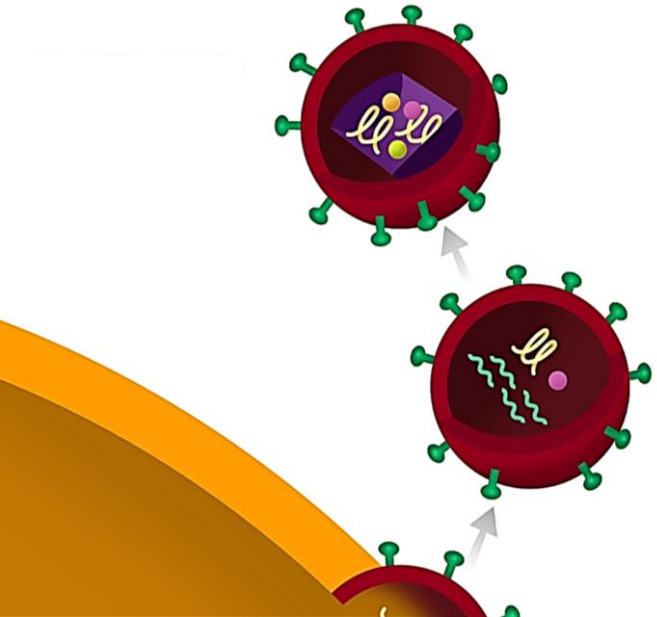
Comparison of Efficacy and Tolerability of Protease Inhibitors



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Disclosure

- Speakers Bureau
  - Pfizer, Astellas, MSD, Janssen, AztraZeneca, GSK, DKSH, BMS, AbbVie, Meiji, Siam, Daiichi, Takeda, Sanofi, Mylan, DCH Auriga, Biopharm, BLHua, Roche, Berlin, Zuellig Pharma, Medtronic, Biogenetech
- Congress Travel
  - Astellas, Pfizer, MSD, Janssen, BMS, AbbVie, Siam, Daiichi, Takeda, DKSH
- Research Grant
  - Gilead, MSD, BMS, Daiichi, Biopharm, Medicago

Outline

- Thailand National Guidelines
- Comparison of PIs: potency and efficacy
- Comparison of PIs: tolerability
- Pharmacokinetic enhancers

Thailand National Guidelines: First-line Regimen

Standard regimen (3 drugs)

NRTIs (backbone)			INSTIs (recommend)
TAF TDF	3TC FTC	+	DTG

NRTIs (alternative)			NNRTI (alternative)		
ABC AZT	3TC	+	EFV	OR	RPV

Optional regimen (2 drugs)

Regimen	Remarks
DTG + 3TC	• Contraindication to TDF and TAF • Considerations ➢ HBsAg negative ➢ Baseline VL <500,000 copies/mL or CD4 >200 cells/mm^3 ➢ No 3TC and INSTIs RAMs

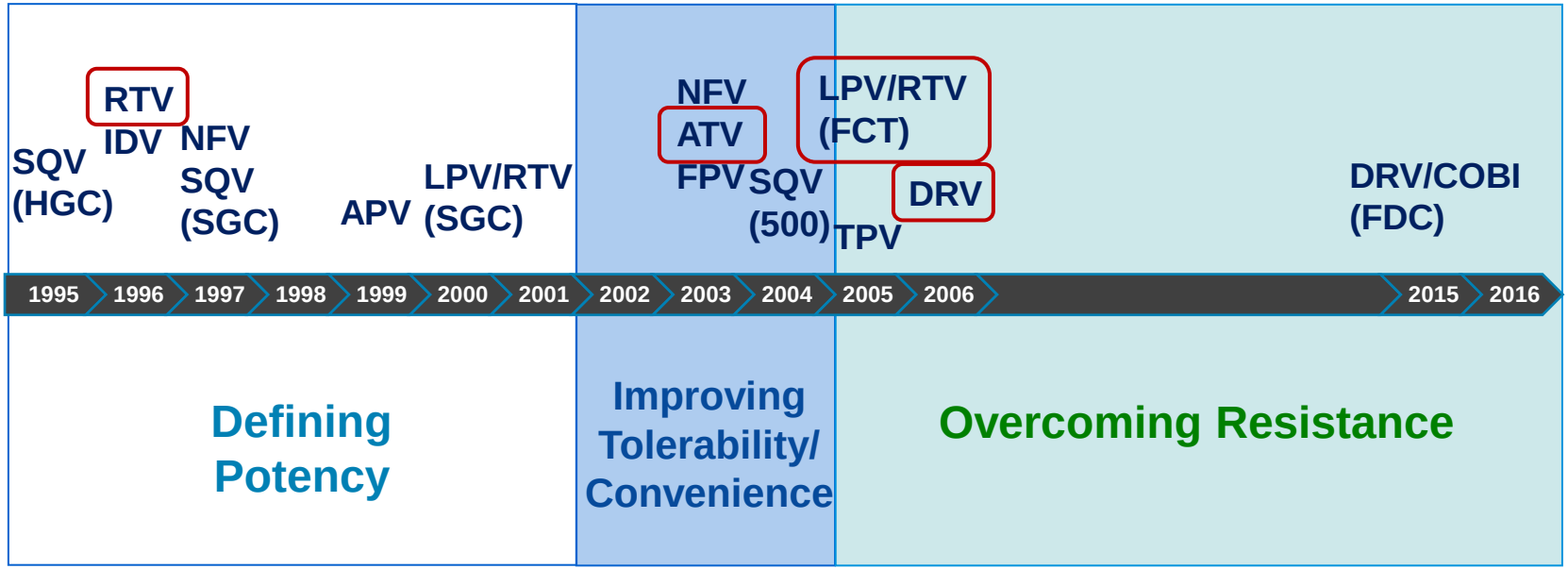
Thailand National Guidelines on HIV/AIDs Diagnosis, Treatment and Prevention 2020/2021. Available from http://thaiaidssociety.org/images/PDF/thai_aids_guidelines_2020_2021.pdf

