

Pharmacokinetic interaction between TMC114/ritonavir and tenofovir disoproxil fumarate in healthy volunteers

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What is already known about this subject

- Tenofovir disoproxil fumarate and some of the HIV protease inhibitors show drug–drug interactions that cannot be predicted based on their metabolic profiles.
- Tenofovir disoproxil fumarate and HIV protease inhibitors are often combined as part of antiretroviral therapy.

What this study adds

- TMC114 (darunavir) is the latest HIV protease inhibitor approved by the US Food and Drug Administration and is used in combination with low-dose ritonavir.
- This study shows for the first time the extent of the drug–drug interaction between tenofovir disoproxil fumarate and TMC114 combined with low-dose ritonavir and compares the interaction observed with other HIV protease inhibitors.

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Aim

TMC114 is a new HIV protease inhibitor, used in combination with low-dose ritonavir (TMC114/r) as a pharmacokinetic enhancer. Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor. Both antiretrovirals show activity against wild-type and resistant HIV. An open-label crossover study was conducted in HIV – healthy volunteers to investigate the potential for a pharmacokinetic interaction between TMC114/r and tenofovir.

Methods

Two groups, each of six volunteers, were evaluated in two consecutive sessions. In session 1, volunteers received TMC114/r (300/100 mg bid) for 7 days, followed by a wash-out period of at least 6 days. In session 2, volunteers received TMC114/r (300/100 mg bid) plus TDF (300 mg qd).

Results

When TMC114/r and TDF were coadministered, tenofovir plasma concentrations (C_{\min} and C_{\max}), and area under the curve ($AUC_{24\text{h}}$) increased by 37%, 24% and 22%, respectively. When TDF and ritonavir were coadministered, TMC114 plasma C_{\min} , C_{\max} and $AUC_{12\text{h}}$ increased by 24%, 16% and 21%, respectively. There were no changes in the urinary excretion of unchanged tenofovir or TMC114 during coadministration. Administration of TMC114/r in HIV – healthy volunteers with or without TDF was well tolerated.

Conclusions

The interaction between TMC114/r and tenofovir is not clinically relevant and no dose adjustments are required when these drugs are coadministered.

Introduction

TMC114 (Prezista™) is a new protease inhibitor (PI), highly active against both wild-type and resistant HIV-1 strains *in vitro* [1]. TMC114 is approved in the USA in combination with ritonavir for the treatment of HIV infection in treatment-experienced adults [2]. TMC114 with low doses of ritonavir (TMC114/r) results in improved pharmacokinetic characteristics compared with TMC114 alone [3]. Ongoing randomized, controlled trials are designed to evaluate the efficacy and safety of TMC114/r in HIV-infected patients. Results of the 24-week primary analyses of studies in the treatment-experienced have shown significant benefits in efficacy outcomes when TMC114/r is compared with investigator-selected control PIs in combination with an optimized background regimen (OBR) [4, 5]. In addition, TMC114/r is generally safe and well tolerated.

Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor (NtRTI) with efficacy in treatment-naive and -experienced patients [6, 7]. Tenofovir has been shown to interact with some PIs and nucleoside analogues; an unexpected finding, as tenofovir does not induce or inhibit cytochrome P450 (CYP) 3A4 metabolism; most of these interactions are deemed not clinically relevant [8]. As TMC114/r will be used in combination with other antiretroviral agents, a pharmacokinetic interaction trial of TMC114/r and TDF was performed in HIV- healthy volunteers.

Methods

Study design

This was an open-label, randomized, two-session cross-over trial to determine the extent of pharmacokinetic interaction between TMC114/r and TDF. The study participants were HIV- healthy volunteers, aged 18–55 years. During session 1, volunteers were randomized into group 1 ($n = 7$) or group 2 ($n = 6$). In session 1, both groups received TMC114/r 300/100 mg bid for 6 days with an additional dose in the morning of day 7. After a wash-out period of 6 days, both groups were administered TDF 300 mg qd for 14 days (session 2). In addition, volunteers in group 1 received TMC114/r 300/100 mg bid from day 8 to day 14, whereas volunteers in group 2 received TMC114/r from day 1 to day 7. No formal sample size calculation was performed. A total of 13 subjects were enrolled to allow for relevant conclusions. A regimen of TMC114/r 300/100 mg bid has been found to be well tolerated in healthy volunteers [3]. This dose is lower than the recommended 600/100 mg bid dose of TMC114/r. TDF is licensed at a dosing regimen of 300 mg qd [8], which was the recommended dose for this study. A wash-out period of at least 6 days between

the two sessions was considered sufficient to avoid carry-over effects from one session to the next.

