The Pharmacology of Integrase Inhibitors

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HIV Viral Life Cycle

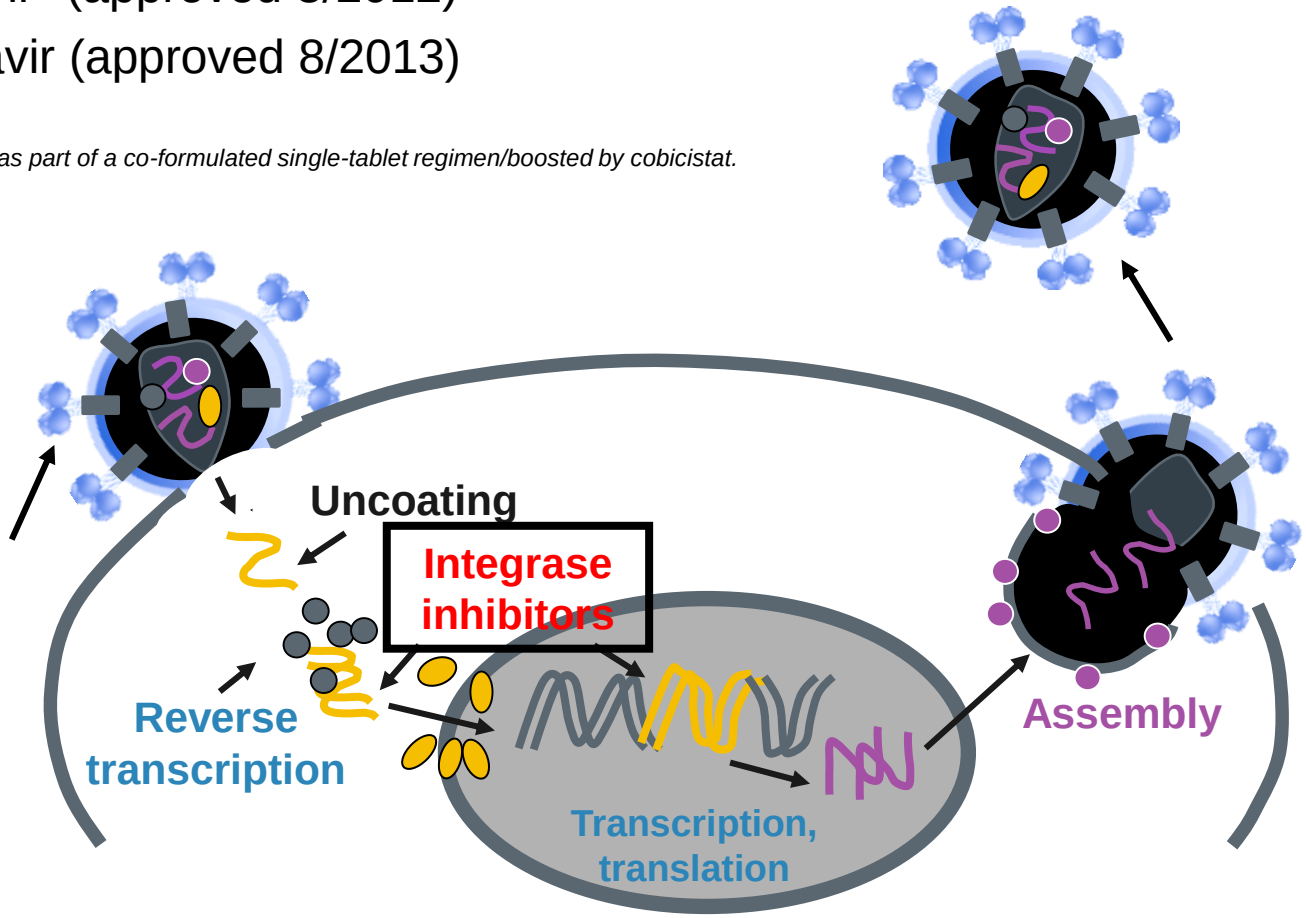
Currently available integrase inhibitors

Raltegravir (approved 10/2007)

Elvitegravir* (approved 8/2012)

Dolutegravir (approved 8/2013)

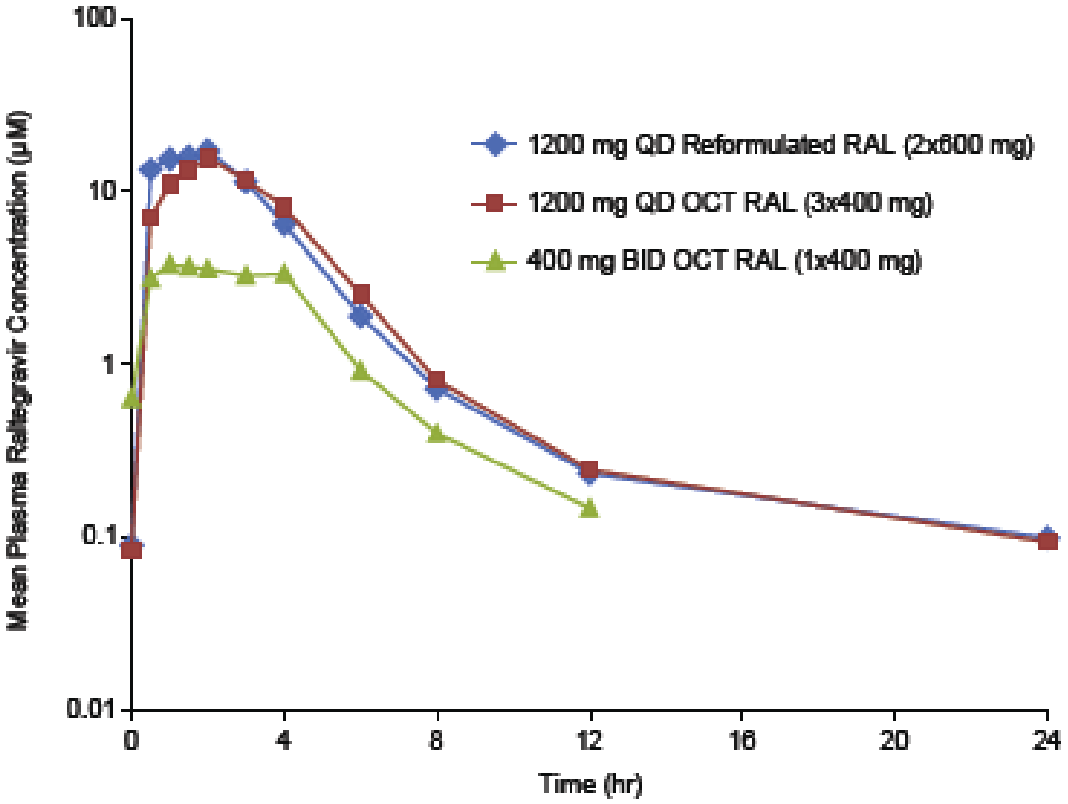
**Currently available only as part of a co-formulated single-tablet regimen/boosted by cobicistat.*



Raltegravir

- Raltegravir dosed at 400 mg BD
- Tx with 100, 200, 400, or 600 mg BD vs placebo for 10 days
- Metabolized by glucuronidation primarily by uridine glucuronosyl transferase (UGT) 1A1
- Low potential for drug interactions
- Half-life ~ 9 h
- Dosed without regard to meals
- Wide intra-patient variability for C_{12h} and $AUC_{0–12h}$ ranged from 1 to 113%, and 1 to 77%
- Large therapeutic window and mild side effect profile (variability less clinically relevant)

Mean plasma concentration profiles for RALTEGRAVIR following administration of multiple doses to healthy subjects for 5 days



Effect of raltegravir on the PK of other drugs

- No effect on the PK of etravirine, maraviroc, tenofovir, hormonal contraceptives, methadone, midazolam or boceprevir …

- Co-administration with DRV/r resulted in modest decrease of DRV plasma concentrations
  - Mechanism unknown?
  - Clinical significance?

Effect of other drugs on the PK of raltegravir

- INDUCERS OF UGT1A1
  - Rifampicin ↓ plasma [RAL] AUC ↓ 40%, C12h ↓ 61%, Cmax ↓ 38% / impact on the efficacy unknown → double dose to 800 mg BD
  - Phenytoin and phenobarbital
  - Efavirenz (C12h ↓ 21%), nevirapine, etravirine (C12h ↓ 34%), rifabutin, glucocorticoids, St. John's wort, pioglitazone may be used RAL 400 mg BD

- INHIBITORS OF UGT1A1
  - Atazanavir/r ↑ plasma [RAL] AUC ↑ 41%, C12h ↑ 77%, Cmax ↑ 24% / no dose adjustement
  - Tenofovir ↑ plasma [RAL] AUC ↑ 49%, C12h ↑ 3%, Cmax ↑ 64%

- OTHER MECHANISMS
  - Antacids containing divalent metal cations ↓ RAL absorption (chelation): co-administration with aluminium and/or magnesium antacids not recommended / ↓ plasma [RAL] C12h ↓ 49-63%
  - Calcium carbonate antacid ↓ plasma [RAL] but not clinically meaningful, no dose adjustment required
  - By increasing gastric pH, omeprazole and famotidine increase raltegravir absorption: ↑ plasma [RAL], no dose adjusment required

Mr A

- 37 yo MSM diagnosed with HIV-infection 2 weeks ago
- Seen in Soho, London
- VL 5,660,523 copies/mL
- CD4 924 (34%)
- Comeds: lamotrigine 100 mg BD, carbamazepine depot 600 mg OD, valproate 1 g BD
- Epilepsy only partially controlled

- “I want to start cART as TasP today…”

What did I do?

