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PHARMACOLOGY

Translational Approach to Predicting the Efficacy of Maraviroc-Based Regimens as HIV Preexposure Prophylaxis

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ABSTRACT Maraviroc-based regimens have been explored as preexposure prophylaxis (PrEP) against human immunodeficiency virus (HIV). In this study, we utilized mucosal tissue drug exposure data, combined with target concentrations generated *in vitro*, in a pharmacokinetic-pharmacodynamic analysis to predict the effects of drug combinations and adherence on PrEP efficacy. Mucosal tissue concentrations of maraviroc were measured in 24 healthy women. The 90% effective concentrations (EC_{90}) of maraviroc (alone and combined with tenofovir and emtricitabine) for protection against HIV were identified in $CD4^+$ T cells. Monte Carlo simulations were performed to identify dosing strategies to protect colorectal and female genital tract (FGT) tissues from HIV infection. Colorectal maraviroc concentrations were 350-fold higher than in the FGT. Under steady-state conditions, our model predicted that one 300-mg dose/week was sufficient to protect colorectal tissue from HIV in 99% of the population, while 300 mg daily would protect the FGT in only 63% of the population. FGT protection increased to >90% when maraviroc was used in combination with tenofovir (5 doses/week) or emtricitabine (3 doses/week). Poor adherence resulted in a drastic decrease in efficacy in the FGT but not colorectal tissue. However, greater forgiveness was seen when maraviroc was combined with tenofovir or emtricitabine, suggesting that maraviroc should not be used alone as PrEP.

KEYWORDS HIV, antiretroviral, translational medicine, dose response, population pharmacokinetics-pharmacodynamics, quantitative pharmacology, preexposure prophylaxis, maraviroc, tenofovir, emtricitabine

Truvada, a fixed-dose combination of 300 mg of tenofovir disoproxil fumarate (TDF) and 200 mg of emtricitabine (FTC), was approved in 2012 by the U.S. Food and Drug Administration (FDA) for use as a preexposure prophylaxis (PrEP) regimen against human immunodeficiency virus (HIV) (1). However, due to toxicity concerns surrounding the long-term use of TDF (2, 3), other antiretrovirals, such as maraviroc (MVC), raltegravir (RAL), and dapivirine (DPV), are also being explored for use as PrEP (4, 5). MVC was approved in 2007 by the FDA for the treatment of HIV (6). It is a C-chemokine receptor type 5 (CCR5) receptor antagonist that prevents coreceptor binding of HIV peptides and subsequently blocks the entry of HIV into target cells. MVC shows rapid, but variable, absorption (maximal plasma concentration from 0.5 to 4 h postdose) and is 76% bound to plasma proteins. It is a substrate for cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) and is primarily eliminated in the feces. MVC achieves higher concentrations in vulnerable tissues where HIV exposure occurs than in blood plasma, with 2-fold-higher concentrations in vaginal tissue (7) and 27-fold-higher concentrations in the rectal tissue (8) after multiple dosing orally. Furthermore, MVC exhibits

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good potency in peripheral blood mononuclear cells (PBMCs; PBMC concentration which leads to 90% of maximal inhibition response [IC_{90}] from multiple [pooled] donors ranges from 1.2 to 2.6 nM against HIV type 1 [HIV-1] Ba-L) (9). Finally, MVC is generally safe and well tolerated for a long duration of use (>5 years) in treatment-experienced patients (10). However, despite favorable pharmacokinetic (PK) attributes and demonstrated *in vitro* potency, MVC has shown mixed results as PrEP. In a humanized mouse model for PrEP, oral MVC was 100% effective in preventing infection by intravaginal challenge (11). Similarly, in a rhesus macaque model, MVC vaginal microbicide gel showed dose- and time-dependent protection against vaginal simian-human immunodeficiency virus (SHIV) challenge, with six of seven macaques protected at the highest (6 mM) dose (12). However, rectal SHIV challenge in six rhesus macaques (13) dosed with MVC orally 24 h prior to challenge and 2 h postchallenge led to infections in five animals. Two phase IV trials reported limited *ex vivo* potency of a single dose of oral maraviroc in vaginal and colorectal tissue (14) and in colorectal tissue only (15). Furthermore, in HPTN069, a phase II clinical trial designed to evaluate the safety and tolerability of MVC alone or in combination with TDF or FTC as PrEP in men who have sex with men (MSM) and in high-risk women, five seroconversions were reported in the MSM cohort: four in the MVC-only arm and one in the MVC-TDF arm (16). This may have been related to issues with low medication adherence due to the finding of low or variable MVC concentrations in their plasma. Based on these data, a combination of MVC with other antiretrovirals (ARVs) may be a more suitable option for use as PrEP.

In this work, we developed a population PK model to characterize the disposition of MVC in plasma, colorectal tissue, and lower female genital tract (FGT) tissue. The model was combined with 90% effective concentration (EC_{90}) targets against HIV derived from human $CD4^+$ T cell culture systems to explore the effect of adherence on overall PrEP efficacy for MVC monotherapy. MVC exposure targets were combined with efficacy targets previously published for TFV and FTC alone (17) to generate synergy model-derived efficacy targets to explore the potential prophylactic efficacy of MVC combined with either TDF or FTC.

