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Clinical and Metabolic Overview of Atazanavir:

2004 Update

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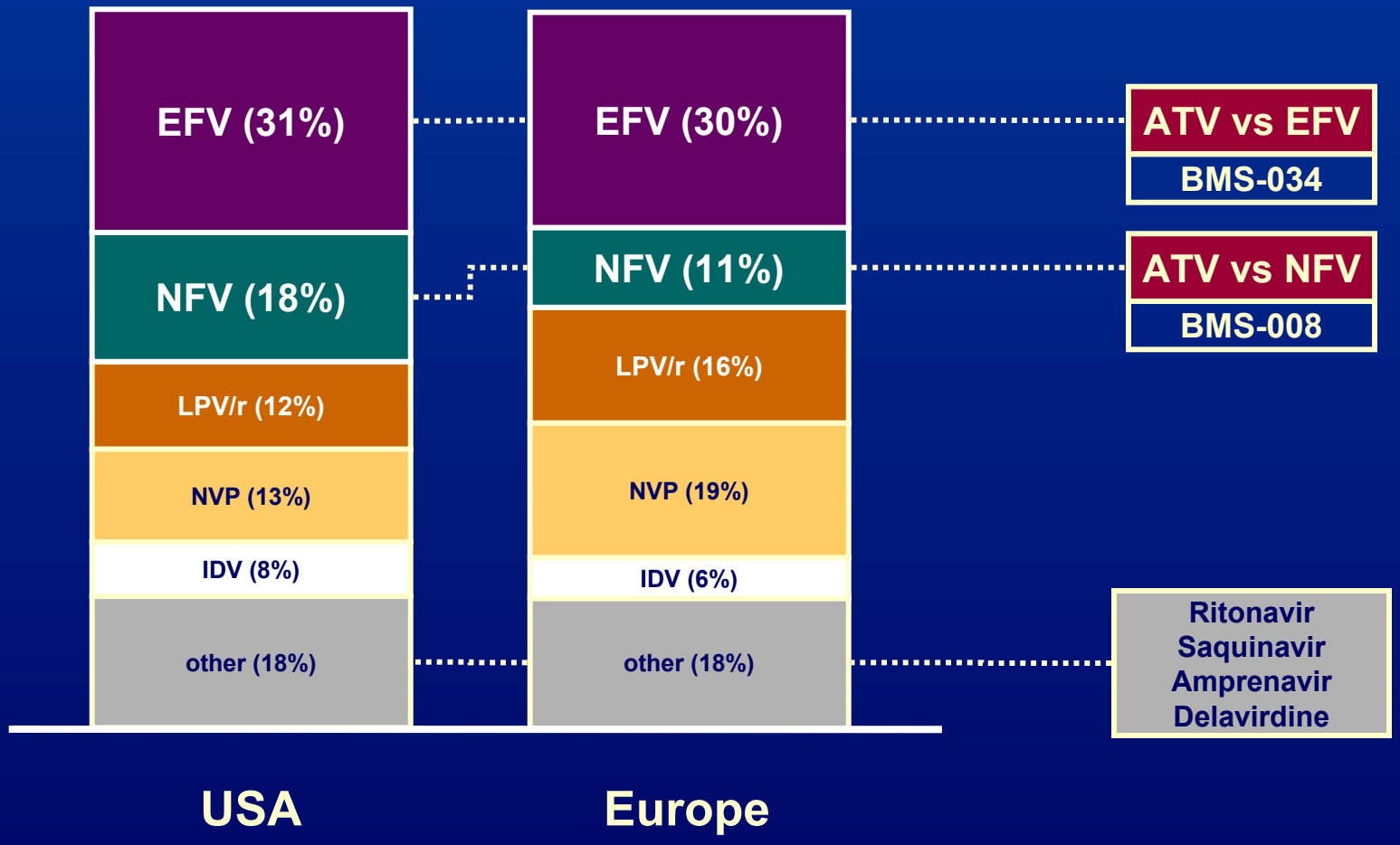
Standard of Care for First-Line HAART

US Department of Health and Human Services: March 2004

Preferred Regimens	# of pills
EFV + 3TC + (AZT, TDF or d4T)	3-5
LPV/r + 3TC + (AZT or d4T)	8-10

Alternative Regimens	# of pills
EFV + FTC + (AZT, TDF, d4T)	3-4
EFV + (3TC or FTC) + (ddI or ABC)	3-5
NVP + (3TC or FTC) + (AZT, d4T, ABC or ddI)	4-5
ATV + (3TC or FTC) + (AZT, d4T or ABC)	4-5
IDV/r + (3TC or FTC) + (AZT, d4T or ABC)	8-11
NFV + (3TC or FTC) + (AZT, d4T or ABC)	12-14
SQV/r + (3TC or FTC) + (AZT, d4T or ABC)	14-16
(FOS or FOS/r) + (3TC or FTC) + (AZT, d4T or ABC)	6-8
LPV/r + FTC + (AZT, d4T or ABC)	8-9

Third Agent Usage Patterns: First Line Therapy



Sources: ISIS USA, ISIS EU, **2003**

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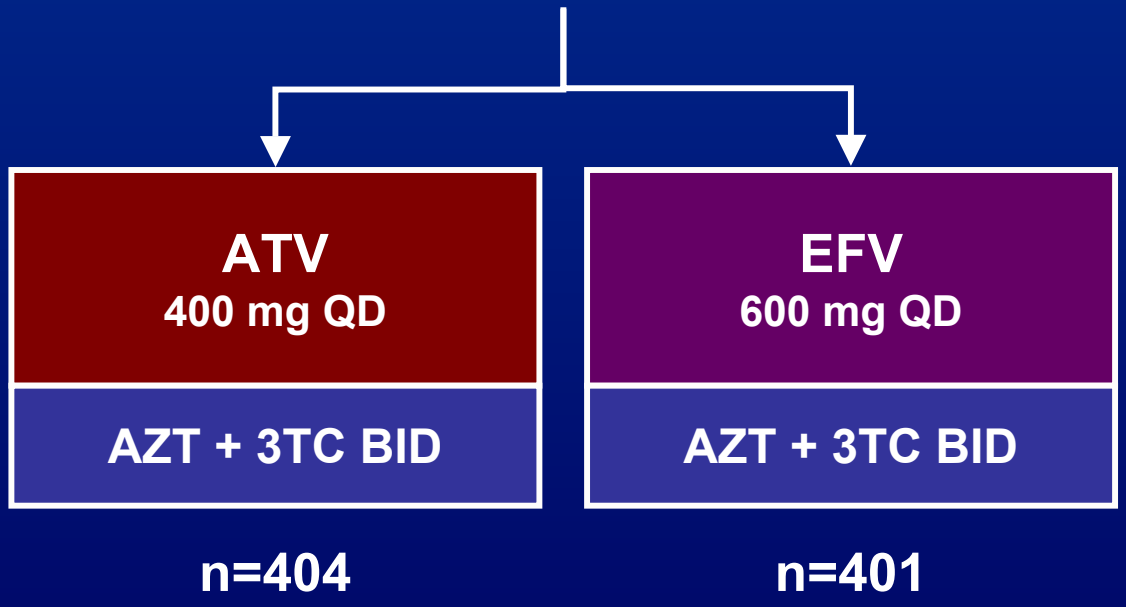
Efficacy as First-Line HAART

