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Effects of a Protein-Rich Drink or a Standard Meal on the Pharmacokinetics of Elvitegravir, Cobicistat, Emtricitabine and Tenofovir in Healthy Japanese Male Subjects: A Randomized, Three-Way Crossover Study

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Abstract

This study investigated the effects of ingested food types on the pharmacokinetics of elvitegravir, cobicistat, emtricitabine, and tenofovir as a single-tablet regimen (STR) in Japanese HIV-negative healthy subjects. In this open-label, randomized, three-way crossover study, the pharmacokinetic profiles of elvitegravir, cobicistat, emtricitabine, and tenofovir were evaluated when administered with a standard breakfast, under fasting conditions, or with a nutritional protein-rich drink. All subjects (N = 11) received a single morning dose of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (150/150/200/300 mg). Administration under fasting conditions resulted in decreases in the mean AUC_{inf} of elvitegravir and tenofovir by 50% and 28%, respectively, relative to administration with a standard breakfast, whereas the bioavailabilities of elvitegravir and tenofovir were comparable when administered with a standard breakfast or a nutritional protein-rich drink. Under fasting conditions, it appears that the bioavailabilities of elvitegravir and tenofovir were not equivalent to those when they were administered with either type of food, although they were bioequivalent to each other under fed conditions. Cobicistat and emtricitabine were bioequivalent under all conditions. These findings suggest that elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate should be administered with food, and that the bioavailability of elvitegravir and tenofovir is not affected by the type of meal ingested.

Keywords

elvitegravir, stribild, Japanese, food effect, pharmacokinetics

Elvitegravir is a novel low-molecular-weight integrase strand transfer inhibitor (INSTI) with antiviral activity, originally developed by Japan Tobacco, Inc. (Tokyo, Japan). It was discovered through screening assays of human immunodeficiency virus type 1 (HIV-1) integrase inhibitory activity using HIV-1 integrase obtained after genetic engineering of the full-length genome sequence of the NL4-3 strain of HIV-1.[1]

Cobicistat, marketed by Gilead Sciences, Inc. (Foster City, CA), is a new chemical entity and structural analogue of ritonavir with no antiretroviral activity. It is a more specific, mechanism-based CYP3A inhibitor than ritonavir that enhances or "boosts" the exposure of CYP3A substrates. Cobicistat inhibits human CYP3A selectively and potently with metabolic activation-dependent activity. It enhances the bioavailability of coadministered drugs such as elvitegravir, which are metabolized by CYP3A and decreases their clearance. The activity of cobicistat as a booster is equivalent to that of low-dose ritonavir. Cobicistat has no antiretroviral activity, and can therefore be used as a booster without concern that drug-resistant virus strains may develop, even in regimens that do not contain a protease inhibitor.[2]

Abbreviations: AUC, area under the plasma concentration–time curve; BMI, body mass index; C_{24}, concentration at 24 hours post-dose; CI, confidence interval; C_{max}, maximum plasma concentration; CYP3A, cytochrome P450 3A; EVG/COBI/FTC/TDF, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; GMR, geometric mean ratio; HIV-1, human immunodeficiency virus type 1; STR, single-tablet regimen; T_{max}, time to reach C_{max}.

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A single-tablet regimen (STR) of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF, Stribild®) contains 150 mg of elvitegravir and 150 mg of cobicistat, as well as 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate, which are the recommended backbones for initial treatment of HIV-1-infected patients. It is the first INSTI-containing combination tablet that can be taken once daily for treatment of HIV-1 infection,[3] and the Antiretroviral Guidelines for Adults and Adolescents recommend EVG/COBI/FTC/TDF STR as the preferred regimen for antiretroviral therapy-naive patients.[4] EVG/COBI/FTC/TDF STR was approved in August 2012 in the USA, March 2013 in Japan, and May 2013 in the EU, and is currently available commercially as a new treatment option for patients who wish to take fewer tablets less frequently.

