Title:

A Pharmacokinetic/Pharmacodynamic Model to Predict Effective HIV Prophylaxis Dosing Strategies for People Who Inject Drugs

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List of nonstandard abbreviations:

BQL: below the quantitation limit; dATP: deoxyadenosine triphosphate; dCTP: deoxycytidine

triphosphate; FTC: emtricitabine; HIV: human immunodeficiency virus; PrEP: pre-exposure

prophylaxis; PWID: people who inject drugs; TAF: tenofovir alafenamide; TFV: tenofovir; TDF:

tenofovir disoproxil fumarate; TFVdp: tenofovir diphosphate; FTCtp: emtricitabine triphosphate

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Abstract

The goal of this work was to evaluate dosing strategies for tenofovir disoproxil fumarate (TDF),
tenofovir alafenamide (TAF), and emtricitabine (FTC) for pre-exposure prophylaxis (PrEP) with
injection drug use with a pharmacokinetic/pharmacodynamics analysis of concentration data
generated from two single-dose clinical studies conducted in healthy women. Population
pharmacokinetic models were developed using measured intracellular metabolite, endogenous
nucleotide competitors, and extracellular parent drug concentrations. Intracellular metabolite
concentrations were normalized to endogenous competitors and compared to an EC_{90} target for
PrEP efficacy. Monte-Carlo simulations were used to select effective dose strategies of single
agents (TAF, TDF, FTC) and combinations (TDF+FTC, TAF+FTC). Daily dosing, intermittent
dosing, and event-driven dosing at varying dosage amounts were explored. When combined,
both TDF+FTC and TAF+FTC provided quick (0.5 h) and durable (up to 84 and 108h,
respectively) protection of ≥99% after a single dose. When dosed twice per week, protection
remained at 100%. Single-agent regimens provided lower estimates of protection than either
combination tested. Here, the application of pharmacokinetic modeling to in vitro target
concentrations demonstrates the added utility of including FTC in a successful PrEP regimen.
While no TAF-based PrEP data are yet available for comparison, this analysis suggests
TAF+FTC could completely protect against percutaneous exposure with as little as 2 doses per
week.

Introduction

As part of a comprehensive harm reduction program for people who inject drugs (PWID),

(opioid treatment facilities, syringe services programs, etc.), the Centers for Disease Control and

Prevention (CDC) recommends pre-exposure prophylaxis (PrEP) with once daily tenofovir

(TFV) disoproxil fumarate (TDF), alone or in combination with emtricitabine (FTC), to prevent

HIV (US Public Health Service, 2014). This recommendation is based on the Bangkok Tenofovir

Study (Choopanya *et al.*, 2013), which found a 49% risk reduction in participants taking TDF

compared to placebo. The combination of TDF+FTC has never been studied in a PWID

population, despite showing benefit in other settings (Grant *et al.*, 2010; Baeten *et al.*, 2012).

TDF and FTC are known to work synergistically (Cottrell *et al.*, 2016), have different

pharmacokinetic profiles in various tissues (Patterson *et al.*, 2011; Cottrell *et al.*, 2015;

Dickinson *et al.*, 2015), and are available in a co-formulated product. Additionally, the

combination is attractive in the event of exposure to HIV with resistance-associated mutations.

Tenofovir alafenamide (TAF) was approved as a co-formulated tablet with FTC in 2016. When

compared to TDF, TAF has a more advantageous pharmacokinetic and safety profile (Ruane *et

al.*, 2013) in the treatment of HIV, and is currently in clinical trials for its use in preventing HIV

transmission from sexual exposure. Given these facts, the feasibility of TAF+FTC for prevention

of HIV transmission for PWID is appealing; however, the efficacy of TAF for PrEP is still

unknown.

The Bangkok Tenofovir Study was largely conducted in a directly-observed-therapy

(DOT) setting. While DOT can improve HIV virologic outcomes in PWID (Altice *et al.*, 2007;

Berg *et al.*, 2011), DOT may not be a sustainable option for PrEP outside of a medication

assisted treatment program for opioid dependence. Antiretroviral therapy and engagement in

care, for HIV treatment or prevention, can be especially difficult for people with substance use

disorder, with or without other mental health disorders. The use of event-driven PrEP among the

men who have sex with men (MSM) population has shown benefit (Molina *et al.*, 2015), but on-

demand dosing has not yet been studied in PWID.