- ***BMS-034: ATV vs EFV***

ATV vs EFV in Treatment-Naïve Patients

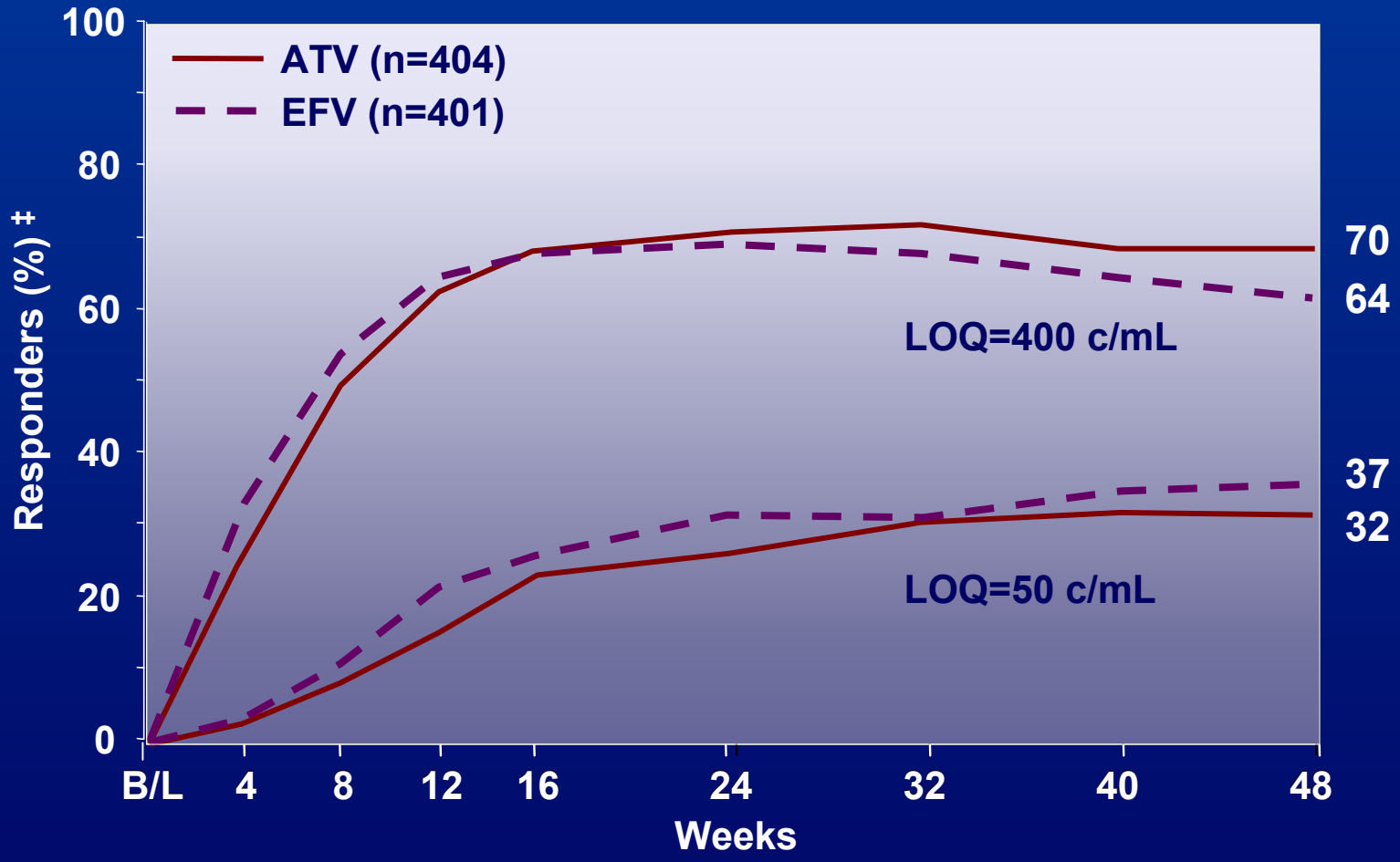
BMS-034

Phase III, double-blind, multicenter trial in ARV-naïve patients, randomized 1:1



Adapted from: Squires K *et al*. 42nd ICAAC, San Diego, Sep 2002. **Oral presentation H-1076**

48 Week Virological Response (ITT)



Analysis: TLOVR: Time to Loss of Virological Response (ITT: NC=F)
‡Responders at each visit are patients who had achieved and maintained HIV-1 RNA <400 copies/mL (<50 copies/mL) without discontinuation by that visit.

Adapted from: Squires K *et al*. 42nd ICAAC, San Diego, Sep 2002. **Oral presentation H-1076**

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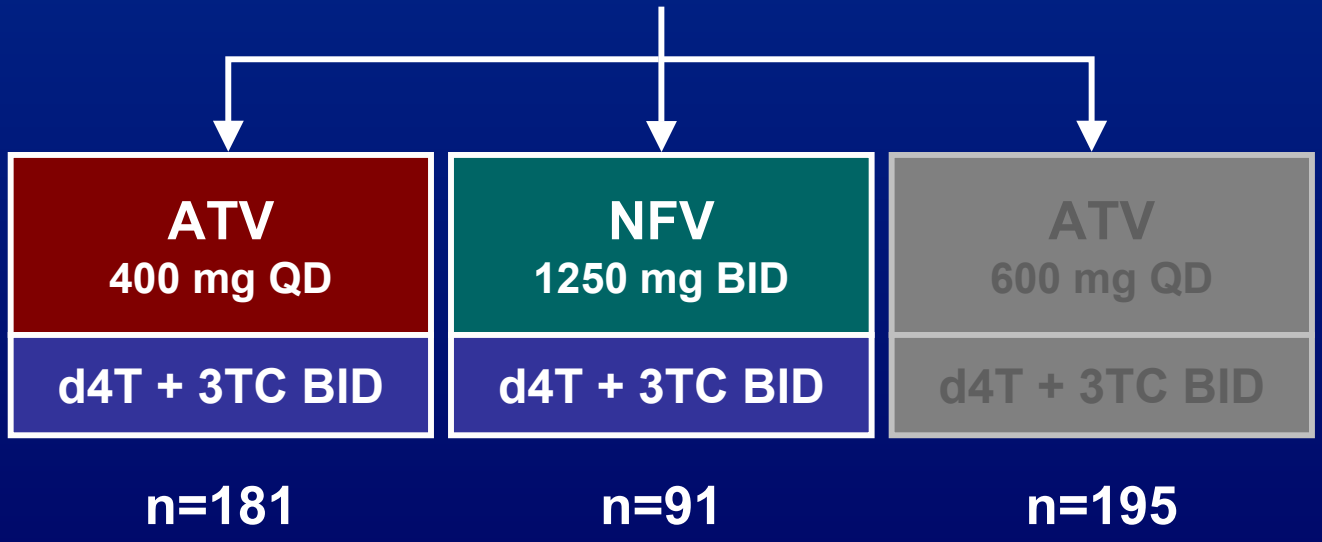
Efficacy as First-Line HAART

- ***BMS-008: ATV vs NFV***

ATV vs NFV in Treatment-Naïve Patients

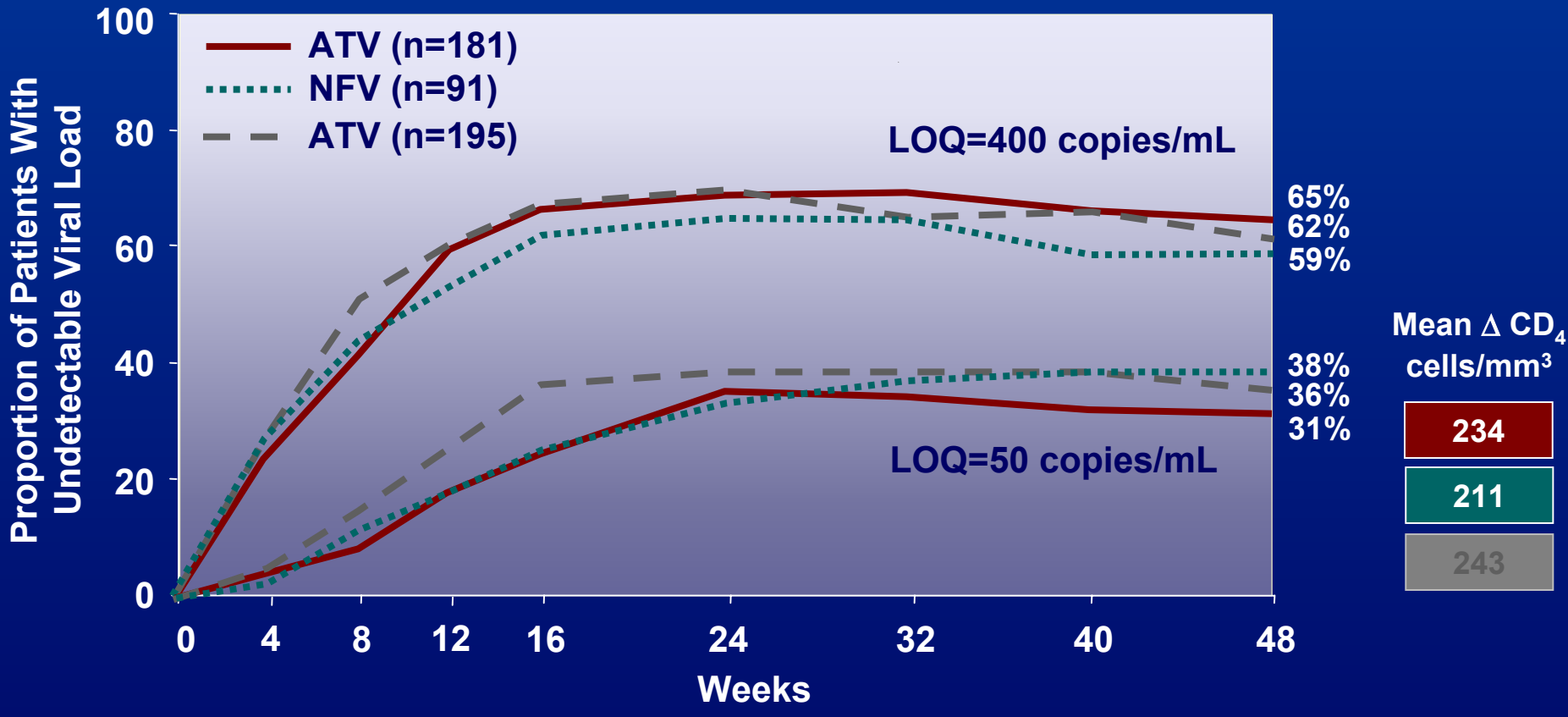
BMS-008

Phase II, 48-week, multicenter trial in antiretroviral (ARV)-naïve patients blinded to ATV dose, randomized 2:1:2