The pharmacokinetics of elvitegravir, cobicistat, emtricitabine, and tenofovir, the four components of EVG/COBI/FTC/TDF STR, have been studied before in healthy subjects[5] and HIV-1-infected patients[6] in the USA. The oral bioavailability of elvitegravir and tenofovir is affected by food intake.[3,7] A food interaction study showed that the mean AUC_{inf} and C_{max} of these components of EVG/COBI/FTC/TDF STR administered orally were increased by 34% and 24%, respectively, when administered with a meal (373 kcal, 20% fat), as compared with fasting conditions.[7] Therefore, in a clinical setting, it is recommended that EVG/COBI/FTC/TDF STR be taken with a meal.[3] Although EVG/COBI/FTC/TDF STR has been approved for marketing in Japan and has already been administered to HIV-1-infected patients, the pharmacokinetics of these components have not yet been evaluated in Japanese subjects. In previous studies of the effects of food on pharmacokinetics, meals of approximately 400 and 800 kcal were evaluated,[3,7] but the effects of meals containing fewer calories, such as protein-rich drinks, have remained unknown. If exposure to EVG/COBI/FTC/TDF STR administered with a protein-rich drink containing fewer calories was equivalent to that when administered with a standard breakfast, then patients treated with EVG/COBI/FTC/TDF STR would have more meal options.

The objectives of our present study were to confirm the effects of fasting conditions and two types of meal (a nutritional protein-rich drink and a standard meal) on the pharmacokinetics of elvitegravir, cobicistat, emtricitabine, and tenofovir in Japanese subjects taking the EVG/COBI/FTC/TDF single-tablet formulation.

Methods

This food-effect study was conducted at Kyushu Clinical Pharmacology Research Clinic (Fukuoka, Japan) in compliance with the ethical principles of the Declaration of Helsinki and the Guideline for Good Clinical Practice of the Japanese Ministerial Ordinance. The protocol was reviewed and approved by the Pharmaceuticals and Medical Devices Agency (Tokyo, Japan) and the Institutional Review Board of Kyushu Clinical Research Clinic. All subjects provided written informed consent to participate prior to underdoing any study-related assessment, procedures or treatment.

Study Design and Participants

This was a randomized, open-label, single-dose, three-treatment, three-period, three-sequence crossover study conducted in healthy Japanese male subjects to investigate the pharmacokinetics, short-term safety and tolerability of EVG/COBI/FTC/TDF STR administered under fasting conditions and two different fed conditions (a standard breakfast and a nutritional protein-rich drink). EVG/COBI/FTC/TDF STR, which contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 300 mg of tenofovir disoproxil fumarate in one tablet (supplied by Torii Pharmaceutical Co., Ltd, Tokyo, Japan), was used as the study drug. The study subjects were 12 HIV-negative healthy Japanese males aged between 20 and 45 years, who were selected based on screening assessment results including BMI, medical history, physiological tests (ECG and vital signs), and laboratory tests (hematology, blood biochemistry, immunology, and urinalysis).

Prior to the first dose of the study drug, the subjects were randomized to three panels, each of which included four subjects. In three sessions, panel 1 received treatments A, B, and C (defined as *Study treatments*), panel 2 received treatments B, C, and A, and panel 3 received treatments C, A, and B, by random allocation of treatment sequences. The treatment period was divided into Periods 1, 2, and 3, with a 7-day interval between Periods 1 and 2 and between Periods 2 and 3. In each treatment period, subjects were admitted to the study center on the day before treatment, and the study drug (study treatment) was administered the following day (Day 1). Subjects were placed under the supervision of the investigators until their discharge after the end of assessment on Day 3.

Study Treatments

Subjects were required to fast overnight for at least 10 hours (except for water intake) before each administration. On Day 1 in each treatment period, a single dose of the EVG/COBI/FTC/TDF STR was given with 200 mL of water either under fasting conditions or within 5 minutes after ingestion of a standard breakfast (treatment A: one ham, cheese and egg sandwich, one tuna, lettuce and tomato sandwich, 1 cup of white peach jelly, and 160 g of apple juice; total calories: 413 kcal, 11.4 g protein, 9.6 g fat, and 72.2 g carbohydrate) or a nutritional drink rich in proteins (treatment C: Ensure Liquid 250 mL [Abbott Japan Co., Tokyo, Japan]; total calories: 250 kcal,

8.8 g protein, 8.8 g fat, and 34.3 g carbohydrate). The entire meal had to be consumed within 30 minutes. Subjects were prohibited from consuming any food other than the treatment A or C meal until after collection of the 4-hour pharmacokinetic sample, and were prohibited from drinking any water for 1 hour before and after drug administration, except for the 200 mL given with the study treatment.

