Session 4: HIV Prevention and Cure

Clinical Case: Potential Challenges of Drug Interactions of Long-Acting Agents

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Clinical case:
Potential challenges of drug interactions of long-acting agents

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Global HIV Clinical Forum 2020

Case presentation

- Adrian 29 year-old MSM
- Multiple male sexual partners per month, condom use inconsistent
- BMI: 28 kg/m^2
- Currently on PrEP with TDF/FTC
- Last control: HIV antigen/antibody negative, HBsAg negative,
- eGFR 90 mL/min/1.73 m^2
- Chemsex (ecstasy, methamphetamine)
- Medications: occasionally antacids, St John’s Wort (mild depression)

Case presentation

- Adrian heard that Cabotegravir is more efficient than TDF/FTC to prevent HIV infection
- Would Cabotegravir PrEP be suitable for Adrian?

Press release on May 2020

Global HIV Prevention Study Ends Early After Injectable Cabotegravir Shows High Efficacy

HPTN 083
an HIV prevention clinical trial

Study population: MSM and transgender women at high risk for HIV acquisition (n = 4570).

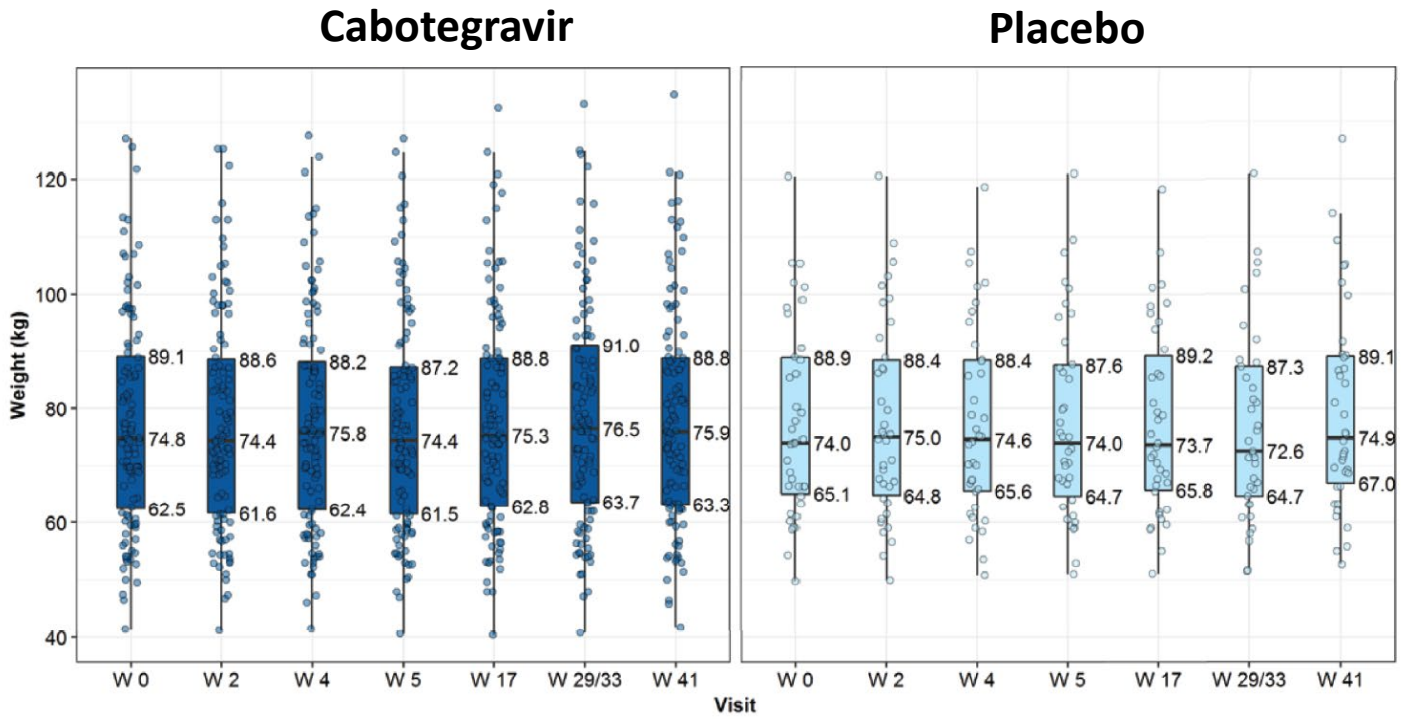
Randomized, double-blind study comparing:
- cabotegravir **600 mg** im every 8 weeks
- TDF/FTC 245/300 mg oral once daily

Results:
- overall 50 incident HIV infections (incidence 0.79%)
- 38 infections with TDF/FTC (incidence **1.21%**)
- 12 infections with cabotegravir (incidence **0.38%**)

Cabotegravir and weight gain

Evaluation of weight gain in HPTN077

Population (n = 177): median age: 31.5 years; 66% female; median BMI: 26.6 kg/m^2 (IQR: 23.4-32.7)



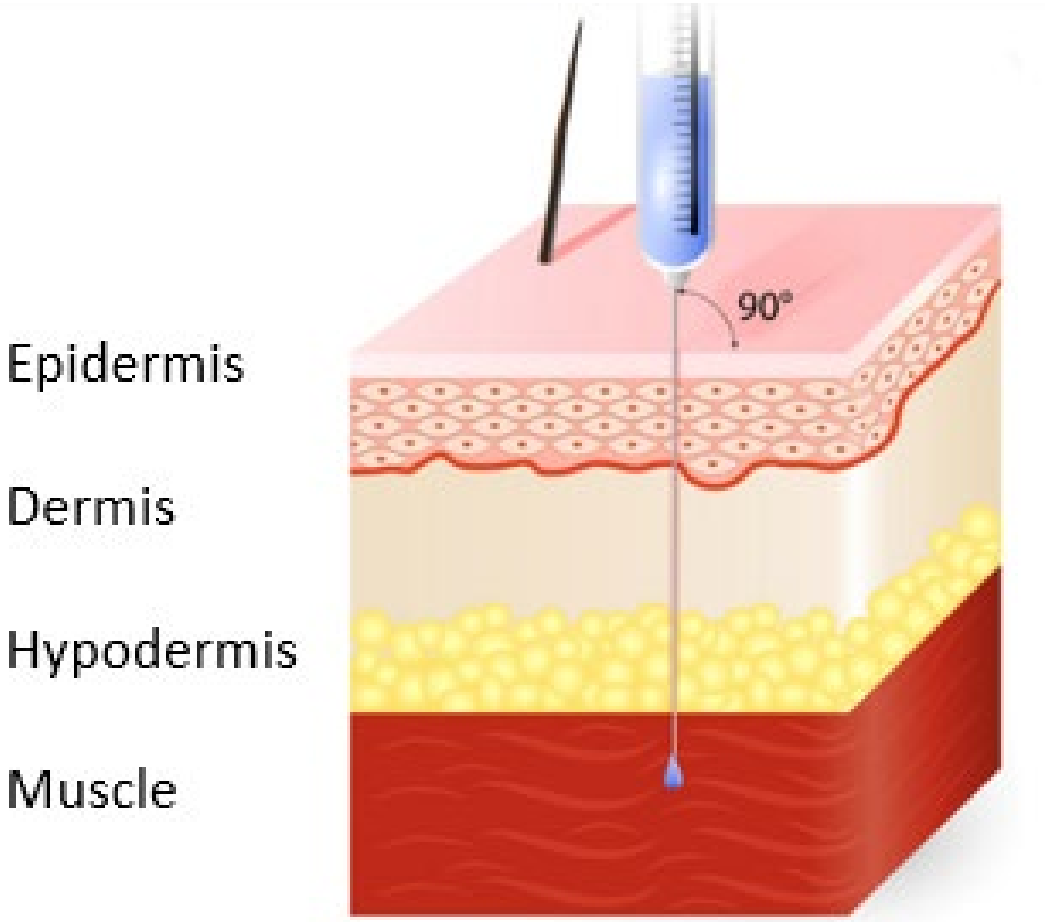
from W0 to W41: + 1.1 kg

from W0 to W41: + 1.0 kg

No differences in weight gain between cabotegravir and placebo arms.
No differences among ethnic groups or sex.

