

# Long-acting Cabotegravir/Rilpivirine after Bariatric Surgery. A good idea in theory.....

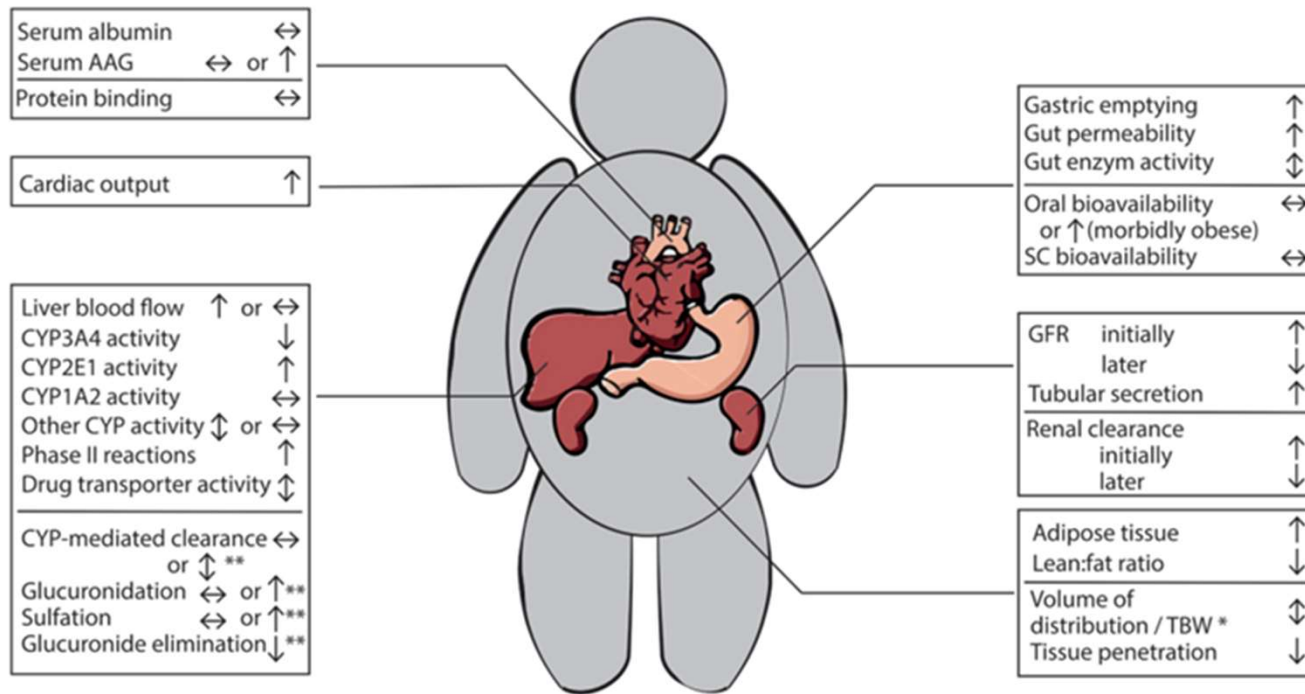
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# Introduction