Pharmacokinetic Assessments

In each session, the full pharmacokinetic profiles of elvitegravir, cobicistat, emtricitabine, and tenofovir were assessed. Serial samples were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 14, 16, 20, 24, 36 and 48 hours post-dose. Blood sampling times were based on the known concentration–time profiles of each analyte to allow accurate assessment of their pharmacokinetics. Blood samples were collected by venipuncture into a Venoject II® plastic whole blood tube (VP-DK050K, TERUMO, Tokyo, Japan) containing anticoagulant (spray-dried K2 ethylenediaminetetraacetic acid [EDTA]), and the tube was inverted several times to mix the blood and the anticoagulant. To harvest the plasma, tubes were centrifuged for 10 minutes at 3,000 rpm in a refrigerated centrifuge at 4°C. Separated plasma samples were stored below −70 °C until analysis.

The plasma concentrations of elvitegravir, cobicistat, emtricitabine, and tenofovir were measured using validated high-performance liquid chromatography/tandem mass spectrometry (HPLC-MS/MS) methods, as described previously.[5,8] The assays were performed by QPS, LLC (Newark, DE). For elvitegravir and cobicistat, 50 μL of human plasma was spiked with respective deuterated internal standards and processed by solid-phase extraction. Solid-phase extraction was performed using a TOMTEC Quadra 96® system. The plasma samples were loaded onto a Waters OASIS™ HLB SPE plate (10 mg), and then the plates were washed with water/methanol/formic acid solution, and eluted with acetonitrile/water/formic acid solution. The internal standards were supplied by Gilead Sciences, Inc. The compounds were detected by MS/MS in the selected reaction monitoring mode using electrospray ionization with positive polarity, and the following ion transitions were monitored: m/z 448 → 344 for elvitegravir, m/z 456 → 344 for the internal standard of elvitegravir, m/z 776 → 606 for cobicistat, and m/z 784 → 614 for the internal standard of cobicistat. The limit of quantification was 20 ng/mL for elvitegravir, and 5 ng/mL for cobicistat. The calibration curves were linear from 20 to 10,000 ng/mL for elvitegravir and from 5 to 2,500 ng/mL for cobicistat. The inter-assay precision range (%CVs) for elvitegravir at 20 and 10,000 ng/mL was 2.8–8.1, and the range for cobicistat at 5 and 2,500 ng/mL was 3.9–8.3. The inter-assay accuracy range (%RE) was −8.0 to 5.7 for elvitegravir and −0.3 to 9.7 for cobicistat. Elvitegravir and cobicistat in the frozen matrix were stable for 585 days at −70°C, and 365 days at −60 and −80°C, respectively. All samples were analyzed within the storage stability window.

For emtricitabine and tenofovir, 100 μL of human plasma was deproteinized using 300 μL of methanol solution containing the two internal standards (^{13}C, $^{15}N_2$-double-labeled emtricitabine and deuterated tenofovir), which were supplied by Toronto Research Chemicals (Ontario, Canada). The compounds were detected by MS/MS in the selected reaction monitoring mode using electrospray ionization with positive polarity, and the following ion transitions were monitored: m/z 248 → 130 for emtricitabine, m/z 251 → 133 for the internal standard of emtricitabine, m/z 288 → 176 for tenofovir, and m/z 294 → 182 for the internal standard of tenofovir. The limit of quantification for emtricitabine and tenofovir was 5 ng/mL. The calibration curves were linear from 5 to 3,000 ng/mL for emtricitabine and tenofovir. The inter-assay precision range (%CVs) for emtricitabine at 5 and 3,000 ng/mL was 1.4–5.7, and the range for tenofovir at 5 and 3,000 ng/mL was 2.4–6.5. The inter-assay accuracy range (%RE) was −7.8 to 2.4 for emtricitabine and −4.7 to 2.0 for tenofovir. Emtricitabine and tenofovir in a frozen matrix were stable for 340 days at −70°C.

Safety Assessments

Safety was assessed on the basis of subjective symptoms, objective findings, physiological tests (vital signs and electrocardiogram), and laboratory tests (hematology profile, chemistry profile, and urinalysis), and changes that were assessed as clinically significant by the investigator were handled as adverse events. Adverse events were investigated from the screening assessment until Day 3 in Period 3. Laboratory tests were performed at the screening assessment, and on Days 1 and 3 in each treatment period.

