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Decreased absorption of dolutegravir and tenofovir disoproxil fumarate, but not emtricitabine, in an HIV-infected patient following oral and jejunostomy-tube administration

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Abstract

The use of enteral feeding tubes to administer antiretroviral medication administration is necessary in certain patients with human immunodeficiency virus (HIV) infection. However, adequacy of drug exposures after these administration routes are largely unknown, making dosing recommendations and the attainment of viral suppression challenging in this patient population. This report describes a patient with advanced HIV infection and a complicated medical history, including long-term intractable nausea/vomiting necessitating antiretroviral medication administration via a Roux-en-Y jejunostomy (J)-tube. Pharmacokinetic assessments were performed to compare differences in antiretroviral drug absorption and plasma exposure following oral and J-tube administration of dolutegravir, tenofovir disoproxil fumarate, and emtricitabine. Results were also compared to published pharmacokinetic data in HIV-infected individuals. Exposure to dolutegravir and tenofovir were similar between J-tube and oral administration routes, whereas emtricitabine exposure was 38% lower when administered via J-tube. However, in

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comparison to reference data in HIV-infected individuals taking these medications orally, exposure to dolutegravir and tenofovir was 75%–76% and 55%–61% lower, respectively, following both routes of administration. Emtricitabine exposure was similar to and 71% higher than reference data following J-tube and oral administration, respectively. This report highlights the importance of performing pharmacokinetic assessments in patients with the potential for impaired drug absorption to ensure antiretroviral treatment success.

Keywords

antiretroviral; dolutegravir; emtricitabine; HIV; J-tube; pharmacokinetics; tenofovir disoproxil fumarate; therapeutic drug monitoring

Introduction

The use of enteral feeding tubes for medication administration is necessary in some patients. However, data comparing medication absorption and subsequent drug exposures between oral and enteral feeding tube routes are limited. Drug absorption may be altered when administered through an enteral feeding tube due to the physicochemical properties and formulation of the drug, the need to crush tablets, and the physical characteristics of the gastrointestinal (GI) region into which drugs are being administered.¹ Specifically, direct medication administration into the jejunum may alter drug absorption for a number of reasons related to bypassing the stomach and duodenum, including less absorptive surface area, differences in pH and subsequent drug ionization², and variable presence of drug-metabolizing enzymes and efflux transporters along the small intestine.^{3, 4}

For antiretroviral therapy, adequate drug exposure is critical to achieving and maintaining virologic suppression of human immunodeficiency virus (HIV). Subtherapeutic antiretroviral concentrations may result in virologic failure, disease progression, and/or the development of drug resistance. Here, we report on pharmacokinetic (PK) assessments performed following oral and jejunostomy (J)-tube administration of the antiretroviral medications dolutegravir, tenofovir disoproxil fumarate (DF), and emtricitabine in a patient with advanced HIV infection and a Roux-en-Y jejunostomy.

Case Report

The patient was a 47-year-old African-American man diagnosed with HIV in 1999. He was non-adherent to his HIV care, and received antiretroviral treatment intermittently until 2007, when he presented with complaints of intractable nausea/vomiting, a CD4 T-cell count of 13 cells/mm³, and plasma HIV-1 RNA (viral load (HIV-VL)) >750,000 copies/mL. The patient was diagnosed with disseminated *Mycobacterium avium complex* infection and began appropriate treatment. However, his symptoms of nausea/vomiting persisted.

Since 2007, the patient's medical history was significant for recurrent pneumonias (including *Pneumocystis*), herpes zoster, *Clostridium difficile*-associated diarrhea, azole- and echinocandin-resistant *Candida* esophagitis, anemia, reactive airway disease requiring home oxygen, and medication non-adherence related to decreased appetite, nausea/vomiting, and

depression. A J-tube was inserted in 2008 for medication administration in the setting of persistent and intractable nausea/vomiting. This was revised in 2012 via a Roux-en-Y jejunojejunostomy with new J-tube insertion and partial small bowel resection. Between 2013 and 2016, the patient continued to experience nausea/vomiting with no identified etiology, and his weight declined from 133 kg to 59 kg for a total weight loss of 74 kg. Multiple computed tomography scans of the abdomen performed in 2016 could not identify any etiologies to explain his symptoms, and no gross anatomical abnormalities were found.