Landovitz R et al. Clin Infect Dis 2020

Obesity and drug delivery in the muscle



- Cabotegravir injection performed in gluteal muscle.
- Muscle has rich vascular supply favoring drug absorption.
- Subcutaneous adipose tissue has less vascular supply which may result in less drug absorption.
- Injection technique is critical to ensure drug is not deposited in subcutaneous adipose tissue.
- Cabenuva label indicates that longer needle lengths may be required for patients with higher BMI to ensure that drug is delivered im.

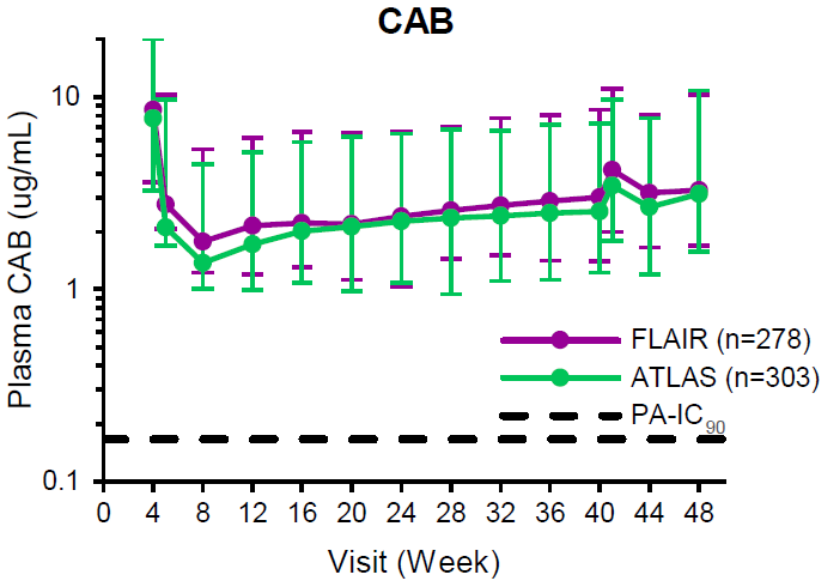
Cabenuva Canadian product monograph March 2020

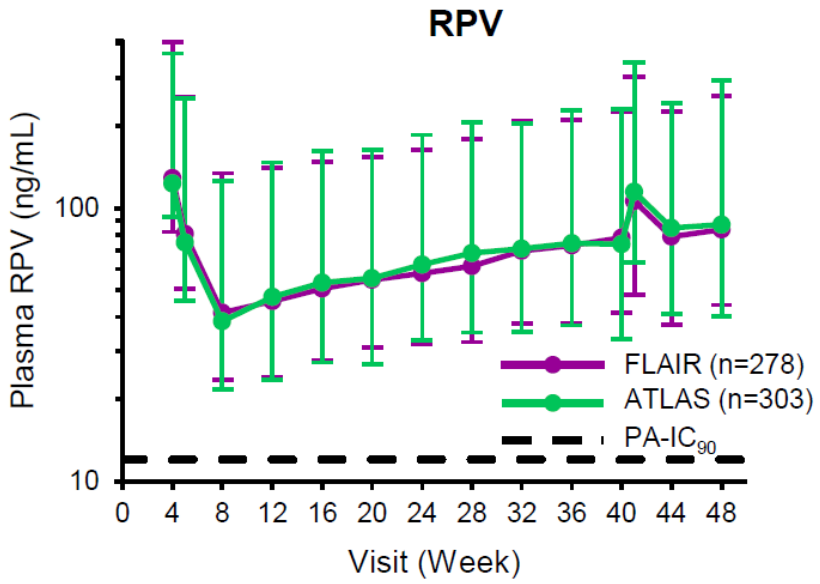
Cabotegravir and rilpivirine plasma levels

Median (5th and 95th percentile) plasma CAB and RPV trough levels over time

Oral lead-in: CAB/RPV 30/25 mg QD for 4 weeks
Initial im dose: CAB/RPV **600**/900 mg im at week 4
Maintenance im dose: CAB/RPV 400/600 mg im from week 8 and every 4 weeks thereafter

	FLAIR	ATLAS
Median BMI:	24.1 (17.3-44.9)	25.5 (15.3-50.9)
Proportion female:	22%	33%



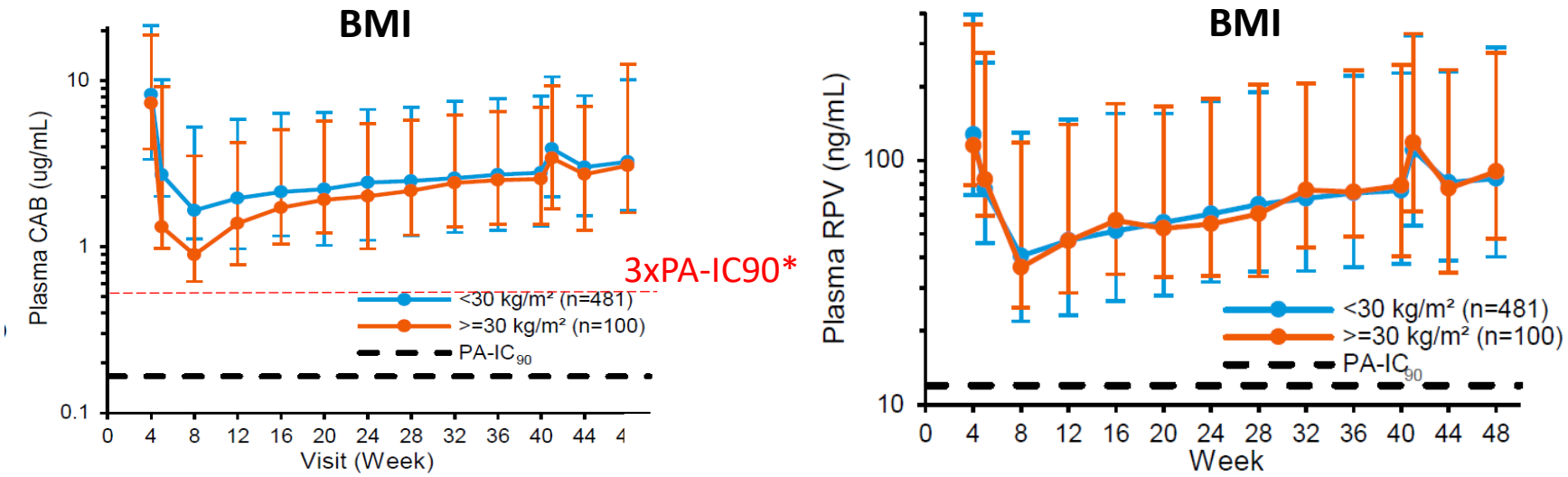


Patel P et al. ID week 2019

Cabotegravir and rilpivirine plasma levels in obese vs non-obese

Median (5th and 95th percentile) plasma CAB and RPV trough levels over time

In FLAIR and ATLAS: 17% participants had BMI ≥ 30 kg/m²
13% were male with BMI ≥ 30 kg/m²
27% were female with BMI ≥ 30 kg/m²



