resistance in naive patients with CCR5 tropic virus.

### Data Analysis

To estimate the parameters of the viral dynamics model, viral load data were modeled using the nonlinear mixed effects software package NONMEM.<sup>16</sup> Its general nonlinear differential equation model (PREDPP subroutine ADVAN6) was used with its First-Order Conditional Estimation Method. For each individual patient, from study A4001007, 2 efficacy parameters were calculated:  $\log_{10}$  viral load decline from baseline to day 11 and rate constant of viral load decrease between days 2 and 11 (lmlist function in S-PLUS).

### Simulation Plan

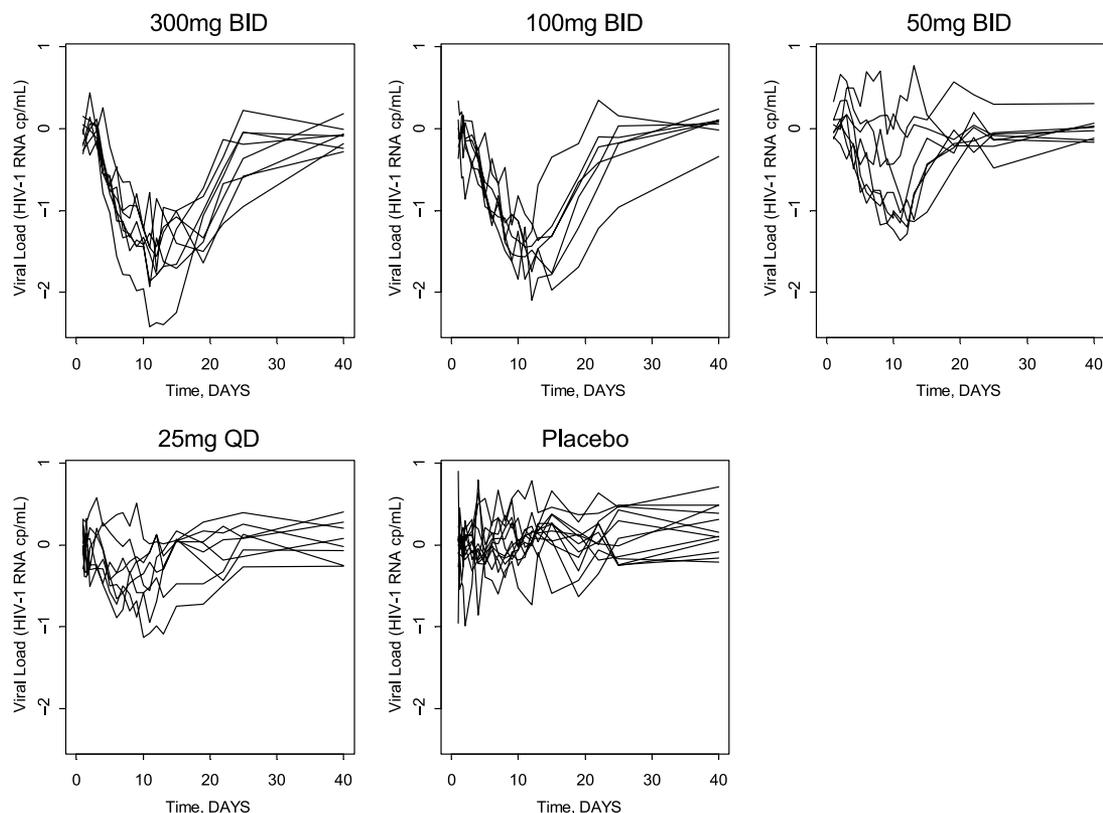
The PK-PD-Disease model was used to simulate decline of HIV-1 RNA plasma levels for 400 patients per treatment arm. The maraviroc dosing regimens simulated were as follows: 150 mg twice daily fed, 150 mg twice daily fasted, and 300 mg once daily fasted. The drug was administered for 10 days as monotherapy. HIV-1 RNA measurements were

performed daily for 40 days after the start of treatment. Simulations for study A4001015 were performed assuming a similar patient population in terms of baseline viral load and basic reproductive ratio at the start of the treatment as that of the A4001007. The plasma HIV-1 RNA levels from each simulated patient were  $\log_{10}$  transformed and subtracted from baseline values. Then, for each simulated treatment arm, the 5th, 50th, and 95th percentiles of the difference were calculated, plotted, and reported for day.<sup>11</sup> Monte Carlo simulations were carried out in the Trial Simulator software package.<sup>17</sup> The statistical analyses were performed using S-PLUS, (version 6, Professional edition).<sup>18</sup>

