

Drug-Drug Interactions With Long-Acting Antivirals: Difficult to Study, Easy to Manage?



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Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Burger reported receiving consulting or advisor fees paid to his institution from Merck Sharp & Dohme and grants paid to his institution from Merck Sharp & Dohme, Gilead Sciences, Inc, and ViiV Healthcare. (Updated October 15, 2026)

Slide 2

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe the drug-drug interaction profile of long-acting antiretrovirals
- List potential challenges in performing drug-drug interaction studies with long-acting antiretrovirals
- Explain the value of physiologically-based pharmacokinetic (PBPK) modeling in predicting drug-drug interactions between strong enzyme inducers and lenacapavir

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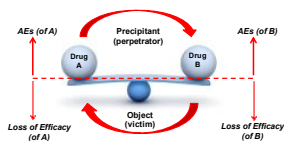
Outline of my presentation

- The basics of drug-drug interactions (DDIs) (in 5 minutes)
- How to study DDIs with new drugs
- DDI profiles of long-acting ART
 - CAB/RPV
 - LEN
 - ISL/LEN
- Discussion & Conclusions

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Concept of Precipitant and Object of DDIs



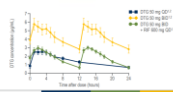
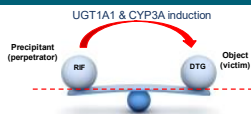
Need to understand:
The disposition or handling of each drug
The therapeutic window of each drug

Personal Communication:
Professor D J Back

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Example of a DDI: Rifampicin + Dolutegravir



Personal Communication:
Professor D J Back

Dooley et al. JAIDS 2013

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Two important concepts in PK DDIs: inhibition & induction

- Drugs can **inhibit** metabolic enzymes and drug transporters, leading to **increased** concentrations of relevant substrates (three categories: weak, moderate, strong)
- Drugs can **induce** metabolic enzymes and drug transporters, leading to **reduced** concentrations of relevant substrates (three categories: weak, moderate, strong)

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Two important differences between PK DDIs based on inhibition & induction

- **Inhibition** starts directly at the first dose, becomes maximal at steady-state, and stops when concentrations of the inhibitor have disappeared (usually, when dosing has stopped. Exception: long-acting!)
- **Induction** requires 1-2 weeks before becoming maximal, remains present 1-2 weeks after dosing of the inducer has stopped.

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Understanding (or predicting) PK DDIs

- Assess which drug has which role: precipitant or object
- Assess the mechanism: inhibition and induction

→ *what kind of intervention is needed?*

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How to study DDIs with new drugs

Preclinical studies

- give an indication whether a drug is a substrate of metabolic enzymes and/or drug transporters (object)
- give an indication whether a drug is able to inhibit or induce hepatic enzymes and/or drug transporters (precipitant)

These data determine which clinical DDI studies need to be performed during clinical development

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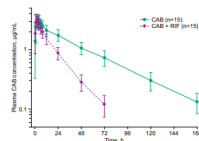
Cabotegravir/rilpivirine (CAB/RPV) - 1

Antimicrobial Agents
and Chemotherapy®

Effect of Rifampin on the Single-Dose Pharmacokinetics of Oral Cabotegravir in Healthy Subjects

S. L. Ford¹, R. Sutton¹, Y. Luo¹, Z. Zhang¹, A. Terasaki¹, C. Trossa¹, F. Patel¹, W. Sprenkle¹

2017 (B1) 400487-17



Effect of rifampin on rilpivirine AUC even larger: ~80% (Edurant SmPC)

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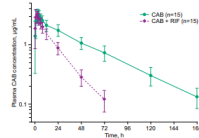
Cabotegravir/rilpivirine (CAB/RPV) - 2

Antimicrobial Agents
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2017 (B1) 400487-17



Effect of rifampin on rilpivirine AUC even larger: ~80% (Edurant SmPC)

Co-administration of rifampin and cabotegravir and rilpivirine (oral or l.m.) is contra-indicated

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Cabotegravir/rilpivirine (CAB/RPV) - 3

A single i.m. administration of LA CAB/RPV can lead to detectable plasma levels up to 52 weeks or even longer; this makes DDI studies in healthy volunteers unfeasible

Plasma (ng/mL)

Time (weeks)

Legend:

- LA CAB (open circles)
- LA RPV (filled circles)
- LA CAB (open squares)
- LA RPV (filled squares)
- LA CAB (open triangles)
- LA RPV (filled triangles)
- LA CAB (open diamonds)
- LA RPV (filled diamonds)

Source: Spreen et al JAIDS 2014

[illegible]

