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REVIEW ARTICLE

Implications of Bariatric Surgery on the Pharmacokinetics of Antiretrovirals in People Living with HIV

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Abstract

Bariatric surgery is increasingly applied among people living with HIV to reduce obesity and the associated morbidity and mortality. In people living with HIV, sufficient antiretroviral exposure and activity should always be maintained to prevent development of resistance and disease progression. However, bariatric surgery procedures bring various gastrointestinal modifications including changes in gastric volume, and acidity, gastrointestinal emptying time, enterohepatic circulation and delayed entry of bile acids. These alterations may affect many aspects of antiretroviral pharmacokinetics. Some drug characteristics may result in subtherapeutic exposure and the potential related risk of treatment failure and resistance. Antiretrovirals that require low pH, administration of fatty meals, longer intestinal exposure, and an enterohepatic recirculation for their absorption may be most impacted by bariatric surgery procedures. Additionally, some antiretrovirals can interact with the polyvalent cations in supplements or drugs inhibiting gastric acid, thereby preventing their use as these comedications are commonly prescribed post-bariatric surgery. Predicting pharmacokinetics on the basis of drug characteristics solely proved to be challenging, therefore pharmacokinetic studies remain crucial in this population. Here, we discuss general implications of bariatric surgery on antiretroviral outcomes in people living with HIV as well as drug properties that are relevant for the choice of antiretroviral treatment in this special patient population. Additionally, we summarise studies that evaluated the pharmacokinetics of antiretrovirals post-bariatric surgery. Finally, we performed a comprehensive analysis of theoretical considerations and published pharmacokinetic and pharmacodynamic data to provide recommendations on antiretrovirals for people living with HIV undergoing bariatric surgery.

1 Introduction

Obesity, defined as a body mass index (BMI) > 30 kg/m^2, is a manifestation reported in as much as 40% of women and 20% of men living with HIV infection in the USA [1]. Similarly, reports from lower-income to upper-income countries indicate that obesity trends in people who live with HIV (PLWH) are comparable to those in the general population [2–5]. Table 1 summarises the reported incidences of obesity among PLWH in various countries. Additionally, many observational and randomised clinical studies have detected an association between increased body weight and the intake of some newer antiretrovirals (ARVs), particularly integrase strand transfer inhibitors and tenofovir alafenamide fumarate [reviewed in [6]].

Yet, half of deaths in PLWH have been linked to non-infectious complications [7]; of those, cardiovascular disease represents the most frequent cause of non-AIDS mortality [8, 9]. Elevated risks for cardiovascular disease and metabolic disorders (e.g. abdominal fat accumulation, dyslipidaemia and diabetes mellitus) have been shown to be significant contributors for the shorter survival in PLWH [8–12]. Given the negative consequences of obesity on cardiovascular disease risk and the general health,

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Key Points

Gastrointestinal modifications after bariatric surgery may alter antiretroviral' pharmacokinetics and activity.

Investigating physiochemical properties and clinical outcomes of a drug can predict its performance after bariatric surgery.

Dolutegravir, darunavir and most nucleoside analogue reverse transcriptase inhibitors are successful drug candidates post-bariatric surgery.

more emphasis is currently placed on weight-management strategies in the regular care of PLWH [13, 14].

Bariatric surgery (BS) is becoming popular as the most effective surgical option to overcome severe obesity and the metabolic dysregulation when lifestyle changes fail to achieve weight goals [15]. Moreover, incidences of cancer, stroke and overall mortality were found to be significantly lower in obese subjects who start losing weight post-BS compared with their matched non-operated obese controls in a prospective intervention study [16]. The current European and American guidelines acknowledge BS as the most efficient intervention for obesity and its related comorbidities in adults with a BMI $\geq$ 40 kg/m^2, or a BMI $>$ 35 kg/m^2 with one or more comorbidity [17–19].

Despite being safe and effective in PLWH in terms of BMI and comorbidity reduction as reported in small studies [20, 21] and clinical cases [22–24], BS causes several physiological and anatomical alterations in the gastrointestinal (GI) tract. As a consequence, this may impact the pharmacokinetics of orally administered drugs, mainly absorption and bioavailability [25]. In the case of subtherapeutic exposure to ARVs, the development of resistance may occur, potentially leading to treatment failure and HIV progression [26, 27].

Drug absorption is a multifactorial event that is dependent on physiochemical properties of the drug; including lipophilicity, solubility and the drug–drug interaction (DDI) profile. In addition, other factors may play a role in drug absorption such as gastric pH, gastric volume and motility, inlet of bile secretions and intestinal absorption area [25, 28]. In this review, we sought to discuss the effects of BS on the pharmacokinetics and pharmacodynamics of ARVs in PLWH. Based on the theoretical knowledge as well as published data, we evaluate the suitability of several ARVs as treatment options post-BS.

2 Methods

For the effect of BS on ARV exposure and efficacy, PubMed and Google Scholar searches were conducted between February 2021 and May 2021. A detailed list of terms used for the search can be found in the Electronic Supplementary Medicine. Literature was retrieved from all types of

Table 1 Incidence of obesity among people living with HIV in various countries

Country	State/city	Before ARV initiation		After ARV initiation		Follow-up in months	Period of estimation	References
		Overweight (*N*)	Obese (*N*)	Overweight (*N*)	Obese (*N*)			
Brazil	Rio de Janeiro	21.7% (1794)	7.9% (1794)	40.3% (1794)	18.3% (1794)	± 49	2000–15	[110]
Dominican Republic		27% (133)	18% (133)	42% (133)	24% (133)	± 24	2007–13	[5]
Ivory Coast	Abidjan	19.7% (755)	7.2% (755)	24.8% (597)	9.2% (597)	± 24	2008–14	[3]
Nigeria		19.6% (8819)	7.5% (8819)	35.7% (8,819)	26.5% (8819)	± 60	2004–9	[2]
North America	USA and Canada	Mean = 30% (135,914)	Mean = 14% (135,914)	22% became overweight from normal BMI (13,591)	18% became obese from normal/overweight BMI (13,591)	± 36	1998–2010	[4]
USA	Alabama	24% (681)	20% (681)	31% (681)	25% (681)	±24	2000–8	[111]
	San Diego-Maryland (military beneficiaries)	54% (661)		46% (661)	17% (661)	±54	2004–5	[112]

Overweight = BMI ≥25 to <30 kg/m^2, obesity = BMI ≥30 kg/m^2 [113]

ARV antiretroviral, *BMI* body mass index

human-related reports published in English. Additional literature has been retrieved via backward reference searching from the key published reports. Registration information files from the European Medicines Agency and the US Food and Drug Administration were used, and current guidelines were also screened. Moreover, manually retrieved published articles and conference abstracts were investigated and included when relevant.

3 Theoretical Implications of BS on the Pharmacokinetics and Pharmacodynamics of ARVs

Among several surgical options, Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most popular bariatric procedures [29]. When RYGB is performed, a stomach pouch of approximately one ounce is preserved and attached directly to the jejunum. In SG, around 80% of the stomach body is resected, leaving a tube-shaped gastric pouch with no anastomosis with any intestinal parts (Fig. 1) [30]. Sleeve gastrectomy is considered a restrictive procedure, while RYGB combines both restrictive and malabsorptive features. Because of these differences, distinct alterations occur in the GI tract, which may impact the pharmacokinetics of orally administered drugs. We discuss the implications of BS on ARVs in Sect. 3, and discuss the ARV-specific literature data in Sect. 5. Table 2 summarises the main considerations for ARV use post-BS.

