Pharmacokinetics of Dolutegravir When Administered With Mineral Supplements in Healthy Adult Subjects

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Abstract

All commercially available integrase inhibitors are 2-metal binders and may be affected by co-administration with metal cations. The purpose of this study was to evaluate the effect of calcium and iron supplements on dolutegravir pharmacokinetics and strategies (dose separation and food) to attenuate the effects if significant reductions in dolutegravir exposure were observed. This was an open-label, crossover study that randomized 24 healthy subjects into 1 of 2 cohorts to receive 4 treatments: (1) dolutegravir alone, fasting; (2) dolutegravir with calcium carbonate or ferrous fumarate, fasting; (3) dolutegravir with calcium carbonate or ferrous fumarate with a moderate-fat meal; (4) dolutegravir administered 2 hours before calcium carbonate or ferrous fumarate, fasting. Plasma dolutegravir AUC(0–1), Cmax, and C24 were reduced by 39%, 37%, and 39%, respectively, when co-administered with calcium carbonate while fasting and were reduced by 54%, 57%, and 56%, respectively, when co-administered with ferrous fumarate while fasting. Dolutegravir administration 2 hours before calcium or iron supplement administration (fasted), as well as administration with a meal, counteracted the effect. Dolutegravir and calcium or iron supplements can be co-administered if taken with a meal. Under fasted conditions, dolutegravir should be administered 2 hours before or 6 hours after calcium or iron supplements.

Keywords
dolutegravir, calcium carbonate, ferrous fumarate, pharmacokinetics, drug interaction

Integrase strand transfer inhibitors (INSTIs) represent a novel class of antiretroviral drugs designed to block the action of the viral integrase enzyme, which is responsible for insertion of the viral genome into the host cellular DNA. Dolutegravir (Tivicay®; ViiV Healthcare, Research Triangle Park, North Carolina) is an HIV INSTI that has been approved for the treatment of HIV infection in adult and pediatric (12 years and older) patients who are treatment-naive, treatment-experienced but INSTI-naive, and treatment-experienced and INSTI-resistant. Studies in healthy subjects demonstrate that dolutegravir is well tolerated, has low to moderate pharmacokinetic (PK) variability, and achieves therapeutic concentrations with once-daily dosing without the need for PK boosting.1,2 Phase III studies in treatment-naive and treatment-experienced subjects demonstrate that dolutegravir has sustained antiviral activity in combination with various background therapies in HIV-infected adults. Furthermore, in vitro experiments suggest that dolutegravir retains activity against viral strains harboring major INSTI-resistant mutations selected for by both raltegravir and elvitegravir, 2 previously approved INSTIs.3,4 These data have been confirmed in clinical studies demonstrating dolutegravir’s activity in subjects with resistance to raltegravir.5

The mechanism of action of INSTIs involves binding to magnesium in the active site of the integrase enzyme, preventing insertion of HIV viral DNA into the host cell DNA. As such, drugs in this class are susceptible to chelation-type drug interactions with divalent and trivalent metal cations. Previous studies with the INSTIs raltegravir and elvitegravir6,7 have shown clinically significant effects of concomitant administration with antacids, which were significantly improved for elvitegravir when its dosing was separated from antacids by 2 and 4 hours. In a study with dolutegravir, concurrent...
administration of Maximum Strength Maalox \(^8\) (containing Al\(^{3+}\) and Mg\(^{2+}\); Novartis Consumer Health, Parsippany, New Jersey) under fasted conditions decreased dolutegravir mean area under the plasma concentration-time curve (AUC), maximum observed plasma concentration (C\(_{\text{max}}\)), and plasma concentration at 24 hours post-dose (C\(_{24}\)) by 74\%, 72\%, and 74\%, respectively, and administration of Maalox 2 hours after dolutegravir administration decreased dolutegravir mean AUC, C\(_{\text{max}}\), and C\(_{24}\) by 26\%, 18\%, and 30\%, respectively.\(^8\) These data resulted in the recommendation that concomitant administration of dolutegravir and antacids should be avoided. Dolutegravir can be administered 2 hours before or 6 hours after antacids.

