**Predicting pharmacokinetics of a tenofovir alafenamide subcutaneous implant using PBPK modelling**

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**Running Title: PBPK modelling of TAF implant**

**Abstract**

**Background and Objectives:** Long-acting (LA) administration using a subcutaneous (SC) implant presents opportunities to simplify administration of antiretroviral drugs, improve pharmacological (PK) profile and overcome sub-optimal adherence associated with daily oral formulations. Tenofovir alafenamide (TAF) is a highly potent nucleoside reverse transcriptase inhibitor (NRTI) and an attractive agent for LA delivery, with a high potency and long intracellular half-life. The aim of this study was to predict minimum TAF doses required to achieve concentrations effective for HIV pre-exposure prophylaxis (PrEP). Daily drug-release requirements were then ascertained by averaging across the dosing interval.

**Methods:** A TAF PBPK model was developed and partially qualified against available oral single- and multiple-dose pharmacokinetics. The models were assumed to be qualified when simulated values were within 2-fold of observed mean. TAF SC implants were simulated in five hundred individuals reporting predicted TAF plasma, tenofovir (TFV) plasma concentrations for various release rates. Intracellular TFV diphosphate (TFV-DP) concentrations were also simulated in peripheral blood cells, cervical and rectal tissues. The minimum dose predicted to achieve intracellular TFV-DP levels above target concentration of 48 fmol/106 cells for a month was identified.

**Results:** TAF, TFV and TFV-DP concentrations for release rates between 1.0 and 1.6 mg/day were simulated. The PBPK model indicated a minimum release of 1.4 mg/day TAF is necessary to achieve TFV-DP concentrations above the identified target in PBMCs. TFV-DP cervical and rectal tissue concentration were predicted to be between 1.5 - 2.0 fmol/106 cells and 0.9 – 1.1 fmol/106 cells respectively for release rates between 1.3 – 1.6 mg/day.

**Discussion:** These simulations provide target minimum doses for LA TAF PrEP in humans. Based on the generated results, multiple implants delivering a total of 1.4 mg/day of TAF subcutaneously could provide protections levels for approximately 6-months to 1 year. This modelling may inform future design of SC implants to mitigate adherence-issues for effective PrEP applications.

## Introduction

Human immunodeficiency virus (HIV) is a global epidemic with an estimated 37.9 million people currently living with the virus [[1](#_ENREF_1)]. Although existing antiretroviral (ARV) regimes for treatment and pre-exposure prophylaxis (PrEP) have dramatically reduced the incidence of new infections annually over the last decade, an estimated 1.7 million people became newly infected in 2018; sex workers and clients of sex workers, men who have sex with men (MSM), people who inject drugs (PWID)s, transgender women (TGW), and their partners accounted for over half of these new infections globally [[1](#_ENREF_1)]. In sub-Saharan Africa, young women and adolescent girls accounted for two out of three new HIV infections that occurred in 2017 in the region [[2](#_ENREF_2)]. Development and implementation of more HIV prevention options for these high-risk populations are key to decreasing the incidence of new infections and overall prevalence of the virus [[3](#_ENREF_3), [4](#_ENREF_4)].

Tenofovir disoproxil fumarate (TDF), a prodrug of tenofovir, and emtricitabine (FTC; F) was FDA approved for treatment of HIV in 2004 and for PrEP in 2012 as the once-daily oral combination FTC/TDF (Truvada™) [[5](#_ENREF_5)]. Oral PrEP has been successful among serodiscordant heterosexual couples, MSM, and TGW when they are able to adhere to daily pill-taking regimens [[6](#_ENREF_6), [7](#_ENREF_7)] . However, several social, behavioural, and biological factors can contribute to reduced user-adherence and effectiveness of oral PrEP (e.g. poor accessibility to healthcare clinics for monthly refills, dosing-fatigue, social stigma of taking ARVs in public, and lower drug sequestration in vaginal tissues than rectal tissues) [[8-11](#_ENREF_8)]. Studies in women have shown that suboptimal adherence to oral PrEP yielded no protection [[12](#_ENREF_12), [13](#_ENREF_13)] and nearly perfect adherence (doses up to 6 to 7 per week) was needed to achieve complete protection via the vaginal route of exposure [[10](#_ENREF_10), [14](#_ENREF_14)].