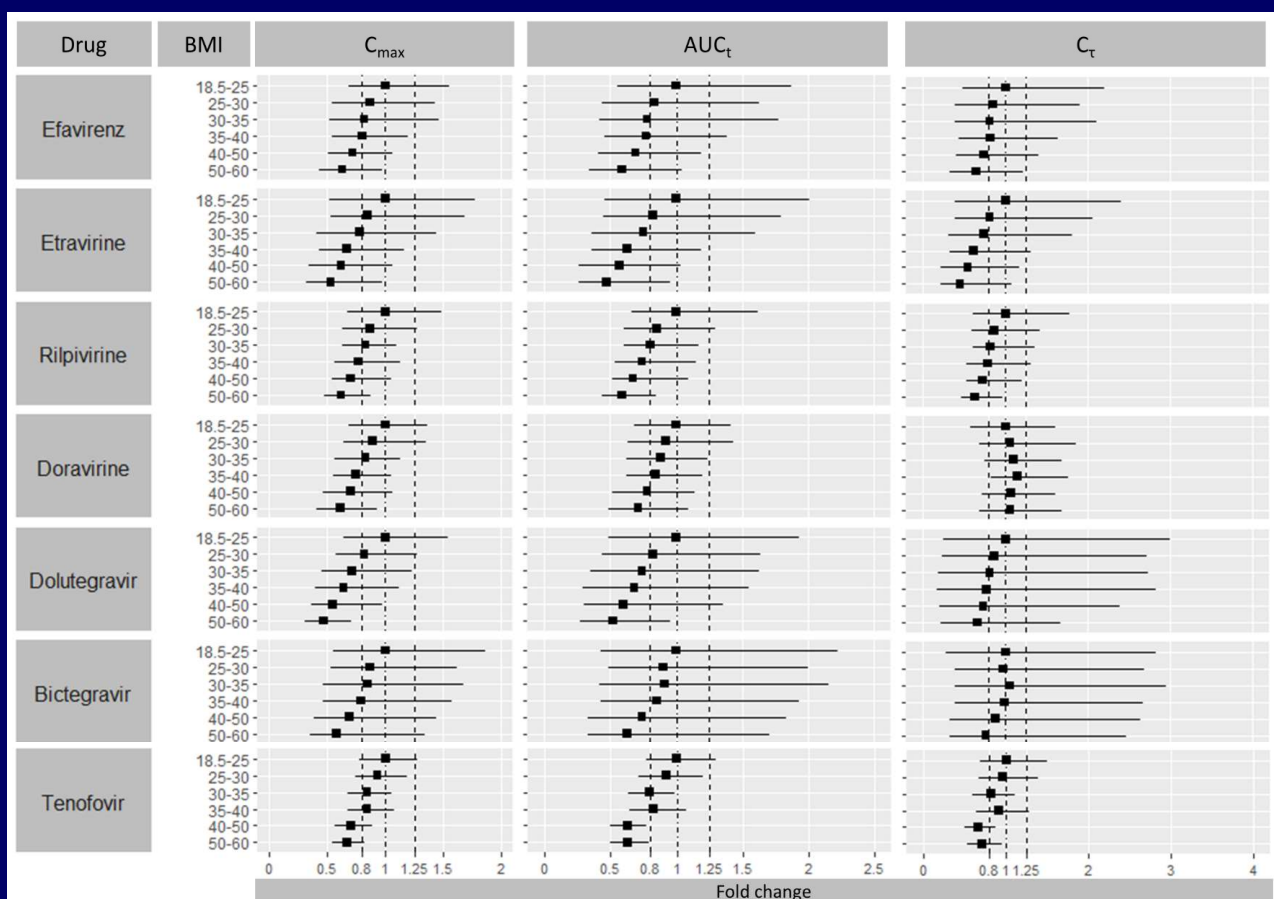
- Increasing rates of obesity in people with HIV
- Aging population
- Side effect of newer ARVs (INSTIs, TAF)
- Antiretroviral PK can be influenced by both weight & bariatric surgery
- Bariatric surgery is emerging as an effective treatment option for obesity

# Impact of Obesity on Drug Dispostion



# Reduced exposure of ARVs as BMI increases

Effect of obesity on PK parameters of selected antiretrovirals:



Data are expressed as geometric mean and 5<sup>th</sup> and 95<sup>th</sup> percentile.

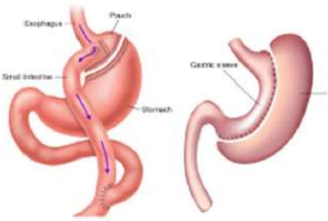
- Our simulations showed that obesity reduces the exposure of all investigated ARVs.
- Greatest decreases with etravirine, lowest change with doravirine
- C<sub>t</sub>rough less impacted due to greater redistribution of drug from the tissue into the bloodstream.

Berton M et al., Clinical Infectious Diseases [epub ahead of print].  
Slide courtesy of M. Berton.

# % of virtual obese individuals with C<sub>T</sub> levels below the clinical target concentration threshold

	Darunavir / ritonavir	Efavirenz	Etravirine	Rilpivirine	Doravirine	Dolutegravir	Bictegravir	Raltegravir
Target threshold (ng/mL)	550	700	300	50	230	300	760	20
BMI 18.5-25 kg/m <sup>2</sup>	10	1	<b>21</b>	<b>4</b>	19	9	8	0
BMI 25-30 kg/m <sup>2</sup>	0	4	41	6	18	9	3	0
BMI 30-35 kg/m <sup>2</sup>	0	3	38	4	8	15	3	0
BMI 35-40 kg/m <sup>2</sup>	3	3	54	11	2	15	4	0
BMI 40-50 kg/m <sup>2</sup>	1	4	<b>58</b>	<b>24</b>	12	14	7	0
BMI 50-60 kg/m <sup>2</sup>	0	9	<b>72</b>	<b>45</b>	11	13	6	0

- Predicted % of virtual obese individuals with C<sub>T</sub> levels below the clinical target concentration threshold were similar to those observed in the SHCS data.
- Etravirine and rilpivirine present the highest risk of suboptimal exposure in individuals with BMI > 40 kg/m<sup>2</sup>.