## RESULTS

### Patient Characteristics

In the study A4001007, 32 patients received active treatment for 10 days. From those, only 31 were included in the analysis. One patient in the 100-mg twice-daily treatment arm was excluded from the analysis because this patient had dual tropic virus at baseline and therefore did not meet the inclusion criteria. Baseline HIV-1 RNA calculated as the mean of screening, baseline, and predose measurements, was 4.58  $\log_{10}$  copies/mL (SD 0.50). The mean CD4 count was 544 cells/ $\mu$ L. The mean  $\log_{10}$  viral load declines from baseline to day 11 for placebo, 25 mg once daily, 50 mg



**FIGURE 2.** HIV-1 RNA  $\log_{10}$  decline from baseline for the 4 treatment arms. Baseline was calculated as a mean of 3 predose viral load measurements. One patient in the 100 mg twice daily treatment arm who had a dual tropic virus at baseline was excluded from the analysis.

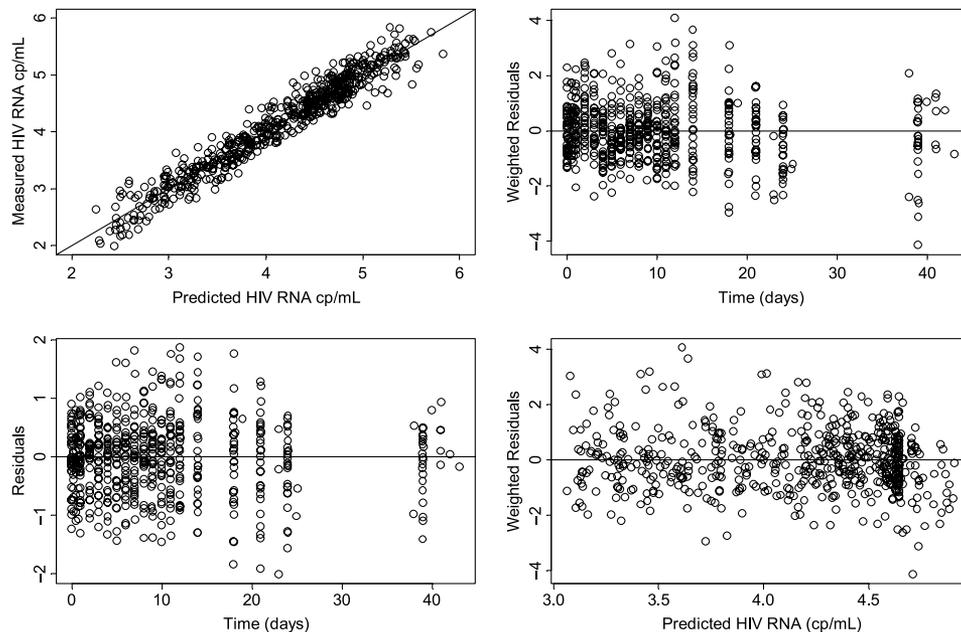


FIGURE 3. Goodness-of-fit plots for the disease model.

twice daily, 100 mg twice daily, 300 mg twice daily were 0.02 [range: -0.45 to 0.56], -0.43 [range: -1.08 to 0.02], -0.66 [range: -1.37 to 0.40], -1.42 [range: -1.84 to -1.04], and -1.60 [range: -2.42 to -0.78], respectively. Figure 2 shows the viral load decline by treatment group. HIV-1 RNA plasma levels continued to decline for a few days after the administration of the last dose. At follow-up (day 40), viral load was at levels similar to baseline values.