Long-acting (LA) methods (e.g. lasting longer than 2 - 3 months between dosing intervals) offer a promising strategy for users to overcome some of the documented adherence challenges. Two ARV drugs, cabotegravir and rilpivirine, are currently in late stage clinical development as an intramuscular LA injection for HIV treatment. The latest results show that the combination of cabotegravir and rilpivirine LA as maintenance therapy provided viral suppression equivalent to existing daily oral therapy FTC/TDF [[15-17](#_ENREF_15)]. Cabotegravir LA as a stand-alone agent is also being compared to FTC/TDF for prevention in two Phase 3 studies among a population of healthy MSM and TGW who have sex with men (NCT02720094) and healthy women (NCT03164564). Evidence suggests persistent sub therapeutic levels of cabotegravir in plasma occurs long after secession, requiring a “tailing” regimen of oral PrEP to prevent risk of antiviral resistant infection [[18](#_ENREF_18)]. Implants systems containing highly potent ARVs are also in development as LA methods. These systems are inserted subcutaneously in the upper arm during a minimally invasive surgical procedure and can provide efficacious concentrations for months to years with no clinical follow up until implant removal or replacement. They can also be removable in case of an adverse event, an advantage over LA-injectable formulations. Some implants are made of bioabsorbable material designed to degrade after the therapeutic-use window, thus eliminating the need for an additional clinic visits to remove the depleted implant [[19](#_ENREF_19)]. Several groups are developing implants with the NRTI Tenofovir Alafenamide (TAF) [[19-22](#_ENREF_19)]. TAF is approved for oral treatment as the combination F/TAF (Descovy®) and more recently for PrEP in at-risk adult and adolescent males. Like TDF, TAF is a tenofovir prodrug, but is about 10 times more potent, has an improved safety profile and longer intracellular half-life of the active metabolite tenofovir diphosphate (TFV-DP) [[23](#_ENREF_23)]. Unlike TDF, TAF is not approved for HIV PrEP in women at risk of infection from the vaginal route of exposure, but plans to evaluate efficacy for HIV PrEP among this population are ongoing. TAF is an attractive single agent for LA administration due to its superior potency (lower target plasma concentrations) and low dose long intracellular half-life.

Physiologically based pharmacokinetic (PBPK) modelling is a computational approach to simulate pharmacokinetics in humans. PBPK models mimic human anatomy and physiology through anthropometric equations and combine drug physicochemical data (e.g. log P, pKa, molecular weight), and *in vitro* data (protein binding, apparent permeability, blood-to-plasma ratio, intrinsic clearance) to describe drug disposition kinetics. PBPK models are increasingly used to support candidate selection during drug discovery, dose selection for clinical development, facilitating regulatory submissions and optimising therapy post market approval across different sub-populations [[26](#_ENREF_26)].

The aim of this study was to develop a TAF PBPK model and simulate the minimum dose suitable as a subcutaneous implant in virtual healthy women. The developed model was qualified against observed data of oral administration, and then used to simulate theoretical LA options. The minimum daily dose for the subcutaneous implant was evaluated such that the intracellular concentration of TFV-DP was above the target concentration of 48 fmol/106 cells [[6](#_ENREF_6), [21](#_ENREF_21)] at the end of a 4-week interval. Given the unanswered scientific question of whether mucosal drug concentrations play an important role for PrEP, in addition to systemic drug levels [[27](#_ENREF_27)], cervical and rectal tissue concentrations of TFV-DP were also simulated.

## Methods

A whole-body PBPK model was described using Simbiology (MATLAB v.2018b, MathWorks, Natick, MA, USA) and a virtual population of 500 healthy adult women was used in this study considering a previously published model framework [[28](#_ENREF_28)]. The PBPK model assumed 1) a well-stirred model i.e. the drug distribution across organs and tissues is instant and uniform 2) blood-flow limited first order kinetics to describe drug distribution [[29](#_ENREF_29)] and 3) no drug reabsorption from colon. This study is based on computational data generated by the model; so, no ethics approval was needed.