- van Luin et al. J Clin Pharmacol, 2009: no interaction between lamotrigine and RAL
- Not studied but low potential for an interaction between valproate and RAL
- http://www.hiv-druginteractions.org: co-administration not studied but could potentially decrease raltegravir concentrations as it is mainly glucuronidated by UGT1A1 and in vitro data suggest that carbamazepine induces UGT1A1. Consider TDM for raltegravir.

TDF/FTC/RAL 800 mg BD and fingers crossed…

Elvitegravir

What is Stribild?

- Integrase based Single Tablet Regimen

- Each Stribild tablet contains:
  - Integrase - Elvitegravir
  - Pharmacokinetic enhancer - Cobicistat
  - NRTI – Emtricitabine
  - N(t)RTI – Tenofovir Disoproxil Fumerate

- The use of a PK enhancer will result in drug-drug interactions that need to be understood
  - Extensive experience exists with RTV
  - Prescribers and pharmacists need to be aware of the potential drug-drug interactions of Stribild

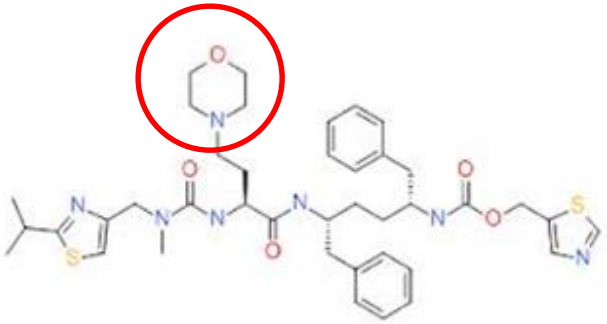
Elvitegravir/cobicistat

- **Cobicistat** inhibits CYP3A4 >> CYP2D6, CYP2B6
- **Cobicistat** inhibits P-gp and BCRP (intestine), OATP1B1 and OATP1B3 (liver); MATE-1 (kidney)
- **Elvitegravir** is a modest inducer of CYP2C9

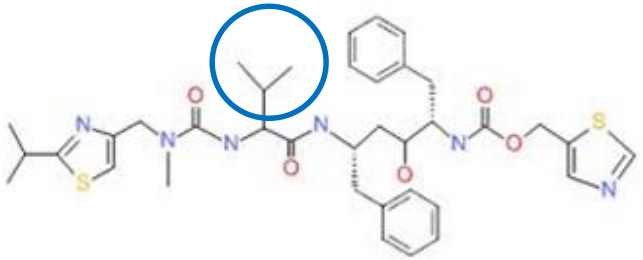
What is cobicistat?

- Designed as a CYP3A inhibitor (and also CYP2D6 and transmembrane transporters)
- No HIV activity
- Developed to boost elvitegravir but also available to boost PIs
- Trials with additional agents ongoing
- Able to be co-formulated into STR

Cobicistat is structurally similar to RTV



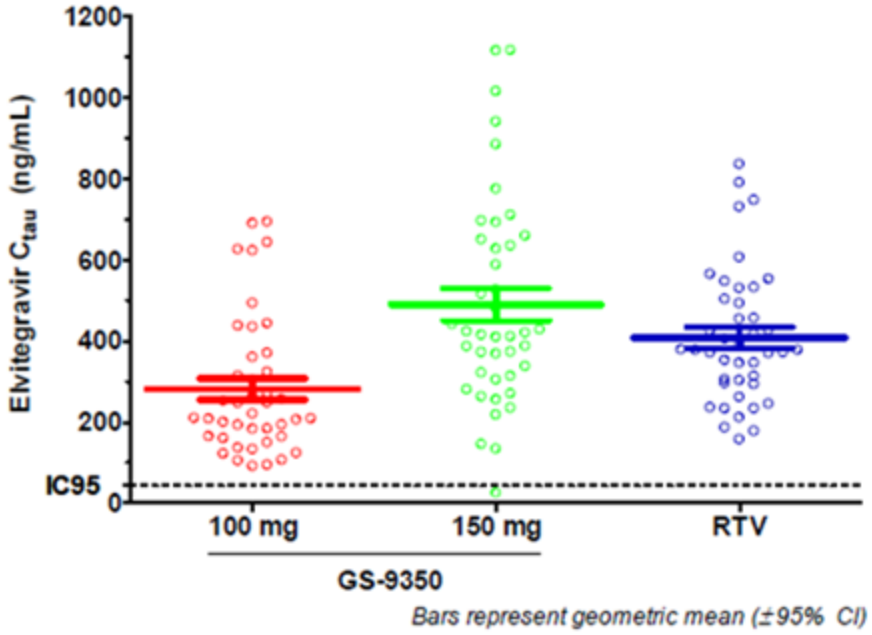
Cobicistat



Ritonavir

Comparative effects of cobicistat and RTV on elvitegravir *in vivo*

Mean EVG PK (n=42)	EVG/COBI 100mg	EVG /COBI 150mg	EVG/RTV 100mg
AUC_{tau}(ng.hr/ml)	21100	27000	22500
C_{max} (ng/ml)	2250	2660	2500
C_{tau} (ng/ml)	282	490	409



- Cobisistat effectively boosts EVG
- High EVG trough concentrations maintained with cobisistat 150mg
  - 11-fold above the protein binding-adjusted IC_{95} (44.5ng/ml)
  - Low within-subject variability (15%CV)

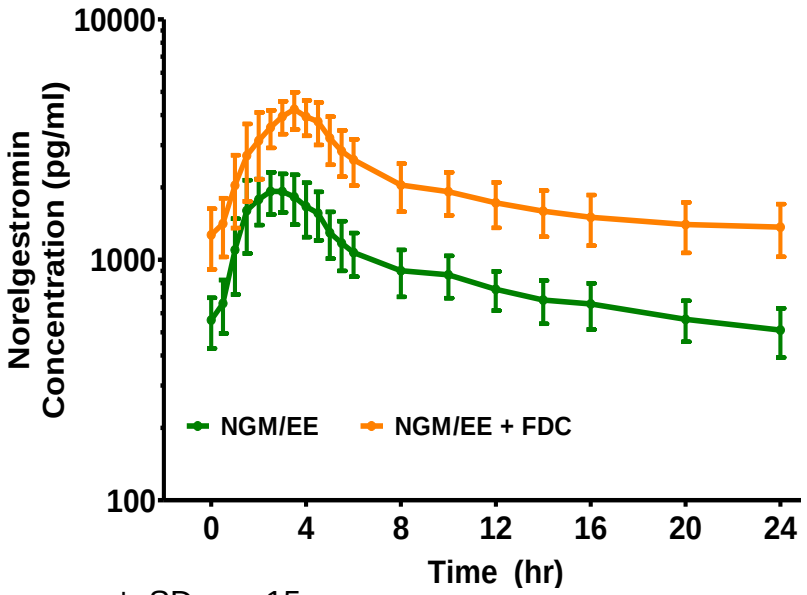
Mathias A et al, GS-9350: A Pharmacoenhancer Without anti-HIV Activity. 2010.Clincial pharmacology and therapeutics,87:3

Common drugs that can be used with STRIBILD

Drug Class	Drug Name
Acid reducing agents	Antacids (separate Stribild and antacid administration by at least 4 hours)[4] Omeprazole[1] (Taken 2 hours before Stribild), Famotidine[1]
HMG CoA reductase Inhibitors	Rosuvastatin[2], Pravastatin[4], Fluvastatin[4] Atorvastatin[4]: The lowest possible dose of atorvastatin should be administered with careful safety monitoring.
Hormonal contraceptives	Hormonal contraceptive should contain at least 30 µg Ethinylestradiol and contain Norgestimate as the progestagen[3]
Macrolide antibiotics	Clarithromycin[4] Monitoring is recommended for patients with ClCr < 90 mL/min. For patients with ClCr < 60 mL/min, alternative antibacterials should be considered.
Narcotic analgesics	Methadone[5], Buprenorphine[5], Naloxone[5]
PDE 5 Inhibitor Please refer to the SPC for further interactions	Sildenafil[4] (not exceeding 25mg in 48 hours) Vardenafil[4] (no more than 2.5mg in 72 hours) Tadalafil[4] (no more than 10mg in 72 hours)

1.Mathias A et al. IWCHPT, Miami, April 2010. Poster no 13
2.Ramanathan S et al. IWCHPT Barcelona April 2012. Abstract oral presentation no 03
3.German P et al. IWCHPT Miami, April 2010. oral presentation
4.Stribild SPC 2013
5.Bruce R, et al. ICAAC 2012. San Francisco, CA 2012. Abstract A-1250.

