Bioequivalence study of two oral tablet formulations containing tenofovir disoproxil fumarate in healthy volunteers

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Abstract

Tenofovir disoproxil fumarate (TDF, CAS 147127-20-6) is a nucleotide reverse transcriptase inhibitor which is indicated in combination with other antiretroviral agents for the management of HIV-1 infection. The objective of this study was to compare the rate and extent of absorption and to assess the bioequivalence between a new pharmaceutical equivalent tablet formulation containing 300 mg of TDF and the innovator product. A randomized, single-center, open-label, single-dose, two-way crossover bioequivalence study in 40 healthy adult subjects was conducted. Dosing was separated by a wash-out period of 14 days. Blood samples were collected over 48 h and plasma levels of tenofovir (TFV) were determined by a validated HPLC assay. Rate and extent of absorption were similar between products. The 90 % confidence interval (CI) of the ratio of the geometric means for log-transformed C_{max}, AUC_{last} and AUC_{inf} values were used to assess bioequivalence between the two formulations using the equivalence interval of 80 and 125 %. In healthy subjects, the point estimate and 90 % CI of the ratios of C_{max}, AUC_{last} and AUC_{inf} values were 0.99 (0.92–1.02), 0.99 (0.95–1.03) and 0.93 (0.85–1.02), respectively. Both treatments exhibited similar tolerability and safety. It was concluded that the new pharmaceutical product was bioequivalent to the innovator.

Key words

- **CAS 147127-20-6**
- **Nucleotide reverse transcriptase inhibitor**
- **Tenofovir, bioequivalence, healthy volunteers**

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1. Introduction

Tenofovir disoproxil fumarate (TDF, CAS 147127-20-6) is an orally bioavailable ester-derived prodrug which is converted *in vivo* by serum and tissue esterases to tenofovir (TFV), an acyclic nucleotide. Intracellular phosphorylation of TFV yields the active metabolite, tenofovir diphosphate, which is a competitive inhibitor of HIV-1 reverse transcriptase, leading to the prevention of DNA chain elongation and termination of viral DNA growth [1–3]. TFV was approved by the Food and Drug Administration (FDA) in October 2001 and is indicated for use in combination with other antiretroviral agents for the management of HIV-1 infection [4–6].

The pharmacokinetics (PK) of TFV following oral administration of 300 mg has been well characterized in HIV-infected and healthy adult subjects. After oral administration, tenofovir concentrations increase over 1 to 3 h (T_{max}) with a maximum concentration (C_{max}) of approximately 300 ng/ml and a mean area under the plasma concentration-versus-time curve (AUC) at steady state of approximately 3000 ng · h/ml is observed [7–9]. When administered with a high fat meal (700–1000 calories containing 40–50 % fat), TFV's AUC and C_{max} are increased by 40 % and 14 %, respectively. TFV is primarily eliminated unchanged in the urine by a combination of glomerural filtration and active tubular secretion. The once-daily dosing schedule is supported by TFV serum elimination half-life of 12 to 17 h and the long half-life of the intracellular metabolite between 10 to 50 h [9, 10].

A new pharmaceutical equivalent oral tablet formulation containing TFV 300 mg has been developed and the objective of the present study was to evaluate and compare its rate and extent of absorption to that of the innovator product in healthy volunteers under fed condition.

2. Subjects and methods

2.1 Study design and methodology

A randomized, balanced, single-center, open-label, single-dose, two-way crossover bioequivalence study in 40 healthy adults subjects under fed condition was carried out. The study was conducted at the pharmacokinetics unit of FP Clinical Pharma Clinical (Buenos Aires, Argentina) between August and November 2009. The study protocol and the Informed Consent Form (ICF) were approved by an Institutional Review Board, by an Independent Ethic Committee and by the local Regulatory Agency (ANMAT) before study start-up. The procedures were carried out in accordance with ICH-GCP guidance, FDA guidance for conducting bioavailability and bioequivalence studies for oral administered drugs and the principles enunciated in the latest version of the Declaration of Helsinki [11–14]. All subjects volunteered to participate by signing the ICF.

The volunteers were randomly assigned to receive either a single 300 mg oral tablet of TDF Leuzan® as test preparation (batch No. LB1), manufactured by Richmond Laboratories (Buenos Aires, Argentina), or a single 300 mg oral tablet of the innovator product as reference preparation (batch No. L03809) purchased at a local pharmacy. The treatments were administered under fed condition in two different dosing periods separated by a 14-day wash-out period according to a predetermined randomized schedule. Subjects were not allowed to either crush or chew the study medication.

