LONG ACTING AGENTS FOR HIV INFECTION

Are DDIs and polypharmacy still a concern?

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17th Residential Course on
Clinical Pharmacology of Antiretrovirals

Long acting antiretroviral drugs for treatment and prevention

CAB + RPV (i.m.; 1x/1 or 2 months)
Integrase inhibitor + NNRTI

Ibalizumab (i.v.; every 2 weeks)
Monoclonal Ab, attachment inhibitor

Lenacapavir (s.c.; 1x/6 months)
Capsid inhibitor

Leronlimab (s.c.; 1x/week)
Monoclonal Ab, CCR5 antagonist

UB-421 (i.v.; 1x/1 or 2 weeks)
Monoclonal Ab, attachment inhibitor

Cabotegravir (i.m.; 1x/2 months)
Integrase inhibitor

Dapivirine (vaginal ring; 1x/month)
NNRTI

Lenacapavir (s.c.; 1x/6 months)
Capsid inhibitor

Islatravir (implant; 1x/year)
Reverse transcriptase translocation inh.

CAB + VRC07-523LS (i.m.; 1x/month; iv; 1x/8 weeks)
Integrase inhibitor + bnAb

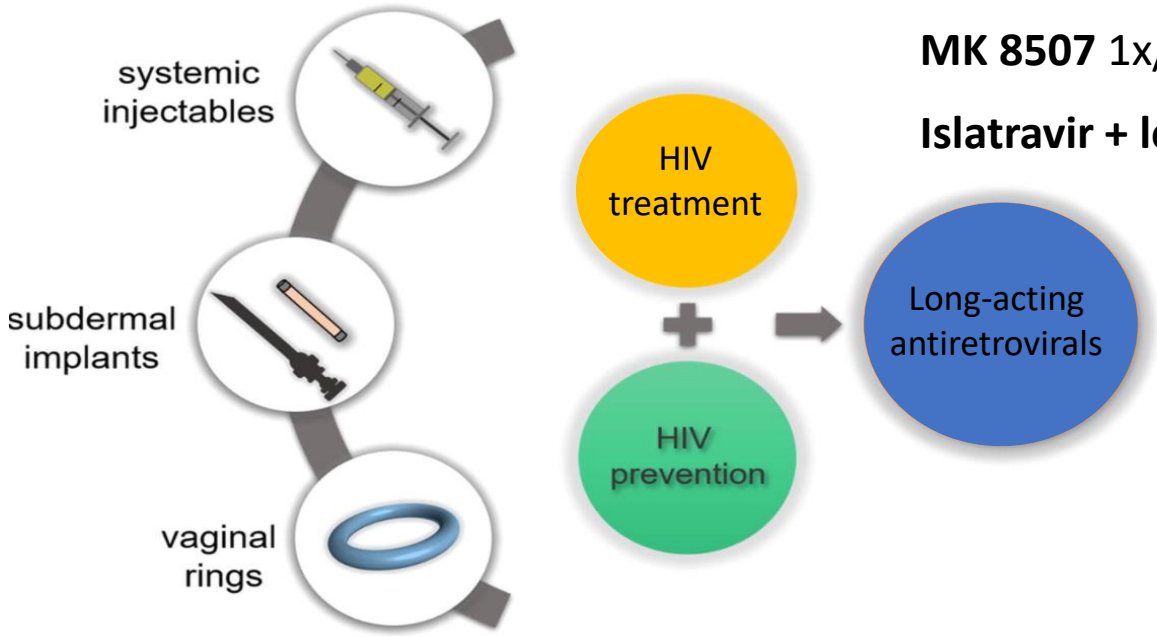
Albuvirtide + 3BNC117 (i.v.; 1x/month)
Fusion inhibitor + bnAb

Oral administration

Islatravir 1x/month

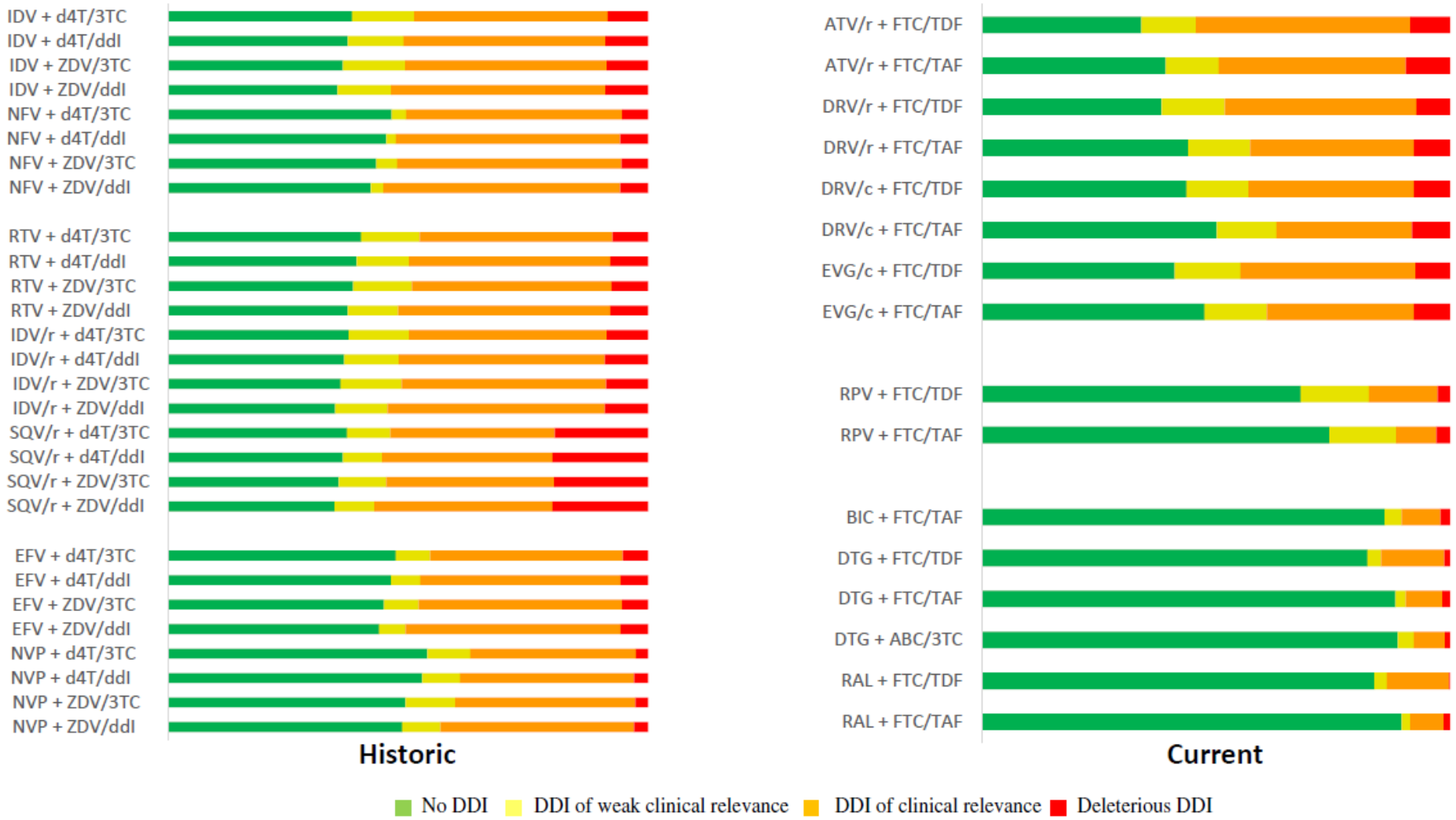
MK 8507 1x/week

Islatravir + lenacapavir 1x/week



Adapted from Krovi S et al. Adv Drug Deliv Rev 2021; Chandiwana NC,….Flexner C. AIDS 2021

Interaction profiles of first-line ARV regimens in 1999 and 2019



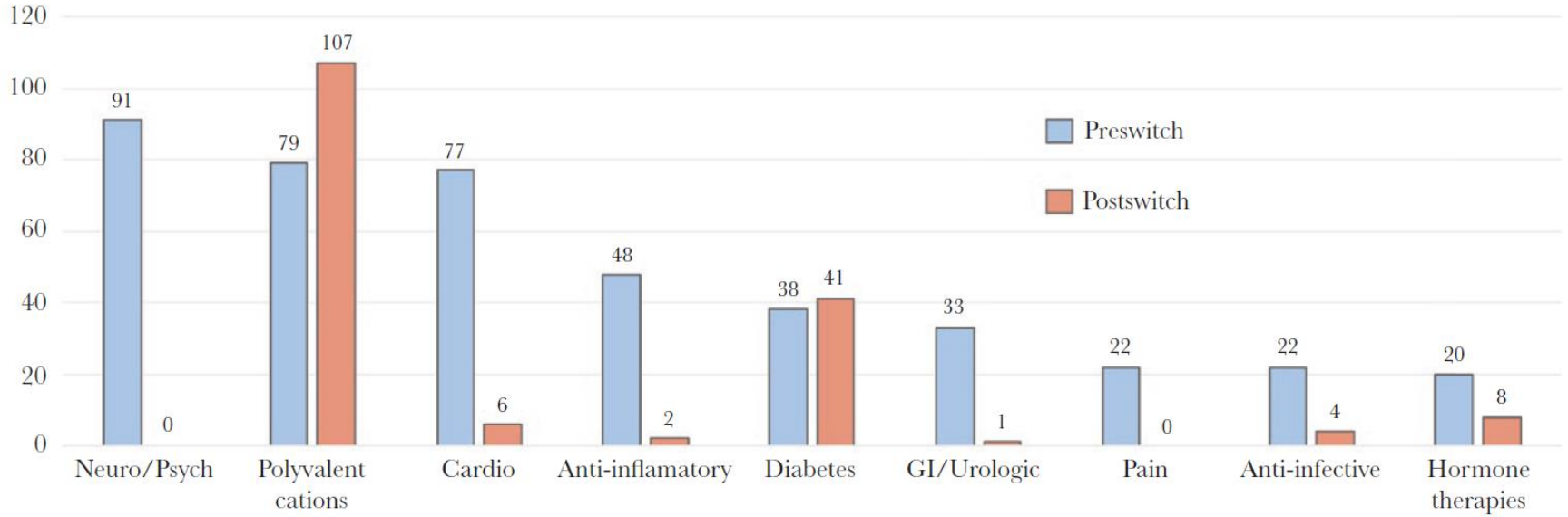
Gibbons S et al. HIV Med 2019

Prevalence of DDIs before/after switching to unboosted integrase inhibitor

Study evaluating changes in prevalence of drug-drug interactions in 411 PLWH before and after switching ART to a bictegravir containing regimen. DDI analyzed using University of Liverpool DDI database and atributed a score 0 (no DDI), 1 (potential DDI) and 2 (contraindicated DDI).

➔ Baseline DDI scores were 1.4 and decreased by 1 point after switch to bictegravir

Subjects with at least 1 DDI between their ART and selected comedications pre- and post-switch



Are DDIs and polypharmacy a concern with long acting agents?