(Versions of this work were presented at the American Society of Clinical Pharmacology and Therapeutics Meeting, Orlando, FL, March 2018.)

RESULTS

Demographics of the clinical study. Between April 2012 and August 2013, 25 healthy women were enrolled in the clinical trial. In the 300-mg cohort, one participant was not able to provide samples and was withdrawn from the analysis, leaving a total of 24 evaluable participants. Each dosing cohort included eight participants.

PK analysis and population pharmacokinetic model. The population PK model was developed with a total of 264 plasma concentrations, 24 tissue concentrations in the female genital tract, and 24 tissue concentrations in the rectal tissue. The vaginal tissue and cervical tissue concentrations were not significantly different from each other ($P = 0.07$) and were thus averaged into one FGT tissue concentration per subject in order to simplify the model (see Fig. S1 in the supplemental material). At all doses, MCV concentrations were 100 times higher in the rectal tissue than in the FGT tissue. Concentrations also continued to increase at 48 h in the rectal tissue. A linear 10-compartment model best fit the clinical trial data (Fig. 1). Despite a 2-peak phenomenon shown in plasma with the 150-mg and 300-mg concentrations, models implementing complex absorption profiles were unstable, and a simple linear absorption profile was ultimately selected. Five transit compartments were used to describe the increasing rectal tissue concentrations past 24 h. The volume of distribution in both the tissue compartments was fixed to physiologically relevant volumes (100 ml for the FGT tissue and 170 ml for the rectal tissue) (Y. Fedoriw, personal communication, May 2014). Steady-state concentrations were predicted to occur after a single dose in the FGT tissue and after 10 doses in the rectal tissue based on the estimated half-life in the tissue. The PK model parameters are listed in Table S1, and goodness-of-fit plots are shown in Fig. S2. Exploratory analysis was performed to evaluate covariates, but

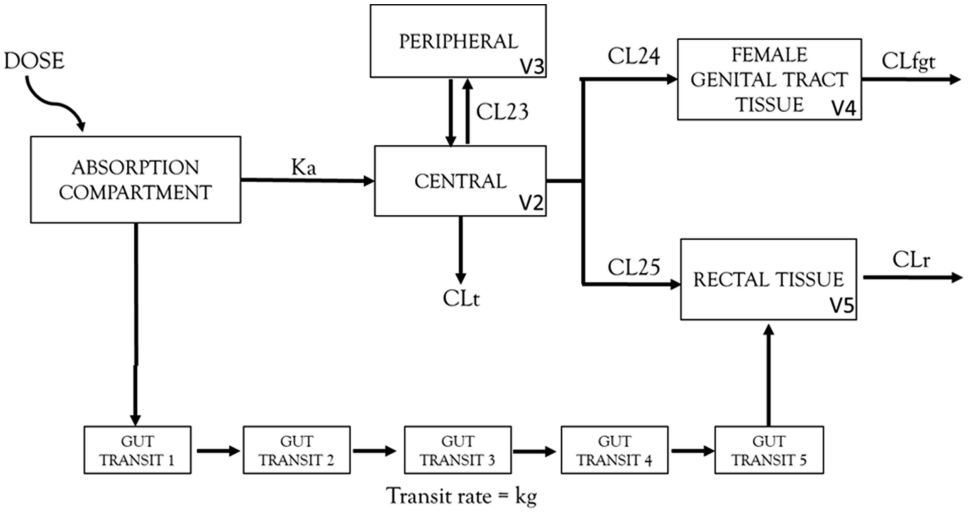

FIG 1 Structure of the population pharmacokinetic model for maraviroc to describe the disposition in the plasma, female genital tract tissue, and rectal tissue. A 10-compartment population PK model was fitted to the data. Maraviroc distribution in plasma was described by a simple 2-compartment model with linear clearance. Distribution into rectal tissue was described by the use of 5 transit compartments with similar transit rates in order to account for delayed second peak in rectal tissue concentration. Volume of distribution in the female genital tract and rectal tissue was fixed to physiologically relevant values, and the clearance out of the two compartments was estimated. Ka, absorption constant; V2, central volume; V3, peripheral volume; V4, volume of female genital tract tissue; V5, volume of rectal tissue; CLt, total clearance; CL23, distributional clearance in plasma; CL24, distributional clearance from plasma to female genital tract; CL25, distributional clearance from plasma to rectal tissue; CLfgt, clearance out of female genital tract tissue; CLr, clearance out of rectal tissue.

because of the lack of significant relationships and the limited data, covariate modeling was not performed.

Concentration-response relationships in CD4$^+$ T cells. Unbound MVC targets for protective efficacy against HIV-1 pseudovirus were investigated, and the best fit for the exposure-response maximum-effect (E_{max}) model is shown in Fig. 2. The EC_{50} of protein-unbound MVC in CD4$^+$ T cells was 0.68 ng/ml, and the Hill coefficient was 0.73. The EC_{90} protein-unbound target for inhibition of viral infection was 14.02 ng/ml.