A high-fat breakfast was administered 30 min before dosing. It was comprised approximately of 800–1000 total calories: 500–600 cal from fat, 250 cal from carbohydrate and 150 cal from protein. Mouth checks were performed after each dosing. Then, subjects remained under fasting condition until after the 4-h pharmacokinetic blood sampling time point. A standard lunch and afternoon meal were administered after the 4^{th} and 8^{th} hour of drug administration, respectively.

2.2 Study population

The sample size was calculated using the formula developed by Marzo and Balant [15]. A total of 40 healthy male and female subjects (nonpregnant and nonlactating) between 21 and 50 years of age were enrolled. Inclusion criteria included Body Mass Index (BMI) between 19 and 27 kg/m^2. Female subjects of childbearing potential (i. e. not surgically sterile or at least 2 years postmenopausal) were required to have a negative pregnancy test at screening and to agree to use a highly effective contraception method (not hormonal) while on study treatment and for three weeks after the last dose of study drugs. Laboratory values, electrocardiograms and chest x-rays for all subjects had to be within normal range. Negative test for HIV, hepatitis B and C viruses were also required.

Subjects were excluded if they had a history or current manifestations of gastrointestinal disease or surgery, or hepatic, cardiovascular, respiratory, renal, hematopoietic, neurological, endocrine-metabolic diseases. Volunteers were not allowed to use medicine of any kind within the previous two weeks and throughout the study execution. Other standard exclusion criteria for bioavailability/bioequivalence studies were adopted for subject enrollment [12].

2.3 Sample collection and bioanalytic procedures

Serial blood samples for pharmacokinetic assessments were collected over a 48 h period at the following points: 0 (predose), 0.5, 1.0, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 and 48 h after oral administration of each treatment. For each sample, approximately 10 ml of blood was collected into Vacutainers containing EDTA as an anticoagulant.

Blood samples were centrifuged and separated plasma was frozen at –20 °C until analysis. TFV concentration in human plasma was determined by a validated HPLC/fluorescence method [16]. The lower limit of quantification of TFV was 5 ng/ml and the relationship between concentration and peak area ratio (TFV: internal standard) was found to be linear within the range of 5 ng/ml to 1000 ng/ml. Full methodological validation was carried out according to FDA guidance for bioanalytical method validation [17].

2.4 Pharmacokinetic evaluation

The plasma concentration-time data after oral administration of a single dose of test and reference treatment were analyzed using a noncompartmental pharmacokinetic model (WinNonlin, version 5.2; Pharsight, Mountain View, CA, USA). The maximum plasma concentration and the corresponding sampling time were defined as C_{max} and T_{max}, respectively. The elimination half-life ($T_{1/2}$) was estimated as $\ln 2/\lambda$. The slope of the log-linear regression function (λ) was the first order rate constant associated with the terminal portion of the curve estimated by linear regression of time *vs.* log-concentration. The area under the plasma concentration-time curve from the time of dosing to the last measurable concentration (AUClast) was calculated using the trapezoidal rule. The AUC from dosing time extrapolated to infinity based on the last observed concentration was defined as AUC_{inf} which was calculated by the equation $AUC_{inf} = AUC + (Cn/\lambda)$ where Cn is the last measurable concentration and λ is the slope of the log-linear regression function. A pharmacokinetic rule was generated to treat data coming from samples presenting values less than the lower level of quantification in bioanalytic assays. Subjects who experienced emesis at or before 2 times the median time to maximum concentration (T_{max}) for the analyte were excluded from the PK analysis set [12].

2.5 Safety assessment

Physical examination, hematology, platelets count, serum chemistry (liver function panel, creatinine, urea, fasting glucose, uric acid, calcium, phosphorous, bicarbonate, potassium, sodium, lactic acid), urinalysis, were performed at screening (Day –21 to –1) and at study termination for safety purposes (Day 17). A 12-lead electrocardiogram and a chest x-ray were also carried out at screening. For females with childbearing potential, serum pregnancy test was performed at screening and on urine samples previous to each dosing. An abbreviated physical examination was also performed on the morning before drug administration. Vital signs (systolic and diastolic blood pressure in supine position and heart rate) were recorded during screening, immediately before drug administration, and 4, 12 and 72 h after drug administration.