Spreen et al JAIDS 2014

Slide

Cabotegravir/rilpivirine (CAB/RPV) - 4

In the absence of a clinical DDI study, physiologically-based PK (PBPK) modelling might be an alternative

Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213174Orig1s001.pdf

Beatores et al. CPT Pharmacometrics & Syst Pharmac 2024; 13(5): 761-68

The diagram illustrates the human lymphatic system. On the left, a blue vertical cylinder represents the 'Venous' system. On the right, a red vertical cylinder represents the 'Artery'. A central column lists various organs and tissues: Lung, Adipose, Bone, Brain, Gut, Heart, Kidney, Muscle, Pancreas, Skin, Thymus, and Testis. A yellow box labeled 'Lymph Node' is positioned between the Venous system and the Lung. A network of red lines connects these organs to the lymphatic system. A legend on the right shows a box labeled 'Interstitial space' with arrows pointing to 'Lymphatic space' and 'Blood space'.

Battista et al. *CPT Pharmacom & Syst Pharma* 2024; 13(2): 781-84

Slide

Cabotegravir/rilpivirine (CAB/RPV) - 5

Predicting Drug-Drug Interactions Between Rifampicin and Long-Acting Cabotegravir and Rilpivirine Using Physiologically Based Pharmacokinetic Modeling

David A. Auld¹, Paul Hsieh², Jason Smith³, David Park⁴, Christine Mendenhall⁵, Andrew Hsieh⁶, and Brian Steward⁷

The Journal of Infectious Diseases • 2019;219(12):20

Management of Drug-Drug Interactions Between Long-Acting Cabotegravir and Rilpivirine and Comedications With Inducing Properties: A Modeling Study

David Steward¹, William Hwang², Kelly Smith³, Michael Rodriguez⁴, and Carlos Mendez del Rio⁵

Clinical Infectious Diseases • 2019;70(10):28

Predicted effect of rifampin administration on trough levels of LA CAB/RPV:

CAB: -46%	CAB: -62%
RPV: -82%	RPV: -40%

The two models agree to the same conclusion = contra-indication, though actual predictions vary to some extent

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The Journal of Interpersonal Violence 27(12):2515-2531

Clinical Infectious Diseases® 2012;54(7):1235–36

CAB: -46%

CAB: -62%

RPV: -82%

RPV: -40%

The two models come to the same conclusion = contra-indication, though actual predictions vary to some extent

Q14a

Open Forum Infectious Diseases

BRIEF REPORT

Long-Acting Cabotegravir/Rilpivirine Concentrations in Combination With Intravenous Rifampin: A Case Report

Shannon W. Stangor

Joshua P. Stangor

Anthony Padgett

Ryan Wilkins

Kristine E. Evans

and Sara R. Bane

Complex case of a TB/HIV-co-infected patient where only parenteral medication was possible, including rifampin and CAB/RPV.

7 days after administration of a 600/900 CAB/RPV loading dose, drug levels were:

CAB: 0.455 mg/L (ref.: approx. 4 mg/L) **89% ↓**

RPV: < 0.005 mg/L (ref.: approx. 0.133 mg/L) **>96% ↓**

OFID 2023

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Clinical experience with rifampin & CAB/RPV (2)

Rapid onset and offset of the interaction between rifampicin and long-acting cabotegravir/rilpivirine: A pharmacokinetic case report

Emilie M. Gilling

Lisanne A. H. Bevers

Wouter L. Smits

Rosa H. Elias

Annelies Verbon

David M. Burger

Berend J. van Welzen

Patient stable on LA CAB/RPV required MRSA eradication therapy including RIF 600mg BID.

RIF was started 6 weeks after last LA dose

Drug levels were measured before and at Day 7 of RIF treatment:

CAB: 2.08 → 0.90 mg/L (**57% ↓**)

RPV: 0.126 → 0.022 mg/L (**83% ↓**)

Br J Clin Pharmacol 2026; in press

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Discussion of clinical cases

- Both cases were not exactly similar as the scenarios used in PBPK modelling
- Impact of a strong inducer like rifampin was greatest for RPV
- Modelling scenarios with increased dosing of CAB/RPV did not lead to therapeutic levels

CAB/RPV remains contra-indicated with strong enzyme inducers

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What else can be said about DDIs with LA CAB/RPV?

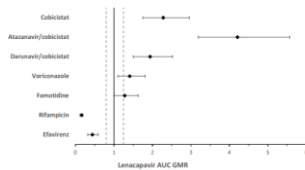
- Logically, there is no interaction with gastric acid-reducing agents as seen with oral RPV or with cations and oral InSTI
- RPV is a CYP3A substrate, so DDIs with CYP3A inhibitors (e.g., clarithromycin) remain clinically relevant
- DDI alerts (e.g., QTc prolongation) may be presented up to 6 months after last administration (depending on the system): clinically relevant?