**Pharmacokinetics**

Pharmacokinetic data from study A4001007 in HIV-positive subjects with restricted food intake indicate that maraviroc absorption was rapid but variable, with  $T_{max}$  generally occurring between 1 and 4 hours after dosing. There was no evidence of maraviroc accumulation at any dose. Exposures to maraviroc, as measured by  $C_{max}$  and area under the curve of 0 to 12 seems slightly lower than those seen in healthy volunteer studies where the volunteers were fasted. However, the patient data are consistent with data generated in healthy volunteers where similar food restrictions were in place. Pharmacokinetic parameters of maraviroc on days 1 and 10 from study A4001007 are presented elsewhere.<sup>14</sup>

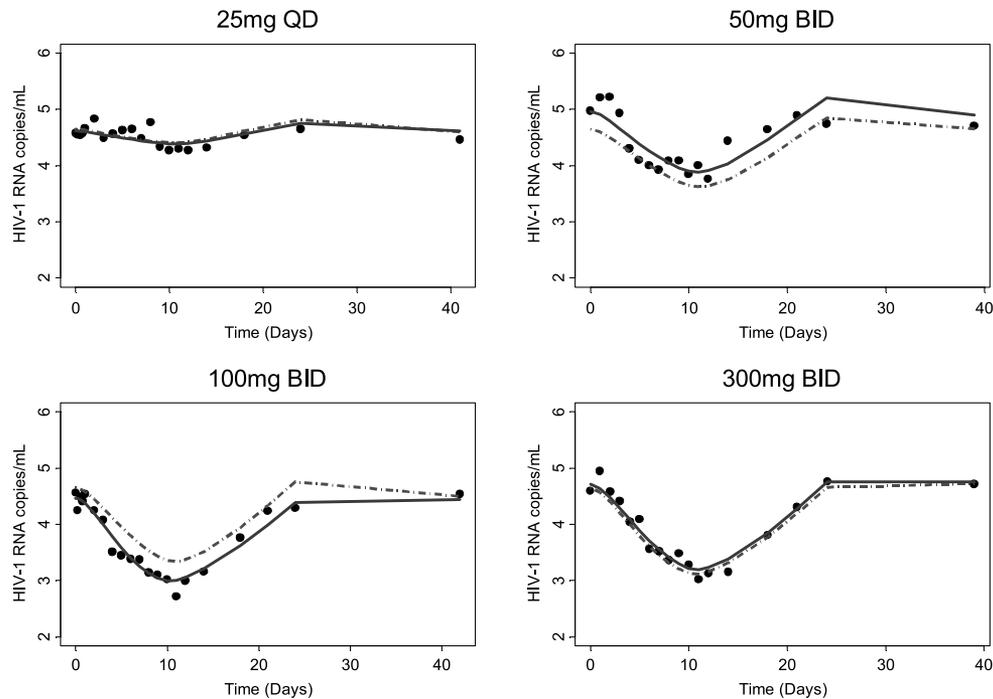
**The Model**

The viral dynamics model was fitted simultaneously to the HIV-1 RNA decline data from all patients using the nonlinear mixed effects approach. This approach allows the integration of the information from all HIV-1 RNA measurements, from day 1 to follow-up. Goodness-of-fit plots show that the model describes the data reasonably well (Fig. 3). Figure 4 shows the measured, the population-predicted, and the individual-predicted viral load time profiles for 4 patients included in the analysis from each dose group.

The parameters derived from the viral dynamic model were used to calculate the average viral inhibition fraction and basic reproductive ratio for each treatment group after 10 days of treatment with maraviroc and are summarized in Table 1. The mean rate of exponential decline of HIV-1 RNA ( $\log_{10}$  copies/mL) per dose group is presented in Table 1. Only the 300 mg twice daily dose was able to bring the basic reproductive ratio below 1 in all patients. The 300 mg twice daily dose provided an estimated inhibition fraction of 0.93; it is possible that higher levels of inhibition could be seen at higher doses (Fig. 5).

**Simulations**

The PK-PD-Disease model was used to perform simulations to assess the impact of food intake and dosing interval on viral load decline. The simulated viral load results for 300 mg once daily (fasted) were compared with the results for the 150 mg twice daily fasted treatment arm. The simulations predicted that once-daily regimens would be equivalent to twice-daily regimens with half the dose; that is, the viral load decline for 150 mg twice daily is equivalent to 300 mg once daily. The model estimated that the impact of food on viral load would be attenuated, with a reduction of 14% in mean viral load decline with food intake. Figure 6 shows the 5th, 50th, and 95th percentiles of viral load for the 400 simulated patients, along with results from study A4001015. Simulated results were in agreement with the actual measured data obtained in study A4001015, as shown in Table 2. A pooled analysis from studies A4001007 and A4001015 was performed. The average inhibition fraction was estimated using Eq. (1), with maraviroc plasma concentrations and a typical  $IC_{50}$  value. The results indicated that the inhibition fraction obtained with 100 mg once daily