Effect of EVG/COBI on norgestimate PK



mean ± SD, n = 15

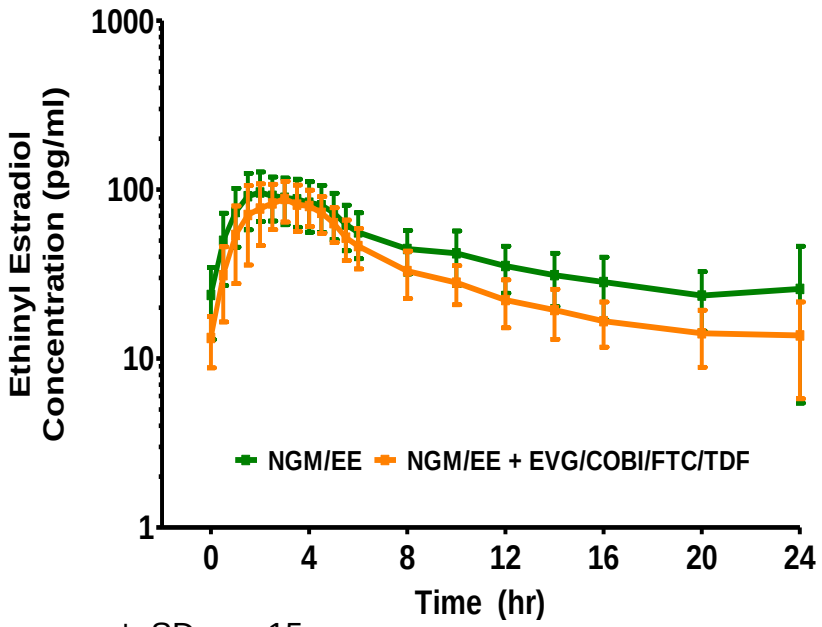
- NGMN exposure is increased with FDC plus NGM/EE versus NGM/EE alone
  - Increases in NGMN have been previously documented[1]
  - Potential effect on NGMN clearance since conversion is esterase mediated [5,6]

NGMN Parameter	NGM/EE	NGM/EE + FDC	GMR (90% CI)
AUC_{tau} (pg·hr/ml)	21400 (17.1)	48300 (17.7)	226 (215, 237)
C_{max}(pg/ml)	2150 (15.4)	4460 (14.5)	209 (200, 217)
C_{tau} (pg/ml)	510 (23.1)	1370 (24.7)	267 (243, 292)

n = 15, mean (%CV); FDC: EVG/COBI/FTC/TDF

German P et al. IWCHPT Miami, April 2010. oral presentation

Effect of EVG/COBI on ethinyloestradiol PK



mean ± SD, n = 15

- EE AUC_{tau} and C_{tau} are decreased with FDC plus NGM/EE versus NGM/EE alone
  - EE is metabolized by sulphation, oxidation and glucuronidation
  - EVG is a modest PXR inducer; COBI has minimal effects on PXR
  - **Induction of glucuronidation?**

EE Parameter	NGM/EE	NGM/EE + FDC	GMR (90% CI)
AUC_{tau} (pg·hr/ml)	1050 (32.1)	775 (26.1)	75.0 (69.4, 81.0)
C_{max}(pg/ml)	106 (30.7)	98.6 (27.8)	94.1 (85.5, 104)
C_{tau} (pg/ml)	25.8 (78.9)	13.7 (57.8)	56.5 (51.9, 61.5)

n = 15, mean (%CV); FDC: EVG/COBI/FTC/TDF

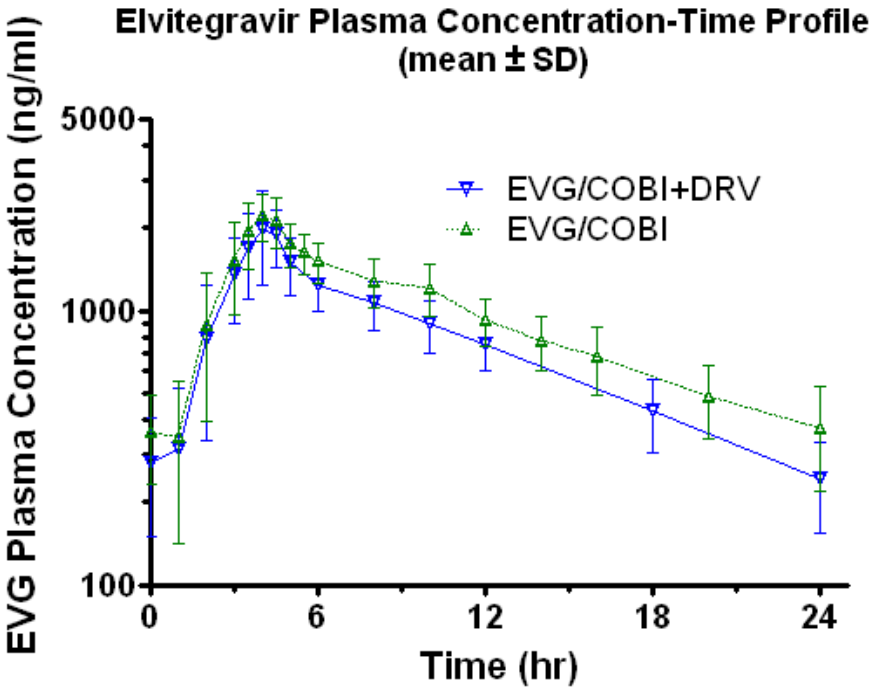
German P et al. IWCHPT Miami, April 2010. oral presentation

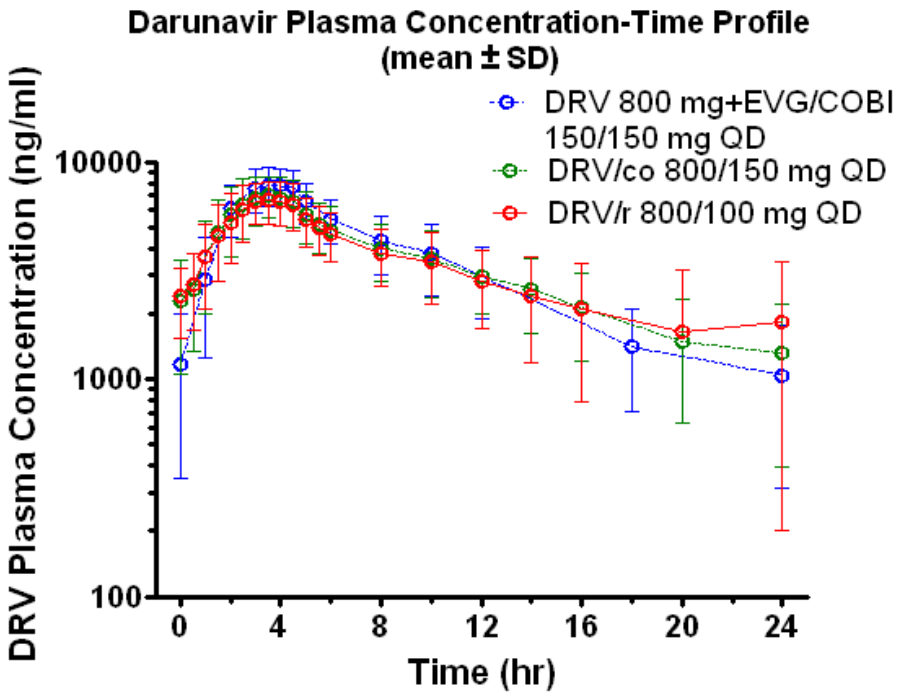
Drugs contraindicated with STRIBILD

Drug Class	Drug Name
Alpha 1 adrenoceptor antagonist	Alfuzosin
Antiarrhythmics	Amiodarone, Quinine
Anticonvulsants	Carbamazepine, Phenobarbital, Phenytoin
Antimycobacterial	Rifampicin
Ergot derivatives	Dihydroergotamine, Ergometrine, Ergotamine
GI motility agent	Cisapride
Herbal products	St John's wort (*Hypericum perforatum)*
HMG CoA reductase Inhibitors	Lovastatin, Simvastatin
Neuroleptic	Pimozide
PDE 5 Inhibitor	Sildenafil (for pulmonary arterial hypertension)
Sedative/hypnotics	Triazolam, oral midazolam