Adapted from: Sanne I *et al*. 41st ICAAC, Chicago, Dec 2001. **Oral presentation I-667**

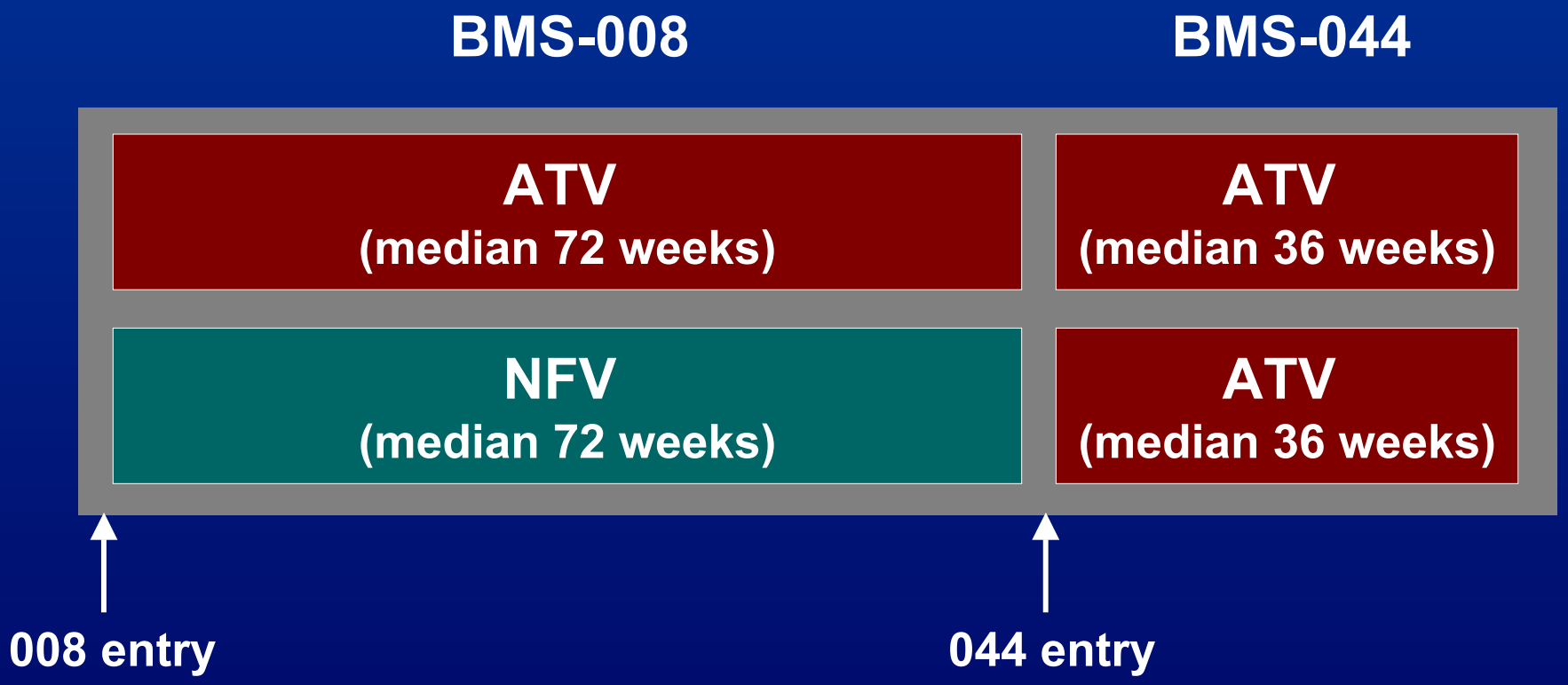
48 Week Virologic Response (ITT*)



*Analysis: TRWPF: Treatment Response Without Prior Failure (ITT: NC=F)

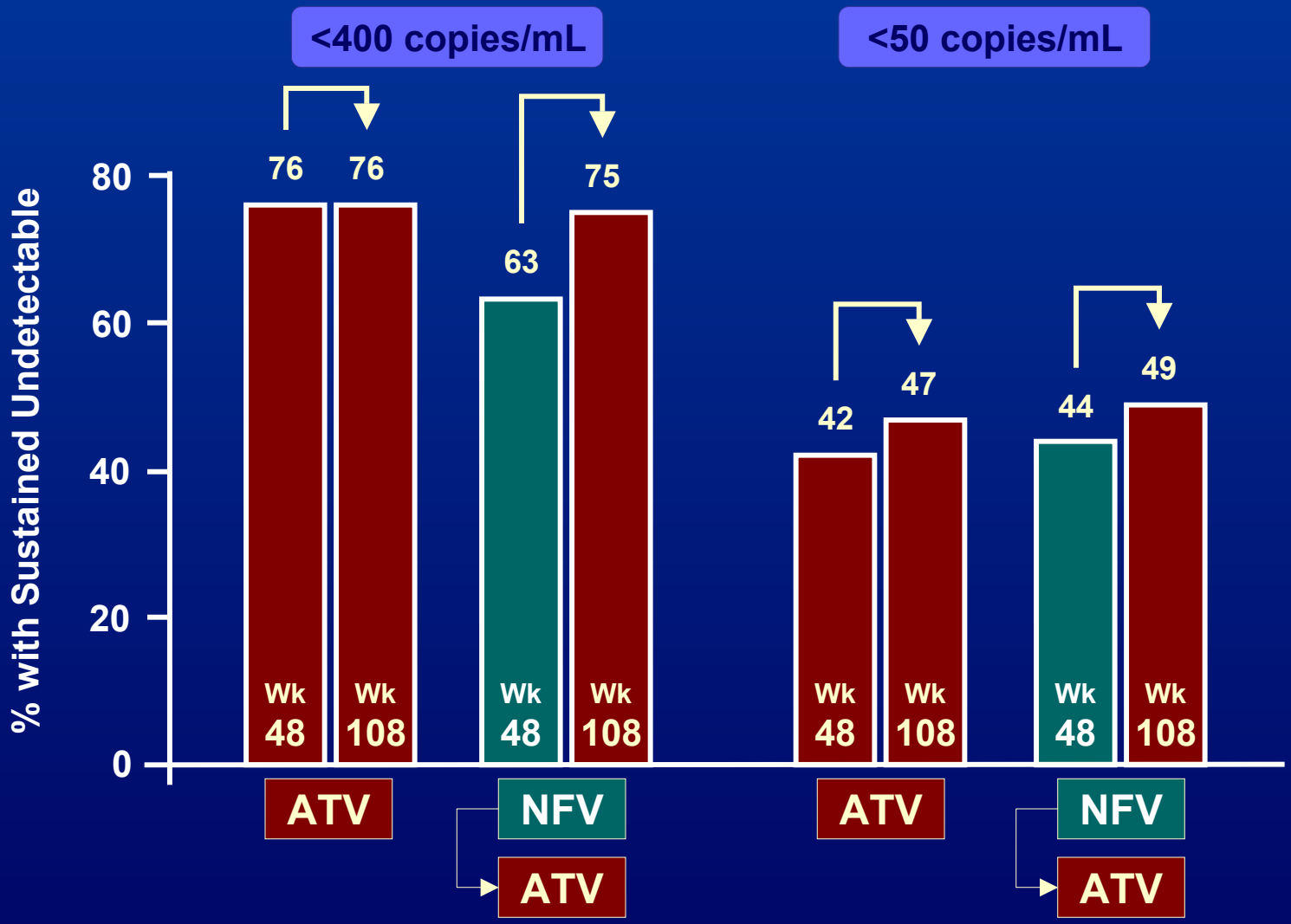
Adapted from: Sanne I *et al*. 41st ICAAC, Chicago, Dec 2001. **Oral presentation I-667**