All study medication was taken with food. TMC114 was formulated as an oral aqueous solution of 20 mg ml⁻¹ containing vitamin E-d- α -tocopheryl polyethylene glycol 1000 succinate and polyethylene glycol 400 as main solubilizing agents, while ritonavir and TDF were obtained as commercially available capsules and tablets, respectively.

Full pharmacokinetic profiles of TMC114 and ritonavir were determined on day 7 of session 1 and on day 14 (group 1) or day 7 (group 2) of session 2. Full pharmacokinetic profiles of tenofovir were determined on day 7 and day 14 of session 2 for both groups. On days when samples were taken for pharmacokinetic analysis, TMC114, ritonavir and/or TDF were ingested within 15 min after a standard breakfast. Volunteers fasted for 8 h before breakfast and resumption of normal water and food intake was allowed 2 and 4 h after breakfast, respectively.

The study protocol was reviewed and approved by the appropriate institutional ethics committee(s) and health authorities, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all volunteers.

Pharmacokinetic assessments

TMC114 and ritonavir in plasma and urine were determined simultaneously using a validated LC-MS/MS method. The lower limit of quantification in plasma was 10.0 ng ml⁻¹ for TMC114, 5.00 ng ml⁻¹ for RTV and 20.0 ng ml⁻¹ for tenofovir. The lower limit of quantification in urine was 20.0 ng ml⁻¹ for TMC114 and 1.00 μ g ml⁻¹ for tenofovir. The precision and accuracy for the TMC114 (40, 400 and 8000 ng ml⁻¹) and ritonavir (20, 200, 4000 ng ml⁻¹) quality control (QC) samples in plasma and urine were <12% and 16%, respectively, and met the predefined criteria of <20% for the low QC and 15% for the medium and high QC samples, respectively [9]. Concentrations of tenofovir in plasma and in urine were determined using a high-performance liquid chromatography method with fluorescence detection. The precision and accuracy for the tenofovir QC (75, 750 and 15 000 ng ml⁻¹) samples in plasma and urine were <11% and met the predefined criteria.

During session 1, predose plasma concentrations of TMC114 and ritonavir were assessed on days 4 and 6. For pharmacokinetic analysis of TMC114 and ritonavir, day 7 blood samples were taken predose and 0.5, 1, 1.5, 2, 3, 4, 6, 9 and 12 h postdose. During session 2, predose plasma concentrations of TMC114, ritonavir and teno-

fovir were assessed on days 11 and 13 (group 1) or days 4 and 6 (group 2). For pharmacokinetic analysis of TMC114 and ritonavir, blood samples were taken on day 14 (group 1) or day 7 (group 2), predose and 0.5, 1, 1.5, 2, 3, 4, 6, 9 and 12 h postdose. On day 7 and day 14 of session 2, tenofovir concentrations were determined in blood samples taken predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12 and 24 h postdose for both groups.

Predose urine samples were taken on day 1 of session 1 and days 1 and 8 of session 2. For pharmacokinetic analysis of urine during session 1, output was collected on day 7 over a 12-h period following study drug dosing. During session 2, urine output was collected on day 14 (group 1) or day 7 (group 2) over a 24-h period after dosing.

Safety assessments

Volunteers were monitored regularly throughout the study for cardiovascular parameters, blood pressure and biochemical characteristics of blood and urine. Adverse events (AEs) were recorded. All safety evaluations were graded according to the AIDS Clinical Trials Group/World Health Organization grading scales.

Statistical methods

Descriptive statistics were calculated for the plasma concentrations of TMC114, ritonavir and tenofovir, and the urinary concentrations of TMC114 and tenofovir. Pharmacokinetic data for TMC114, ritonavir and tenofovir were analysed by noncompartmental methods using WinNonlin Professional™ software (version 3.3; Pharsight Corp., Mountain View, CA, USA). Analyses included area under the curve from time of administration to 12 h postdosing ($AUC_{12\text{ h}}$) or 24 h postdosing ($AUC_{24\text{ h}}$), predose plasma concentrations ($C_{0\text{ h}}$), minimum (C_{min}) and maximum (C_{max}) plasma concentrations, average steady-state plasma concentrations ($C_{\text{ss,av}}$) and time to reach C_{max} (t_{max}). The percentage of administered drug excreted in urine (D_{urine}) from 0 to 12 h, 12–24 h and 0–24 h after dosing was also analysed by noncompartmental methods, using Microsoft Excel® software (version 2000; Microsoft, Redmond, WA, USA).