### Anatomy and physiology

Simulations were conducted in females between the ages of 18 and 60 years, weighing between 40-120 kg (76.4 ± 30.9 kg) having a BMI between 18 – 40 kg/m2 (29.2 ± 12.51 m) [[30](#_ENREF_30)]. Various anthropometric equations that relied on the characteristics of the individual (age, weight, BMI, height and body surface area) were used to derive the anatomical components – organ weights and volumes and blood flow rates [[31](#_ENREF_31)]. Mean and standard deviations were provided for each of these components and inbuilt functions of the model were used to generate a random unique female individual for every simulation thus generating a population over multiple simulations.

A compartmental absorption and transit (CAT) model was used to describe effective absorption kinetics within the oral TAF model used for qualification [[32](#_ENREF_32)]. The CAT model consisted of seven compartments representing the stomach, various parts of the small intestine – duodenum, jejunum and ileum. An absorption rate equivalent to 6.24 h-1 derived from the two-compartmental population pharmacokinetic model was used [[33](#_ENREF_33)]. The absorption model did not account for drug solubility and assumed that all drug is in solution, readily available for absorption. An apparent systemic clearance of 149 L/h was used due to the unavailability of in vitro data [[33](#_ENREF_33)]. Drug specific parameters used in this study are shown in Table 1.

First-order kinetics were used to describe drug distribution across the multi-compartmental model [[34](#_ENREF_34)]. The tissue to plasma partition coefficients were computed by equations obtained from Poulin and Theil [[35](#_ENREF_35)]. A subcutaneous (SC) compartment was added to this previously published whole-body PBPK model [[36](#_ENREF_36)] to describe zero-order TAF release from the implant.

### Model qualification

The TAF PBPK model was qualified against available pharmacokinetic data for TAF, TFV and TFV-DP from various clinical studies [[37-39](#_ENREF_37)]. The models were assumed to be qualified if 1) the mean simulated pharmacokinetic parameters - area under the curve (AUC) and maximum concentration (Cmax) were within ± 50% from the mean observed values and 2) the simulated and the observed pharmacokinetic data points vs. time had an absolute average fold error (AAFE) less than two. A value of AAFE = 1 is representative of an exact match to the observed data.

The PBPK model was initially qualified against available oral data for 8 mg and 25 mg TAF given once daily on day 1 [[37](#_ENREF_37)] and day 14 [[38](#_ENREF_38)]. Once the TAF model was qualified, using the observed TAF plasma concentration and the pharmacokinetic curves of TFV on day 1 and day 14 [[37](#_ENREF_37), [38](#_ENREF_38)] and TFV-DP on day 1 [[39](#_ENREF_39)], the rate of change of TAF to TFV/TFV-DP (Kin) and the rate of elimination of TFV/TFV-DP (Kout) (as shown in Figure 1) were estimated by trial and error (Equation 1) using 25 mg TAF. In this model, TFV-DP concentrations refer to concentration in peripheral blood mononuclear cells (PBMCs). The estimated Kin and Kout were then used to further validate available TFV and TFV-DP pharmacokinetics for multiple 5 mg, 8 mg, 10 mg, 25 mg and 40 mg TAF doses.

(1)

Where C is the plasma concentration of TFV or intracellular TFV-DP and CTAF is the plasma concentration of TAF at time t.

The estimated values of Kin and Kout were 0.035 ± 0.007 h-1 and 0.03 ± 0.006 h-1 for TFV plasma concentration and 0.465 ± 0.05 h-1 and 0.011 ± 0.001 h-1 for TFV-DP intracellular concentration respectively.



**Figure 1** Diagrammatic representation of TFV/TFV-DP concentration dependent on Kin, Kout and TAF plasma concentration

### 2.3 Model prediction

The qualified PBPK model was used for dose prediction of implants through the subcutaneous route of administration. A range of zero-order release rates were simulated from 1.0 – 1.6 mg/day, and the minimum amount required per day was identified such that the TFV-DP intracellular concentration in PBMCs were above the target concentration of 48 fmol/106 cells for the entire dose interval [[6](#_ENREF_6), [21](#_ENREF_21)]. Additionally, TFV-DP concentrations in cervical and rectal tissue were also simulated. An average ratio of 0.031 and 0.02 for TFV-DP cervical/TFV-DP PBMC and TFV-DP rectal/TFV-DP PBMC respectively, as described in clinical studies [[39](#_ENREF_39)], were applied (see Supplementary Section).

