Blood plasma and seminal plasma population pharmacokinetics of emtricitabine and tenofovir

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Introduction

Sexual transmission of human immunodeficiency virus (HIV) is the main way of HIV infection spreading, with semen being one of the most important sources of HIV infections. The use of combined antiretroviral treatments (cART) resulted into significant decrease in blood plasma (BP) HIV load. A parallel decay in HIV-RNA levels both in plasma and seminal plasma (SP) has been reported in numerous studies. However, other studies have described discordance between BP HIV load and SP HIV load (spVL). Thus, despite a suppressed BP HIV load, spVL could be detectable for some patients receiving cART (~ 10%). One determinant of HIV shedding in the male genital tract could be the penetration of antiretroviral drugs in this compartment. Available data on FTC and TFV seminal plasma concentrations are sparse, despite these drugs are recommended in first-line regimen for HIV treatment and are intended to be used as a pre- and post-exposure prophylaxis agents.

The aims of this study were: (i) to describe FTC and TFV blood plasma and seminal plasma pharmacokinetics in a large population of HIV-1 infected men; (ii) to evaluate FTC and TFV penetration in the male genital tract by SP-to-BP exposures ratios at steady state; and (iii) to assess the impact of FTC and/or TFV seminal plasma exposures on the seminal plasma HIV load.

Methods

Patients, treatments, sampling

Our study populations included HIV-1 infected men having sex with men from the Evarist ANRS-EP 49 study. These men received stable cART and had a suppressed BP HIV load for at least 6 months. FTC and TFV BP and SP concentrations were measured using a validated high-performance liquid chromatography tandem mass spectrometry method. For FTC, 122 and 117 men were included for the BP and SP analyzes respectively. A total of 236 BP concentrations and 209 SP concentrations were available. For TFV, 129 and 123 men were included for BP and SP analyzes respectively. A total of 248 BP concentrations and 217 SP concentrations were available.

Modeling

Data were analyzed by a population approach, using the software program Monolix version 4.1.4. Parameters were estimated using the stochastic approximation expectation maximization (SAEM) algorithm. FTC and TFV BP pharmacokinetics were described by two-compartment models. Addition of an effect compartment with different input and output constants was used to describe FTC and TFV SP pharmacokinetics.

Statistical Analysis

Mixed effects logistic regressions with random effect on individuals were performed with R software in order to evaluate the impact of FTC and/or TFV seminal plasma exposures on the spVL detectability.

Results

**FPC Results**

**Parameter** | **Estimate (SE)** | **RSE (%)** | **Parameter** | **Estimate (SE)** | **RSE (%)**
--- | --- | --- | --- | --- | ---
ka (h−1) | 0.51 (0.03) | 1.2 | ka (h−1) | 0.31 (0.03) | 28
CL/F (l/h) | 14.8 (2.4) | 1.27 | CL/F (l/h) | 11.1 (2.4) | 0.13 | 12
Vc/F (l) | 51.6 (11) | 3.2 | Vc/F (l) | 25.5 (11) | 0.22 | 12
Q/F (l/h) | 8.1 (2.6) | 0.13 | Q/F (l/h) | 3.5 (2.6) | 0.053 | 10
VP/F (l) | 106 (44) | 0.339 | VP/F (l) | 33 (44) | 0.339 | 6
F_R in CL/F (0.178) | 35 | 0.357 | 7

**TFV Results**

**Parameter** | **Estimate (SE)** | **RSE (%)** | **Parameter** | **Estimate (SE)** | **RSE (%)**
--- | --- | --- | --- | --- | ---
ka (h−1) | 1.35 (0.41) | 0.0963 | ka (h−1) | 0.31 (0.04) | 28
CL/F (l/h) | 45.8 (3) | 0.0339 | CL/F (l/h) | 16 (3) | 0.146 | 48
Vc/F (l) | 268 (16) | 0.197 | Vc/F (l) | 97 (19) | 0.194 | 45
Q/F (l/h) | 197 (39) | 0.197 | Q/F (l/h) | 39 (19) | 0.194 | 45
VP/F (l) | 1630 (43) | 0.826 | VP/F (l) | 43 (8) | 0.826 | 7
F_R in CL/F (0.591) | 13 | 0.263 | 8
F_R in CL/F (0.260) | 34 | 0.374 | 7

Visual Predictive Check for FTC BP concentrations (left) and SP concentrations (right)

Visual Predictive Check for TFV BP concentrations (left) and SP concentrations (right)

**Conclusion**

These are the first population models describing FTC and TFV pharmacokinetics in blood plasma and seminal plasma. FTC and TFV seminal plasma concentrations were higher than plasma blood concentrations. FTC and TFV accumulate in seminal plasma and the median SP-to-BP AUC0–24 ratios were estimated at 2.91 and 2.24 respectively. TFV penetration in the male genital tract seems to be more variable than FTC penetration (CV SP-to-BP AUC0–24 ratios 125 % vs 54.7 %). For FTC, SP AUC0–24 were higher than BP AUC0–24 for more than 99 % of the men compared to 87 % for TFV.