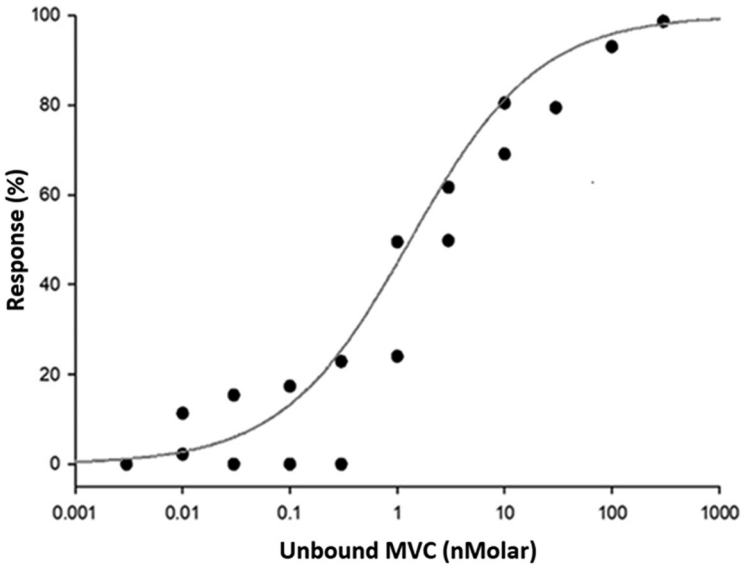

FIG 2 Concentration-response analysis and E_{max} model for maraviroc in CD4$^+$ T cells. The EC_{50} of protein-unbound MVC in CD4$^+$ T cells was 0.68 ng/ml, and the Hill coefficient was 0.73. The EC_{90} protein-unbound target for inhibition of viral infection was 14.02 ng/ml.

The noncompetitive-interaction model demonstrated a synergistic effect ($\Psi < 1$) for both combinations, MVC and TFV ($\Psi = 0.51$) (Fig. 3a) and MVC and FTC ($\Psi = 0.48$) (Fig. 3b). A 3-dimensional surface plot showed that the combinations fit the surface of the model predictions without bias.

Efficacy simulations. The results of the pharmacokinetic-pharmacodynamic (PK-PD) simulations are shown for the FGT tissue and rectal tissue across one to seven doses per week for MVC alone and for the two-drug combinations in Fig. 4. In the FGT, with MVC alone, 63% of the virtual subjects with 100% adherence achieved the target concentration needed for HIV-1 protection. With declining adherence (from six doses/week to one dose/week), the percentage of the population attaining the target concentration declined rapidly (Fig. 4a). The combination of MVC with FTC demonstrated >90% protection with at least 30% adherence. The combination of MVC with TFV demonstrated >90% protection with at least 85% adherence. In rectal tissue, however, administration of four doses/week of MVC alone was associated with >99% protection (Fig. 4b).

In order to predict the pericoital efficacy of MVC-based regimens, we simulated the concentration-time profile of MVC in vulnerable tissues (Fig. 5) after an on-demand Ipergay dosing regimen (two doses 2 to 24 h before coitus, one dose 24 h after coitus, and one dose 48 h after coitus) and up to 14 days postcoitus. When MVC was used alone, protection was achieved in 88% and 98% of the virtual population in FGT tissue (Fig. 5a) and rectal tissue (Fig. 5b), respectively. Protection dropped off rapidly in the FGT tissue, and only 15% of the virtual subjects were predicted to be protected by the 4th day postcoitus without additional doses of MVC. The combination of TFV and MVC in the FGT tissue led to an increase in efficacy predictions, with 65% of virtual subjects protected by the 4th day postcoitus. In comparison, with the combination of MVC and FTC, it was predicted that >96% of the virtual population would be protected by the 4th day postcoitus. In the rectal tissue, the use of MVC alone was predicted to protect 100% of the virtual population up to the 4th day postcoitus, followed by a sharp decline in efficacy. For the combination of TFV and MVC, it was predicted that >90% of the virtual population would be protected in rectal tissue up to 10 days postcoitus, while the combination of FTC and MVC was predicted to have only a marginal increase in efficacy compared to that of MVC alone (>90% of the virtual population protected up to the 5th day postcoitus).

DISCUSSION

While PrEP has shown efficacy in preventing HIV in high-risk populations (18), long-term use of TDF-based prevention strategies has been associated with renal nephropathy (2) and a reduction in bone mineral density (3) in 15% of PrEP users, highlighting the need for other approaches to prevent HIV. Furthermore, large HIV PrEP trials (19–22) have shown various efficacies in MSM and women. Using a similar model-based approach (17), we previously estimated that women would need at least 6 doses of Truvada per week to achieve protective concentrations in the FGT, while MSM would need more than two doses per week to reach adequate concentrations for protection in the rectal tissue. Therefore, while efficacy in HIV prevention trials has been linked with high adherence in women (23), adherence to oral TDF-based PrEP has generally been approximately 30% (20).