3.1 GI Volume and Motility

Bariatric surgery decreases the surface area of the stomach (SG, RYGB) and intestine (RYGB) and, thus, alters the absorption capacity of oral medication. Gastric motility might be interrupted in restrictive surgery, leading to slower or less disintegration and dissolution of orally administered medications, a step that is a prerequisite for absorption [31, 32]. Altered gastric motility affects gastric emptying time, which is a rate-limiting step for the absorption of some drugs [33]. Both gastric motility and emptying time are found to be highly decreased after SG [34].

Additionally, RYGB includes bypassing parts of the intestine (duodenum and proximal jejunum) and, therefore, minimises the exposure to the mucosal layer [35]. It is worth noting that the absorptive capacity of the GI is limited, not only by the surface area of absorption, but also by other factors, mainly the intestinal transit time. The duodenum and proximal jejunum have the largest area of absorption per unit length. However, they have the fastest transit time (6 and 18 min, respectively), making distal parts (e.g. Ileum) responsible for around 62% of intestinal absorption because of the long transit time (~ 120 min) [36]. A very rapid intestinal transit time can decrease absorption. Nevertheless, intestinal adaptation is a documented phenomenon in short bowel cases, where mucosal hypertrophy compensates for

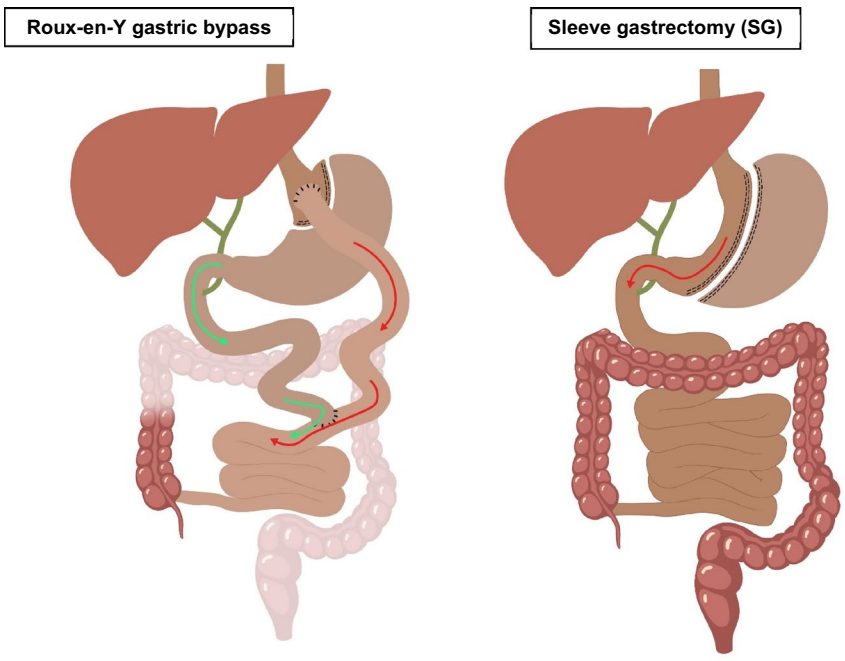

Fig. 1 Types of common weight loss procedures

Table 2 Summary of main drug considerations that affect their pharmacokinetics post-BS

	Recommendation
Absorption site	Drugs with a main absorption site at the level of stomach and stomach ± duodenum should be closely monitored for reduced absorption after SG and RYGB, respectively
Bioavailability	When a drug has a low bioavailability, reduced absorption has relatively a greater impact
pH dependency	Drugs that have a dependency on high or low pH degree for their absorption might be absorbed differently post-BS
Enterohepatic circulation	In RYGB, the enterohepatic circulation is altered, which may affect the bioavailability of drugs with an intensive enterohepatic recirculation
High lipophilicity (log P) and food intake	Drugs that have high lipophilicity and/or requires an intake with (fat)food for their absorption might be less absorbed owing to the delayed entry of bile acids in RYGB and restricted food intake after RYGB and SG
Large dosage forms	If swallowing difficulties emerge post-BS, consider alternative formulations including crushed tablets and oral solutions, however, monitor for dumping syndrome
Interaction profile	A special caution should be made for drugs that interact with post-surgery medications (nutritional supplements + PPIs)

BS bariatric surgery, *log P* lipophilicity, *PPIs* proton pump inhibitors, *RYGB* Roux-en-Y gastric bypass, *SG* sleeve gastrectomy

the short intestinal length achieving near normal absorption with time [37]. Overall, changes in the GI surface area and motility may not necessarily hinder drug absorption. In theory, ARVs that are absorbed in the stomach or proximal intestine, as well as slow-release formulations are the agents at higher risk to be impacted by BS. Rilpivirine is an ARV that has been reported to be absorbed in the upper intestine [38], and one extended-release formulation of an ARV exists for nevirapine 400 mg.

3.2 Gastric Acidity

The gastric pH can affect all aspects of drug dissolution and solubility. Malabsorptive procedures are shown to increase the gastric pH directly as well as > 1-year post surgery [39–41]. Restrictive procedures, however, increase the pH to a lower extent (6.4 vs 4.9) [40], and the effect was not present at 1-year post-surgery [40, 41]. The suggested mechanism of the increase in pH is the removal of most acid-producing cells with the transected stomach [42]. Additionally, patients require a concomitant intake of proton pump inhibitors (PPIs) post-BS to prevent GI complications [43, 44]. Eventually, this can hinder drug ionisation, and thus, the absorption of ARVs with low-pH-dependent solubility, such as rilpivirine [45] and atazanavir [46]. In addition, disintegration of some solid-form medications is reduced in higher gastric pH [28].

Drug dissolution of ARVs has not been investigated in vivo post-BS. In a cellular model, lipophilicity and cellular permeability of raltegravir were found to be pH dependent and were sharply lower after increasing the pH of the extracellular media from 5 to 9. This same study showed that the PPI omeprazole did not alter raltegravir permeability [47].

3.3 Role of Drug Formulation

Drug disintegration is the preliminary step for drug solubility within the GI medium. This step is crucial for absorption, and it is widely variable among different drug formulations [42]. Additionally, reducing the stomach volume post-BS is expected to reduce gastric mixing and the subsequent drug disintegration [28]. Moreover, reduced diameter of the gastrojejunostomy or gastric sleeve may create gastrodynia and restrict the continuous passage of large or multiple tablets [22], which could explain the non-adherence to ARVs in some patients post-BS [44]. When such scenarios occur, medication management post-BS should include the use of liquid formulation, chewable/crushable tablets, openable capsules that can be sprinkled on food and non-oral drug forms (e.g. intramuscular) when available. Caution is warranted because of the development of dumping syndrome when using liquid formulations with non-absorbable sugars [31]. Using formulations of delayed dissolution, such as extended-release or enteric-coated ARV options should be avoided post-BS [42], although structural evidence of reduced efficacy is lacking. Importantly, ARV exposure must be re-assessed when changing drug formulations.

