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BRIEF REPORT

Evaluation of Dolutegravir- and Bictegravir-Based Antiretroviral Regimen Utilization in Patients who Cannot Take Medications by Mouth

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A retrospective review of patients unable to take medications by mouth showed short interruptions of therapy for most patients. In a secondary analysis, our data showed maintenance and/or achievement of viral suppression for most patients. A retrospective review of intensive care patients unable to take antiretrovirals by mouth showed 56.6% of patients experiencing a transient interruption in therapy. Additionally, our case series further supports previous literature on crushing dolutegravir and bictegravir regimens to maintain and achieve viral suppression.

Keywords. HIV; bictegravir; crushed; dolutegravir.

As HIV treatment has advanced, the life expectancy of patients with HIV (PWH) has increased [1, 2]. Older age, coupled with ongoing HIV immune activation, can lead to cardiovascular, pulmonary, and other adverse health events that may require intensive care unit (ICU) admission [1]. In the ICU setting, interruption of antiretroviral therapy (ART) is a concern due to nothing by mouth (NPO) status, endotracheal (ET) tube placement for ventilation, enteral feeding tube (EFT) placement, or head and neck cancers requiring crushed ART. In these situations, crushing ART can be crucial to avoid missed doses. Previous studies have demonstrated that incorrect administration of oral medication through an EFT is a frequent cause of medication errors, resulting in increased toxicity or decreased effectiveness [3]. Case studies and series describe successful use of crushed dolutegravir (DTG)-based regimens, which guided our hospital's use of this crushed therapy [4–9]. Fewer case studies detail crushed or dissolved tenofovir alafenamide (TAF) and/or bictegravir (BIC)-emtricitabine-tenofovir alafenamide regimens, with some studies showing loss of virologic suppression when used in patients with uncontrolled viremia [10–16].

In accordance with the current literature, our institution currently supports crushed DTG as part of ART for any PWH and crushed BIC as part of BIC/emtricitabine/tenofovir alafenamide only for PWH with suppressed viral loads when unable to take medications by mouth. Here we provide a summary of PWH receiving crushed DTG or BIC regimens in our health system intensive care units between July 1, 2020, and June 30, 2022, and a case series describing 7 patients with HIV viral loads before and after crushed therapy. All data were collected manually in the electronic medical record.

The primary objective quantified the percentage of PWH admitted to the ICU and unable to take medications orally who received all DTG and BIC regimen doses without an interruption of therapy, defined as delay in antiretroviral therapy >24 hours. Additional objectives defined the patient population(s) receiving crushed ART. A case series evaluated HIV viral load documented within ~3 months of admission and after administration of at least 3 days of crushed ART for patients with corresponding viral load results. Three days was selected due to the unlikely impact of a short duration of crushed ART on viral load, considering the half-life of the ART included in this study. HIV virologic suppression was defined as an HIV RNA PCR showing <50 copies/mL. Patients were excluded if they did not have documentation of needing crushed DTG or BIC in the electronic medical record. While not excluded, no patients had received a long-acting injectable integrase inhibitor given the timeframe of the study.

We identified 53 PWH unable to take medications by mouth who qualified for crushed ART (DTG n = 37, BIC n = 16) while admitted to the ICU. Most patients were male (n = 46, 86.8%), with the majority being either White (n = 25, 47.2%) or Black (n = 26, 49.1%). Eighteen (34%) had infectious disease (ID) consult before the need for crushed ART. Almost all patients (n = 49, 95.5%) were treatment-experienced, having previously taken antiretroviral therapy before admission. Of these, 38 (77.6%) were virologically suppressed at inclusion. Thirty-seven patients received DTG regimens, with the most common being DTG + emtricitabine/tenofovir alafenamide (n = 15). Sixteen patients received a BIC regimen (most commonly BTG/emtricitabine/tenofovir alafenamide, n = 15). The most common indication for crushed therapy was mechanical ventilation (n = 44, 83%), with other indications being NPO except medication (n = 4, 7.5%) and malnutrition (n = 5,

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9.4%). Six patients required a therapy change at the time of ART crushing due to unsuppressed viral load (n = 2), inability to crush initial therapy (with switch to DTG regimen in all cases, n = 2), and caregiver knowledge deficit (n = 3). The median duration of ET tube placement (interquartile range [IQR]) was 5 (0–24) days, with 51% having ET tube placement >5 days. The median duration of crushed therapy (IQR) was 10.5 (3.25–18.75) days. Eight patients (15%) had crushed ART initiated on a weekend.