## Results

#### 3.1 Model qualification

The comparison of observed and predicted pharmacokinetic parameters and the tables comparing the AUC, Cmax of TAF, TFV and TFV-DP for different dosing regimens are shown in the Supplementary Section (Supplementary figure 1). The simulated pharmacokinetic parameters are in the agreeable two-fold limit from the mean observed values except for the TFV Cmax of single 10 mg TAF oral dose which exceeds the limit by 6%. The difference in the simulated pharmacokinetic parameters – AUC and Cmax of plasma TAF and TFV on day 14 for 8 mg and 25 mg OD TAF was less than 50% from the observed mean however the difference between observed and simulated for single oral doses of 5 mg and 10 mg AUC was between 10 and 50% and Cmax between 90 and 107% for plasma TFV. The difference in the intracellular TFV-DP AUC and Cmax for the single TAF doses of 5 mg and 10 mg was between 10 to 35%.

#### 3.2 Model prediction

Pharmacokinetics of TAF, TFV and TFV-DP for various release amounts per day from the implant are presented in Table 2 and the intracellular TFV-DP concentrations in cervical and rectal tissues for various release rates are reported in Table 3. The model indicated that a minimum release of 1.4 mg TAF per day is necessary to achieve TFV-DP intracellular concentration above the target concentration of 48 fmol/106 cells. The simulated TAF implant plasma concentrations were predicted to reach a steady level within half a day (assuming constant uninterrupted release from the implant). However, TFV and TFV-DP concentrations required a longer interval of time (up to 14 days) as shown in Figure 1-2.

## Discussion

This study developed a PBPK model for TAF to inform the minimum dose required for a subcutaneous implant to achieve protection against HIV infection in healthy adult women. The PBPK model was qualified against TAF oral formulations and the model simulations were in agreement with the clinically observed pharmacokinetic data. The observed data considered for this study comprised of both single- and multiple-dose studies of TAF in a healthy population. Qualification against both single- and multiple-dose scenarios improved the performance and confidence of the TAF PBPK model for long-term simulations. This study focused on the use of TAF as a single agent and therefore clinical studies during which no other concomitant drugs were administered were considered for model qualification, but co-administration with other drugs may affect TAF pharmacokinetics. The model qualification resulted in simulations well within 2-fold of the mean observed values. The difference in the Cmax of plasma TFV for both – 5 mg and 10 mg doses were on the higher side (98-107%) which may be due to the low values of Cmax for these doses (0.8 and 1.5 ng/ml for 5 mg and 10 mg respectively). However, since the simulated AUC and Cmax values of plasma TAF and TFV for multiple doses of 8 mg and 25 mg were within 50% from the mean observed values, the model was considered qualified and the long-term performance was better than for a single dose. The simulated TFV-DP intracellular concentration in healthy individuals was also compared with observed data and the mean values were within the two-fold limit (data not shown) [[40](#_ENREF_40)].