Most ARVs are available only as tablet formulations, and most of them cannot be crushed based on the manufacturer's recommendations [48]. In addition, several ARVs are available as single-tablet combinations, thus even if one agent can be crushed, data on crushing for the other components may not exist [49]. These data are critical because in the immediate period post-BS, patients are often only able to take crushed or liquified medications [50]. In the absence of data, the crushing or suspending of

Table 3 Advice on bariatric surgery and NRTI selection in people living with HIV

	Drug properties related to absorption/exposure					Literature data			Data related to drug intake		
	Absorption site[27]	F [114]	pH-dependency, pKa[115]	Enterohepatic loop	Log P [115]	C_{trough} (dose, surgery type, time since surgery)	Ratio before/after surgery	Viral load	Alternative formulations[48]	intake with food[48]	DDI with polyvalent/gastric pH inhibitors[72]
NRTI											
Abacavir (+++)	Proximal small intestine (likely) and Duodenum (probably)	83%	No, 5.77 (b)	-	1.2	24.5. ng/mL (600mg (crushed), SG, 3 d)[84] 58.5. ng/mL (600mg (intact), SG, 11 d)[84] 103.3 ng/mL (600mg (intact), SG, 42 d)[84]	0.35 (3 d)[84] 0.17 (11 d)[84] 0.08 (42 d)[84]	6/6 UD[50, 81, 84, 85]	oral solution	-	No
	+					+			+		
Emtricitabine (+++)	NA	93%	No	-	-1.4	88 ng/mL (QD,200mg, SG, 1 m)[75] 446 ng/mL (QD,200mg, SG, 3 m)[75] 147 ng/mL (QD,200mg, RY,12m)[35] 57 ng/mL (QD,200mg, RY, 24 m)[89] 20 ng/mL (QD,200mg, TGRY, 8 Y)[83] 97 ng/mL (QD,300mg PrEP, SG, 24m)[82]	2.9 (12m)[35]	15/15 UD[27, 35, 50, 75, 81, 83, 89]	Capsule opened and sprinkled	-	No
	+					+			+		
Lamivudine (+++)	Duodenum and jejunum (likely)	80-85%	No	-	-1.4	102 ng/mL (BID, 150mg, SG, 2 m)[75] 46.1 ng/mL (BID, 150mg, RY, pregnant, 9 Y)[86] 72 ng/mL (300mg (crushed), SG, 3 d)[84] 111. ng/mL (300mg (intact), SG, 11 d)[84] 161 ng/mL (300mg (intact), SG, 42 d)[84]	0.90 (3 d)[84] 0.54 (11 d) [84] 0.37 (42 d)[84]	4/4 UD[50, 75, 84, 86]	crushed tablet	-	No
	+					+			+		
Tenofovir alafenamide (+)	Small intestine (likely)	NA	No, 5.12 (b)	-	-1.5	11 ng/mL (QD, -, RY, 12m)[35]	-	-	Crushed tablet	Yes	No
	-					+			-		
Tenofovir disoproxil (+++)	Small intestine (likely)	25-40%	No, 3.74 (b)	-	1.6	34 ng/mL (QD,300mg, SG, 1 m)[75] 86 ng/mL (QD,300mg, SG, 3 m)[75] 34 ng/mL (QD,245mg, SG, 1 m)[79] 40 ng/mL (QD,245mg, SG, 3 m)[79] 32 ng/mL (QD,245mg, SG, 6 m)[79] 47 ng/mL (QD,245mg, SG, 12 m)[79] 40 ng/mL (QD,300mg, RY, 24 m)[89] 20 ng/mL (QD,245 mg, TGRY, 8 Y)[83] 89 ng/mL (QD, -, TGRY, 1 m)[80] 119 ng/mL (QD, -, TGRY , 3 m)[80] 19 ng/mL (QD,300mg PrEP, SG, 24m)[82]	0.72 (1 m)[79] 0.85 (3 m)[79] 0.68 (6 m)[79] 1.0 (12 m)[79] AUC: 1.0 (1 m)[80] 1.0 (3 m)[80]	13/14 UD[27, 79] [50, 75, 80, 89]	crushed tablet	Yes	No
	+					+			+		

AUC area under the concentration–time curve, *BID* twice daily, C_{trough} trough concentration, *d* days, *DDI* drug–drug interaction, *F* bioavailability, *log P* lipophilicity, *m* months, *NA* not available, *NRTI* nucleoside reverse transcriptase inhibitor, *PreP* pre-exposure prophylaxis, *QD* once daily, *RY* Roux-and-Y, *SG* sleeve gastrectomy, *TGRY* total gastrectomy Roux-and-Y, *UD* undetectable, *w* weeks, *y* years

ARVs is not recommended. Available alternative formulations of ARVs are listed in Tables 3, 4, 5 and 6.

3.4 Role of Drug Properties

The physiochemical properties of a drug (e.g. water solubility, lipophilicity and affinity for protein binding) determine drug distribution [36]. Both malabsorptive and restrictive procedures create a smaller gastric pouch that holds a lesser amount of (fatty) food. Moreover, the entry of pancreatic secretions and bile secretions in the intestine is delayed and equally the exposure of drugs/food to those active compounds. This could result in a significant reduction in the lipid intake [31, 51]. Lipophilic drugs need bile acids for their dissolution and solubility [52].

Especially in malabsorptive procedures, the upper intestinal parts undergo anatomical changes, which may influence the enterohepatic recirculation of bile secretion. Lipophilic drugs rely on enterohepatic recirculation, which may influence their steady-state concentrations [53]. Although Simonen et al. reported that in a fasting state, serum levels of bile acids were two-fold higher after RYGB as a compensation mechanism, the lipid absorption is still reduced because of the delayed entry of bile acids to the intestine and the

Table 4 Advice on bariatric surgery and NNRTI selection in people living with HIV

	Drug properties related to absorption/exposure					Literature data			Data related to drug intake		
	Absorption site[27]	F[114]	pH-dependency, pKa[115]	Enterohepatic loop	Log P[115]	C_{trough} (dose, surgery type, time since surgery)	Ratio before/after surgery	Viral load	Alternative formulations[48]	intake with food[48]	DDI with polyvalent/gastric pH inhibitors[72]
NNRTI											
Doravirine (++)	NA	64%	No, 7.34 (a)	-	2.19	NA	-	NA	No	-	No
	+					-			+		
Efavirenz (++)	jejunum (mainly)+ duodenum (possibly)[116]	40-45%[117]	No,	Possible[118]	4.6	Na	-	6/6 UD[50, 81]	crushed tablet	-	No
	-					+			+		
Etravirine (++)	NA	NA	No, 4.13 (b)[119]	-	3.67	1690 ng/mL (16u, SG)[24]	-	3/3 UD[81]	Crushed tablet	Yes	No
	NA					+			+		
Nevirapine (++)	Jejunum and ileum	75-90%	No, 5.06 (b)	Possible[120]	2.5	2545 ng/mL (BID,200mg, SG, 2m)[75]	-	1/1 UD[75]	Crushed tablet	-	No
	-					+			+		
Rilpivirine (oral) (+)	upper Small intestine[38]	NA	Yes, lower uptake by higher pH 5.16 (b)	-	4.86	150 ng/mL (QD,25mg, SG, 1m)[75]	-	1/1 UD[75]	Crushed tablet	Yes	PPI Antacids H2 blockers
	-					+			-		

BID twice daily, C_{trough} trough concentration, *d* days, *DDI* drug–drug interaction, *F* bioavailability, *log P* lipophilicity, *m* months, *NA* not available, *NNRTI* non-nucleoside reverse transcriptase inhibitors, *PPI* proton pump inhibitor, *QD* once daily, *SG* sleeve gastrectomy, *UD* undetectable

limited food intake after the surgery [54]. The lipophilicity and enterohepatic characteristics of currently used ARVs are listed in Tables 3, 4, 5 and 6.