2.6 Statistical analysis

The following pharmacokinetic parameters: C_{max}, AUC_{last}, and AUC_{inf} were analyzed using natural log-transformed data. These PK variables were compared by means of ANOVA for a

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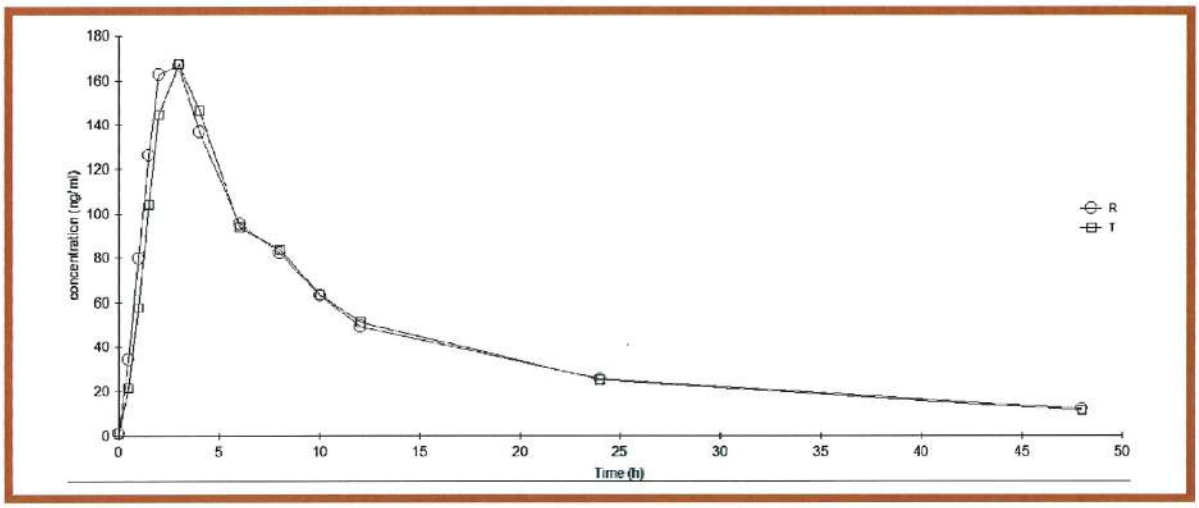

Fig. 1: Mean plasma concentration-time profile of TFV (n = 39) following single-dose administration of 300 mg test and reference tablets.

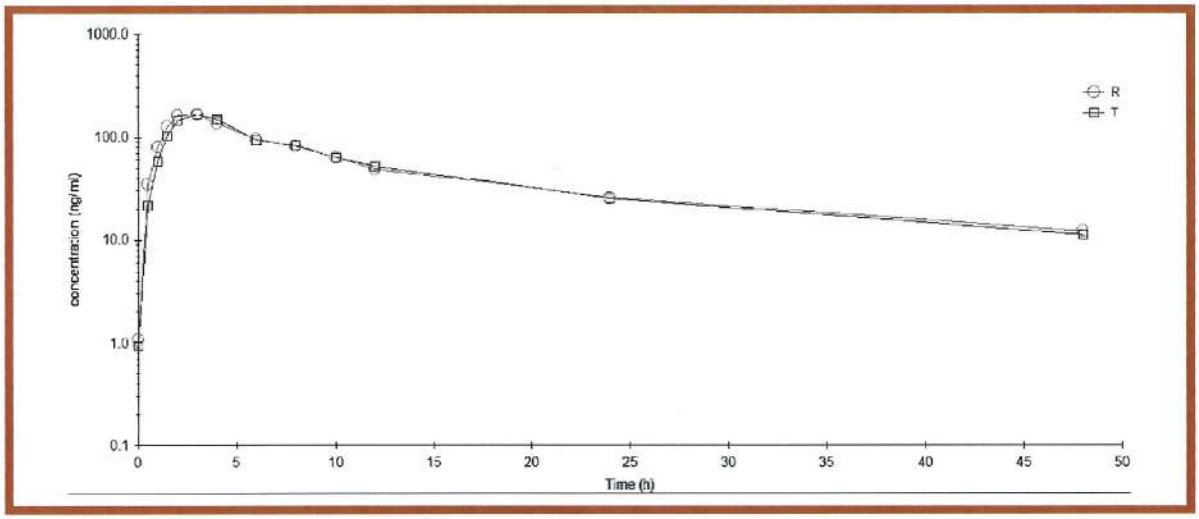

Fig. 2: Mean plasma log-concentration time profile of TFV (n = 39) following single-dose administration of 300 mg test and reference tablets.

