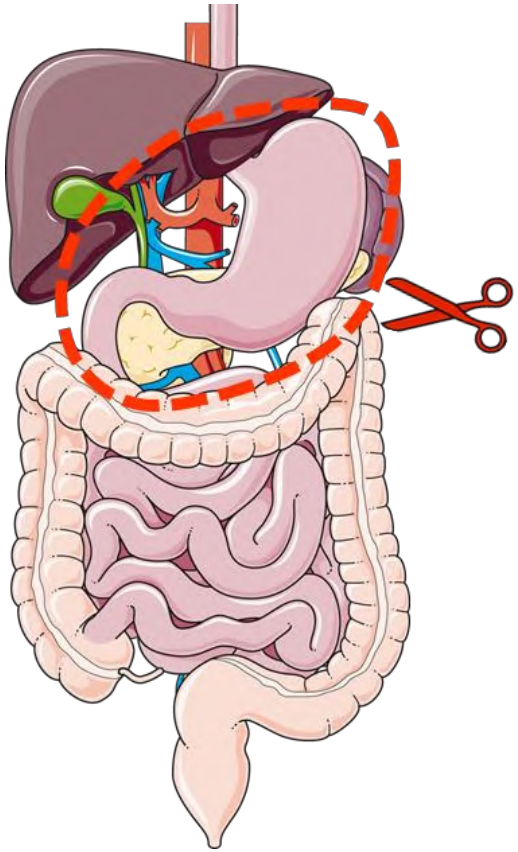
Effect of Gastrointestinal Surgery on ARV Absorption

Bariatric Surgery



Adapted from: www.smart.servier.com

Note: Gastrointestinal surgery does not affect the absorption of ARVs administered intramuscularly (e.g., cabotegravir/rilpivirine), subcutaneously (e.g., enfuvirtide, lenacapavir), vaginally (e.g., dapivirine), or by infusion (e.g., albuvirtide, ibalizumab).

Potential Key Changes after Bariatric Surgery

	Sleeve Gastrectomy	*Roux-en-Y Gastric Bypass*
Gastric motility	Likely impaired	Likely impaired
Gastric volume	Decreased	Decreased
Gastric pH	Increased	Increased
Surface area	No change or possible decrease	Decreased contact with stomach and intestinal surface
First pass metabolism	Not affected	Potentially reduced since proximal small intestine has high CYP3A4. Also bypass some transporter activity.

Site of Absorption of ARVs and Relevant DDIs after Bariatric Surgery

ARV	*Site of Absorption*	*AUC (fasting vs fed)*	*Relevant DDIs Post-surgery*
Abacavir	Duodenum		
Atazanavir	Small intestine	↓ 33%	PPI (contraindicated); Antacid/H2RA (caution)
Bictegravir	Unknown	↑ 24%	Divalent cations (separate administration)
Darunavir	Small intestine	↓ 30% (bioavailability)	
Dolutegravir	Proximal small intestine	↓ 66% (*cf* high fat meal)	Divalent cations (separate administration)
Etravirine	Unknown	↓ 50%	
Emtricitabine	Likely duodenum		
Lamivudine	Duodenum, jejunum		
Lopinavir	Jejunum		
Raltegravir	Ileum		Divalent cations (separate administration)
Rilpivirine	Unknown	↓ 40%	PPI (contraindicated); Antacid/H2RA (caution)
Ritonavir	Unknown		
Tenofovir-DF	Likely duodenum	↓ 40%	

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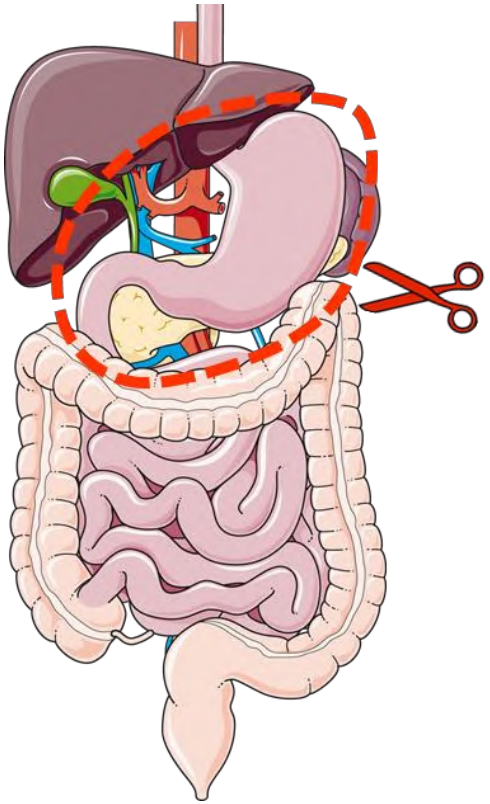