In September 2016, the patient was referred to the National Institutes of Health (NIH) for enrollment in a protocol to manage patients with antiretroviral treatment failure ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01976715) NCT01976715). This study was reviewed and approved by the National Cancer Institute's Institutional Review Board. At enrollment, his CD4 count was 8 cells/mm³ and HIV-VL was 20,365 copies/mL. His virus had multiple resistance mutations to nucleoside and non-nucleoside reverse transcriptase inhibitors and protease inhibitors, but no documented resistance mutations to integrase strand transfer inhibitors (Table 1).⁵ His antiretroviral treatment history since 2007 is detailed in Figure 1, with his most recent regimen consisting of once-daily dolutegravir 50 mg with co-formulated tenofovir DF 300 mg/emtricitabine 200 mg. He was not taking any prescription or over-the-counter medications known to interact with his antiretroviral medications.

The patient was previously advised by an outside provider to take his antiretroviral medications orally instead of by J-tube to enhance absorption. However, this resulted in significant nausea/vomiting up to 3–4 times per week and persistent non-adherence. As part of the study protocol, the patient was admitted to the hospital for 7 days to receive his antiretroviral drugs under directly observed therapy (DOT) in order to assess the virologic efficacy of his prescribed antiretroviral therapy. During this inpatient admission, PK assessments with HIV-VL monitoring were performed following both J-tube and oral administration. These were conducted to determine whether impaired absorption of his antiretroviral medications was responsible for his virologic failure, and to compare antiretroviral drug exposure following each route of administration. HIV-VLs were collected on Days 1, 3, 5, and 8 of the admission. The PK assessments are further detailed under the Methods and Results sections.

The patient did not experience any nausea/vomiting following antiretroviral medication administration throughout the inpatient admission and tolerated his antiretroviral therapy well. The patient's HIV-VL declined from 37,620 copies/mL on day 1 to 1,011 copies/mL on day 8, a 1.57 log₁₀ decline. At his week 2 protocol visit after the DOT admission, the patient reported nausea/vomiting since discharge. He underwent another J-tube replacement in the interim, and subsequently experienced worsening abdominal pain, with weight loss of another 7 kg. He also reported missing doses of his antiretroviral medications subsequent to these symptoms, resulting in a rebound of his HIV-VL to 15,530 copies/mL. Shortly thereafter, he had a 10-day admission at an outside hospital for severe abdominal pain, dehydration, and possible pneumonia. His J-tube was evaluated and determined to be patent. He returned to the NIH after discharge from the outside hospital, which was 5 weeks after his DOT visit, and reported ongoing abdominal pain with nausea/vomiting in addition to poor medication adherence. His HIV-VL had further increased to 55,984 copies/mL. As he

was not tolerating any medications, further adjustments to his antiretroviral regimen were not possible at that time. One week later, he presented to an emergency department with severe abdominal pain and hypotension. An emergency exploratory laparotomy was performed, and it was noted that part of his small bowel had twisted around his J-tube. Immediately post-surgery, he developed a myocardial infarction and cardiac arrest. The patient died 10 days after surgery.

Methods

During the 7-day inpatient DOT admission, after breakfast, dolutegravir 50 mg (Tivicay®, ViiV Healthcare, Research Triangle Park, NC) and the fixed-dose combination tablet of tenofovir DF 300 mg/emtricitabine 200 mg (Truvada®, Gilead, Foster City, CA) were administered via J-tube on days 1–3, orally on day 4, and then J-tube administration was resumed. Medications administered via J-tube were crushed, mixed with 3–5 mL of water, given immediately, and flushed with ~10 mL of water. The patient was pre-medicated with ondansetron before administration of his oral antiretroviral medications on day 4, and his antiretroviral medications were given as intact tablets.

Blood was collected for PK analysis at time 0 (pre-dose), 1, 2, 4, and 24 hours post-dose on days 3 (J-tube administration) and 4 (oral administration). Samples were centrifuged at 3200 rpm for 10 minutes at 4°C after collection, stored at –80°C, and then shipped on dry ice to the University of North Carolina Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Core (Chapel Hill, NC) for further analysis. Dolutegravir, tenofovir, and emtricitabine plasma concentrations were measured using standard protein precipitation followed by liquid chromatography and tandem mass spectrometry (LC-MS/MS) analysis. Isotopically labeled dolutegravir-¹³C,_{d5}; tenofovir-¹³C; and emtricitabine-¹³C, ¹⁵N were used as internal standards, resulting in analyte calibration ranges of 50–10,000 ng/mL for dolutegravir; 1–4,000 ng/mL for tenofovir; and 50–4,000 ng/mL for emtricitabine. Precision and accuracy of calibration standards and quality controls were within 15% (20% at the lower limit of quantitation; LLOQ).