Shafer J et al. Open Forum Infect Dis 2021

What is the drug-drug interaction risk for

Cabotegravir + rilpivirine

Cabotegravir

Ibalizumab

Lenacaprevir

Islatravir

MK 8507

MERCK Nov 2021

Decreases in total lymphocyte and CD4+ T-cell counts were observed in study participants randomized to receive ISL+MK-8507. A review by the external Data Monitoring Committee (eDMC) determined that this effect was related to treatment with the combination of ISL+MK-8507; the greatest decreases were seen in the arms of the study receiving the highest doses of MK-8507 (200 mg and 400 mg). At the recommendation of the eDMC, Merck is stopping dosing in the trial, with continued monitoring of study participants. The company has notified investigators

In light of the findings from the MK-8591-013 study, Merck conducted a review of trends in total lymphocyte and CD4+ T-cell counts in company-sponsored clinical trials of ISL across all indications and dosing regimens. A dose-dependent decrease in lymphocyte counts was observed in an ongoing Phase 2 trial (MK-8591-016), which is evaluating monthly ISL (60 mg and 120 mg) for PrEP in participants at low-risk of HIV-1 infection. In this population of HIV-1 uninfected participants, the mean decreases were in the normal range and there was no increase in clinical adverse events (AEs) related to infection. In addition, a small, treatment related mean decrease in CD4+ T-cell counts

Cabotegravir + rilpivirine

- First approved long-acting injectable antiretroviral therapy for virologically suppressed adults with HIV
- Administration every 4 weeks demonstrated noninferiority to oral ART through week 96 both in the ATLAS and FLAIR studies
- ATLAS-2M found similar efficacy through 96 weeks for administration every 8 weeks instead of 4 weeks

1x/month intramuscular administration

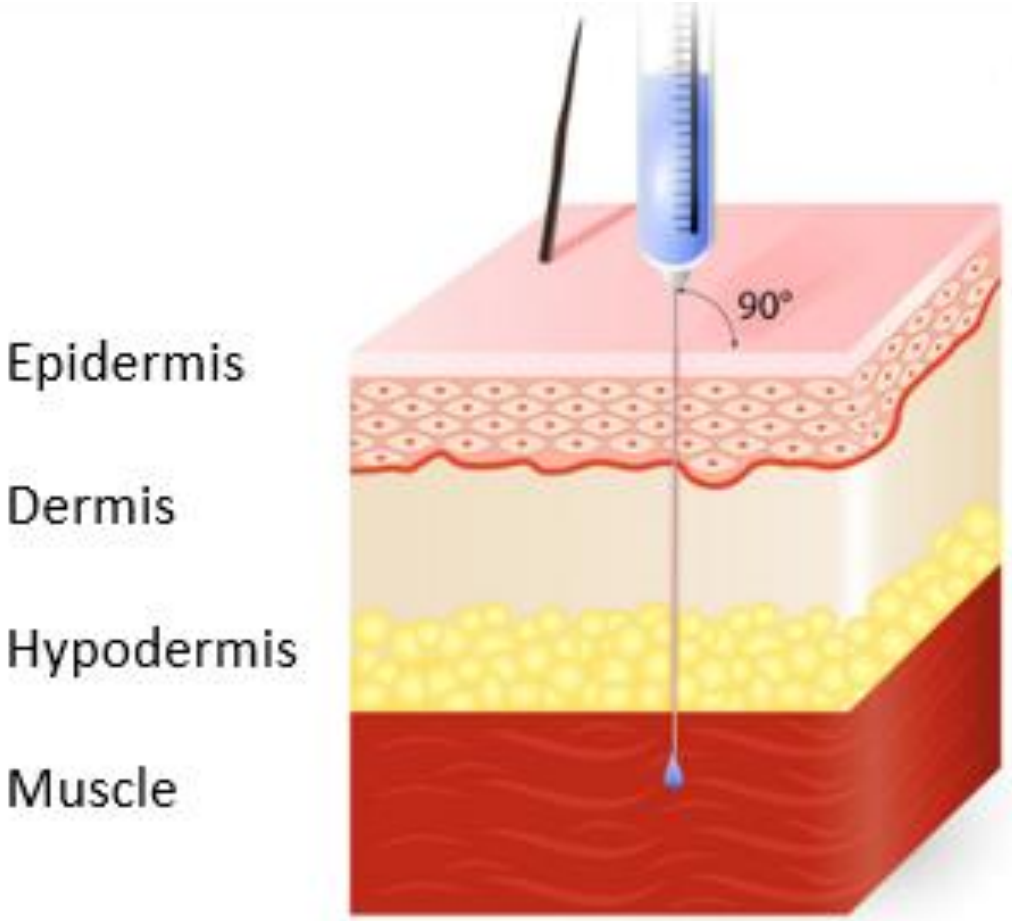
	Initial injection	Maintenance
Cabotegravir	600 mg	400 mg
Rilpivirine	900 mg	600 mg

1x/every 2 months intramuscular administration

	Initial injections (1 month apart)	Maintenance (2 months apart)
Cabotegravir	600 mg	600 mg
Rilpivirine	900 mg	900 mg

Swindells S et al. AIDS 2021; Orkin C et al. Lancet HIV 2021; Jaeger H et al. Lancet HIV 2021
Vocabria and Rekambys Summary of Product Characteristics 2021; Cabenuva Highlights of Prescribing Information 2021

Intramuscular administration

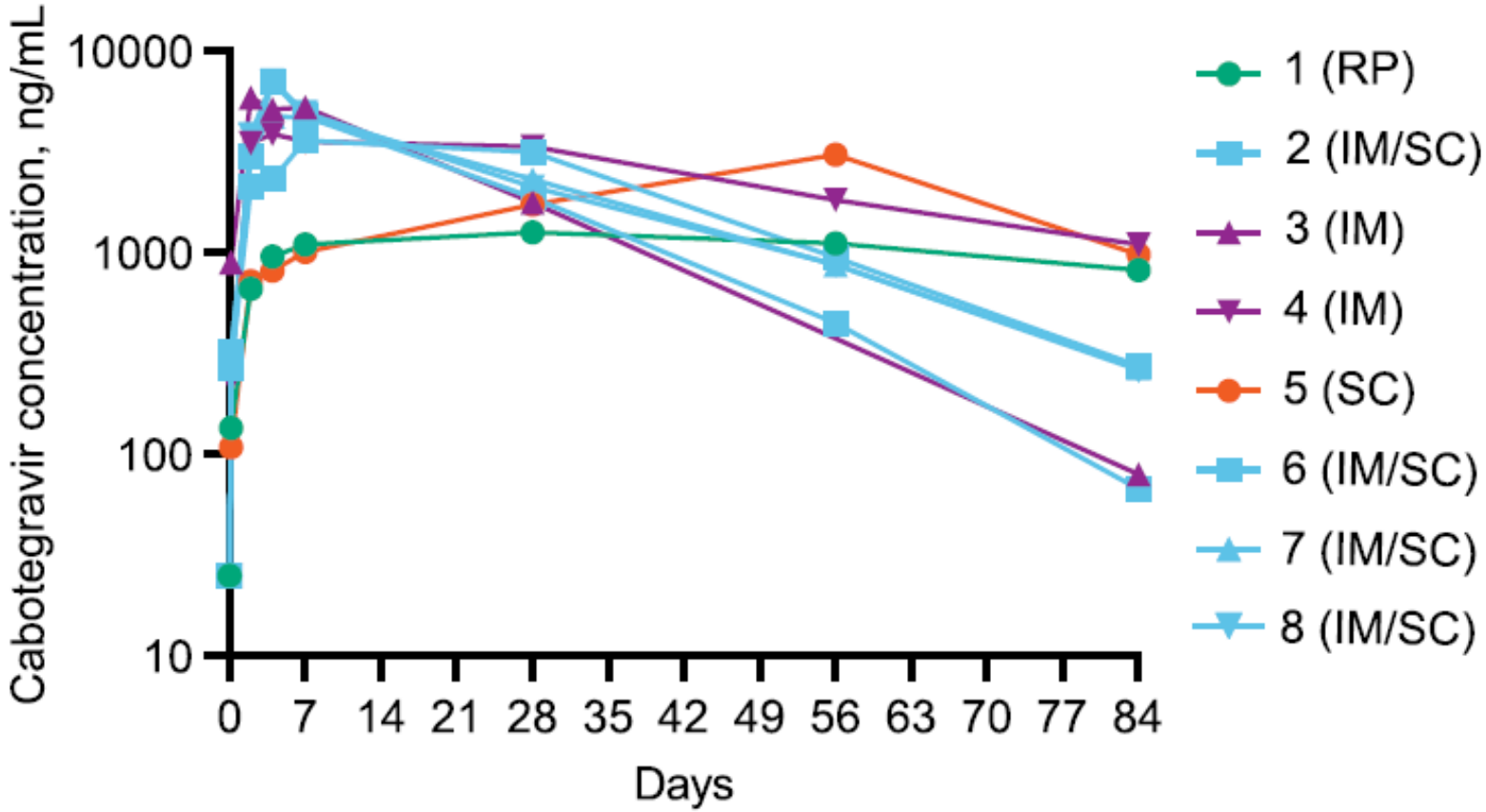


- Injection performed in gluteal muscle.
- Muscle has rich vascular supply favoring drug absorption.
- Subcutaneous adipose tissue has less vascular supply which may result in less drug absorption.
- Injection technique is critical to ensure drug is not deposited in subcutaneous adipose tissue.
- Labels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

Vocabria and Rekambys Summary of Product Characteristics 2021; Cabenuva Highlights of Prescribing Information 2021

Impact of injection on rate of cabotegravir absorption

8 participants (4 men + 4 women) were administered cabotegravir LA 600 mg under ultrasonographic-guided injections in gluteal muscle. Cabotegravir LA depot locations varied: IM compartment (2); combined IM/SC (4), SC (1) and retro-peritoneal cavity (1).