Results from the phase II HPTN069 study in women highlight the ongoing challenge of low adherence in HIV prevention trials. Despite a favorable reduction in side effects with MVC-based PrEP regimens, only 60% of women were adherent to daily doses of the study drug (24) (in the MSM group of HPTN069, adherence was 77%) (16). However, our analysis shows that less than 20% of the population would be protected by MVC monotherapy in the FGT with a similar adherence rate. Our model suggests that the combination of MVC and TFV may be slightly more forgiving of low adherence (~40% protection at three doses/week), but MVC combined with FTC is the most forgiving of poor adherence (~90% protection at two doses/week) in the FGT. This is consistent with results from our previous pharmacometric modeling analysis showing that FTC

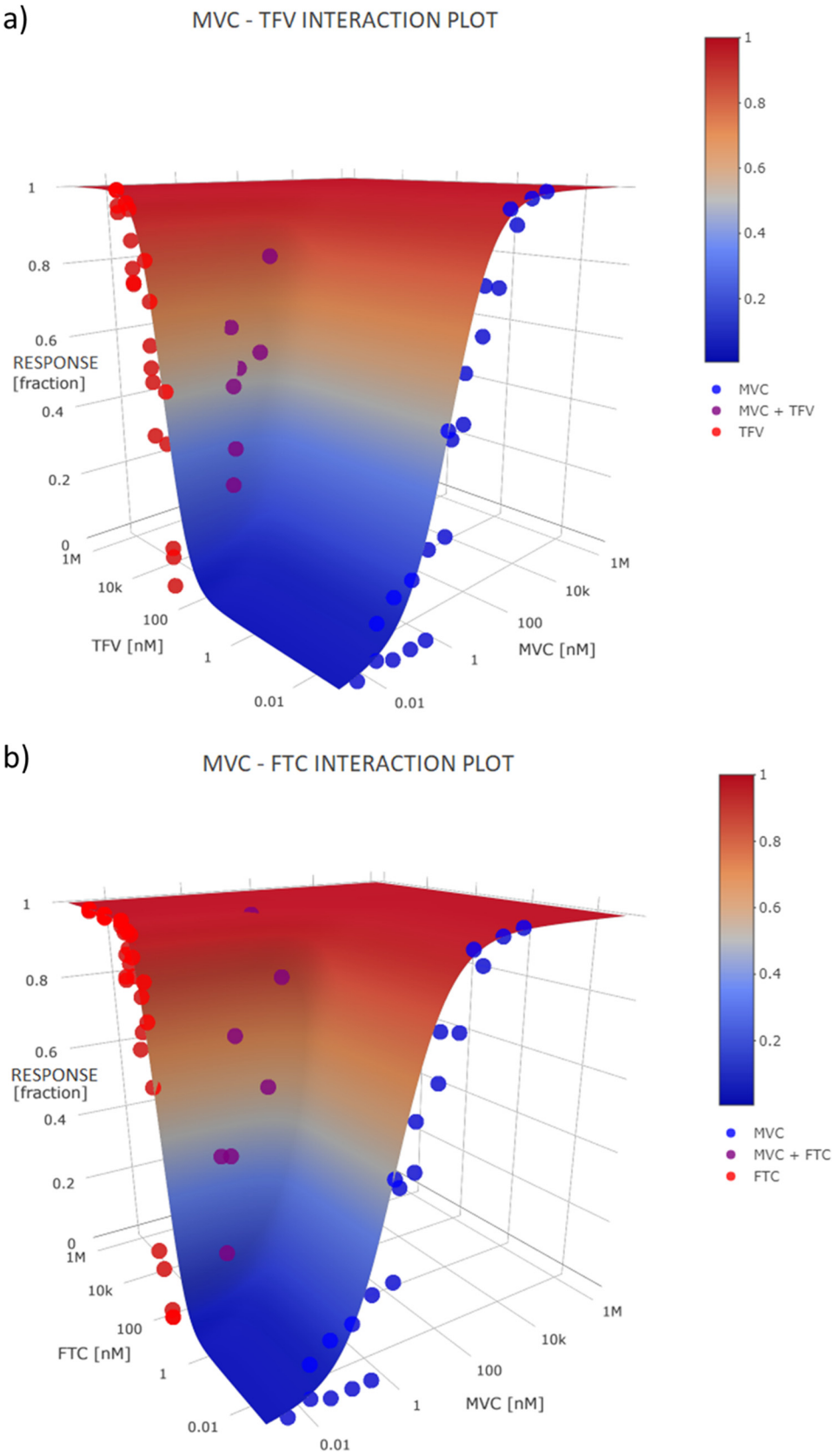

FIG 3 Three-dimensional surface plots showing the interaction between maraviroc (MVC) and tenofovir (TFV) (a) and MVC and emtricitabine (FTC) (b). The combinations fit the surface of the model predictions well, without any bias.