Studies have indicated that a 90% effective concentration (EC90) for TFV-DP is between 26 to 48 fmol/106 cells, and therefore 48 fmol/106 cells was considered as the conservative target concentration [[6](#_ENREF_6), [21](#_ENREF_21)], since no standardised target concentration for prophylactic use of TAF has been identified. For the model predictions, simulations starting with 0.1 mg/day were gradually increased to identify the minimal release from the implant per day to achieve TFV-DP concentration above the target concentration. Only data for simulations conducted with release over 1.0 mg/day are presented in Table 2. A declining trend in the plasma concentration – time curve is observed for conventional implants due to the physical degradation and the declining amount of drug and the surface area of the implant. However, the PBPK model assumes 100% bioavailability from the subcutaneous environment and a constant drug release from the implant with no physical changes (no degradation of the implant) and therefore Figures 2 and 3 show a steady curve at the end of the 4-week period without a decline in TAF plasma concentrations. Figure 2 and 3 show that longer timescales are likely to be needed to reach steady concentration for TFV-DP compared to TFV and TAF. The mean simulated intracellular TFV-DP concentrations for 1.4 mg/day are over the target concentration of 48 fmol/106 cells (Figure 2). However, the implant is predicted to need at least 14 days to reach that level of protection if this is experimentally confirmed. This may warrant additional oral doses to compensate for the low TFV-DP levels immediately following implantation. The variability observed in the simulated pharmacokinetics mean that potentially a higher dose per day (>1.6 mg per day) might be necessary to protect all individuals (TFV-DP levels >48 fmol/106 cells). A minimum dose of 1.4 mg/day would result in 42 mg monthly, 126 mg quarterly and 252 mg every 6 months. Recent efforts of a biodegradable implant containing up to 115 mg TAF demonstrated a tuneable release rate between approximately 0.2 and 0.9 mg/day and a sustained zero-order release of TAF at approximately 0.3 mg/day for over 6-months *in-vitro* [[19](#_ENREF_19)]. Multiple implants may thus be needed to achieve protection for a target duration of 6-months to 1 year in humans. Notably, a recent study among reproductive aged women in sub-Saharan Africa suggested that multiple implants was acceptable for PrEP, provided that an increased number of rods afforded a longer duration of protection [[41](#_ENREF_41)].

Although the presented PBPK model was successfully qualified against available data and minimum daily implant dose was identified, there are some important limitations. The effect of transporters such as P-gp, have not been directly accounted for due to current data limitations, and this may affect TAF pharmacokinetics [[42](#_ENREF_42)]. Also, there is evidence of granuloma formation for injectable formulations [[43](#_ENREF_43)] that can change the pharmacokinetics, and this may also occur for subcutaneous implants when the normal foreign body response results in a thick fibrous capsule formed around the implant [[43](#_ENREF_43)]. The model does not account for potential toxicity of TAF delivered subcutaneously. Local reactivity was noted with TAF implants releasing from 0.15 mg/day to 1.8 mg/day in different animal species [[20](#_ENREF_20), [44](#_ENREF_44), [45](#_ENREF_45)], and with doses greater than 1.0 mg/day specifically in Beagles [[45](#_ENREF_45)]. Recently, Su et al. reported marked inflammation with their TAF implant in New Zealand White (NZW) rabbits and rhesus macaques with doses from 0.13 mg/day up to 0.78 mg/day after 4- and 12-week durations [[22](#_ENREF_22)]. It is thus critical for a minimum protective dose of TAF to exist below the threshold of toxicity and be delivered safely in humans via the subcutaneous route of administration over long durations.

## Conclusion

A PBPK model for a theoretical subcutaneous TAF implant is presented along with the minimum dose needed to provide protection against HIV. The PBPK model was qualified against available data from existing oral formulations and the predictions suggest a dose of at least 1.4 mg/day are needed to sustain mean intracellular TFV-DP concentrations over 48 fmol/106 cells. This approach may be valuable to support the design of future LA SC implants, addressing problems such as sub-optimal adherence and pill fatigue associated with oral drug delivery that are known to impact the success of PrEP.

## Acknowledgements

This study was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (R24 AI 118397).

**Author contributions**

All the authors in this manuscript contributed to the study design. RR designed the model, performed the simulations and analysis. ZD provided the description of implant. RR, ZD and MS wrote the manuscript with inputs from CF and AO. All the authors contributed towards the writing and reviewing of the final manuscript.

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**7 Tables**

**Table 1** Physicochemical properties, *in vitro* and population pharmacokinetic data of tenofovir alafenamide

|  |  |
| --- | --- |
| Property | **Tenofovir Alafenamide** |
| Molecular weight | 476.474 [[46](#_ENREF_46)] |
| Solubility in water | 4.86 mg/ml [[46](#_ENREF_46)] |
| log Po: w | 1.6 [[46](#_ENREF_46)] |
| pKa | 3.96 [[46](#_ENREF_46)] |
| Blood-to-plasma ratio | 1.5 (mean of 0.6 and 2.4 was considered) |
| Protein binding | 80 % [[46](#_ENREF_46)] |
| Absorption rate | 6.24 h-1 [[33](#_ENREF_33)] |
| Apparent clearance | 149 L/h [[33](#_ENREF_33)] |
| Oral bioavailability | 0.53 (assumed since 47.2 ± 4.62% is excreted in faeces) [[33](#_ENREF_33)] |

log Po: w – Partition coefficient between octanol and water; pKa – logarithmic value of the dissociation constant.