Additionally, the oral bioavailability of a drug depends on the extent of the first-pass metabolism (i.e. presystemic metabolism at the level of the intestine and liver) [42, 55]. Cytochrome 450 (CYP) isozymes, mainly CYP3A4, are the major enzymes involved in first-pass metabolism [55]. Cytochrome 450 enzymes are more abundant in the proximal intestine compared with the distal intestine [28]. Physiologically based pharmacokinetic (PK) modelling predicted that the extent of intestinal first-pass metabolism for CYP3A4 substrates is decreased after RYGB surgery [56]. Conversely, the expression of hepatic CYP3A4 is upregulated post-RYGB, leading to an increased first-pass hepatic metabolism [56]. However, more data are warranted for ARVs that are major substrates for CYP3A4.

3.5 DDI

3.5.1 Mineral Supplements

Micronutrient deficiency constitutes mid-term to long-term complications post-BS [30]. Established guidelines advise including several minerals and multivitamins for a routine, long-term, nutrient compensation post-BS [57]. Importantly, integrase strand transfer inhibitors (INSTIs) interact with mineral supplements containing divalent cations, which are often administered post-BS. Integrase strand transfer inhibitors chelate with magnesium at the active site of viral integrase enzyme, thereby preventing the insertion of viral DNA into the host cellular DNA [58]. The co-administration of calcium or magnesium has been shown in vitro to decrease the cellular permeability of raltegravir as free divalent metals (calcium and magnesium) attach to the divalent metal chelating motif of raltegravir [47]. Such binding is thought to occur in the GI tract, thereby resulting in reduced absorption of INSTIs (i.e. raltegravir, elvitegravir, bictegravir, oral cabotegravir and dolutegravir).

Song et al. compared the pharmacokinetics of dolutegravir alone vs dolutegravir when co-administered with calcium or iron supplements under fasting or fed conditions in healthy subjects [59]. Under fasting conditions, coadministration with calcium carbonate decreased dolutegravir area under the concentration–time curve (AUC) from zero to infinity, maximum concentration (C_{max}) and C_{24} by 39%, 37% and 39%, respectively, while iron coadministration decreased these dolutegravir PK parameters by 54%, 57% and 56%, respectively. The effect of the minerals on

Table 5 Advice on bariatric surgery and PPI selection in people living with HIV

	Drug properties related to absorption/exposure					Literature data			Data related to drug intake		
	Absorption site[27]	F[114]	pH-dependency, pKa[115]	Enterohepatic loop	Log P[115]	C_{trough} (dose, surgery type, time since surgery)	Ratio before/after surgery	Viral load	Alternative formulations[48]	intake with food[48]	DDI with polyvalent/gastric pH inhibitors[72]
PI											
Atazanavir (-)	Intestinal of unknown site	NA	Yes, lower uptake by higher pH 4.42 (b)	-	4.5	640 ng/mL op 12u (-, SG)[24] 722 ng/mL (QD,300mg/r, SG, 3 m)[75] 178 ng/mL (QD,300mg/r, TGRY, 1 m)[80] 150 ng/mL (QD,300mg/r, TGRY, 3 m)[80]	0.65[24] 3.6 (1m)[80] 4.3 (3m)[80]	6/8 UD[24, 27, 80, 81]	Suspension, capsule opened	Yes	PPI Antacids H2 blockers
	-					-				-	
Darunavir (+++)	Small intestine (likely)	37-82%	No, 2.39 (b)	possible[121]	1.8	Not quantifiable at 16h (SG)[24] 2270 ng/mL (QD,800mg/r, SG, 1 m)[75] 2602 ng/mL (BID,600mg/r, RY, 24 m)[89] 1166 ng/mL (BID,600 mg, RY, 3 d)[35] 3350 ng/mL (BID,600 mg, RY, 10 w)[35] 3140 ng/mL (QD,800 mg, RY, 12 m)[35]	1.49 (3d)[35]	11/11 UD[24, 35, 50, 75, 81, 89]	Suspension	Yes	No
	+					+				+	
Lopinavir (++)	Small intestine (most probably Jejunum)	NA	No	Yes[122]	3.9[27]	4864 ng/mL (BID,400mg/r, RY, 4 m)[94] 1920 ng/mL (BID,600mg/r, RY, pregnant, 9 Yr.)[86]	-	NA (short follow-up)[86, 94]	Solution	Yes	No
	-					+				+	
Boosters											
Ritonavir* (++)	Unknown but probably stomach)[16]	NA	Yes[27], 2.84 (b)	-	3.9	54 ng/mL (BID,100mg, RY, 24 m)[89] 410 ng/ml (BID,100mg, RY, 17 d)[94] 60 ng/mL (BID,150 mg, RY, pregnant, 9Y)[86] Not quantifiable (-, SG)[24] 40 ng/mL (BID, 100 mg, RY, 3 d)[35] 384 ng/mL (BID, 100 mg, RY, 10 w)[35] 298 ng/mL (QD,100 mg, RY, 12 m)[35]	1.49 (3d)[35]	2/2 UD (with lopinavir)[86, 94] 10/10 UD (with darunavir)[24, 89] [35, 81] 2/3 UD (with atazanavir)[81]	Solution	-	No
	-					+				+	
Cobicistat* (++)	NA	NA	No, 6.69 (b)	-	4.36	NA	-	2/2 UD[50]	NA	-	No
	-					+				+	
*The final recommendation related to the use of the pharmacokinetic booster depends on the boosted ARV drug											

BID twice daily, C_{trough} trough concentration, *d* days, *DDI* drug–drug interaction, *F* bioavailability, *log P* lipophilicity, *m* months, *NA* not available, *PPI* proton pump inhibitor, *QD* once daily, *RY* Roux-and-Y, *SG* sleeve gastrectomy, *TGRY* total gastrectomy Roux-and-Y, *UD* undetectable, *w* weeks, *y* years

[a]The final recommendation related to the use of the pharmacokinetic booster depends on the boosted antiretroviral

dolutegravir was mitigated when dolutegravir was given with a meal. Reduced exposures have also been reported for other INSTIs (i.e. raltegravir, elvitegravir and bictegravir) in the presence of divalent cations, which can lead to treatment failure [60].

Drug–drug interactions between mineral supplements and INSTIs are generally managed by separating drug intake. Therapeutic drug monitoring is also recommended as a means to prevent sub-therapeutic drug concentrations and related risk of treatment failure. Noteworthy, DDIs with divalent cations are avoided with the intramuscular administration of the injectable long-acting INSTI, cabotegravir; however, such DDIs are still relevant for the oral lead-in phase.