HIV-infected patients may take mineral supplements in combination with their antiretroviral medications. Calcium supplementation is commonly used in HIV-infected patients. Iron supplementation may also be used in HIV-infected patients with anemia. As both of these mineral supplements have the potential to interact with dolutegravir, this study was performed to evaluate the potential of calcium and iron supplements to decrease dolutegravir exposure in healthy adult subjects and to assess 2 possible strategies for combined use if an interaction was observed. The first strategy was a 2-hour separation, as this was shown to be effective in attenuating the interaction with Maalox.\(^8\) The second strategy involved the administration of dolutegravir and the supplement with a meal because the presence of food modestly increases dolutegravir exposure\(^9\) and because mineral supplements are often administered with food.

### Methods

#### Study Design and Subjects

Prior to study initiation, the study protocol, amendments, and consent forms were reviewed and approved by the institutional review boards for the study site (Quintiles Early Clinical Development, Overland Park, Kansas), and all subjects provided signed consent. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and its amendments, consistent with good clinical practices and local regulatory requirements.

This was an open-label, randomized, 2-cohort, 4-period crossover study that was designed to evaluate the effects of calcium carbonate and ferrous fumarate on the PK of dolutegravir in healthy adult subjects. The study was conducted between December 2012 and March 2013.

Calcium carbonate was selected for this study because of its higher elemental calcium content compared with calcium citrate, and a clinically relevant dose of 1,200 mg calcium carbonate (containing \(~480\) mg elemental calcium) was used. Among iron supplements, ferrous fumarate contains a higher quantity of elemental iron than ferrous sulfate and ferrous gluconate, thus it was selected for this study to represent a worst case, and the standard dose of 324 mg ferrous fumarate (containing \(~107\) mg elemental iron) was used.

Eligible subjects were male or female adult subjects ranging from 18 to 65 years of age; had a body mass index (BMI) within the range of 18.5–31.0 kg/m\(^2\); and were judged to be healthy on the basis of physical examination, medical history, 12-lead electrocardiogram (ECG), and laboratory testing. Excluded subjects were those with a pre-existing condition interfering with normal gastrointestinal anatomy or motility; hepatic dysfunction, renal dysfunction, or both that could have interfered with the absorption, metabolism, or excretion of the study drugs; or positive test for hepatitis B surface antigen, hepatitis C antibody, or HIV antibody. Subjects were prohibited from ingesting any prescription or non-prescription drugs, including vitamins, herbal supplements, and dietary supplements, within 7 days or 5 half-lives (whichever was longer) before the first dose of study medication.

This study was planned to enroll 24 eligible subjects who were randomized into 1 of the 2 cohorts (calcium or iron) (Table 1) and received each of 4 treatments in a randomized fashion: (1) a single dose of dolutegravir 50 mg administered under fasted conditions (Treatment A); (2) a single dose of dolutegravir 50 mg co-administered with a single dose of calcium carbonate (Treatment B) or ferrous fumarate (Treatment E) under fasted

| Table 1. Study Treatment Description |
|------------------------------------|
| Cohort | Treatment | Description |
|--------|-----------|-------------|
| 1 | A | A single dose of dolutegravir 50 mg administered under fasted conditions |
| B | A single dose of dolutegravir 50 mg co-administered with a single dose of calcium carbonate 1,200 mg under fasted conditions |
| C | A single dose of dolutegravir 50 mg co-administered with a single dose of calcium carbonate 1,200 mg with a moderate-fat (30%) meal |
| D | A single dose of dolutegravir 50 mg administered under fasted conditions 2 hours prior to administration of a single dose of calcium carbonate 1,200 mg |
| 2 | A | A single dose of dolutegravir 50 mg administered under fasted conditions |
| E | A single dose of dolutegravir 50 mg co-administered with a single dose of ferrous fumarate 324 mg under fasted conditions |
| F | A single dose of dolutegravir 50 mg co-administered with a single dose of ferrous fumarate 324 mg with a moderate-fat (30%) meal |
| G | A single dose of dolutegravir 50 mg administered under fasted conditions 2 hours prior to administration of a single dose of ferrous fumarate 324 mg |
conditions; (3) a single dose of dolutegravir 50 mg co-administered with a single dose of calcium carbonate (Treatment C) or ferrous fumarate (Treatment F) with a moderate-fat meal (approximately 30% fat); and (4) a single dose of dolutegravir 50 mg administered under fasted conditions 2 hours prior to administration of a single dose of calcium carbonate (Treatment D) or ferrous fumarate (Treatment G). Each dosing session was separated by a washout period of at least 7 days. During each treatment period, the subjects were admitted to the unit on Day −1 and were housed in the unit until the Day 3 postdose assessments were completed. A follow-up visit was conducted within 7–14 days after the last dose of study drug.