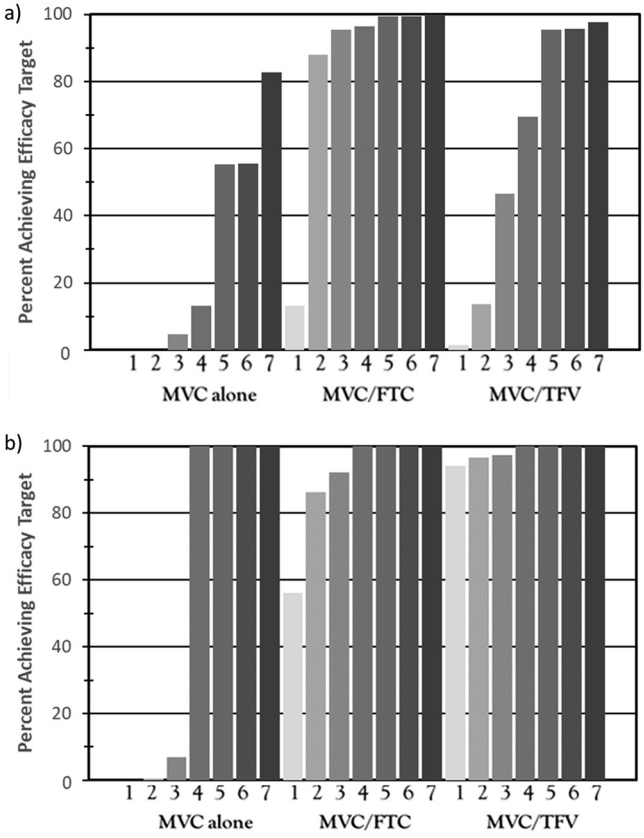

FIG 4 Simulations for protection in female genital tract (FGT) tissue (a) and rectal tissue (b) based on patient adherence (given by number of doses per week). Maraviroc was predicted to show increased efficacy combined with emtricitabine in the FGT (>90% protection at two doses/week) and combined with tenofovir in the rectal tissue (>90% protection with one dose/week).

preferentially accumulates in the FGT compared to TFV (17). In the rectal tissue, our model predicted >90% protection with at least four doses/week of MVC, with protection quickly dropping off with poorer adherence. MVC in combination with either TFV or FTC was more forgiving of poorer adherence (90% protection achieved with 1 dose/week or 3 doses/week, respectively). These data suggest that MVC in combination with either TFV or FTC would show enhanced effectiveness as PrEP compared to that of the monotherapy regimen. Our conclusions agree with those of McGowan et al. (25), who showed that MVC alone showed limited viral suppression in an *ex vivo* rectal biopsy system compared to MVC in combination with either TFV or FTC.

While modeling and simulation analyses do not predict an individual's risk of becoming infected, they may be useful to inform overall forgiveness of PrEP regimens in clinical trials or populations. The modeling framework that was developed in this study could be used to test other ARV drug combinations used in PrEP as well as different dosing regimens or strategies. Such models could also be used to explain biological differences in drug concentration or efficacy at the target site. For example, our group has previously identified pharmacological limitations that may explain the diverging results of TDF-based HIV prevention trials in MSM versus women, despite similar adherence patterns, and outlined estimated minimum adherence requirements for efficacy (17). Strict adherence in women (six or seven doses a week) but not men (two or three doses a week) resulted in at least 90% of the population achieving the efficacy target for protection.

In this work, we used a similar approach to look at MVC-based strategies for HIV prevention. The E_{max} parameters we report here for MVC in protecting $CD4^+$ T cells from HIV infection, accounting for protein binding, have not been previously reported.