Table 6 Advice on bariatric surgery and INSTI selection in people living with HIV

	Drug properties related to absorption/exposure					Literature data			Data related to drug intake		
	Absorption site[27]	F[114]	pH-dependency, pKa[115]	Enterohepatic loop	Log P[115]	C_{trough} (dose, surgery type, time since surgery)	Ratio before/after surgery	Viral load	Alternative formulations[48]	intake with food[48]	DDI with polyvalent/gastric pH inhibitors[72]
INSTI											
Bictegravir (+)*	NA	NA	No	-	1.28	-	-	-	No	-	Mineral supplements Antacids containing divalent cations
	+					-			-		
Cabotegravir (oral) (+)*	NA	NA	No,	-	1.04	-	-	-	Short term therapy followed by intermuscular injections	-	Mineral supplements Antacids containing divalent cations
	+					-			-		
Dolutegravir (+++)	Small intestine	41-66%	No	Yes[123]	0.98	1740 ng/mL (QD,50mg, SG)[75] 900 ng/mL (QD,50mg, SG, 14 m)[75] 1410 ng/mL (50mg (crushed), SG, 3 d)[84] 1230 ng/mL (50mg (intact), SG, 11 d)[84] 2347 ng/mL (50mg (intact), SG, 42 d)[84] 0.5 mg/L at 11h (QD, 50mg, RY, 14 d)[78]	≈ 1[75] 0.69 (3 d)[84] 0. 74 (11 d)[84] 0.39 (42 d)[84]	8/9 UD [50, 75, 84, 85] 4/4 UD (2 were temporarily on dolutegravir BID after the surgery)[78]	Crushed tablet	-#	Mineral supplements Antacids containing divalent cations
	+					+			+		
Elvitegravir (+)*	NA	NA	6.16 (a)	-	3.66	-	-	1/1 UD[50]	Crushed tablet	Yes	Mineral supplements Antacids containing divalent cations
	-					+			-		
Raltegravir (+)	Ileum	NA	Yes&, 5.52 (a)	possible[124]	-0.39	372 ng/mL at 16h (SG, -)[27] 83 ng/mL (BID, 400mg, SG, 1m)[75]		9/11 UD[27] [50, 75, 81]	Crushed tablet	-	Mineral supplements Antacids containing divalent cations
	-					-			+		

(a) acid, *(b)* base, *BID* twice daily, C_{trough} trough concentration, *d* days, *DDI* drug–drug interactions, *F* bioavailability, *h* hours, *INSTIs* integrase strand transfer inhibitors, *m* months, *NA* not available, *PPI* proton pump inhibitor, *QD* once daily, *RY* Roux-and-Y, *SG* sleeve gastrectomy, *TGRY* total gastrectomy Roux-and-Y, *UD* undetectable

[a]Data on bictegravir, cabotegravir and elvitegravir are limited and, therefore, these antiretrovirals are not recommended

[b]Dolutegravir is preferably to be taken with food in the presence of class resistance mutations

[c]Higher absorption when combined with a PPI but lower cellular uptake and 9-fold lower cell permeability at higher pH [47]

Advice on bariatric surgery and antiretroviral therapy in HIV:

Green agents (+++) are preferred agents after bariatric surgery based on ≥2 favourable properties related to absorption (+); and ≤1 viral failure in the literature (+); and less ≤1 intake restriction (+)

Red agents (+) are not recommended because of unfavourable drug properties, or potential impaired efficacy after bariatric surgery, or lack of information

White agents (++) are not preferred because of insufficient information but may be an option for individual complex cases under close monitoring

3.5.2 Gastric Acid Inhibitors

Antacids can affect ARV exposure via two mechanisms: chelation, as these agents contain polyvalent cations, and/or drug absorption, as these agents increase gastric pH. Antacids containing divalent cations essentially lower the absorption of INSTIs. A clinical study of Kiser et al. demonstrated that when coadministered with magnesium-containing and aluminium-containing antacids, the trough concentration (C_{trough}) of raltegravir was reduced by 67% with 75% of subjects having a C_{trough} below the 95% inhibitory concentration of raltegravir (15 ng/mL) [61]. Similarly, Patel et al. reported a 74% decrease in the AUC of dolutegravir when co-administered with an antacid. Conversely, PPIs did not alter dolutegravir exposure, thereby demonstrating that its absorption is not impacted by changes in gastric pH [62].

Recommendations on how to administer INSTIs with mineral supplements or antacids can be found in the Liverpool HIV Drug Interactions website [63]. Additionally, the exposure of some ARVs can be reduced in a higher pH medium after the administration of antacids, PPIs or H2 receptor antagonists. Prevalence of gastroesophageal reflux disease (GERD) in obese individuals is reported to be twice as high as that of non-obese individuals [64]. Proton pump inhibitors are considered the gold standard treatment for GERD and may require a life-long maintenance therapy [65]. Moreover, although RYGB was reported to be beneficial for GERD remission or improvement in the majority of patients [66], SG was shown to raise the incidence of de novo GERD [66, 67]. Currently, PPIs are routinely prescribed post-BS to minimise the risk of GI complications [68, 69] including ulceration [70], gastritis and extra-digestive syndrome [71]. The protease inhibitor atazanavir and oral rilpivirine have an absorption that is pH dependent and therefore their coadministration with PPIs and H2 receptor antagonists is not recommended [72]. Although this is not relevant for the long-acting intramuscular rilpivirine, it is still important to consider during the oral lead-in phase.

4 Role of the Surgery Type

The restrictive procedure preserves digestive continuity, causing less malabsorptive nutritional deficiency and fewer GI complications such as dumping syndrome, diarrhoea and obstruction [73, 74]. In theory, this procedure is expected to have a lower impact on drug absorption and consequently may have a lower effect on the pharmacokinetics of ARVs. Pourcher et al. proposed that the optimal procedure for PLWH should be characterised by a lower risk of complications, have no implanted foreign substances, less absorption disruption and a convenient weight loss, all of which is likely to be achieved with SG [75]. In addition, Panko et al. suggested that, based on clinical experience, the fear of ARV malabsorption or difficulties in swallowing the medications constitute major concerns for PLWH who are considering BS. Thus, PLWH may find restrictive procedures preferable, as they do not present the issue of malabsorption [50].

Two studies compared the HIV outcomes between PLWH undergoing restrictive vs malabsorptive procedures, but did not include a pharmacokinetics analysis [26, 76]. The study of Akbari et al. showed no substantial difference between SG and RYGB in terms of CD4 count, viral loads (VLs) and overall disease progression among 56 patients [26]. Moreover, El Kamari et al. conducted a multi-center, retrospective, long-term analysis to compare weight loss and comorbidities between SG and RYGB in PLWH. Rates of weight loss and comorbidities remission were comparable after 6 months. At the 2-year and 3-year follow-ups, patients who underwent SG regained their weight and their dyslipidaemia and hypertension worsened, which was not observed after RYGB. CD4 counts were similar after both surgeries at all timepoints [76]. These results are consistent with data obtained from non-HIV infected individuals showing a tendency for weight gain and comorbidity progression after SG but not after RYGB [77].