TAF, TDF, and FTC are metabolized to active intracellular metabolites by host

phosphatases (Anderson *et al.*, 2011). TFV diphosphate (TFVdp) is the active metabolite of both

TAF and TDF, and FTC triphosphate (FTCtp) is the metabolite of FTC. These metabolites work

by acting as nucleotide analogues and are reverse transcribed into the HIV DNA in HIV-infected

cells. Incorporation of either TFVdp or FTCtp into HIV DNA results in chain termination and

prevention of viral replication. In order to be incorporated into HIV DNA, these metabolites

must compete with their analogous, naturally occurring nucleotide, referred to here as

endogenous nucleotides. TFVdp is an adenosine triphosphate analogue, and FTCtp is a cytosine

triphosphate analogue. Both metabolites have long intracellular half-lives: about 6 days for

TFVdp and 1.6 days for FTCtp (Anderson *et al.*, 2011). Since PWID would be exposed to HIV

via direct inoculation in blood (rather than through tissues as in sexual exposure), drug

concentrations at that site, i.e. peripheral blood mononuclear cells (PBMCs) were considered

especially relevant. To investigate the potential benefit of TDF or TAF, with or without FTC,

pharmacokinetic modeling of the active metabolites and their endogenous nucleotide

competitors, dATP and dCTP, in PBMCs was used in combination with a previously described

pharmacodynamic model (Cottrell *et al.*, 2016) to simulate effective dosing regimens in a PWID

population.

Materials & Methods

Study Design

Concentrations of TFV, TAF, FTC, TFVdp, and FTCtp from two previously reported

oral, single-dose pharmacokinetic studies in healthy women (NCT010330199 and

NCT02357602) (Cottrell *et al.*, 2016, 2017) were analyzed. Both studies were approved by the

University of North Carolina's Biomedical Institutional Review Board. Details of the study

design and bioanalytical analysis were described previously (Cottrell *et al.*, 2016, 2017). Briefly,

72 women were enrolled to receive either TDF (150, 300, or 600mg; n=8/arm), FTC (100, 200,

400 mg; n=8/arm), or TAF (5, 10, 25 mg; n=8/arm). For TDF and FTC, plasma was collected at

0.5, 1, 2, 3, 4, 6, 9, 12, 18, 24, 36, and 48h post-dose; PBMCs were collected at 1, 3, 6, 12, 24,

36, and 48 h post-dose. For TAF, plasma was collected 1, 3, 6, 12, 24, 72, 168, 240, and 336h

post-dose and PBMCs were collected 3, 6, 12, 24, 72, 168, 240, and 336h post-dose. All analytes

were measured by LC-MS/MS methods with the following lower limits of quantitation (LLOQ):

TFV and FTC (5ng/mL); TFVdp, FTCtp, dATP, and dCTP (0.02ng/ml, normalized by cell

count); and TAF (0.05ng/mL). TAF was only measured in subjects enrolled in the 25mg arm.

Doses of TDF, FTC, and TAF and concentrations were converted to micromolar (µM)

units to allow co-modeling of all analytes. Molecular weights (gram/mole; g/mol) used for

conversion were: TDF, 635.52; FTC, 247.248; TAF, 476.466; TFV, 287.216. The estimate of

PBMC volume was one cell equivalent to 282 femtoliters (fl) (Rodriguez *et al.*, 2000).

Model Development and Evaluation

Parent (TFV, TAF, FTC) and metabolite (TFVdp, FTCtp) data were co-modeled in

NONMEM (v7.3, ICON Development Solutions, Ellicott City, MD) using the ADVAN6

subroutine and the first-order conditional (TDF,FTC) or Laplacian (TAF) estimation method

with interaction. Pirana and Perl-speaks-NONMEM (PsN) were used for the population model

development (Lindbom *et al.*, 2005; Keizer *et al.*, 2011). Data visualization was conducted in R

(v 3.3.2, R Foundation for Statistical Computing, Vienna, Austria) using R Studio (v 1.0.136,

RStudio, Boston, MA) (R Core Team, 2016) and the tidyverse and Xpose4 packages.