Thailand National Guidelines: Second-line Regimen

First-line regimen	Resistance associated mutations	Second-line regimen
DTG + **NRTIs**	NRTIs RAMs	• 2 active NRTIs + DTG • **Boosted PI** + DTG • 2 active NRTIs + **boosted PI** • RPV + DTG
NNRTI + **NRTIs**	NRTIs RAMs	• NRTIs + **boosted PI** • NRTIs + DTG
	NNRTIs RAMs + M184V/I	• 2 active NRTIs + **boosted PI** • 2 active NRTIs + DTG
	NNRTIs RAMs + NRTIs RAMs	• **Boosted PI** + DTG
Boosted PI + **NRTIs** OR **RAL**	NRTIs RAMs + no PIs RAMs	• 2 active NRTIs + DTG • RPV + DTG
	NRTIs RAMs + PIs RAMs	• 2 active NRTIs + **boosted PI** (genotypic resistance test)
NRTIs + **EVG/c OR RAL**	M184V/I + INSTIs RAMs	• Consult expert

Thailand National Guidelines on HIV/AIDs Diagnosis, Treatment and Prevention 2020/2021. Available from http://thaiaidssociety.org/images/PDF/thai_aids_guidelines_2020_2021.pdf

Evolution of The Protease Inhibitors Class



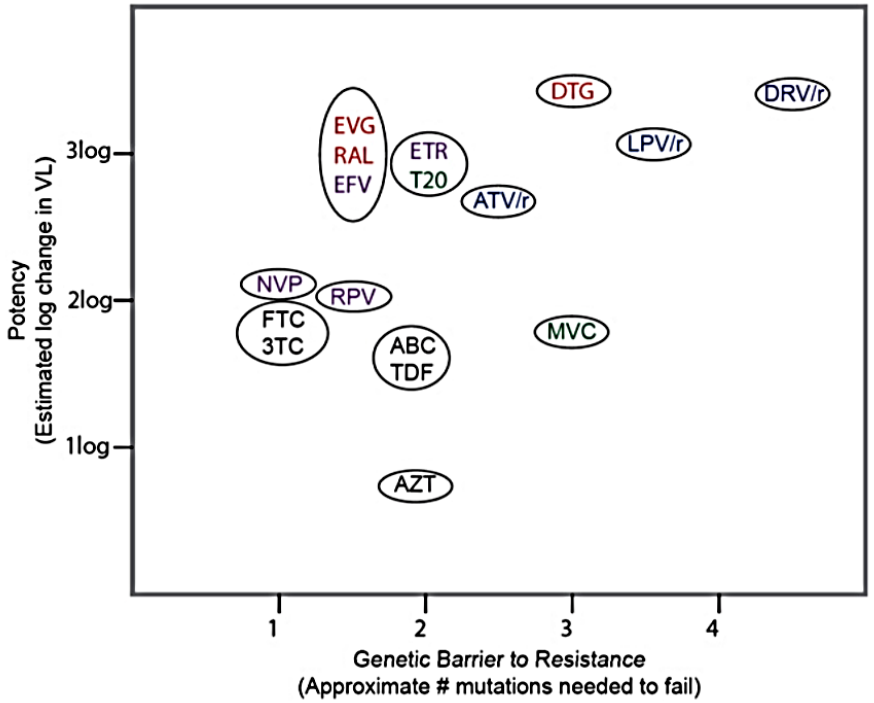
FCT: Film-coated tablet, HGC: Hard-gel capsule, FDC: Fixed-dose combination, SGC: Soft-gelatin capsule

Available in Thailand

Cihlar T, et al. Curr Opin Virol 2016;18:50-6. Approved drug products with therapeutic equivalence evaluations March 20, 2020 edition.

ARV Potency vs Genetic Barrier to Drug Resistance

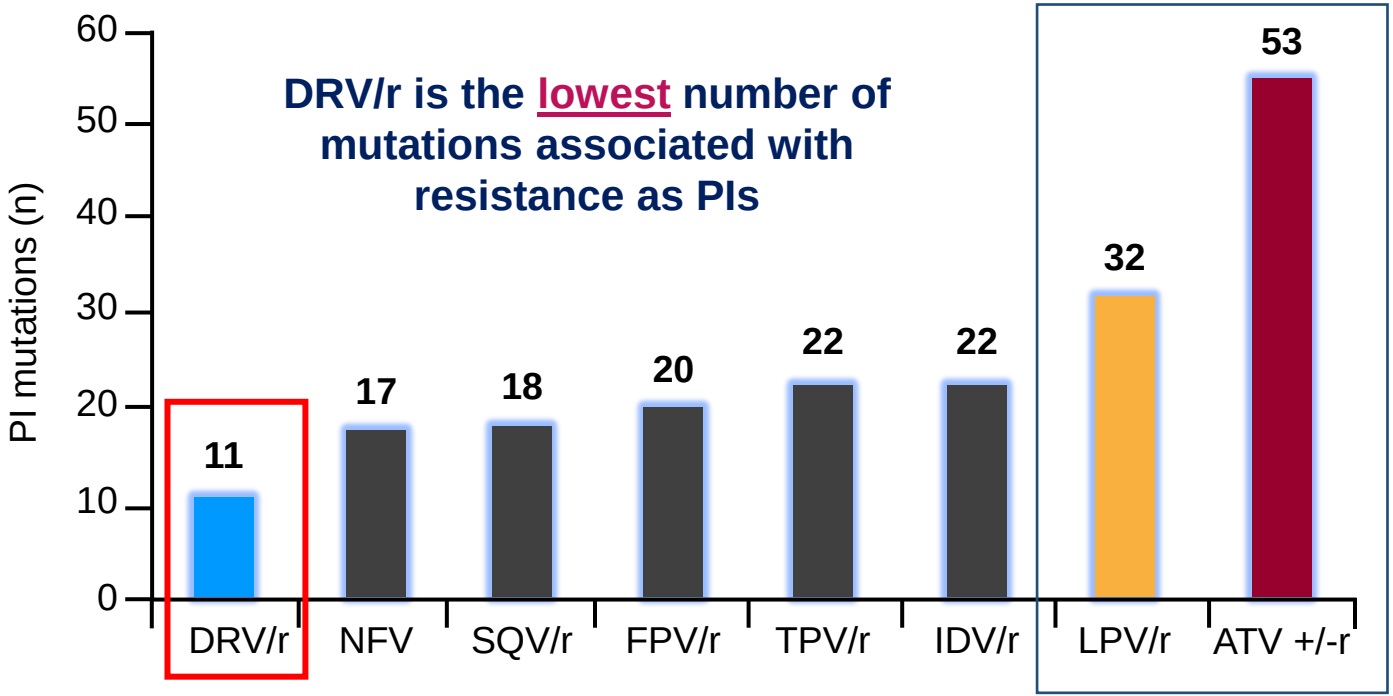
- ARV's intrinsic antiviral potency combined with its genetic barrier to resistance influences
  - Its ability to protect an ART regimen from VF
- There is essentially no cross-resistance between drug classes
- **LPV/r** and **DRV/r** have high genetic barriers to resistance
  - Multiple DRMs are required before antiviral activity is compromised