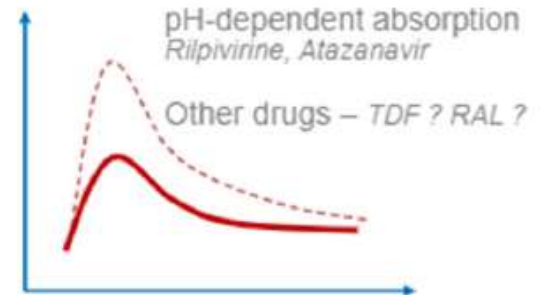
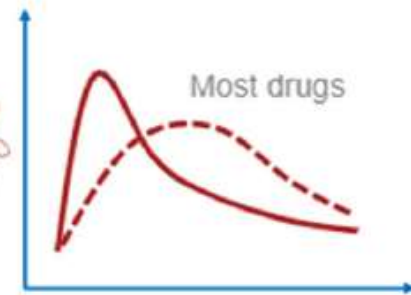
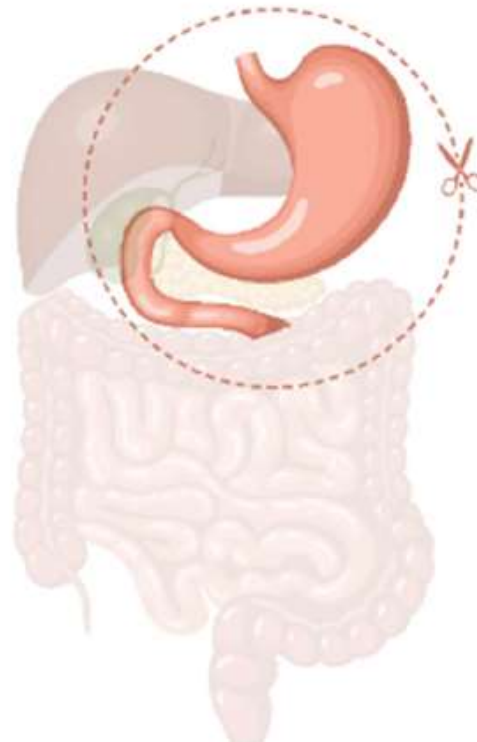
Roux-en-Y  
Gastric Bypass

Sleeve  
Gastrectomy

# Gastric Surgery: influence on drug PK

## Gastrectomy

- Many ARVs absorbed in the stomach onwards
- Plenty of redundancy in absorptive mucosa
- Delayed peak ( $T_{max}$ )
- Issue with pH-dependent absorption



## Impact of Bariatric Surgery on ARVs

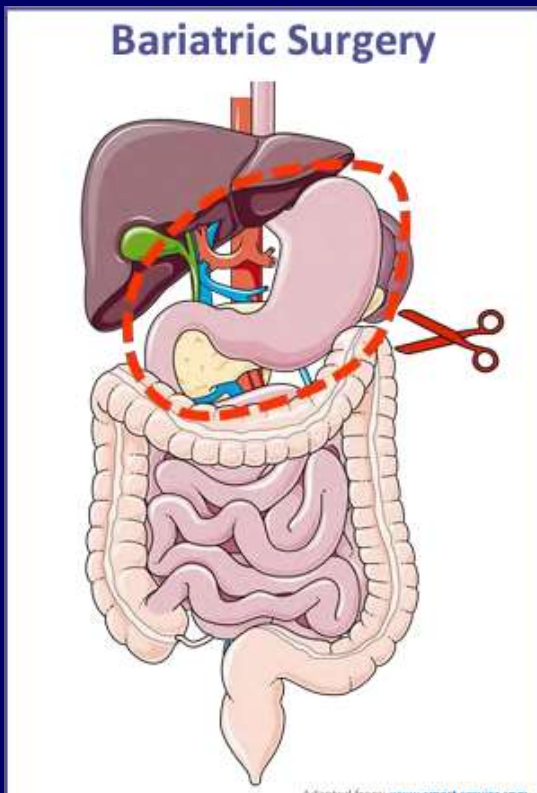
Drug	Description	Operation	PK effect
TDF	Case report	RYGB	↔
	Series (N=8)	SG	↔
	Series (N=4)	SG	Transient/reversible TFV ↓
	Series (PreP; N=4)	SG, others	TFV Ctrough ↓
TAF	No Data		
3TC	Case	SG	No PK
	Case	SG	↑ PK post op
	Case (pregnant)	SG	↓ PK (pregnant reference)
ABC	Case	SG	↑ PK post op
	Series (N=2)	SG	↔

