Achievement of virologic suppression with HIV antiretroviral therapy in a patient also taking multiple daily cation supplement doses: A case report and review of the literature

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Purpose: To describe a case report of antiretroviral regimen selection, with considerations for drug-supplement interactions, for a patient living with HIV with complicated nutrition needs.

Summary: A 56-year-old white female with a history of sleeve gastrectomy was initiated on coformulated bictegravir/emtricitabine/tenofovir alafenamide for treatment of HIV infection. Her baseline HIV viral load was 139,790 RNA copies/mL, and the baseline CD4 cell count was 544 cells/mm³. The patient additionally had a nutritional supplement regimen of twice-daily calcium and twice-daily multivitamins with minerals following sleeve gastrectomy. Due to binding interactions between polyvalent cations and bictegravir and the potential impact on antiretroviral efficacy, construction of a daily medication schedule to avoid interactions between the antiretroviral regimen and the supplements while promoting optimal dosing of each supplement was necessary; however there is currently no guidance on twice-daily cation dosing with coadministered bictegravir and limited guidance on multivitamin coadministration in this context. A review of the available literature on bictegravir interactions and pharmacokinetic parameters was performed. A dose separation strategy was utilized to design a regimen that maximized separation of doses of supplements from doses of bictegravir/emtricitabine/tenofovir alafenamide while minimizing interaction potential. At follow-up 8 weeks after regimen initiation, the HIV viral load was undetectable (<40 copies/mL) and the CD4 cell count had increased to 821 cells/mm³.

Conclusion: Integrase strand transferase inhibitor interactions with polyvalent cations in nutritional supplements can be avoided or mitigated with attention to timing of each
dose and optimizing separation strategies. This case report shows the potential for alleviating such interactions through optimal dose scheduling.

**Keywords**: antiretroviral, drug interaction, human immunodeficiency virus, integrase inhibitor, polyvalent cations
Key Points

- Use of bictegravir and other integrase strand transferase inhibitors requires special considerations to avoid interactions with polyvalent cations that can result in treatment failure.

- Current primary literature and tertiary reference data on optimal dosing strategies for integrase strand transferase inhibitors and polyvalent cations are limited.

- In the case described here, HIV virologic suppression was achieved and maintained by designing a daily medication schedule that optimized strategies for separation of doses of bictegravir and polyvalent cations including calcium and multivitamins.
Integrase strand transferase inhibitors (INSTIs) were first approved for treatment of HIV type 1 (HIV-1) infection in 2007 and have become first-line recommended agents for both treatment-naive and treatment-experienced patients.\textsuperscript{1,2} INSTIs function at the active site of the viral integrase enzyme, where they tightly bind and chelate the divalent metal ions in the catalytic core domain of the enzyme, preventing integration of viral DNA into host cell DNA.\textsuperscript{2} This same mechanism of chelating to divalent or trivalent metal ions (aluminum, calcium, iron, magnesium, zinc, or combination products containing these cations) within the gastrointestinal tract can lead to decreased absorption of INSTIs, resulting in decreased drug levels and potentially virologic failure and the emergence of resistance.\textsuperscript{3,4}

Here we describe a patient with newly diagnosed HIV-1 infection treated with the INSTI bictegravir coformulated with emtricitabine and tenofovir alafenamide who required supplementation with cations multiple times per day following sleeve gastrectomy.

\textbf{Case presentation}

A 56-year-old Caucasian cisgender female presented to our HIV clinic following a new diagnosis of HIV-1 infection and was initiated on coformulated bictegravir/emtricitabine/tenofovir alafenamide within 5 days of HIV diagnosis. Her past medical history included hypertension and hyperlipidemia, and her past surgical history included laparoscopic sleeve gastrectomy 3 years prior to HIV diagnosis. Her weight at the first visit was 92.9 kg. The patient’s current medications at the time of the first visit included lovastatin 40 mg daily, lisinopril/hydrochlorothiazide (20 mg/12.5 mg daily), vitamin D\textsubscript{3} 2,000 units daily, and calcium citrate 500 mg daily. Her baseline viral load was 139,790 RNA copies/mL, with a baseline CD4 cell count of 544 cells/mm\textsuperscript{3},
with no mutations present on baseline genotyping. Due to the presence of calcium citrate on the patient’s medication list, she was instructed to take bictegravir/emtricitabine/tenofovir alafenamide at the same time as calcium citrate along with food per instructions in the prescribing information. The patient had a rapid initial response to treatment, with the viral load decreasing to 67 RNA copies/mL and the CD4 count increasing to 756 cells/mm³ within 3 weeks of treatment following initiation of antiretroviral therapy (ART).