ARVs appearing together in the same ellipse should be considered to have roughly equivalent potencies and genetic barriers to resistance.

Clutter DS, et al. Infect Genet Evol 2016;46:292-307. Pozniak AL, et al. Lancet 2014;383;2191-3.

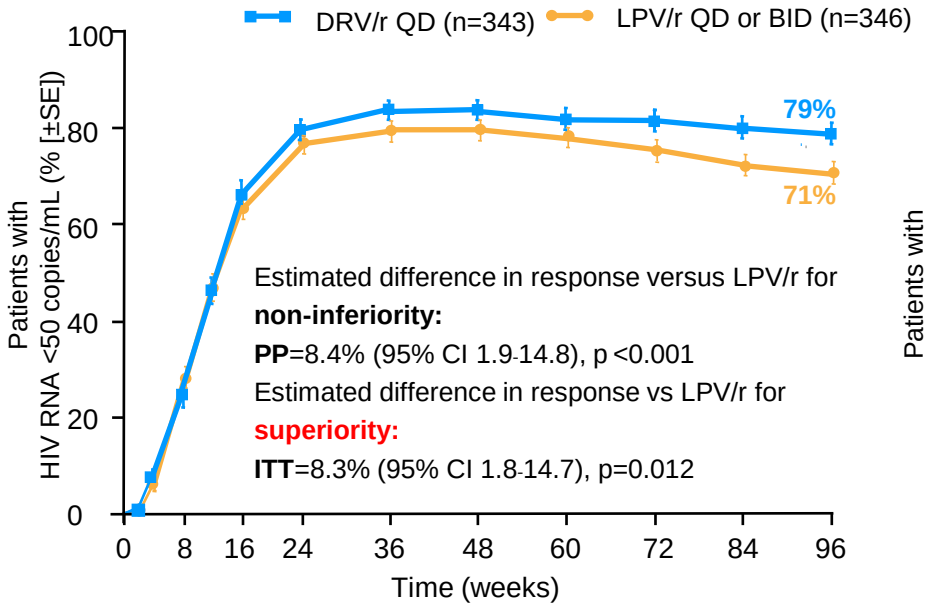
Number of Mutations in Protease Gene Associated With Resistance to PIs



Johnson VA, et al. Top Antivir Med 2016;24:132-41.

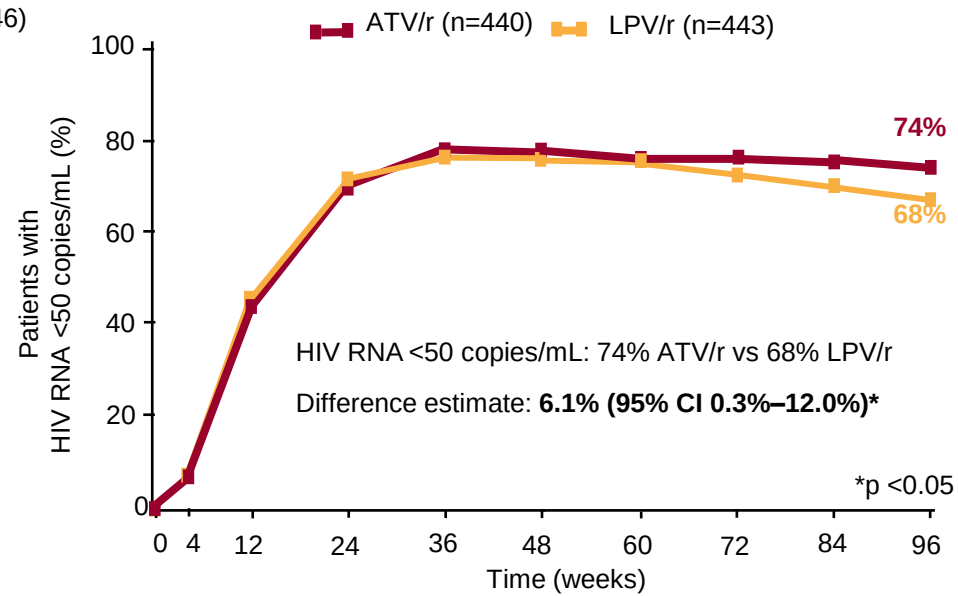
ARTEMIS[1] and CASTLE[2]

ARTEMIS: HIV RNA <50 copies/mL to Week 96 (ITT TLOVR)*



*Estimated from a logistic regression model including treatment and stratification factors (baseline $\log_{10}$ viral load and baseline CD4 count)

CASTLE: HIV RNA <50 copies/mL to Week 96 (ITT CVR, NC=F)