Models tested included one, two, and three compartment plasma models with zero and 1st

order absorption and elimination. Conversion of parent to metabolite was tested using 1st order

and Michaelis-Menten kinetics (Chen *et al.*, 2016), and transit compartments. Parent amounts,

assumed to be primarily renally excreted rather than metabolized, were linked to metabolite

concentrations using micro-rate constants. The M3 method was used to account for data below

the quantitation limit (BQL) (Beal, 2001).

Inter-individual variability (IIV) was assumed to be normally distributed with mean of

zero and variance ω^2, and exponentially associated with the population parameters. Covariance

among IIVs was explored based on correlation. Proportional and combined additive and

proportional residual variability models were assessed separately for each analyte, and were

assumed to be normally distributed with a mean of zero and a variance σ^2. Due to the

homogeneity of the study population, covariate analysis was not performed. Final model

selection was determined using a combination of the precision of parameter estimates, Akaike

information criterion, goodness-of-fit plots, and physiologic plausibility. Prediction-corrected

visual predictive checks (PC-VPCs) were generated using nominal sample times to evaluate

model appropriateness.

Simulations

Monte Carlo simulations of TFVdp and FTCtp in PBMCs were performed for 1000

virtual subjects, each taking 300mg TDF, 200mg FTC, or 25mg TAF (conventional treatment

doses for each drug) based on the final model developed for each drug. Dosing regimens included conventional treatment dose, double dose (i.e., a dose of 600mg TDF, 400mg FTC, or 50mg TAF), steady-state dosing with 1-7 equally-spaced conventional treatment doses/week, and on-demand dosing in which subjects took a double dose 24 or 2 hours prior to exposure followed by a single, standard treatment dose 24 and 48h after exposure (Molina *et al.*, 2015). dCTP and dATP concentrations were randomly selected from the log-normal distribution of those analytes (presented as log[analyte]~N(mean, standard deviation)): log[dCTP]~N(0.35, 0.47); log[dATP]~N(-0.99, 0.38). Ratios of TFVdp to dATP and FTCtp to dCTP were subsequently calculated by dividing the concentration of metabolite by the concentration of endogenous nucleotide.

Protective Effect

The active metabolite to endogenous nucleotide ratio that was 90% effective (EC90) in prevention of transmission (0.29 for TFVdp:dATP and 0.07 for FTCtp:dCTP) was used when any of the drugs were assessed as monotherapy (Cottrell *et al.*, 2016). A pharmacodynamic interaction model (**Equation 1**) of TFVdp:dATP and FTCtp: dCTP ratios was used to determine the simulated protected effect when each of the TFV prodrugs was combined with FTC. The 50% effective concentration (EC_{50}) and Hill (H) coefficients for each drug ratio and the synergy parameter (ψ) were previously established and fixed (Cottrell *et al.*, 2016). Parameters were: EC_{50}, $_{TFVdp}$ 0.086, H_{TFVdp} 1.81; EC_{50}, $_{FTCtp}$ 0.077, H_{FTCtp} 1.88; ψ 0.63. Because the active metabolites have long half-lives, to allow for consistency in modeling and to align with clinical standards for trough monitoring (i.e. vancomycin), ratios were assessed 30 minutes prior to next dose for steady-state dosing. If ratios were greater than the EC_{90}, they were declared above target for the dosing interval.

$$(Eq. 1)\ E\ =\ \frac{\left(\frac{TFV}{\psi \times EC_{50,TFVdp}}\right)^{H_{TFVdp}}+\left(\frac{FTC}{\psi \times EC_{50,FTCtp}}\right)^{H_{FTCtp}}+\left(\frac{TFV}{\psi \times EC_{50,TFVdp}}\right)^{H_{TFVdp}}\times\left(\frac{FTC}{\psi \times EC_{50,FTCtp}}\right)^{H_{FTCtp}}}{1+\left(\frac{TFV}{\psi \times EC_{50,TFVdp}}\right)^{H_{TFVdp}}+\left(\frac{FTC}{\psi \times EC_{50,FTCtp}}\right)^{H_{FTCtp}}+\left(\frac{TFV}{\psi \times EC_{50,TFVdp}}\right)^{H_{TFVdp}}\times\left(\frac{FTC}{\psi \times EC_{50,FTCtp}}\right)^{H_{FTCtp}}}$$