- 4 weeks following the first injection, median cabotegravir levels were 46% lower in obese vs non-obese

=> slower absorption resulting in initial lower trough that increases over time with no difference at week 32

- RPV is not affected by BMI

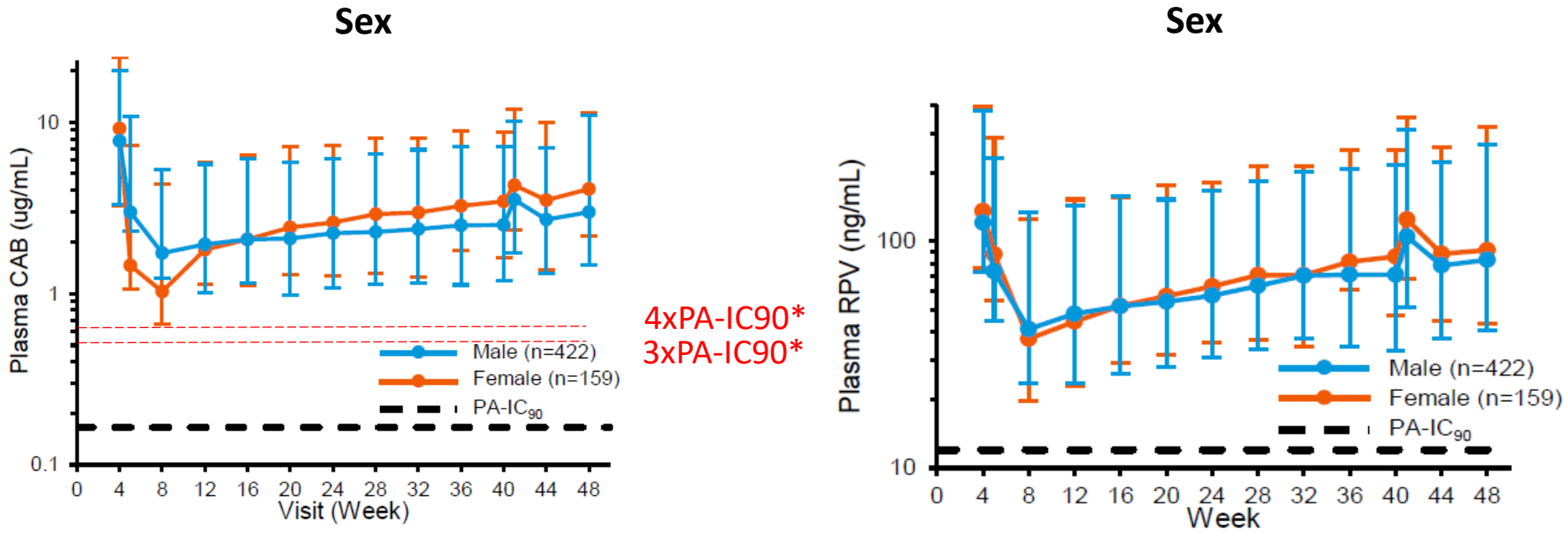
* in a low dose rectal challenge model, plasma CAB concentrations > 3x PA-IC90 provided 100% protective efficacy, 1-3 x PA-IC90 provided 97% protective efficacy

Andrews CD et al. Science 2014

Patel P et al. ID week 2019

Cabotegravir and rilpivirine plasma levels in female vs men

Median (5th and 95th percentile) plasma CAB and RPV trough levels over time



- 4 weeks following the first injection, median cabotegravir levels were 40% lower in female vs male
- RPV is not affected by sex

- in a low dose rectal challenge model, plasma CAB concentrations > 3x PA-IC90 provided 100% protective efficacy, 1-3 x PA-IC90 provided 97% protective efficacy
- In a vaginal challenge model, plasma CAB concentrations > 4x PA-IC90 provided 87% protective efficacy

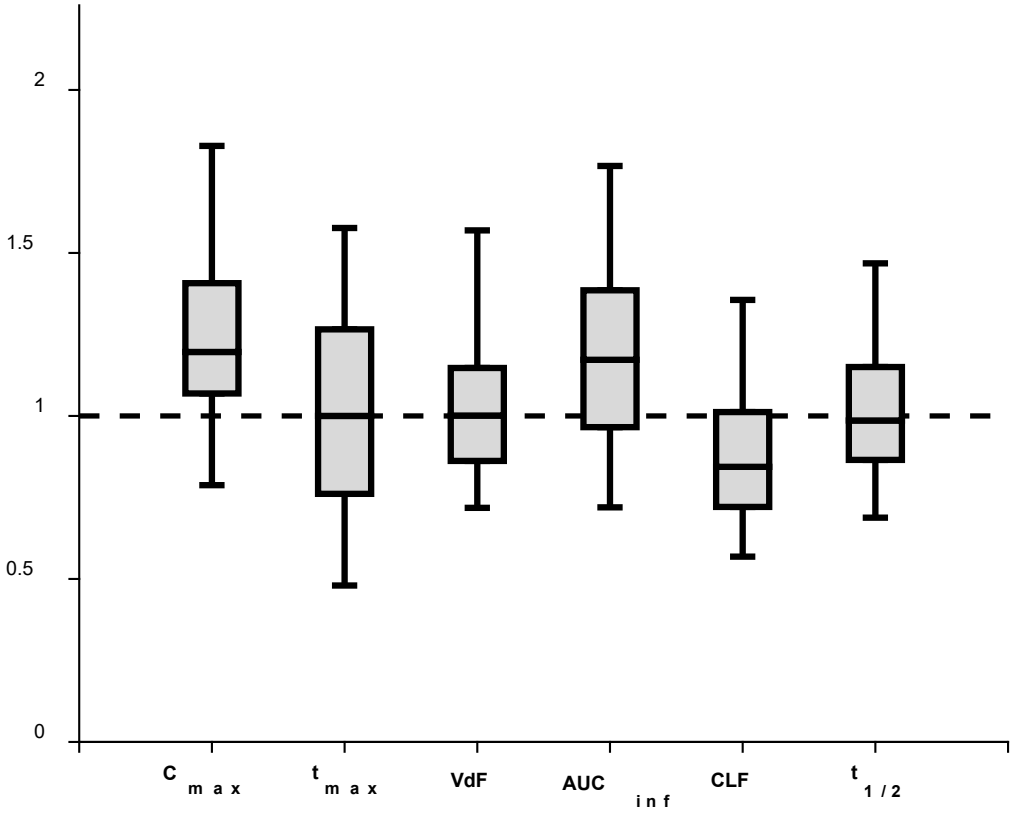
Andrews CD et al. Science 2014

Patel P et al. ID week 2019

Gender effect on the pharmacokinetics of oral and iv drugs

Meta analysis of existing studies (n = 64) comparing gender PK

Data represent ratio women/men



Parameter	Difference
C_{max}	↑ 20%
t_{max}	0%
AUC_{inf}	↑ 17%
CLF	↓ 11%
VdF	0%
$t_{1/2}$	-1%

Explained by differences in body weight and metabolism resulting in reduced first pass effect and hepatic metabolism.