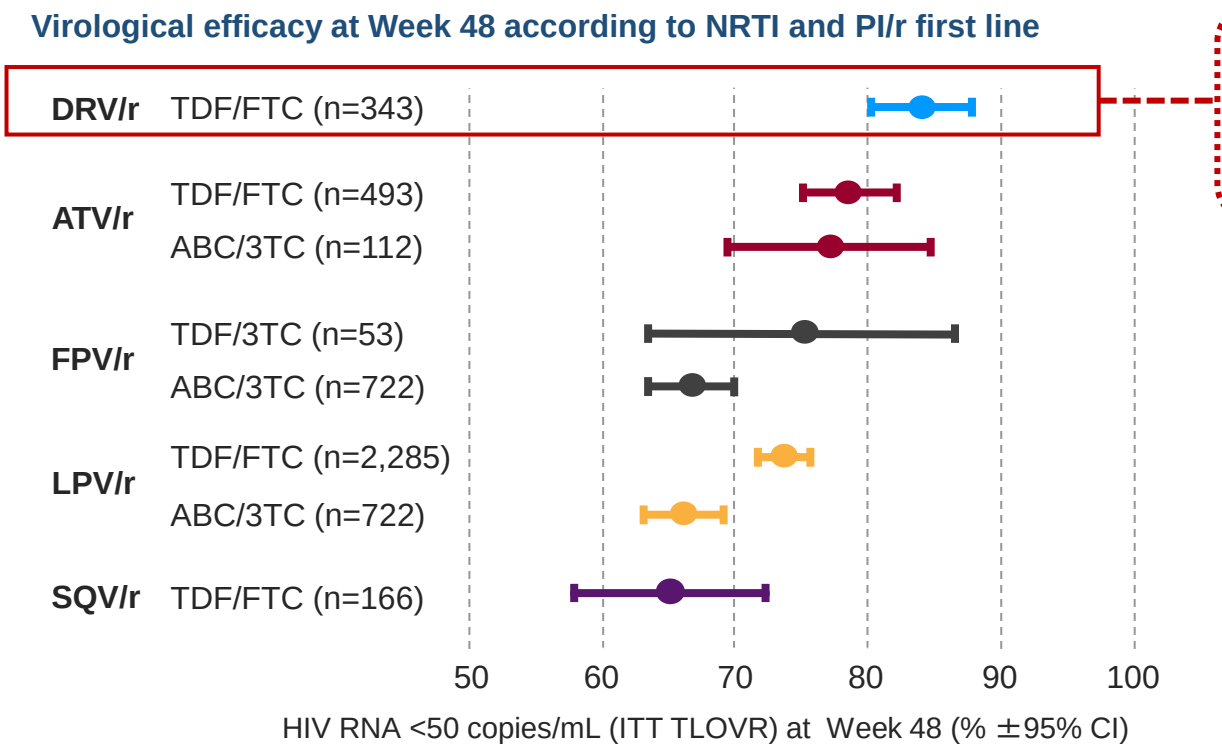


Supporting analyses:
ITT – TLOVR: HIV RNA <50 c/mL: ATV/r 70%, LPV/r 63%; 6.6% (0.4–12.7%)
OT – VR-OC: HIV RNA <50 c/mL: ATV/r 89%, LPV/r 88%; 1.6% (–3.1–6.2%)

1. Mills AM, et al. AIDS 2009;23:1679-88. 2. Molina JM, et al. J Acquir Immune Defic Syndr 2010;33:323-32.

Efficacy in Treatment-naive Patients

- Meta-analysis of efficacy at Week 48

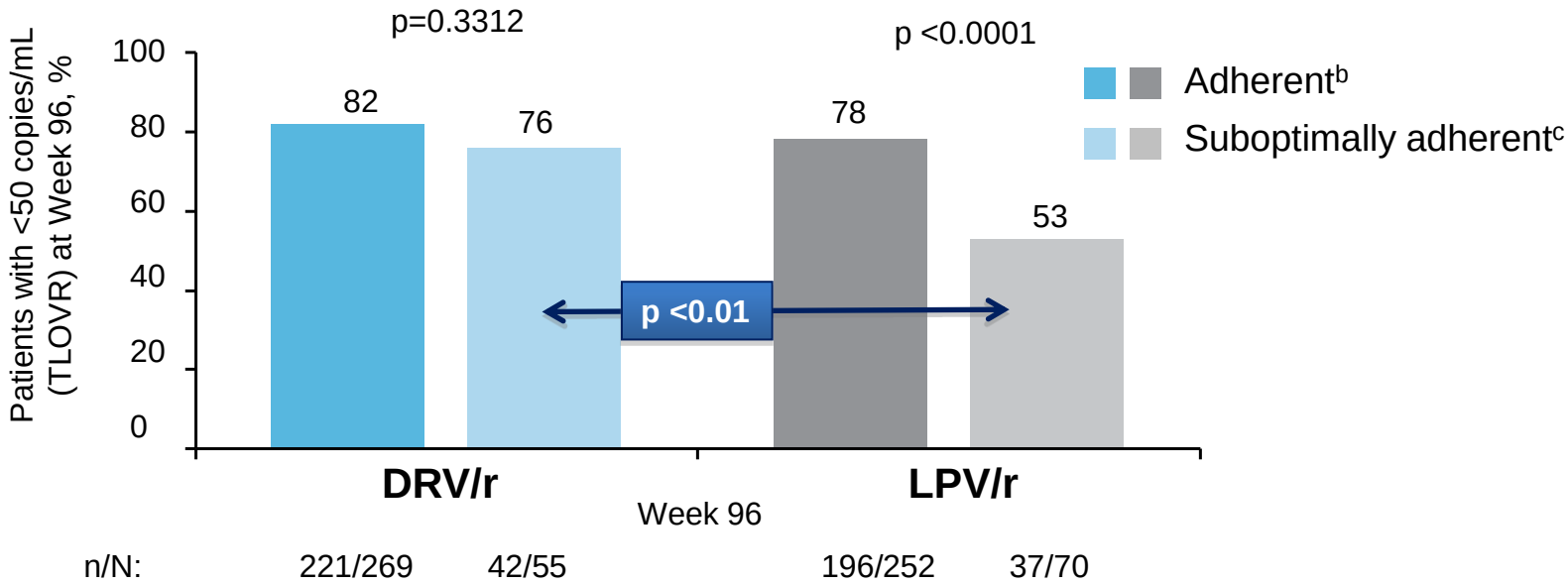


DRV/r is the highest virological efficacy as protease inhibitors

Hill A, et al. HIV Med 2009;10:527-35.