Results

Study Population and PK Observations

Of 288 TFV plasma samples collected, one (0.3%) was below the quantitation limit

(BQL). One participant in the FTC arm had unusable samples due to improper storage, leaving

276 available for analysis and one (0.4%) was BQL. There were 166 and 161 TFVdp and FTCtp

samples for analysis in the TDF and FTC arms, respectively. Five (3.6%) TFVdp samples and

one (0.6%) FTCtp sample were BQL. TAF was measured in plasma from participants taking

25mg TAF. All samples collected beyond 6h post-dose were BQL, resulting in 23 samples for

evaluation. Of these, 5 (22%) were BQL, all occurring at the 6h time point. Women enrolled in

both studies had median ages of 22 and 27 years (**Table 1**). There were no significant differences

in age or weight between the groups (*p*=0.1). The majority of participants were white (72%) and

non-Hispanic (96%).

Population PK Analysis

A two-compartment model with first-order absorption and elimination best described

FTC plasma pharmacokinetics, with saturable metabolite formation. A one-compartment model

described FTCtp, with first-order transfer of metabolite back to plasma. A two-compartment

model with delayed absorption best described the plasma TFV (from TDF) pharmacokinetics. A

one-compartment model with first-order formation from plasma TFV and clearance out of the

body best described the TFVdp data. The elimination rate of TFVdp following dosing with TDF

could not be estimated because its half-life was longer than the sampling period of 48h, so it was

fixed to a value consistent with the TAF data (0.0125 h^{-1}). A one-compartment model with an

additional transit compartment for metabolite conversion best described the TAF and TFVdp

data. Since the time to maximum concentration is 0.48h after dosing (Ruane *et al*., 2013) and the

earliest time point in this study was 1h, absorption phase could not be characterized and the rate

constant was fixed to 2.8 h^{-1}.

Simulated concentration-time profiles for TFV and TFVdp (TDF), FTC and FTCtp

(FTC), and TAF and TFVdp (TAF) following dosing with TDF 300mg, FTC 200mg, and TAF

25mg are shown in **Figure 1**. Population pharmacokinetic parameter estimates are provided in

Supplemental Table 1; model schematics for each drug are presented in **Supplemental Figures**

1-3; example model code is presented in **Supplemental File 1**. All fixed effect parameters were

estimated with acceptable precision [residual standard error (RSE%) ≤30%]. Shrinkage of

random effects parameters was ≤50%. Diagnostic plots did not reveal any model

misspecification and estimated parameters were physiologically plausible. Inter-individual

variability for the clearance parameter was higher in patients receiving TAF (>65%) compared to

those receiving TDF or FTC (<35%). All three models captured the central tendency of the data

well and were deemed suitable to generate simulations.

Simulations and Efficacy

With on-demand dosing, a single dose of TDF is predicted to provide protection in 2%

and 50% of the population at the time of HIV exposure if TDF is taken 2h or 24h prior

(**FIGURE 2**). All other dosing combinations are expected to provide near 100% protection at

time of exposure, regardless of initial dose time. TDF+FTC provides protection for up to 120h

post-exposure whereas TAF+FTC provides protection for 192h post-exposure in >99% of the

population. At steady-state, the model predicts TDF alone provides the least efficacy based on

the target EC_{90} (**FIGURE 3**). Taking 1, 4, or 7 doses per week of TDF is predicted to provide 3,

72, and 92% protection. Taking the same number of TAF doses per week is predicted to provide

16, 100, and 100% protection. FTC is predicted to provide similar efficacy as TAF. When

combining FTC with either TDF or TAF, as few as two doses per week should provide near

100% protection.

A single dose of TDF is expected to maximally provide 44% protection at 48h after

dosing. (**FIGURE 4**) Comparatively, a single dose of TAF would provide 100% protection

between 3-36h after the dose with >90% protection 60h after the dose. FTC would provide >90%

protection between 0.5-84h after a dose. Using twice the clinical dose, the time to maximal

protection with TDF is shortened to 28h, where 80% protection is expected. TAF should provide

near 100% protection 2h after the dose and remain near 100% through 72h, with 90% protection

through 120h. FTC provides near 100% protection through 144h. Combining FTC with TDF or

TAF results in protection >90% for 144h and 176h after dosing, respectively.