Durable Response with ATV



Adapted from: Murphy R *et al*. 10th CROI, Boston, Feb 2003. **Poster 555**

Sustained Virologic Response to 108 Weeks



ATV 600mg not shown

Adapted from: Murphy R *et al*. 10th CROI, Boston, Feb 2003. **Poster 555**

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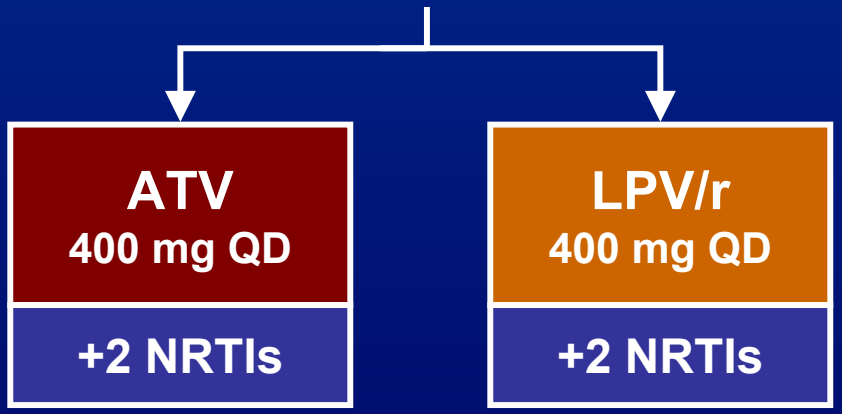
Efficacy in Treatment-Experienced Patients

- ***BMS-043: ATV vs boosted LPV***

ATV vs LPV/r in PI-Experienced Patients

BMS-043

Ongoing phase III, open-label, multicenter study, randomized 1:1
Patients were screened for prior PI failure

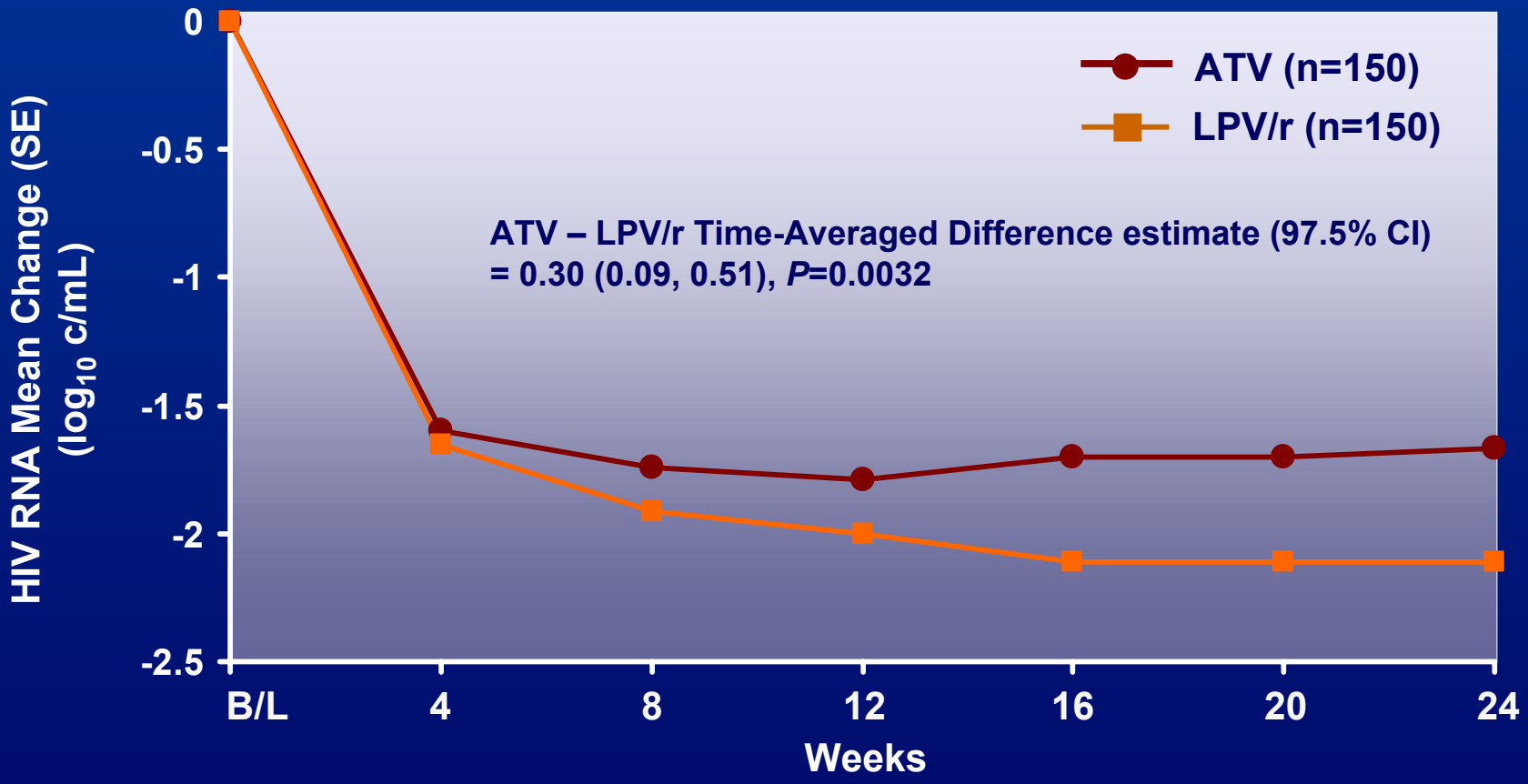


n=150 **n=150**

NRTI backbone: Physician choice

Adapted from: Cohen C *et al*. 2nd IAS, Paris, July 2003. **Oral presentation 117**

Viral Load Change Through Week 24



ATV (n)	150	141	140	134	135	130
LPV/r (n)	150	144	143	138	138	135

Adapted from: Cohen C *et al*. 2nd IAS, Paris, July 2003. **Oral presentation 117**

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Efficacy in Highly Treatment-Experienced Patients

- ***BMS-045: boosted ATV vs boosted LPV***

ATV/r vs LPV/r: Study Design

Patient Treatment History (N=358)	
Baseline Regimen	**ARV History**
PI or NNRTI	**Failed ≥2 regimens and failed ≥1 from each class**

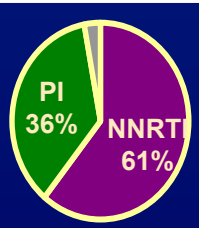
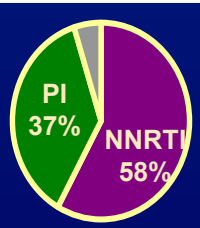
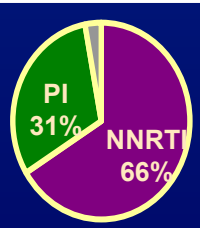
Randomization 1:1:1

	ATV 300 mg QD + RTV 100 mg	LPV 400 mg BID + RTV 100 mg	ATV 400 mg QD SQV 1200 mg QD
	n=120	n=123	n=115
Wk 1-2	Maintain NRTIs	Maintain NRTIs	Maintain NRTIs
Wk 2-48	TDF + 1 NRTI	TDF + 1 NRTI	TDF + 1 NRTI