PIs Adherence and Virologic Response

- Suboptimal adherence to DRV/r has less effect on virologic response compared to suboptimal adherence to LPV/r



[a]viral load <50 copies/mL, TLOVR; [b]Week 4-96 mean adherence >95%; [c]Week 4-96 mean adherence ≤95%; n, number of patients with <50 copies/mL; N, number of patients who completed the questionnaire

Orkin C, et al. HIV Med 2013;14:49-59.

Tolerability Comparison

ARTEMIS: difference in efficacy between the DRV/r and LPV/r arms was driven by combination of adverse events and virological failure[1]

Incidence (Week 96), n (%)	DRV/r n=343	LPV/r n=346
Discontinuations	59 (17)	81 (23)
Adverse event	13 (4)	32 (9)
Lost to follow-up	18 (5)	11 (3)
Virological failure	3 (1)	8 (2)
Other	5 (1)	10 (3)
Pregnancy	6 (2)	3 (1)
Non-compliance to study protocol	3 (1)	7 (2)
Withdrew consent	11 (3)	10 (3)

CASTLE: discontinuations were primarily due to adverse events[2]

Incidence (Week 96), n (%)	ATV/r n=438	LPV/r n=440
Discontinuations	72 (16)	95 (21)
Adverse event	13 (3)	22 (5)
Death	6 (1)	5 (1)
Lack of efficacy	16 (4)	10 (2)
Other	1 (<1)	1 (<1)
Lost to follow-up	10 (2)	13 (3)
Non-compliance	12 (3)	16 (4)
Pregnancy	5 (1)	7 (2)
No longer meets study criteria	4 (<1)	3 (<1)
Withdrew consent	5 (1)	18 (4)

1. Mills AM, et al. AIDS 2009;23:1679-88. 2. Molina JM, et al. J Acquir Immune Defic Syndr 2010;33:323-32.

Hepatotoxicity and Gastrointestinal Side Effect

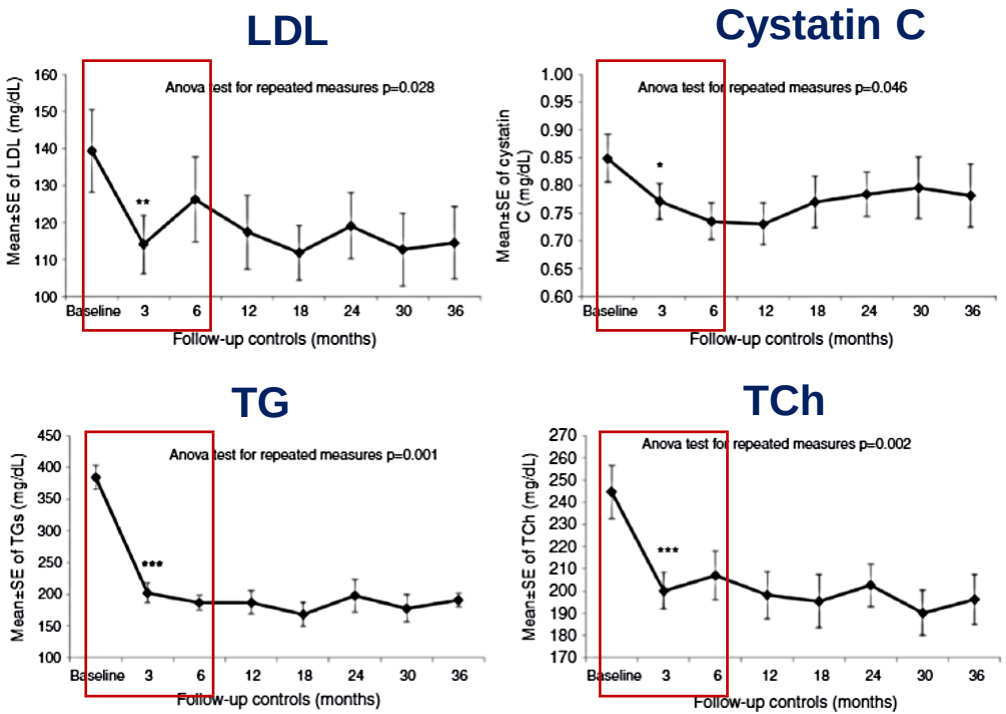
Grade 2-4 AEs at least possibly related to treatment over 96 Weeks (≥2% incidence)*

	ARTEMIS[1]		CASTLE[2]	
	DRV/r n=343	LPV/r n=346	ATV/r n=440	LPV/r n=443
Any grade 2-4 AE at least possibly related to treatment, n (%)*	80 (23)	119 (34)	133 (30)	140 (32)
Gastrointestinal AEs, n (%)				
Diarrhea	14 (4)†	38 (11)	11 (2)	54 (12)
Nausea	6 (2)	10 (3)	18 (4)	33 (8)
Hyperbilirubinemia, n (%)	4 (1)	17 (5)	33 (7)	1 (<1)
Jaundice, n (%)	ns	ns	18 (4)	0 (0)

*Excludes laboratory abnormalities reported as AEs; † p <0.001 vs LPV/r; ns=not specified
Results cannot be directly compared because of different study designs and populations

1. Mills AM, et al. AIDS 2009;23:1679-88. 2. Molina JM, et al. J Acquir Immune Defic Syndr 2010;33:323-32.

Switching to DRV/r Improves Lipid Profile



Lipid profile of patients: total cholesterol (TCh), LDL cholesterol (LDL), cystatin C and triglycerides (TGs) at baselineand at different controls of follow-up. *p < 0.05, **p < 0.01, ***p < 0.001 contrast analysis versus the previous follow-up control

- Switching to DRV/r in 13 patients previously on LPV/r and FPV/r
- At the end of the study, TG 47%, TCh 18%, and LDL 18% significant reduced
- TCh/HDL ratio has improved
- CD4 counts were increased
- Significant reduction of cystatin C 8% and microalbuminuria 35%

Ucciferri C, et al. Braz J Infect Dis 2016;20:401-2.