**FIGURE 4.** Measured and predicted HIV-1 RNA  $\log_{10}$  (copies/mL). Dotted line represents the population mean curve, bold solid line represents the individual predictions, and circles represent the measured values.

and 50 mg twice daily were 0.54 and 0.50, respectively. For 300 mg twice daily and 300 once daily, the average inhibitions were 0.84 and 0.81, respectively.

## DISCUSSION

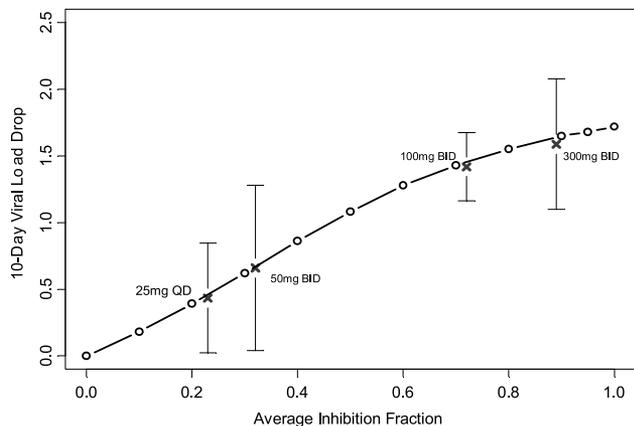
A model-based decision-making approach was used during the development program of maraviroc. This approach was implemented before any clinical data were available. The model was updated each time that new clinical data became available, and the results from simulations were used to make decision for the next planned studies. One of the advantages of a model-based approach is that it allows the integration of all information, not only the clinical data generated during a trial but also data from the literature and clinical studies of other drugs. Another advantage of this approach is that it allows the analysis of pooled data from several studies. The use of mixed effects modeling techniques allow simultaneous analysis of all HIV-1 RNA

measurements collected during a clinical trial. By doing so, all the information available can be used to interpret the results from clinical studies. In contrast, with the traditional statistical analyses, only mean baseline and day 11 (or day 6) measurements of HIV-1 RNA are used, whereas the rest of the time-point measurements are ignored. This approach also has the advantage of integrating all relevant information, such as PK, virus susceptibility, and viral load information gathered during the clinical trial.

By modeling the time-course of plasma HIV-1 RNA after the administration of maraviroc, we were able to predict the doses required to achieve biologically meaningful differences between treatment arms. Although the results of comparisons between different treatment arms presented here using a modeling approach are consistent with standard statistical methods currently used for analysis of clinical trial data, the standard statistical methods are not suited for extrapolation to new doses and regimens. Standard methods do not integrate information from all dose groups simultaneously.

**TABLE 1.** Estimates of the Inhibition Fraction and Basic Reproductive Ratio for Treatment Arms From Study A4001007 (With Minimum; Maximum Values)

Treatment Arm	N	Decay Rate of $\log_{10}$ HIV-1 RNA, $\text{day}^{-1}$	Estimated Inhibition Fraction	Estimated Basic Reproductive Ratio
		Mean $\pm$ SD	Mean [Max; Min]	Mean [Max; Min]
25 mg qd	8	0.20 $\pm$ 0.14	0.24 [0.38; 0.15]	6.91 [17.0; 2.87]
50 mg bid	8	0.29 $\pm$ 0.31	0.53 [0.74; 0.34]	9.70 [41.3; 1.17]
100 mg bid	7	0.41 $\pm$ 0.20	0.78 [0.86; 0.64]	1.28 [2.35; 0.61]
300 mg bid	8	0.58 $\pm$ 0.12	0.93 [0.96; 0.88]	0.41 [0.76; 0.11]



**FIGURE 5.** Predicted inhibition fraction in function of mean viral load drop for study A4001007 (solid line). Crosses represent the doses tested. Bars represent the SD.