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Pharmacokinetics of ARVs following Bariatric Surgery

Antiretroviral	*Sleeve Gastrectomy*	*Roux-en-Y Gastric Bypass*
Abacavir (ABC)	↔[1]	
Atazanavir (ATV)	↓[1], ↓[2], ↓[3]	
Bictegravir (BIC)		↓ (2 months)[4]
Darunavir (DRV)	↔[2]	↓ (3 days)[5], ↔ (10 weeks)[5], ↔[6]
Dolutegravir (DTG)		↔ (3 patients)[7], ↓ (1 patient)[7], ↔[2]
Emtricitabine (FTC)	↔[1], ↔[8], ↔[2]	↑ (2 months)[4]↓ (3 days)[5], ↔ (10 weeks)[5], ↔[6], ↓[9]
Etravirine (ETR)	↔[3]	
Lamivudine (3TC)	↔[1]	↔[10], ↓[11]
Lopinavir (LPV)		↓[11], ↔[12]
Raltegravir (RAL)	↓[1], ↔[2]	
Ritonavir (RTV)	↔[1],	↓ (3 days)[5], ↑ (10 weeks)[5], ↓[6], ↔[12]
Tenofovir alafenamide (TAF)		↑ (2 months)[4]
Tenofovir-DF (TDF)*	↔[1], ↓[8], ↓[13]	↔[5], ↓[6], ↓[9]

** Individuals receiving TDF for PrEP (i.e. uninfected) had decreased tenofovir exposure.*

Conclusions

- Data limited to individual case reports or case series.
- Timing of sample collection post-surgery varies.
- Pharmacokinetics are more likely to be altered in the early stage post-surgery.
- Following sleeve gastrectomy, decreased exposure of ATV, RAL and possibly TDF (data from one study).
- Following Roux-en-Y gastric bypass surgery, data are highly variable and in part related to time of study post-surgery. Evidence of decreased exposure of BIC, DRV, DTG, FTC, 3TC, LPV, RTV, TDF.
- TDM (if available) will help to guide dosing.

Recommendations

Antiretroviral	*Prescribing Recommendation*
Atazanavir; Rilpivirine	Avoid due to impaired absorption as a result of increased gastric pH
Integrase Inhibitors	Separate administration from mineral supplements
Dolutegravir; Etravirine; Tenofovir-DF	Exposure reduced in fasted condition, administer with food
Dolutegravir (DTG)	Consider DTG 50 mg twice daily in the early phase post-surgery. Determine maintenance dose by performing TDM (where feasible).
Darunavir/ritonavir (DRV/r)	Consider DRV/r 600 mg twice daily in the early phase post-surgery. Determine maintenance dose by performing TDM (where feasible).

References

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3. Fysekidis M *et al.* Obes Surg 2015; 25(2): 229-233.
4. Tempestilli M et al. J Antimicrob Chemother 2021; 76(12):3320-3322.
5. Baettig V *et al.* AIDS 2018; 32(13): 1903-1905.
6. MacBrayne C *et al.* Ann Pharmacother 2014; 48(6): 816-819.
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10. Razonable R *et al.* 14th Int AIDS Conf, Barcelona, 2002; B10386.
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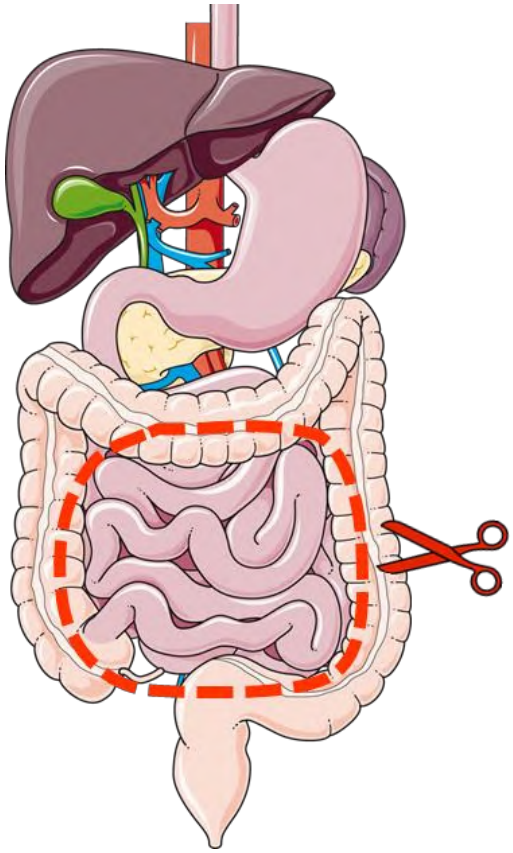
Effect of Gastrointestinal Surgery on ARV Absorption

Small Bowel Resection



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Potential Key Changes after Small Bowel Resection Surgery (and Pancreaticoduodenectomy)

Absorption	Impact on absorption will depend on the amount of bowel removed.
Intestinal transit	Likely more rapid – i.e. less time for absorption
Bile salt absorption	Disrupted and can lead to choleretic diarrhoea and decreased absorption of some drugs
Fat absorption	Disrupted leading to malabsorption of some drugs
Bacterial overgrowth	Possible effect on absorption?
Additional medications	Possible effect on absorption?

