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# Gemfibrozil Concentrations are Significantly Decreased in the Presence of Lopinavir/ritonavir

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## Abstract

**Objective:** To determine the influence of a two-week course of lopinavir-ritonavir on the pharmacokinetics of the triglyceride-lowering agent, gemfibrozil.

**Methods:** The study was conducted as an open label, single-sequence pharmacokinetic study in healthy human volunteers. Gemfibrozil pharmacokinetic parameter values were compared using a students *t* test after a single 600 mg dose was administered to healthy volunteers before, and after two weeks of lopinavir-ritonavir (400/100 mg) twice daily.

**Results:** Fifteen healthy volunteers (8 males) completed the study. All study drugs were generally well-tolerated and no subjects withdrew participation. The geometric mean ratio (GMR, 90% CI) for gemfibrozil area under the plasma concentration-time curve ($AUC_{0-\infty}$) after 14 days of lopinavir-ritonavir compared to baseline was 0.59 (0.52, 0.67) ($P < 0.001$). All 15 study subjects experienced a reduction in gemfibrozil $AUC_{0-\infty}$ after lopinavir-ritonavir (range: −6% to −74%). The GMRs for gemfibrozil apparent oral clearance (Cl/F) and maximum concentration ($C_{max}$) were 1.69 (1.41, 1.97) and 0.67 (0.49, 0.86) after 14 days of lopinavir-ritonavir versus baseline, respectively ($P < 0.0001$ and 0.01, respectively). Gemfibrozil elimination half-life did not change after lopinavir-ritonavir administration ($P = 0.60$).

**Conclusion:** Lopinavir/ritonavir significantly reduced the systemic exposure of gemfibrozil by reducing gemfibrozil absorption. Clinicians treating HIV-infected patients with hypertriglyceridemia should be aware of this drug interaction.

### Keywords

drug interaction; lopinavir-ritonavir; gemfibrozil; HIV

## Introduction

Dyslipidemia continues to be common in HIV-infected individuals [1]. The natural history of HIV infection is characterized by decreased levels of total, low-density lipoprotein (LDL), and

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high-density lipoprotein (HDL) cholesterol, as well as increased triglyceride levels [2]. In addition to dyslipidemia associated with HIV infection, the HIV protease inhibitors have been associated with elevations in LDL, total cholesterol, and triglyceride levels [2]. The nucleoside reverse transcriptase inhibitor stavudine has been associated with lipid perturbations as well [3]. The overall prevalence of hyperlipidemia disorders in patients receiving protease inhibitor-containing highly active antiretroviral therapy (HAART) has been estimated at 27%-57% and increases with duration of therapy [4]. As a result, cardiovascular complications are now being reported in this population [5,6].

In addition to cardiovascular disease, HIV infected individuals whose lipid profiles are marked by significant hypertriglyceridemia (> 1000 mg/dL) may be at risk for the development of pancreatitis [1,7]. These individuals are often treated with a fibric acid derivative (fibrate) such as gemfibrozil, alone or in combination with an HMG-CoA reductase inhibitor (statin) medication [7]. However, gemfibrozil, alone, or in combination with a statin, frequently fails to reduce triglyceride concentrations to normal levels [8,9,10]. In addition, a recent study in over 7,000 subjects showed that HIV-infected patients who began gemfibrozil therapy had substantially smaller decreases in triglyceride levels compared to non-HIV infected individuals (44.2% vs. 59.3%; $P < 0.001$) [11]. Persisting hyperlipidemia (including hypertriglyceridemia) in HIV-infected patients receiving lipid-lowering therapy may be due to the complex and multifactorial nature of lipid abnormalities in patients with HIV infection [12]. An unexplored possibility, is that a drug interaction exists between gemfibrozil and one or more antiretroviral medications, and that this interaction contributes to gemfibrozil's frequent inability to normalize triglyceride concentrations in HIV-infected HAART recipients.