To assess the impact of coadministration with TDF on TMC114 and ritonavir pharmacokinetic characteristics, treatment with tenofovir (session 2) was used as the test and treatment without tenofovir (session 1) was used as the reference. Similarly, to assess the impact of coadministration of TMC114/r on the pharmacokinetic parameters of tenofovir, treatment with TMC114/r was used as the test and treatment without TMC114/r was used as the reference. Data for both test and reference in

this case were from session 2. The primary plasma pharmacokinetic variables were $C_{0\text{ h}}$, C_{min} , C_{max} , as well as $AUC_{12\text{ h}}$ (for TMC114 and ritonavir) or $AUC_{24\text{ h}}$ (for tenofovir) on a logarithmic scale. The primary urine pharmacokinetic parameters were $D_{\text{urine},0-12\text{ h}}$ for TMC114 and $D_{\text{urine},\text{total}}$ for tenofovir. Only paired observations for test and reference were included in the statistical analyses.

The least square (LS) means of the AUC, C_{min} , C_{max} and $C_{0\text{ h}}$ for each treatment group were estimated using a linear, mixed-effects model. The model controlled for period and randomization group as fixed effects and volunteer (nested in randomization group) as a random effect. Period effects were considered significant at the 5% level and sequence effects were considered significant at the 10% level. Where period and sequence effects were not significant, they were not retained in the model. A 90% confidence interval (CI) was constructed around the difference between the LS means of test and reference. T_{max} was analysed by the nonparametric Koch test, using the bioequivalence module of WinNonlin Professional™ software (version 3.3; Pharsight Corp.).

Results

Pharmacokinetic data

Data from 12 HIV– healthy volunteers were available for analysis of pharmacokinetic parameters. When TDF and ritonavir were coadministered, TMC114 mean plasma $C_{0\text{ h}}$, C_{min} , C_{max} and $AUC_{12\text{ h}}$ of TMC114 increased by 12%, 24%, 16% and 21%, respectively, as shown in Figure 1 and Table 1. Urinary excretion of unchanged TMC114 was not significantly altered. The LS means of $D_{\text{urine},0-12\text{ h}}$ for TMC114 were 6.3% and 6.8% with and without tenofovir, respectively.

When TMC114/r was coadministered, the $C_{0\text{ h}}$, C_{min} , C_{max} and $AUC_{24\text{ h}}$ for tenofovir increased by 36%, 37%, 24% and 22%, respectively, as shown in Figure 2 and Table 2. Coadministration of TMC114/r had no effect on the urinary excretion of tenofovir. The LS means of $D_{\text{urine},\text{total}}$ for tenofovir were 34.9% and 33.6% with or without TMC114/r, respectively.

The pharmacokinetic characteristics of ritonavir were not significantly affected when coadministered with TDF and TMC114, with LS mean ratios for $C_{0\text{ h}}$, C_{min} , C_{max} and $AUC_{12\text{ h}}$ being 0.95, 0.92, 0.87 and 0.94, respectively, compared with administration of TMC114/r alone. Based on predose plasma concentrations, steady-state conditions for TMC114, ritonavir and tenofovir were reached on the days when full pharmacokinetic profiles were taken. No significant sequence or period effects were observed ($P > 0.1$).

Safety and tolerability

Overall, TMC114/r was generally well tolerated when used alone or in combination with TDF. The most commonly reported AEs during the trial were gastrointestinal (diarrhoea, flatulence and loose stools) and headache. All reported AEs were classified as mild and no grade 3 or 4 abnormality of biochemistry parameters was recorded.

Discussion

We report here the steady-state pharmacokinetic characteristics of TMC114, ritonavir and tenofovir during

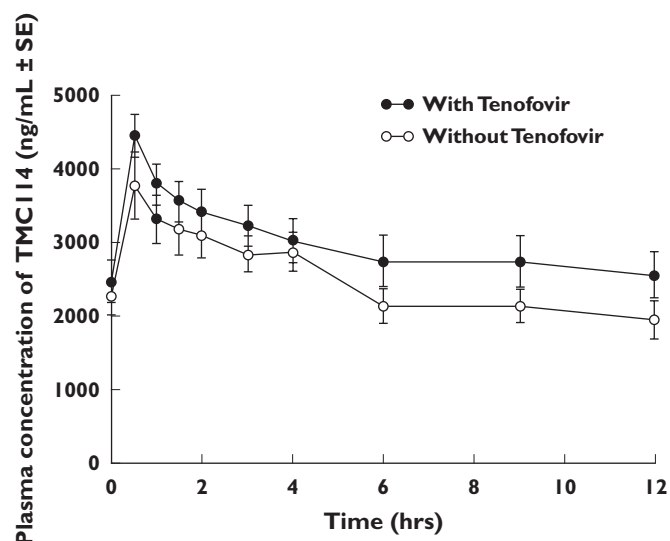


Figure 1

Profile of mean plasma concentration of TMC114 over time, in the presence or absence of a steady-state concentration of tenofovir. With Tenofovir, (●—●); Without Tenofovir, (○—○)