Stribild SPC 2013

DRV is not recommended with Stribild

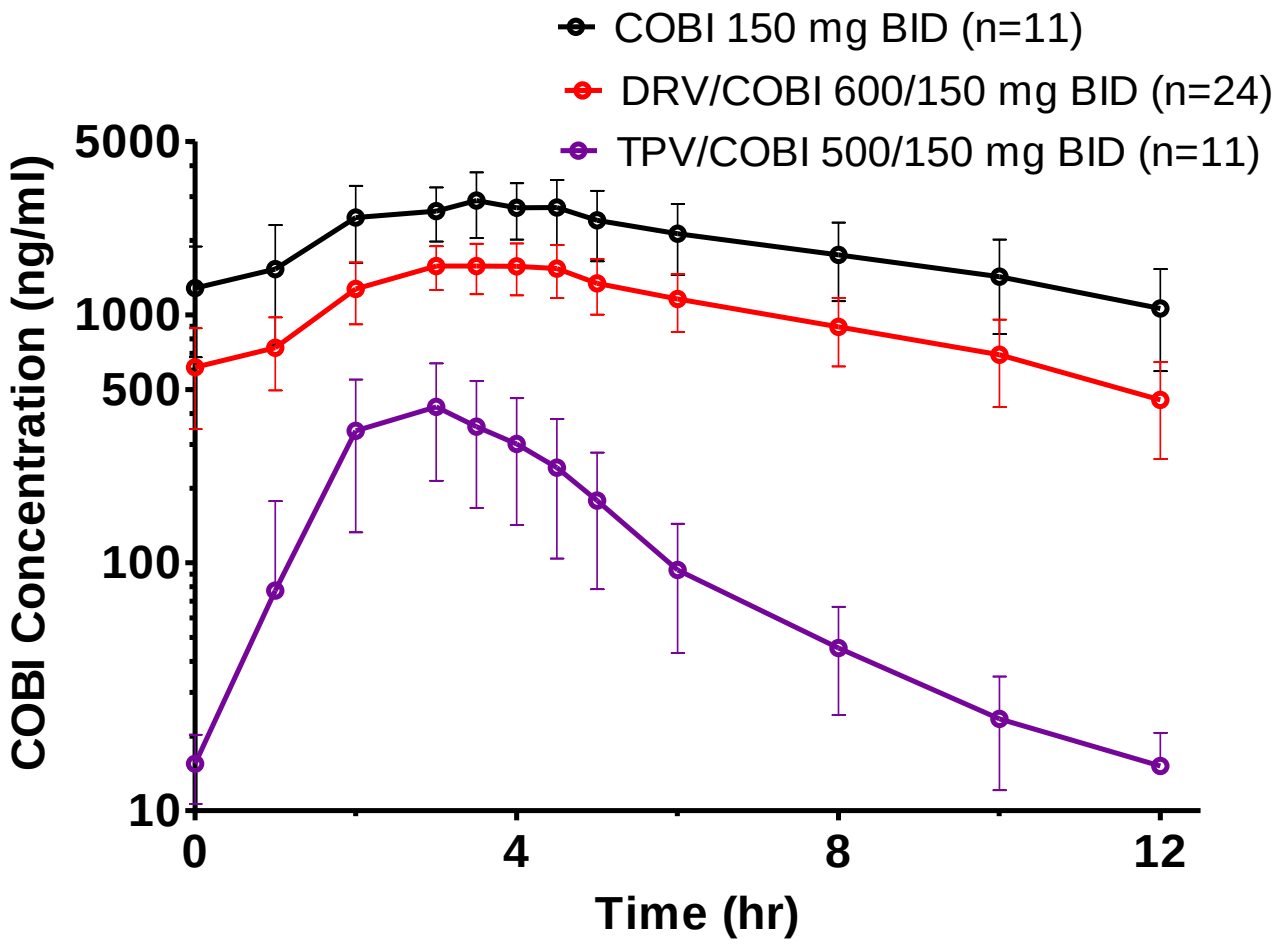




- EVG Ctrough lower with EVG/COBI + DRV vs EVG/COBI
- DRV Ctrough lower with EVG/COBI + DRV vs DRV/COBI

Ramanathan S et al IWCPHT April 2012 O-8

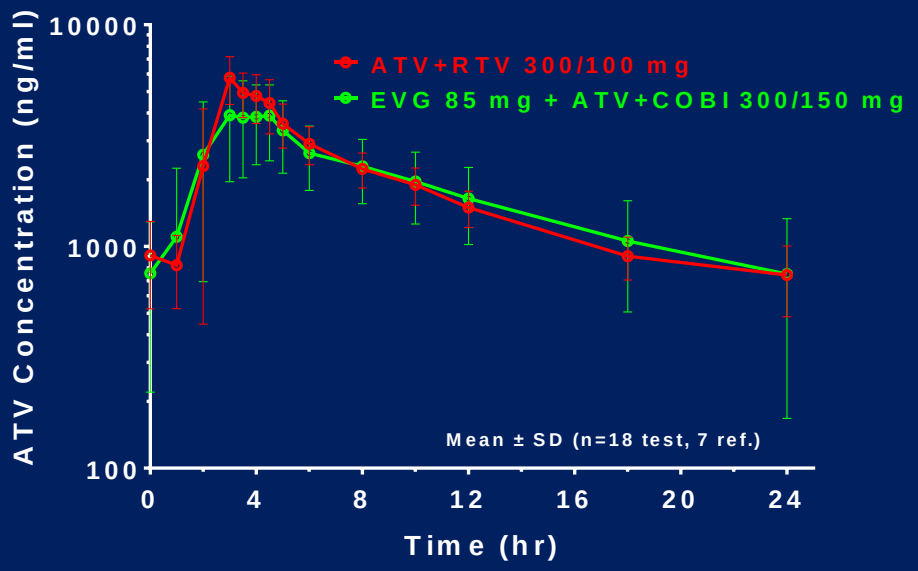
Cobicistat concentration is also reduced by darunavir

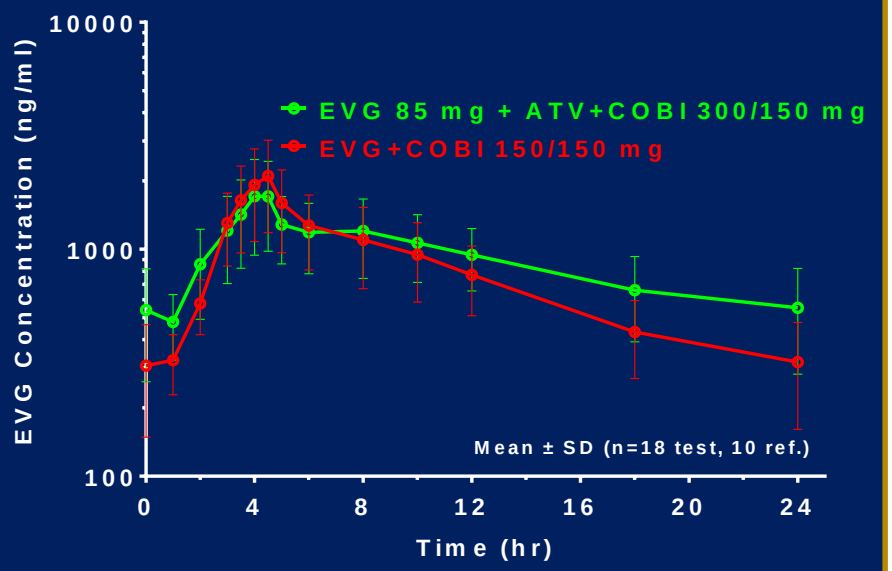


Ramanathan S et al IWCPHT April 2012 O-8

EVG + COBI + ATV

EVG 85mg QD + COBI 150mg QD + ATV 300mg QD





Effect on Concentration

↑ elvitegravir (EVG)

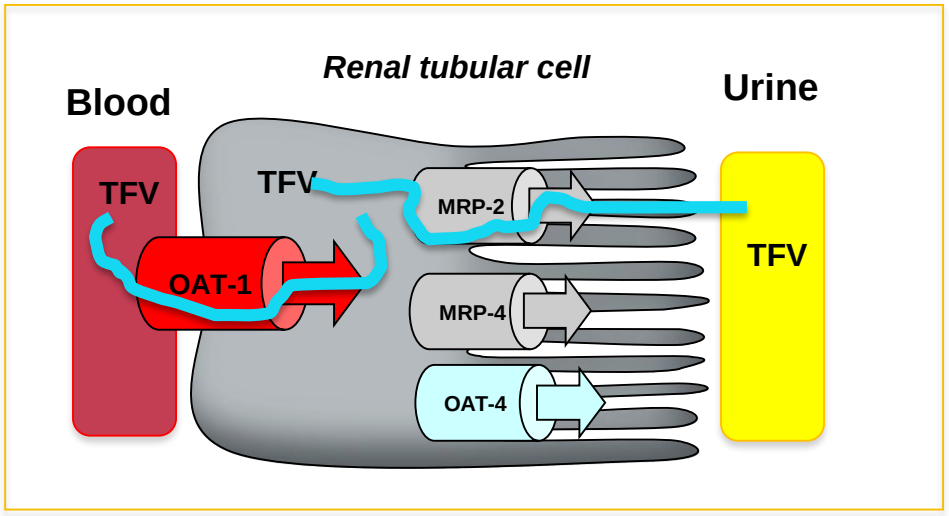
↔ atazanavir (ATV)

Coadministration of COBI-boosted EVG + ATV 300mg requires a dose reduction of EVG to 85mg, but does not require modification of ATV or COBI[a]

Ramanathan S, et al. IWCPHT 2012; Barcelona. 0_03

[a] Data not shown

Renal elimination and DDIs?