Drug concentrations following both administration routes were plotted and compared against oral reference PK data in HIV-infected individuals, which were digitized from published reports (Graph Digitizer v2.0).^{6–8} Area-under-the-concentration-time-curve (AUC) was calculated based on exact time after dose rather than nominal time using non-compartmental analysis with linear-up/log-down trapezoidal rule (Phoenix WinNonlin v6.3, Certara USA, Inc., Princeton, NJ). Maximum concentration (C_{max}) and concentration at the end-of-the-dosing-interval (C_{τ}) were based on direct observation of measured data.

Results

PK results are detailed in Figure 2 and Table 2. When comparing dolutegravir and tenofovir exposures between J-tube vs oral administration, the AUCs for each drug were similar between administration routes. Dolutegravir and tenofovir C_{max} were 26% and 21% higher, respectively, with J-tube administration in comparison to oral. However, when compared to reference PK data in HIV-infected patients^{6, 7}, the overall exposures to dolutegravir and

tenofovir were 75%–76% and 55%–61% lower, respectively, following both administration routes. The AUC of emtricitabine was 38% lower when given by J-tube in comparison to oral. However, emtricitabine exposure following J-tube administration was comparable to reference data in HIV-infected patients, and was 71% higher when given orally.⁸ C_{τ} was comparable between administration routes for all antiretroviral medications, but dolutegravir and tenofovir C_{τ} values were 71%–78% and 42%–43% lower than reference data, respectively. Elimination rates for both dolutegravir and tenofovir were similar to reference PK data. The terminal elimination phase for emtricitabine could not be determined.

Discussion

To our knowledge, this is the first report comparing the PK differences of these three antiretroviral agents when administered orally or via J-tube. PK assessments were performed in this patient to assess whether impaired drug absorption was contributing to his antiretroviral treatment failure, and to identify which administration route would provide optimal antiretroviral drug exposure.

The PK results revealed a number of findings. Most notably, dolutegravir and tenofovir exposures were 74%–75% and 55–61% lower, respectively, following both oral and J-tube administration compared to reference PK data in HIV-infected individuals.^{6, 7} Elimination rates for both dolutegravir and tenofovir were consistent with reference PK data, suggesting that reduced absorption was the primary cause for decreased drug exposure. The AUC of emtricitabine was comparable or higher than HIV-infected individuals following both administration routes.⁸ Despite the lower exposure to dolutegravir and tenofovir, a 1.57 $\log_{10}$ decline in the patient's HIV-VL was observed between day 1 and 8 of the DOT period, indicating effectiveness of his prescribed regimen when given daily by DOT, and confirming that non-adherence was a key reason for his virologic failure.

There are no published data demonstrating whether dolutegravir and tenofovir DF have altered absorption when administered via J-tube, although these data are available for several other drugs.⁹ Neither dolutegravir nor tenofovir DF undergo significant first-pass metabolism by cytochrome P450 enzymes. Dolutegravir is highly permeable across the GI tract¹⁰ and its absorption is not acid-dependent¹¹, though it is poorly soluble in aqueous solutions at low pH levels. The absorption site of tenofovir DF is not well-characterized¹², but its solubility is increased in acidic solutions, suggesting that the proximal region of the small intestine is the most likely site of absorption.¹³ As the bioavailability of tenofovir DF is only ~25%, even small alterations in absorption could have a significant impact on overall drug exposure.¹⁴ Because of its high permeability and solubility, emtricitabine is highly bioavailable (~93%), possibly rendering it less susceptible to altered absorption following J-tube administration.^{8, 13} In addition, the apparent differences in emtricitabine exposure by administration route observed in this patient may be partly due to extrapolation of the elimination phase between 4 and 24 hours. Emtricitabine PK typically follows a multi-compartment model, which was not captured with the selected sampling time points. Collection of additional time points between 4 and 24 hours was not feasible due to the patient's underlying anemia. However, selection of multiple time points between 0 to 4

hours allowed for adequate characterization of the patient's drug absorption following both administration routes.