Pharmacokinetic and Statistical Analysis

Descriptive statistics of pharmacokinetic parameters were calculated from the plasma concentrations of elvitegravir, cobicistat, emtricitabine, and tenofovir for each treatment method using a non-compartmental method with WinNonlin Enterprise (version 5.3; Pharsight Corporation, Mountain View, CA). The pharmacokinetic parameters estimated for each analyte were: maximum plasma concentration (C_{max}), concentration at 24 hours post-dose (C_{24}), time to reach C_{max} (t_{max}), half-life ($T_{1/2}$), area under the plasma concentration–time curve from the time of administration up to the last time point with a measurable concentration post-dose (AUC_{last}), and AUC extrapolated to infinity (AUC_{inf}). AUC_{last} was calculated by linear trapezoidal summation. AUC_{inf} was calculated as the sum of AUC_{last} and C_{last}/λ_z, where C_{last} denotes the last

measurable concentration and λ_z represents the elimination rate constant determined by linear regression of the terminal points of the ln-linear plasma concentration–time curve.

Statistical analyses for the plasma pharmacokinetic parameters of elvitegravir, cobicistat, emtricitabine, and tenofovir compared test treatments B and C versus treatment A (reference). EVG/COBI/FTC/TDF STRs have been administered under fed conditions throughout clinical development, and in clinical pharmacokinetic studies a standard breakfast has been used. This determined the choice of the standard breakfast treatment (treatment A) as the reference treatment.

The primary pharmacokinetic parameters of interest for each analyte were C_{max} and AUC_{inf} on a logarithmic scale. The least square (LS) means of the pharmacokinetic parameters were estimated using linear mixed effect modeling, controlling for treatment, sequence, and period as fixed effects, and for subject as a random effect. The ratio of LS means of the test treatment (i.e., fasted or protein-rich drink) and reference treatment (i.e., standard breakfast) value was calculated for each treatment, and 90% confidence intervals (CIs) were constructed. Both the ratios of LS means and the 90% CIs were retransformed to the original scale. Treatment and period effects were considered significant at the 5% level, and sequence effects were considered significant at the 10% level. A food effect on any pharmacokinetic parameter was considered to exist if the 90% CIs of the geometric least-squares mean ratio (GMR) of the test treatment relative to the reference treatment fell outside the equivalence boundaries of 0.80–1.25.

Safety assessment data were evaluated by descriptive statistics and frequency tabulations.

Results

Demographic Characteristics

A total of 12 male subjects were randomized to three treatment sequences, each comprising four subjects. One subject withdrew after the first administration in Period 1. All subjects were of Japanese origin. The demographic data [mean (±standard deviation)] for the 12 subjects who were assigned to the treatments were: age 32.2 (±8.4) years, height 172.1 (±4.8) cm, body weight 59.6 (±3.9) kg, and BMI 20.1 (±1.1) kg/m^2.

Pharmacokinetics

The mean elvitegravir plasma concentration–time profiles following the study treatments are shown in Figure 1A. These profiles were comparable for both treatments A and C under fed conditions. In comparison, administration under fasting conditions (treatment B) resulted in a lower mean elvitegravir plasma concentration–time profile. The