Drug	Description	Operation	PK effect
DRVr	Case (bd)	RYGB	↔
	Case (bd)	RYGB	Transient ↓ (in therapeutic range)
	Case (od)	SG	Therapeutic range
	Series (od; N=7)	SG	No PK (6), undetectable (1)
DRVc	Case	SG	No PK
ATV(r)	Series (4; 3 boosted)	SG	Unboosted ↓ PK pre, ↓↓ PK, 2 failures
	Case	SG	(NB: RTV in normal range)
	Series	SG/RYGB	↓ PK
	Series	banding	2 ATV failures 1 ATV failure

Drug	Description	Operation	PK effect
EFV	3	SG	
NVP	Case	SG	↔
ETR	6	SG	
RPV	No Data		↓ PK likely - AVOID
DOR	No Data		

Drug	Description	Operation	PK effect
DTG (od)	Series (N=6)	SG/RYGB/banding (2 each)	All suppressed
	Series (N=4)	RYGB	(↓) PK (in therapeutic range)
	Case	SG	↑ PK post op
RTG	Series (N=7)	SG	↓ PK in 3/7 V failures
EVG	Case	SG	No PK

# Effect of Bariatric Surgery on ARV absorption



- PK changes after sleeve gastrectomy or gastric bypass
  - ↓ gastric motility, volume, ↑ pH, possible ↓1<sup>st</sup> pass effect
  - Avoid atazanavir, oral rilpivirine
- ↓ ARV exposures reported (esp early post-surgery)
  - Consider temporary ↑ ARV dose and/or TDM
- PrEP: ↓ tenofovir
  - some suggestions to double TDF/F for 1<sup>st</sup> month
  - Use daily vs. event-driven PreP
- Role of LA-CAB/RPV (or IM CAB) for treatment/PreP????



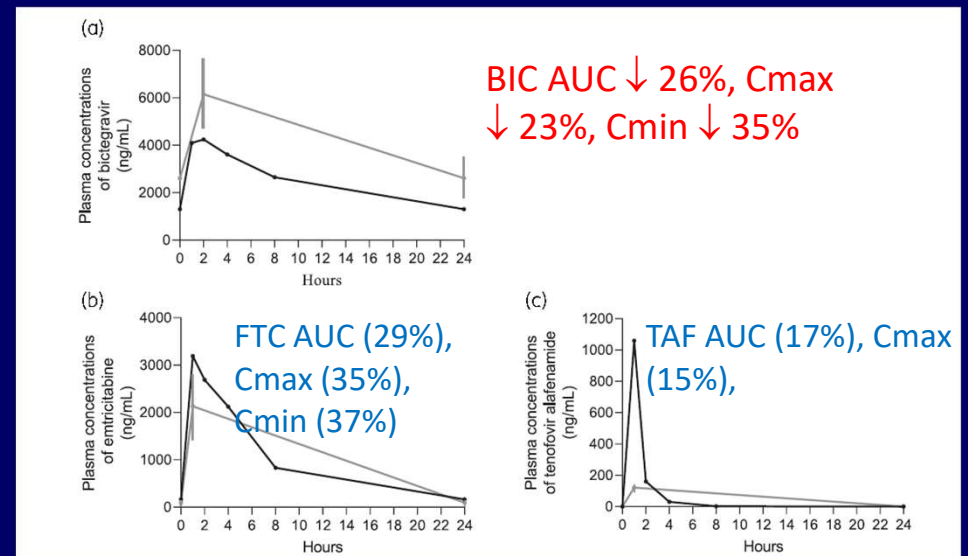
## Additional considerations for oral ARVs post-bariatric surgery