Stader F. EACS Conference 2019

Case presentation

- Adrian 29 year-old MSM
- Multiple male sexual partners per month, condom use inconsistent
- BMI: 28 kg/m^2
- Currently on PrEP with TDF/FTC
- Last control: HIV antigen/antibody negative, HBsAg negative,
- eGFR 90 mL/min/1.73 m^2
- Chemsex (ecstasy, methamphetamine)
- Medications: occasionally antacids, St John's Wort (mild depression)

Cabotegravir metabolism

	Cabotegravir	Effect of Cabotegravir on UGTs, CYPs, transporters
Metabolism	**UGT1A1** (minor UGT1A9)	No inhibitory or inducing effects on: CYPs UGTs
Transport	P-gp, BCRP High intestinal permeability (inhibitors unlikely to impact CAB absorption) OATP1B1/3, OAT3, MRP2, MRP3, MRP4	No clinically significant inhibitory effects on: P-gp, BCRP, MRP4, MRP2, OATP1B1/3, OCT1/2, BSEP, MATE1, MATE2K, OAT1/3
$T_{1/2}$	oral: 41 hours im: 5.6-11.5 weeks	

Cabenuva Canadian product monograph March 2020; Reese MJ et al. Xenobiotica 2016; Taskar K et al. CROI 2019

Drug-drug interactions with Chemsex

Cabotegravir does not interact with Chemsex

Drug	Metabolism	Interaction Potential	
		Cobicistat Ritonavir	*BIC, CAB, DOR, DTG, RAL, MVC, RPV, NRTIs*
Benzodiazepines: *Midazolam, Triazolam*	CYP3A4	High	Low
Benzodiazepines: *Others*	CYP3A4	High	Low
Cocaine	CYP3A4 (minor)	Low-moderate	Low
Ecstasy (MDMA)	CYP2D6	Limited CYP2D6 inhibition, but small PK changes could be significant due to non-linear PK.	Low
GHB	GHB dehydrogenase CYP?	Unknown. Caution due to GHB **narrow therapeutic index**	Low
Ketamine	CYP3A4	High	Low
Mephedrone	CYP2D6	Limited CYP2D6 inhibition	Low
Methamphetamine	CYP2D6	Limited CYP2D6 inhibition, but small PK changes could be significant due to non-linear PK.	Low

www.hiv-druginteractions.org

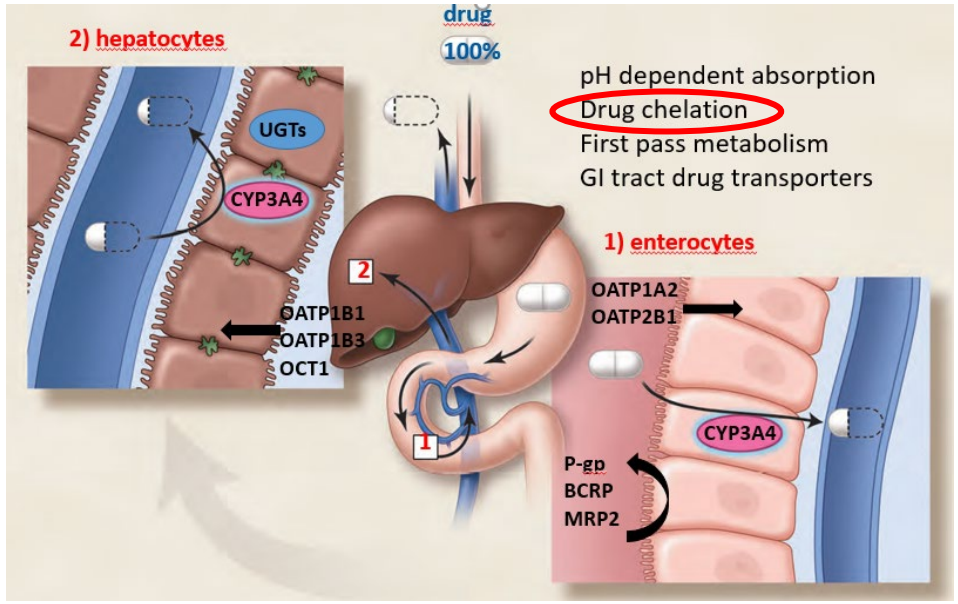
Drug-drug interactions with antacids

oral lead-in

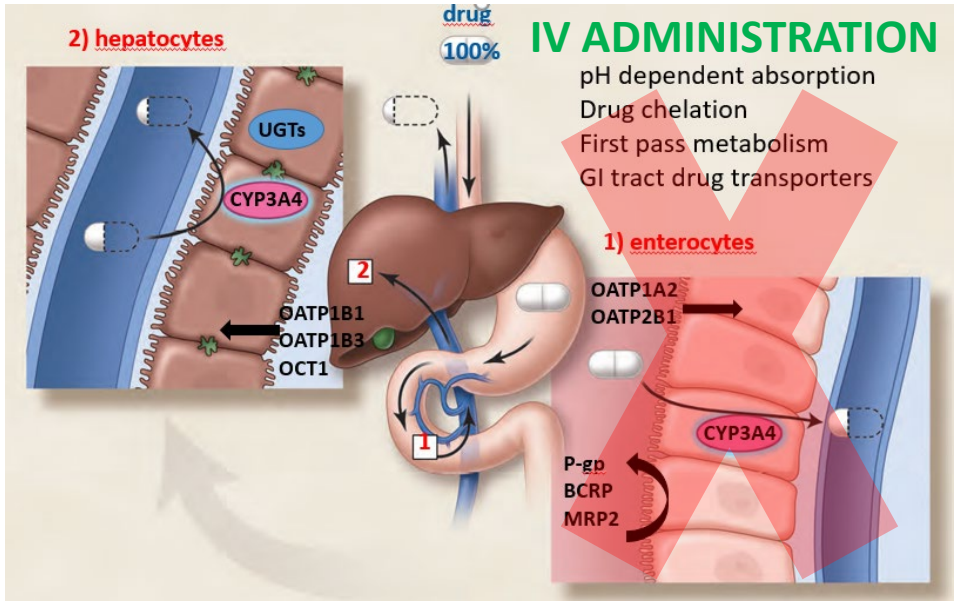
Potential Interaction
Cabotegravir [oral] (CAB oral)
Antacids

im injection

No Interaction Expected
Cabotegravir/rilpivirine [long acting] (CAB/RPV LA)
Antacids



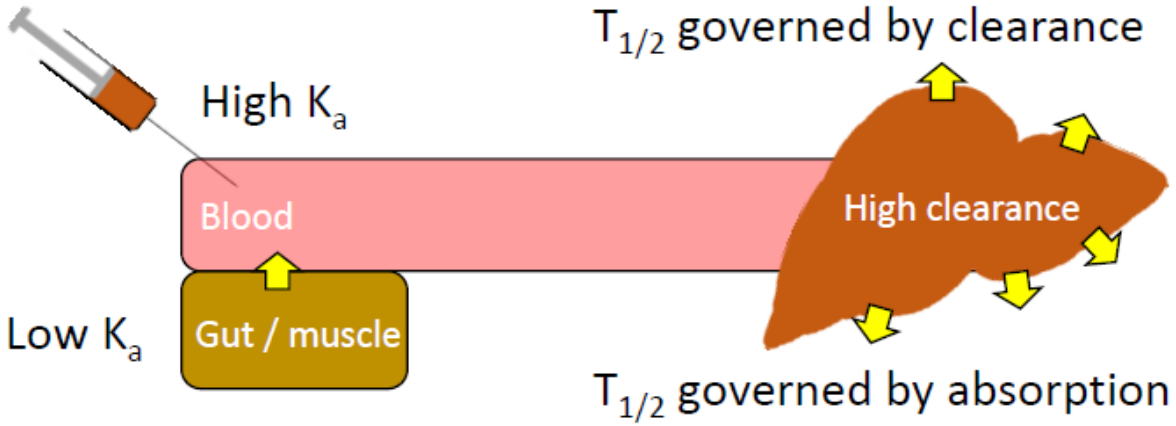
Administer antacids 2 h before or 4 h after oral cabotegravir