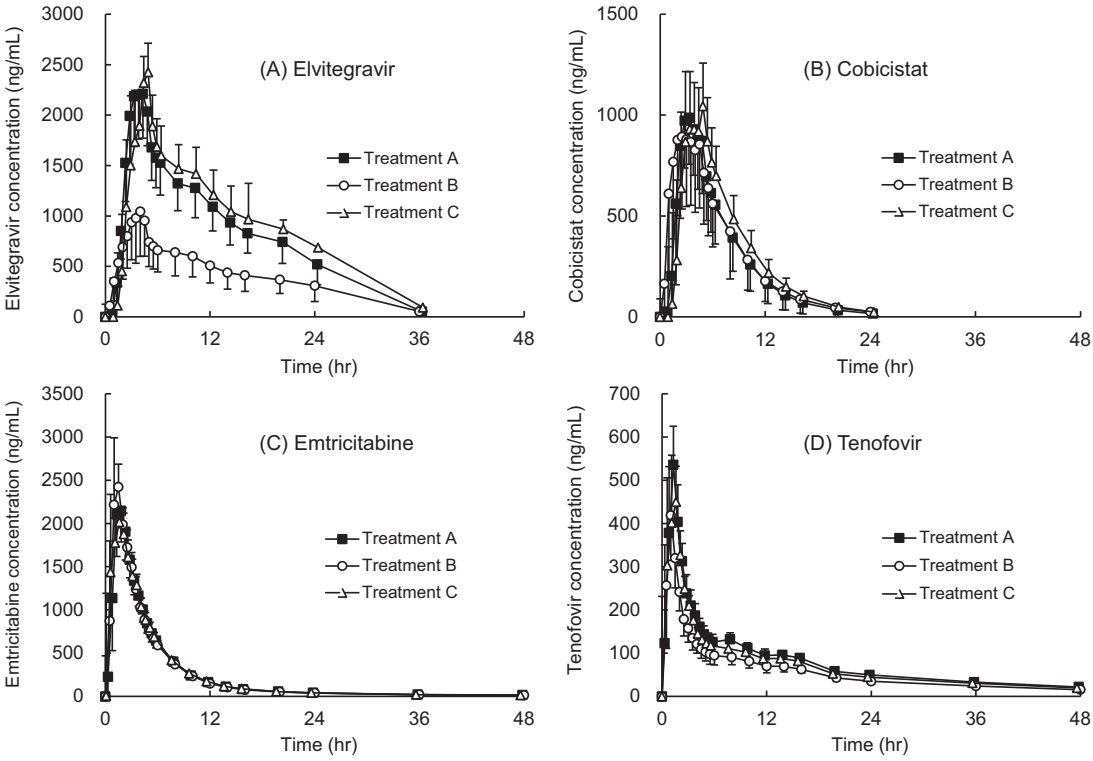

Figure 1. Mean (±standard deviation) plasma concentration-time profiles of (A) elvitegravir, (B) cobicistat, (C) emtricitabine, and (D) tenofovir administered with different meals. Treatments were follows: treatment A = standard breakfast, treatment B = fasted conditions, treatment C = protein-rich drink.

plasma elvitegravir concentration reached C_{max} within 4 hours post-dose in all of the treatment groups. The corresponding elvitegravir pharmacokinetic parameters and the test versus reference treatment comparisons are listed in Table 1. For assessment of the LS mean ratio, a single oral dose of EVG/COBI/FTC/TDF STR in a fasted state (treatment B) resulted in 55% and 50% decreases in C_{max} and AUC_{inf} for elvitegravir, respectively, as compared with those following administration with a standard breakfast (treatment A). The 90% CIs of GMR for elvitegravir pharmacokinetic parameters were below 0.8–1.25, indicating that a fasted state was not bioequivalent to the standard meal arm. The C_{max} and AUC_{inf} values for elvitegravir in the protein-rich drink group (treatment C) were comparable to those in the standard breakfast group. The 90% CIs of GMR for elvitegravir AUC_{inf} were within the boundary of 0.8–1.25, while the upper limit of the 90% CI of GMR for elvitegravir C_{max} was narrowly above the lack of a food effect boundary (1.27) after administration with a protein-rich drink, indicating that the two fed conditions were bioequivalent to each other.

The mean plasma cobicistat concentration–time profiles are shown in Figure 1B. The plasma cobicistat concentration following administration with a standard breakfast (treatment A) reached C_{max} at 2.5 hours post-dose. The plasma cobicistat concentration–time profiles were comparable among the treatment groups. The C_{max} and AUC_{inf} values for cobicistat following administration in a fasted state (treatment B) and with a nutritional protein-rich drink (treatment C) were comparable to those following administration with a standard breakfast (treatment A) (Table 1), the corresponding 90% CIs of the GMR for cobicistat C_{max} and AUC_{inf} falling within the bioequivalence limit, indicating the lack of any food effect.

The mean plasma emtricitabine concentration-time profiles are shown in Figure 1C. The plasma emtricitabine concentration following administration with a standard breakfast (treatment A) reached C_{max} at 1.5 hours post-dose. The plasma emtricitabine concentration–time profiles were comparable among the treatment groups. The pharmacokinetic parameters of emtricitabine are presented in Table 2. The C_{max} and AUC_{inf} values for emtricitabine following administration with a standard breakfast were comparable to those following administration under fasting conditions (treatment B) and after ingestion of a protein-rich drink (treatment C). The corresponding 90% CIs of the GMR for emtricitabine pharmacokinetic parameters were within 0.8–1.25, indicating that all conditions were bioequivalent for emtricitabine.