Pharmacokinetics of ARVs Following Small Bowel Resection

Antiretroviral (via NG tube)	*Pharmacokinetic change described in case report**
Darunavir	Peak plasma concentration within normal range but rapidly eliminated
Etravirine	Markedly decreased plasma concentrations
Lopinavir	Markedly decreased plasma concentrations
Maraviroc	Plasma concentrations within normal range
Raltegravir	Decreased plasma concentrations.
Ritonavir	Markedly decreased plasma concentrations

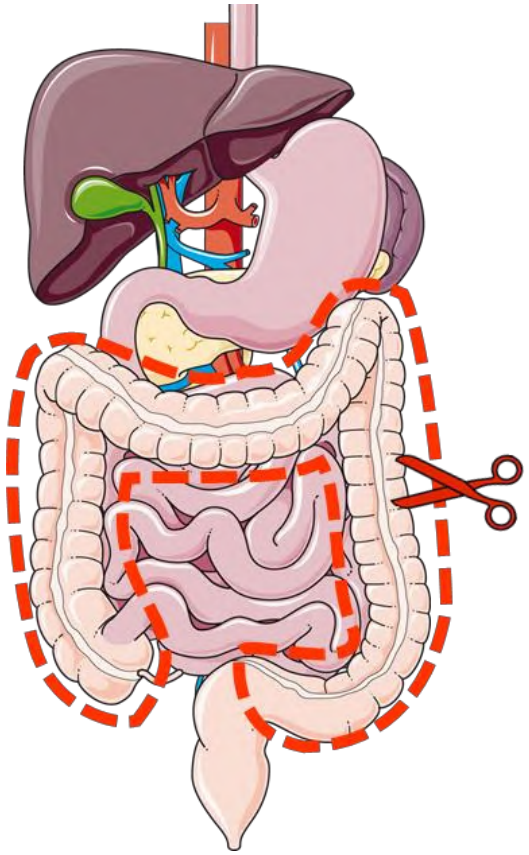
** Ikuma M et al. Intern Med 2016; 55(20):3059-3063.*

Conclusions

- Limited data (case report) but evidence of decreased exposure of most ARVs studied.
- TDM (if available) will help to guide dosing.

Effect of Gastrointestinal Surgery on ARV Absorption

Colonic Resection



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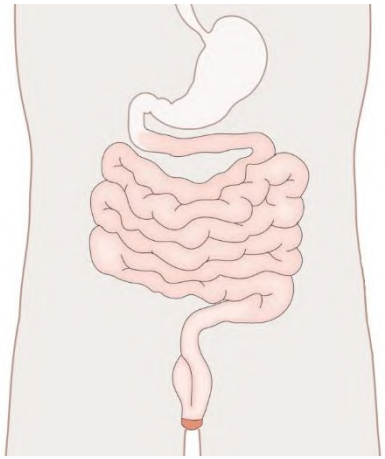
Potential Key Changes After Colonic Resection

	Part Removal	*Total Colectomy*
Absorptive Capacity	Little change	Absorptive site for some drugs is removed. No evidence that this impacts ARVs.
Enterohepatic recycling (EHC)	Probably little change	Lack of EHC may impact drugs undergoing extensive hepatic conjugation and biliary excretion, e.g., raltegravir.

Effect on Local Delivery of PrEP

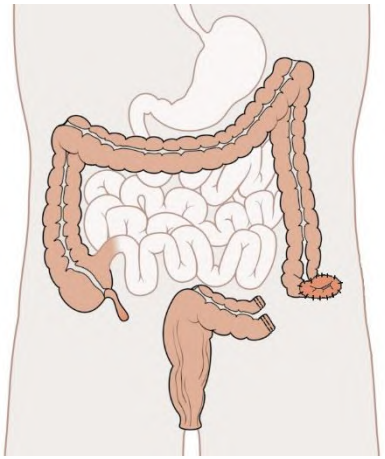
Ileoanal Anastomosis

No effect – pouch functions as new rectum



Colostomy/Ileostomy

No delivery to the rectal stump



Conclusions

- Impact on absorption of ARVs likely to be limited
- No local delivery of oral PrEP (FTC/TDF) to the rectal stump following colostomy/ileostomy. Daily PrEP, rather than event-driven PrEP, is recommended.