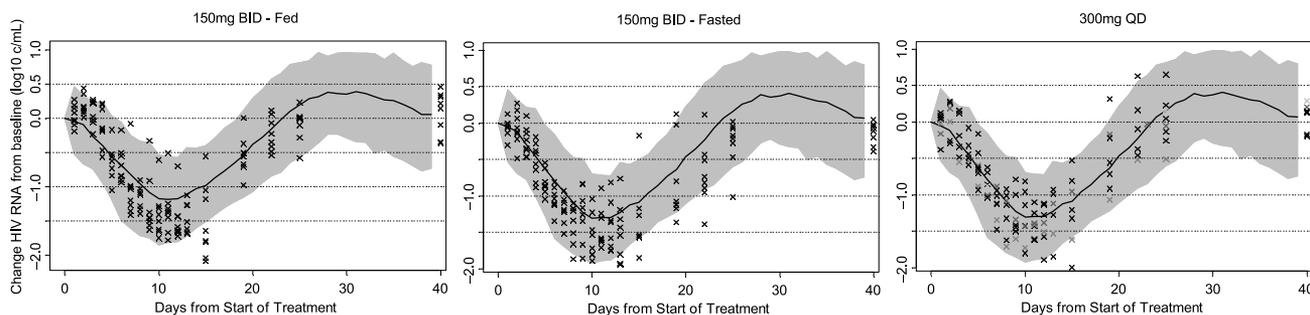
The modeling approach can be used to validate HIV-1 RNA measurements as a biomarker for viral inhibition. Although viral load measurement is useful to distinguish among treatments with weak efficacy, it fails to differentiate between potent doses or regimens as was demonstrated elsewhere.<sup>19</sup> The estimation of the inhibition fraction gives information regarding treatment potency and can be used as a measure of treatment efficacy. As such, we were able to obtain information regarding how much efficacy we could potentially gain by increasing the dose (Fig. 5).

The mean decay rate of actively infected cells expressed as the rate of exponential decline of HIV-1 RNA for 8 patients who received 300 mg twice daily of maraviroc was estimated to be  $-0.58 \pm 0.12 \text{ day}^{-1}$ . No information on decay rate has been published for the 2 other CCR5 antagonists that were in development. The decay rate of actively infected cells following administration of these compounds were therefore estimated from the mean viral load data available and must be interpreted with caution. Aplaviroc given as 600 mg twice daily for 10 days showed similar results to 300 mg twice daily maraviroc.<sup>20,21</sup> Another CCR5 inhibitor, vicriviroc (former SCH 417690), showed a decay rate of the mean viral load following monotherapy 50 mg twice daily that is lower than that seen for maraviroc 300 mg twice daily.<sup>22,23</sup> These results are similar to the one obtained with a 200-mg total daily dose of

maraviroc.<sup>19</sup> A retrospective comparison has indicated that maraviroc resulted in a greater initial rate of decline than reported for several other antiretroviral drugs given as monotherapy. The decline rates induced with protease inhibitors, NNRTIs and NRTIs were reported as  $-0.41 \pm 0.16 \text{ day}^{-1}$  for 23 patients receiving ritonavir, indinavir, or nevirapine<sup>24</sup> and  $-0.34 \pm 0.09 \text{ day}^{-1}$  for 20 patients receiving ritonavir (600–1200 mg twice-daily).<sup>25</sup> In another study, the decay rate for ritonavir 1200 mg twice daily was  $-0.47 \pm 0.16 \text{ day}^{-1}$ .<sup>26</sup> Gruzdev reported a decline rate for 900 mg twice daily of TMC125 of  $-0.33 \text{ day}^{-1}$ .<sup>27</sup> Louie et al reported an average decay rate of  $-0.48 \pm 0.15 \text{ day}^{-1}$  after treatment with tenofovir.<sup>28</sup> Emtricitabine showed decay rates of  $-0.55 \text{ day}^{-1}$  for 200 mg twice daily and  $-0.48 \text{ day}^{-1}$  for 200 mg once daily.<sup>29</sup> However, the initial decline rates for HIV-1 RNA in patients receiving combination therapy were faster than those observed with 300 mg twice daily of maraviroc. Perelson et al reported an average rate of virus decline for 8 patients receiving nelfinavir, zidovudine, and lamivudine of  $-0.79 \pm \text{day}^{-1}$ .<sup>30</sup> Noterman et al reported an average rate of  $-0.61 \pm 0.19 \text{ day}^{-1}$  for 15 patients receiving ritonavir, zidovudine, and lamivudine.<sup>31</sup> It has been shown that the initial decline rate in plasma HIV-1 RNA during combination therapy is predictive of longer-term clinical outcome.<sup>32</sup> Polis et al also analyzed the initial rate of virus decline as a predictor of drug efficacy and concluded that virus decay rate constants at day 6 after treatment initiation are major correlates of long-term virologic response.<sup>33</sup>