Study Objectives

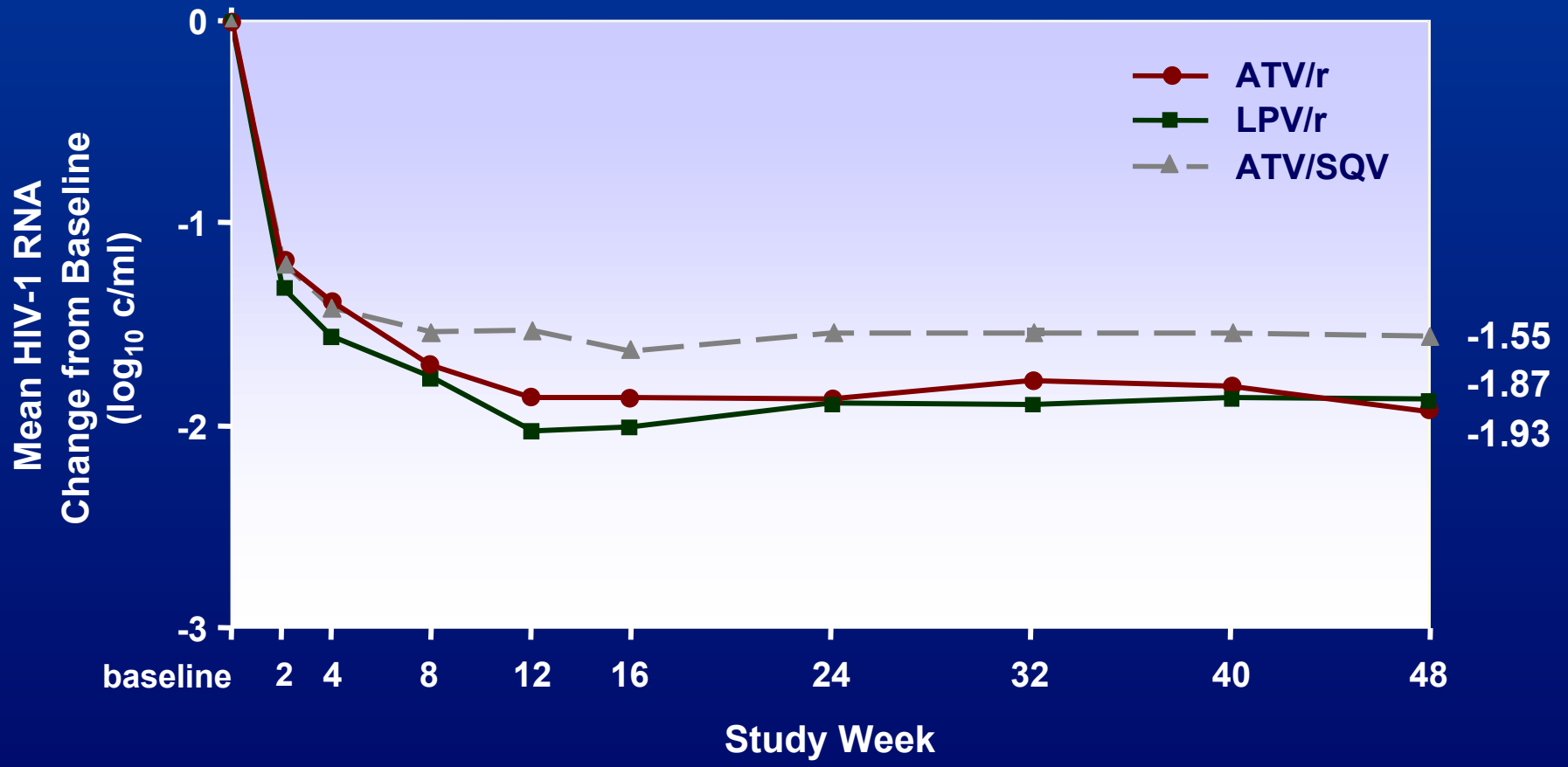
- **Primary Objective**
  - Compare magnitude of plasma HIV RNA reduction from baseline for ATV/r, ATV/SQV, and LPV/r in patients with multiple virologic failures through 48 weeks
- **Secondary Objectives**
  - Virologic response rates: <400 and <50 c/mL through 48 weeks
  - CD4 cell count changes from baseline
  - Metabolic parameters: changes from baseline through 48 weeks
    - Total cholesterol (TC)
    - Fasting LDL cholesterol (LDL-C)
    - HDL cholesterol (HDL-C)
    - Fasting triglycerides (TG)
  - Safety and tolerability

Treatment History: Baseline Characteristics

	ATV 300 mg QD RTV	LPV 400 mg BID RTV	ATV 400/SQV
Prior ARV use (median)			
Randomized, N	120	123	115
Prior NRTI use, weeks (range)	269 (40-782)	265 (0.1-679)	255 (25-762)
Prior PI use, weeks (range)	133 (0.1-321)	136 (0.1-346)	127 (0.1-470)
Prior NNRTI use, weeks (range)	78 (0.1-227)	69 (0.1-304)	86 (7-192)
Preceding regimen (PI or NNRTI)			

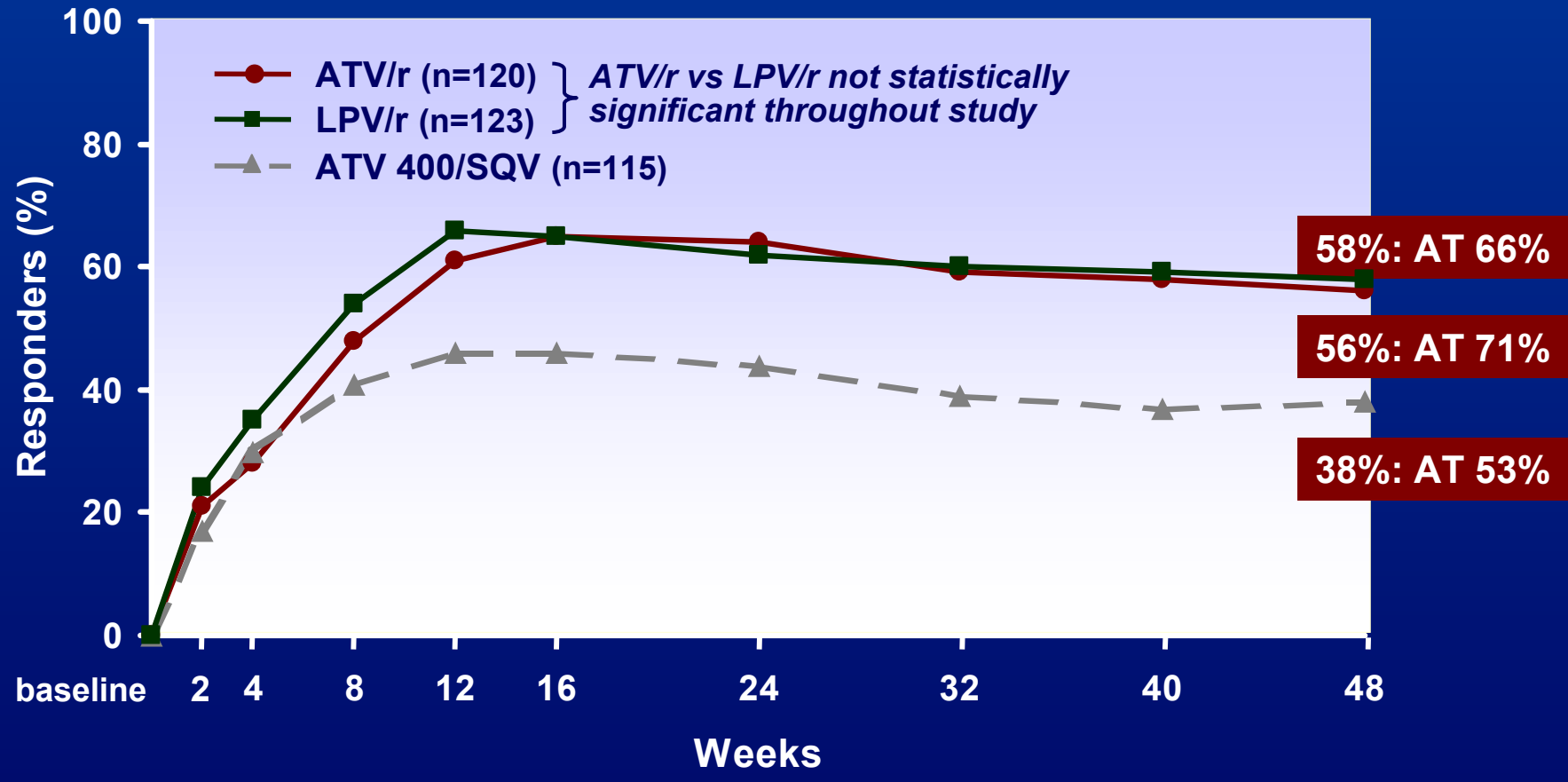
Adapted from: Clotet B *et al*. 2nd IAS, Paris, July 2003. **Oral presentation 118**
Zala C *et al*. 9th EACS, Warsaw, Poland, Oct 2003. Oral presentation F7/2

Primary Endpoint: Virologic Efficacy Through 48 Weeks



Time Averaged Difference Estimate:
ATV/r - LPV/r: 0.13 log_{10} c/mL. [97.5% CI: -0.12, 0.39]
ATV/SQV - LPV/r: 0.33 log_{10} c/mL. [97.5% CI: 0.07, 0.60]

