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ANTIVIRAL AGENTS

Case Report of Increased Exposure to Antiretrovirals following Sleeve Gastrectomy

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ABSTRACT Bariatric surgery is increasingly performed in morbidly obese HIV patients. Limited data exist regarding antiretroviral drug exposure after bariatric surgery. We report a case of a morbidly obese HIV patient who underwent sleeve gastrectomy. Abacavir, lamivudine, and dolutegravir therapeutic drug monitoring was performed at several time points pre- and postsurgery. Significantly increased levels were measured, particularly for abacavir, whose levels increased ~12-fold. Several mechanistic explanations for these findings are discussed.

KEYWORDS antiretrovirals, bariatric surgery, obesity, sleeve gastrectomy

Obesity prevalence among people living with HIV (PLWH) is rising. Weight gain after initiation of antiretroviral (ARV) therapy may be attributed to the general health gains associated with ARV commencement and to the ARV therapy itself, particularly integrase inhibitors. Accordingly, bariatric surgery (BS) is increasingly being performed in PLWH (1). Several types of BS are currently available, such as gastric bypass, gastric banding, and sleeve gastrectomy (SG). Because of the complexities related to ARV therapy and the crucial importance of maintaining an uninterrupted adequate exposure to ARV, it has been recommended that SG, being restrictive rather than malabsorptive, may pose a lesser risk of unwanted effects on ARV absorption and should be preferred for PLWH.

Despite the growing popularity of BS in PLWH, little is known regarding its effects on ARV exposure. The short- and long-term effects of BS on the anatomy, physiology, and function of the upper gastrointestinal tract (UGIT) and other systems may alter the pharmacokinetics and disposition of various medications, including ARVs. Although most ARVs are absorbed in the small intestine (2), various aspects of BS might alter their absorption, such as changes in UGIT function and pH, diet, food and fluid intake, medication forms (i.e., liquid or crushed formulations instead of solid dosage forms), and concomitant medications. Several case reports and small series have been published describing various medical outcomes of BS in PLWH, including weight loss and related comorbidities, such as diabetes, hyperlipidemia, and hypertension. As for HIV-related parameters, most reports followed viral load and CD4 counts, whereas only few published studies have reported peri-BS ARV therapeutic drug monitoring (TDM) (2). Limited data suggest that drug exposure is generally not significantly altered after BS. Exceptions to this include raltegravir and atazanavir, which exhibited lower concentrations after BS, accompanied by loss of viral suppression (3).

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TABLE 1 Therapeutic drug monitoring of abacavir, lamivudine, and dolutegravir before and after sleeve gastrectomy

TDM[a]	Timing relative to SG[b]	Tablet form	Plasma concentrations (ng/ml) of[c]:		
			ABC	3TC	DTG
1	1 mo pre-SG	Intact	8.7	60	919
2	1 day pre-SG	Crushed	8.8	65	980
3	3 days post-SG	Crushed	24.5	72	1,410
4	11 days post-SG	Intact	58.5	111	1,230
5	6 wk post-SG	Intact	103.3	161	2,347
Trough levels in prescribing information leaflets			<30	42	1,110

[a]TDM, therapeutic drug monitoring.
[b]SG, sleeve gastrectomy.
[c]ABC, abacavir; 3TC, lamivudine; DTG, dolutegravir.

We report a case of an HIV patient treated with a single-tablet regimen of abacavir (ABC) 600 mg, lamivudine (3TC) 300 mg, and dolutegravir (DTG) 50 mg (Triumeq, ViiV Healthcare, UK), in which TDM for all three components was performed before and after SG. Informed consent was received from the patient.

A 36-year-old man was diagnosed with HIV in 2008, with a baseline CD4 count of 366 cells/μl and an HIV plasma viral load of 76,000 copies/ml. Medical history included appendectomy, minor depressive disorder, and smoking. Weight at diagnosis was 83 kg (height, 178 cm; body mass index (BMI), 26.2 kg/m^2). ARV treatment with tenofovir disoproxil fumarate, emtricitabine, and ritonavir-boosted atazanavir was initiated 1 year later.

The patient reported good ARV adherence, constantly maintaining an undetectable viral load. CD4 counts rapidly increased, exceeding 500 cells/μl as of 2010. In 2017, treatment was simplified to a single-tablet regimen of abacavir-lamivudine-dolutegravir, maintaining efficacy, tolerability, and adherence.

Starting in 2015, the patient's body weight gradually increased, peaking at 138 kg (BMI, 43.6 kg/m^2) by the end of 2018, accompanied by impaired fasting glucose and fatty liver disease. Consequently, the patient decided to undergo BS, and SG was recommended.

