The Cellular Pharmacology of F-TAF in dried blood spots "TAF-DBS"

IDENTIFIERS:
Colorado Multiple Institutional Review Board: 16-0972
NCT02962739

FUNDING SUPPORT:
Gilead Sciences

PHARMACEUTICAL SUPPORT:
Study Drug Donated by Gilead Sciences

IND SPONSOR:
Exempt

PRINCIPAL INVESTIGATOR
Peter L. Anderson, Pharm.D.

Version 2.0
22 June 2017

PROTOCOL

Full Title: The Cellular Pharmacology of F-TAF in dried blood spots

Short Title: **TAF-DBS**

Clinical Phase: I-II

IND Sponsor: **Exempt**

Principal Investigator: Peter L. Anderson, Pharm.D.

Sample Size: Approximately 36 who complete the study timeline. IRB approvals will be sought for 72 subjects to allow for screen failures and drop outs.

Study population: HIV-uninfected adult participants at low risk for HIV infection. All participants must have a creatinine clearance >60 ml/min (MDRD equation) and no contraindicated medical conditions or medications.

Participating sites: The University of Colorado Anschutz Medical Campus.

Study Design: Approximately 36 HIV negative subjects will be enrolled. Enrollment will target approximately half women and one third African-Americans or Latino. However, strict quotas will not be imposed. Enrollment will proceed without the need to meet specific race/gender targets. Participants will be randomized to one of 6 sequences consisting of two directly observed dosing regimens, 33%/67%, 33%/100%, 67%/33%, 67%/100%, 100%/33%, and 100%/67%, expressed as % of daily dosing. Each dose regimen will have a duration of approximately 12 weeks. DBS/blood will be collected every week and hair will be collected at 3 week intervals. There will be a 12 week washout period between dose regimens. Additional samples will be collected during this washout period to determine elimination kinetics in hair and DBS/blood.

The 33% and 67% dosing regimens will skip doses spaced by days (i.e. 67% is two daily doses followed by skipping a day, repeated for 12 weeks; 33% dosing is a daily dose followed by two skipped days, repeated for 12 weeks).

Study Duration: For participants, the study lasts for approximately 36 weeks. Recruitment and enrollment will continue for approximately one year, the total study duration is approximately two years.

Study Regimen: Volunteers will receive 200mg and 25mg of emtricitabine and tenofovir alafenamide fumarate (F-TAF) according to the regimens outlined above. This medication will be donated by Gilead Sciences, and managed by the University of Colorado Hospital Investigational Pharmacy.

Primary objectives:

1) Define the expected concentrations and dose-proportionality for TFV-DP in DBS using directly observed F-TAF therapy at 33%, 67%, and 100% of daily dosing.

2) Establish a model to predict adherence rate to F-TAF by level of TFV-DP in DBS.

STATISTICAL CONSIDERATIONS

Primary outcomes

Primary outcome 1. The study was powered on dose proportionality of TFV-DP in DBS. Means, variances and dose proportionality will utilize measured concentrations at steady-state (Css at 12 weeks). Measured values will be validated with fitted values from PK modeling approaches (eg NONMEM).(22) The sample size was based upon demonstrating dose proportionality. Under the power model, $Css=a(dosing)^{b}e$, dose proportionality dictates the 90% CI for b is in (0.8, 1.25).(23) We assume an incomplete block design with each subject receiving 2 (of 3) doses, providing 6 permuted dose sequences (figure 2). An estimate of within subject CV was 2*max(CV) = 0.20 based on 5 replicate TFV-DP DBS samples from 2 subjects. Assuming a significance level of 0.05, we estimate a sample size of n=36 subjects (6 per dose sequence).(23) If dose proportionality is not shown, we will consider dose as a predictor of log(Css) as a linear ($b\neq1$) or a categorical effect interacted with time. Secondary outcomes such as the effects of race, gender and genetics, will be evaluated with models utilizing likelihood ratio tests and AIC to compare nested and non-nested models. (23-27)

Primary outcome 2. The goal is to determine DBS TFV-DP cut points associated with adherence levels. For the primary analyses, we will attempt to discriminate 33%, 67% and 100% dosing based upon TFV-DP in DBS. Power calculations conservatively assume a single measured Css observation at week 12, dose as a categorical predictor and 1 dose regimen per subject. Sample sizes of n=16 for each regimen achieve 90% power to detect a difference of 0.27 (0.30) between the area under the ROC curve (AUC) under the null hypothesis of 0.50 and an AUC under the alternative hypothesis of 0.77 (0.80) using a two-sided z-test at a significance level of 0.05. In practice, a proportional odds logistic approach which allows for an ordinal outcome (25, 26, 28) and extensions which control for correlations between repeated measurements on a subject will be utilized. (29) Finally, we will employ PK models from aim 1 to simulate TFV-DP for other dose regimens to estimate cut points for adherence rates other than 33%, 67% and 100%.

Enrollment/Stratification/Randomization/Blinding Procedures

This is a randomized open label observational study. Each subject will be randomized to one of 6 possible dosing regimens shown in the table below (Table 1). For each study period, block randomization will be used to ensure that Dosing Groups are balanced across enrollment time. The randomization will be programmed using R software (http://cran.r-project.org/ , The R Foundation for Statistical Computing).

Table 1: All possible randomization scenarios

Dosing group	1	2	3	4	5	6
Period 1	33	33	67	67	100	100
Period 2	67	100	33	100	33	67
N (36 total)	6	6	6	6	6	6

Participant Enrollment Follow-Up
Enrollment will be discussed at PSRT meetings every 6 months.

Planned Interim Analyses and Stopping Guidelines
Because the study is non-therapeutic and relatively small (N<100) the study team will monitor for safety as described above, but not efficacy.

Assays will be performed real time for the first 6 participants to evaluate if the half-life of TFV-DP in RBC is similar for TAF vs TDF. An analysis will be conducted at week 6 or 8 to assess TFV-DP by fitting the following equation: $Ct=Css*(1-e^{-K*t})$, where Ct is TFV-DP in DBS at time t, Css is the fitted steady state concentration, k is the fitted first-order elimination rate constant. Note the dose is not required for this equation. For comparison, we will run simulations of TFV-DP in DBS during TDF therapy using data from our ongoing DOT-DBS study (COMIRB 13-0427). If TFV-DP kinetics are similar for TAF and TDF, we would expect the fitted k to be similar between DOT-DBS and the present study. This interim analysis will only detect very large differences. We will meet as a study team (PSRT and Dr. Sam MaWhinney) to assess comparability, and will make decisions about potential study design alterations at this meeting. If study alterations are deemed to be needed, they will be submitted to the IRB prior to implementation.