The mean plasma tenofovir concentration-time profiles are shown in Figure 1D. The plasma tenofovir concentration following administration with a standard breakfast (treatment A) reached C_{max} at 1.5 hours post-dose. Statistical comparisons of tenofovir are presented in Table 2. Administration in a fasted state (treatment B) resulted in 28% decreases in both C_{max} and AUC_{inf} for tenofovir, compared with those following administration with a standard breakfast (treatment A), whereas the C_{max} and AUC_{inf} values for tenofovir following administration with a nutritional protein-rich drink (treatment C) were comparable to those following administration with a

Table 1. Summary and Statistical Comparison of Elvitegravir and Cobicistat Pharmacokinetic Parameters Administered With Different Meal Types and Under Fasting Conditions

	Treatment A: Standard Breakfast (Reference; n = 11)	Treatment B: Fasted Conditions (Test; n = 11)	Treatment C: Protein-Rich Drink (Test; n = 11)
Elvitegravir			
T_{max} (h)	3.5 (2.5–4.0)	4.0 (3.0–4.5)	4.0 (3.0–4.5)
C_{max} (ng/mL)	2,306 ± 473	1,068 ± 443	2,554 ± 416
AUC_{inf} (ng*h/mL)	28,870 ± 5,907	14,873 ± 5,128	32,164 ± 8,126
C_{24} (ng/mL)	519 ± 201	309 ± 156	686 ± 359
$T_{1/2}$ (h)	4.3 ± 1.0	6.4 ± 1.8	5.1 ± 1.9
Least-squares means ratio for test to reference (90% confidence interval)			
C_{max}	—	0.45 (0.39–0.51)	1.12 (0.98–1.27)
AUC_{inf}	—	0.50 (0.45–0.55)	1.10 (1.00–1.22)
Cobicistat			
T_{max} (h)	2.5 (2.0–4.5)	2.0 (1.0–4.5)	3.5 (2.0–4.5)
C_{max} (ng/mL)	1,078 ± 233	1,027 ± 291	1,137 ± 220
AUC_{inf} (ng*h/mL)	6,720 ± 2,491	7,324 ± 3,228	7,507 ± 2,592
C_{24} (ng/mL)	16 ± 19	24 ± 35	23 ± 25
$T_{1/2}$ (h)	3.1 ± 0.5	3.4 ± 0.6	3.3 ± 0.6
Least-squares means ratio for test to reference (90% confidence interval)			
C_{max}	—	0.93 (0.86–1.02)	1.05 (0.96–1.15)
AUC_{inf}	—	1.06 (0.96–1.17)	1.11 (1.01–1.23)

Values are shown as mean ± standard deviation except T_{max}, which is shown as median (range).

Table 2. Summary and Statistical Comparison of Emtricitabine and Tenofovir Pharmacokinetic Parameters Administered With Different Meal Types and Under Fasting Conditions

	Treatment A: Standard Breakfast (Reference; n = 11)	Treatment B: Fasted Conditions (Test; n = 11)	Treatment C: Protein-Rich Drink (Test; n = 11)
Emtricitabine			
T_{max} (h)	1.5 (1.0–2.5)	1.0 (1.0–2.0)	1.5 (1.0–3.0)
C_{max} (ng/mL)	2,302 ± 346	2,598 ± 464	2,380 ± 472
AUC_{inf} (ng*h/mL)	11,062 ± 1,205	11,278 ± 1,360	11,113 ± 692
C_{24} (ng/mL)	41 ± 5.0	39 ± 7.7	41 ± 5.9
$T_{1/2}$ (h)	13 ± 2.1	13 ± 2.4	12 ± 1.1
Least-squares means ratio for test to reference (90% confidence interval)			
C_{max}	—	1.13 (1.04–1.23)	1.03 (0.95–1.13)
AUC_{inf}	—	1.02 (0.97–1.07)	1.00 (0.96–1.05)
Tenofovir			
T_{max} (h)	1.5 (0.5–2.0)	1.0 (0.5–2.0)	2.0 (1.0–2.5)
C_{max} (ng/mL)	613 ± 127	450 ± 115	554 ± 158
AUC_{inf} (ng*h/mL)	4,321 ± 475	3,155 ± 605	3,902 ± 676
C_{24} (ng/mL)	50 ± 6.3	35 ± 6.9	45 ± 7.6
$T_{1/2}$ (h)	16 ± 1.0	16 ± 1.9	16 ± 1.4
Least-squares means ratio for test to reference (90% confidence interval)			
C_{max}	—	0.72 (0.61–0.86)	0.90 (0.76–1.07)
AUC_{inf}	—	0.72 (0.65–0.79)	0.89 (0.81–0.98)

Values are shown as mean ± standard deviation except T_{max}, which is shown as median (range).

standard breakfast. In terms of the LS mean ratio and the 90% CIs, it appears that in a fasted state, the bioavailability of tenofovir is not equivalent to that for either of the fed conditions. Relative to the standard meal, the AUC_{inf} for tenofovir was within the lack of a food effect boundary after administration with a nutritional protein-rich drink, though C_{max} was slightly lower (0.76), indicating that the two fed conditions were bioequivalent to each other.