Discussion

TFVdp and FTCtp work by acting as nucleotide analogues and are reverse transcribed into the HIV DNA. Incorporation of either TFVdp or FTCtp results in HIV DNA chain termination and inhibition of viral replication. TFVdp and FTCtp compete with their endogenous nucleotides dATP and dCTP. When TFVdp and FTCtp are present, they must reach a threshold to be preferentially incorporated into DNA. Because this threshold is inherently dependent upon the endogenous nucleotide pool within an individual, we chose to use the ratio of TFVdp to dATP and FTCtp to dCTP as our pharmacodynamic targets. This method has been previously validated using in vitro data (Cottrell *et al.*, 2016) and was cited as an efficacy target in a non-human primate PrEP study (García-Lerma *et al.*, 2011).

In this analysis, we show the rapid accumulation of FTCtp and the prolonged half-life of TFVdp in PBMCs are both necessary to protect PWID from HIV infection. Complete protection could be achieved with either TDF+FTC or TAF+FTC dosed twice weekly for those engaged in frequent and routine injection drug use, or dosed on-demand as little as 2h prior to exposure for those who inject less frequently. Our data support the CDC recommendation of TDF alone as a viable option, where our prediction of daily TDF would provide 92% protection. For patients unable to take TDF, daily TAF could provide complete protection. However, when TDF or TAF are combined with FTC, additional individuals will be protected if using fewer doses. Due to the synergistic efficacy of FTCtp and TFVdp (Cottrell *et al.*, 2016), a combination product could protect 100% of the population with two doses per week with a single dose providing protection at least 84h after a dose.

This analysis was based upon the assumption of preventing infections caused by blood-borne transmission of wild-type HIV. Nucleoside reverse transcriptase inhibitor associated

mutations, such as M184V and K65R, generally decrease viral fitness (Wertheim *et al.*, 2017).

However, the M184V mutation, which confers FTC resistance but increases TDF/TAF

sensitivity, is common among people failing antiretroviral therapy (Wainberg *et al.*, 2011).

Primary resistance with M184V can occur in 7-23% of new HIV infections (Wainberg *et al.*,

2011), thus PrEP with FTC alone is not recommended in practice. Despite perfect adherence,

PrEP may not be able to protect against multi-drug resistant virus (Knox *et al.*, 2017).

We chose to evaluate protection conferred by a single conventional treatment dose of

each drug and combination. A 300mg dose of TDF was expected to provide a maximum of 44%

protection, whereas FTC, TAF, TDF+FTC, and TAF+FTC all reached 100% protection and

sustained it for up to 3.5 days after dosing. To determine if weekly dosing was a viable option,

double doses of all drugs and combinations were tested. At 7 days after a double dose of

TAF+FTC, 93% of the population is expected to be protected compared to 24, 38, 53, and 78%

with TDF, FTC, TAF, and TDF+FTC respectively.

Additionally, we chose to look at multi-dose and event-driven strategies for each drug

and combination: evaluating 1-7 doses per week and utilizing an event-driven strategy around

the time of injection. On-demand strategies were evaluated starting 2 or 24h prior to injection.

FTC, TAF, TDF+FTC, and TAF+FTC were estimated to provide 100% protection whether taken

2 or 24h prior to event with protection up to 192 h for TAF+FTC. Conversely, due to the much

lower TFVdp concentrations associated with TDF than TAF, TDF was estimated to only protect

2 and 50% if taken 2 or 24h prior to event, respectively. With 3 doses per week, TAF and FTC

were estimated to provide 100% protection whereas the same level of protection could be

achieved with 2 doses per week of either TAF+FTC or TDF+FTC.