Safety evaluations including clinical laboratory tests (serum chemistry, hematology, and urinalysis), vital sign monitoring, and 12-lead ECG were performed during each treatment period. All adverse events (AEs) were closely monitored throughout the entire treatment phase and at the follow-up evaluation.

Blood samples (2 mL for each collection) were collected at predose (within 15 minutes prior to dosing) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours postdose on Day 1 for the determination of plasma concentrations of dolutegravir. Blood samples were drawn into potassium ethylenediaminetetraacetic acid (K2 EDTA)-containing tubes via venipuncture or through a cannula and kept chilled on ice until centrifugation. Plasma was separated by centrifugation at 4 °C and stored at −20 °C until analysis.

Bioanalytical Methods
Plasma samples were analyzed for dolutegravir concentrations by Pharmaceutical Product Development (PPD; Middleton, Wisconsin). Analysis was performed using a validated analytical method based on protein precipitation, followed by high-performance liquid chromatography with tandem mass spectrometry analysis. The lower and higher limits of quantification were 20 ng/mL and 20,000 ng/mL, respectively, using a 25-μL aliquot of EDTA-treated plasma. Linear regression analysis calculations were performed using PPD Assist LIMS, version 5.

Quality control samples, prepared at 5 different concentrations and stored under the same conditions as study samples, were analyzed with each batch of samples against separately prepared calibration standards. The bias for the analysis of dolutegravir was −2.3%–1.7%, with precision values of 3.4%–4.7% (within-day) and ≤2.3% (between-day).

Pharmacokinetic Data Analysis
Plasma dolutegravir concentration-time data were analyzed by noncompartmental methods using WinNonlin (Version 5.3; Pharsight Corporation, Mountain View, California). Pharmacokinetic parameter calculations were based on the actual sampling times recorded during the study. Pharmacokinetic parameters that were determined included Cmax, AUC from time zero to the time of last quantifiable concentration (AUC[0–t]), AUC from time zero extrapolated to infinity (AUC[0–∞]), C24, and time of occurrence of Cmax (tmax). The blood sampling scheme of this single dose study allowed for an almost complete characterization of AUC(0–∞) as indicated by AUC(0–t) representing more than 90% of AUC(0–∞); therefore, AUC(0–t) is not presented.

One subject had nonzero predose dolutegravir concentrations in Periods 2, 3, and 4; however, the values were <5% of Cmax and were set to zero.

Statistical Analysis
In order to have 8 evaluable subjects in each cohort, the sample size of 12 subjects was chosen based on the within-subject variability of dolutegravir and feasibility to address the objectives of the study. A lack-of-effect boundary was predefined based on accumulated knowledge of the PK/pharmacodynamic relationship of dolutegravir, as follows30: interactions between dolutegravir and either calcium carbonate or ferrous fumarate were not considered to be clinically significant if the observed decrease in the AUC or Cmax of dolutegravir was less than 70% (ie, estimates for the test to reference ratio were ≥0.3). For a sample size of 8, the associated 90% confidence interval for this ratio was 0.23–0.40, assuming a within-subject coefficient of variation of 33%.

Following loge-transformation, AUC(0–∞), Cmax, and C24 of dolutegravir in each cohort were separately analyzed using a PROC MIXED procedure in SAS (SAS Institute, Inc, Cary, North Carolina) with period, sequence, and treatment as fixed effects and subject as random effect in the model. Point estimates and their associated 90%CIs were considered for the differences in PK parameter values between the test and reference treatments. Dolutegravir given alone under fasted conditions was considered to be the reference treatment, and the test treatments were dolutegravir co-administered with calcium carbonate or ferrous fumarate under fasted conditions, dolutegravir co-administered with calcium carbonate or ferrous fumarate with a moderate-fat meal, and dolutegravir given 2 hours prior to administration of calcium carbonate or ferrous fumarate under fasted conditions. Additional comparisons with dolutegravir co-administered with calcium carbonate or ferrous fumarate under fasted conditions as reference treatment and dolutegravir co-administered with calcium carbonate or ferrous fumarate with a moderate-fat meal as test treatment were also performed. The point estimates and their associated 90%CIs were then back-transformed to provide point estimates and 90%CIs for the ratios of PK parameters from test to reference treatments on the original scale. Tmax was analyzed nonparametrically for
the treatment differences of interest using the Wilcoxon’s Matched-Pairs method. The point estimates and 90% CIs for the median differences were calculated.