No significant period or sequence effects were seen for any of the comparisons, and the mean $T_{1/2}$ of each analyte was generally comparable among all the treatments (Tables 1 and 2).

Safety

The EVG/COBI/FTC/TDF STR was generally well tolerated, irrespective of whether it was administered under fasted or fed conditions. No deaths, serious adverse events, or discontinuations due to any of the treatment-related adverse events reported previously were observed in this study. A total of 3 adverse events occurred in 1 (8.3%) of the 12 subjects given a single dose of EVG/COBI/FTC/TDF STR with a nutritional protein-rich drink. These events comprised one case each of headache, nausea, and vomiting. These adverse events were mild or moderate, and were considered to have been attributable to the stress of having to live in a group. Any causal relationship with the study drug was ruled out in all cases. No clinically significant changes in other physiological parameters or laboratory test values were found.

Discussion

The present randomized, open-label, single-dose, three-treatment, three-period, three-sequence crossover study involving HIV-negative healthy adult Japanese subjects was designed to determine the pharmacokinetic characteristics of EVG/COBI/FTC/TDF STR when administered with a standard breakfast and with a nutritional protein-rich drink, as well in a fasted state. This represents the first study in which EVG/COBI/FTC/TDF STR has been administered to Japanese subjects, and the effect of taking a nutritional protein-rich drink, which had never been evaluated previously, was also assessed as a new meal condition.

Compared with administration with a standard breakfast, administration in a fasted state resulted in 50% and 55% decreases in the mean AUC_{inf} and C_{max} values for elvitegravir, and the 90% CIs of GMR for elvitegravir pharmacokinetic parameters were below the equivalence limits, indicating that bioavailability in a fasted state was not equivalent to that of administration with a standard meal. By contrast, these values following administration with a nutritional protein-rich drink were essentially comparable to those following administration with a standard breakfast, the two fed conditions appearing to be bioequivalent to each other, and the 90% CI of GMR being narrowly above the upper limit of equivalence (1.25) for elvitegravir C_{max} (1.27). No changes in cobicistat or emtricitabine pharmacokinetics were observed among the three treatment regimes, that is, administration in a fasted state and with two types of

meals, confirming that all of the treatments involving cobicistat and emtricitabine were bioequivalent. On the other hand, administration in a fasted state resulted in an approximate 30% decrease of AUC_{inf} and C_{max} for tenofovir compared with administration with a standard breakfast. However, the 90% CI for tenofovir AUC_{inf} following administration with a nutritional protein-rich drink was within the equivalence limits following administration with a standard breakfast. While C_{max} was slightly lower, this was not considered to be clinically relevant. These results revealed that the contents of a meal taken before administration of EVG/COBI/FTC/TDF STR did not affect the pharmacokinetics of each analyte, and suggested that EVG/COBI/FTC/TDF STR can be administered with a light meal such as a nutritional protein-rich drink if patients cannot take a standard meal. The advantage of being able to take EVG/COBI/FTC/TDF STR without regard to meal type is that it imposes less of a burden on the patient, thus ensuring better compliance.

The effect of food on the bioavailability of each component following administration of EVG/COBI/FTC/TDF STR has been evaluated previously in 24 healthy adult non-Japanese subjects.[7] This revealed that although the AUCs of cobicistat and emtricitabine were unaffected by food, the bioavailability of elvitegravir and tenofovir was decreased by 26% and 19%, respectively, in a fasted state, compared with administration with a meal of 373 kcal containing 20% fat. These findings were consistent with those of the present study. It is generally known that a hydrophobic drug becomes more soluble when given with a meal, leading to increased absorption of the drug. Elvitegravir is a hydrophobic drug,[3] and this increase in bioavailability may be partly attributable to higher drug solubility in the presence of food.