After near complete oral absorption (oral bioavailability ≅ 100%), gemfibrozil undergoes hepatic metabolism by several pathways [13-15]. Oxidation of a ring methyl group forms a hydroxyl methyl and carboxyl metabolite [14,15]. There is a paucity of information regarding which enzymes are involved in these oxidative processes [14]. Gemfibrozil also undergoes glucuronide conjugation primarily by uridine 5′-diphosphate (UDP) glucuronosyltransferase isoenzyme (UGT) 2B7 [16]. Approximately 70% of the drug and its metabolites are excreted in the urine as glucuronide conjugates [14]. UGT2B7 is also involved in the metabolism of the anticonvulsants valproic acid and lamotrigine [17,18], both of whose plasma concentrations may be reduced by approximately 50% in the presence of the protease inhibitor combination lopinavir-ritonavir (19,20). If lopinavir-ritonavir reduces gemfibrozil plasma concentrations by a similar magnitude, this may partially explain why triglyceride concentrations frequently fail to normalize in HIV-infected patients receiving gemfibrozil and concurrent lopinavir-ritonavir-containing HAART. Due to the potentially serious consequences of inadequately treated hypertriglyceridemia, we examined the influence of lopinavir-ritonavir administration for two weeks on gemfibrozil pharmacokinetics in healthy human volunteers.

## Methods

### Study Subjects

The study population consisted of 15 HIV-negative individuals receiving no other concomitant medications (including prescription, over-the-counter, or herbal preparations) for at least 30 days prior to and throughout study participation. To be included in the current study, subjects were required to be 18-50 years of age, test HIV negative (ELISA) and be free of concurrent illnesses per medical history, physical exam, and screening laboratory values. Screening laboratory values were required to be within institutional normal ranges, except for fasting total cholesterol and triglycerides, which were each required to be below 270 mg/dL. Females of child-bearing potential were required to have a negative serum pregnancy test within 7 days of commencing lopinavir-ritonavir and to practice abstinence or use effective non-hormonal methods of birth control during the study. Subjects were required to be non-smoking for at

least 6 weeks prior to study participation and to refrain from smoking during the entire study period. In addition, subjects were not permitted to ingest fruit juices (grapefruit juice, orange juice, apple juice etc.) during the course of the investigation.

All participants gave written informed consent, and clinical research was conducted according to guidelines for human experimentation as specified by the US Department of Health and Human Services. This study was approved by the National Institute of Allergy and Infectious Diseases Institutional Review Board.

## Study Design and Treatments

This study was conducted as an open-label, single series design in an outpatient HIV clinic. In each subject, the gemfibrozil pharmacokinetic profile on study day 1 served as the "control arm" of the study; it was compared to the gemfibrozil pharmacokinetic profile on day 14 of lopinavir-ritonavir dosing. Any changes in gemfibrozil pharmacokinetics observed in subjects were attributable to the co-administration of lopinavir-ritonavir. Since ritonavir is no longer used as a single protease inhibitor in clinical practice, our study aim was to document the clinical relevance of lopinavir-ritonavir causing any modulation of gemfibrozil pharmacokinetics. Lopinavir-ritonavir was chosen for use in this study given its status as a one of the preferred protease inhibitor combinations recommended for the treatment of HIV in antiretroviral treatment-naïve individuals [21].

After an overnight fast, subjects took a single 600 mg gemfibrozil tablet (Teva Pharmaceuticals, USA) with 240 mL of water and waited 30 minutes prior to receiving a standard light breakfast. Blood samples for determination of gemfibrozil plasma concentrations were collected into heparinized tubes at time 0 (pre-dose), 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours following the dose. Blood was centrifuged after collection and plasma was harvested and frozen at −80 °C until the time of analysis.

Following gemfibrozil pharmacokinetic sampling, subjects were allowed a 1-5 week lee-way period before starting lopinavir-ritonavir (Kaletra, Abbott Laboratories, North Chicago, IL) 400/100 mg ( given as two 200/50 mg tablets) twice daily with food, continuing for 14.5 days. This extended lee-way period was incorporated into the protocol in an attempt to avoid conflicts with subject's schedules. However, in actuality the median time between gemfibrozil pharmacokinetic sampling and the start of lopinavir-ritonavir dosing was 8 days (range: 8-15 days). To monitor adherence, a pill count was conducted prior to dispensing the medication and when subjects returned for their second pharmacokinetic sampling period. On day 14 of lopinavir-ritonavir administration subjects took their a.m. lopinavir-ritonavir dose with a light breakfast 30 minutes after receiving gemfibrozil 600 mg, and they took their p.m. lopinavir-ritonavir dose in the usual manner. Blood was drawn for pharmacokinetic sampling of gemfibrozil as on day 1; additional blood was drawn for laboratory safety monitoring.