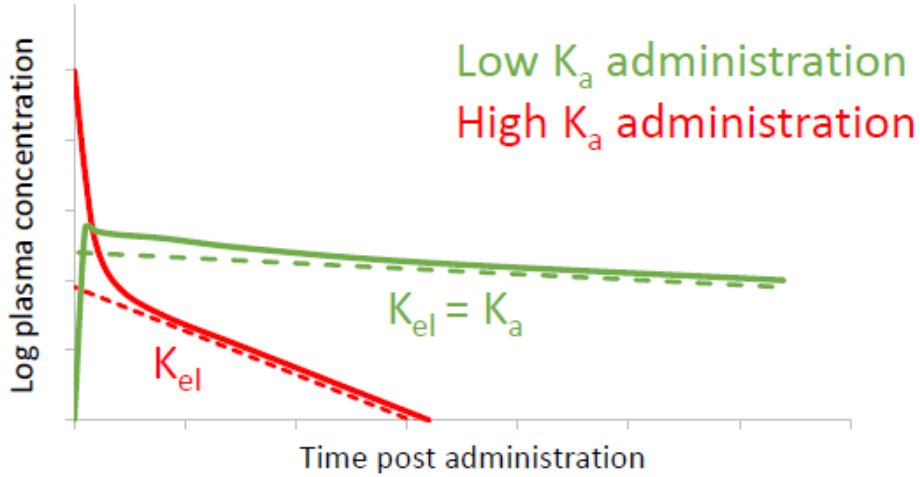


No chelation with im administration

Intramuscular administration characterized by flip-flop pharmacokinetics

In case of flip-flop pharmacokinetics, the rate of absorption is slower than rate of elimination ($K_{el} > K_a$)





In presence of strong inducers, AUC is decreased as elimination rate increases but $t_{1/2}$ remains constant as it is controlled by absorption rate.

Courtesy of Prof. Owen A

Drug-drug interactions with strong inducers

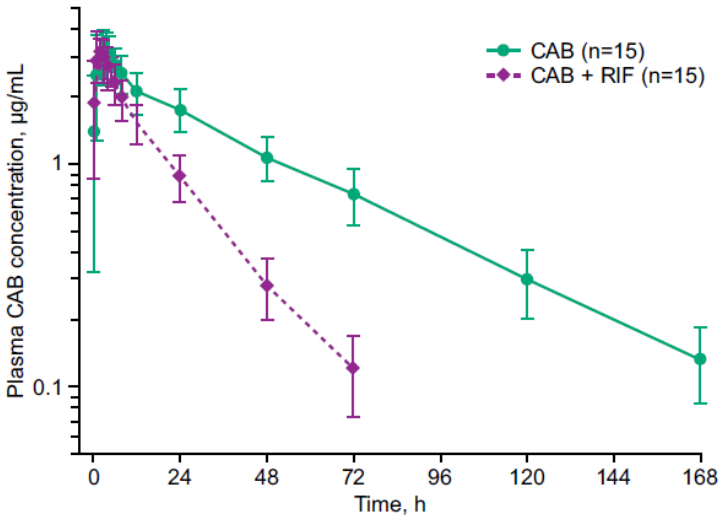
No Interaction Expected
Emtricitabine/Tenofovir-DF (FTC/TDF, PrEP)
St John's Wort

Do Not Coadminister
Cabotegravir [oral] (CAB oral)
St John's Wort

Do Not Coadminister
Cabotegravir/rilpivirine [long acting] (CAB/RPV LA)
St John's Wort