Atazanavir and Kidney Stones

- ATV/r exposure is associated with increased rate of renal stones compared with EFV, LPV/r, and DRV/r

Outcomes	ATV/r (n=1,206)	EFV, DRV/r, and LPV/r combined cohort (n=4,449)	p-value
No. of patients with kidney stones	24	24	
Prevalence of kidney stones per 1,000 patients (95% CI)	20 (13-30)	5.4 (3.2-7.6)	<0.001
Event rate per 1,000 pt-yrs of exposure, n (95% CI)	7.3 (4.7-10.8)	1.9 (1.2-2.8)	<0.001

- Kidney stones was **3.8x** higher in individuals on ATV compared with those in EFV, DRV/r and LPV/r combined cohort

Rockwook N, et.al. AIDS 2011;25:1671-3.

Protease Inhibitors and Kidney Function

- Impact of PIs on the evolution of urinary markers
- Renal abnormalities
  - Microalbuminuria, macroalbuminuria, or proteinuria and/or glycosuria (without hyperglycemia), hematuria, and/or hypophosphatemia, or eGFR <60 mL/min/1.73 m^2
- Significant risk for renal impairment with **ATV/r** and **LPV/r**

Drugs	Hazard ratio* (95% CI)	p-value
LPV/r	1.69 (1.1-2.6)	0.017
ATV/r	1.52 (1.14-2.03)	0.004
DRV/r	1.31 (0.94-1.81)	0.108
EFV	1.00	

*Adjusted for gender, age at start of HAART, baseline eGFR, HBsAg, prior exposure to TDF and IDV and total duration of TDF exposure

Rockwood N, et al. J Antivir Antiretrovir 2012,4:2.

Improved Kidney Function After Switching to DRV/r

- The UK CHIC study (n=1430)
  - Median age 45 years, 79% were men, 76% had undetectable VL, and median eGFR 93 mL/min/1.73 m^2
- Improved kidney function in patients who switch from ATV or LPV to DRV

Table 2. eGFR slope estimates in individuals who switch from either atazanavir (/r) or lopinavir (/r) to darunavir (/r).

Regimen	*N*	Mean change in eGFR per year (95% CI)		*P* value*
		Pre switch	Post switch	
A. All switchers				
Unadjusted estimates				
All switchers	1430	−0.87 (−1.21, −0.53)	0.51 (0.25, 0.77)	<0.001
Atazanavir	577	−0.94 (−1.38, −0.49)	0.90 (0.47, 1.34)	<0.001
Lopinavir	853	−0.78 (−1.29, −0.28)	0.27 (−0.05, 0.59)	<0.001
Adjusted estimates**				
All switchers	1430	−0.67 (−1.03, −0.31)	0.86 (0.59, 1.12)	<0.001
Atazanavir	577	−0.84 (−1.31, −0.36)	1.23 (0.80, 1.66)	<0.001
Lopinavir	853	−0.57 (−1.09, −0.05)	0.62 (0.28, 0.96)	<0.001
D. Patients who did not receive TDF prior to switch (regardless of TDF use post switch)†				
Atazanavir	158	−0.22 (−1.17, 0.72)	0.51 (−0.20, 1.22)	0.240
Lopinavir	351	0.20 (−1.25, 1.66)	0.52 (−0.04, 1.09)	0.695

*Pre vs. post switch eGFR slopes
**Model includes age, sex, ethnicity, eGFR at switch, CD4 count, undetectable viral load (yes/no) and cumulative TDF exposure

Sophie J, et al. AIDS 2017;31:485-92.

Dosage and Pill Burden of Protease Inhibitors

	DRV/r	LPV/r	ATV/r
Dosage form (adult)	 800/100 600/100	 100/25 200/50	 300/100 200
Pill burden			
• Naïve treatment	• 800/100 QD (2 tabs)	• 400/100 BID • 800/200 QD (4 or 8 tabs)	• 400 QD • 300/100 QD (2 tabs)
• Experienced treatment	• No DRV-RAMs: 800/100 QD (2 tabs) • With DRV-RAMs: 600/100 BID (4 tabs)	• With ≥3 LPV-RAMs: 400/100 BID • 800/200 QD (4 or 8 tabs)	• 300/100 QD (2 tabs)

Drug Boosting – How Does It Work?

Possibilities to overcome these issues

- Ingestion of larger doses
- More frequent dosing

Drug boosting

→ **Higher pill-count and potentially adherence issues**

- Drug-boosting is based on drug-drug interaction
- Inhibition of cytochrome P450 3A4 (CYP3A4) isoenzymes decreases the inactivation of PIs when passing the liver after initial uptake from the intestine
- Example: **Boosting DRV with RTV increases its bioavailability 11-fold**

- Cytochrome P450 enzymes are oxidases that:
  - Unmask or add polar groups to drugs, make drugs more water soluble
  - Inactivate drugs or activate pro-drugs or turn them into non-toxic metabolites

Cobicistat: An Alternative Booster to RTV[1]

Disadvantages of RTV[2]

- Antiviral activity with the risk to develop PI-resistance in non-PI-containing regimens
- Poor solubility limits the coformulation of RTV with other ARVs
- Tolerability issues and numerous drug-drug interactions