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Lenacapavir (LEN) DDIs: as an Object (studied with oral LEN)(1)

- LEN is a substrate of CYP3A, UGT1A1 and P-gp



Marzolini et al. Expert Opin Drug Metab & Toxicol 2025

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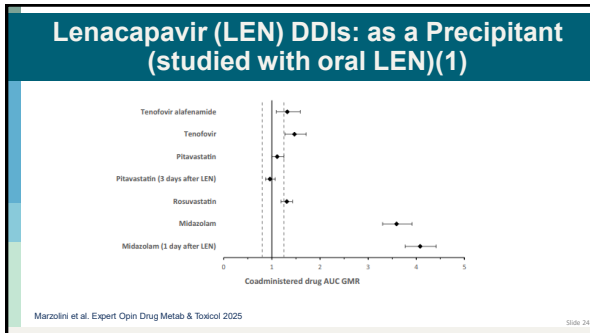
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Lenacapavir (LEN) DDIs: as an Object (studied with oral LEN)(2)

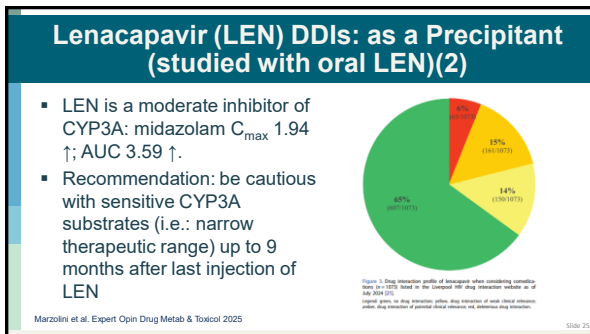
- LEN is a substrate of CYP3A, UGT1A1 and P-gp
- Rifampin (strong inducer) = **contra-indication**
- Moderate inducers (EFV, rifabutin) = **not recommended**
- Atazanavir/cobicistat (strong inhibitor of all three pathways) = **contra-indication**
- Inhibition of 1 or 2 pathways (e.g. DRV/c) = **not relevant** (escape pathway)

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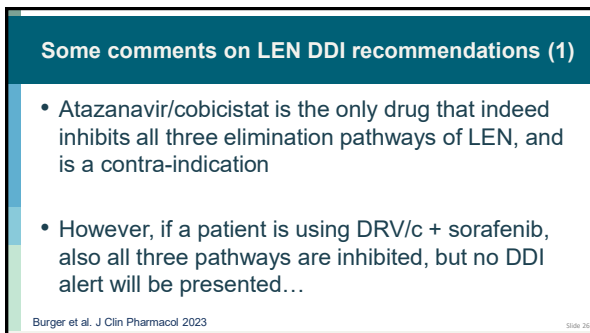
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Some comments on LEN DDI recommendations (2)

As LEN is a moderate CYP3A inhibitor, CYP3A substrates that are initiated several months after the last LEN injection are still prone to a DDI. Is the system working?

Clinical reports

A precautionary tale of lenacapavir drug-drug interactions: A case series of two persons living with HIV receiving long-acting injections

Patricia Pearce Fulco¹, Elizabeth Winthrop² and Gonzalo M. Bearnson³

STDT & AIDS

International Conference on
Drug Therapy & AIDS
Abstract #1067
October 18-22, 2019
San Francisco, CA, USA
[http://www.stdtandids.org](#)
S Stage

Case 1: clopidogrel was prescribed 2 months after last LEN injection; no DDI alert was generated

Case 2: patient used daily inhalations of fluticasone (not included in medication list) and developed Cushing syndrome

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Recently, the LEN PREP product label was updated with new DDI recommendations (1)

Physiologically Based Pharmacokinetic Modelling to Inform Lenacapavir Dose Regimen when Co-Administered with Rifamycins

Sara Salerno¹, Yvira Lukacska¹, Ramoth Palapattay¹, Remo Singh¹, Ana Ruiz Garcia¹

¹Takeda Sciences, Inc., Foster City, California, USA; Tsimakios Plus, Inc., Lancaster, California, USA

¹Presenting author

Abstract 1003, The 20th International Meeting on Clinical Pharmacology of HIV Infection, and other scientific drug development, Indianapolis, 1-4 September 2024 (poster #1003)

 **CLINICAL PHARMACOLOGY 2025**
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Recently, the LEN PrEP product label was updated with new DDI recommendations (2)

Magnitude of Interaction Expected to be Less with LEN SC by Avoiding Pre-Systemic Metabolism

we developed a PK model to propose dosing recommendations for co-administration of SC LEN with rifampicin or rifabutin that can maintain safe and efficacious LEN concentrations.