**Results**

**Subject Demographics and Accountability**
A total of 24 subjects (12 in each cohort) were enrolled in the study, and 21 completed the study as planned. No subjects were prematurely withdrawn from the study because of AEs. One subject in Cohort 1 was prematurely withdrawn from the study because of a protocol deviation (positive urine drug screen on Day −1 of Period 3). Two subjects in Cohort 2 were prematurely withdrawn from the study: 1 subject was lost to follow-up (Day 2, Period 1), and 1 subject was withdrawn because of a protocol deviation (positive urine drug screen on Day −1 of Period 3). The overall mean age and BMI of the subjects were 33.2 years and 26.1 kg/m², respectively. The majority of subjects were male (58%) and white (71%).

**Safety Evaluation**
Dolutegravir 50 mg was generally well tolerated when administered alone and in combination with calcium carbonate 1,200 mg or ferrous fumarate 324 mg. All AEs in both cohorts were Grade 1 in severity. Six subjects (50%) in Cohort 1 experienced AEs. No individual AE occurred in more than 1 subject. Six subjects (50%) in Cohort 2 experienced AEs. Contact dermatitis and headache were reported in 3 subjects each, yet none of these were considered related to study drug. All other AEs occurred in 1 subject each. No consistent, treatment-related, or clinically significant changes in mean or median hematology or clinical chemistry values were observed in the study. No clinically significant changes in vital signs or ECGs were observed during the study.

**Pharmacokinetics of Dolutegravir**
The plasma concentration-time profiles of dolutegravir after administration of dolutegravir alone and in combination with calcium carbonate or ferrous fumarate are presented in Figure 1 (calcium carbonate) and Figure 2 (ferrous fumarate), and the dolutegravir PK parameters are presented in Table 2.

Co-administration of dolutegravir with either calcium carbonate or ferrous fumarate under fasted conditions resulted in reduction in plasma dolutegravir exposures as follows: plasma dolutegravir AUC(0–∞), C_{max}, and C24 were reduced by approximately 37%–39% with calcium carbonate and by approximately 54%–57% with ferrous fumarate (Table 3). Co-administration of dolutegravir with calcium carbonate or ferrous fumarate under fed conditions counteracted the interaction and provided plasma exposures comparable to dolutegravir alone under fasted conditions. Similarly, dolutegravir administer under fasted conditions 2 hours prior to administration of a single dose of calcium carbonate or ferrous fumarate resulted in plasma exposures comparable to dolutegravir alone. Co-administration of dolutegravir with calcium carbonate or ferrous fumarate had no effect on t_{max} of dolutegravir (Tables 2 and 3).

**Discussion**
The current study evaluated the effect of calcium and iron supplements on dolutegravir plasma exposure, as well as strategies (dose separation and food) to attenuate the effects of these supplements if significant reductions in dolutegravir exposure by these agents were observed. Unlike antacids that are taken "as needed" and are often taken after meals, calcium and iron supplements are usually taken on a chronic basis and are usually taken with a meal. The use of these supplements is common in HIV-infected patients because of increased risk of

![Figure 1. Mean plasma concentration-time profiles of dolutegravir (50 mg, single dose) administered with and without calcium carbonate (CC) (1,200 mg, single dose).](image1)

![Figure 2. Mean plasma concentration-time profiles of dolutegravir (50 mg, single dose) administered with and without ferrous fumarate (FF) (324 mg, single dose).](image2)
osteoporosis due to drugs (eg, tenofovir)\textsuperscript{11} or disease and because of anemia.\textsuperscript{12}

Consistent with the mechanism of action, INSTIs lend themselves to interactions with metal cation-containing medications. As such, both calcium and iron supplements (calcium carbonate 1,200 mg and ferrous fumarate 324 mg) significantly reduced dolutegravir plasma exposure under fasted conditions. Plasma dolutegravir