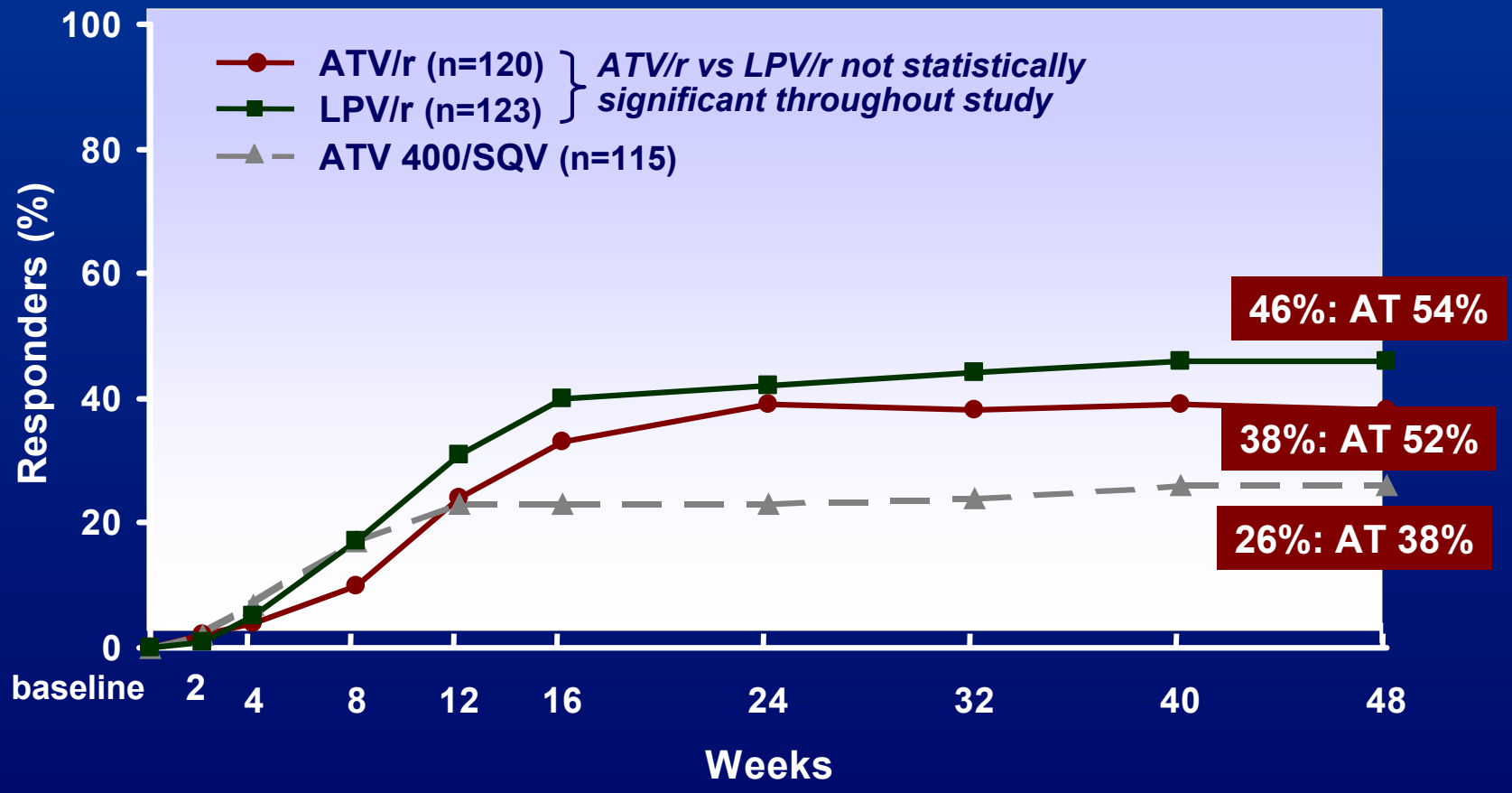
Virologic Response < 400 c/mL Through 48 Weeks (ITT)



Time to Loss of Virologic Response (TLOVR)
Difference Estimate (95% CI): < 400 c/mL

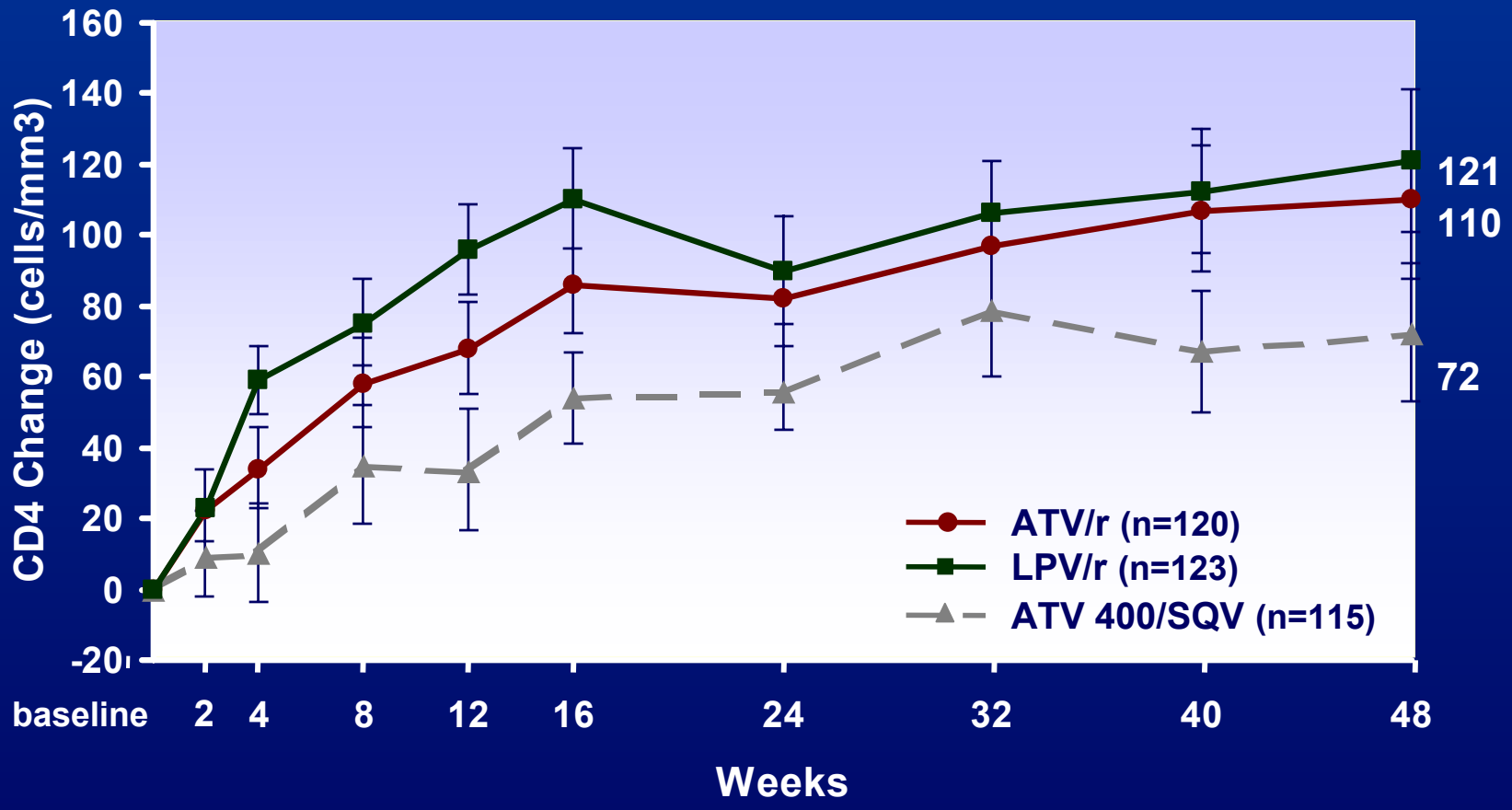
ATV 300/r – LPV/r: -1.9 (-14.3, 10.6)

Virologic Response < 50 c/mL Through 48 Weeks (ITT)



Time to Loss of Virologic Response (TLOVR)
Difference Estimate (95% CI): < 50 c/mL
ATV 300/r – LPV/r: -8.0 (-20.4, 4.4)

CD4 Cell Count Change from Baseline Through 48 Weeks



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Efficacy Summary

Efficacy Conclusions From ATV Trials

Treatment naïve

- Once-daily ATV is the only PI to demonstrate durable efficacy compared to EFV, a standard of care (ATV vs EFV, study 034)

Maintaining first-line

- Once-daily ATV provides durable efficacy with virologic control maintained through 108 weeks (ATV vs NFV, study 008, 044)

Switching

- Virologic suppression was maintained or improved after switching from NFV to once daily ATV (NFV⇨ATV, study -044)

PI-experienced

- In highly treatment-experienced patients, once-daily ATV/r demonstrated comparable potency/viral control to twice daily LPV/r, a standard of care (ATV/r vs LPV/r, study -045)