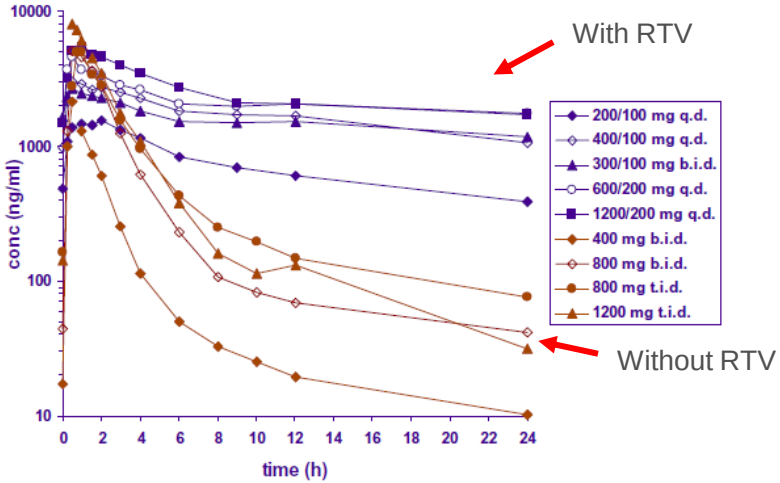
COBI is a structural analogue of RTV

- No intrinsic antiviral activity
- Improved physicochemical properties
- Similar potency[3] in boosting ATV,[4] DRV[5], and EVG[6] compared to RTV
- In Thailnand, will be available soon as DRV/COBI

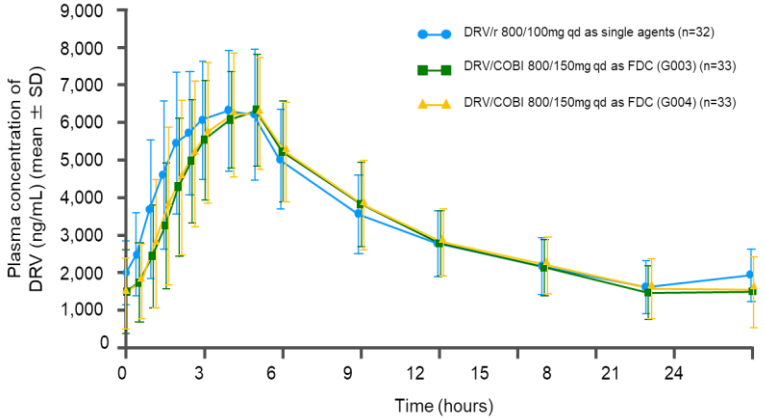
1. Marzolini C, et al. J Antimicrob Chemother 2016;71:1755-8. 2. Hsu A, et al. Clin Pharmacokinet 1998;35:275-91. 3. Mathias AA, et al. Clin Pharmacol Ther 2010;87:322-9.
4. Elion R, et al. AIDS 2011;25:1881-6. 5. Kakuda TN, et al. J Clin Pharmacol 2014;54:949-57. 6. German P, et al. J Acquir Immune Defic Syndr 2010;55:323-9.

Boosting Increases PI Plasma Concentration

Pharmacologic boosting of DRV by RTV[1]



DRV/COBI is bioequivalent to DRV/r[2]



- Boosting DRV with RTV increases plasma concentrations significantly
- Cobicistat is structurally similar to RTV
- It has been proven to be non-inferior vs RTV regarding its boosting capacity

1. Hoetelmans R, et al. CROI 2003. Poster 549. 2. Kakuda TN, et al. J Clin Pharmacol. 2014;54:949-57.

DRV/COBI Shows Significant Lipid Profile Improvement After Switch From DRV/RTV

Lipid parameter	Baseline	Week 24	P-value
Total population (n=299)			
Use of lipid-lowering agents (%)	12%	12%	--
TC (mg/dL) [median (IQR)]	190 (162, 216)	184 (154, 211)	0.085
LDL-c (mg/dL) [median (IQR)]	111 (92, 136)	109 (84, 132)	0.530
HDL-c (mg/dL) [median (IQR)]	44 (38, 54)	45 (38, 54)	0.440
TG (mg/dL) [median (IQR)]	167 (93, 187)	124 (87, 175)	**0.018**
Subjects with TC ≥200 mg/dL, LDL-c ≥130 mg/dL and/or TG ≥ 200 mg/dL (%)	52%	45%	0.112
Subjects with hypercholesterolemia at baseline (TC >200 mg/dL and/or LDL-c >130 mg/dL) (n=124)			
TC (mg/dL) [median (IQR)]	231 (209, 243)	212 (189, 239)	**0.001**
LDL-c (mg/dL) [median (IQR)]	144 (131, 161)	131 (113, 152)	**0.047**
HDL-c (mg/dL) [median (IQR)]	45 (40, 54)	52 (44, 59)	**0.002**
TG (mg/dL) [median (IQR)]	157 (109, 209)	131 (101, 202)	**0.025**
Subjects with hypertriglyceridemia at baseline (TG >200 mg/dL) (n=64)			
TC (mg/dL) [median (IQR)]	207 (182, 232)	191 (158, 215)	0.067
LDL-c (mg/dL) [median (IQR)]	109 (84, 121)	105 (83, 127)	0.299
HDL-c (mg/dL) [median (IQR)]	40 (36, 45)	40 (36, 48)	0.381
TG (mg/dL) [median (IQR)]	352 (223, 389)	229 (131, 279)	**<0.001**

Echeverría P, et al. HIV Med 2017;18;782-6.

COBI vs RTV DDI Profiles With Co-medications 1

Therapeutic class	Drug	Metabolic pathway/comments	RTV	COBI
Anaesthetics	propofol	UGT1A9, UGT1A8+CYP2B6	↓	↔
Analgesics	diamorphine	Deacetylation+UGT2B7, UGT1A1	↓	↔
	dihydrocodeine	CYP2D6+UGT2B7 > CYP3A4	↓↑	↑
	hydromorphone	UGT2B7	↓	↔
	morphine	UGT2B7, UGT1A1	↓	↔
	pethidine	CYP2B6 > CYP3A4	↓	↑
Antibacterials	sulfadiazine	CYP2C9	↓	↔
Anticoagulants	acenocoumarol	CYP2C9>CYP1A2, CYP2C19	↓	↔
	eltrombopag	UGT1A1, UGT1A3+CYP1A2, CYP2C8	↓	↔
	phenprocoumon	CYP2C9, CYP3A4	↓↑	↑
	warfarin	CYP2C9>CYP1A2, CYP3A4	↓	↑
Anticonvulsants	lamotrigine	UGT1A4	↓	↔
	valproate	UGT1A6, UGT1A9, UGT2B7+CYP2C9, CYP2C19	↓	↔
Antidepressants	agomelatine	CYP1A2	↓	↔
	bupropion	CYP2B6	↓	↔
	duloxetine	CYP2D6, CYP1A2	↓↑	↑
	sertraline	CYP2B6>CYP2C9, CYP2C19, CYP2D6, CYP3A4	↓	↑