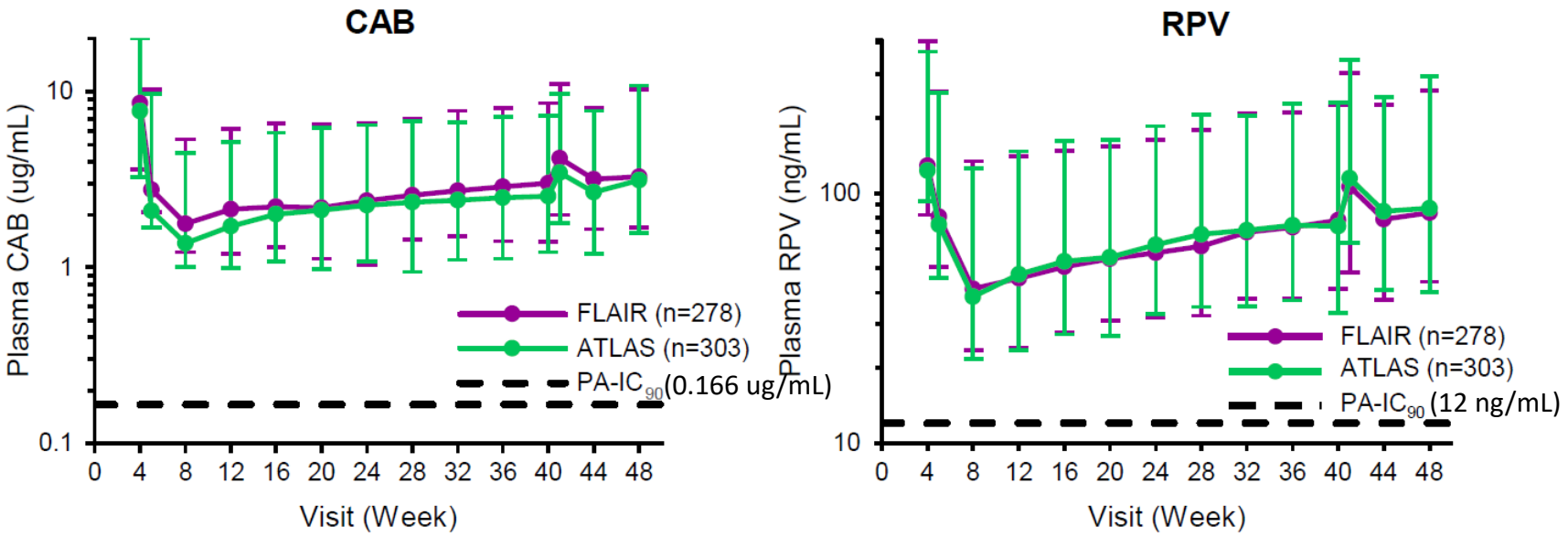
Jucker BM et al. Br J Clin Pharmacol 2021

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%

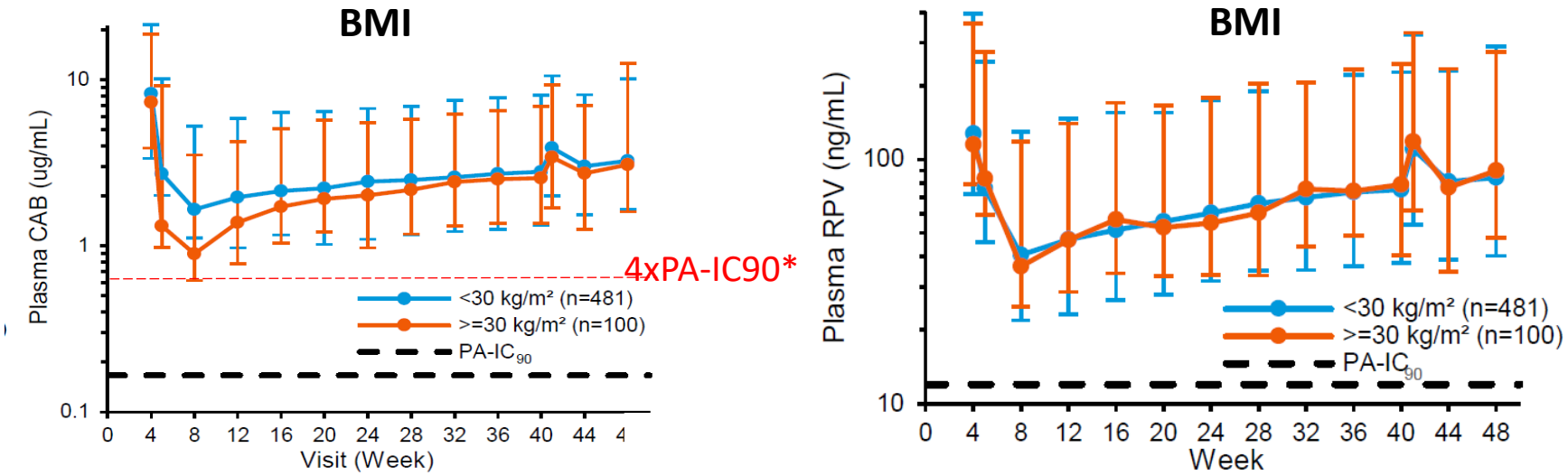


Patel P et al. ID week 2019

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

* ≥4x PA-IC90 trough, clinical threshold associated with efficacy in participants with HIV infection in phase II and III trials

Patel P et al. ID week 2019

Predictors of virologic failure to long-acting cabotegravir and rilpivirine

Efficacy data of long-acting cabotegravir and rilpivirine dosed intramuscularly every 4 to 8 weeks were pooled from phase 3/3b FLAIR, ATLAS or ATLAS-2M studies through week 48 (1039 participants) to examine the influence of baseline viral and participant factors, dosing regimen and drug concentrations on confirmed virologic failure occurrence using a logistic regression model.

Baseline factors	Virologic success[a] *n* (%)	CVF[b] *n* (%)
None of the three factors	694/732 (94.8)	3/732 (0.41)
Any one of the three baseline factors	261/272 (96.0)	1/272 (0.37)
HIV-1 subtype A6/A1 alone	90/95 (94.7)	1/95 (1.1)
BMI $\geq$30 kg/m^2 alone	147/153 (96.1)	0/153 (0)
RPV RAM(s) alone	24/24 (100)	0/24 (0)
At least two of the three baseline factors	25/35 (71.4)	9/35 (25.7)
RPV RAM(s) + HIV-1 subtype A6/A1	2/3 (66.7)	1/3 (33.3)
RPV RAM(s) + BMI $\geq$30 kg/m^2	7/10 (70.0)	3/10 (30.0)
HIV-1 subtype A6/A1 + BMI $\geq$30 kg/m^2	16/21 (76.2)	4/21 (19.0)
All three baseline factors	0/1 (0)	1/1 (100)
TOTAL	980/1039 (94.3)	13/1039 (1.25)
[95% CI (exact method)]	(92.74–95.65)	(0.67–2.13)

➔overall 1.25% of participants experienced confirmed virological failure.

➔RPV resistance associated mutations, HIV-1 subtype, higher BMI (associated with week 8 CAB trough concentration) and lower week 8 RPV trough concentrations were associated with increased odds of confirmed virological failure.

➔only combination of at least 2 baseline factors was associated with increased confirmed virological failure.

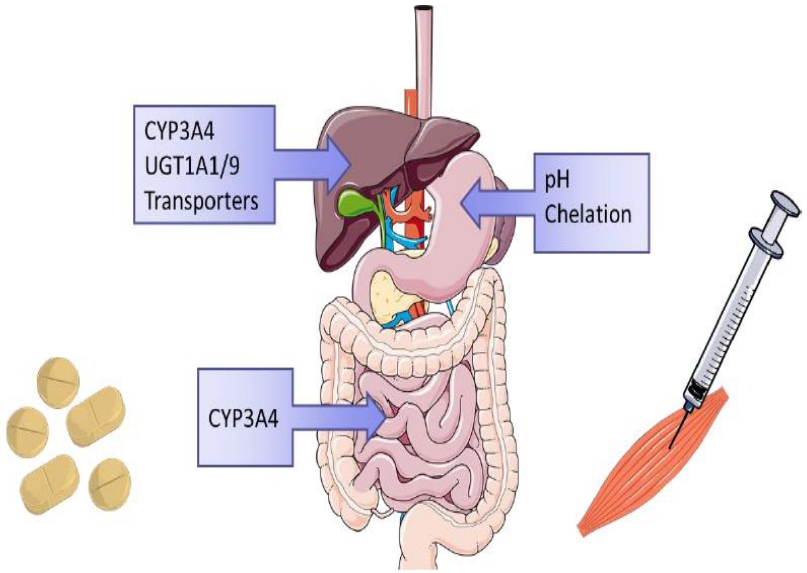
Cutrell AG et al. AIDS 2021

Cabotegravir and rilpivirine metabolism

	Cabotegravir	Rilpivirine
Metabolism	**UGT1A1** >UGT1A9	**CYP3A4**
Transport	P-gp, BCRP High intestinal permeability (inhibitors unlikely to impact CAB absorption) OATP1B1/3, OAT3, MRP2, MRP3, MRP4	
Effect on UGTs, CYPs, transporters	No inhibitory or inducing effects on CYPs, UGTs. No inhibition of transporters at clinically relevant concentrations except for OAT1/3 (IC50: 0.81/0.41 uM).	No inhibitory or inducing effects on: CYPs or UGTs. No clinically significant inhibitory effects on drug transporters.

Reese MJ et al. Xenobiotica 2016; Taskar K et al. CROI 2019; Hodge D et al. Clin Pharmacokinet 2021

Drug-drug interactions with oral vs im administration



	Oral administration	*Intramuscular administration*
Stomach/intestine	• Change in gastric pH • Chelation with divalent cations • Inhibition/induction of CYP3A4 and transporters	• Bypassed
Liver	• Inhibition/induction of CYP3A4, UGT1A1/9, transporters	• Inhibition/induction of CYP3A4, UGT1A1/9, transporters

Examples of drugs interacting with oral, but not intramuscular, administration

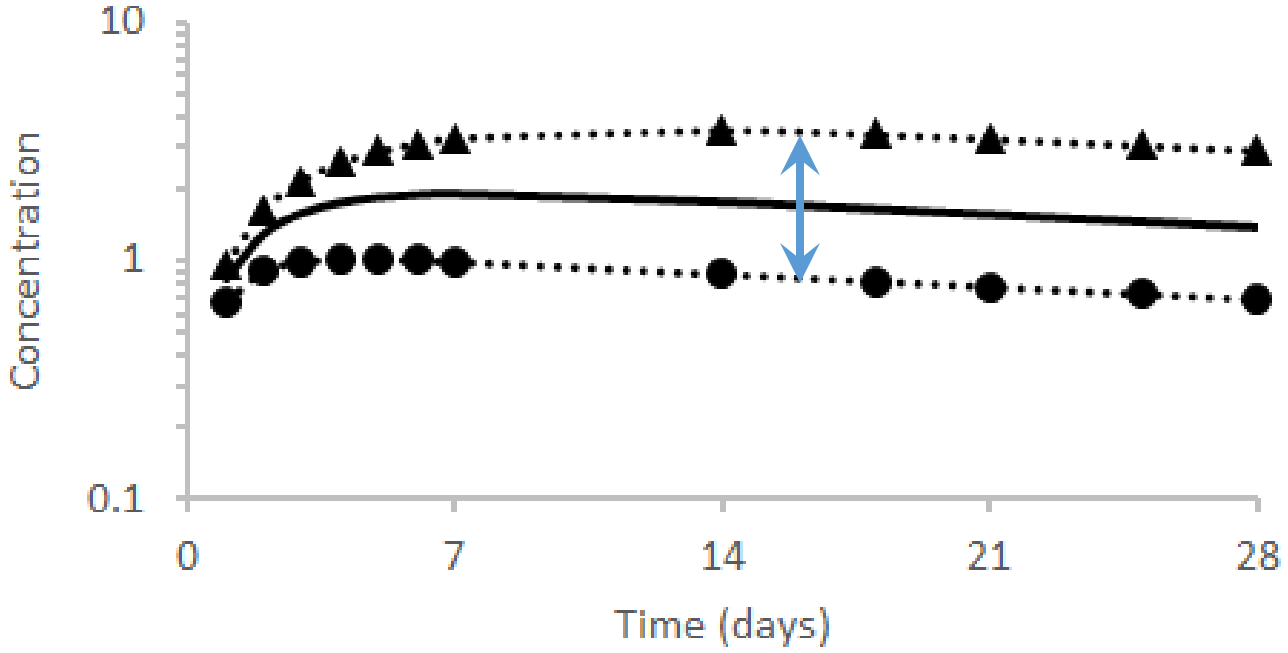
Cabotegravir	*Rilpivirine*
Antacids	Antacids
Calcium	Famotidine
Iron	Lansoprazole
Magnesium	Liraglutide
Multivitamins containing divalent cations	Omeprazole
Orlistat	Orlistat
Strontium ranelate	Pantoprazole
	Rabeprazole
	Ranitidine

Intramuscular administration characterized by flip-flop pharmacokinetics

In case of flip-flop pharmacokinetics, the rate of absorption is slower than rate of elimination ($K_{el} > K_a$).
Thus, the net effect from a DDI is a parallel upward (inhibitor) or downward (inducer) shift in the concentration-time course and no change in elimination rate.

