Antiretroviral Drug-Drug Interaction Profile of Long-Acting Cabotegravir and Rilpivirine

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Differential Impact of Pharmacokinetic-Based DDIs on CAB + RPV LA

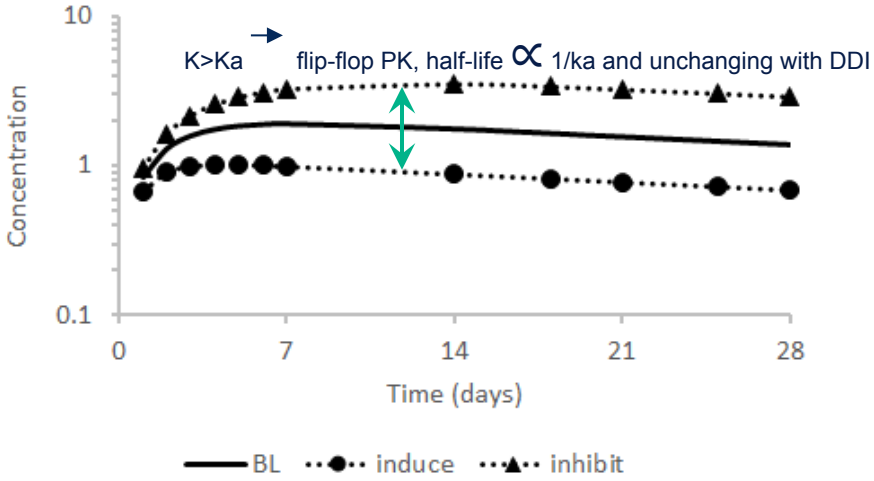
- **Cabotegravir (CAB) and rilpivirine (RPV) is the first long-acting (LA), two-drug antiretroviral regimen administered monthly or every 2 months for the maintenance of HIV-1 virologic suppression**
- CAB + RPV LA is administered as separate gluteal IM injections from which drug is slowly absorbed into systemic circulation resulting in sustained plasma concentrations over time
- CAB is metabolized via UGT1A1 with minor UGT1A9 component and RPV is metabolized by CYP3A; neither are inducers or inhibitors of metabolic enzymes

- Metabolic (CYP/UGT) inducers and inhibitors as perpetrators of DDIs affect the victim drug's elimination half-life through changes in CL and overall drug exposure (AUC)
- For drugs with flip-flop PK, the net effect from a drug interaction is a parallel upward (inhibitor) or downward (inducer) shift in the concentration-time course and no change in elimination rate (Figure)

- **Few clinically relevant PK-mediated DDIs exist during active CAB + RPV LA therapy:**
  - Strong metabolic inducers are contraindicated
  - Use caution with sensitive OAT1/3 substrate drugs with narrow therapeutic index (methotrexate)
  - Use caution in individuals receiving chronic systemic anticoagulation given IM delivery of CAB + RPV LA
  - Use caution with drugs with a known risk of Torsade de Pointes
- **Following CAB + RPV LA discontinuation, there are no clinically relevant DDIs during LA PK tail**
  - No DDI-based restrictions with alternate ART: PIs, NNRTIs, NRTIs, INIs, entry inhibitors, and ibalizumab
  - Metabolic inducers will not hasten removal of CAB + RPV LA
- **Drugs that may be used without restriction with CAB + RPV LA include:**
  - Hormonal contraceptives (combination or progestin-only; oral or parenteral), HBV and most HCV antivirals, most antibiotics (including IM formulations), gastric acid–modifying agents, polyvalent cation products, and drugs for other co-morbidities

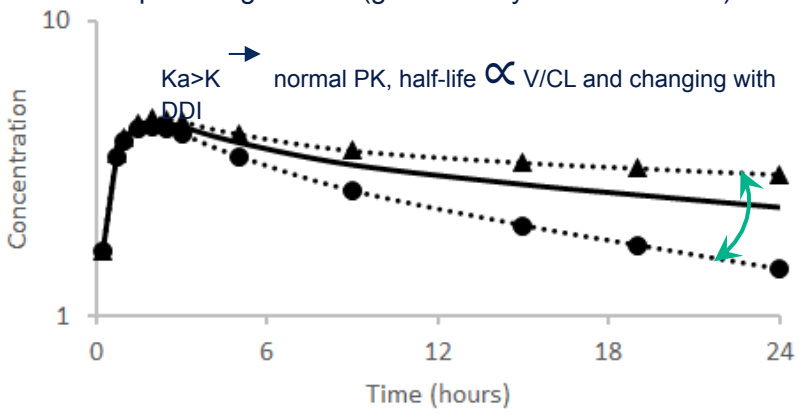
Conc-time profile for LA drugs with flip-flop PK with DDI