Table 2. Summary of Plasma Dolutegravir Pharmacokinetic Parameters

| Treatment                                      | Geometric Mean (Coefficient of Variation, %) |
|------------------------------------------------|---------------------------------------------|
| Pharmacokinetic Parameters                     | Dolutegravir 50 mg Single Dose + Calcium Carbonate (CC) 1,200 mg Single Dose |
|                                                  | Dolutegravir Alone, Fasted (n = 12)          |
| AUC(0–\infty) (\mu g \cdot h/mL)                | 35.6 (62.3)                                 |
| C\textsubscript{max} (\mu g/mL)                 | 1.98 (45.9)                                 |
| C24 (\mu g/mL)                                  | 0.542 (66.0)                                |
| t\textsubscript{max} (h)                        | 3.00 (0.50, 6.00)                           |
| Dolutegravir + CC, Fasted (n = 12)              |                                             |
| AUC(0–\infty) (\mu g \cdot h/mL)                | 21.8 (66.3)                                 |
| C\textsubscript{max} (\mu g/mL)                 | 1.25 (45.0)                                 |
| C24 (\mu g/mL)                                  | 0.332 (74.1)                                |
| t\textsubscript{max} (h)                        | 2.00 (0.50, 12.00)                         |
| Dolutegravir + CC, Fed (n = 11)                 |                                             |
| AUC(0–\infty) (\mu g \cdot h/mL)                | 39.2 (46.6)                                 |
| C\textsubscript{max} (\mu g/mL)                 | 2.13 (30.4)                                 |
| C24 (\mu g/mL)                                  | 0.588 (54.3)                                |
| t\textsubscript{max} (h)                        | 3.00 (1.00, 6.02)                           |
| Dolutegravir 2 h Prior + CC, Fasted (n = 11)     |                                             |
| AUC(0–\infty) (\mu g \cdot h/mL)                | 33.8 (56.8)                                 |
| C\textsubscript{max} (\mu g/mL)                 | 1.98 (46.1)                                 |
| C24 (\mu g/mL)                                  | 0.493 (58.1)                                |
| t\textsubscript{max} (h)                        | 3.00 (1.00, 4.00)                           |

AUC, area under the plasma concentration-time curve; AUC(0–\infty), AUC from time zero extrapolated to infinity; C\textsubscript{max}, maximum observed plasma concentration; t\textsubscript{max}, time of occurrence of C\textsubscript{max}.

osteoporosis due to drugs (eg, tenofovir)\textsuperscript{11} or disease and because of anemia.\textsuperscript{12}

Consistent with the mechanism of action, INSTIs lend themselves to interactions with metal cation-containing medications. As such, both calcium and iron supplements (calcium carbonate 1,200 mg and ferrous fumarate 324 mg) significantly reduced dolutegravir plasma exposure under fasted conditions. Plasma dolutegravir

Table 3. Statistical Comparisons of Plasma Dolutegravir Pharmacokinetic Parameters

| Treatment                                      | Ratio of Geometric Least-Squares Means (90%Confidence Interval) |
|------------------------------------------------|---------------------------------------------------------------|
| Pharmacokinetic Parameters                     | Dolutegravir 50 mg Single Dose + Calcium Carbonate (CC) 1,200 mg Single Dose |
|                                                  | Dolutegravir + CC, Fasted vs. Dolutegravir Alone, Fasted       |
| AUC(0–\infty) (\mu g \cdot h/mL)                | 0.61 (0.47, 0.80)                                             |
| C\textsubscript{max} (\mu g/mL)                 | 0.63 (0.50, 0.81)                                             |
| C24 (\mu g/mL)                                  | 0.61 (0.47, 0.80)                                             |
| t\textsubscript{max}                            | -0.76 (–1.75, 0.24)                                           |
| Dolutegravir + FF, Fasted vs. Dolutegravir Alone, Fasted |                                             |
| AUC(0–\infty) (\mu g \cdot h/mL)                | 1.09 (0.84, 1.43)                                             |
| C\textsubscript{max} (\mu g/mL)                 | 1.07 (0.83, 1.38)                                             |
| C24 (\mu g/mL)                                  | 1.08 (0.81, 1.42)                                             |
| t\textsubscript{max}                            | 0.37 (–1.50, 2.00)                                            |
| Dolutegravir 2 h Prior + CC, Fasted vs. Dolutegravir Alone, Fasted |                                             |
| AUC(0–\infty) (\mu g \cdot h/mL)                | 0.94 (0.72, 1.23)                                             |
| C\textsubscript{max} (\mu g/mL)                 | 1.00 (0.78, 1.29)                                             |
| C24 (\mu g/mL)                                  | 0.90 (0.68, 1.19)                                             |
| t\textsubscript{max}                            | 0.00 (–1.00, 1.00)                                            |
| Dolutegravir + CC, Fed vs. Dolutegravir Alone, Fasted |                                             |
| AUC(0–\infty) (\mu g \cdot h/mL)                | 1.78 (1.36, 2.33)                                             |
| C\textsubscript{max} (\mu g/mL)                 | 1.70 (1.32, 2.18)                                             |
| C24 (\mu g/mL)                                  | 1.76 (1.33, 2.33)                                             |
| t\textsubscript{max}                            | 0.88 (–2.00, 2.75)                                            |