Salerno et al. Antiviral PK workshop 2025; abstract #9

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Recently, the LEN PrEP product label was updated with new DDI recommendations (3)

Rifampicin* Initiated with Supplemental LEN Initiation Regimen Dosing Beginning Day 3 of LEN¹ Regimen Maintains Target LEN Concentrations

Parameter	Predicted/Observed Parameter Ratio
Area Under the Curve (AUC)	1.00
Peak	1.00
Time to Peak	1.00

Rifampicin can be started with supplemental dosing at least 2 days after starting LEN initiation regimen

Salerno et al. Antiviral PK workshop 2025; abstract #9

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Various responses by regulatory authorities on the proposed DDI recommendations

- US FDA: proposal for DDI management with supplemental LEN doses accepted for all strong and moderate CYP3A inducers (but only for existing LEN users, only for PrEP)
- Canadian FDA: proposal only accepted for rifampin
- EMA: proposal **NOT** accepted
 - "... the predictions rely on unstable assumptions"

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ISL DDI profile

Table 6: Drug Interactions: Changes in Pharmacokinetic Parameter Values of Islatravir in the Presence of Co-administered Drug

Co-administered Drug	Regimen of Islatravir	Regimen of Islatravir	Parameter	Mean Ratio (95% CI) of Islatravir Pharmacokinetic Parameter Values in the Presence of Co-administered Drug
Isatravir	100 mg QD	2.75 mg QD	AUC ₀₋₂₄	1.00
Isatravir	100 mg QD	2.75 mg QD	C _{max}	1.00
Isatravir	100 mg QD	2.75 mg QD	T _{1/2}	1.00
Isatravir	100 mg QD	2.75 mg QD	CL _{CR}	1.00
Isatravir	100 mg QD	2.75 mg QD	CL _{ES}	1.00
Isatravir	100 mg QD	2.75 mg QD	CL _{EB}	1.00
Isatravir	100 mg QD	2.75 mg QD	CL _{EB}	1.00
Isatravir	100 mg QD	2.75 mg QD	CL _{EB}	1.00
Isatravir	100 mg QD	2.75 mg QD	CL _{EB}	1.00
Isatravir	100 mg QD	2.75 mg QD	CL _{EB}	1.00

Based on this interaction studies conducted with islatravir, no clinically significant drug interactions have been observed following the co-administration of islatravir and the following drugs: didanosine, didanosine and TDF, and oral contraceptives containing ethyl-estradiol and norgestrel. Indinavir, zalcitabine, zalcitabine.

ICP Substrates		
Anti-viral antiviral antiviral	1 SL-TP	Co-administration is contraindicated with lamivudine or emtricitabine.
Nucleoside		
antiviral antiviral antiviral	1 SL-TP	Co-administration with these nucleoside antiretrovirals is not recommended as ICP substrates may cause a decrease in the intracellular concentration of SL-TP.
ATC Substrates		
antiviral antiviral	1 SL-TP	Co-administration with zalcitabine is not recommended as it may cause an increase in plasma concentrations of islatravir.

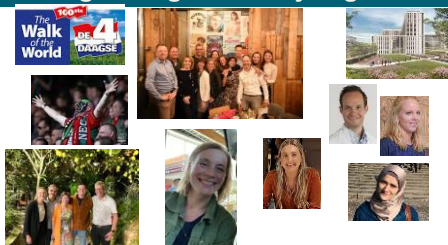
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Conclusions

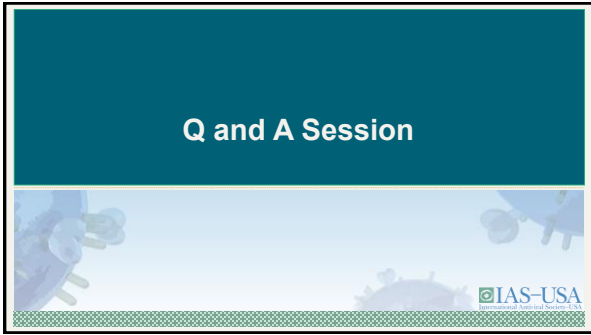
- DDIs with LAART ≠ DDIs with oral ART
- No DDIs based on absorption with parenteral ART
 - E.g., PPIs + RPV; cations + INSTIs
- With LA ART being CYP3A substrates, susceptibility to inducers and inhibitors not different from oral ART; what is the value of PBPK modelling?
- Please be aware of DDIs weeks or months after last LA injection

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Thank you for your attention & greetings from Nijmegen



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