**Table 2** TAF subcutaneous implant pharmacokinetic predictions at different zero-order release rates for 28 consecutive days

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Simulated** | |
| **Release rate** | **Compound** | **AUC (ng.h/ml)** | **Css (ng/ml)** |
| **1.6 mg/day** | TAF, plasma | 899 ± 193 | 1.341 ± 0.287 |
| TFV, plasma | 1064 ± 414 | 1.683 ± 0.682 |
| TFV-DP, PBMCs\* | - | 56.59 ± 15.84 |
| **1.5 mg/day** | TAF, plasma | 806 ± 134 | 1.202 ± 0.199 |
| TFV, plasma | 950 ± 369 | 1.497 ± 0.498 |
| TFV-DP, PBMCs\* | - | 51.72 ± 13.54 |
| **1.4 mg/day** | TAF, plasma | 769 ± 148 | 1.146 ± 0.221 |
| TFV, plasma | 899 ± 296 | 1.418 ± 0.482 |
| TFV-DP, PBMCs\* | - | 49.26 ± 10.32 |
| **1.3 mg/day** | TAF, plasma | 715 ± 135 | 1.067 ± 0.202 |
| TFV, plasma | 811 ± 307 | 1.249 ± 0.492 |
| TFV-DP, PBMCs\* | - | 46.26 ± 11.09 |
| **1.2 mg/day** | TAF, plasma | 678 ± 109 | 1.011 ± 0.163 |
| TFV, plasma | 768 ± 274 | 1.212 ± 0.451 |
| TFV-DP, PBMCs\* | - | 42.95 ± 10.16 |
| **1.0 mg/day** | TAF, plasma | 556 ± 96.3 | 0.831 ± 0.167 |
| TFV, plasma | 609 ± 196 | 0.986 ± 0.238 |
| TFV-DP, PBMCs\* | - | 35.53 ± 8.797 |

Values are represented as mean ± standard deviation. AUC is measured for 28 days (672 hours) subsequent to implant administration, Css – steady state concentration, \*Intracellular concentrations represented in fmol/106 cells. TAF – tenofovir alafenamide, TFV – tenofovir, TFV-DP – tenofovir diphosphate, PBMCs – peripheral blood mononuclear cells.

**Table 3** TFV-DP cervical and rectal PK for a subcutaneous implant at different zero-order release rates for 28 consecutive days

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Simulated** | | |
| **Release rate** | **TFV-DP IC** | **TFV-DP cervical** | **TFV-DP rectal** |
| **1.6 mg/day** | 56.6 ± 15.8 | 1.72 ± 0.38 | 1.11 ± 0.25 |
| **1.5 mg/day** | 51.7 ± 13.5 | 1.63 ± 0.42 | 1.05 ± 0.27 |
| **1.4 mg/day** | 49.3 ± 10.3 | 1.52 ± 0.32 | 0.98 ± 0.21 |
| **1.3 mg/day** | 46.3 ± 11.1 | 1.45 ± 0.36 | 0.94 ± 0.23 |

Values are represented as mean ± standard deviation. TFV-DP concentrations represented in fmol/106 cells, IC – intracellular concentration in peripheral blood mononuclear cells. An average ratio of **0.031** and **0.02** for TFV-DP cervical/TFV-DP PBMC and TFV-DP rectal/TFV-DP PBMC was used for computation of TFV-DP concentrations in cervical and rectal tissues respectively.

**8 Figures**

**Figure 1** TAF and TFV pharmacokinetics at a constant release of 1.4 mg/day TAF implant through the subcutaneous tissue for 28 days are illustrated but duration of exposure would ultimately be defined by the total amount of TAF containing within an implant, standard deviation (SD) represents 1\*SD

**Figure 2** TFV-DP pharmacokinetics at a constant release of 1.4 mg/day TAF implant through the subcutaneous tissue for 28 consecutive days. The red line represents the target intracellular concentration of 48 fmol/106 cells, standard deviation (SD) represents 1\*SD