Oral cabotegravir + rifampicin

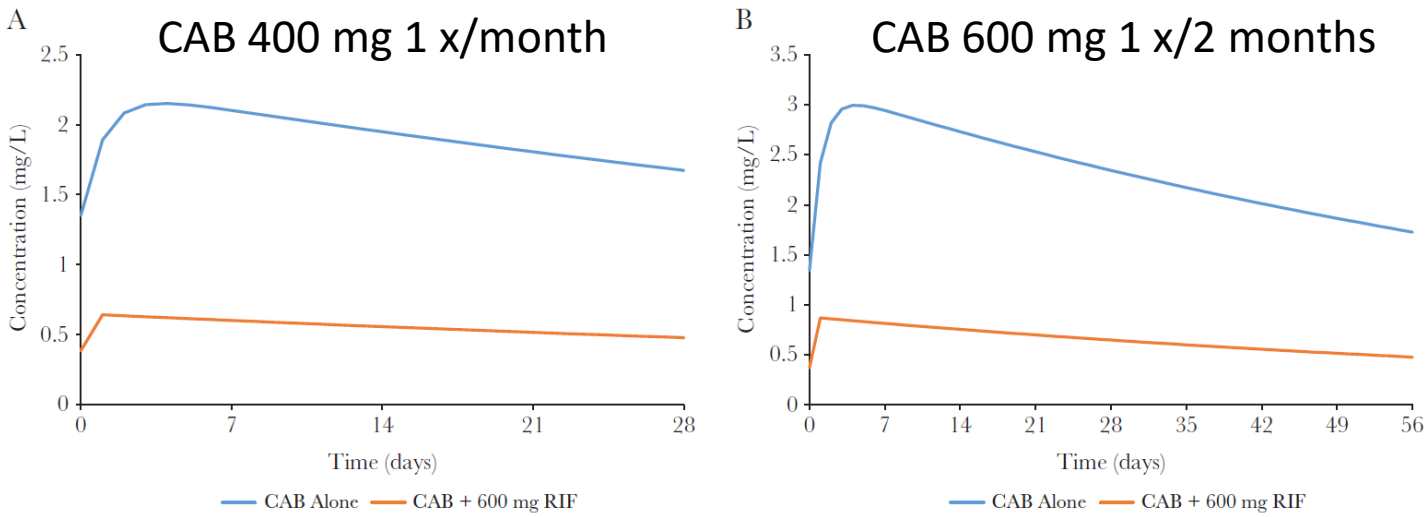
CAB AUC↓ by 59%; $t_{1/2}$↓ by 57%



Cabotegravir im + rifampicin

CAB AUC↓ by 41%; $t_{1/2}$ ↔

CAB AUC↓ by 46%; $t_{1/2}$ ↔



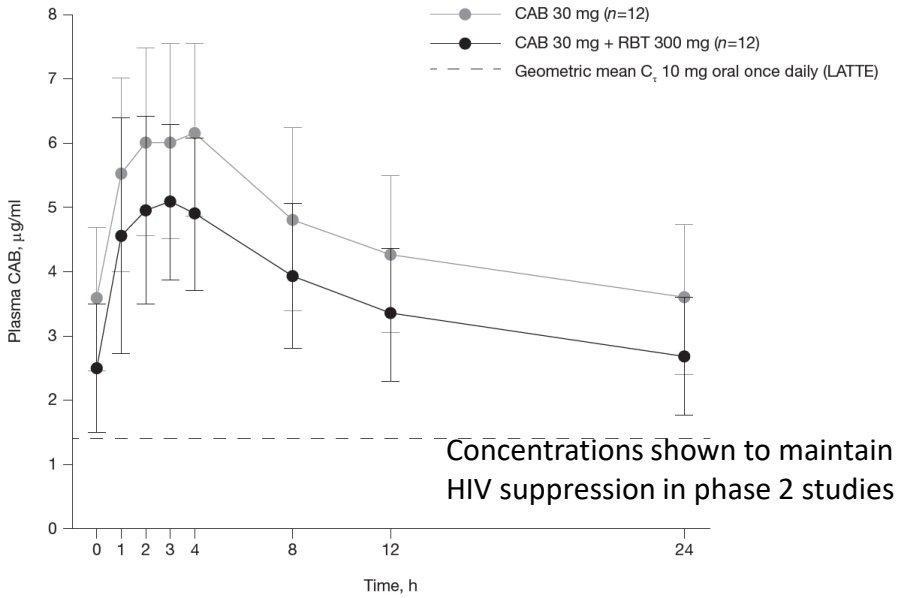
Ford SL et al. AAC 2017

Rajoli RKR et al. JID 2019

What about moderate inducers

Oral cabotegravir + rifabutin

CAB AUC ↓ by 21%; Ctrough ↓ by 26%

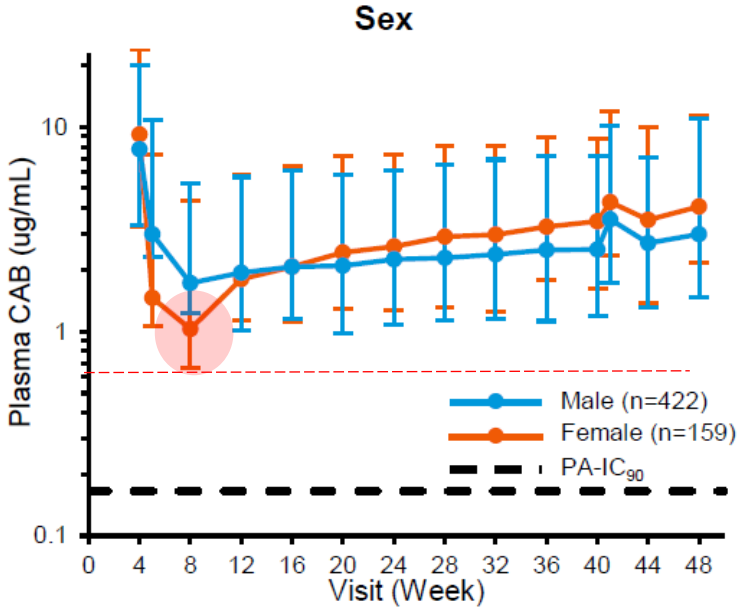


Concentrations shown to maintain HIV suppression in phase 2 studies

No Interaction Expected
Cabotegravir [oral] (CAB oral)
Rifabutin

Ford SL et al. Antiviral Ther 2019

Current gap: DDI in special populations



4xPA-IC90

Could DDI with moderate inducers become relevant in an obese woman in the early phase of cabotegravir injection?

HPTN 084 Long-acting Injectable For the Epidemic

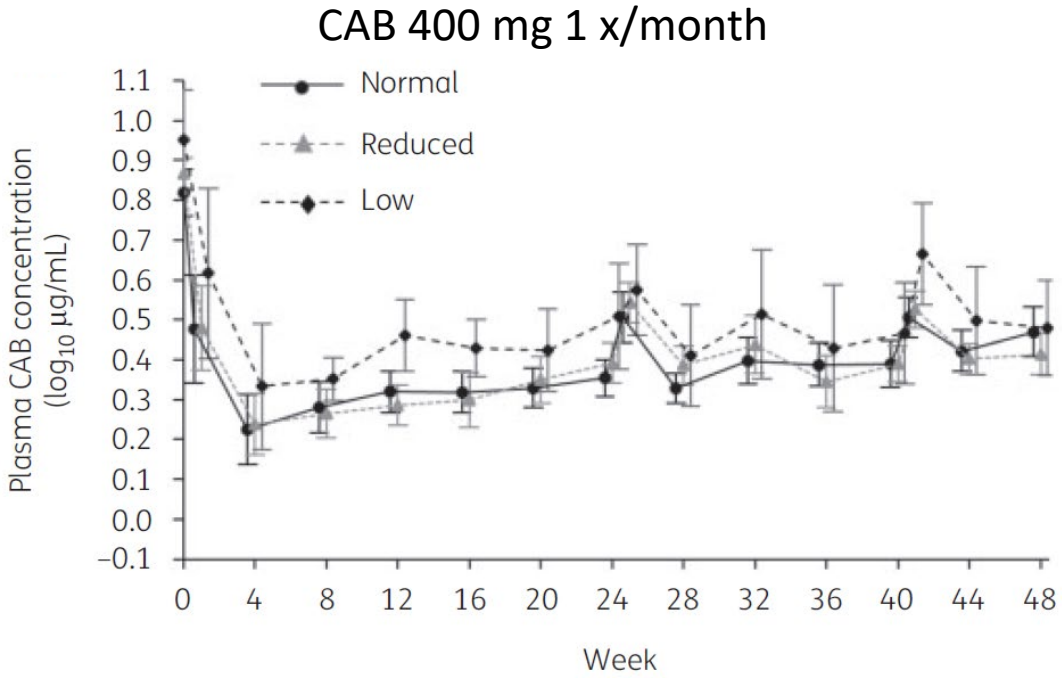
Ongoing phase III study evaluating efficacy and safety of CAB LA compared to oral PrEP in women

What about strong inhibitors of UGT1A1

DDI predictions using PBPK modelling

Substrate – Inhibitor/Inducer DDI Enzyme	CAB AUC Ratio* Geometric Mean (5th-95th percentile) Predicted	CAB Cmax Ratio* Geometric Mean (5th-95th percentile) Predicted
Cabotegravir – Atazanavir UGT1A1 Inhibition	1.11 (1.04, 1.20)	1.02 (1.01, 1.04)
Cabotegravir – Mefenamic Acid UGT1A9 Inhibition	1.10 (1.04, 1.18)	1.02 (1.01, 1.03)

Effect of UGT1A1*6 and UGT1A1*28 (reduced function) on CAB pharmacokinetics



Genetic variations resulted in modest elevations of oral cabotegravir exposure (28-50% increase) and im cabotegravir exposure (16-24%).

Taskar K et al. 20th PK Workshop 2019

Patel P et al. J Antimicrob Chemother 2020

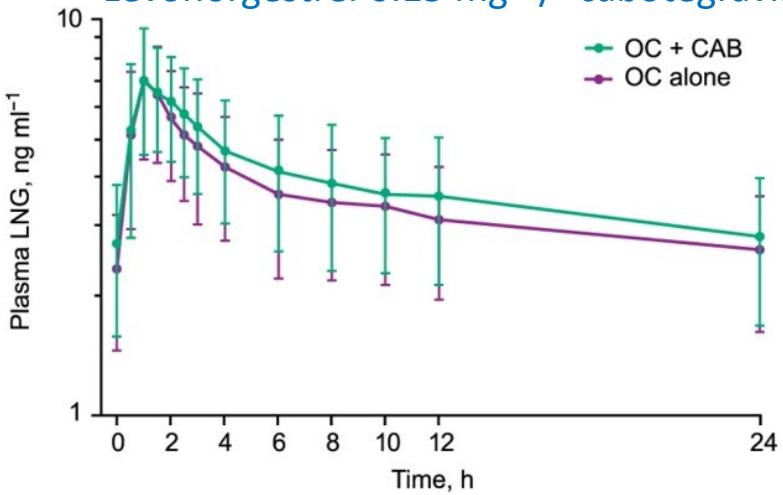
Case presentation

- Adrian is considering undergoing gender reassignment and wonder whether cabotegravir does interact with hormones