## Gemfibrozil analysis

Using a newly developed high performance liquid chromatography method in our laboratory, gemfibrozil and clofibric acid internal standards were separated and detected by tandem mass spectrometry using multiple reaction monitoring (MRM). The separation was performed on an Acquity BEH RP18, 2.1 × 50 mm, 1.7μm analytical column preceded by an Vanguard BEH RP18, 2.1 × 5 mm, 1.7μm pre-column (Waters Corp., Milford, MA, USA) using a mobile phase gradient starting with a 50:50 (v/v) mixture of acetonitrile (ACN) and 5.0mM ammonium formate (buffer) adjusted to pH 3.0 with formic acid at a flow rate of 0.300 ml/min. Gemfibrozil and clofibric acid internal standard were isolated from human plasma by an off-line solid-phase extraction (SPE) method using Oasis MAX 1cc/30mg cartridges (Waters).

Calibration curves for gemfibrozil were linear from 0.020 μg/mL – 20.0 μg/mL with $R^2 >$ 0.998. Percent errors, as a measure of accuracy, were <15% and the inter- and intra-assay coefficients of variation for gemfibrozil were 3.6-5.1% and 2.1-5.3%, respectively, at three different drug concentrations. The limit of quantitation for gemfibrozil was 0.020 μg/mL and the limit of detection was 0.010 μg/mL.

### Pharmacokinetic Analysis

Gemfibrozil pharmacokinetic parameters were determined using noncompartmental methods with WinNonlin Professional computer program (version 5.0; Pharsight Corporation, Mountain View, CA). Maximum plasma concentrations ($C_{max}$) and time to reach $C_{max}$ ($T_{max}$) were determined by visual inspection of the concentration-time profiles. The elimination rate constant ($\lambda_z$) was estimated as the absolute value of the slope of a linear regression of a natural logarithm of concentration versus time using at least 3 points on the line. Half-life ($T_{1/2}$) was calculated as $\ln 2/\lambda_z$. Area under the concentration vs. time curve (AUC) from 0 hours to the last quantifiable concentration ($AUC_{0\text{-last}}$) was determined using the linear trapezoidal rule. AUC from time 0 to infinity ($AUC_{0\text{-}\infty}$) was determined by dividing the last measured concentration by the elimination rate constant ($\lambda_z$) and adding this value to $AUC_{0\text{-last}}$. Apparent oral clearance (CL/F) was estimated as dose divided by $AUC_{0\text{-}\infty}$ and apparent volume of distribution (V/F) was estimated as dose divided by the product of $AUC_{0\text{-}\infty}$ and $\lambda_z$.

### Statistical Analysis

Sample Size was calculated with regard to reported variability in gemfibrozil area under the concentration vs. time curve (AUC) in healthy volunteers (75 μg•hr/mL with a relative standard deviation of 35%) [22]. Based on these data and $\alpha = 0.05$, a sample size of 13 yielded 81% power to detect a clinically relevant change of 30% in gemfibrozil AUC with concomitant lopinavir-ritonavir. Gemfibrozil pharmacokinetic parameters derived pre- and post lopinavir-ritonavir exposure (Days 1 and 14, respectively) were compared using a paired Students *t* test. Statistical significance was defined a priori as $\alpha < 0.05$ (SYSTAT Software, version 11; Richmond, CA, USA).

## Results

Fifteen subjects (8 males) screened for, and completed the study. The average age and weight of the study participants was 37 (± 10) yrs. and 78 (± 18) kg, respectively. Gemfibrozil geometric mean pharmacokinetic parameter values and geometric mean ratios (GMRs) are displayed in Table 1. Gemfibrozil $AUC_{0\text{-}\infty}$ and $C_{max}$ were significantly decreased with lopinavir-ritonavir (Fig. 1). All 15 study subjects experienced a decrease in gemfibrozil $AUC_{0\text{-}\infty}$ (GMRs ranged from 0.26 to 0.94 for $AUC_{0\text{-}\infty}$), and 12 of 15 subjects experienced a decrease in gemfibrozil $C_{max}$ (GMRs ranged from 0.35 to 2.12 for $C_{max}$) with the addition of lopinavir-ritonavir. Gemfibrozil Cl/F and V/F were each significantly increased by 69% following lopinavir ritonavir (Table 1); this increase was observed in all 15 subjects for Cl/F, where GMRs ranged from 1.06 to 3.83, and in 12 of 15 subjects for V/F, where GMRs ranged from 0.76 to 5.20. Gemfibrozil $T_{max}$ and half-life were not significantly changed by lopinavir-ritonavir (Table 1).