Therefore, SG may cause fewer physiological alterations and consequently may impact less ARV pharmacokinetics. However, RYGB has been shown to achieve more sustainable weight loss and comorbidity remission. Importantly, the time post-BS seems to be a major factor to define the extent of PK variation. Many studies showed that BS affects the plasma concentrations of ARVs the highest during the early period post-BS, and the concentrations returned to population or pre-surgery levels after approximately 6 months for tenofovir and dolutegravir [78, 79] or even earlier (10 weeks) for darunavir [35]. Yet, there are limited data comparing the effect of the type of surgery on the pharmacology of ARVs. As such, patients' and physicians' preferences should determine the procedure type.

5 Overview of ARV PK Studies After BS

5.1 Nucleoside Reverse Transcriptase Inhibitors

Two studies have shown no considerable effect on tenofovir disoproxil fumarate (TDF) or emtricitabine exposure post-BS in PLWH [80, 81]. The first study measured tenofovir concentrations at 1 and 3 months after RYGB and showed no effect on plasma C_{trough} [80]. Similarly, a case series of eight patients demonstrated no significant decrease in tenofovir or emtricitabine concentrations at 3 months post-SG [81]. In contrast, data from a case series of individuals with GI disorders ($n = 4$; SG, chronic diarrhoea, terminal ileitis and celiac disease) on TDF as a pre-exposure prophylaxis (PrEP)

reported a significantly decreased C_{trough} of tenofovir (but not emtricitabine) [19 ng/mL vs 138 ng/mL in healthy PrEP users] [82]. None of the four patients seroconverted after > 1 year of follow-up [82]. The patient that underwent SG had the surgery 2 years before starting PrEP; therefore, other factors may have contributed to the low tenofovir exposure. Nevertheless, the study recommended an increase in TDF dosage or to use an alternative PrEP in individuals with GI disorders, including SG [82].

As RYGB is essentially a subtotal gastrectomy, results from gastrectomised patients might be extrapolated to those undergoing RYGB [36]. In this regard, Roelofsen et al. investigated the pharmacokinetics of TDF and emtricitabine as a PrEP in a non-obese patient who had undergone a full gastrectomy ~ 9 years prior to the PK analysis. With the standard dose of TDF/emtricitabine (245/200 mg), the AUC from 0 to 24 hours were 73.2% (tenofovir) and 43.7% (emtricitabine) lower compared with reference values. Trough concentrations were also 2.5-fold and 4-fold lower for emtricitabine and tenofovir compared with reference values (both 0.02 mg/L vs 0.08 and 0.05 mg/L, respectively). After doubling the dose, the AUC from 0 to 24 h increased by 148.9% (15.9 h mg/L) for emtricitabine and by 132.5% for tenofovir (3.7 h mg/L). The authors suggested that with a standard dose of TDF/emtricitabine, patients undergoing a gastrectomy may show a long-term sub-prophylactic exposure, which therefore requires dose doubling [83].

Abacavir exposure after SG has been investigated in one case report [84] and two case series [81, 85]. Trough concentrations of abacavir in one case were reported to be ~ 7-fold and 12-fold-higher at 11 days and 42 days post-SG (58.5 and 103.3 ng/mL), respectively, compared with baseline levels from the same patient (8.7 ng/mL). This patient also had a higher C_{trough} of lamivudine (161 ng/mL, 2.7-fold) and atazanavir (2347 ng/mL, 2.5-fold) at day 42 post-SG compared with pre-surgery concentrations (60 and 919 ng/mL, respectively) [84]. By contrast, C_{trough}, C_{max} and AUC of abacavir after surgery were within the population range in two cases at 3 and 6 months post-SG [81, 85]. Furthermore, Badowski et al. showed that in two patients on abacavir-containing regimes, VL was undetectable at 9 months after both RYGB and SG. [85].

Three cases were reported for lamivudine post-SG [75, 84] or post-RYGB in a pregnant woman [86]. Post-SG, twice-daily concentrations of lamivudine 150 mg showed a C_{trough} of 102 ng/mL at 2 months post-SG, but without any control data for comparison [75]. The second case reported a 2.5-fold increase in concentrations of once-daily lamivudine at 6 weeks post-SG compared with pre-surgery concentrations. The patient was subsequently switched from abacavir/lamivudine/dolutegravir to a dual therapy with dolutegravir/lamivudine for treatment simplification and the VL remained undetectable [84]. Finally, in the pregnant woman who had RYGB approximately 9 years prior to the analysis, plasma concentrations of twice-daily lamivudine were considerably lower than those published for pregnant controls with HIV (C_{max} of 0.69 µg/mL vs ~ 110 µg/mL). Nonetheless, viral suppression was maintained during the pregnancy and the infant was born HIV negative [86]. In all cases, the patients maintained viral suppression post-BS.

Amongst commonly used nucleoside reverse transcriptase inhibitors, lamivudine, emtricitabine, and abacavir have favourable pharmacokinetic and pharmacodynamic characteristics post-BS with no considerable changes in exposure concentrations or evidence on viral failure. While TDF has favourable characteristics after SG and RYGB, its use after total gastrectomy should be cautious and under close monitoring. Data are lacking for tenofovir alafenamide post-BS and, therefore, this nucleoside reverse transcriptase inhibitor is not recommended.

5.2 Non-nucleoside Reverse Transcriptase Inhibitors

Published data on nevirapine are limited to one case who underwent SG and showed a C_{trough} of 2545 ng/mL at 12 h post-dosing [87]. This patient was receiving twice-daily nevirapine 200 mg as part of a combination ARV treatment and was virologically suppressed at > 1-year post-SG. Other than the potential disadvantage of undergoing enterohepatic circulation, nevirapine has in theory favourable properties for patients post-BS (Table 4). Once more clinical data are available, nevirapine could be recommended for patients post-BS. However, it is advised to avoid the prolonged-release formulation of nevirapine for patients post-BS as no PK data exist.

Three and six patients who received efavirenz and etravirine, respectively, as part of their ARV regime maintained viral suppression post-SG [24, 50, 81]. Data on patients after RYGB are lacking as well as comparative measurement for drug exposure before and after surgery, making it difficult to draw conclusions from the current literature. Caution is advised with oral rilpivirine, as it relies on gastric acidity for solubility and absorption [88]. In addition, rilpivirine interacts with gastric acid inhibitors [72], although no study compared its exposure pre-BS and post-BS.

Overall, few data are available for non-nucleoside reverse transcriptase inhibitors use post-BS, thus making it difficult to assess whether these agents are suitable for use post-BS. Rilpivirine should be avoided as it has unfavourable pharmacokinetics and restrictions related to intake (Table 4). The novel non-nucleoside reverse transcriptase inhibitor,

doravirine, seems to have favourable drug characteristics, but clinical data post-BS are missing.