LA drugs concentration time profile with flip-flop PK in presence of interacting drug

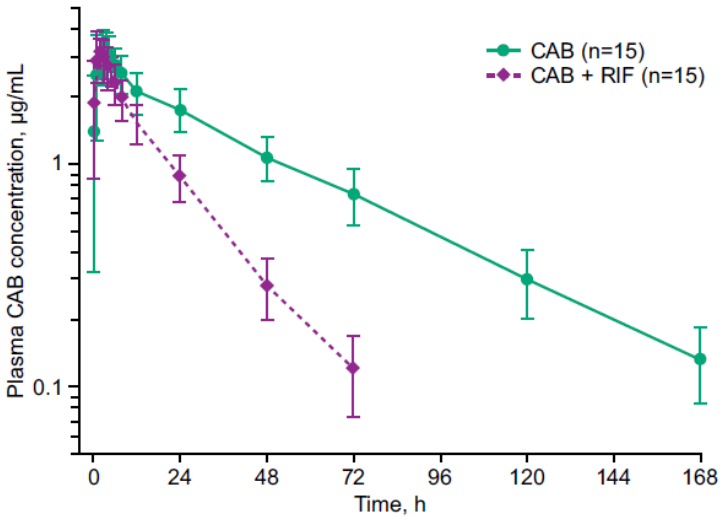
DDIs do not impact drug half-life (governed by absorption rate)



Drug-drug interactions with strong inducers

Cabotegravir oral + rifampicin

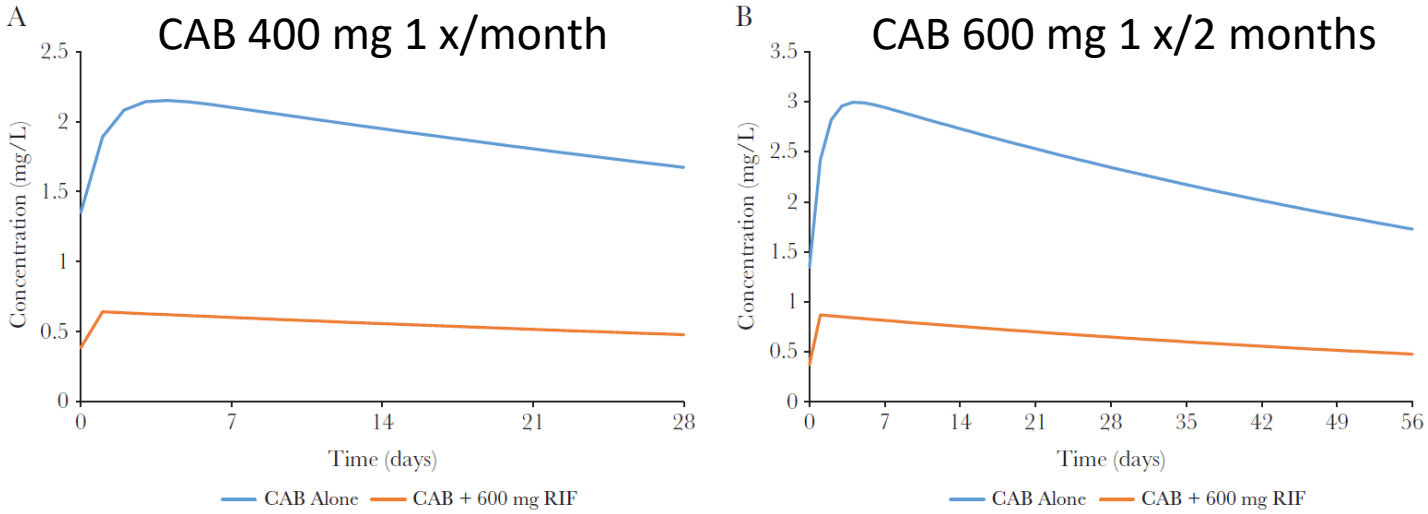
CAB AUC↓ by 59%; $t_{1/2}$ by 57%



Cabotegravir im + rifampicin (first maintenance dose)

CAB AUC↓ by 41%; $t_{1/2}$ ↔

CAB AUC↓ by 46%; $t_{1/2}$ ↔



Magnitude of drug-drug interaction with im administration is predicted to be more pronounced after multiple maintenance doses.

Ford SL et al. AAC 2017

Rajoli RKR et al. JID 2019

Drug-drug interactions with strong inhibitors of UGT1A1

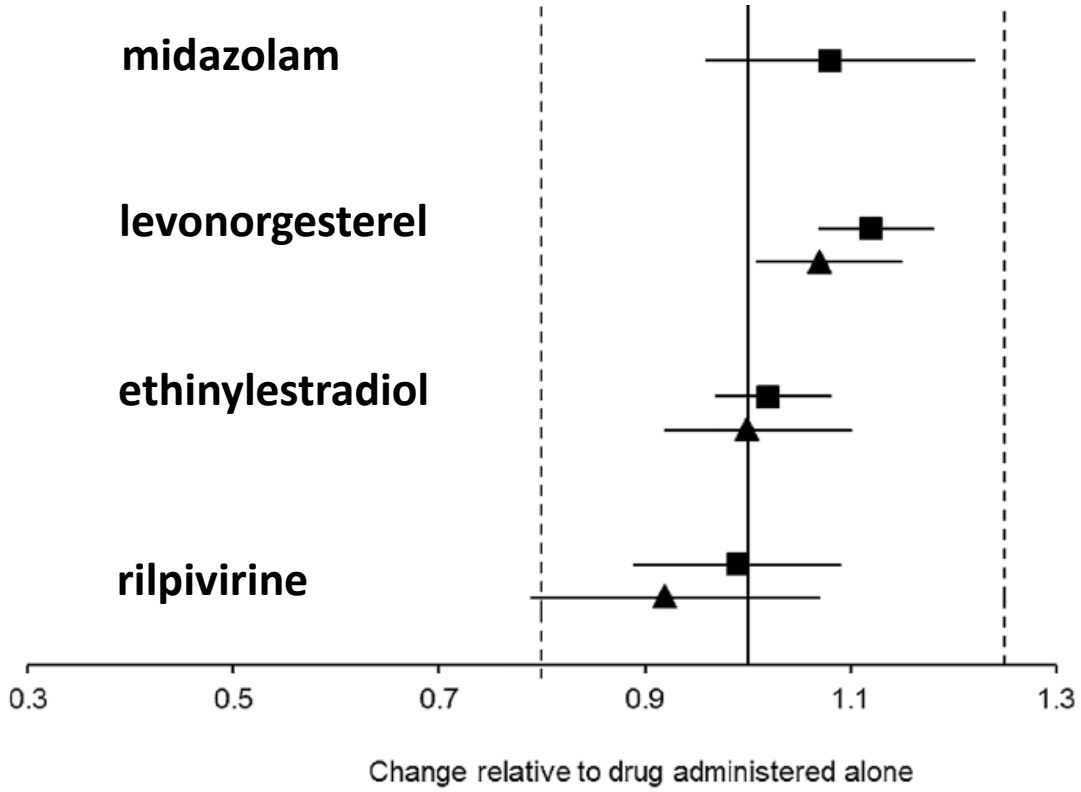
Predictions using CAB PBPK Model

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)

Taskar K et al. 20th PK Workshop 2019

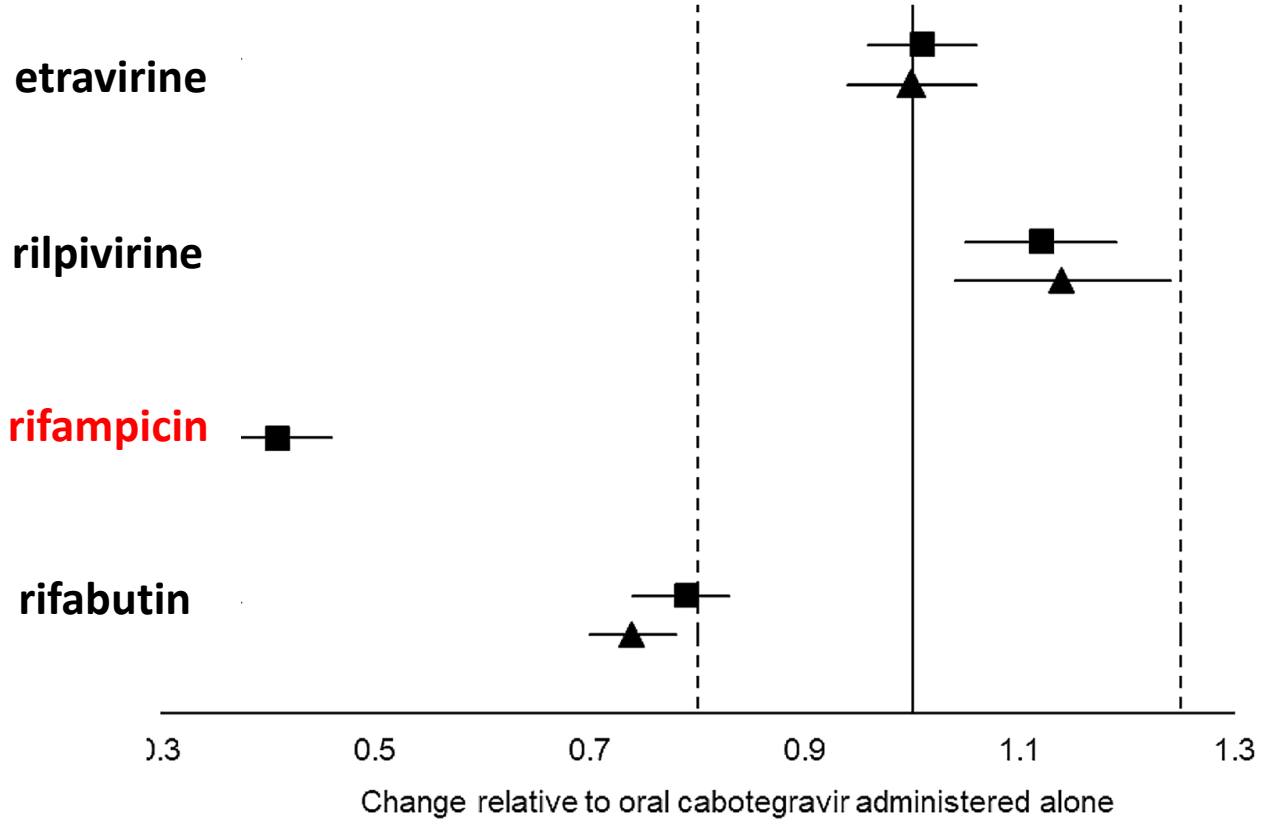
Drug-drug interactions studies with cabotegravir