All study drugs were generally well-tolerated and no subjects withdrew participation. Side effects associated with lopinavir-ritonavir dosing included mainly Grade 1 nausea and diarrhea. As expected, lopinavir-ritonavir was associated with increases in total cholesterol, triglycerides, and LDL cholesterol compared to baseline. Mean triglycerides increased 73% from 77 mg/dL (pre-lopinavir-ritonavir) to 133 mg/dL (post- lopinavir-ritonavir); elevations

in total cholesterol and LDL cholesterol were less marked at + 8% (177 to 191 mg/mL) and +11% (110 to 122 mg/dL), respectively. No additional laboratory abnormalities were observed.

## Discussion

Gemfibrozil pharmacokinetic parameters in this study were not entirely consistent with those previously reported in patients with normal renal function [23,24]. We believe this is due to the sensitivity of our HPLC/MS assay (LLQ = 0.020 μg/mL) , which allowed us to measure gemfibrozil plasma concentrations 24 hrs post-dose. In comparison, previous studies used a less sensitive HPLC assay (LLQ = 1.0 μg/mL) and were thus limited to 12 hr sampling. [23-25]. As a result of extended sampling, we were able to characterize the slower terminal elimination phase of gemfibrozil and thus observed an average gemfibrozil half-life of 4.4 hrs compared to 1-2 hrs reported in previous studies that truncated post-dose sampling at 12 hrs. This increase in half-life we noted (i.e. reduction in $\lambda_z$) likely contributed to the increase in apparent volume of distribution (V/F) we observed compared to previously reported values (37L vs approximately 10 L for a 70 kg individual) since V/F was estimated as dose divided by the product of $AUC_{0-\infty}$ and $\lambda_z$[26].

In this study, two weeks of lopinavir-ritonavir administration resulted in a 41% decrease in gemfibrozil $AUC_{0-\infty}$. Due to the fact that a defined dose-response relationship exists between gemfibrozil and its ability to reduce triglyceride concentrations, the magnitude of the interaction we observed between lopinavir-ritonavir and gemfibrozil is likely to be clinically relevant [27] At approved doses (600 mg twice daily), HIV-negative patients can typically expect triglyceride reductions of 40-50% after 3-5 months of treatment with gemfibrozil. [28-30] When gemfibrozil was administered at 50% of its standard daily dose (600 mg once daily) to 10 HIV-negative individuals with hypertriglyceridemia, the average reduction in triglyceride concentrations was only 16% (range −34% to +14%) after 9 weeks of therapy [27]. Because gemfibrozil displays linear pharmacokinetics, [25] a 50% reduction in the daily gemfibrozil dose (600 mg once daily) would be expected to produce an approximate 50% reduction in the drug's AUC, which is similar in magnitude to the 41% reduction in gemfibrozil AUC with lopinavir-ritonavir. These data are consistent with studies that show suboptimal reductions in triglyceride levels in HIV-infected patients receiving protease inhibitor-containing HAART [8-11].

The precise mechanism of the interaction between gemfibrozil and lopinavir-ritonavir cannot be determined from our study. The influence of lopinavir-ritonavir on gemfibrozil pharmacokinetics, which is hallmarked by reductions in gemfibrozil AUC and $C_{max}$ without a subsequent change in half-life, does not appear to be due to induction of hepatic (or intestinal) UGT2B7 or gemfibrozil oxidation by lopinavir-ritonavir, as these enzymatic processes do not exhibit an appreciable first-pass effect on gemfibrozil pharmacokinetics [13,14]. Alternatively, one would expect induction of gemfibrozil metabolism via glucuronidation or oxidation, to primarily alter (reduce) the terminal elimination of the drug, which we did not observe.