The model predictions for 300 mg once daily were within the 5th to 95th percentiles of distribution of 400 simulated patients (Fig. 6) and were not biased. For 150 mg twice daily, the predictions were slightly biased during the first days of treatment; however, around day 11, they were not biased. The measured HIV-1 RNA from study A4001015 fell within the 5th to 95th percentile distribution of the simulated data. Frequency of administration has little impact on efficacy, as judged by both viral load drop and average inhibition fraction.

As previously stated, the area-under-the-curve plasma concentration-time for maraviroc decreased by 50% in the presence of food. The model estimated that the impact of food on viral load would be attenuated, with a reduction of 14% in mean viral load decline with food intake 150 mg twice daily. However, the results from study A4001015 revealed a reduction in mean viral load decline of only 8%. This discrepancy may be explained by the lack of pharmacokinetic



**FIGURE 6.** Measured and model simulated HIV-1 RNA log<sub>10</sub> (copies/mL) for study A4001015. The shaded area represents the 90% CI.

**TABLE 2.** Measured and Predicted Viral Load Decline for Fed and Fasted Regimens and for Once- and Twice-Daily Regimens

Treatment Arm	Measured*	[Max; Min]	Predicted†	CI: [5%–95%] <sup>‡</sup>
150 mg bid fasted	–1.45	[–1.71; –0.90]	–1.30	[–1.67; –0.82]
150 mg bid fed	–1.34	[–1.79; –0.51]	–1.12	[–1.52; –0.58]
100 mg qd	–1.13	[–1.70; –0.43]	–0.81	[–1.32; –0.32]
300 mg qd	–1.35	[–1.62; –0.95]	–1.30	[–1.76; –0.83]

\*Mean decrease from baseline and day 11 in HIV-1 RNA, log<sub>10</sub> copies/mL.

†Median (50% ile) decrease from baseline and day 11 in HIV-1 RNA, log<sub>10</sub> copies/mL.

‡In study A4001015, patients in the fed treatment groups (150 mg bid and placebo) took their morning and evening doses within 30 minutes of a high-fat breakfast or an evening meal, respectively.

CI indicates confidence interval.

data on maraviroc 150 mg twice daily given with food and by the fact that maraviroc exhibits nonlinear PK. Another possible explanation for the bias in the results is that the healthy volunteer studies were carried out under more strict experimental conditions than study A4001015, which was an outpatient study.

The PK-PD-Disease model was updated when results from the second monotherapy study were available and extended to incorporate resistant viral strains. Resistance to each drug was characterized by an IC<sub>50</sub> “step.” Simulations were performed to assess the ability of a phase 2B study with maraviroc given as combination to provide information to select phase 3 doses. The results from the simulations showed that given the high response rates of triple regimens, it would not be possible to differentiate between doses with a short- or medium-term trial with modest patient numbers. Therefore, differences between doses would only be seen when the combination therapy started to fail and resistance developed. Based on these results, it was decided that a stand-alone phase 2B would not allow appropriate dose selection.

Compliance and trial outcome components were added to the extended PK-PD-Disease model described in “Methods” to simulate a phase 3 trial response. To assist in dose selection for phase 3, long-term combination-therapy response was plotted against short-term monotherapy response. Based on this analysis, it was decided to take 2 doses into large-scale trials. Modeling and simulation activities for phase 3 are outside the scope of this article; results have been presented elsewhere.<sup>34</sup>

## CONCLUSIONS

Simulations based on the integrated PK-PD-Disease model have been performed to better understand the complexity of the interactions and to support the design of phase IIa clinical trials of new anti-HIV drugs. This modeling has aided the analysis and interpretation of the clinical data. The use of model-based approach for selecting doses can accelerate drug development by replacing some arms or trials with simulations.

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