Pharmacometric models are limited by the data used to generate them. For the TDF

model, a 48-hour sampling window was not long enough to capture the elimination phase of

TFVdp due to its extended half-life. We fixed this parameter to a value comparable to the one

from the TAF model. In addition, the first-order process failed to capture the rapid generation of

TFVdp within the first two hours, while using the saturable model only described it well at the

300 mg dose level. We chose the model with first-order TFVdp conversion given that it fit the

data across doses better and is easier to interpret. The model is able to reasonably predict the

TFVdp steady-state trough concentrations (Chen *et al.*, 2016) which were more relevant for this

exercise. FTC had minimal limitations as sampling times allowed for adequate estimation of

absorption and elimination of both FTC and FTCtp. Additionally, non-linearity was observed in

the dose range studied and implemented in the model.

For TAF model development, only the highest dosing arm (25 mg) had detectable TAF

plasma concentrations and the earliest time point was one-hour post-dose. The literature-

referenced time to maximum concentration for TAF is ~0.5 hours (Ruane *et al.*, 2013) and would

not have been adequately captured in the pharmacokinetic model had the absorption rate

constant, Ka, not been fixed. Since data for TAF was only available for three time points and the

last time point had several values below the quantification limit, a TAF plasma model could not

precisely be developed. A two-compartment model has been reported (Gaur *et al.*, 2016), but

was not supported by our data. Due to these limitations, a one-compartment model was used. The

lack of data and/or compartmental misfit could explain the high inter-individual variability of

TAF clearance and the inability to estimate volume inter-individual variability. However, the M3

method is the gold standard when modeling datasets with large proportions of values below the

quantification limit (Beal, 2001), and was utilized to maximize the knowledge gained from these

data. The model also assumes that the conversion of TAF to TFVdp, and the subsequent

elimination of TFVdp, are linear across the 5-50 mg dose range, which may not be the case

based on early steady-state data (Ruane *et al.*, 2013). However, the single-dose data used in this

analysis were linear (Cottrell *et al.*, 2017). This raises an important consideration when using

single-dose data for multi-dose simulations: elimination may not continue to be linear as

concentrations increase. Unfortunately, the model was not able to account for this. However, if

concentrations of TFVdp in PBMCs did increase due to non-linear elimination, the model

developed would under-predict efficacy rather than over-predict, making this a conservative

estimate of PrEP efficacy in a PWID population.

The paucity of Phase III clinical data to evaluate the efficacy of PrEP among PWID

limits the ability of clinicians to present their patients with scientifically-informed options to

prevent HIV infection. The Bangkok Tenofovir Study used a modified-intent-to-treat analysis in

which two participants were excluded because they were HIV-positive at enrollment, and found

a 48.9% reduction in HIV. Among participants adherent at least 71% of the time, without

missing ≥2 consecutive doses, and who had detectable drug concentrations, there was a 73.5%

reduction in HIV transmission in the TDF group (Choopanya *et al.*, 2013). This corresponded to

our analysis in which 71.2 and 82.5% of the population is expected to be protected with 4-5

doses of TDF per week. This is particularly striking because our analysis was based on the

pharmacokinetic profiles of young, healthy women and not persons chronically ill from injection

drug use. While acute kidney injury has been noted as a sequelae of injection drug use (Wilson *et

al.*, 2017), normal renal function was assumed in this analysis. Other population models for

tenofovir and emtricitabine pharmacokinetics include a covariate effect of creatinine clearance

on parent drug clearance; such a function could be considered for this model, however given that

clinical studies evaluating TDF+FTC for PrEP exclude participants with reduced renal function,

the Bangkok Tenofovir Study included, we did not implement this covariate in our model. Thus,

any renal impairments associated with injection drug use in real-world patients would need to be

taken into consideration, as the relationship between renal impairment and increasing tenofovir

concentrations, and subsequent toxicity, is well-described (Hall *et al.*, 2011). However, in

individuals with creatinine clearance > 50ml/min, these medications require no dosage

adjustment and have been used long-tern with an acceptable adverse effect profile. The safety is

such that the FDA recently approved TDF+FTC for long-term use in adolescents for PrEP

(Office of Communication 2018), an age cohort where the risk-benefit relationship was not

always clear. In those with creatinine clearance < 50 ml/min, continued use of TDF, particularly

for PrEP, requires an individual weighing of HIV acquisition risk compared to risk of further

renal impairment. TAF, on the other hand, has a more favorable safety profile compared to TDF,

especially in regards to renal function (Ruane *et al*., 2013). Future work using the strategies

highlighted in this modeling exercise in the PWID population will be needed to ensure our

parameter estimates from healthy volunteers are comparable.