Instead, lopinavir-ritonavir appeared to produce a significant reduction in gemfibrozil bioavailability (F); this is supported by the significant (and similar) reductions observed in gemfibrozil $C_{max}$ and AUC with lopinavir-ritonavir and by the fact that gemfibrozil apparent oral clearance (CL/F) and apparent volume of distribution (V/F) increased to an identical extent with the addition of lopinavir-ritonavir (i.e. a similar reduction in F, would result in similarly increased estimations of apparent oral clearance and volume).

A potential mechanism for the apparent increase in gemfibrozil absorption with concurrent lopinavir-ritonavir is modulation of presystemic gemfibrozil transport by lopinavir-ritonavir; unfortunately, little information is available regarding which enterocyte proteins are involved

in the intestinal transport of gemfibrozil. Hepatic organic anion transport polypeptide 1B1 (OATP1B1) may be inhibited by lopinavir-ritonavir [31]; however, hepatic inhibition of OATP1B1 would be expected to produce an increase in gemfibrozil exposure assuming that gemfibrozil, itself an inhibitor of OATP1B1 [32], is also an OATP1B1 substrate. Originally thought to be liver-specific, OATP1B1 is also expressed in the intestine [33]. Inhibition of OATP1B1 in the intestinal tract by lopinavir-ritonavir could theoretically reduce gemfibrozil absorption (again, assuming gemfibrozil is an OATP1B1 substrate); however, the role of OATP1B1 in the intestine is questionable since it was incapable of transporting the common OATP substrate, fexofenadine [33]. To this end further study is necessary to elucidate gemfibrozil transport *in vivo* to determine the mechanism by which lopinavir-ritonavir reduced the systemic availability of gemfibrozil.

An additional point for consideration is the possibility that gemfibrozil, which is 98.6% bound to albumin in plasma, underwent significant protein binding displacement when combined with lopinavir-ritonavir [34]. This could potentially result in a transient increase in free (unbound) gemfibrozil concentrations that subsequently return to pre-interaction levels. As a result, total (bound plus unbound drug) gemfibrozil concentrations would be expected to decrease, without a noticeable change in the drug's half-life; such a scenario would be consistent with our findings. Since unbound (pharmacologically active) gemfibrozil concentrations would be unaltered in this case, dosage increases to compensate for reduced gemfibrozil exposure would be inappropriate. However, both lopinavir and ritonavir have a higher binding affinity for alpha-1 acid glycoprotein (to which gemfibrozil does not bind) versus albumin [35,36], perhaps making this scenario less likely. Moreover, ritonavir displaces other highly protein bound drugs only to a small degree even at higher concentrations (5 mg/L) than those achieved when the drug is administered at boosting doses of 100 mg twice daily ($\cong$ 0.5 mg/L) [36,37].

Even though the precise mechanism of the interaction between lopinavir-ritonavir and gemfibrozil is unknown, a more imminent concern for clinicians is how this interaction should be managed in the clinical setting. The first option would be to avoid lopinavir-ritonavir, but this may not be practical or feasible for many patients, particularly if one chooses to avoid all ritonavir-containing regimens based on the assumption that ritonavir is the culpable agent in the interaction between gemfibrozil and lopinavir-ritonavir. Another approach to avoiding this interaction might involve substituting gemfibrozil with another triglyceride-lowering agent such as fenofibrate. However, given fenofibrate chemical similarity to gemfibrozil (both are fibric acid derivatives), an interaction with ritonavir and/or lopinavir-ritonavir cannot be ruled out. Statins could be used as an alternative, or in addition to, gemfibrozil; however, statins are more effective in reducing cholesterol than triglycerides, and again clinical experience suggests that they are relatively ineffective in lowering the latter [7]. Moreover, serious drug interactions between certain statins and protease inhibitors are well-described [7]. Another option is to increase the gemfibrozil dose, but due to the unknown risks of increased gemfibrozil exposure (elevated creatinine kinase, rhabdomyolysis, etc.) this approach should be initiated within the controlled environment of a clinical trial.