Our multidisciplinary clinic is part of an academic medical center in a suburban location that is composed of a variety of medical and social services, including an embedded dietician and an embedded clinical pharmacist. Three weeks after initiation of ART the patient was seen by the dietician, who noted concerns regarding weight maintenance after initiation of ART and management of nutritional needs. Upon the meeting with the clinic dietician, it was determined that the patient had insufficient intake of numerous vitamins and minerals. A plan to increase or initiate new nutritional supplements was developed. A daily regimen that included calcium citrate 600 mg twice daily, a multivitamin tablet with minerals twice daily, vitamin B₁₂ 500 µg daily, and vitamin D₃ 2,000 units daily was initiated. The specific multivitamin product contained 200 mg of calcium, 11 mg of zinc, 50 mg of magnesium, and 18 mg of iron per tablet. In crafting the patient’s nutrition and supplement regimen, the clinic pharmacy team was consulted to help ensure this regimen would avoid interactions with ART.

After performing a literature review and consulting available pharmacokinetic (PK) and drug interaction data, a regimen stipulating specific timing of supplements throughout the day was designed. The daily schedule was based on available data showing the ability to coadminister bictegravir/emtricitabine/tenofovir alafenamide with supplements that contain calcium together with food. The following schedule was
created: bictegravir/emtricitabine/tenofovir alafenamide taken with calcium citrate 600 mg in the morning with breakfast; the first multivitamin dose given at least 4 hours after bictegravir/emtricitabine/tenofovir alafenamide and calcium; the second dose of calcium citrate 600 mg taken with dinner; and the second multivitamin dose taken at bedtime along with vitamin D and vitamin B₁₂. Approximately 8 weeks after initiation of the supplement schedule, the patient returned to the clinic for a follow-up visit, at which she reported 100% adherence to both ART and her supplements. Repeat viral load testing at this time indicated an undetectable load (<40 copies/mL), and the CD4 count had increased to 821 cells/mm³. At a follow-up appointment 3 months later, the viral load remained undetectable (<40 copies/mL) and the CD4 count had increased to 839 cells/mm³. The patient continued to report 100% adherence to all medications.

**Discussion**

The supplement regimen for this patient was constructed on the basis of the PK studies and pharmacodynamic parameters of bictegravir. Phase 1 PK studies of bictegravir with repeated administration at steady state showed rapid absorption of bictegravir, with median time to maximum plasma concentration ($t_{\text{max}}$) values occurring in 1.3 to 2.7 hours.⁶ PK studies summarized in the prescribing information identify a $t_{\text{max}}$ of bictegravir (when given as bictegravir/emtricitabine/tenofovir alafenamide) of 2 to 4 hours when the drug is administered with or without food.⁵ This data is indicative of bictegravir being rapidly absorbed from the gastrointestinal tract. PK studies support the coadministration of bictegravir and calcium with food. The administration of 1,200 mg of calcium carbonate together with 50 mg of bictegravir (the amount contained within coformulated bictegravir/emtricitabine/tenofovir alafenamide) in a fed state led to nonsignificant impacts on maximum concentration ($C_{\text{max}}$) achieved (a mean ratio of
measured to standard $C_{\text{max}}$ of 0.9) as well as area under the curve (AUC) (a mean ratio of measured to standard AUC of 1.03).\textsuperscript{5} In the fasted state, calcium carbonate decreased both the $C_{\text{max}}$ and AUC substantially (mean ratios of 0.58 and 0.67, respectively).\textsuperscript{5} In additional PK studies, antacids containing magnesium, calcium, and aluminum administered 2 hours after bictegravir had little impact on absorption, with AUC decreasing by only 13%.\textsuperscript{7}

The prescribing information for bictegravir contains guidance on coadministration of polyvalent cations. Calcium and iron supplements can be coadministered with bictegravir with food, but in the fasted state routine coadministration is not recommended.\textsuperscript{5} Furthermore, multivitamins may contain additional polyvalent cations of concern such as magnesium and zinc. Bictegravir should be given 2 hours before or 6 hours after supplements containing magnesium or aluminum.\textsuperscript{5} There is no manufacturer data regarding the coadministration of bictegravir and zinc, but a case report described virologic rebound occurring in a patient taking both bictegravir and zinc.\textsuperscript{8} PK literature for multivitamins and combination products containing multiple cations is limited. Clinical practice guidelines and prescribing information place multivitamins into the same section as other polyvalent cations, with guidance specifically based on the individual cation products, which can be confusing for clinicians and patients to interpret.\textsuperscript{1,5} There is further discordance in tertiary references, as the Liverpool Drug Interaction Database recommends administration of bictegravir and multivitamins containing divalent cations simultaneously with food.\textsuperscript{9} Additionally, to our knowledge there is no published literature describing separation strategies in patients requiring multiple daily administrations of polyvalent cations. Thus, the design of our patient’s medication schedule was based on the assumption of rapid bictegravir absorption (within 2-4
hours), labeling instructions for calcium and magnesium as individual entities, and with intent to separate the multivitamin from calcium citrate administration.