Effect of cabotegravir on comedications



➔ **Cabotegravir has a low potential to cause PK DDIs**

Effect of comedications on cabotegravir

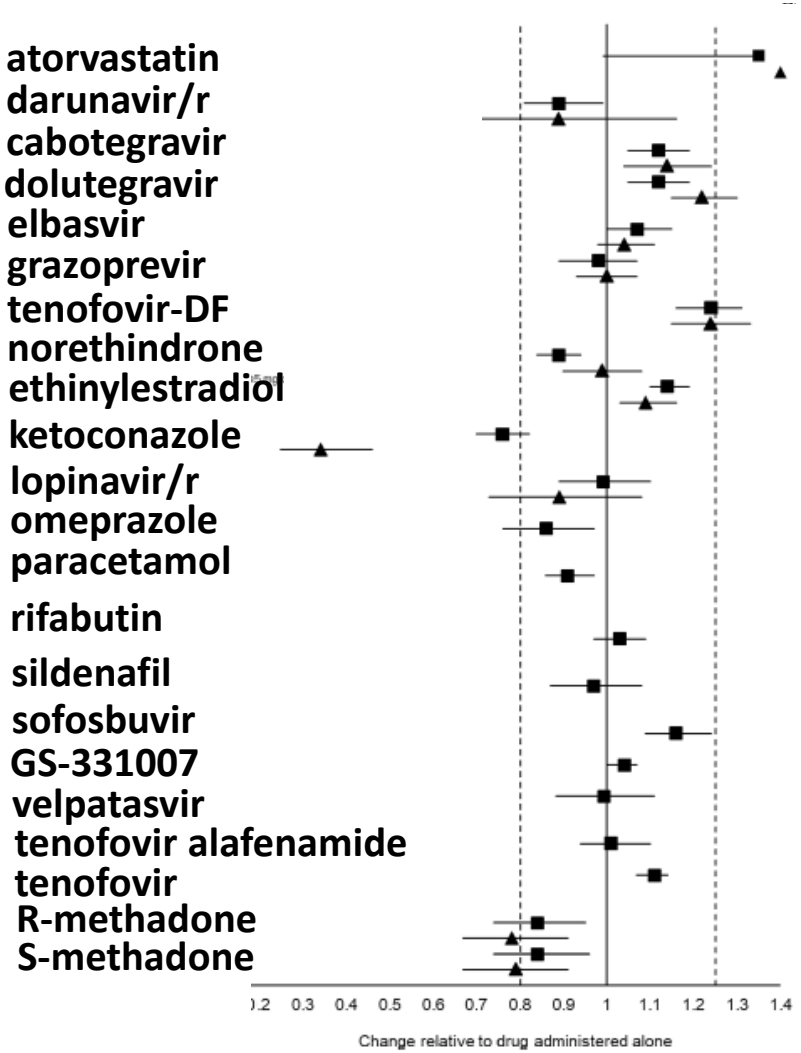


➔ **Cabotegravir is impacted by strong inducers whereas moderate inducers cause a smaller decrease.**

Hodge D et al. Clin Pharmacokinet 2021

Drug-drug interactions studies with rilpivirine

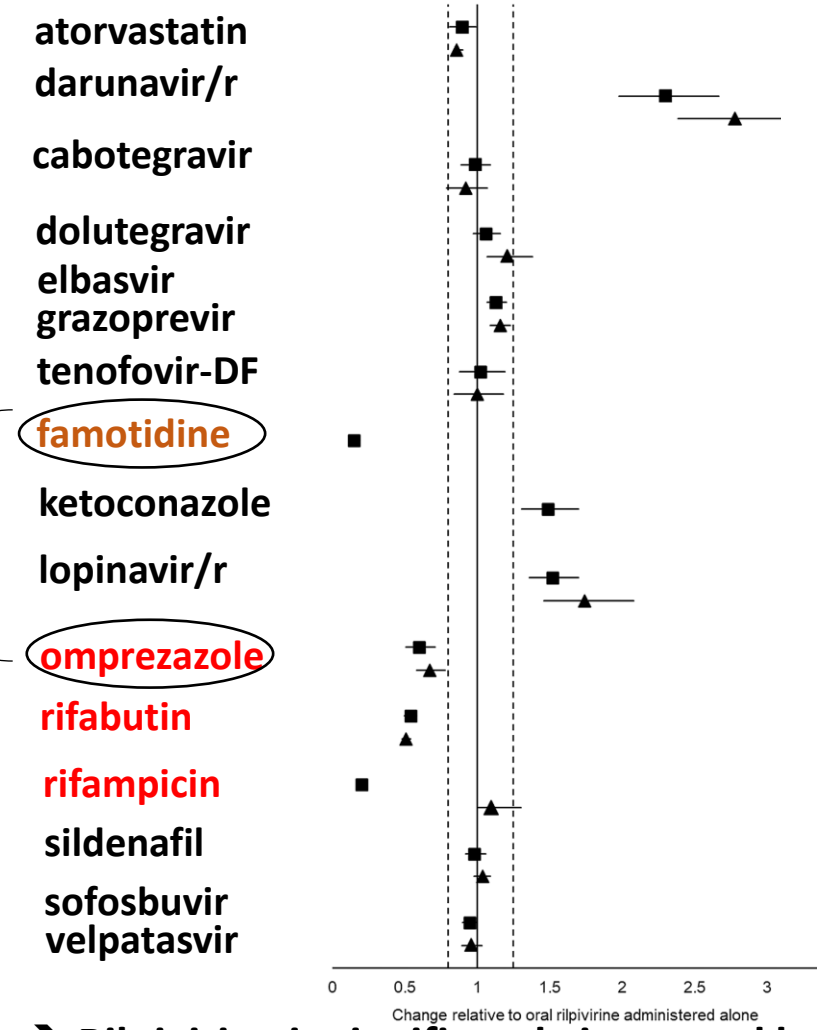
Effect of rilpivirine on comedications



➔ **Rilpivirine has a low potential to cause PK DDIs**

Effect of comedications on rilpivirine

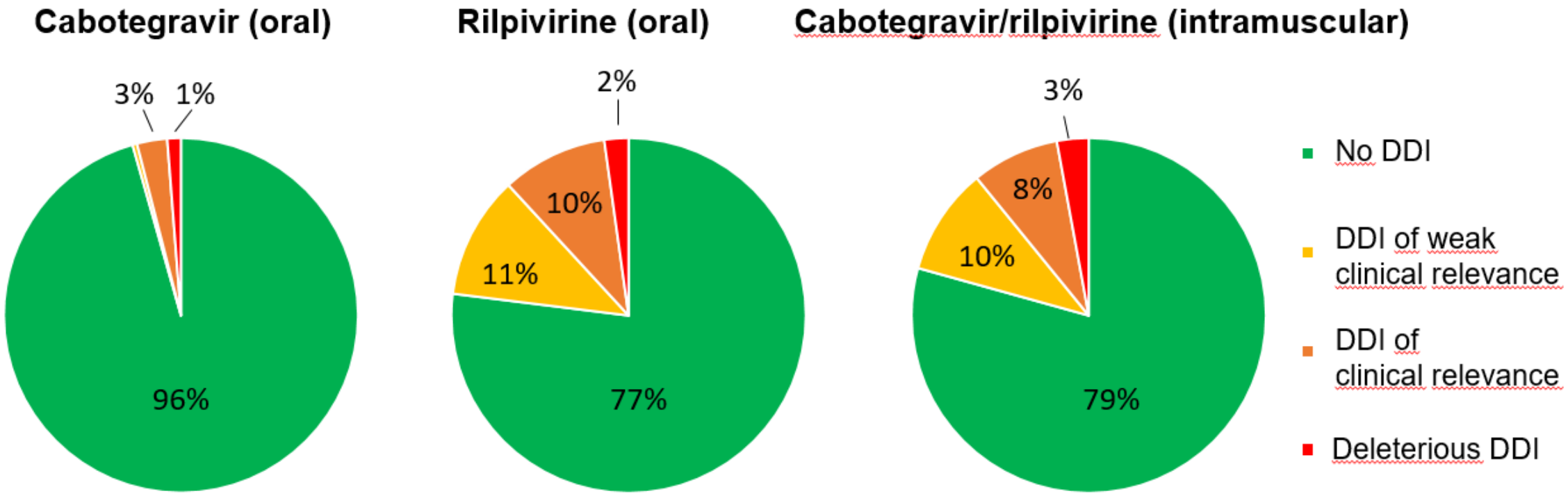
only for oral rilpivirine



➔ **Rilpivirine is significantly impacted by strong and moderate inducers.**

Hodge D et al. Clin Pharmacokinet 2021

DDI profile of oral and LA cabotegravir/rilpivirine considering >700 comeds



Red: strong and moderate inducers
Amber: coadministration with drugs with known risk QT prolongation
Amber: coadministration with NTI substrate of OAT1/3
Yellow: coadministration with drugs with possible risk QT prolongation
Yellow: coadministration with strong inhibitors