AUC, area under the plasma concentration-time curve; AUC(0–\infty), AUC from time zero extrapolated to infinity; C\textsubscript{max}, maximum observed plasma concentration; t\textsubscript{max}, time of occurrence of C\textsubscript{max}.

Table 3. Statistical Comparisons of Plasma Dolutegravir Pharmacokinetic Parameters

| Treatment                                      | Ratio of Geometric Least-Squares Means (90%Confidence Interval) |
|------------------------------------------------|---------------------------------------------------------------|
| Pharmacokinetic Parameters                     | Dolutegravir 50 mg Single Dose + Ferrous Fumarate (FF) 324 mg Single Dose |
|                                                  | Dolutegravir + FF, Fasted vs. Dolutegravir Alone, Fasted       |
| AUC(0–\infty) (\mu g \cdot h/mL)                | 0.46 (0.38, 0.56)                                             |
| C\textsubscript{max} (\mu g/mL)                 | 0.43 (0.35, 0.52)                                             |
| C24 (\mu g/mL)                                  | 0.44 (0.36, 0.54)                                             |
| t\textsubscript{max}                            | 1.00 (0.00, 2.00)                                             |
| Dolutegravir + FF, Fed vs. Dolutegravir Alone, Fasted |                                             |
| AUC(0–\infty) (\mu g \cdot h/mL)                | 0.98 (0.81, 1.20)                                             |
| C\textsubscript{max} (\mu g/mL)                 | 1.03 (0.84, 1.26)                                             |
| C24 (\mu g/mL)                                  | 1.00 (0.81, 1.23)                                             |
| t\textsubscript{max}                            | 0.00 (–1.00, 2.00)                                            |
| Dolutegravir 2 h Prior + FF, Fasted vs. Dolutegravir Alone, Fasted |                                             |
| AUC(0–\infty) (\mu g \cdot h/mL)                | 0.95 (0.77, 1.15)                                             |
| C\textsubscript{max} (\mu g/mL)                 | 0.99 (0.81, 1.21)                                             |
| C24 (\mu g/mL)                                  | 0.92 (0.74, 1.13)                                             |
| t\textsubscript{max}                            | -0.75 (–1.50, 0.25)                                           |
| Dolutegravir + FF, Fed vs. Dolutegravir Alone, Fasted |                                             |
| AUC(0–\infty) (\mu g \cdot h/mL)                | 2.14 (1.76, 2.61)                                             |
| C\textsubscript{max} (\mu g/mL)                 | 2.41 (1.97, 2.94)                                             |
| C24 (\mu g/mL)                                  | 2.28 (1.85, 2.81)                                             |
| t\textsubscript{max}                            | -1.00 (–2.00, 1.00)                                           |