Using the available PK data for bictegravir, the administration of bictegravir/emtricitabine/tenofovir alafenamide along with calcium during the morning meal was planned on the basis of available data showing absorption would not be impaired. While our patient was taking calcium citrate rather than calcium carbonate, there is no literature regarding drug interactions with INSTIs and calcium citrate specifically; thus we extrapolated from the current labeling recommendations. Published evidence indicates that both calcium citrate and calcium carbonate are fully absorbable when taken with meals, so the doses of calcium citrate were given with breakfast and dinner. With less data available for polyvalent cations besides calcium, it was planned for the multivitamin to be administered at least 4 hours after bictegravir/emtricitabine/tenofovir alafenamide under the assumption that this would allow time for bictegravir absorption to occur as well as to follow labeling guidance for the magnesium component. With this scheduling in place the patient’s first multivitamin was to be taken around noon, the second dose of calcium was taken with dinner in the afternoon to early evening, and the second multivitamin dose was to be taken in the evening around bedtime.

While this patient’s multivitamin product included zinc (11 mg per tablet) and this was previously associated with virologic failure in the study by Rock and colleagues, the patient in the study by Rock et al was receiving 300 mg of zinc per day, taken in divided doses approximately every 3 hours, along with a vial of zinc solution at an unknown concentration every 3 hours. As our patient’s overall daily dose of zinc was significantly lower than this, we felt our separation strategies would overcome potential interactions. As multivitamin products are widely available over the counter (OTC) and
such products contain variable quantities of individual vitamins and minerals, it is imperative to identify dosages of polyvalent cations while designing regimens and separation strategies for patients on INSTIs. This further highlights the importance of medication reconciliation including OTC and herbal products.

While absorption was further complicated in this patient’s case due to sleeve gastrectomy, a recent review of available data indicates that patients living with HIV maintain high rates of virologic suppression following bariatric surgery, including sleeve gastrectomy.\textsuperscript{11} Sleeve gastrectomy is a bariatric surgical procedure in which approximately 90\% of the stomach is removed.\textsuperscript{12} This can impact absorption of medications by interrupting gastric motility and delaying gastric emptying time; thus absorption of antiretrovirals that are primarily absorbed in the stomach or proximal intestine may be hindered by bariatric surgery.\textsuperscript{12} The exact site of absorption for bictegravir/emtricitabine/tenofovir alafenamide is unknown, and absorption data specific to bictegravir are lacking. One case report described use of bictegravir/emtricitabine/tenofovir alafenamide in a 64-year-old female following sleeve gastrectomy.\textsuperscript{13} The patient maintained virologic suppression, but therapeutic drug monitoring of this particular patient showed a decrease in bictegravir PK parameters (AUC, $C_{\text{max}}$, and trough concentrations) relative to values in clinical trial populations along with increased emtricitabine and tenofovir alafenamide plasma concentrations.\textsuperscript{13} While this report did not describe additional nutritional supplementation, we were encouraged that the patient’s previous bariatric surgery did not appear to be associated with adverse virologic outcomes. As bictegravir/emtricitabine/tenofovir alafenamide remains a preferred therapy in clinical practice guidelines, more data regarding use in patients living with HIV who have undergone bariatric surgery is needed.
While the outcomes of our patient case are encouraging overall, more literature is needed to identify optimal strategies for separation of nutritional supplements and INSTIs, particularly in patient populations requiring multiple products at multiple doses per day. Multivitamin products are often placed into other categories in package labeling and in tertiary databases, which can result in confusion as individual cations may have discordant administration instructions. Decisions such as those in this patient case should be made by a multidisciplinary team, using available PK and pharmacodynamic literature and patient-specific data to design an optimal regimen.

Conclusion

A patient with newly diagnosed HIV infection with a history of sleeve gastrectomy required nutritional supplements containing polyvalent cations multiple times per day. This case shows that by using available PK and pharmacodynamic data, bictegravir/emtricitabine/tenofovir alafenamide can be administered along with polyvalent cations, including multiple-daily dosing, while avoiding drug-supplement interactions that could result in virologic rebound and treatment failure. More studies are needed to further identify optimal dosing strategies.
Disclosures

The authors have declared no potential conflicts of interest.
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