5.3 Protease Inhibitors

Darunavir (DRV) is a protease inhibitor that can be boosted either with ritonavir (DRV/r) or cobicistat (DRV/c). Data on DRV/c are limited to one case report showing viral suppression after switching to DRV/c post-SG, with no further PK data [50]. Ten published cases exist for DRV/r post either SG ($n = 8$) or RYGB ($n = 2$). After RYGB, DRV/r has been given twice daily at a dose of 600/100 mg with TDF/emtricitabine [35, 89]. In one case, concentrations of DRV/r experienced a transient reduction after surgery (3 days), while remaining within the therapeutic range (1166 ng/mL), before returning to population plasma concentrations by week 10 and week 48 [35]. The other case showed also a normal plasma concentration at 12 months post-RYGB (2602 ng/mL) [89]. Eight cases in the literature underwent SG and were taking DRV/r 800/100 mg once daily [24, 75, 81]. One case taking DRV/r (plus raltegravir, abacavir and lamivudine) reported a therapeutic plasma concentration of DRV (2270 ng/mL) at 1-month post-SG [75]. The other seven cases reported no PK data ($n = 6$) [81], or undetectable concentrations for DRV or ritonavir 16 hours post dosing ($n = 1$) [24]. Importantly, virological control was reported in all ten cases on DRV-containing regimes regardless of the surgery type or ARV combinations. Noteworthy, DRV should be taken with food to achieve an optimal exposure, which may be challenging for patients with a reduced stomach pouch. However, a small amount of food consumed with darunavir was shown to be sufficient, which should be achievable post-BS [90, 91].

Four studies showed subtherapeutic exposure including some cases with subsequent virologic failure both with ritonavir-boosted or unboosted atazanavir post-BS [24, 76, 81, 85]. A study of 17 PLWH with undetectable VLs who underwent SG showed that 3 months post-SG, the VL of 12 patients remained undetectable while five showed detectable concentrations. Two unsuppressed patients taking ritonavir-boosted atazanavir (ATZ/r) plus abacavir/lamivudine or atazanavir plus raltegravir showed significantly lower C_{trough} post-SG. Subsequently, ARV was changed, and VL became undetectable [81]. Similar results of suboptimal atazanavir/r exposure were reported in a clinical case post-SG period; however, the VL remained undetectable [24]. Furthermore, among 23 virologically suppressed individuals undergoing SG or RYGB, two patients receiving atazanavir-containing therapy showed a detectable VL [76]. Finally, a case series showed that treatment with atazanavir (with raltegravir, emtricitabine and tenofovir) in one patient after gastric banding failed to achieve viral suppression, which was resolved after switching to a dolutegravir-based regime [85]. One explanation is that for atazanavir, dissolution and absorption are highly dependent on low gastric pH, and at neutral pH, the drug is considered to be insoluble [92]. Another explanation for the reduced serum concentrations of atazanavir is its high lipophilicity [80], this factor needs further investigation.

Only two variable cases have been reported for boosted lopinavir after a total gastrectomy with RYGB. In a pregnant patient with HIV who has been gastrectomised 9 years prior, C_{trough} for twice-daily lopinavir and ritonavir (600/100 mg) were within the therapeutic range, thus not requiring dose adjustment [93]. The other patient was taking lopinavir/ritonavir 400/100 mg twice daily and had also a therapeutic concentration (4864/410 ng/mL) 4 months post-surgery [94].

To date, DRV boosted with ritonavir is the most suitable protease inhibitor based on both literature and drug considerations provided food intake is guaranteed. In contrast, atazanavir holds the highest risk for lower absorption, DDI and a subsequent viral failure (Table 5).

5.4 INSTIs

Data on the first-line agent, dolutegravir, seem to favour use post-BS, with few cases suggesting the need for a twice-daily dosing in some patients. A case series showed that 9 months post-BS, viral suppression was maintained in 6/6 patients treated with dolutegravir-containing regimes after SG ($n = 2$), RYGB ($n = 2$) or gastric banding ($n = 2$) [85]. Piso et al. reported that plasma concentrations of dolutegravir were slightly decreased in four subjects directly after RYGB, but remained above therapeutic thresholds [78]. In two patients, dolutegravir dose was temporarily increased to twice daily during the early 2 months and 7 months post-RYGB to overcome a marginal plasma exposure (0.5 mg/L) or slow viral decay, respectively [78]. In the studies above, dolutegravir was combined with either, abacavir/lamivudine or tenofovir/emtricitabine and all patients achieved a durable viral inhibition [78, 85].

However, dolutegravir may be sensitive to a high pH environment post-BS. Given that it is a weak acid (pKa = 8.2), elevated pH in the GI after surgery may increase dolutegravir ionisation [95]. Thus, dolutegravir solubility in the stomach fluids could increase and consequently its absorption. This hypothesis could explain the outcome of a recent case report in which C_{trough} of abacavir, lamivudine and dolutegravir were elevated at week 6 post-BS (103, 161 and 2374 ng/mL, respectively) compared with those measured 1-month pre-SG (8.7, 60 and 919 ng/mL, respectively) [84]. In addition to the potential effect of increased pH, the authors suggest other possible mechanisms for the elevated concentrations post-SG, including alterations in gut microbiota and reduced

glucuronidation of abacavir and dolutegravir. However, this assumption requires further evaluation, as PK studies showed no major interaction between dolutegravir and PPIs [62].

The same study investigated the effect of crushing abacavir/dolutegravir/lamivudine tablet on plasma exposure post-SG and found no substantial effect on abacavir and lamivudine concentrations, but a modest increase in dolutegravir exposure [84]. A similar effect on dolutegravir exposure (AUC from zero to infinity: +26% and C_{max}: +30%) and approximately no change in lamivudine and abacavir concentrations after crushing abacavir/dolutegravir/lamivudine tablets were detected in an open-label randomised trial on 22 healthy volunteers [96]. However, higher dolutegravir concentrations after crushing did not exceed those after a three times-daily intake or intake in a fed state and were judged acceptable by the authors.

For raltegravir, Amouyal et al. demonstrated that in PLWH, SG may impair the absorption of raltegravir resulting in viral rebound in some cases [81]. Seven patients were treated with a raltegravir-containing regime, in whom three showed detectable VL 3 months post-SG, and four remained virally suppressed. The virologic failure was accompanied with a significant reduction in raltegravir plasma exposure. The authors hypothesised that virologic failure is driven by concomitant use of calcium after the surgery. However, one-third of patients with a detectable VL was taking atazanavir/raltegravir and became virologically suppressed after switching to etravirine/raltegravir [81]. These data suggest that treatment with raltegravir, particularly combined with atazanavir, may increase the risk of virologic failure.

Several mechanisms may contribute to the impaired absorption of raltegravir post-BS. An in vitro study indicated that as pH increases, a charge is introduced at the active site of raltegravir preventing the drug from penetrating across the phospholipid bilayer of the cell membrane [47]. This mechanism is plausible, as gastric pH is increased after RYGB. Additionally, Roberts et al. reported PLWH taking raltegravir with no detectable VL for 10 months who demonstrated detectable VL 1 month after coadministration of calcium carbonate 1 g plus vitamin D_3 three times a day to prevent osteoporosis [97]. The HIV-1 phenotype showed resistance to raltegravir and emtricitabine. After switching to abacavir, lamivudine, tenofovir and ritonavir-boosted atazanavir, the VL became rapidly undetectable. Considering that raltegravir resistance is rare in naïve patients and that compliance was good in this case, the authors suggested that viral rebound was likely due to the interaction with calcium, and the subsequent subtherapeutic exposure to raltegravir [97]. Thus, raltegravir poses several challenges and risks for PLWH post-BS. A comprehensive analysis of raltegravir exposure and virologic response post-BS is essential to determine its suitability in this special population.

