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HIV Viral Rebound Due to a Possible Drug–Drug Interaction between Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide and Calcium-Containing Products: Report of 2 Cases

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Abstract

Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) is a potent fixed-dose, once-daily regimen for HIV-1 treatment and has rare emergence of drug resistance. We report a potential drug–drug interaction in 2 female patients both receiving treatment for HIV and cerebral toxoplasmosis: one case between E/C/F/TAF with calcium carbonate and a second case involving leucovorin as calcium salt. Both cases resulted in rise in HIV RNA levels and emergence of M184 V mutation and resistance to elvitegravir and raltegravir. To the best of our knowledge, these 2 cases are the first reports of rapid emergence of mutation from coadministration of E/C/F/TAF and calcium.

Keywords

HIV/AIDS, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, calcium, mutation emergence, resistance

What Do We Already Know about This Topic?

The manufacturer of elvitegravir recommends separation of administration from aluminum, magnesium or calcium-containing antacids without providing specific data regarding calcium salts.

How Does Your Research Contribute to the Field?

The cases describe new data on clinically significant drug interaction between elvitegravir and simultaneously administered calcium, leading to resistance-associated mutations and ultimately, treatment failure.

What Are Your Research's Implications toward Theory, Practice, or Policy?

Clinicians should check for all forms of calcium for possible drug interaction with elvitegravir while advising the patient to separate the administration of the 2 medications.

Introduction

Elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg (E/C/F/TAF) is a relatively new antiretroviral combination having potent and durable activity against HIV-1.^{1,2} It is a single tablet, once-daily (QD) regimen containing an integrase strand transfer inhibitor, a pharmacokinetic booster, and inhibitor of CYP3A, and 2 nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs). It was well tolerated and showed a low frequency of emerging resistance during clinical trials.^{3,4} Drug–drug interactions have been described including aluminum and magnesium hydroxide-containing antacids, which decrease the absorption of elvitegravir.⁵ The package insert recommends separating the

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administration of antacids containing aluminum, magnesium hydroxide, or calcium carbonate from E/C/F/TAF by at least 2 hours.⁶ We encountered 2 cases wherein resistance to E/C/F/TAF unexpectedly emerged during treatment of HIV-1. Both patients were also being managed for cerebral toxoplasmosis. We speculate that coadministered calcium may have limited absorption of the anti-retroviral, leading to acquired resistance.

Case 1

A 42-year-old woman with no known history of HIV infection or treatment, presented to the hospital in January 2017, following a near syncopal episode and chronic generalized weakness. Brain magnetic resonance imaging (MRI) showed multiple ring-enhancing lesions in the right internal capsule and basal ganglia with extensive vasogenic edema and a midline shift of 7 mm. She had an emergent left frontal burr hole and a placement of left extraventricular drain for hydrocephalus and a stereotactic needle biopsy of the brain confirmed cerebral toxoplasmosis. She was also diagnosed with HIV at this time and her plasma HIV viral load in January 2017 was 66 500 copies/mL and her CD4 T-cell count was 10 cells/mm³. The genotype at this time demonstrated no reverse transcriptase (RT) gene mutations, but the following protease gene mutations: L10V, M36I, L63P, H69H/Y, A71T/A, and I93L. Integrase genotype was not performed as there have been no reports of resistance to integrase inhibitors among treatment naive individuals.

On admission in January, the patient was started on oral sulfadiazine 1000 mg every 6 hours, pyrimethamine 75 mg daily, and leucovorin 15 mg daily. She quickly developed profound neutropenia and the regimen was changed to oral atovaquone 1500 mg twice daily (BID) and clindamycin 600 mg intravenous (IV) every 6 hours. The patient tolerated the new treatment regimen, and in February 2017, E/C/F/TAF was started. One month later in March 2017, the HIV viral load decreased to 347 copies/mL and CD4 T-cell count increased to 36 cell/ μ L.

In March 2017, the patient's symptoms improved, and she was discharged to a skilled nursing facility to continue the treatment of toxoplasmosis with IV clindamycin and oral atovaquone which also served as *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis, E/C/F/TAF for HIV, and fluoxetine for depression. In April 2017, her HIV viral load further declined to 64 copies/mL.