The length of PrEP dosing required to provide adequate protection is a concern. While

we show that two doses per week of TDF+FTC or TAF+FTC would provide near 100%

protection, we did not specifically analyze the duration of time at which the ratio must exceed

the efficacy target nor the effect of multiple HIV exposures within a dosing interval. However,

since a single dose would provide protection for 84 and 108h, respectively, we believe as long as

the second dose is taken within that time frame, protection should be maximal.

Lastly, this analysis has been conducted with the assumption that PWID are only exposed

to HIV via injection drug use and not via other concurrent routes. This likely does not apply to

all PWID, and should be considered in the context of dosing strategies to protect mucosal

surfaces for HIV infection (Cottrell *et al.*, 2016). Women are particularly vulnerable and less

than daily dosing has not been demonstrated effective for vaginal HIV exposure. Furthermore,

less than daily dosing may be more challenging to adhere to (Bekker *et al.*, 2018). A person's

entire risk profile should be taken into account when considering PrEP.

In summary, to our knowledge, this is the first pharmacokinetic/pharmacodynamic model

to evaluate TDF, TAF, and FTC for PrEP in a PWID population. We demonstrate data consistent

with the Bangkok Tenofovir Study and provide characterization of the intracellular interactions

necessary to protect cells from HIV infection. These data can be used to inform future clinical

studies and potentially policy decisions in the absence of specific clinical investigations. This

approach can also be extended to evaluate the efficacy of dosing scenarios for other compounds

under investigation for PrEP. Because of the limitations highlighted, these data should not be

used to make clinical decisions at this time, but should be used to design clinical studies to

evaluate PrEP for PWID.

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Footnotes:

Previous Presentations: Portions of this work have been presented at HIV Research for Prevention (HIVR4P) [17-21 October 2016, Chicago, Illinois, Poster P21.12LB] and American Conference on Pharmacometrics 8 [14-19 October 2017, Fort Lauderdale, Florida, Poster T-081].

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Legends for Figures

Figure 1: Concentrations of Parent Drug and Metabolites in Plasma and PBMCs

Figure 1. Median (minimum-maximum) concentration of tenofovir (TFV), emtricitabine (FTC), tenofovir alafenamide (TAF), tenofovir diphosphate (TFVdp), and emtricitabine triphosphate (FTCtp) in plasma (left) and peripheral blood mononuclear cells (PBMCs; right) after a single dose of 300mg tenofovir disoproxil fumarate (TDF), 200mg FTC, or 25mg TAF. All data are represented for TDF and FTC; TAF data are represented through 48h of study (total study 14 days; 48h data point imputed).

Figure 2: Protection Using On-Demand Dosing

Figure 2 depicts pharmacokinetic/pharmacodynamic (PK/PD) simulations of protection using on-demand dosing in which a double dose of the indicated drug is taken 24 hours (left) or 2 hours (right) prior to HIV exposure followed by a standard doses 24 and 48 hours after exposure. TDF, tenofovir disoproxil fumarate; TAF tenofovir alafenamide; FTC emtricitabine. Standard dose: 300mg TDF, 25mg TAF, 200mg FTC.

Figure 3: Protection Using Steady-State Dosing

Figure 3 depicts the proportion of population above the target at the end of the dosing interval in 1-7 equally-spaced doses of the target drug each week. TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; FTC, emtricitabine.

Figure 4: Single and Double Dose Protection Simulations

Figure 4 depicts pharmacokinetic/pharmacodynamic (PK/PD) simulations of protection when a single dose (left) and a double dose (right) of the indicated drug(s) is taken. TDF, tenofovir disoproxil fumarate; TAF tenofovir alafenamide; FTC emtricitabine. Standard dose: 300mg TDF, 25mg

Table 1: Demographics of Participants

	TDF (n=24)	FTC (n=24)	TAF (n=24)
Age[a], years	27 (21-38)	22 (20-39)	25 (19-46)
Weight[a], kg	66.85 (50.8-94.7)	62.75 (46.3-90.3)	68.54 (50.53-107.05)
Race[b]			
White	16 (66.7)	18 (75)	20 (83.3)
Black	7 (29.2)	4 (16.7)	4 (16.7)
Asian	1 (4.2)	1 (4.2)	0
Native American	0	1 (4.2)	0
Ethnicity[b]			
Hispanic	0	0	3 (12.5)
Non-Hispanic	24	24	21 (87.5)

[a]Data expressed as median (minimum-maximum).