Use of elvitegravir boosted with cobicistat (plus emtricitabine and tenofovir) is limited to one case post-SG with no PK data [50]. Similarly, data on the use of bictegravir post-BS are lacking. Thus, both agents are not recommended post-BS (Table 6).

Amongst INSTIs, dolutegravir is the most suitable agent for use post-BS, particularly if separated from polyvalent-containing agents. Close monitoring of drug exposure is still warranted.

5.5 Boosters

Outcomes of PK boosters (ritonavir, cobicistat) post-BS are variable and seem dependent on the boosted drug. Data on the use of the newer booster, cobicistat, in the settings of BS are limited to two patients where cobicistat was combined with darunavir or elvitegravir with no reported viral rebound [50]. Plasma concentrations of cobicistat were not measured in this study. Currently, more data are available to support the use of ritonavir, rather than cobicistat, post-BS (Table 5).

6 Successful ARV Candidates Post-BS

When evaluating available literature on BS outcomes among PLWH, comprehensive PK data are limited with a large variability in the type of BS, type of ARV used and timing after ARV measurements post-BS. Not surprisingly, conflicting data have been reported, making it difficult to draw reliable recommendations for some ARV drugs. HIV-related guidelines such as the HIV/AIDS Treatment Guidelines (Department of Health and Human Services) and the European AIDS Clinical Society do not include "obesity" or "bariatric surgery" conditions when discussing the selection (and dosing) of ARVs. This makes it difficult for physicians to determine the best ARV treatment options for their patients. As such, a theoretical framework for evaluating the impact of BS on ARV outcomes combined with an interpretation of the limited clinical data may represent the best strategy. Here, we present such an integrated analysis Tables 3, 4, 5 and 6.

Based on drug aspects discussed here, a favourable PK profile of any ARV candidate post-BS should in theory fulfil many criteria, including; (1) Favourable absorption conditions (i.e. no dependency of [fat] food or low gastric pH); (2) Absorption site past stomach and duodenum; (3) Hydrophilic drug (low lipophilicity); (4) No major first-pass metabolism; (5) No interaction with divalent-containing supplements or antacids; (6) Availability of alternative formulations (i.e. liquid, crushed and immediate-release formulations); and 7. Therapeutic drug monitoring protocols and validated methods are available for individualised treatment. However, predicting pharmacokinetics

based on drug properties proved to be challenging owing to the complexity of BS and individual drug properties [98]. Monitoring ARV exposure and activity is crucial in this population.

Based on the criteria above and the availability of supporting clinical data, the following agents could be recommended: abacavir, emtricitabine, lamivudine, TDF, ritonavir-boosted darunavir and dolutegravir. Despite this recommendation, patients should be informed that some instructions remain crucial, such as food intake with darunavir and separated intake of cations with dolutegravir.

Another promising agent is doravirine. This drug meets several preferred PK properties (# 1,2,4,5,7) while another (#6) could be easily investigated. In addition, doravirine is marketed as a co-formulated regime with TDF/lamivudine, which are among the preferred nucleoside reverse transcriptase inhibitor backbones as discussed above. Finally, doravirine has been demonstrated to be an effective switch regime in the DRIVE-SHIFT trial, where patients were virally suppressed on various regimes for > 6 months [99]. Normally, patients who are candidates for BS are also required to be virally suppressed. However, candidates for BS or subjects who underwent BS were most likely not represented in the DRIVE-SHIFT trial. Clinical trials on the pharmacokinetics, safety and efficacy of doravirine post-BS are warranted.

Recently, long-acting injectable ARV therapy containing rilpivirine and cabotegravir has been demonstrated to be non-inferior to oral ARV therapy and was approved for use in Europe and USA. Being administered directly to the systemic circulation, long-acting injectable ARV therapy may solve many absorption and bioavailability challenges post-BS [100]. However, multi-level barriers slow down the large-scale implementation of long-acting ART. Issues from a provider perspective (i.e. staff capacity and training, clinic capacity, cold chain), a patient's perspective (i.e. injection tolerability, adherence to visits) and a pharmacological perspective (extended DDI, missed doses, pharmacokinetic "tail") are all pressing needs to be met [101]. Additionally, the high BMI at the initial period post-BS may negatively affect the C_{trough} of long-acting cabotegravir as seen in phase IIa trials [102], although the effect was not persistent until week 48 [103]. Taken together, long-acting ART is an interesting domain for investigation and, when optimised, could provide a valuable alternative for BS candidates.

7 Discussion and Future Perspectives

An accurate extrapolation of dosing recommendations is difficult owing to the multifactorial physiological changes post-BS. As such, therapeutic drug monitoring should be performed during the early post-BS phase. An optimal therapeutic drug monitoring protocol should include a baseline level (pre-BS) and at least one short-term (1–6 weeks) and one long-term (3–6 months) post-BS ARV drug measurement. Measuring both C_{trough} and maximum drug concentrations is beneficial to detect alterations during absorption and elimination phases, and to define the appropriate drug exposure. As BS candidates are indicated for multiple follow-up visits and laboratory tests after the surgery (e.g. vitamin deficiency tests), therapeutic drug monitoring sampling could be easily implemented in their routine blood analysis.

Overall, the performance of bariatric interventions in the HIV population has not been investigated in large-scale or randomised clinical trials. In this population, assessing the safety and efficacy of this surgery requires considering the obesity and the HIV outcomes in parallel. Factors including excess body weight, remission of comorbidities as well as CD4 counts, VL and ARV exposure are all essential parameters to monitor [26]. Other individual factors may influence the outcome of the surgery, including technical skills of the surgery centres [104], the patients characteristics [30] and the willingness to change a lifestyle after surgery [105]. All these factors are difficult to standardise or to anticipate.

Recently, alterations in gut microbiota post-BS have been shown to be instant, perpetual and independent of surgery [107]. A possible influence of alterations in the gut microbiome on ARV pharmacokinetics has been suggested for abacavir and dolutegravir. Both drugs are inactivated by uridine 5′-diphospho-glucuronosyltransferase, forming glucuronide conjugates, a procedure that could be reversed via ß-glucuronidase enzymes. Several species of bacteria are ß-glucuronidases producers, such as *Bacteroides* sp. and *Escherichia coli,* whose abundance increase post-BS [108]. Increasing levels of ß-glucuronidase enzymes in the gut environment could regenerate the active forms and increase exposure concentrations of the two drugs [109]. However, such assumptions should be interpreted carefully as the gut microbiome is influenced by diet, antibiotics and demographic parameters. With such limitations, the translation of these assumptions into pharmacological or clinical decisions is not yet feasible.

The literature compilation for this review was initially conducted as a systematic review. However, because of limited data collected via the automated search, a manual search provided most of the reported literature. Therefore, this review is probably limited by the publication bias and the possibility of missing relevant reports. Other less common bariatric procedures, such as gastric banding and jejunoileal bypass, were not extensively discussed here, but might be still performed in some clinical centres.

To our knowledge, this is the first review to discuss the potential mechanisms responsible for PK changes of ARVs after BS together with a panel of clinical recommendations. This work highlights many areas for future investigations and identifies gaps to be addressed in order to optimise ARV treatment in this special patient population.

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