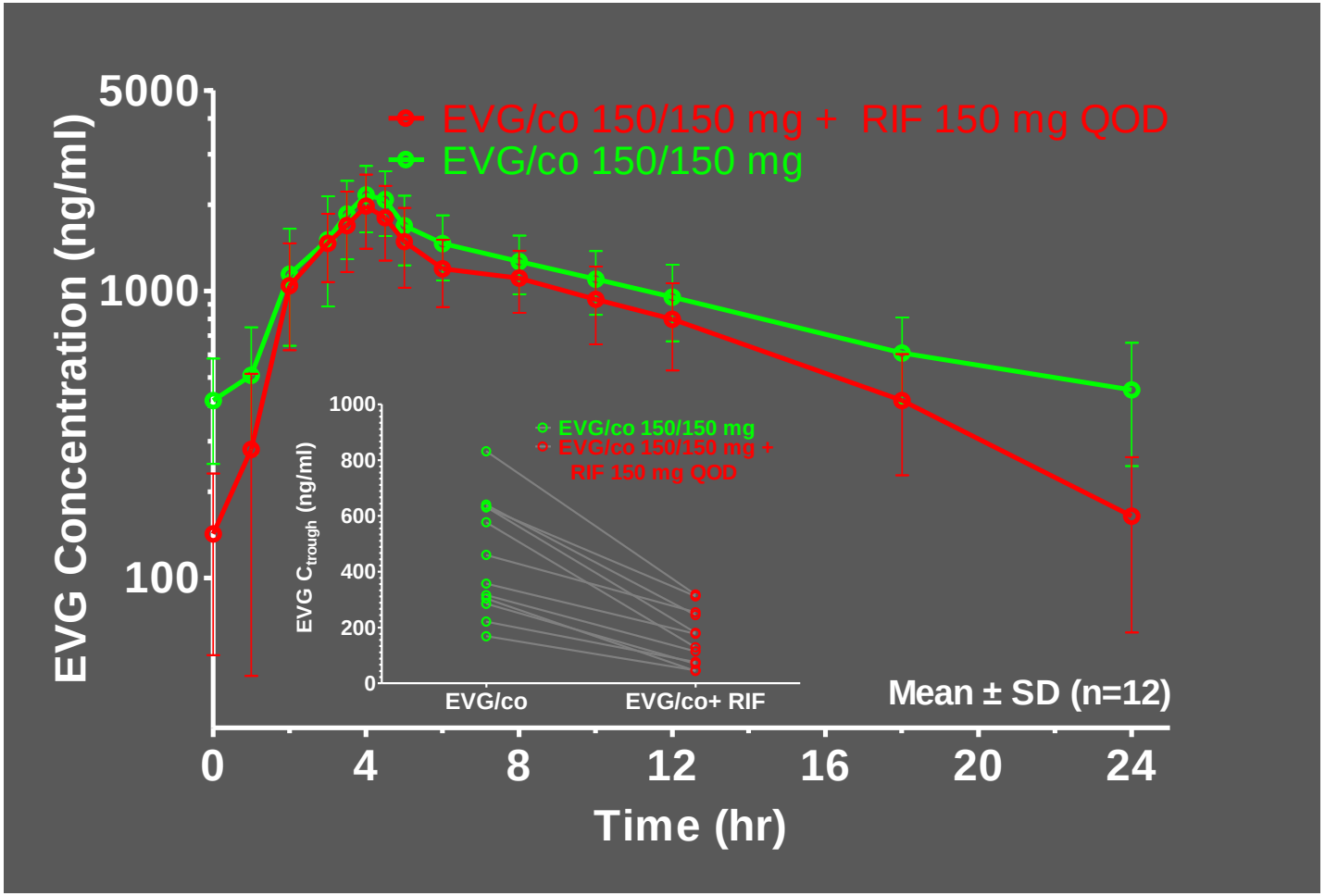


- If OAT-1 is inhibited by the co-administered drug, plasma concentrations of TFV are increased and may lead to potential systemic toxicity
- If MRP-2 is inhibited by the co-administered drug intracellular concentrations of TFV are increased and cause renal toxicity

Co-administration of EVG/COBI with commonly used drugs in HIV

Co-medication **Antibacterials**	Comment
Amoxicillin Dapsone Doxycycline Metronidazole Trimethoprim/Sulfamethoxazole	A clinically significant interaction is unlikely
Rifabutin	Co-administration of elvitegravir with dose reduced rifabutin is not recommended due to the reduction in elvitegravir Ctrough.
Rifampicin	Co-administration is contraindicated

Rifabutin is not recommended with Stribild: low EVG levels



Ramanathan et al, 13th International Workshop on Clinical Pharmacology of HIV Therapy, April 16-18, 2012, Barcelona, Spain, Abstract #O_03

Co-administration of EVG/COBI with commonly used drugs in HIV

Co-medication **Lipid Lowering Agents**	Comment
Atorvastatin	Co-administration with EVG/COBI could potentially increase atorvastatin concentrations. **Titrate atorvastatin dose and use the lowest possible dose with careful monitoring.**
Fluvastatin	Interactions are not expected
Lovastatin	Co-administration is contraindicated
Pravastatin	Interactions are not expected
Rosuvastatin	Rosuvastatin concentrations are increased but not considered clinically relevant
Simvastatin	Co-administration is contraindicated

www.hiv-druginteractions.org

Rosuvastatin can be used with Stribild

	Rosuvastatin (ROS)PK		
Mean (%CV)	EVG/COBI + ROS	ROS	GMR (90% CI)
AUC (ng.hr/ml)	38	27	138
C_{max} (ng/ml)	5.0	2.7	189
$T_{1/2}$ (hr)	18	21	-

Ramanathan S et al IWCHPT Barcelona April 2012

Co-administration of EVG/COBI with commonly used drugs in HIV

Co-medication **Steroids**	Comment
Budesonide	Co-administration of EVG/COBI is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. If used dose reduction and close monitoring required.
Fluticasone	Co-administration of EVG/COBI is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects. If used dose reduction and close monitoring required.
Prednisolone	EVG/COBI may increase prednisolone concentrations. Careful monitoring of adverse effects is recommended when prednisolone is co-administered.

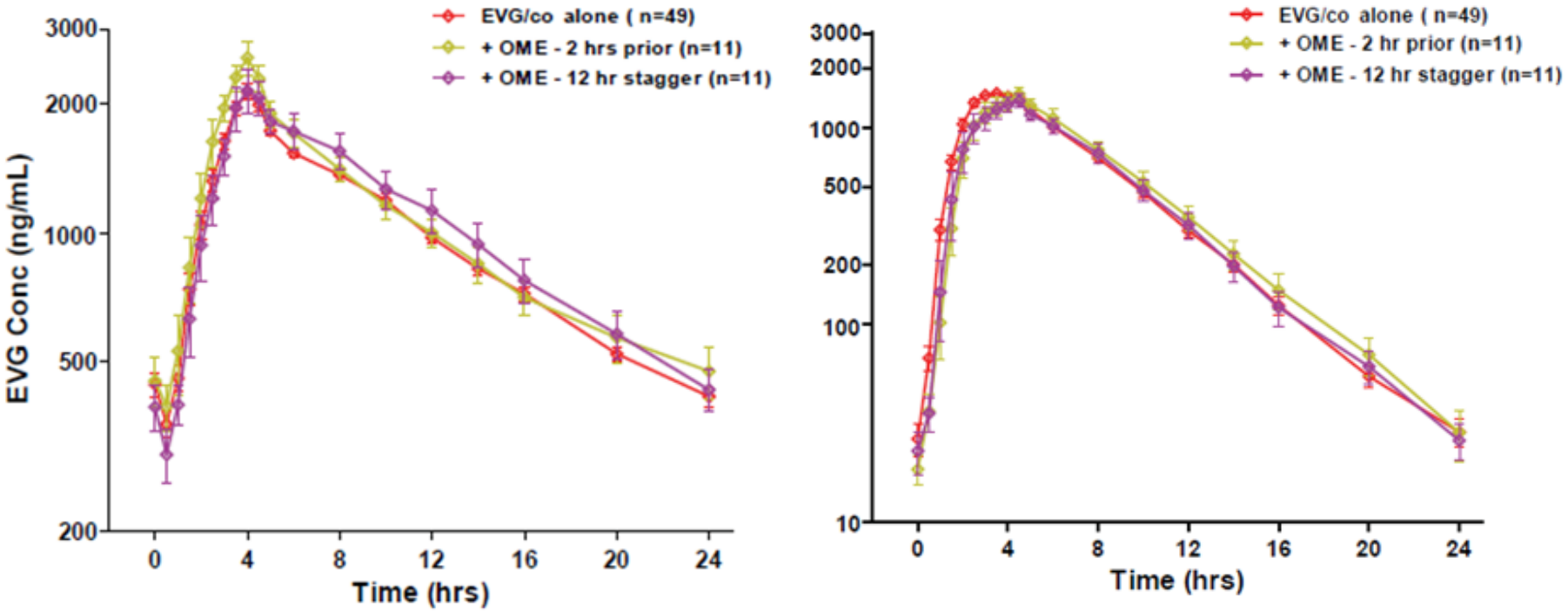
Co-administration of EVG/COBI with commonly used drugs in HIV

Co-medication	Comment
Acyclovir	A clinically significant interaction is unlikely
Atovaquone	A clinically significant interaction is unlikely
Cyclizine	EVG/COBI could potentially increase cyclizine concentrations although to a moderate extent. **No a priori dosage adjustment is required.**
Fluoxetine	EVG/COBI could potentially increase fluoxetine concentrations although to a moderate extent. **No a priori dosage adjustment is recommended but monitor adverse effects.**
Fluconazole	A clinically significant interaction is unlikely

Co-administration of EVG/COBI with commonly used drugs in HIV

Co-medication	Comment
Ferrous sulphate	EVG/COBI should be separated by at least 2 hours from mineral supplements such as ferrous sulphate.
Loperamide	EVG/COBI could potentially increase loperamide exposure . However this interaction is unlikely to result in opioid CNS effects.
Proguanil	A clinically significant interaction is unlikely
Salbutamol	A clinically significant interaction is unlikely
Zopiclone	EVG/COBI could potentially increase zopiclone exposure which could result in increased sedation. **A dosage reduction may be needed.**

Stribild can be used with Proton Pump Inhibitors



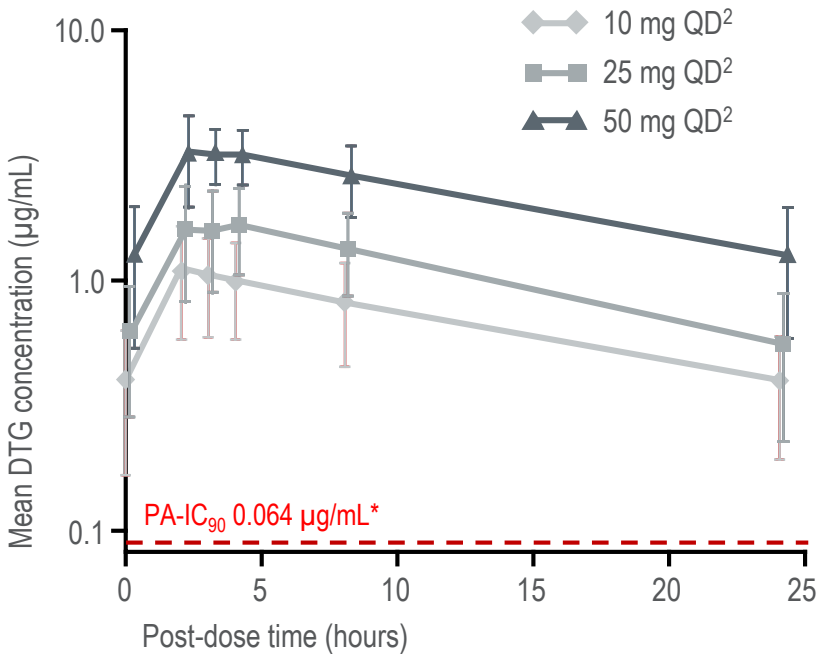
- Administration of EVG/co with (Omeprazole) OME, a PPI, had no effect on the exposure of COBI when the PPI was staggered by 2 or 12 hours from EVG/COBI
- Administration of EVG/co with OME, a PPI, had no effect on the exposure of EVG when the PPI was staggered by 2 or 12 hours from EVG/COBI

Mathias A, et al. 11th International Workshop on Clinical Pharmacology of HIV Therapy 2010. Miami, FL. Poster P13.