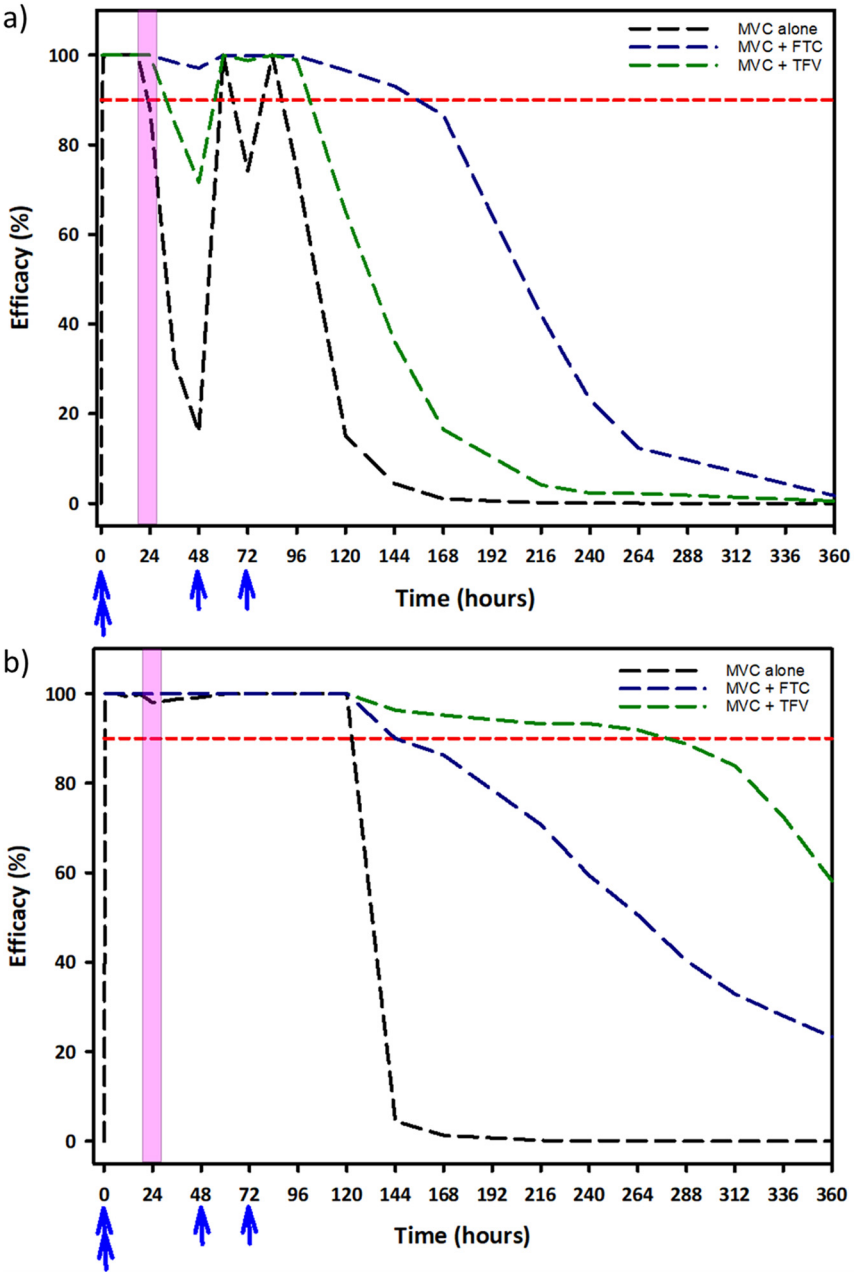

FIG 5 Simulations for protection by the IPERGAY strategy in female genital tract tissue (a) and rectal tract tissue (b). The blue arrows indicate time of dose of preexposure prophylaxis regimen (either maraviroc monotherapy or maraviroc in combination with tenofovir or emtricitabine), and the pink-shaded region represents exposure incident to HIV. The dashed red line represents the 90% efficacy threshold for protection against HIV infection.

Using an interaction model, we demonstrated that MVC showed synergistic antiviral activity in combination with both TDF and FTC. Work previously published by Dorr et al. showed that the antiviral activity of MVC *in vitro* was additive with TFV and mildly synergistic with certain protease inhibitors (9). In our model, we saw similar trends, with the combination of TFV and MVC being less synergistic (higher psi value) than the combination of FTC and MVC. In our simulation of 1,000 subjects, at least three doses of MVC-FTC per week were required for 90% of virtual subjects to attain the target concentration in FGT and rectal mucosal tissues. Given that FTC achieves high concentration in the FGT, the combination may be especially effective as a PrEP strategy in women.

Finally, we evaluated an Ipergay dosing strategy with MVC alone and in combination with FTC and TFV. MVC alone was predicted to protect greater than 90% of the population up to 4 to 5 days postcoitus in the FGT tissue and rectal tissue. While MVC in combination with TFV and FTC prolonged the duration of protection, the magnitude of this effect was dependent on the tissue type, as shown previously (17). Our model predicted that in the FGT, the combination of MVC and FTC would protect >90% of the virtual population up to a week postcoitus. The duration of protection of this combination in the FGT was predicted to be longer than for the combination of TDF and FTC (17), likely due to increased accumulation of MVC in the FGT compared to that of TDF. However, in the rectal tissue, the combination of MVC and FTC showed little additional benefit compared to MVC alone (>90% of virtual population would be protected up to 6 days postcoitus). Similarly, the combination of MVC-TFV was predicted to be highly effective in the rectal tissue, protecting greater than 90% of the virtual population for up to 11 days postcoitus, but was predicted to be only marginally effective in the FGT (>90% of virtual population protected for about 4 days postcoitus). Therefore, while MVC in combination could be an attractive option as an on-demand dosing strategy, different combinations may have to be utilized for men and women to be effective for longer durations, particularly since it is still not known how long the drug would need to be in the tissue in order to be completely protective.

This work has some important limitations. The model for MVC was not able to accurately describe the plasma absorption phase of the PK curve, due to high variability in the data at the lowest dose. However, using data from 24 subjects in this analysis did not support modeling complex absorption profiles to explain multiple peaks in plasma or to capture some of the highest concentrations, and this is shown in the final model diagnostics (Fig. S2b and c). Previously published models (26) have reported similar difficulties in modeling the absorption phase of MVC in plasma. Additionally, the 48-h sampling period did not allow enough time to capture the eventual decline in MVC concentrations in rectal tissue. Having this information would have better informed time to steady state. The tissue concentrations were highly variable, and as a result, the model was not able to adequately capture tissue concentrations at the 12-h postdose time point (particularly in the FGT). Finally, while all tissue concentrations were quantifiable, we used the M5 estimation method for our plasma concentrations below the lower limit of quantification (LLOQ) rather than likelihood estimation methods, and this could have introduced some bias into the model estimates that impact our plasma simulations (27).