Twenty-three patients (43.4%) received all crushed doses appropriately with no interruption in therapy. Of the patients who experienced missed doses, 66.7% (n = 20) received a DTG regimen and 33.3% (n = 10) received a BIC regimen. For the complete population, 539 out of 627 potential crushed ART dose administrations were given appropriately (85.5%), and a median (IQR) of 6.7% (0%–27.3%) of ART doses were missed per patient, equaling a median (IQR) of 2 (1–4) doses missed per patient. The most common reason for a missed ART dose as documented by nursing staff was NPO status (n = 10, 30%), followed by lack of feeding tube and instruction to hold by a licensed independent practitioner (LIP; n = 5, 16.7% for both).

We conducted an exploratory analysis to identify characteristics of patients who experienced missed doses, evaluated using a chi-square or Fisher exact test with effect estimate calculations using relative risk (RR). Presence of ID consult (7/23, 39.1%, vs 9/30, 30%; RR, 0.83; 95% CI, 0.49–1.42) and weekend therapy initiation (2/23, 8.7%, vs 6/30, 20%; RR, 1.41; 95% CI, 0.87–2.28) did not increase the incidence of missed crushed ART doses. ET tube placement for ≥5 days was more common in patients with a missed crushed ART dose than those who did not miss a dose (20/30, 67%, vs 7/23, 30%; RR, 1.92; 95% CI, 1.13–3.29). The secondary analysis evaluating patients with crushed ART with viral load before and after therapy included 7 patients, 4 with a viral load <50 copies/mL and 3 with a detectable HIV viral load at baseline (Table 1). All 4 virologically suppressed patients (3 on a DTG regimen and 1 on a BIC regimen) maintained viral suppression at 4–12-week follow-up after crushed ART. Two treatment-naïve patients achieved virologic suppression at 6 and 13 weeks after a crushed DTG regimen. One patient achieved a significant decrease in viral load, defined by at least a 0.5-$\log_{10}$ decrease in viral load at 10 weeks post–crushed DTG/darunavir/cobicistat. Upon chart review, lack of virologic suppression was due to nonadherence before and after crushed ART. A genotype at week 10 demonstrated new resistance, and ART was changed. All patients in the secondary analysis received tube feeds for >50% of the time on crushed ART through a gastric or duodenal feeding tube. No patients experienced prolonged drug interactions as described in Table 1.

To our knowledge, this is the first study to describe the practicality and efficacy of crushing DTG- and BIC-based ART in a real-world cohort. While only 42.5% of patients received all

Table 1. Case Series of Patients Receiving Crushed Therapy

Patient	Regimen	Baseline CD4, cells/mm^3	Baseline HIV Viral Load, copies/mL	Viral Load Postcrushed, copies/mL	Time After Crushed Doses to Viral Load, wk	Crushed Doses Given Appropriately, %	Duration of Crushed Therapy, d	Diet Order Throughout Crushed Therapy[a]	Maximum Vasopressor Dose, mcg/min (Duration, d)	DDI Drug Duration	ID Consult Timing	Crushing Continued at Discharge
Patients Virologically Suppressed at Baseline												
A	DTG + FTC/TAF	44	<20	< 20	8	100	3	Tube feed	0	9[b]	Before	No
B	DTG + FTC/TAF	353	<20	< 20	4	100	7	Tube feed	0	6[c]	Before	Unsure
C	DTG/ABC/3TC	634	<20	<20	8	91.7	23	Tube feed	19 (4)	0	After	No
D	BIC/FTC/TAF	337	<20	39.8	12	91.7	10	Tube feed	0	0	After	Yes
Patients Not Virologically Suppressed At Baseline												
E	DTG + DRV/c	4	11 200	785	13	87.5	7	Tube feed	0	0	On date	Yes
F	DTG/RPV	217	11 500	< 20	6	94.1	16	Tube feed	34 (13)	0	Before	Yes
G	DTG + FTC/TAF	6	127 000	34	10	92	20	Tube feed	17 (21)	3[c]	On date	Unsure

Abbreviations: 3TC, lamivudine; ABC, abacavir; BIC, bictegravir; DDI, drug–drug interaction; DRV/c, darunavir/cobicistat; DTG, dolutegravir; FTC, emtricitabine; ID, infectious diseases; RPV, rilpivirine; TAF, tenofovir alafenamide.