Dolutegravir

CONSISTENT DOSE-EXPOSURE RELATIONSHIP FOR DOLUTEGRAVIR

DTG PK parameters at Week 2 by dose in the SPRING-1 Phase IIb trial[1,2]



Values shown are geometric means (CV%)

QD dose	C_{max} (µg/mL)	$AUC_{0-\tau}$ (µg·h/mL)	C_{τ} (µg/mL)	IQ†
10 mg[1,2]	1.10 (37)	16.0 (40)	0.30 (71)	4.7
25 mg[1,2]	1.71 (43)	23.1 (48)	0.54 (67)	8.4
50 mg[1,2]	3.40 (27)	48.1 (40)	1.20 (62)	19

- DTG showed low to moderate PK variability[1,2]
- All drug levels were well above the in-vitro PA-IC_{90} of 0.064 µg/mL[1,2]

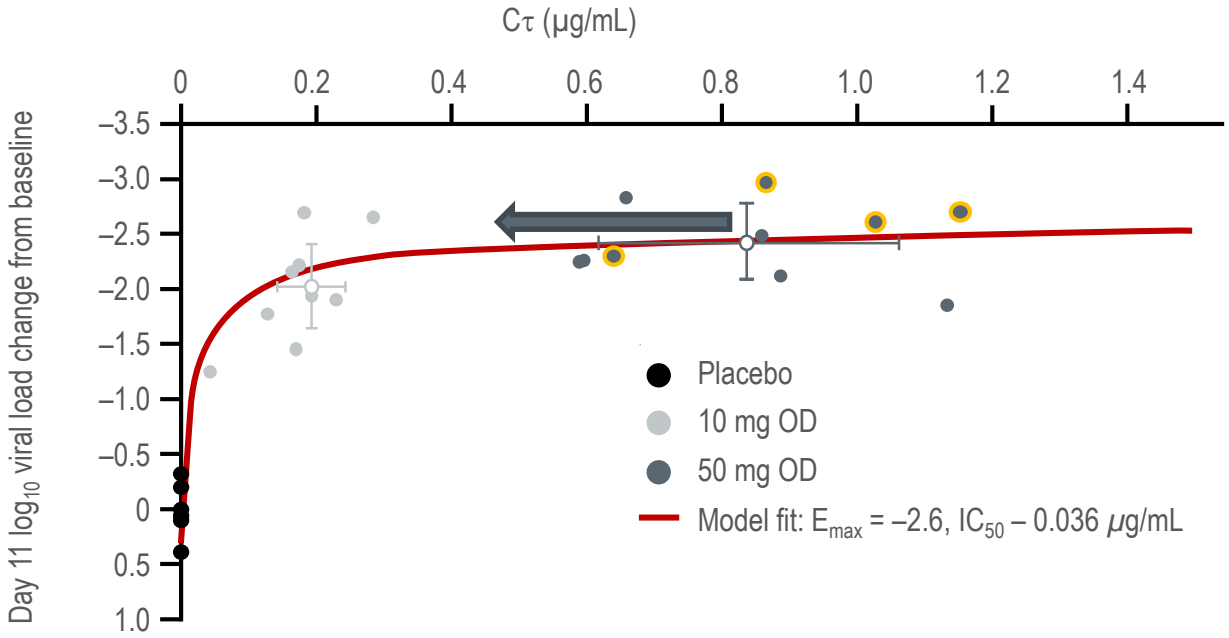
*PA-IC_{90} is the protein-adjusted 90% inhibitory concentration
†Inhibitory quotient is defined as C_{τ}/PA–IC_{90}

1. Adapted from van Lunzen J, et al. Lancet Infect Dis 2012; 12:111–8
2. Adapted from Rockstroh J, et al. HIV10 2010. Abstract O50

Dolutegravir

RELATIONSHIP BETWEEN DOLUTEGRAVIR Ctrough AND VIRAL LOAD REDUCTION

Phase IIa, dose-ranging, placebo-controlled, 10-day monotherapy study



Subjects with HIV-1 RNA <50 c/mL are represented by orange-bordered circles

Open circles with lines denote mean standard deviation

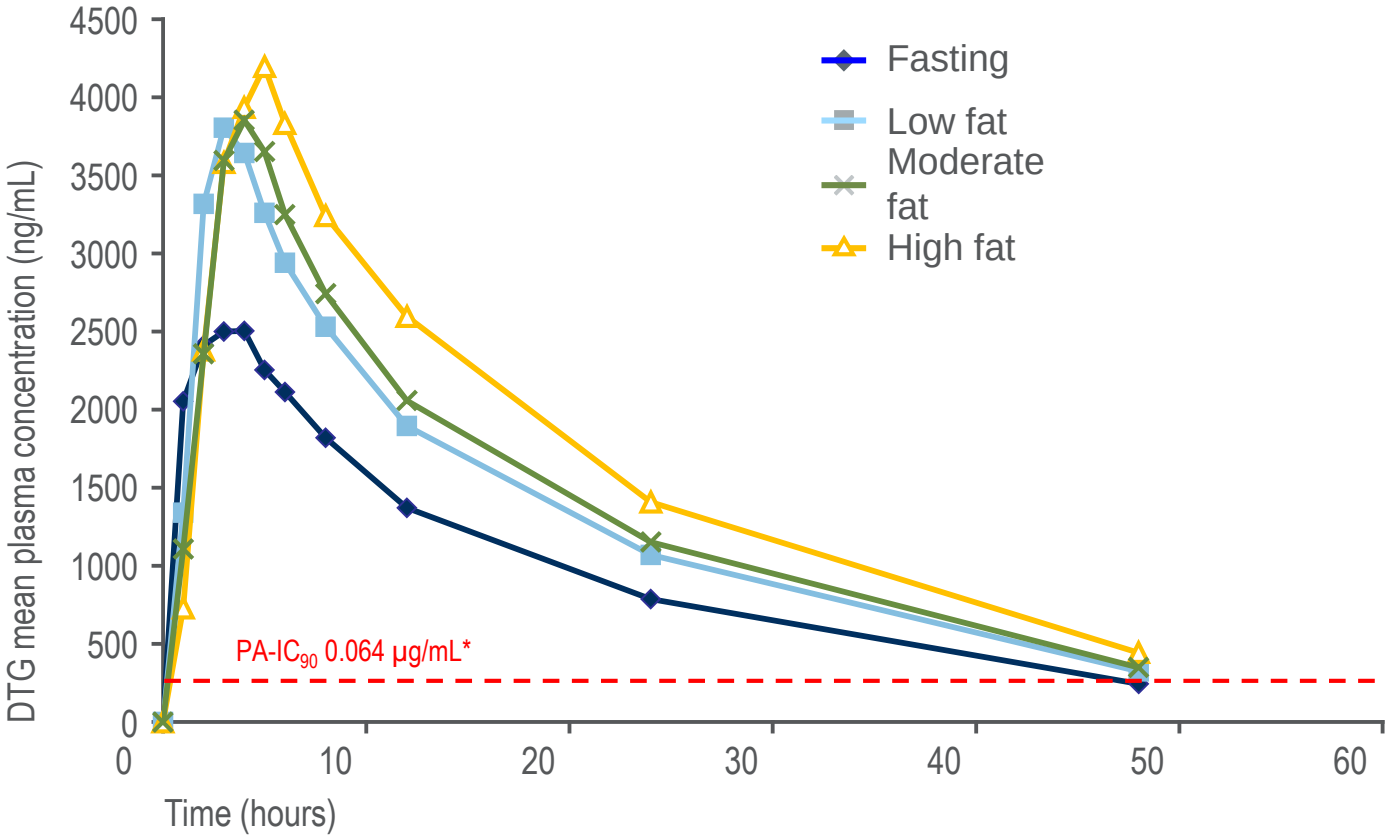
DTG is associated with a well characterised, predictable exposure-response relationship

c/mL, copies/mL; Emax, maximum effect

Adapted from Min S, et al. AIDS 2011; 25:1737–45

Dolutegravir

EFFECT OF FOOD ON DOLUTEGRAVIR EXPOSURE IN HEALTHY VOLUNTEERS



Low, moderate and high fat meals increased DTG† $AUC_{0-\infty}$ by 33%, 41% and 66%, respectively

In integrase-naive patients, dose with or without food. In integrase resistant patients, preferably dose with food

*PA-IC_{90} is the protein-adjusted 90% inhibitory concentration;
†Phase III (50 mg) formulation