In conclusion, PK-PD modeling was used to predict the tissue concentration profile of MVC alone and in combination with standard ARVs to predict efficacy in vulnerable populations with various levels of adherence. From our simulations, adherence significantly affected MVC's efficacy in the FGT. Therefore, if MCV is to be used for PrEP, combining it with FTC might be an effective option in both men and women.

MATERIALS AND METHODS

Clinical trial. A phase I dose-ranging PK study was conducted in healthy women (ClinicalTrials.gov identifier NCT01330199). Each woman was given a single dose of 150 mg, 300 mg, or 600 mg of MVC, which corresponded to 50%, 100%, or 200% of the clinical dose for HIV treatment. Intensive sampling was used for collection of plasma specimens over a 48-h period, including predose (0 h) and the following time points postdose: 0.5, 1, 2, 3, 4, 6, 9, 12, 18, 24, 36, and 48 h. In the case of tissue sampling, each woman contributed one rectal tissue biopsy specimen at a certain time point and one vaginal tissue and cervical tissue biopsy specimen at a distinct time point. Tissue biopsy specimens were collected at either 6, 12, 24, or 48 h. The clinical trial was conducted in accordance with good clinical practice and written consent was obtained from all participants before enrollment into the study. Detailed methodology about the clinical trial and sample collection methods have been published previously (17).

Pharmacokinetic sample analysis. MVC was measured in the plasma, lower FGT tissue, and colorectal tissue by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay which has been described previously (8). In the plasma, the dynamic range of the assay was 5 to 5,000 ng/ml, and accuracy and precision were within 15%. In the tissue, the dynamic range of the assay was 0.02 to 20 ng/ml of tissue homogenate. The precision and accuracy of this assay were within 15% (20% at the lower limit of quantification).

Development of the population pharmacokinetic model. Nonlinear mixed-effects modeling (NONMEM version 7.4; ICON plc) was used to fit a population PK model to the MVC clinical trial

concentration data. MVC concentrations in the plasma, female genital tract tissue, and rectal tissue were log transformed and a log additive error model was used to model residual variability. Samples that were below the limit of quantification (BLQ) were handled by the Beal M5 method (28). The model's predictive performance was evaluated with standard goodness-of-fit plots and by evaluating the plausibility of parameter estimates. One thousand Monte Carlo simulations were performed at each dose using model estimates from the final model, and the model fit was assessed by using visual predictive checks (VPC), stratified by tissue type.

Concentration-response relationships in CD4$^+$ T cells. PBMCs were isolated from buffy coats obtained from 2 donors from the New York Blood Center (Long Island City, NY) and sorted for CD4$^+$ T lymphocytes, using an EasySep negative-selection kit (Stemcell Technologies, Vancouver, Canada). CD4$^+$ T cells were stimulated for 48 h in RPMI medium supplemented with 10% fetal bovine serum (FBS), antibiotics, phytohemagglutinin (PHA; 5 μg/ml), and interleukin 2 (10 U/ml). A total of 1×10^6 resuspended CD4$^+$ T cells/ml were incubated in PHA-free RPMI medium after stimulation along with MVC (0.003 to 1,000 nM) either alone or in combination with TFV (0.3 to 10 μM) or FTC (0.03 to 30 μM) for 24 h. All drugs were obtained from the NIH AIDS Reagent Program. Pseudotyped virus was generated using NL4-3.Luc.R-.E backbone (NIH AIDS Reagent Program) (29, 30) and transfected with *env* expression plasmid from HIV-1JR-CSF, using X-tremeGENE HP (Roche Life Science, Indianapolis, IN). Virions were concentrated 10-fold using a Lenti-X concentrator (Clontech Laboratories, Mountain View, CA). Cells were incubated for 48 h in 25 μl of pseudotyped virus (multiplicity of infection [MOI] of 1) and then lysed with 100 μl of GloLysis buffer. A luciferase assay system kit (Promega) was used to measure relative light units on a Veritas microplate luminometer (Turner Biosystems, Sunnyvale, CA). Infectivity was normalized to infection in the absence of drug and reported as percent inhibition.

Protein binding of maraviroc in macaque mucosal tissue. In order to determine the free fraction of MVC in the mucosal tissues, the protein binding of MVC was determined by rapid equilibrium dialysis in the lower FGT and colorectal tissue of six male and three female adult rhesus macaques. Details of this animal study have been described previously (31). In brief, six male and three female adult rhesus macaques were dosed to steady-state with TFV, FTC, MVC, and RAL. At day 10, the macaques were euthanized by a barbiturate overdose, and tissue reservoirs were collected at necropsy. The vaginal and colorectal tissue sections were snap-frozen in dry ice and placed in aluminum foil. A section of the tissue was reserved to determine the protein binding; the full details are described in the supplemental material.