coadministration in HIV– healthy volunteers. Coadministration of TMC114/r and TDF increased systemic exposure to tenofovir by 22% compared with administration of TDF alone; this is not considered clinically relevant. Administration of TDF had no significant influence on systemic exposure to TMC114. There were no changes in the urinary excretion of unchanged tenofovir or TMC114 during coadministration. Since pharmacokinetic sampling was performed over the dosing interval (12 h), the terminal half-life of TMC114 was not determined.

Pharmacokinetic drug interactions can be complex and unpredictable, and may involve processes such as drug absorption, distribution, metabolism and excretion. Of these processes, effects on metabolism are the most common factors that contribute to drug interactions. The most efficient and well-known enzymes responsible for drug metabolism are the CYP450 enzymes.

Drug interactions between TDF and other PIs have been reported, most notably the reduction in systemic concentrations of atazanavir achieved in the presence of TDF (both with and without ritonavir) [10]. In contrast, coadministration of TDF, saquinavir hard gel and ritonavir has no significant effect on the pharmacokinetic concentrations achieved for any of the three drugs [11, 12]. Systemic exposure to fosamprenavir is not altered by coadministration of TDF, when fosamprenavir is administered in the presence of ritonavir [13]. Similarly, no change is seen in lopinavir or ritonavir concentrations when lopinavir/ritonavir and TDF are coadministered. However, a 32% increase in tenofovir plasma AUC has been observed in the presence of lopinavir and ritonavir, compared with TDF alone [8, 14]. Importantly, the interaction between tenofovir and TMC114/r is of similar

Pharmacokinetic parameter	Without TDF	With TDF	LS mean ratio (90% CI)	P-value
Mean ± SD				
<i>n</i>	12	12	–	–
$C_{0,hr}$, ng ml ⁻¹	2262 ± 908	2473 ± 991	1.12 (0.85, 1.47)	0.50
$C_{min,r}$, ng ml ⁻¹	1845 ± 842	2220 ± 1051	1.24 (0.90, 1.69)	0.26
$C_{max,r}$, ng ml ⁻¹	3971 ± 1385	4448 ± 1008	1.16 (0.94, 1.42)	0.24
$AUC_{12,hr}$, ng h ⁻¹ ml ⁻¹	29837 ± 10345	35755 ± 12582	1.21 (0.95, 1.54)	0.19
Median (range)				
$T_{max,r}$, h	0.5 (0.5–4.0)	0.5 (0.5–0.5)	–	0.09

Table 1

Pharmacokinetic results of TMC114 administered with low-dose ritonavir (TMC114/r), with or without TDF

CI, Confidence interval; LS, least square; *n*, number of volunteers; SD, standard deviation; TDF, tenofovir disoproxil fumarate.

magnitude to that observed with tenofovir and lopinavir/ritonavir, for which no dose adjustments are advised.

To date, the mechanisms of tenofovir–PI interaction are unknown. However, since tenofovir is not metabolized by CYP450 enzymes, interactions are unlikely to be mediated by this pathway [15].

Increases in tenofovir concentrations could theoretically be associated with increased renal side-effects, but the magnitude of this potential problem is unclear. Tenofovir is an acyclic nucleoside phosphate, excreted by glomerular filtration and active tubular secretion in a similar manner to cidofovir and adefovir. Cidofovir and

adefovir are substrates of renal transporter proteins such as human renal organic anion transporter 1 (hOAT1) [16, 17]. Ritonavir is a potent inhibitor of the drug-transporting ATPases P-glycoprotein and multidrug resistance protein 2 (Mrp-2) [18]. Inhibition of Mrp-2-mediated transport could theoretically increase tubular concentrations of tenofovir by reducing its efflux from the kidneys. This hypothesis, however, remains unproven. In the dose ranging studies of TMC114/r plus OBR, TDF was the most frequently used reverse transcriptase inhibitor. TMC114/r plus OBR was generally well tolerated and renal disorders related to tenofovir were infrequent [19–21].

Cilhar and coworkers investigated tenofovir transport by hOAT1, hOAT2 and hOAT3 to assess further the involvement of tenofovir in renal drug interactions [22]. The study showed that at clinically relevant plasma concentrations of tenofovir, this substrate would occupy only a limited fraction of the renal transport capacity and so would not exert an inhibitory effect. Therefore, the authors concluded that renal drug interactions due to the inhibition of active transport are unlikely to occur. Recent data from Ray and colleagues have confirmed that, at the molecular level, there is no evidence of a pharmacokinetic renal drug–drug interaction between lopinavir or ritonavir and tenofovir [23]. This is congruent with our findings, which showed no alteration in tenofovir or TMC114 renal excretion during coadministration.