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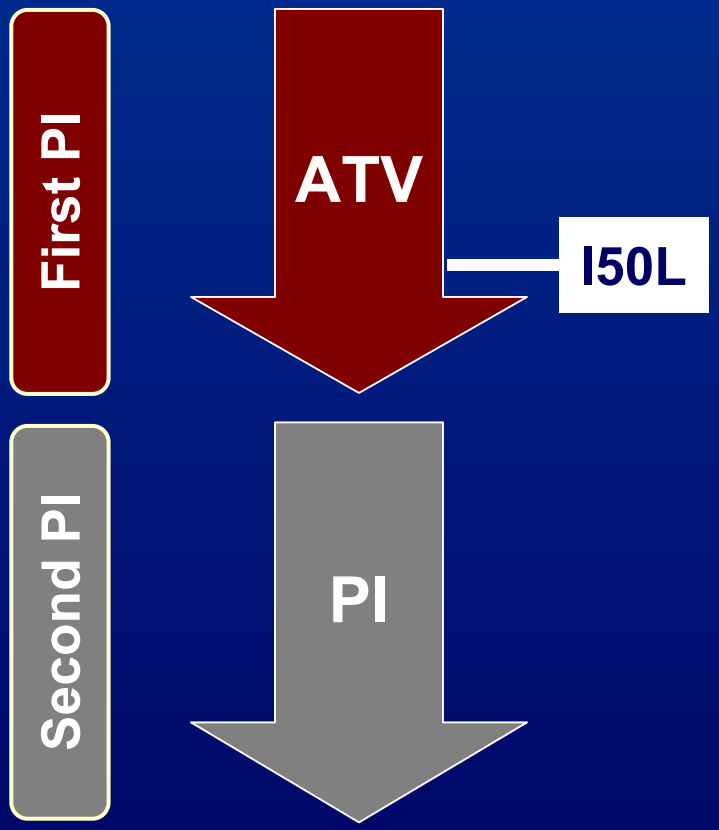
Resistance Profile

- *signature mutation in naïve patients*
- *mutation patterns in PI-experienced patients*
- *increased susceptibility*

Genotypic Resistance to ATV: Naïve Patients—What Do We Know?

ATV Used as Initial PI



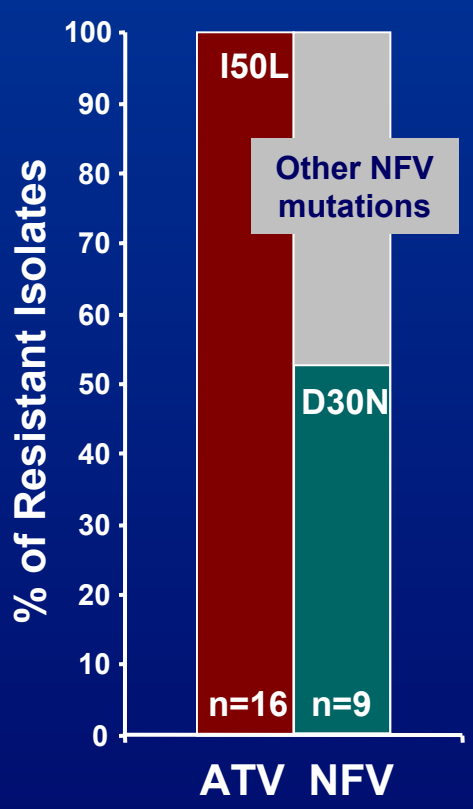
Signature ATV Substitution: I50L

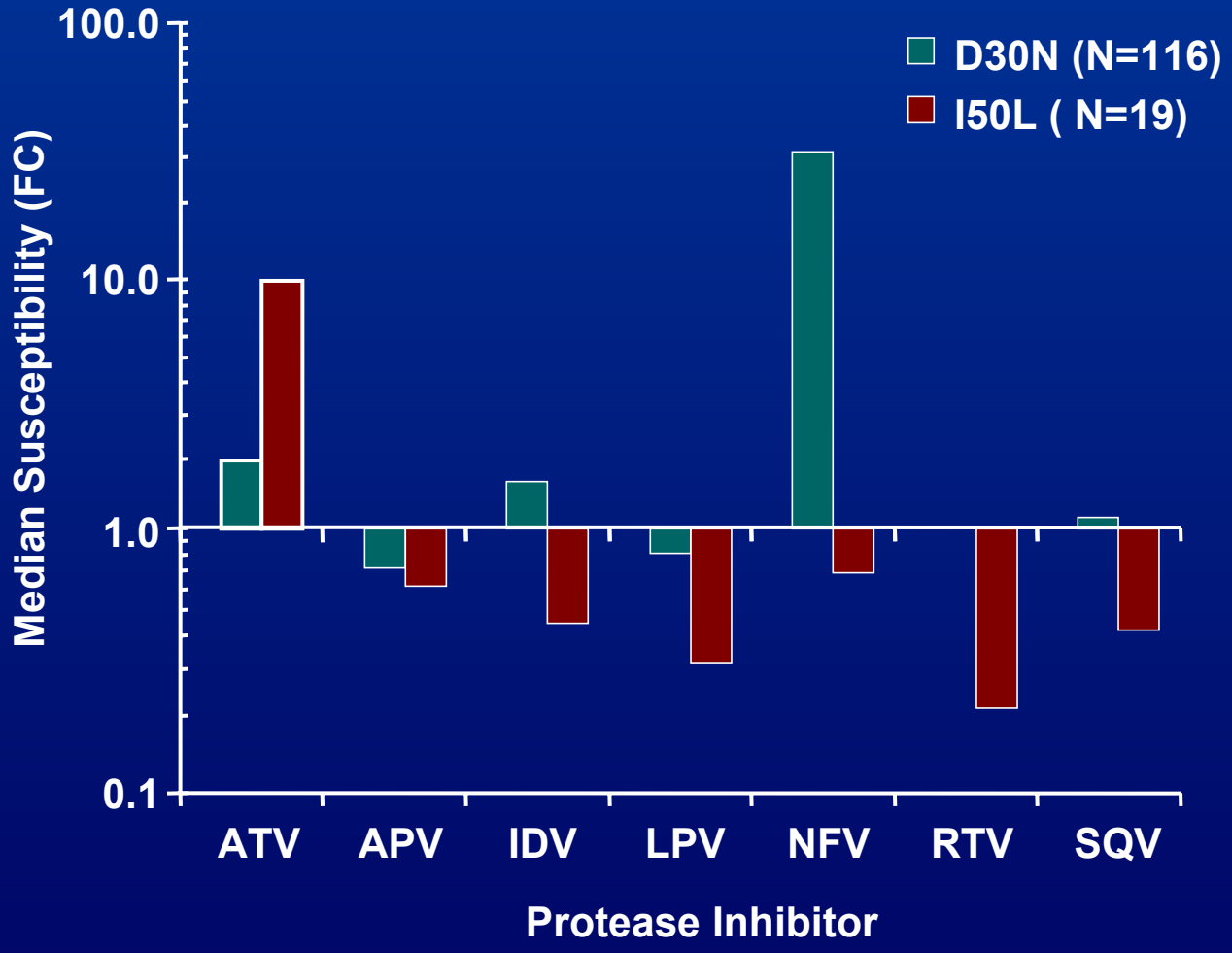
- Substitution at I50L selected in 100% of cases of genotypic resistance
- Occurs in ~2% of all treated patients and ~18% of virologic failures

Lack of Cross-Resistance to I50L

- Distinct from APV-selected I50V
- Does not confer cross-resistance to other members of the PI class; may even confer increased susceptibility to subsequent PIs