2-treatment crossover design. The model included the fixed effects of sequence, period, and treatment. In accordance with scientific standards and international guidelines for bioequivalence studies, bioequivalence was concluded if the 90 % confidence interval (CI) for the ratio of the geometric least-squares means (test treatment/reference treatment) was within the bounds of 80 % to 125 % for the primary PK parameters. All statistical tests used a 5 % level of significance [12, 18].

3. Results

The demographic data and the mean health parameters of all the participants are summarized in Table 1.

3.1 Pharmacokinetics

The data set for TFV analysis included 39 subjects. One subject was excluded because of an emesis episode at 2 h after dosing. Fig. 1 (arithmetic scale) and Fig. 2 (semilog-transformed scale) show mean plasma concentration-time curves after single dose administration of 300 mg of test and reference products. The curves for the two treatments followed a typical profile for a

Table 1: Demographic data and health parameters of subjects (n = 40).

Characteristic	Results
Race Caucasian /Non-caucasian, n (%)	39 (97.5)/1 (2.5)
Gender (male/female), n (%)	17 (42.5)/23 (57.5)
Age (yrs), mean ± SD	35.32 ± 8.89
Height (cm), mean ± SD	168 ± 83
Weight (kg), mean ± SD	71.13 ± 9.41
BMI (kg/m^2), mean ± SD	25.03 ± 2.01

Table 2: Pharmacokinetic parameters of TFV in healthy volunteers (n = 39) after a 300-mg oral single dose of test or reference treatment.

Pharmacokinetic parameter	Reference treatment (n = 39)	Test treatment (n = 39)
C_{max} (ng/ml), mean (SD)	232.675 (87.308)	226.884 (76.229)
T_{max} (h), mean (SD)	2.423 (1.091)	2.718 (0.985)
AUC_{last} (ng · h/ml), mean (SD)	1968.975 (738.928)	1926.333 (618.710)
AUC_{inf} (ng · h/ml), mean (SD)	2657.194 (1417.315)	2366.618 (786.822)
Ke (1/h)	0.046 (0.021)	0.049 (0.022)
Half-life (h), mean (SD)	26.843 (5.592)	26.906 (6.763)

conventional immediate release formulation with long half-lifes and both curves were essentially superimposable. Following the achievement of C_{max}, TFV concentrations declined in a biphasic manner for both the test and reference products. Plasma pharmacokinetic parameters for TFV are summarized in Table 2. TFV formulations showed similar mean T_{max} and half-life values.

The analysis of variance did not show any statistically significant difference between test and reference formulations ($p < 0.05$) in relation to the fixed effect of period, sequence and treatment for the pharmacokinetic parameters analyzed: ln C_{max}, AUC_{last} and AUC_{inf}.

Statistical analysis of TFV pharmacokinetic log-transformed parameters and their geometric least squares mean ratios for the test and reference treatment are presented in Table 3. The limits of the 90 % confidence intervals (CI) for the ratios of C_{max}, AUC_{last}, and AUC_{inf} for their log-transformed data fell well within 80 to 125 %. Coefficients of intra-individual variation for C_{max}, AUC_{last} and AUC_{inf} were 0.19, 0.12 and 0.25; respectively. Coefficients of inter-individual variation for C_{max}, AUC_{last} and AUC_{inf} were 0.28, 0.34 and 0.31, respectively.

Test-reference ratio for the geometric means (%) for all primary pharmacokinetic parameters (AUC_{last}, AUC_{inf}, C_{max}) were close to unity (100 %), and the corresponding 90 % confidence intervals were contained within the bioequivalence bounds of 80–125 %. Morover, the null hypothesis of the Schuirmann two one-sided t-test could be rejected ($p < 0.05$) as shown in Table 3.

3.2 Safety

TFV was well tolerated by all subjects. No clinically significant changes in vital signs (blood pressure, heart rate) and safety laboratory tests were observed after single oral dose administration of TFV 300 mg. A total of 5 non-serious adverse events (AEs) were reported: Two cases of emesis of mild intensity were considered related to the study drug by the investigators, and they resolved without any medication. Another case of emesis of mild intensity was considered not related to the study drug and did not require any medication. One case of earache and one case of dental pain, both of moderate intensity and not related to the study drug, resolved with the use of ibuprofen 400 mg.