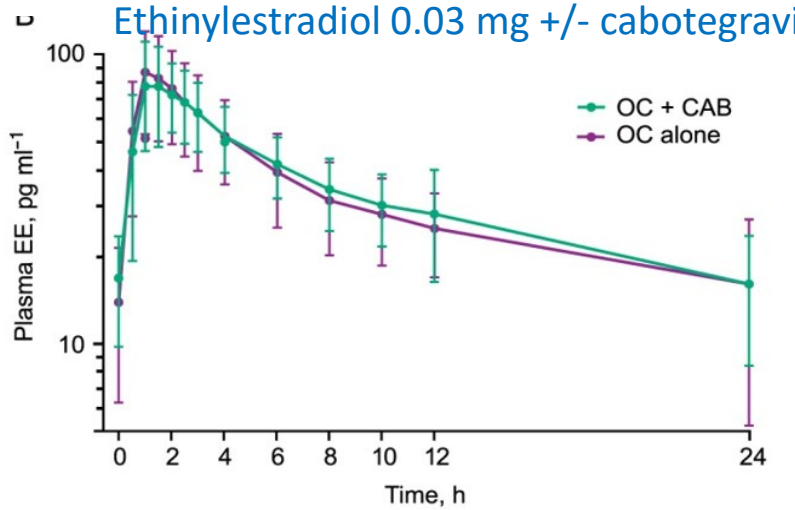
Drug-drug interactions with hormonal contraception

CAB oral

Levonorgestrel 0.15 mg +/- cabotegravir 30 mg



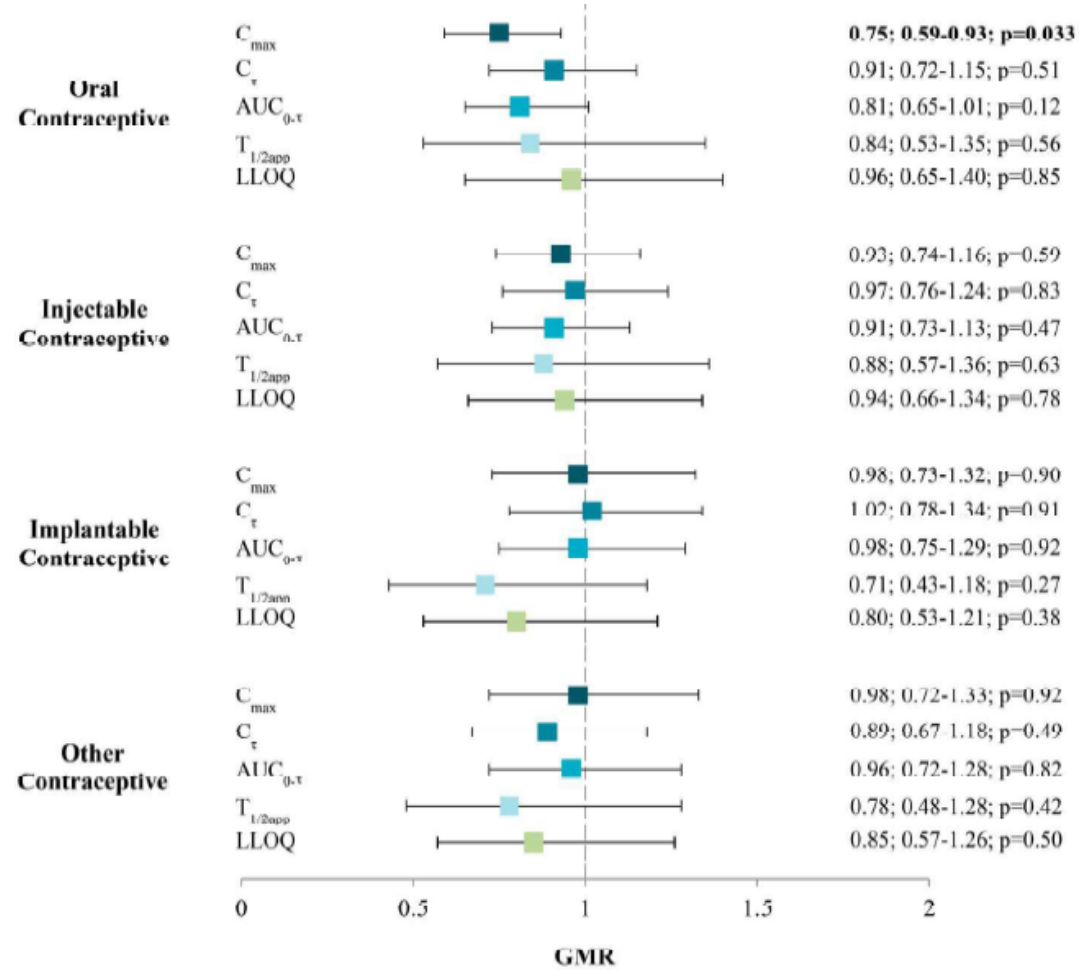
Ethinylestradiol 0.03 mg +/- cabotegravir 30 mg



- No significant effect

Trezza C et al. Br J Clin Pharmacol 2017

CAB LA



- Oral contraceptive associated with lower CAB LA peak but no significant effect on other PK parameters
- Other contraceptives caused no changes in CAB-LA PK

Blair CS et al. JAIDS 2020

Drug-drug interactions with hormone therapy for gender affirming

No significant pharmacokinetic interactions expected with cabotegravir

Estrogen and anti-androgen preparations for use in male to female gender reassignment therapy

		HIV drugs with no predicted effect	HIV drugs predicted to inhibit metabolism	HIV drugs predicted to induce metabolism
Estrogens		CAB, DOR, RPV, MVC, BIC, DTG, RAL ABC, ddI, FTC, 3TC, d4T, TAF, TDF, ZDV	ATV alone, ATV/cobi, DRV/cobi, EVG/cobi	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r, EFV, ETV, NVP
Estradiol oral	*Starting dose*	2 mg/day	1 mg/day	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.
	Average dose	4 mg/day	2 mg/day	
	Maximum dose	8 mg/day	4 mg/day	
Estradiol gel (preferred for >40 y and/or smokers)	*Starting dose*	0.75 mg twice daily	0.5 mg twice daily	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.
	Average dose	0.75 mg three times daily	0.5 mg three times daily	
	Maximum dose	1.5 mg three times daily	1 mg three times daily	
Estradiol patch (preferred for >40 y and/or smokers)	*Starting dose*	25 µg/day	25 µg/day*	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.
	Average dose	50-100 µg/day	37.5-75 µg/day	
	Maximum dose	150 µg/day	100 µg/day	
Conjugated estrogen†	*Starting dose*	1.25-2.5 mg/day	0.625-1.25 mg/day	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.
	Average dose	5 mg/day	2.5 mg/day	
	Maximum dose	10 mg/day	5 mg/day	
Ethinylestradiol	*Starting dose*	No interaction expected, but not recommended due to thrombotic risks	Not recommended	Not recommended
	Average dose			
	Maximum dose			
Androgen Blockers		CAB, DOR, RPV, MVC, BIC, DTG, RAL ABC, ddI, FTC, 3TC, d4T, TAF, TDF, ZDV	ATV alone, ATV/cobi, ATV/r, DRV/cobi, DRV/r, EVG/cobi, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	EFV, ETV, NVP
Spironolactone	*Starting dose*	50 mg/day	No interaction expected. No dose adjustment required.	No interaction expected. No dose adjustment required.
	Average dose	150 mg/day		
	Maximum dose	400 mg/day		
Finasteride	*Starting dose*	2.5 mg/day	Finasteride has a large safety margin. No dose adjustment required.	Increase finasteride dosage as needed based on clinical effects and monitored hormone levels.
	Average dose	2.5 mg/day		
	Maximum dose	5 mg day		
Cyproterone acetate	*Starting dose*	50 mg/day	25 mg/day	Increase cyproterone dosage as needed based on clinical effects and monitored hormone levels.
	Average dose	150 mg/day	75 mg/day	
	Maximum dose	150 mg/day	75 mg/day	
Goserelin	*Starting dose*	3.6 mg/month	No interaction expected. No dose adjustment required.	No interaction expected. No dose adjustment required.
	Average dose	3.6 mg/month		
	Maximum dose	3.6 mg/month		
Leuprorelin acetate	*Starting dose*	3.75 mg/month	No interaction expected. No dose adjustment required.	No interaction expected. No dose adjustment required.
	Average dose	3.75 mg/month		
	Maximum dose	3.75 mg/month		
Triptorelin	*Starting dose*	3.75 mg/month	No interaction expected. No dose adjustment required.	No interaction expected. No dose adjustment required.
	Average dose	3.75 mg/month		
	Maximum dose	3.75 mg/month		