www.HIV-druginteractions; Hodge D et al. Clin Pharmacokinet 2021

Cabotegravir LA for HIV prevention

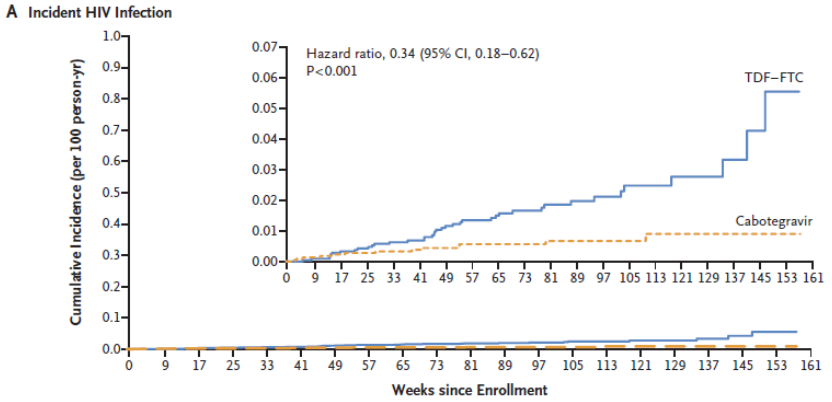
HPTN 083 study

The NEW ENGLAND JOURNAL of MEDICINE 2021

ORIGINAL ARTICLE

Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women

R.J. Landovitz, D. Donnell, M.E. Clement, B. Hanscom, L. Cottle, L. Coelho, R. Cabello, S. Chariyalertsak, E.F. Dunne, I. Frank, J.A. Gallardo-Cartagena, A.H. Gaur, P. Gonzales, H.V. Tran, J.C. Hinojosa, E.G. Kallas, C.F. Kelley, M.H. Losso, J.V. Madruga, K. Middelkoop, N. Phanuphak, B. Santos, O. Sued, J. Valencia Huamaní, E.T. Overton, S. Swaminathan, C. del Rio, R.M. Gulick, P. Richardson, P. Sullivan, E. Piwowar-Manning, M. Marzinke, C. Hendrix, M. Li, Z. Wang, J. Marrazzo, E. Daar, A. Asmelash, T.T. Brown, P. Anderson, S.H. Eshleman, M. Bryan, C. Blanchette, J. Lucas, C. Psaros, S. Safren, J. Sugarman, H. Scott, J.J. Eron, S.D. Fields, N.D. Sista, K. Gomez-Feliciano, A. Jennings, R.M. Kofron, T.H. Holtz, K. Shin, J.F. Rooney, K.Y. Smith, W. Spreen, D. Margolis, A. Rinehart, A. Adeyeye, M.S. Cohen, M. McCauley, and B. Grinsztejn, for the HPTN 083 Study Team*



Incident HIV infection occurred in 52 individuals
13 CAB LA (600 mg/8 weeks) (incidence 0.41/ 100 person per year)
39 oral TDF/FTC (incidence 1.22/100 person per year)

➔ CAB LA superior to daily oral TDF/FTC

FDA NEWS RELEASE

FDA Approves First Injectable Treatment for HIV Pre-Exposure Prevention

Drug Given Every Two Months Rather Than Daily Pill is Important Tool in Effort to End the HIV Epidemic

Approval of APRETUDE on December 20, 2021

Oral Lead-in (at Least 28 Days)	Intramuscular (Gluteal) Initiation Injection (Month 2 and Month 3)	Intramuscular (Gluteal) Continuation Injection (Month 5 and Every 2 Months Onwards)
Oral cabotegravir 30 mg by mouth once daily for 28 days	APRETUDE[a] 600 mg (3 mL)	APRETUDE[b] 600 mg (3 mL)

[a] Should be administered on the last day of oral lead-in or within 3 days thereafter.
[b] Individuals may be given APRETUDE up to 7 days before or after the date the individual is scheduled to receive the injections.

Table 2. Recommended Dosing Schedule (Direct to Injection) for Pre-exposure Prophylaxis in Adults and Adolescents Weighing at Least 35 kg

Intramuscular (Gluteal) Initiation Injection (Month 1 and Month 2)	Intramuscular (Gluteal) Continuation Injection (Month 4 and Every 2 Months Onwards)
APRETUDE[a] 600 mg (3 mL)	APRETUDE[a] 600 mg (3 mL)

[a] Individuals may be given APRETUDE up to 7 days before or after the date the individual is scheduled to receive the injections.

Apretude Highlights of Prescribing Information 2021

Drug-drug interactions with cabotegravir LA for HIV prevention

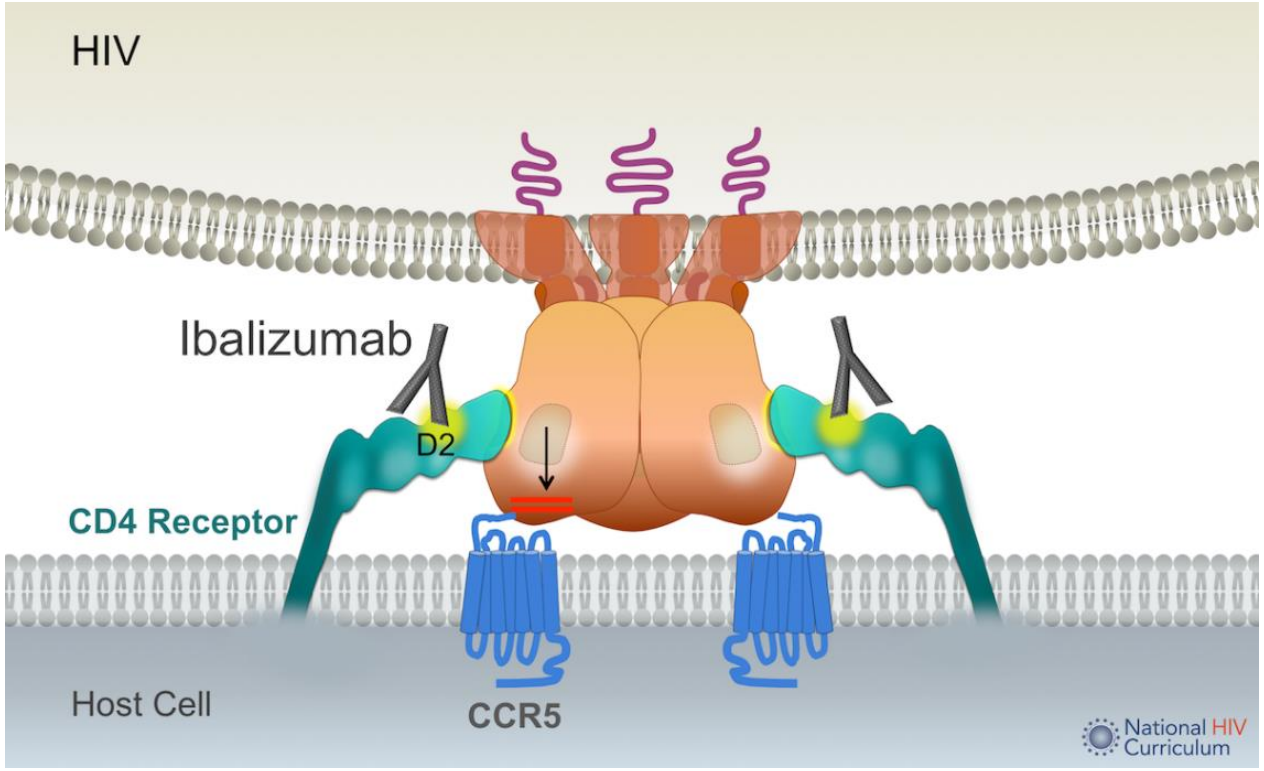
Yellow: coadministration with drugs with possible risk QT prolongation
Yellow: coadministration with strong inhibitors
Amber: coadministration with drugs with known risk QT prolongation
Amber: coadministration with NTI substrate of OAT1/3
Red: strong inducers
➔ Amber: moderate inducers

When rifabutin is started before or concomitantly with the first initiation injection of APRETUDE, the recommended dosing of APRETUDE is one 600-mg (3-mL) injection, followed 2 weeks later by a second 600-mg (3-mL) initiation injection and monthly thereafter while on rifabutin.
When rifabutin is started at the time of the second initiation injection or later, the recommended dosing schedule of APRETUDE is 600 mg (3 mL) monthly while on rifabutin.
After stopping rifabutin, the recommended dosing schedule of APRETUDE is 600 mg (3 mL) every 2 months.

www.hiv-druginteractions.org; Apretude Highlights of Prescribing Information 2021

Ibalizumab

- Monoclonal antibody acting as a CD4-directed post-attachment inhibitor
- In combination with other ARVs in heavily treatment-experienced adults who are failing their current ART regimen
- Ibalizumab is administered as an iv loading dose of 2000 mg followed by maintenance dose of 800 mg every 2 weeks
- Estimated half-life is 72-84 h (note: half-life is less than the 2-3 weeks half-life IgG. This is explained by different clearance mechanisms).



Emu B et al. NEJM 2018; Jacobson JM et al. Antimicrob Agents Chemother 2009

Drug-drug interactions with ibalizumab

No drug-drug interaction studies have been conducted with ibalizumab but no drug interactions are expected given that ibalizumab elimination is driven by binding to CD4 receptor, internalization and degradation.

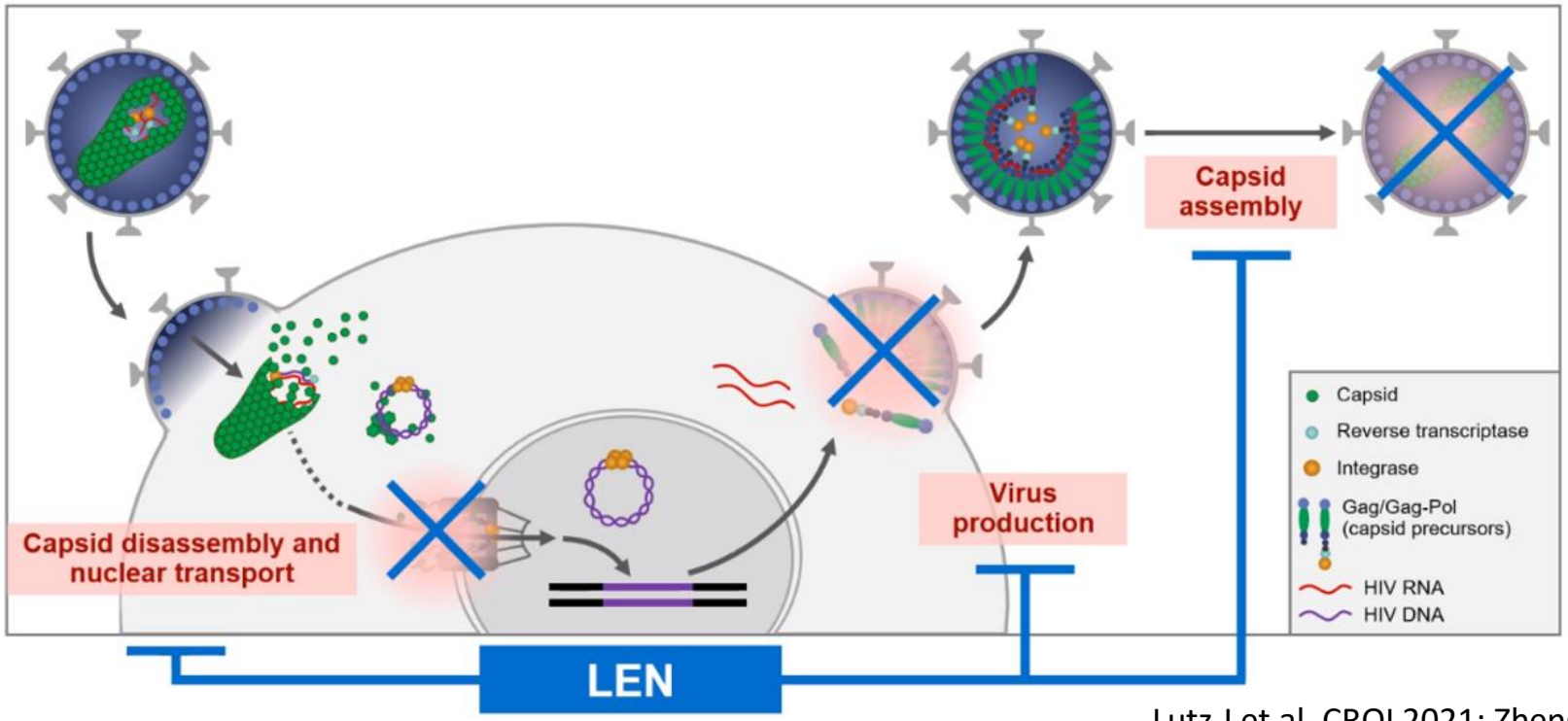
Ibalizumab-uiyk as a bridge therapy for a patient with drug-resistant HIV-1 infection receiving chemotherapy: A case report