In May 2017, per institution's protocol, the patient was started on oral supplement of calcium carbonate 1500 mg (600-mg elemental calcium) QD at the same time as E/C/F/TAF every morning without our knowledge. In July 2017, the HIV viral load increased to 4,840 copies/mL with the CD4 T-cell count of 106 cells/mm³. The HIV genotype at this time reported the RT gene mutations M184V and L100L/F, conferring resistance to emtricitabine and lamivudine, and protease gene mutations L10V, M36I/M, K43R, L63P, H69Y, A71A/V, and I93L. Resistance to protease inhibitors was not predicted as these were minor mutations that do not have substantial effect on phenotype. The virus also exhibited probable resistance to

raltegravir, predicted resistance to elvitegravir, and no predicted resistance to dolutegravir. All medications were reviewed for potential drug interactions, and good adherence was corroborated by the staff and the medication administration record. In August 2017, the regimen was subsequently changed to rilpivirine 25 mg/emtricitabine 200 mg/tenofovir alafenamide 25mg (RPV/F/TAF) and darunavir 800 mg/cobicistat 150 mg, and her repeat HIV viral load was <40 copies/mL with a CD4 T-cell count of 312 cells/mm³ after 3 months on the new regimen.

Case 2

A 35-year-old HIV-1-infected Hispanic woman with no history of AIDS-defining opportunistic illnesses had been prescribed efavirenz 600 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (EFV/FTC/TDF) when she established care in December 2010. The genotype report at that time showed protease gene mutations L63P and V77I, and the patient had prior exposure to zidovudine, lamivudine, didanosine, and nevirapine, since her diagnosis in 2004. Between December 2010 and January 2015, the patient experienced no medical complications and claimed 100% compliance to EFV/FTC/TDF during each visit which was supported by her HIV viral load consistently <20 copies/mL over these years. In 2015, the patient was lost to followup. Unfortunately, she discontinued her medication in June 2016 as she was dealing with an unexpected death of a close family member. The patient reestablished care in October 2016 at which time she was asymptomatic with a HIV viral load of 325 000 copies/mL, and the CD4 T-cell count was 68 cells/mm³. Atovaquone 1500 mg daily was initiated for PJP prophylaxis as the patient reported having extensive rash with trimethoprim/sulfamethoxazole in the past. The genotype performed at this time showed the following protease inhibitor gene mutations: I131/V, E35D, D60E, L63P, I64V, and V77I and RT mutation V106I/V/M conferring resistance to efavirenz and nevirapine. Based on genotype and the patient's history of exposure to multiple medications, an integrase genotype was subsequently ordered in January 2017. There was no predicted resistance to raltegravir, elvitegravir, or dolutegravir. In the meantime, the elevated AST and ALT of 299 IU/L and 475 IU/L prompted an ultrasound of the abdomen, which showed increased echogenicity compatible with a fatty liver. With subsequent improvement of transaminase levels, the patient was started on E/C/F/TAF in March 2017.

One week later, she was admitted with progressively worsening headache for several days with some neck stiffness but without fever, visual disturbances or focal neurological findings. The *Toxoplasma* antibody (immunoglobulin G) was elevated at >5.0 IU/mL, and the brain MRI showed several ring-enhancing lesions consistent with cerebral toxoplasmosis. Because the patient was noted to have developed a diffuse rash along with leukopenia in the past to sulfa-containing medications, she was initially treated with clindamycin 600 mg IV every 6 hours and pyrimethamine 75 mg orally daily along

with leucovorin calcium 25 mg daily. At the time of her admission, her HIV viral load had quickly declined to 2500 copies/mL after 1 week of E/C/F/TAF without any notable adverse reactions. However, E/C/F/TAF was temporarily suspended upon admission to avoid further exacerbation of toxoplasmosis-associated immune reconstitution inflammatory syndrome as well as possible drug–drug interactions. Within a week of toxoplasmosis treatment, pancytopenia was noted and leucovorin calcium was increased to 50 mg BID (8 mg elemental calcium). On hospital day 10, the patient developed diffuse morbilliform rash, fever, and transaminase elevation suspected to be secondary to clindamycin. Clindamycin was discontinued and the regimen was changed to atovaquone 1500 mg BID orally and the same doses of pyrimethamine with leucovorin calcium. The patient became afebrile and the symptoms began to resolve within the next 24 hours.