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



Conc-time profile for oral drugs with standard PK with DDI

DDIs impact drug half-life (governed by elimination rate)



∝:proportional

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Established and Other Potentially Significant Drug Interactions for CAB + RPV LA

	Contraindicated				Consider alternatives[1]	Clinical monitoring recommended
Concomitant drug class	**Anti-convulsants**	**Anti-mycobacterials**		**Glucocorticoid (systemic)**	**Herbal product**	**Macrolide or ketolide antibiotics**	**Narcotic analgesic**
Primary support for DDI guidance	Theoretical	Extrapolation from oral DDI and PK modelling or theoretical		Theoretical	Theoretical	Theoretical	Extrapolation from oral DDI study
Drug name	Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	Rifampicin Rifapentine	Rifabutin	Dexamethasone*	St. John's wort†	Clarithromycin Erythromycin	Methadone
Metabolic enzyme impacted	CYP3A UGT	CYP3A UGT	CYP3A UGT	CYP3A	CYP3A	CYP3A	CYP3A
Effect on concentration	↓ CAB ↓ RPV	↓ CAB ↓ RPV	↓ CAB ↓ RPV ↔ RBT	↓ RPV	↓ RPV	↔ CAB ↑- RPV	↔ CAB ↔ RPV ↓ Methadone

1. Consider alternatives to clarithromycin and erythromycin because of risk of TdP with these drugs.

*More than a single-dose treatment.

†Hypericum perforatum.

↑ = Increase ↓ = Decrease ↔ = No change

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Recommendations Based on Predicted Drug Interactions With CAB + RPV LA

Concomitant drug class (drug name)	Anticipated effect on concentration of CAB + RPV LA or concomitant drug	Clinical comment
Strong UGT1A1/CYP3A inducers (rifampin,* carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and rifapentine)	Decreased CAB and RPV concentrations	Co-administration is contraindicated due to potential for loss of therapeutic effect and development of resistance
Moderate and weak UGT1A1/CYP3A4 inducers (e.g. rifabutin*)		
UGT1A1 inhibitors (e.g. erlotinib, sorafenib)	No clinically relevant drug interaction expected	No dose adjustment necessary
CYP3A4 inhibitors (e.g. ketoconazole)		No clinically relevant drug interaction expected
Antacids containing polyvalent cations (e.g., Mg, Al, or Ca) **Calcium supplements** **Iron supplements**	No drug interaction expected with CAB + RPV LA (parenteral dosing bypasses GI tract)	Depending on type of gastric acid - modifying agent, either contraindicated or to be dosed with separation in time
Proton pump inhibitors (e.g. lansoprazole, esomeprazole, omeprazole, pantoprazole)		
Histamine-2 receptor antagonists (e.g. cimetidine, ranitidine, famotidine, nizatidine)		
Statins (e.g. atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin)	Statins are mostly substrates of CYP3A4, BCRP, and OATP No drug interaction expected	No dose adjustment necessary
HBV medications (e.g. adefovir, entecavir, lamivudine, telbivudine, tenofovir disoproxil fumarate, tenofovir alafenamide)	HBV medications are primarily excreted in urine and are substrates of BCRP, Pgp, and OCT No drug interaction expected	
HCV medications† (e.g. ledipasvir, sofosbuvir, velpatasvir, voxilaprevir, ombitasvir, paritaprevir, dasabuvir, glecaprevir, pibrentasvir, elbasvir, grazoprevir)	HCV medications are mostly substrates of CYP3A4, BCRP, OATP, and Pgp No drug interaction expected	
Opioid dependence treatments (e.g. methadone, buprenorphine)	Methadone and buprenorphine are metabolized by CYP3A4 Clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients	

*Interaction studied.

†CAB + RPV LA has not been studied in patients with hepatitis B co-infection.

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