Statistical analysis. Drug exposure was plotted against percent inhibition of HIV-1 pseudovirus in the *in vitro* CD4$^+$ T cell system and fit to a sigmoidal E_{max} model (SAS version 9.3) to calculate an EC_{90} target using equation 1. E_0 is the response at zero concentration (fixed to 0), E_{max} is the maximal response (fixed to 100), [Cu] is the unbound concentration of maraviroc, β is the Hill slope, and E is the response. Previously published reports have shown that the protein binding of MVC in a cellular system containing 10% FBS is 46%. This protein correction factor was applied to our *in vitro* system to give a measure of unbound MVC concentration in the CD4$^+$ T cell culture systems. The EC_{50} target for MVC was combined with previously determined EC_{50} targets for TDF and FTC (17) by using a noncompetitive interaction model (32) to determine if there was a synergistic interaction between MVC and TFV (equation 2) or MVC and FTC (equation 3). For the interaction models, the EC_{50} values and Hill slopes of MVC, TDF, and FTC were fixed and Ψ was the interaction term. A 3-dimensional goodness-of-fit plot was generated and visually inspected in order to check for bias in the model predictions.

$$E = E_0 + \frac{E_{\max} \times [Cu]\beta}{EC_{50}\beta + [Cu]\beta} \tag{1}$$

$$E = \frac{\left(\frac{\mathrm{TFV}}{\psi \times \mathrm{EC}_{50,\mathrm{TFV}}}\right)^{\mathrm{H}_{\mathrm{TFV}}} + \left(\frac{\mathrm{MVC}}{\psi \times \mathrm{EC}_{50,\mathrm{MVC}}}\right)^{\mathrm{H}_{\mathrm{MVC}}} + \left(\frac{\mathrm{TFV}}{\psi \times \mathrm{EC}_{50,\mathrm{TFV}}}\right)^{\mathrm{H}_{\mathrm{TFV}}} \times \left(\frac{\mathrm{MVC}}{\psi \times \mathrm{EC}_{50,\mathrm{MVC}}}\right)^{\mathrm{H}_{\mathrm{MVC}}}}{1 + \left(\frac{\mathrm{TFV}}{\psi \times \mathrm{EC}_{50,\mathrm{TFV}}}\right)^{\mathrm{H}_{\mathrm{TFV}}} + \left(\frac{\mathrm{MVC}}{\psi \times \mathrm{EC}_{50,\mathrm{MVC}}}\right)^{\mathrm{H}_{\mathrm{MVC}}} + \left(\frac{\mathrm{TFV}}{\psi \times \mathrm{EC}_{50,\mathrm{TFV}}}\right)^{\mathrm{H}_{\mathrm{TFV}}} \times \left(\frac{\mathrm{MVC}}{\psi \times \mathrm{EC}_{50,\mathrm{MVC}}}\right)^{\mathrm{H}_{\mathrm{MVC}}}} \tag{2}$$

$$E = \frac{\left(\frac{\mathrm{FTC}}{\psi \times \mathrm{EC}_{50,\mathrm{FTC}}}\right)^{\mathrm{H}_{\mathrm{FTC}}} + \left(\frac{\mathrm{MVC}}{\psi \times \mathrm{EC}_{50,\mathrm{MVC}}}\right)^{\mathrm{H}_{\mathrm{MVC}}} + \left(\frac{\mathrm{FTC}}{\psi \times \mathrm{EC}_{50,\mathrm{FTC}}}\right)^{\mathrm{H}_{\mathrm{FTC}}} \times \left(\frac{\mathrm{MVC}}{\psi \times \mathrm{EC}_{50,\mathrm{MVC}}}\right)^{\mathrm{H}_{\mathrm{MVC}}}}{1 + \left(\frac{\mathrm{FTC}}{\psi \times \mathrm{EC}_{50,\mathrm{FTC}}}\right)^{\mathrm{H}_{\mathrm{FTC}}} + \left(\frac{\mathrm{MVC}}{\psi \times \mathrm{EC}_{50,\mathrm{MVC}}}\right)^{\mathrm{H}_{\mathrm{MVC}}} + \left(\frac{\mathrm{FTC}}{\psi \times \mathrm{EC}_{50,\mathrm{FTC}}}\right)^{\mathrm{H}_{\mathrm{FTC}}} \times \left(\frac{\mathrm{MVC}}{\psi \times \mathrm{EC}_{50,\mathrm{MVC}}}\right)^{\mathrm{H}_{\mathrm{MVC}}}} \tag{3}$$

Efficacy simulations. Monte Carlo simulations were performed using the final population PK model at various levels of medication adherence to simulate 1,000 virtual subjects administered a 300-mg dose of MVC for PrEP under steady-state conditions. Adherence ranged from daily administration of MVC (seven doses per week) to once-weekly administration of MVC (one dose per week) and was modeled by using different values of interdose interval (II) in the NONMEM data set. For example, perfect adherence was modeled with an II of 24, while an adherence of six doses a week was modeled with an II of 28, and so on. The exposure in rectal tissue were further adjusted for unabsorbed MVC passing through the gut (50.5%) (33), and the exposures in the FGT and rectal tissue were adjusted for the measured tissue protein binding fraction. Under steady-state conditions, the concentrations in tissue at the end of the dosing interval were compared to efficacy targets either for MVC alone (EC_{90} target from E_{max} model) or

for MVC in combination with TFV or FTV (synergy model). Protection was defined as a simulated tissue concentration at the end of the dosing interval that was above the efficacy target defined in the $CD4^+$ T cells. The extent of protection in the virtual subjects was expressed as a percentage of the total simulated population.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.7 MB.

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