In conclusion, results from this investigation offer clear evidence of a potentially significant drug-drug interaction between gemfibrozil and lopinavir-ritonavir. However, further study is necessary to characterize the specific oxidative pathways of gemfibrozil, to identify transport proteins involved in gemfibrozil uptake and/or efflux at the intestinal and hepatic levels, and to characterize the influence of lopinavir-ritonavir on the formation of gemfibrozil's various oxidative and glucuronide metabolites. Once collected, this information should shed light on the precise mechanism by which lopinavir-ritonavir interacts with gemfibrozil and provide helpful information for clinicians managing this interaction in the clinical setting.

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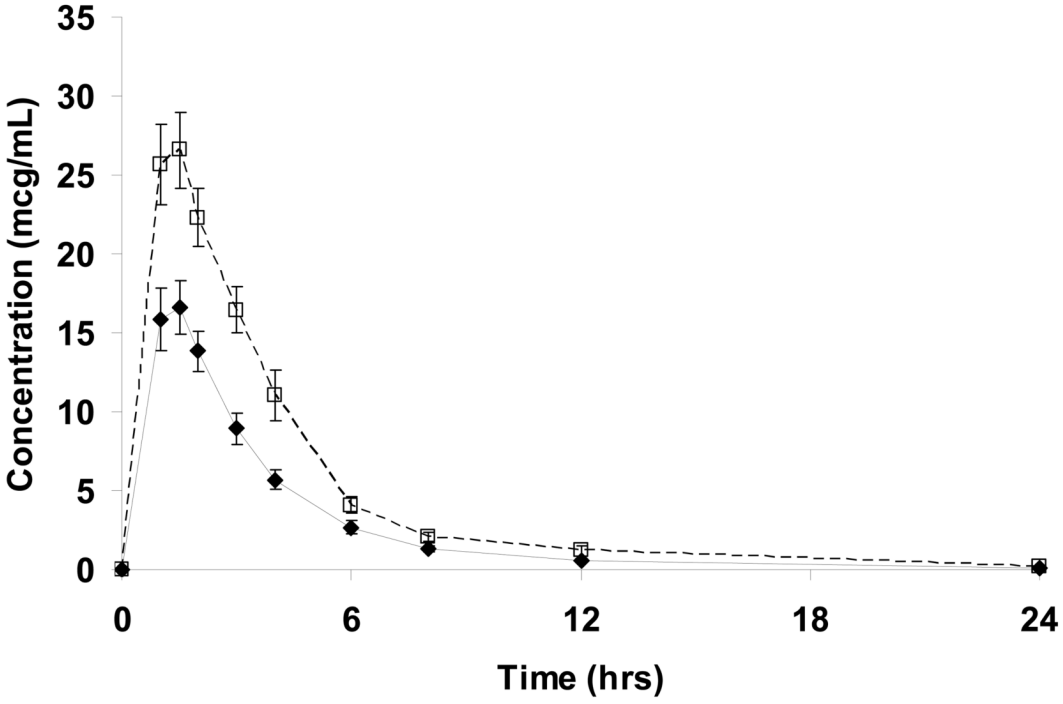


**Figure 1.**
Composite gemfibrozil concentration vs. time curves (arithmetic mean ± SE) in 15 subjects who received the drug alone (open squares, dashed line) and after lopinavir-ritonavir (400/100 mg) twice daily for two weeks (closed diamonds, solid line).

## Table 1

Geometric Mean gemfibrozil Pharmacokinetics (n = 15)

| Pharmacokinetic Parameter | Phase 1 (pre LPV/r | Phase 2 (post LPV/r | GMR Phase 2 vs. Phase 1 (90% CI) | *P** |
|---|---|---|---|---|
| $AUC_{0-\infty}$ (μg·hr/mL) | 104 | 62 | 0.59 (0.52, 0.67) | 0.001 |
| $C_{max}$ (μg/mL) | 28 | 19 | 0.67 (0.49, 0.86) | 0.01 |
| $T_{max}$ (hr) | 1.4 | 1.3 | 0.95 (0.76, 1.13) | 0.56 |
| CL/F (L/hr) | 5.8 | 9.8 | 1.69 (1.41, 1.97) | 0.0001 |
| V/F (L) | 37 | 62 | 1.69 (1.09, 2.28) | 0.011 |
| Half-Life (hr) | 4.4 | 4.4 | 1.0 (0.71, 1.29) | 0.60 |

CI indicates confidence interval; LPV/r, lopinavir-ritonavir; GMR, geometric mean ratio

* Based on a paired Student's *t* test