- Patient HIV+ since 2005 with a new diagnosis of diffuse large B-cell lymphoma.
- Treated with multiple ART treatments over the years, development of multiple resistances.
- Treatment with RPV, DTG, DRV/c at the time of DLBCL diagnosis.
- Planned chemotherapy: rituximab, etoposide, prednisone, doxorubicin, vincristine and cyclophosphamide => DDIs with with DRV/c.
- ARV regimen switched to RPV, DTG + ibalizumab. DRV/c was held on the days the patient received chemotherapy.
- VL became undetectable, patient completed 6 cycles of chemotherapy without any dose limiting toxicities.

Dickter JK et al. J Clin Pharm Ther 2021

Lenacapavir

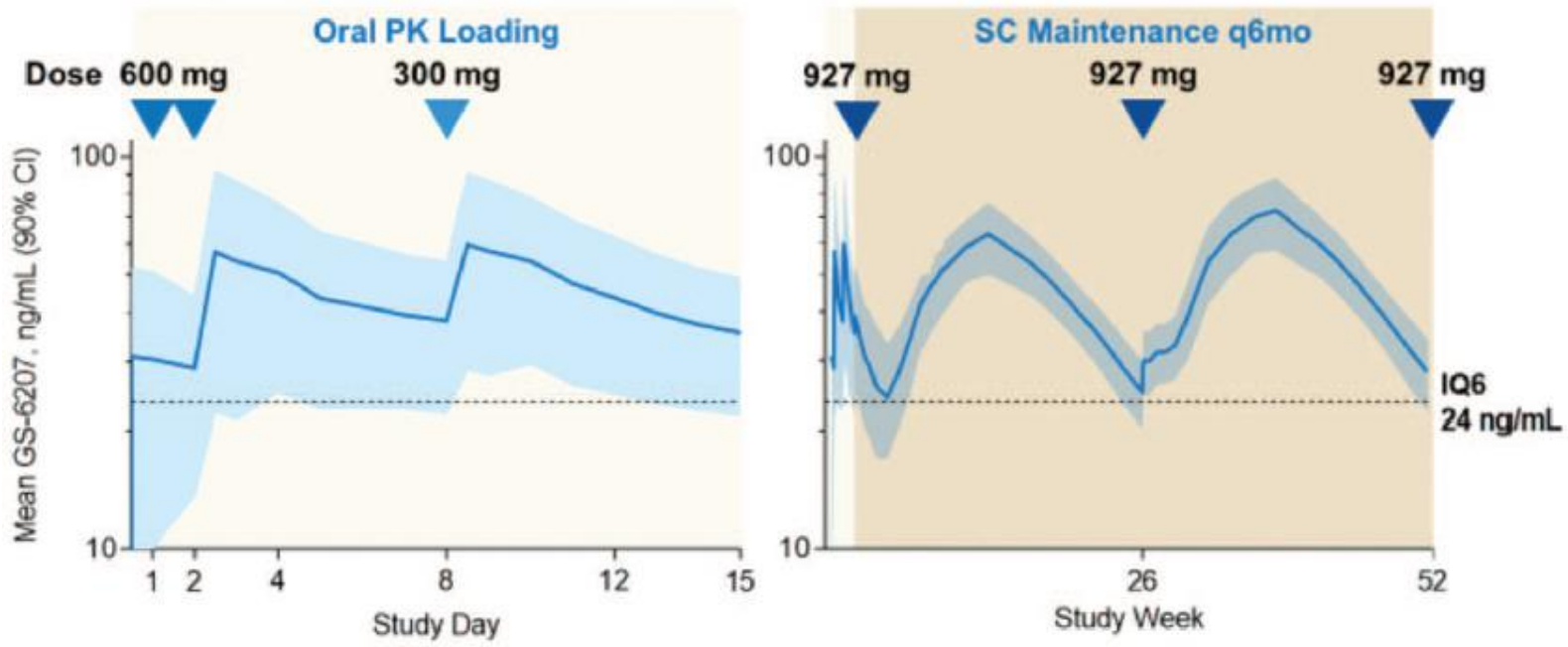
- Lenacapavir is a first-in-class capsid inhibitor which interferes with multiple capsid-dependent functions essential for viral replication: capsid assembly and disassembly as well as nuclear transport and virus production.
- Lenacapavir exhibits antiviral activity at picomolar levels (EC_{50} 0.05 ng/mL) and has no cross resistance to ARV classes.
- In heavily treatment-experienced persons with multidrug-resistant HIV and in treatment naive with HIV, lenacapavir led to high rates of virologic suppression.



Lutz J et al. CROI 2021; Zheng J et al. IDWeek 2018

Lenacapavir dosing

- Lenacapavir has demonstrated adequate pharmacokinetic exposure for up to 6 months after a single sc injection.
- Lenacapavir has a $t_{1/2}$ of 10-12 days (oral) and $t_{1/2}$ of 8-12 weeks (subcutaneous).
- Maintenance dose is 927 mg every 6 months which allow to maintain concentrations >24 ng/mL. Given the slow initial lenacapavir release, an initial oral dosing may be needed to reach sufficient levels faster.



Lutz J et al. CROI 2021; Begley R et al. Int AIDS Conference 2020

Drug-drug interactions with lenacapavir

Lenacapavir	Relevant for DDI
Metabolism	UGT1A1 (major); CYP3A4 (minor)
Transport	P-gp;
Inducer of	no
Inhibitor of	CYP3A4 (moderate); P-gp (weak); BCRP (weak)

Strong Inhibition of:	CYP3A	CYP3A/P-gp	CYP3A/P-gp/UGT
Inhibitor:	VORI	COBI	ATV/COBI
LEN AUC % increase*:	30 (2–67)	130 (80–190)	300 (200–420)

- Strong CYP3A4 and CYP3A4/P-gp inhibitors cause increase in lenacapavir exposure which are not considered to be clinically relevant => coadministration without dose adjustment.
- Strong UGT1A1 inhibitors cause substantial increase in lenacapavir exposure => coadministration not recommended.

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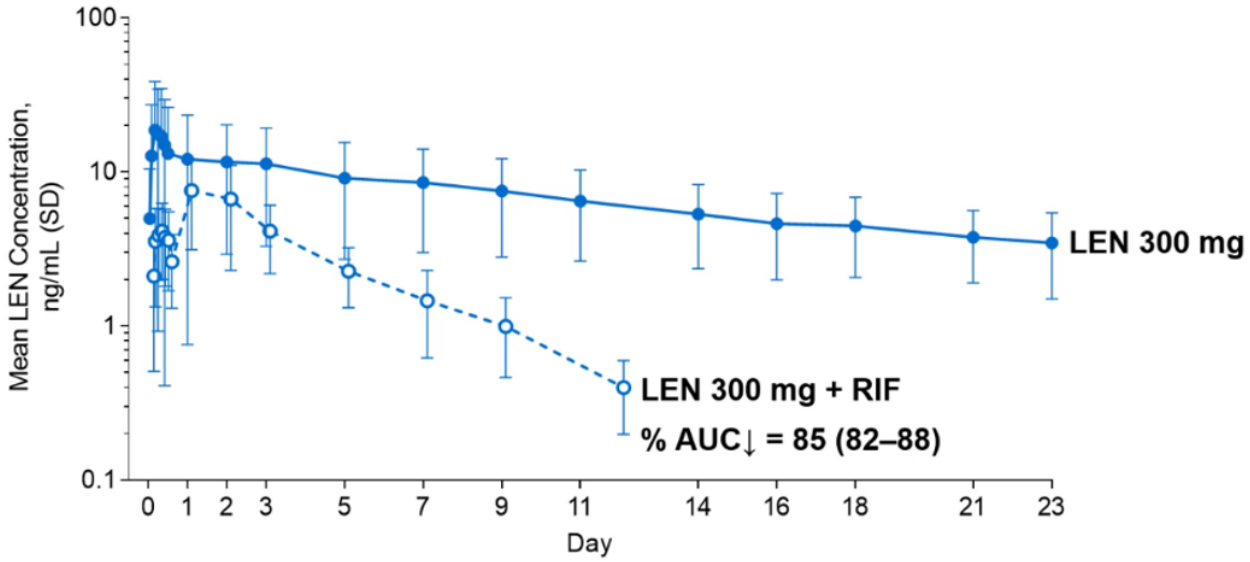
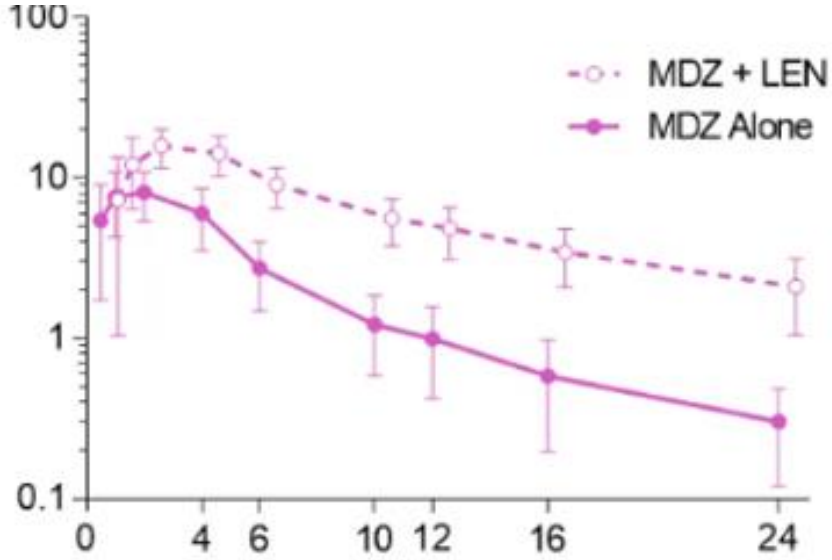
Drug-drug interactions with lenacapavir