↑, potential increase in co-medication exposure by ritonavir or cobicistat pharmacokinetic boosting;
↓, potential increase in co-medication exposure by ritonavir or cobicistat pharmacokinetic boosting;
↔, no clinically significant effect on co-medication exposure.
Information on the metabolic pathway of the co-medication and on the description of the DDI can be found at the Liverpool HIV Drug Interactions web site.[2]

Marzolini C, et al. J Antimicrob Chemother 2016;71:1755-8. Liverpool HIV Drug Interactions. https://www.hiv-druginteractions.org/checker

COBI vs RTV DDI Profiles With Co-medications 2

Therapeutic class	Drug	Metabolic pathway/comments	RTV	COBI
Antidiabetics	gliclazide	CYP2C9>CYP2C19	↓	↔
	glimepiride	CYP2C9	↓	↔
	glipizide	CYP2C9	↓	↔
	nateglinide	CYP2C9>CYP3A4	↓↑	↑
	rosiglitazone	CYP2C8>CYP2C9	↓	↔
	tolbutamide	CYP2C9>CYP2C8,CYP2C19	↓	↔
Antiprotozoals	amodiaquine	CYP2C8	↑	↔
	atovaquone	glucuronidation	↓	↔
	proguanil	CYP2C19>CYP3A4	↓	↔
Antipsychotics	asenapine	UGT1A4, CYP1A2, CYP3A4	↓	↑
	olanzapine	CYP1A2, UGT1A4	↓	↔
Antiretrovirals	efavirenz	cobicistat administered 150 mg once daily is not sufficient to overcome induction by efavirenz, etravirine or nevirapine	a	b
	etravirine		a	b
	nevirapine		a	b
B-blockers	carvedilol	UGT1A1, UGT2B4, UGT2B7+CYP2D6	↓↑	↑
	oxprenolol	glucuronidation	↓	↔
Bronchodilators	theophylline	CYP1A2	↓	↔

↑, potential increase in co-medication exposure by ritonavir or cobicistat pharmacokinetic boosting;
↓, potential increase in co-medication exposure by ritonavir or cobicistat pharmacokinetic boosting;
↔, no clinically significant effect on co-medication exposure.
Information on the metabolic pathway of the co-medication and on the description of the DDI can be found at the Liverpool HIV Drug Interactions web site.[2]
[a]Coadministration is possible when using 600/100 mg of darunavir/ritonavir twice daily, but it is not recommended with 300/100 mg of atazanavir/ritonavir once daily.
[b]Not recommended to be given with once-daily boosting with cobicistat (i.e. 150 mg once daily); cobicistat is not sufficient to overcome the induction effect of efavirenz, etravirine, or nevirapine. Of note: cobicistat is not licensed as a twice-daily boosting agent.

Marzolini C, et al. J Antimicrob Chemother 2016;71:1755-8. Liverpool HIV Drug Interactions. https://www.hiv-druginteractions.org/checker

COBI vs RTV DDI Profiles With Co-medications 3

Therapeutic class	Drug	Metabolic pathway/comments	RTV	COBI
Contraceptives/HRT	oestradiol	CYP3A4, CYP1A2+glucuronidation	↓	↑
	ethinyloestradiol	CYP3A4>CYP2C9, glucuronidation	↓	↑
	norethisterone	CYP3A4, glucuronidation	↓	↑
Cytotoxics	anastrozole	CYP3A4+UGT1A4	↓↑	↑
	dacarbazine	CYP1A2>CYP2E1	↓	↔
	droloxifene	glucuronidation	↓	↔
	epirubicin	UGT2B7	↓	↔
	formestane	partly glucuronidation	↓	↔
	procarbazine	CYP2B6, CYP1A2	↓	↔
Gastrointestinal agents	alosetron	CYP1A2>CYP2C9, CYP3A4	↓	↔
Antihypertensives	irbesartan	glucuronidation+CYP2C9	↓	↔
	labetalol	UGT1A1, UGT2B7	↓	↔
	losartan	CYP2C9	↓	↔
	torasemide	CYP2C9	↓	↔
Immunosuppressants	mycophenolate	UGT1A9, UGT2B7	↓	↔
Lipid-lowering agents	gemfibrozil	UGT2B7	↓	↔
	pitavastatin	UGT1A3, UGT2B7>CYP2C9, CYP2C8	↓	↔
Anti-Parkinson agents	apomorphine	glucuronidation, sulphation	↓	↔
	rasagiline	CYP1A2	↓	↔
	ropinirole	CYP1A2	↓	↔
Other	Dexmedetomidine	UGT1A4, UGT2B10, CYP2A6	↓	↔

↑, potential increase in co-medication exposure by ritonavir or cobicistat pharmacokinetic boosting;
↓, potential increase in co-medication exposure by ritonavir or cobicistat pharmacokinetic boosting;
↔, no clinically significant effect on co-medication exposure.
Information on the metabolic pathway of the co-medication and on the description of the DDI can be found at the Liverpool HIV Drug Interactions web site.[2]

Marzolini C, et al. J Antimicrob Chemother 2016;71:1755-8. Liverpool HIV Drug Interactions. https://www.hiv-druginteractions.org/checker

COBI vs RTV: Conclusions

Difference between COBI and RTV drug profiles

COBI and RTV are interchangeable as inhibitors of CYP3A

COBI is a more-specific CYP3A inhibitor and has no inducing properties → less drug-drug interactions

Comedications primarily metabolized by CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 or mainly glucuronidated are predicted to be affected differently by RTV and COBI

Modified from Marzolini C, et al. J Antimicrob Chemother 2016;71:1755-8.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fit
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