Adapted from Song I, et al. Antimicrob Agents Chemother 2012;56:1627–9

DRUG INTERACTION POTENTIAL OF DOLUTEGRAVIR – AS A PERPETRATOR

- Extensive programme of in-vitro studies examining DTG and potential inhibition (or induction) of enzymes or transport proteins
- Based on these data, DTG is not expected to affect the PK of drugs that are substrates of key cytochrome P-450 enzymes*, UGT1A1, P-gp, BCRP, OATP1B1, OATP1B3, OCT1 and MRP2
- DTG inhibits OCT2 and therefore co-administration with dofetilide* is contraindicated and the interaction with metformin has been studied

*CYP1A2, CYP2A6, CYP2B6, CYP2C8/9, CYP2C19, CYP2D6, CYP3A

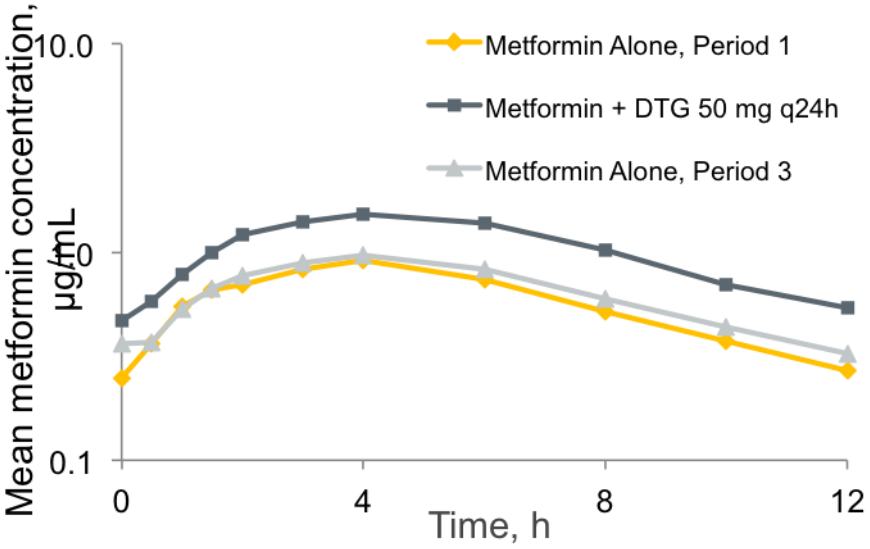
**Dofetilide is an anti-arrhythmic drug which is not licensed in Europe

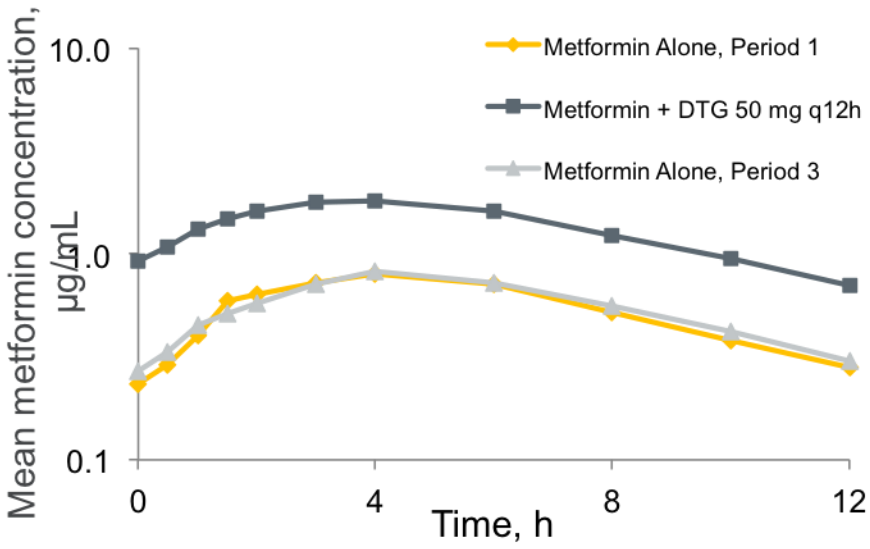
Tivicay SmPC January 2014

Effect of DTG on metformin in HEALTHY SUBJECTS

Plasma exposures of metformin were increased when co-administered with DTG

Dose adjustment of metformin may be considered[1,2]



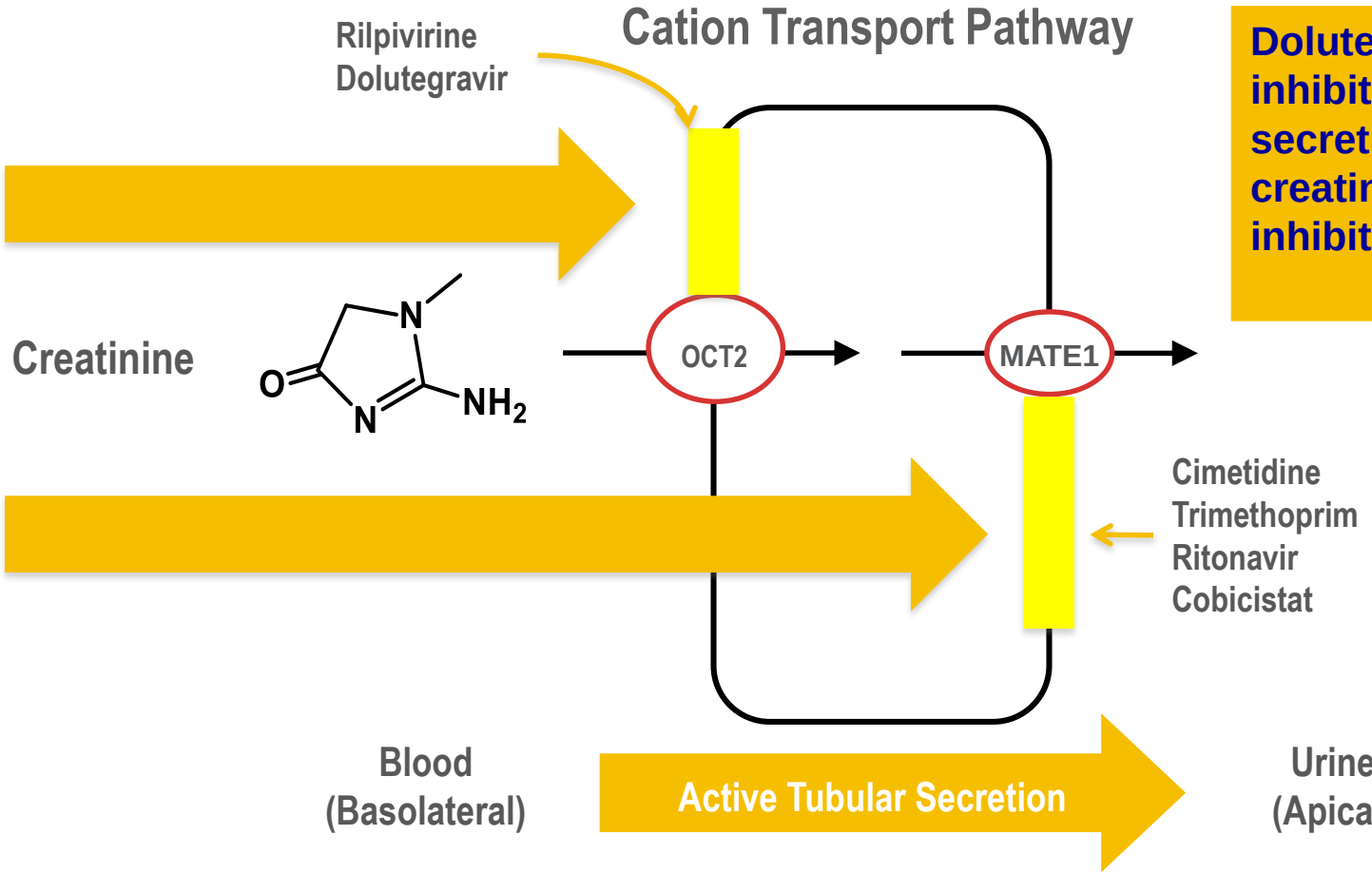


Regimen	C_{max} (µg/mL)[1]	$AUC_{0-\tau}$ (µg·h/mL)[1]	$t_{1/2}$ (hr)[1]
Metformin + DTG (50 mg q24h) vs metformin alone	1.66 (1.53, 1.81)	1.79 (1.65, 1.93)	1.09 (0.954, 1.24)
Metformin + DTG (50 mg q12h) vs metformin alone	2.11 (1.91, 2.33)	2.45 (2.25, 2.66)	1.14 (1.00, 1.29)

Values shown are GLS mean ratio (90% CI)

1. Zong J, et al. HIV Drug Therapy Glasgow 2014. Abstract P052
2. Tivicay US Prescribing Information. ViiV Healthcare, May 2014