We collected blood samples at several time points before and after SG to determine ABC, 3TC, and DTG trough plasma levels. Levels were determined by CoQua Lab (Turin, Italy) using validated liquid chromatography-tandem mass spectrometry methods (Antonio D'Avolio, personal communication). Additional follow-up included routine post-SG care and periodic CD4 and viral load measurements.

The first blood sample for TDM was collected ~1 month before surgery, while the patient was taking a regular intact tablet. Because of the expected alterations in UGIT anatomy and physiology after BS, it is commonly advised to administer medications in a liquid or crushed form during a postoperative phase of several weeks. Because a liquid formulation of ABC-3TC-DTG was not available, we instructed the patient to begin crushing the tablet before intake 4 weeks before surgery. A second blood sample for TDM was drawn just before the surgery, to assess the effect of crushing on drug exposure. The SG procedure was uneventful, and the patient was discharged 2 days later. A third TDM blood sample was drawn 3 days postsurgery, after the patient resumed taking a crushed tablet. Several days later, he reverted to taking the regular intact tablet. Further sampling for TDM was performed 11 days and 6 weeks postsurgery. His weight decreased to 102 kg (BMI, 32.2 kg/m^2) 3 months after the surgery, representing a loss of 61% of his preoperative excess body weight.

Drug concentrations for all five TDM points are presented in Table 1. Before surgery, crushing had no significant effect on ABC and 3TC levels, but those of DTG modestly increased, as expected (4). However, postsurgery levels appeared to be increasing for all three drugs. Compared with the initial presurgery levels (TDM1), the latest postsur-

gery levels (TDM5) presented a 2.5-fold increase in 3TC and DTG levels and a 12-fold increase in ABC levels.

Pharmacokinetic data of ARV after BS are scarce. Generally, the major concern regarding medication management after BS is decreased exposure and consequent reduced efficacy. Surprisingly, in the case presented, exposure to three ARVs was significantly increased after SG, a finding that was not reported previously.

We suggest several explanations for the elevated ARV concentrations measured in our patient after SG. First, ABC is extensively metabolized by UGT1A1 (forming an inactive metabolite). Similarly, DTG is mainly metabolized via glucuronidation by UGT1A1 to form its major inactive metabolite, ether glucuronidated DTG, and is a substrate of UGT1A3, UGT1A9, and CYP3A. Glucuronidation metabolic reactions were reported to be enhanced in individuals with morbid obesity (5). Resultant weight loss, after BS, is expected to be accompanied by loss of glucuronide enzyme-rich adipose tissue and by reduced liver size (6). Consequently, as glucuronidation decreases, postsurgery ABC and DTG plasma levels are expected to increase.

Second, glucuronidation processes are partially dependent on the presence of a uridine diphosphoglucuronic acid cosubstrate. It has been shown that short-term fasting and reduced food intake may deplete this cosubstrate (7), which, in turn, may result in reduced glucuronidation and elevated concentrations of ABC and DTG.

Third, the rapid initial increases in ABC and DTG levels may be related to alterations in gut microbiota after BS, which have recently been shown to be immediate, permanent, and independent of BS type (8). ABC and DTG are inactivated by uridine 5′-diphosphoglucuronosyltransferase, forming glucuronic acid conjugates, a process that may be reversed by β-glucuronidase enzymes. Populations of several bacterial species known to produce β-glucuronidase enzymes, such as *Escherichia coli* and *Bacteroides* spp., were found to increase after BS (9). Because a significant portion of ABC and DTG glucuronidation to inactive metabolites occurs in the gut, the increasingly produced β-glucuronidase enzymes may regenerate the original active forms of ABC and DTG, thus increasing their levels (10). Moreover, DTG undergoes significant enterohepatic recirculation, thereby increasing its exposure to deglucuronidizing gut bacteria, which, in turn, regenerate active DTG.

Fourth, DTG is a weak acid (pKa $\sim$8). As such, the post-SG elevated gastric pH is expected to result in an increased fraction of ionized DTG (11). This form, being more soluble in the aqueous gastric environment, will likely allow for enhanced DTG absorption.

Finally, renal function is altered in morbid obesity and after substantial weight changes. The appropriate method for renal function assessment in obesity is debatable. However, a meta-analysis of surgical weight-loss studies reported a mean 25.6-ml/min reduction in glomerular filtration rate (GFR) in obese patients with normal baseline GFR after BS (12). It has also been demonstrated that obesity-related glomerular hyperfiltration is decreased after significant weight loss. Additionally, BS limits fluid intake by patients, which can further impair renal function. Indeed, our patient reported significantly reduced fluid intake after the surgery ($<$1 liter/day). Because 3TC is excreted unchanged in the urine (70%), reduced renal function may explain increased plasma 3TC concentrations after surgery and consequent weight loss.