Crushing of dolutegravir and tenofovir DF for oral or enteral feeding tube administration has been previously detailed. Oral administration of crushed dolutegravir (with abacavir/lamivudine) in healthy volunteers increases $C_{\max}$ and AUC by 29% and 26%, respectively, compared to intact tablet.¹⁵ In a separate case report, crushed twice-daily dolutegravir with rilpivirine administered via orogastric tube resulted in levels below reported therapeutic ranges for these agents, though virologic suppression was maintained.¹⁶ For tenofovir DF, one case report demonstrated its absorption was not altered when administered via gastrostomy tube.¹⁷ Though helpful for comparison, these results are not directly applicable to our patient as he received his antiretroviral medications via J-tube. Furthermore, marked decreases in dolutegravir and tenofovir exposure were identified, compared to reference PK, even following oral administration of intact tablet in our patient.

The exact mechanism for this patient's decreased dolutegravir and tenofovir DF absorption following oral administration remains unclear. Available records since 2007 did not detail significant surgical resection of his GI tract or a clear etiology for the patient's persistent nausea/vomiting and abdominal pain. A surgical resection performed in 2012 was deemed minor according to available surgical notes, and a short segment of the jejunum (~45 cm) was connected to the abdominal wall for the revised J-tube insertion. Thus, most of the patient's small intestine remained intact following this procedure. Work-up for physiologic and infectious etiologies since the 2012 procedure were unrevealing. Dolutegravir absorption can be reduced if coadministered with polyvalent cation-containing agents.¹¹ However, the patient was not taking any of these interacting medications. Given the patient's long history of nausea/vomiting, in addition to multiple GI surgeries, the overall integrity, function, and motility of his digestive tract may have been compromised. HIV infection itself, particularly during active viral replication and with advanced disease, can contribute to malabsorption¹², impact barrier function¹⁸, alter expression of drug metabolizing enzymes and uptake/efflux transporters along the intestinal tract¹⁹, and cause hypochlorhydria²⁰, which collectively could impact antiretroviral medication absorption.

Although dolutegravir exposure was ~75% lower than reference PK data following both administration routes in this patient, C_T remained above the protein-adjusted 90% inhibitory concentration of 64 ng/mL for wild-type HIV. However, dolutegravir concentrations were expected to fall below 64 ng/mL between 31–32 hours post-dose using extrapolations from this patient's data, making adherence critical. Cumulative data from dolutegravir efficacy studies in treatment-experienced patients have shown lower response rates with median C_T values of 260 ng/mL¹⁰, and 300 ng/mL has been identified as a lower-effect bound at which point twice-daily dolutegravir should be considered.²¹ In this patient, both administration routes resulted in C_T values below these thresholds. With regard to tenofovir, tenofovir DF is metabolized to tenofovir in the GI tract and plasma, and then taken into target lymphoid cells where it is converted to the active moiety, tenofovir-diphosphate.²² Since tenofovir is not the active product, the clinical impact of this patient's lower plasma tenofovir exposure is uncertain. However, tenofovir-diphosphate concentrations in lymphoid cells do increase with increasing plasma tenofovir exposure.²³

Despite the observed virologic response during the patient's 7-day inpatient DOT visit, there was concern for continuing the patient on the same antiretroviral regimen and doses given his low dolutegravir and tenofovir exposures, especially with his cumulative antiretroviral drug resistance mutations and poor medication adherence history. Multiple options were considered, which included increasing the dolutegravir dose to 50 mg twice daily or 100 mg once daily with follow-up PK monitoring as dolutegravir does not demonstrate dose proportionality¹⁰, or switching from dolutegravir to cobicistat-boosted darunavir. A tenofovir- and emtricitabine-based regimen was continued due to the increased viral susceptibility of tenofovir conferred by the patient's M184V mutation, which is continuously selected for in the presence of emtricitabine.²⁴ Switching from tenofovir DF to tenofovir alafenamide, a newer prodrug formulation of tenofovir, was also considered. No changes to emtricitabine were to be made. Unfortunately, attempts to optimize the patient's antiretroviral regimen could not be done due to his clinical deterioration and eventual death in the weeks following his DOT admission.