DRUGS INTERFERING WITH CREATININE TUBULAR TRANSPORTERS

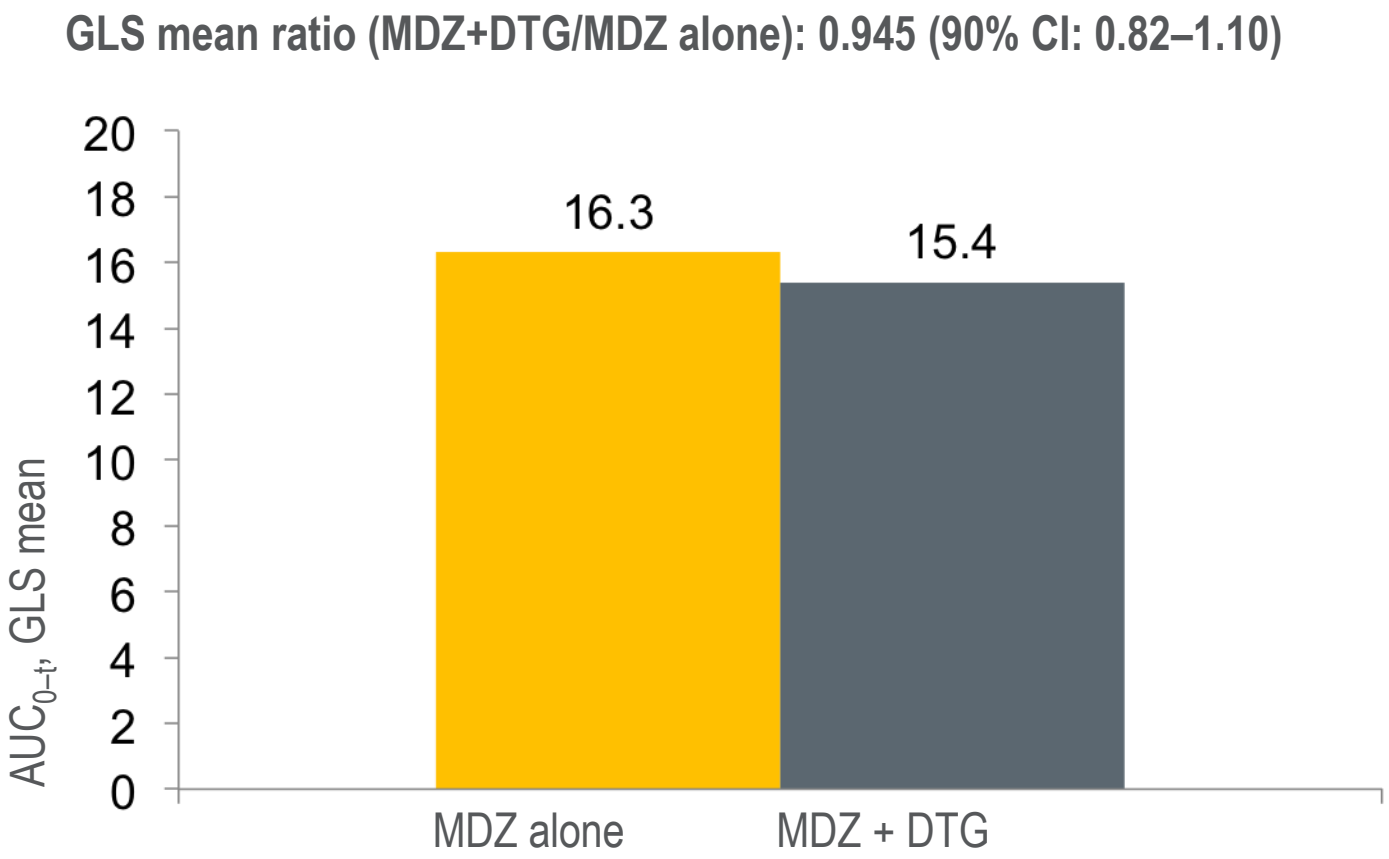


OCT2, organic cation transporter 2
MATE1, multidrug and toxin extrusion transporter 1

Lepist EI, et al. 51st ICAAC 2011. Abstract A1-1724.

IMPACT OF DTG ON CYP3A: STUDY WITH MIDAZOLAM, A CYP3A SUBSTRATE

Plasma MDZ AUC_{0-t} was similar with MDZ + DTG 25 mg versus MDZ alone



CI, confidence interval; GLS, geometric least squares; MDZ, midazolam

Adapted from Min S, et al. Antimicrob Agents Chemother 2010;54:254–8

DRUG INTERACTION POTENTIAL OF DOLUTEGRAVIR – AS A VICTIM

- DTG is metabolised by UGT1A1 with a small contribution from CYP3A.
- Drugs that induce or inhibit these enzymes may decrease or increase DTG exposure

IMPACT OF ARVs ON DOLUTEGRAVIR EXPOSURE

Co-administered drug	DTG C_τ or C_{24} *Geometric mean change*	Recommendation[1]
Protease inhibitors		
DRV/r 600/100 mg BID*	↓38%	No DTG dose adjustment required
ATV 400 mg OD*	↑180%	No DTG dose adjustment required
ATV/r 300/100 mg OD*	↑121%	No DTG dose adjustment required
NNRTIs		
RPV 25 mg OD	↑22%	No DTG dose adjustment required
EFV 600 mg OD	↓75%	DTG 50 mg BID should be given‡
ETR 200 mg BD	↓88%	DTG should not be given with ETR without co-administration of ATV/r, DRV/r or LPV/r
NRTIs		
TDF 300 mg OD	↓8%	No DTG dose adjustment required

*DTG 30 mg OD studied; ‡INI-naive patients; alternative combinations should be considered where possible for INI-experienced patients with certain INI-associated resistance substitutions or clinically suspected INI resistance

C_τ: Trough concentration

1.Tivicay SmPC January 2014

IMPACT OF DRUGS USED TO TREAT TB AND HCV ON DOLUTEGRAVIR EXPOSURE

Co-administered drug	DTG C_τ or C_{24} *Geometric mean change*	Recommendation[1]
Anti-TB drug		
Rifampicin 600 mg OD*	↓72%	DTG 50 mg BID should be given‡
Rifabutin 300 mg OD	↓30%	No DTG dose adjustment required
Anti-HCV drug		
TVR 750 mg every 8 hours	↑37%	No DTG dose adjustment required
BCV 800 mg every 8 hours	↑8%	No DTG dose adjustment required

C_τ: Trough concentration

*DTG 50 mg BID studied

‡INI-naive patients; alternative combinations should be considered where possible for INI-experienced patients with certain INI-associated resistance substitutions or clinically suspected INI resistance

1. Tivicay SmPC January 2014

IMPACT OF OTHER DRUGS ON DTG EXPOSURE

Co-administered drug	DTG C_τ or C_{24} *Geometric mean change*	Recommendation[1]
Oral contraceptives		
Ethinyl estradiol 0.035 mg*	AUC** ↑3%	No DTG dose adjustment required
Norgestromin 0.25 mg*	AUC** ↓2%	No DTG dose adjustment required
Opioids		
Methadone (individualised dose)	↓1%	No DTG dose adjustment required
Steroids		
Prednisone 60 mg OD	↑17%	No DTG dose adjustment required

C_τ: Trough concentration

*DTG 50 mg BID studied; ‡DTG levels not assessed

** C_τ not available in UK SmPC. Values from US Prescribing Information:[2] ↑2% and ↓7% respectively

1. Tivicay SmPC January 2014
2. Tivicay Prescribing Information US August 2013

IMPACT OF ACID-REDUCING AGENTS AND MULTIVITAMINS ON DTG EXPOSURE

Co-administered drug	DTG C_τ or C_{24} *Geometric mean change*	Recommendation
Antacids and supplements≠		
Magnesium / aluminium-containing antacid	AUC*↓74%	Take antacids and supplements a minimum of 2 hours after or 6 hours before DTG[1]
Calcium supplements	↓39%	
Iron supplements	↓56%	
Multivitamins	↓32%	
Acid-lowering agents		
Omeprazole	↓5%	No significant effect observed[2]

C_τ: Trough concentration

*C_τ not available in UK SmPC
≠ Complex binding to polyvalent ions

1. Tivicay SmPC January 2014
2. Patel P et al. J Antimicrob Chemother 2011; 66: 1567–1572

CLINICAL PHARMACOLOGY PROFILE OF DOLUTEGRAVIR VERSUS ELVITEGRAVIR AND RALTEGRAVIR

	DTG[1–3]	RAL[4]	EVG[5,6]
Clinical dose	50 mg QD (INI-naïve), 50 mg BID (INI-resistant)	400 mg BID	150 mg QD boosted with cobicistat
$t_{1/2}$	~14 hours	~9 hours	**EVG** ~12.9 hours (boosted) **Cobicistat** ~3.5 hours
PK variability	Low to moderate	High	Moderate (with boosting)
Food requirement	In INI-naïve patients, take with or without food. In INI-resistant patients, preferably with food	No food restriction, but fat content affects absorption and increases PK variability	Take with food
Protein binding	≥98.9%	83%	98–99%
Metabolism and excretion	UGT1A1 (major), CYP3A (minor), renal elimination <1%	UGT1A1, renal elimination ~9%	**EVG** - CYP3A (major), UGT1A1/3 (minor), renal elimination 6.7% **Cobicistat** – CYP3A and/or CYP2D6-mediated oxidation

1. Tivicay SmPC January 2014; 2. Min S, et al. Antimicrob Agents Chemother 2010;54:254–8 3. Min S, et al. AIDS 2011;25:1737–45; 4. Isentress SmPC August 2013; 5. Stribild SmPC September 2013; 6. Ramanathan S, et al. Clin Pharmacokinet 2011;50:229–44

Cabotegravir

S/GSK1265744

- Carbamoyl pyrodone structure similar to DTG
- Under development as nanoformulated (LAP) and oral formulation

Margolis et al CROI 2014

- The **LATTE Study** enrolled approximately 180 treatment naive patients given the novel InSTI 744 (CABOTEGRAVIR) with ABC/3TC to demonstrate efficacy and safety of 744 given at 10, **30** and 60 mg OD
- Primary goal was to determine whether those suppressed on this NRTIs + InSTI could be switched to a novel 744 plus RPV combination
- This may lead to long-acting formulations of these drugs to be used as maintenance therapy
- Viral suppression at 24 weeks was high and similar in all three doses of 744 and even higher than the TDF/FTC/EFV controls
- Of those suppressed that switched to 744 plus RPV over 90% maintained viral suppression after 24 weeks of maintenance therapy with good tolerability