[a]Tube feed defined as tube feed running >50% of the time the patient was on crushed therapy.

[b]Drug interaction with dexamethasone.

[c]Drug interaction with calcium acetate, not timed appropriately.

crushed ART doses appropriately, our results indicate that patients experienced minimal interruptions in therapy. The nursing staff–documented reasons for missed doses were most commonly NPO status, no feeding tube, and LIP instructed to hold. These holding parameters are concerning as ART therapy interruptions may lead to rebound viremia and resistance development. Therefore, the benefit of continuing therapy often outweighs the risk of crushed administration. This highlights an opportunity for prescriber and nursing education surrounding when to hold vs administer ART in NPO patients. Additionally, the exploratory analysis calls special attention to patients with an ET ≥5 days as they may be most at risk for complications, such as tube dislodgement or clogging. Lastly, the results of our 7-patient case series offer further clinical support on the crushing of DTG and BIC regimens, reinforcing the results of the pharmacokinetic studies and case reports predating our research.

Our case series with viral load results before and after crushed ART included patients receiving DTG + emtricitabine/tenofovir alafenamide, both in treatment-naïve patients and in those receiving ART before admission. Two treatment-naïve patients with advanced infection achieved virologic suppression following administration of crushed therapy for 7 to 20 days, similar to case reports demonstrating suppression after continued crushed DTG/lamivudine/abacavir and crushed DTG, lamivudine, abacavir, and TAF [8, 9]. Use of crushed DTG regimens in virologically suppressed patients has not been described in the previous literature. We described sustained virologic suppression in 3 patients receiving crushed DTG regimens for 3 to 23 days. Our analysis also adds to the literature available for crushed TAF regimens, noting that our most common regimen was crushed DTG plus emtricitabine/TAF. Most case reports and pharmacokinetic analyses evaluating crushed DTG regimens review the DTG/lamivudine/abacavir combination product [4, 5, 8].

Our institutional ART dosing guidelines recommend against the use of BIC/emtricitabine/tenofovir alafenamide in patients without virologic suppression based on outcomes in 2 published case reports [14, 15] where patients with unsuppressed viral loads who were initiated on crushed BIC/emtricitabine/TAF did not achieve suppression and developed resistance. Therefore, our case series only included 1 patient on a BIC regimen who was virologically suppressed at the time of ART crushing.

To improve our own institutional practice, we are pursuing an addition to our ID pharmacist antimicrobial alert system and plan to provide education to prescribers on the proper procedures for crushing these medications. The intent is to prioritize these patients when deemed unable to take medications by mouth, avoid unnecessary missed doses, and encourage interdisciplinary conversations regarding the appropriate administration of these ART regimens.

This study has several limitations. First, the retrospective nature of the study lends itself to an inability to perform efficacy analysis on patients who have received crushed ART and reliance on accuracy of documentation in the medical record. We attempted to mitigate these limitations by performing manual data collection to ensure accuracy and consistency of the data. For example, we were unable to confirm placement of enteral feeding tubes beyond what was documented by the nursing staff. Additionally, while we included multiple centers across the enterprise, the sample size remained small, leading to only 7 patients included in the secondary efficacy analysis. Another limitation noted is that most patients in the secondary analysis did not have documented repeat viral loads until at least 8 weeks after crushed therapy. In this time, there is potential for other factors to influence a patient's viral load, such as nonadherence, interactions, medications changes, etc. The Cleveland Clinic serves as a referral center for the multistate region. As such, many patients do not have outpatient HIV care at our ID clinics. Still, these results show a transient interruption in ART and suggest an opportunity for further intervention by an ID pharmacist and education of staff on the proper procedures for crushing these agents. Lastly, this is the first case series to describe these crushed regimens and significantly adds to the literature available. Further trials should be conducted to validate the results of this study.

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Patient consent. The study design was approved by the local institutional review board committee and did not require informed consent due to its retrospective nature.

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