AUC, area under the plasma concentration-time curve; AUC(0–\infty), AUC from time zero extrapolated to infinity; C\textsubscript{max}, maximum observed plasma concentration; t\textsubscript{max}, time of occurrence of C\textsubscript{max}.
AUC(0–∞), Cmax, and C24 were reduced by 39%, 37%, and 39%, respectively, when co-administered with calcium carbonate under fasted conditions. Plasma dolutegravir AUC(0–∞), Cmax, and C24 were reduced by 54%, 57%, and 56%, respectively, when co-administered with ferrous fumarate under fasted conditions. The expected effects of these metal cation supplements are due to dolutegravir-metal cation chelation resulting in reduced solubility and, therefore, reduced oral absorption as has been seen with other cations.9 Ferrous fumarate 324 mg (containing 107 mg or 1.91 mmol elemental iron) reduced dolutegravir exposure to a greater extent than calcium carbonate 1,200 mg (containing 480 mg or 12 mmol elemental calcium), although it contains a lower quantity of elemental metal cations. Both supplements contain metal cations (calcium or iron) in excess amount to dolutegravir 50 mg (or 0.12 mmol dolutegravir). We hypothesize that one possible explanation for the different effect by iron vs. calcium supplements is a solubility difference in the dolutegravir-iron chelation complex vs. the dolutegravir-calcium chelation complex. Another possible explanation is a higher affinity for iron to the dolutegravir binding site. Such differences are unlikely to be related to the effects on gastrointestinal pH by ferrous fumarate vs. calcium carbonate. Although calcium carbonate may increase gastrointestinal pH to a higher degree than ferrous fumarate, dolutegravir has not shown pH-dependent oral bioavailability in humans, concluded on the basis of a clinical study demonstrating that omeprazole had no effect on dolutegravir exposure.8

Although the study results showed that the effect of calcium/iron supplements on dolutegravir PK did not meet the predefined lack-of-effect boundary, the observed decrease may be clinically significant, especially in individuals who are taking other antiretroviral drugs that are enzyme inducers that further reduce dolutegravir exposure. Therefore, to take a conservative approach, co-administration of dolutegravir and these calcium/iron supplements under fasted conditions is not recommended. While subjects are taking calcium/iron supplements, a separation strategy for dosing under fasted conditions is warranted, similar to the dosing recommendations for metal cation-containing antacids.

Another strategy to counteract the interaction was to give the dolutegravir and the mineral supplement concomitantly with a meal, because food increases the exposure of dolutegravir9 and because mineral supplements are frequently administered with a meal to attenuate gastrointestinal tolerability issues. Administration of the mineral supplement and dolutegravir with a moderate-fat meal resulted in plasma exposures that were similar to dolutegravir administered alone under fasted conditions. The effects of food seem to be different in the presence of metal cation-containing supplement vs. in the absence of supplements. A moderate-fat meal increased dolutegravir AUC by 41% in the absence of added supplement,9 whereas it increased dolutegravir AUC by 78% in the presence of calcium carbonate and by 114% in the presence of ferrous fumarate. Co-administration of dolutegravir and mineral supplements with food may be more relevant for patients because mineral supplements are often taken with a meal to avoid gastrointestinal side effects (ie, iron supplements)13 and enhance absorption (ie, calcium supplements).14 If not administered with a meal, dolutegravir should be administered at least 2 hours before or 6 hours after taking mineral supplements, same as the recommendation for antacids.8 The forms and doses of calcium and iron supplements used in this study, calcium carbonate 1,200 mg and ferrous fumarate 324 mg, contain the most elemental calcium and iron compared with other commonly used supplements (eg, calcium citrate, ferrous gluconate, ferrous sulfate), which represents the “worst case scenario” for potential co-administration of these mineral supplements. Therefore, the effects of calcium and iron from other supplements not evaluated in this study are expected to be lower than or similar to those of calcium carbonate or ferrous fumarate used in the current study. The dose recommendation on the basis of data from calcium carbonate and ferrous fumarate can be generalized to other calcium and/or iron supplements.

This study demonstrates that dolutegravir was well tolerated when given with calcium or iron supplements. It is recommended that dolutegravir and calcium or iron supplements can be co-administered if taken with a meal. Under fasted conditions, dolutegravir should be administered 2 hours prior to or 6 hours after administration of calcium or iron supplements.

**Acknowledgments**

Funding for this work was provided by ViiV Healthcare. All listed authors meet the criteria for authorship set forth by the International Committee of Medical Journal Editors. The authors attest that the funding source did not have an influence on the analysis and reporting of results. We would like to acknowledge the editorial assistance of Jian Zong (Pharstat, Inc.) and Chris Lawrence (MedThink SciCom). These studies were presented at the 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, May 19–21, 2014, Washington, DC.

**Declaration of Conflicting Interests**

IS, JB, NA, BW, and SP are employees of GlaxoSmithKline and hold stock options.

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