To clarify any ethnic differences in pharmacokinetics retrospectively, the mean AUCs of elvitegravir, cobicistat, emtricitabine, and tenofovir upon administration in a fasted state determined in the previous US study to assess the effects of food on bioavailability[7] were compared with those observed in the present study (Tables 1 and 2). This revealed that the AUCs of these components, except for tenofovir, were nearly equivalent between Japanese and non-Japanese subjects. Tenofovir AUC tended to be increased slightly (22.3%) in Japanese subjects; however, it seems unlikely that this increase would be clinically significant. Body weight might also influence tenofovir clearance. Therefore, one possible reason for the increased tenofovir exposure in our present study would have been that the body weight of our Japanese subjects was about 10 kg lower than that of the subjects in the US study. Therefore, it can be considered that the pharmacokinetic profile of EVG/COBI/FTC/TDF STR does not show any marked ethnic differences.

The pharmacokinetics of tenofovir administered as tenofovir disoproxil fumarate alone[9] and as a combination tablet (emtricitabine/tenofovir disoproxil fumarate, Truvada®)[10] had been evaluated previously in healthy Japanese male subjects. Compared with the data for tenofovir exposure following single-dose administration of tenofovir disoproxil fumarate 300 mg or emtricitabine/tenofovir disoproxil fumarate in six subjects in a fasted state, AUC_{inf} for tenofovir was found to be higher in the presence of cobicistat in the present study. No differences in the half-lives of tenofovir were observed following tenofovir monotherapy versus concomitant administration with cobicistat. Tenofovir is renally eliminated and is not a substrate or inhibitor of CYP[11]; also, no clinically significant interactions are evident between tenofovir and many hepatically eliminated drugs.[11,12] Cobicistat inhibits CYP3A as well as many drug transporters including P-glycoprotein.[3] Therefore, any increase in tenofovir AUC may be the result of higher relative bioavailability attributable to co-administration of cobicistat. It has been hypothesized that the mechanism responsible for this interaction is intestinal inhibition of P-glycoprotein by cobicistat, resulting in an increase of tenofovir absorption.[5,13,14] Similar increases in tenofovir absorption have also been reported after co-administration with ritonavir and other protease inhibitors.[15–19] The results for tenofovir obtained in the present study were comparable to those for AUC of tenofovir following administration in combination with ritonavir and other protease inhibitors.

Previous clinical pharmacokinetic/pharmacodynamic studies of 10-day elvitegravir monotherapy in HIV-infected patients have indicated a clear association between the antiviral activity and the plasma trough concentration (C_{tau}).[1,20] Administration of elvitegravir with cobicistat resulted in a substantially higher C_{tau} and robust antiviral activity. Elvitegravir demonstrated a sufficient effect when the mean C_{tau} was approximately 10-fold the 95% inhibitory concentration (IC_{95}), adjusted for the in vitro protein-binding rate (45 ng/mL).[1,20,21] Population pharmacokinetics analysis in phase 2 and 3 studies has indicated that the mean C_{tau} value in HIV-infected patients administered cobicistat-boosted elvitegravir was 451 ng/mL (%CV; 58).[6] The virological response rates (participants with $\leq$50 copies/mL HIV RNA at 48 weeks) in the phase 2 and 3 studies conducted for C_{tau} estimation were more than 90%.[22,23] On the basis of these results, we consider that the target C_{tau} value would be nearly 10-fold the IC_{95}. The mean C_{24} obtained in the present study was nearly 10-fold the IC_{95} under all treatment conditions, that is, administration with a standard breakfast, in a fasted state, and with a nutritional protein-rich drink.

The present study was conducted in healthy adult subjects, and no differences in elvitegravir pharmacokinetics were observed between them and HIV-1-infected

patients.[1,6] Therefore, it seems that these results can be extrapolated to the target population of HIV-1-infected patients.

In conclusion, the mean AUC_{inf} of elvitegravir and tenofovir administered as components of EVG/COBI/FTC/TDF STR were shown to be decreased by 50% and 28%, respectively, following administration in a fasted state, relative to administration with a standard breakfast, whereas exposure to elvitegravir and tenofovir was comparable following administration with a nutritional protein-rich drink and with a standard breakfast. Food or a nutritional drink did not reduce the bioavailability of cobicistat or emtricitabine. On the basis of our results, it is recommended that EVG/COBI/FTC/TDF STR be given with food, and that no restrictions on the type of food ingested are necessary.

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Declaration of Conflicting Interests

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