[b]Data expressed as number (percentage).

TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; TAF, tenofovir alafenamide.

TAF, 200mg FTC.

Figure 1

Tenofovir, Emtricitabine, and Tenofovir Alafanamide Concentrations in Plasma
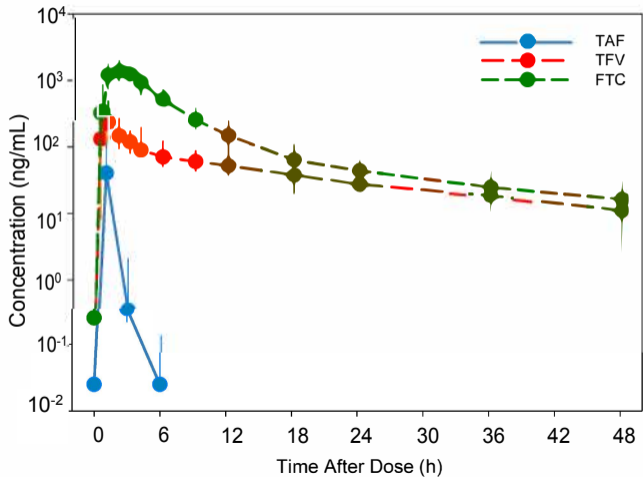
Tenofovir Diphosphate and Emtricitabine Triphosphate Concentrations in PBMCs
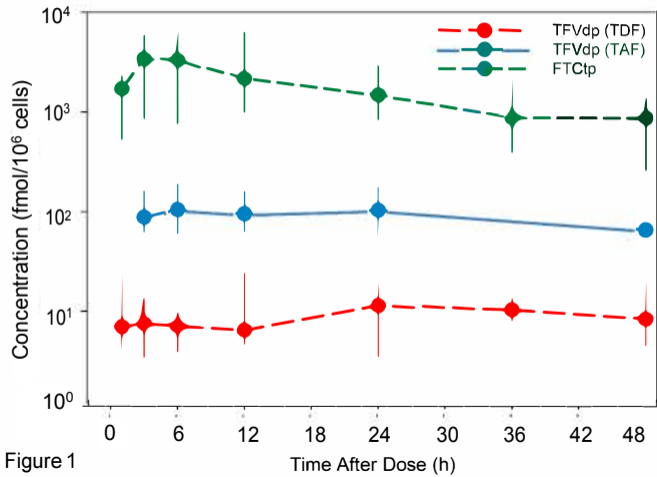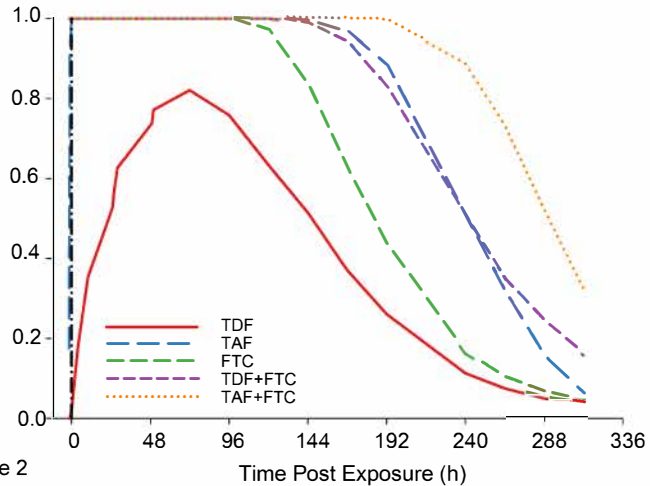
Figure 2

Steady-State Dosing Simulations

Proportion >EC_{90} vs Number of Doses per Week

Legend:
- TDF
- TAF
- FTC
- TDF+FTC
- TAF+FTC

Figure 3

Figure 4