4. Discussion

The objective of the present study was to evaluate and compare rate and extent of absorption of a new pharmaceutical equivalent tablet formulation containing 300 mg TFV to that from the innovator product in healthy volunteers; and secondarily to assess bioequivalence between them. Our results showed that no significant differences were found in terms of rate and extent of absorption between test and reference products, as indicated by C_{max} and AUC comparisons and also by the superimposable plasma tenofovir concentration-time curves. Considering that 90 % CIs of the ratios of μT/μR for the PK parameters (C_{max} and AUCs log-transformed) were found to be within the predetermined range (80 %–125 %) and the Schuirmann two one-sided t-test procedure (probability of exceeding limits of acceptance) found all probability values <0.05, the null hypothesis that the estimated parameters exceeded limits of acceptance was rejected.

To our knowledge, no further bioequivalence studies evaluating TDF as a single dose formulation have been previously reported in the literature.

Table 3: Bioequivalence analysis for TFV following oral single-dose administration of either test or reference treatment (300 mg).

Pharmacokinetic parameter	Reference GeoLSM[a]	Test GeoLSM[a]	Ratio (% Reference)	CI 90 % Classical	Two one-sided t-test Schuirmann	p	Power of the analysis
Ln(C_{max}), ng/ml	218.55	216.77	99.18	92.12 to 106.78	P(0 < 80 %) = 0.0000 P(0 > 125 %) = 0.0000	$p < 0.05$	1.00
Ln(AUC_{last}), ng · h/ml	1843.89	1831.45	99.33	95.02 to 103.83	P(0 < 80 %) = 0.0000 P(0 > 125 %) = 0.0000	$p < 0.05$	1.00
Ln(AUC_{inf}), ng · h/ml	2397.02	2243.47	93.59	85.15 to 102.87	P(0 < 80 %) = 0.0000 P(0 > 125 %) = 0.0000	$p < 0.05$	0.99

[a] Geo LSM: geometric least squares mean.

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Parameters of bioavailability are in good agreement with a previous report where a triple fixed-dose combination of TDF (300 mg)/efavirenz (600 mg)/emtricitabine (200 mg) in a single tablet formulation was compared to the individual dosage forms administered to 45 healthy subjects in a randomized, single-dose, crossover study. In this previous study, the TFV mean ± SD values for C_{max}, AUC_{last} and AUC_{inf} were 325 ± 34.2 ng/ml and 353 ± 29.6 ng/ml, 1950 ± 32.9 ng · h/ml and 1970 ± 32.8 ng · h/ml, 2310 ± 29.2 ng · h/ml and 2320 ± 30.3 ng · h/ml, for the test and reference drug, respectively [19].

The pharmacokinetic profile of TFV described in this study did not differ from previous pharmacokinetic studies carried out in HIV-infected adults with mean calculated AUC_{last} reported values: 2093 ng · h/ml [7], 3000 ng · h/ml [8], 2290 ng · h/ml [20].

In our study, mean calculated AUC_{last} from test and reference product (1926.3 and 1968.9 ng · h/ml, respectively) and C_{max} (226.8 and 232.6 ng/ml, respectively) were slightly lower than previously described mean values (3179 ng · h/ml, AUC_{last} and 375 ng/ml, C_{max}) obtained when a 300 mg dose of TDF was administered under fed condition (high-fat breakfast meal) in HIV-infected adults [7]. This result could be explained by the quite large interindividual variability of tenofovir pharmacokinetics, being the source of variability incompletely understood [21]. The presence of food could have probably increased the variability by interacting with absorption mechanisms. T_{max} values from both products were over 2 h, correlating well with the increased T_{max} observed when TDF was administered from fasted to fed condition, possibly reflecting delay in TFV absorption by concomitant food administration [2, 7]. Mean TFV half-life values (26.9 and 26.8 h) for the test and reference products did not differ from previously reported data [7, 9, 19].

In a previous pharmacokinetic study carried out in healthy volunteers, the most common adverse events reported during treatment with TDF were gastrointestinal disorders, fatigue, headache, somnolence, and dizziness [20]. However, in the present study, only two cases of emesis of mild intensity related to the study drug were observed.

In conclusion, the point estimate of 90 % CI for the log-transformed C_{max}, AUC_{last} and AUC_{inf} were in the range of 80–125 %. Type II error of the statistical test was close to the unity, indicating adequate sample size. No statistically significant difference were found for fixed effects when ANOVA test was applied to the ln C_{max}, AUC_{last} and AUC_{inf}. Both formulations were similar in terms of rate and extent of absorption. This study demonstrated that the new pharmaceutical equivalent TDF formulation is also bioequivalent to the reference product. The finding that the test and reference products are pharmaceutically equivalent and bioequivalent implies that the products are interchangeable.

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Conflict of Interest

The authors state no conflict of interest in relation to the present study.

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