Issue	Post-surgery	ARVs impacted
Food requirements	Limited intake	Rilpivirine, PIs
Tablet size	Often preference for liquids	Often limited information on crushing ARVs; volume of liquid formulations
Drug interactions	Gastric acid reducing agents	Atazanavir, rilpivirine
	Cations, supplements	INSTIs

# Bictegravir/tenofovir alafenamide/emtricitabine in bariatric surgery

- 2 case reports:
  - 56 yo Caucasian female [wt 92.9 kg] post sleeve gastrectomy, required BID multivitamins and calcium supplements. Remained virologically suppressed by introducing adequate spacing.
  - 64 yo Caucasian female [wt not indicated] post gastrectomy with Roux-en-Y reconstruction. Bictegravir PK decreased 2 months post surgery, remained virally suppressed.

- Reduced exposures of BIC post-surgery:



# How about using LA-cabotegravir-rilpivirine post-bariatric surgery?

## Benefits

- Bypasses GI tract: no DDIs with oral medications or food requirements
- Not reliant on the gut for absorption post-surgery
- No manipulation of formulation required
- Dosed bi-monthly
- Decrease stigma and pill fatigue

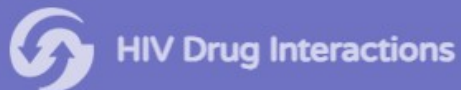
## Potential drawbacks

- No data in clinical trials of patients with BMI  $\geq 30$  kg/m<sup>2</sup> (range BMI 30-54 kg/m<sup>2</sup>)
- High BMI was identified as risk factor for virologic failure
- Longer needles difficult to source
- Window for injection is  $\pm 7$  days from due date, reliable clinic appointment attendance is key
  
- NB: skip oral lead-in to avoid DDIs post surgery

# Predictors of HIV-1 Virologic Failure to Long-acting Cabotegravir/Rilpivirine

- Week 152 data - pooled analysis of FLAIR/ATLAS/ATLAS-2M
  - N=1651; 1.4% had confirmed virologic failure (CVF)
- $\geq 2$  baseline factors associated with increased risk of CVF:
  - RPV RAMS
  - HIV-1 subtype A6/A1
  - BMI  $\geq 30$  kg/m<sup>2</sup>
- Lower CAB Ct<sub>trough</sub><sub>week4</sub> and CAB & RPV Ct<sub>trough</sub><sub>week44</sub> ( $\leq 1^{\text{st}}$  quartile) significant as additional factors, but did not improve prediction of CVF beyond  $\geq 2$  baseline factors

# Questions? Resources



- [www.hiv-druginteractions.org/prescribing-resources/hiv-guidance-gastric-surgery](http://www.hiv-druginteractions.org/prescribing-resources/hiv-guidance-gastric-surgery)
- Zino et al. Clin Pharmacokinet 2022;61:619-35
- Role of TDM to guide dosing?

A screenshot of the HIV/HCV Drug Therapy Guide website. The header shows the logo with a red ribbon and the text "HIV//HCV DRUG THERAPY GUIDE". Below the header, it identifies the drug as "BICTEGRAVIR (BIKTARVY®) HIV INTEGRASE INHIBITOR". A "PROPERTIES MENU SHOW ALL" section lists various drug properties. Two pink arrows point to the "INFORMATION ON CRUSHING/LIQUIDS:" and "ABSORPTION: IMPACT OF BARIATRIC SURGERY:" entries.

**HIV//HCV**  
DRUG THERAPY GUIDE

**BICTEGRAVIR (BIKTARVY®) HIV INTEGRASE INHIBITOR**

PROPERTIES MENU SHOW ALL

OTHER DRUG NAME(S):

PHARMACOLOGY / MECHANISM OF ACTION:  
ACTIVITY:

DOSAGE FORMS:

INFORMATION ON CRUSHING/LIQUIDS: ←

DOSING:  
ADULT:  
PEDIATRIC:  
SPECIAL INSTRUCTIONS FOR PEDIATRIC PATIENTS:  
GERIATRICS:  
ADJUST IN RENAL DYSFUNCTION:  
ADJUST IN LIVER DYSFUNCTION:

ABSORPTION: EFFECT OF FOOD:

ABSORPTION: IMPACT OF BARIATRIC SURGERY: ←

- <https://hivclinic.ca/app/>