Conclusion

Although HIV-VL monitoring provided an indication of the effectiveness of this patient's regimen, PK analysis revealed significantly lower exposures to dolutegravir and tenofovir following both oral and J-tube administration compared to historical HIV-infected controls. The mechanism for this decreased exposure, especially following oral administration, is unclear. Therapeutic drug monitoring while the patient received DOT provided an objective means of understanding this patient's altered drug absorption and the necessity of modifying the dosing of his antiretroviral medications.

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Figure 1. Patient's antiretroviral treatment history, plasma HIV RNA, and CD4 Counts from 2007–2016. ATV/r = ritonavir-boosted atazanavir; DRV/r = ritonavir-boosted darunavir; DTG = dolutegravir; ETR = etravirine; FTC = emtricitabine; RAL = raltegravir; TDF = tenofovir disoproxil fumarate

Figure 2.

Concentration vs. time curves for (a) dolutegravir (DTG), (b) tenofovir (TFV), and (c) emtricitabine (FTC) following J-tube and oral administration, with comparisons to reference PK data in HIV-infected populations. Blood samples for PK analysis were drawn at time 0 (pre-dose), 1, 2, 4, and 24 hours post-dose following J-tube (Day 3) and oral (Day 4) administration for comparisons between administration routes. Oral reference PK data in HIV-infected individuals were digitized from published reports (Graph Digitizer v2.0).⁶⁻⁸

Table 1**Cumulative Antiretroviral Drug Resistance Mutations for this Patient**

Antiretroviral Class	Mutations	Interpretation ⁵
PI	Major: L90M	Low-level resistance to ATV and LPV
	Minor: A71V	Susceptible to DRV
NRTI	T69N, M184V, K219E	High-level resistance to 3TC, FTC
		Low-level resistance to ABC
		Susceptible to TFV, ZDV
NNRTI	K103N, Y181C	High-level resistance to EFV, NVP
		Intermediate resistance to ETR, RPV
INSTI	None	Susceptible to RAL, EVG, DTG

Key: 3TC = lamivudine, ABC = abacavir, ATV = atazanavir, DRV = darunavir, DTG = dolutegravir, EFV = efavirenz, ETR = etravirine, EVG = elvitegravir, FTC = emtricitabine, INSTI = integrase strand transfer inhibitor, LPV = lopinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse-transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, RPV = rilpivirine, TFV = tenofovir, ZDV = zidovudine.

Table 2

PK Parameters following J-tube and Oral Administration with Comparisons to PK Data in HIV-infected Individuals

Administration Route	DTG			TFV			FTC		
	AUC _{0-τ} (ng*hr/mL)	C _{max} (ng/mL)	C _τ (ng/mL)	AUC _{0-τ} (ng*hr/mL)	C _{max} (ng/mL)	C _τ (ng/mL)	AUC _{0-τ} (ng*hr/mL)	C _{max} (ng/mL)	C _τ (ng/mL)
J-tube	13680	1610	219	1237	160	28	10532	1200	120
Oral	13211	1280	163	1436	132	28	17087	1920	123
HIV-infected ⁶⁻⁸	55026	4796	753	3179	375	50 ^a	10000	1800	90
J-tube:Oral ^b	1.04	1.26	1.34	0.86	1.21	1.00	0.62	0.63	0.98
J-tube:HIV-infected ^c	0.25	0.34	0.29	0.39	0.43	0.56	1.05	0.67	1.33
Oral:HIV-infected ^d	0.24	0.27	0.22	0.45	0.35	0.57	1.71	1.07	1.37

Key: AUC_{0-τ} = area-under-the-concentration-time curve over the dosing interval, C_{max} = maximum concentration; C_τ = concentration at the end-of-the-dosing interval; DTG = dolutegravir; FTC = emtricitabine; J-tube = jejunostomy tube; TFV = tenofovir

^aExtrapolated data from graphical presentation

^bRatio of patient-specific PK parameters between J-tube vs. oral routes

^cRatio of patient-specific PK parameters between J-tube administration vs. population average steady-state PK data from HIV-infected individuals given the same oral dose of antiretroviral medications⁶⁻⁸

^dRatio of patient-specific PK parameters between oral administration vs. population average steady-state PK data from HIV-infected individuals given the same oral dose of antiretroviral medication⁶⁻⁸