This interaction study between TMC114/r and tenofovir has been conducted at a TMC114 dose lower than the recommended dosage and with an oral solution. Exposure (AUC) to TMC114 has been found to increase less than dose proportionally. In HIV-infected patients receiving TMC114/r doses of 400/100 mg bid or 600/

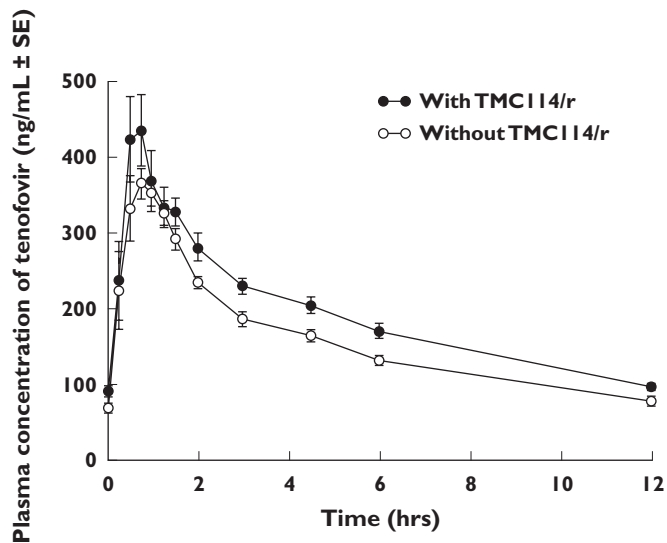


Figure 2

Profile of mean plasma concentration of tenofovir over time, in the presence or absence of a steady-state concentration of TMC114 and ritonavir. With TMC114/r, (●—●); Without TMC114/r, (○—○)

Table 2

Pharmacokinetic results of tenofovir, with or without coadministration of TMC114 and ritonavir (TMC114/r)

Pharmacokinetic parameter	Without TMC114/r	With TMC114/r	LS mean ratio (90% CI)	P-value
Mean ± SD				
n	12	12*	—	—
C _{0h} , ng ml ⁻¹	67.4 ± 14.3	88.9 ± 17.0	1.36 (1.17, 1.58)	0.003
C _{min} , ng ml ⁻¹	65.6 ± 13.4	86.8 ± 15.7	1.37 (1.19, 1.57)	0.001
C _{max} , ng ml ⁻¹	423 ± 75.2	528 ± 106	1.24 (1.08, 1.42)	0.01
AUC _{24h} , ng h ⁻¹ ml ⁻¹	3789 ± 499	4633 ± 735	1.22 (1.10, 1.35)	0.003
Median (range)				
T _{max} , h	1.5 (0.5–2.5)	1.0 (1.0–4.0)	—	0.74

CI, Confidence interval; LS, least square; n, number of volunteers; SD, standard deviation. *n = 11 for C_{0h} and C_{min}.

100 mg bid regimens, a considerable overlap in exposure to TMC114 was obtained with these two dosing regimens. The 50% increase in dose between the 400/100 mg bid and 600/100 mg bid regimens resulted in only a 29% increase in median TMC114 exposure [24]. On this basis, the results of this study conducted with the TMC114/r 300/100 mg bid regimen is considered applicable to subjects receiving the recommended 600/100 mg bid dosing regimen. Since no clinically relevant interaction was observed, and no dose adjustment is recommended with the 300/100 mg bid regimens, it is reasonable to extrapolate this finding to the 600/100 mg bid regimen on account of the overlap in TMC114 exposures seen with these dosing regimens. In addition, in the TMC114/r clinical trials in HIV-infected patients, analysis of covariance was used to investigate the impact of the covariate of concomitant use of TDF on the pharmacokinetics of TMC114. This analysis showed that the concomitant use of TDF did not significantly influence the exposure to TMC114. The geometric mean TMC114 AUC_{24 h} was 114 898 and 121 890 ng h⁻¹ ml⁻¹ for subjects without (*n* = 21) and with (*n* = 98) concomitant use of TDF, respectively, in the combined analysis of the dose ranging studies when using the recommended dose of TMC114/r 600/100 mg bid. This further supports the conclusion that the observed interaction between TMC114/r and tenofovir in this study is not clinically relevant and no dose adjustments are required when these drugs are coadministered.

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