LEN + rifampicin => 85% decrease in LEN exposure



LEN + midazolam => 3 fold increase in midazolam exposure



LEN + efavirenz => 56% decrease in lenacapavir exposure

➔ Inducers of CYP3A4/UGT/P-gp should be avoided
➔ Caution is needed with sensitive CYP3A4 substrates

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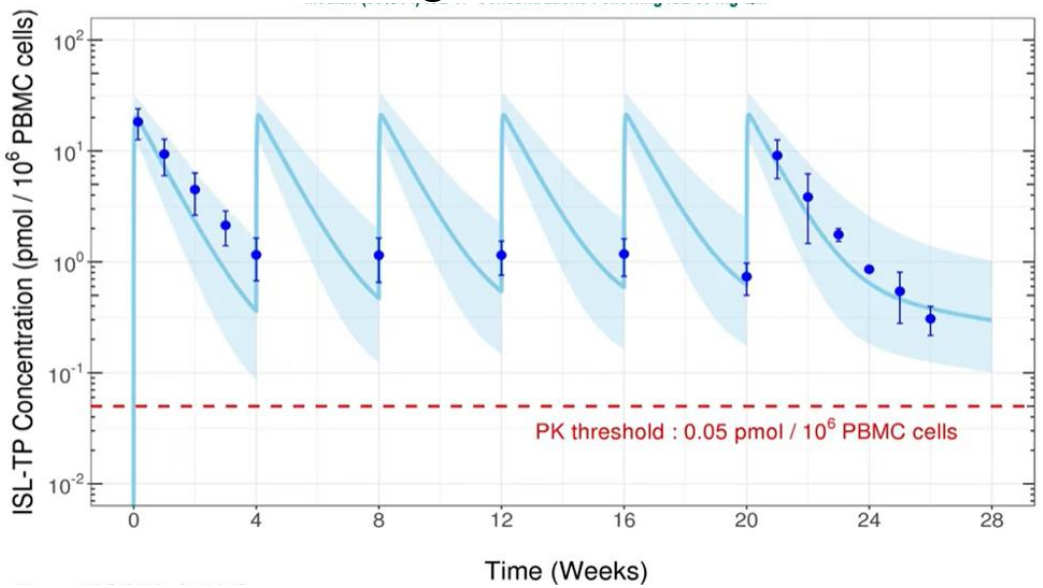
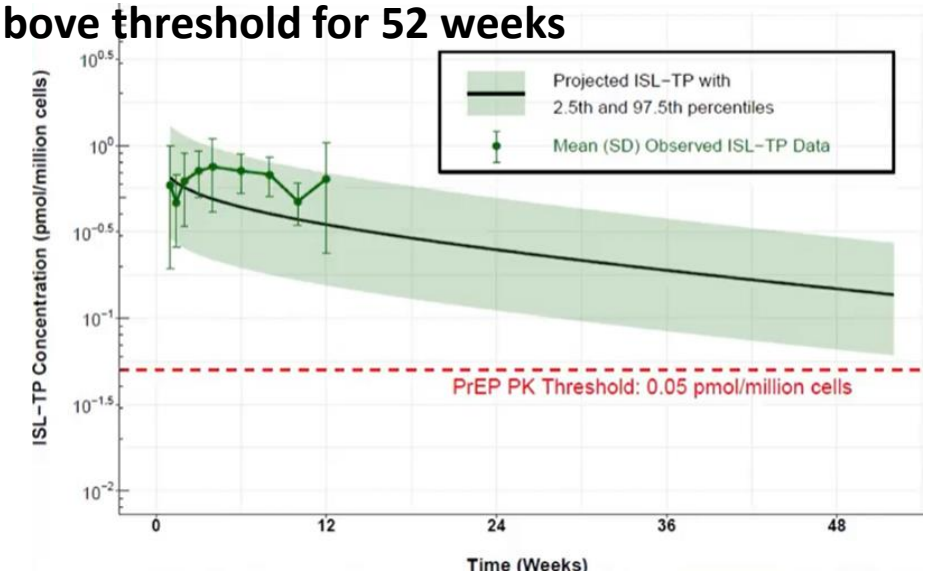
Islatravir

- Islatravir is a first-in-class nucleoside reverse transcriptase translocation inhibitor which blocks primer translocation and causes chain termination during viral transcription.
- Islatravir is phosphorylated intracellularly into the active metabolite islatravir triphosphate (long intracellular $t_{1/2}$ of 118-171 hours).
- Islatravir triphosphate PK threshold is set as 0.05 pmol/10^6 PBMC cells

Islatravir 60 mg oral 1x/month for PrEP



Islatravir 56 mg implant projected to reach concentrations above threshold for 52 weeks



Markowitz M & Grobler JA Curr Op HIV & AIDS 2020; Patel M et al. CROI 2021; Matthews RP et al. CROI 2021

Drug-drug interactions with islatravir

- Islatravir is metabolized by deaminase-mediated metabolism and is eliminated renally
- Islatravir is not a substrate or inhibitor of renal transporters
- Islatravir does not inhibit or induce UGT, CYP or transporters

➔ Islatravir is unlikely to be a victim or perpetrator of drug-drug interactions

Islatravir Risk of Interaction with Metabolic Enzymes

Enzyme	Mechanism of Inhibition	Islatravir IC_{50} (μM) [a]	Maximum Unbound Plasma Concentration [b] ($I_{max,u}$) to $K_{i,u}$ [c] Ratio (μM)	Intestinal Concentration [d] (I_{gut}) to $K_{i,u}$ [c] Ratio (μM)	DDI Potential [f]
CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6	Reversible	>100	<0.019	N/A	Low risk
CYP3A4	Reversible	>200	<0.010	<8.2	Low risk
UGT1A1	Reversible	>100	N/A	<16.4	Low risk [g]
CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4	Time dependent	>50	N/A	N/A	Low risk [h]

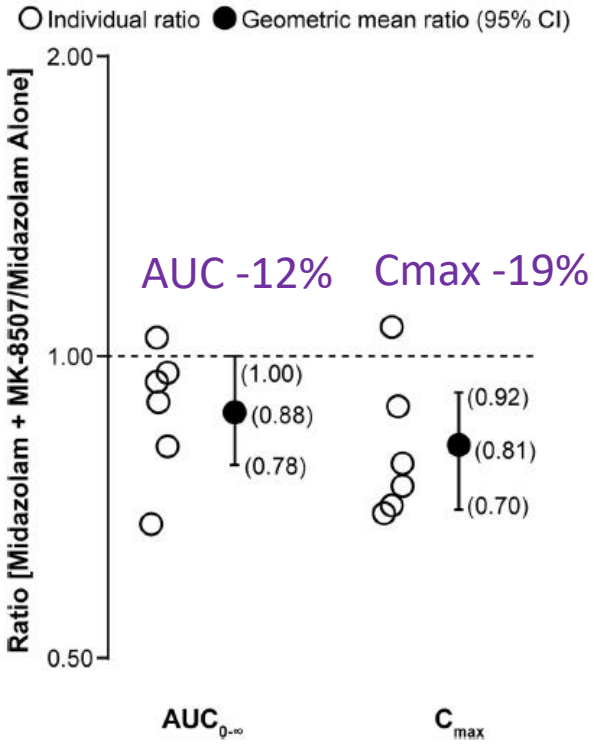
Islatravir Risk of Interaction with Drug Transporters

Transporter	Islatravir IC_{50} (μM) [a]	Maximum Unbound Plasma Concentration [b] ($I_{max,u}$) to IC_{50} Ratio (μM)	Intestinal Concentration [d] (I_{gut}) to IC_{50} Ratio (μM)	Maximum Unbound Inlet Concentration [e] ($I_{in,max,u}$) to IC_{50} Ratio	DDI Potential [f]
OATP1B1, OATP1B3, OCT1	>300	N/A	N/A	<0.035	Low risk
OAT1, OAT3, OCT2	>100	<0.010	N/A	N/A	Low risk
MATE1, MATE2K	>75	<0.013	N/A	N/A	Low risk
BCRP	>100	<0.010	<8.2	N/A	Low risk
MDR1 P-gp	>200	<0.005	<4.1	N/A	Low risk

Bleasby K et al. Viruses 2021

MK-8507

- MK-8507 is a non-nucleoside reverse transcriptase in development
- Doses >100 mg achieved plasma concentrations at day 7 associated with antiviral efficacy
- MK-8507 shown to induce CYP3A4 in vitro however clinical DDI study with midazolam showed a modest decrease in midazolam AUC (-12%) and AUC (-19%). Based on these data, MK-8507 is considered to be not a meaningful inducer of CYP3A4.



Ankrom W et al. Antimicrob Agent Chemother 2021

Conclusions

- LA antiretroviral drugs have a lower risk for drug-drug interactions comparable to unboosted ARV
- LA are not devoid of hurdles, need to better understand:

  - relevance of certain DDIs in special population
  - management of certain DDIs in case of inaugural diseases
  - management of DDIs in case of missed injection visits
  - theoretical risk of developing resistances during the PK tail will need to be carefully evaluated

Acknowledgements

University Hospital Basel

Mattia Berton

Sara Bettonte

Felix Stader

UNIVERSITY OF LIVERPOOL

David Back

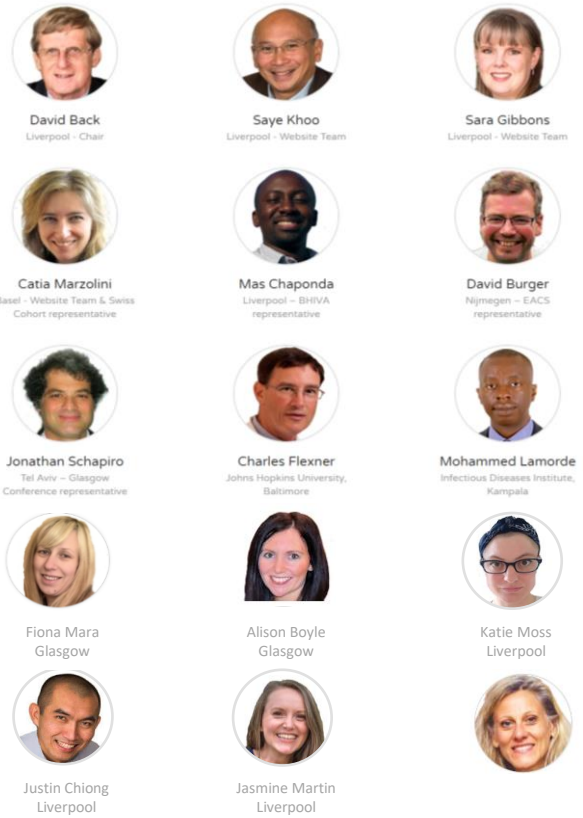
Saye Khoo

Daryl Hodge

Sara Gibbons

HIV Drug Interactions

Liverpool website team & editorial board



Funding

FNSNF Swiss National Science Foundation

OPO STIFTUNG

isaac dreyfus bernheim FONDATION/STIFTUNG

Adolf & Mary Mil Stiftung