The patient was discharged from the hospital in April 2017 with atovaquone, pyrimethamine, and leucovorin calcium only, and E/C/F/TAF was restarted. In July 2017, her CD4 T-cell count was 265 cells/mm³ but HIV viral load increased to 91 300 copies/mL. A repeat genotype performed at this time showed the M184I mutation, conferring resistance to lamivudine and emtricitabine, and probable resistance to raltegravir, predicted resistance to elvitegravir but no predicted dolutegravir resistance. The patient adamantly and repeatedly confirmed 100% adherence to both the antiretroviral and toxoplasmosis regimens. She confirmed taking E/C/F/TAF with breakfast every morning along with leucovorin calcium, atovaquone, and pyrimethamine. She denied use of magnesium/aluminum hydroxide or calcium carbonate antacids, vitamins, herbal supplements, or any other medications that had not been prescribed. She was no longer symptomatic from toxoplasmosis, and the repeat brain MRI showed interval decrease in size of the ring-enhancing lesions and complete resolution of vasogenic edema, suggesting adherence to her toxoplasmosis medications and adequate absorption. In August 2017, her regimen was changed to RPV/F/TAF and atazanavir 300 mg/cobicistat 150 mg. Based on her impressive history of allergic reactions to sulfa-containing medications and clindamycin, any sulfa-containing medication including darunavir was avoided. In January 2018, the HIV viral load was <40 copies/mL and CD4 T-cell count of 317 cells/mm³.

Discussion

Two cases are presented wherein resistance to E/C/F/TAF emerged during treatment of an HIV infection. Both patients had been treated for cerebral toxoplasmosis, had clinically improved, and brain imaging demonstrated progressive resolution of lesions. All medications were reviewed in detail, and both patients were interviewed carefully to assess their compliance and administration of the medication with food. Pharmacy refill records and the medication administration records from the nursing facility were examined, and there were no indications of lapses in dosing.

Virologic failure was, in both cases, unexpected. We considered several possible explanations. In our first case, resistance to integrase inhibitors was not evaluated at baseline. As such, we cannot exclude primary integrase resistance. However, we have not observed primary integrase resistance in our clinic population, and transmitted integrase resistant HIV-1 is extremely rare in the literature.⁴ Our second patient discontinued her antiretroviral medications for a minimum of 4 months, which resulted in RT mutation V106, conferring resistance to NNRTIs. Although M184V/I was not reported at this time, it was possible that this mutation was archived. Once E/C/F/TAF was initiated, M184V/I may have reemerged, causing resistance to emtricitabine. This less than optimal regimen may have led to the emergence of elvitegravir resistance mutation. Phase 3 studies have, however, reported a 0.9% overall emergence of resistance to integrase inhibitor after 144 weeks of E/C/F/TAF.⁴

We speculate, however, that coadministration of calcium may have affected absorption of the antiviral agents. In general, serum concentrations of integrase inhibitors are decreased by compounds that contain metal cations, such as those found in multivitamins and antacids, if they are taken concurrently or in a close time frame.^{7–9} Divalent and trivalent cations bind to elvitegravir, forming an insoluble chelate complex and cause decreased absorption of elvitegravir. Simultaneous administration of elvitegravir with a single dose of antacid-containing aluminum and magnesium resulted in reduction in the serum concentration of elvitegravir by more than 40%, in comparison to elvitegravir alone.⁷ When aluminum or magnesium-containing antacid was dosed 4 hours apart from elvitegravir, the effect was minimal. Coadministration of calcium with elvitegravir has not been studied, specifically. Similar reductions in serum concentrations have been described with raltegravir and 1200-mg elemental calcium, as well as dolutegravir and 500-mg elemental calcium.^{8,9} As such, the manufacturer of E/C/F/TAF recommends the staggered dosing of any antacid including calcium from E/C/F/TAF.⁶ This recommendation was communicated to the skilled nursing team to avoid concurrent administration in the future. The second patient only received calcium in the form of leucovorin calcium salt. The patient's daily dose of leucovorin 100 mg contained approximately 8 mg of elemental calcium.¹⁰ It may be argued that such a small amount of calcium would not result in a clinically significant interaction. However, having reviewed other plausible causes including nonadherence, malabsorption, and other drug interactions, this possibility remains. Of note, it is estimated that 50% of medications are manufactured as salt forms to improve pharmaceutical properties as in atorvastatin calcium and omeprazole magnesium.¹¹

Previous studies with the integrase inhibitors raltegravir, elvitegravir, and dolutegravir have shown significant effects of concomitant administration with antacids. However, clinical relevance of this interaction has not been described. To the best of our knowledge, these 2 cases are the first reports of rapid emergence of mutation and HIV viral rebound from coadministration of E/C/F/TAF and calcium, possibly even at low

doses. It may be prudent to avoid simultaneous coadministration of E/C/F/TAF with any form of calcium and to check the salt forms of all the medications.

Declaration of Conflicting Interests

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