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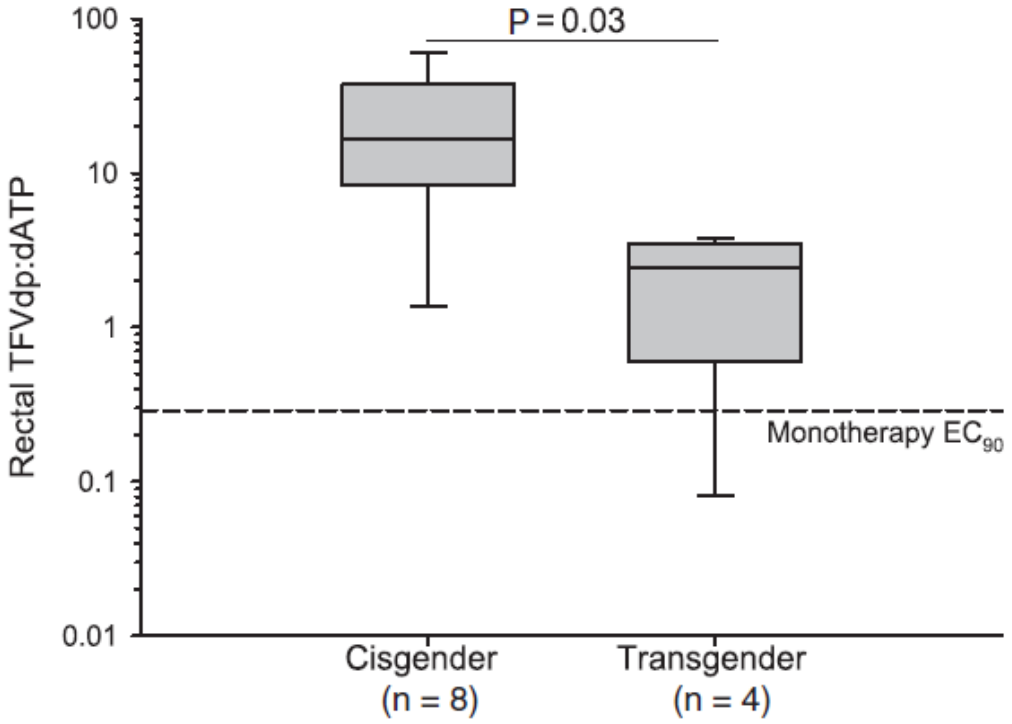
Feminizing hormone therapy and lower rectal tissue tenofovir diphosphate

Tenofovir-DP and endogenous nucleotide ratio in rectal tissue



- median TFVdp:dATP was **7-fold lower** in rectal tissue (but not PBMC) in transgender women taking feminizing hormones
- no differences in FTCtp:dCTP in blood or rectal tissue
- no increase in rectal HIV RNA or DNA was observed
- additional studies are needed to determine the clinical implication

Cottrell ML et al. Clin Infect Dis 2019

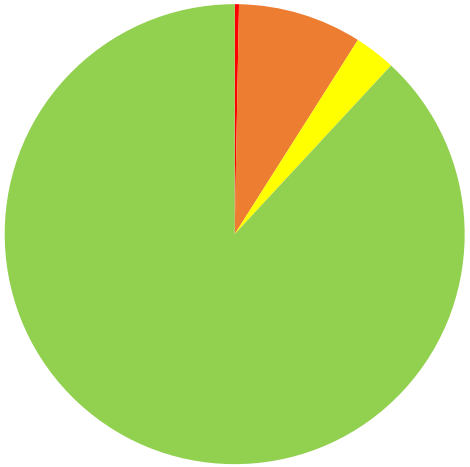
PK study in transgender women using PrEP showed modestly lower plasma FTV exposure however FTVdp levels were not reduced in PBMC. The authors mention that there is no need to adjust PrEP.

Cirrincione LR et al. J Antimicrob Chemother 2020

Drug-drug interactions profiles of PrEP

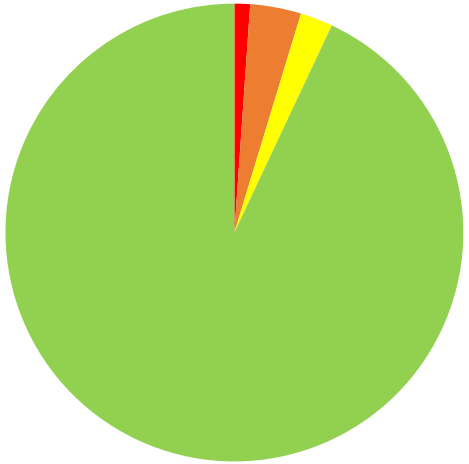
n = 724 comedications

TDF/FTC



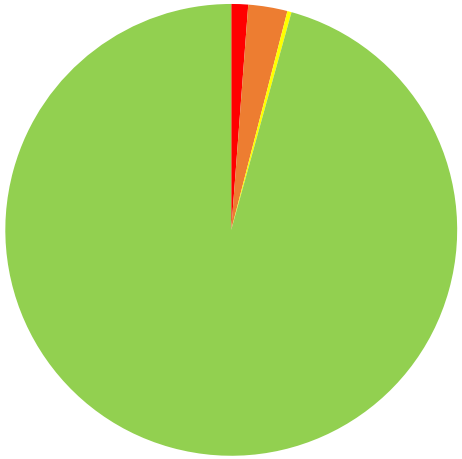
- Nephrotoxic agents
- Inhibitor intestinal transporters
- Inhibitor renal transporters

TAF/FTC



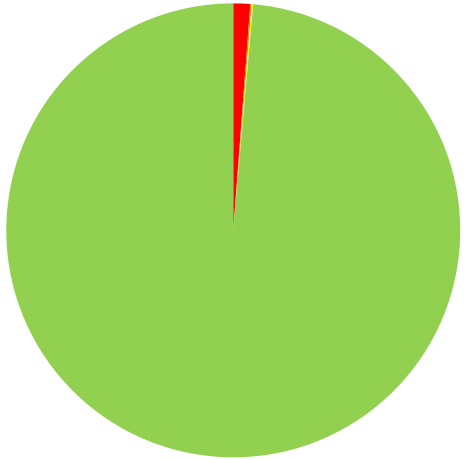
- Strong inducers
- Inhibitor intestinal transporters

CAB oral



- Strong inducers
- Divalent cations

CAB LA



- Strong inducers

no interaction

interaction of clinical relevance

Interaction of weak clinical relevance

deleterious interaction

www.hiv-druginteractions.org

Would cabotegravir PrEP be suitable for Adrian

- No interaction with Chemsex
- No interactions with antacids (separate intake oral CAB from antacids)
- Major interaction with SJW => change antidepressant
- No interaction with gender transitioning drugs

Conclusions

- Cabotegravir LA and oral PrEP have a low risk for drug-drug interactions.
- Better understanding is needed with regard to cabotegravir exposure-response relationship for prevention in both men and female.
- Better understanding of cabotegravir PK is needed in special populations.

Acknowledgements

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HIV Drug Interactions

Liverpool website team & editorial board