Our patient reported no short-term adverse effects that may be related to the significantly increased exposure to the three ARVs. No clinical or laboratory abnormalities have been detected so far. However, long-term increased exposure to ABC whose levels have increased 12-fold raises concern of potential serious adverse effects. These might include an increased risk of cardiovascular disease (although causality has not been established) and neurological and hepatic toxicities. Therefore, we decided to switch the patient to a two-drug regimen consisting of DTG and 3TC alone.

In conclusion, this is the first published report of sequential pre- and postsurgery TDM of combined DTG, ABC, and 3TC. It illustrates the challenging complexity of ARV administration in the growing population of obese HIV patients undergoing BS. Further

research and TDM and PK data are required to construct a safe and effective strategy for successfully continuing ARV therapy in these patients.

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REFERENCES

1. Sharma P, McCarty TR, Ngu JN, O'Donnell M, Njei B. 2018. Impact of bariatric surgery in patients with HIV infection: a nationwide inpatient sample analysis, 2004–2014. AIDS 32:1959–1965. https://doi.org/10.1097/QAD.0000000000001915.
2. Cimino C, Binkley A, Swisher R, Short WR. 2018. Antiretroviral considerations in HIV-infected patients undergoing bariatric surgery. J Clin Pharm Ther 43:757–767. https://doi.org/10.1111/jcpt.12755.
3. Amouyal C, Buyse M, Lucas-Martini L, Hirt D, Genser L, Torcivia A, Bouillot JL, Oppert JM, Aron-Wisnewsky J. 2018. Sleeve gastrectomy in morbidly obese HIV patients: focus on anti-retroviral treatment absorption after surgery. Obes Surg 28:2886–2893. https://doi.org/10.1007/s11695-018-3308-7.
4. Roskam-Kwint M, Bollen P, Colbers A, Duisenberg-van Essenberg M, Harbers V, Burger D. 2018. Crushing of dolutegravir fixed-dose combination tablets increases dolutegravir exposure. J Antimicrob Chemother 73:2430–2434. https://doi.org/10.1093/jac/dky191.
5. Blouin RA, Kolpek JH, Mann HJ. 1987. Influence of obesity on drug disposition. Clin Pharm 6:706–714.
6. Xu J, Kulkarni SR, Li L, Slitt AL. 2012. UDP-glucuronosyltransferase expression in mouse liver is increased in obesity- and fasting-induced steatosis. Drug Metab Dispos 40:259–266. https://doi.org/10.1124/dmd.111.039925.
7. Price VF, Jollow DJ. 1988. Mechanism of decreased acetaminophen glucuronidation in the fasted rat. Biochem Pharmacol 37:1067–1075. https://doi.org/10.1016/0006-2952(88)90512-6.
8. Paganelli FL, Luyer M, Hazelbag CM, Uh HW, Rogers MRC, Adriaans D, Berbers RM, Hendrickx APA, Viveen MC, Groot JA, Bonten MJM, Fluit AC, Willems RJL, Leavis HL. 2019. Roux-y gastric bypass and sleeve gastrectomy directly change gut microbiota composition independent of surgery type. Sci Rep 9:10979. https://doi.org/10.1038/s41598-019-47332-z.
9. Magouliotis DE, Tasiopoulou VS, Sioka E, Chatedaki C, Zacharoulis D. 2017. Impact of bariatric surgery on metabolic and gut microbiota profile: a systematic review and meta-analysis. Obes Surg 27:1345–1357. https://doi.org/10.1007/s11695-017-2595-8.
10. Zhang J, Zhang J, Wang R. 2018. Gut microbiota modulates drug pharmacokinetics. Drug Metab Rev 50:357–368. https://doi.org/10.1080/03602532.2018.1497647.
11. Dahan A, Miller JM, Hilfinger JM, Yamashita S, Yu LX, Lennernas H, Amidon GL. 2010. High-permeability criterion for BCS classification: segmental/pH dependent permeability considerations. Mol Pharm 7:1827–1834. https://doi.org/10.1021/mp100175a.
12. Chang AR, Grams ME, Navaneethan SD. 2017. Bariatric surgery and kidney-related outcomes. Kidney Int Rep 2:261–270. https://doi.org/10.1016/j.ekir.2017.01.010.