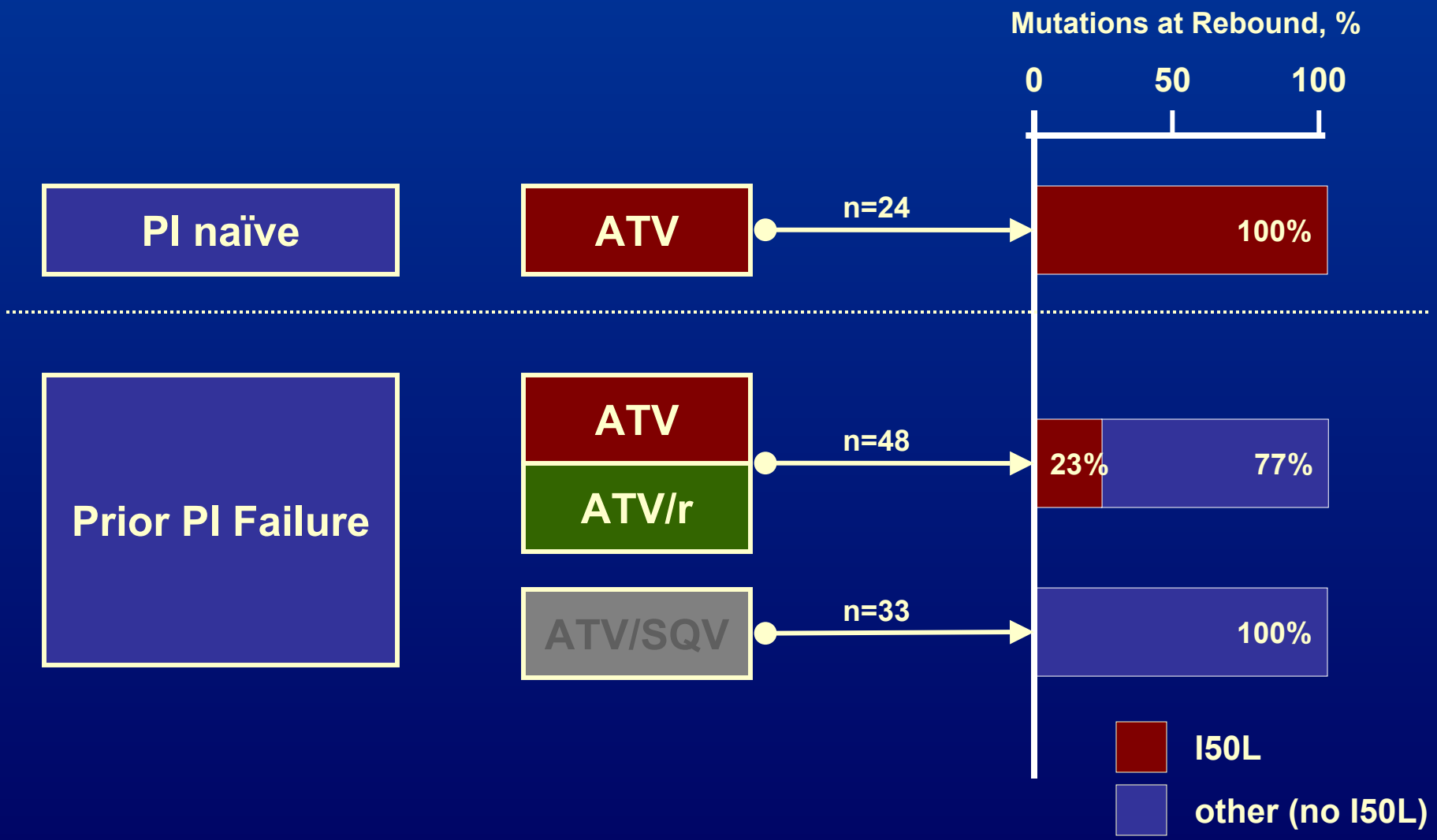
I50L Is Distinct From D30N





Data are from studies 007 and 008.

ATV Resistance Pathways



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Metabolic Evaluation

- *blood lipids*
- *glucose and insulin parameters*
- *body shape changes*

Regression of lipodystrophy in HIV-infected patients under therapy with the new protease inhibitor atazanavir

Georg Haerter[a], Burkhard J. Manfras[a], Markus Mueller[b], Peter Kern[a] and Andreas Trein[c]

AIDS 2004, Vol 18 No 6:952-5.

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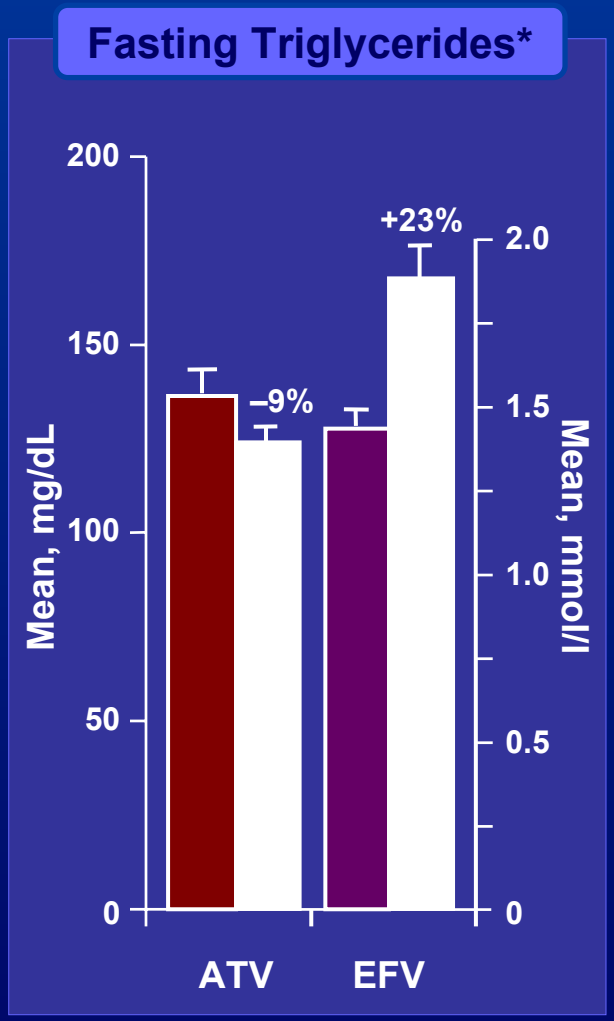
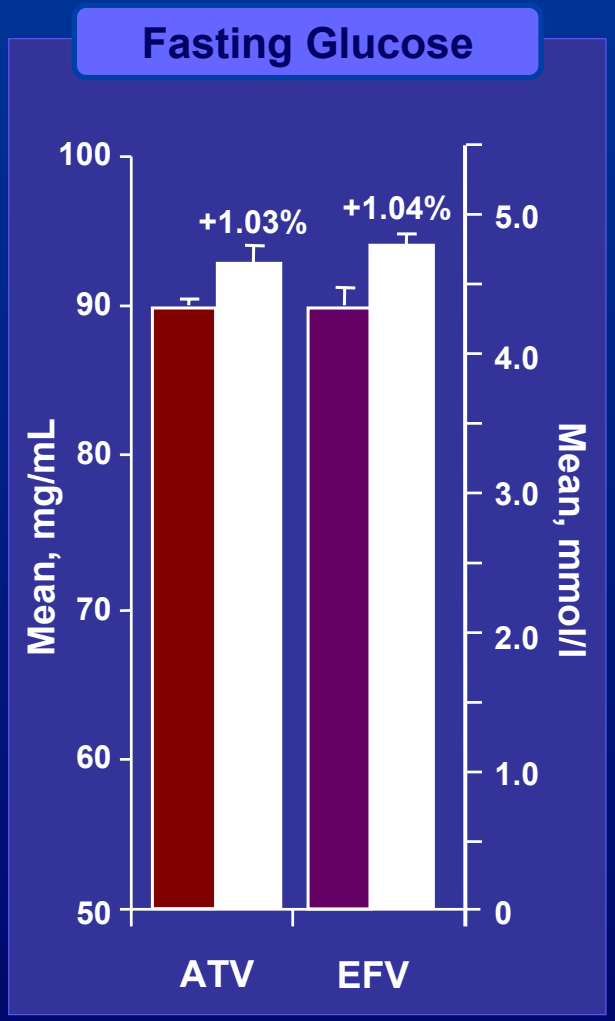
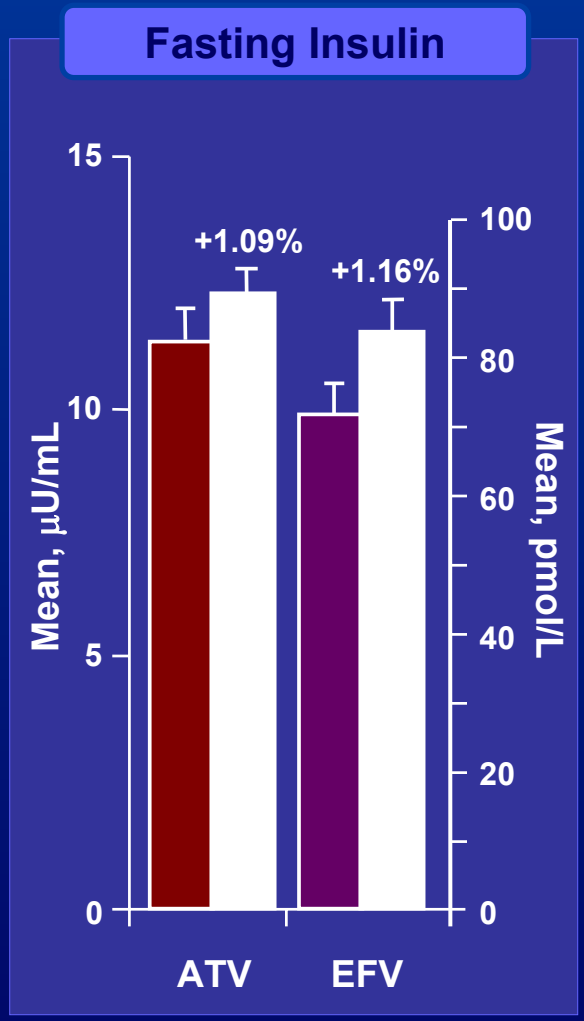
Effects upon Glucose and Insulin Parameters

- ***BMS-034: ATV vs EFV, naïve***

Metabolic Profile: Triglycerides, Glucose, and Insulin







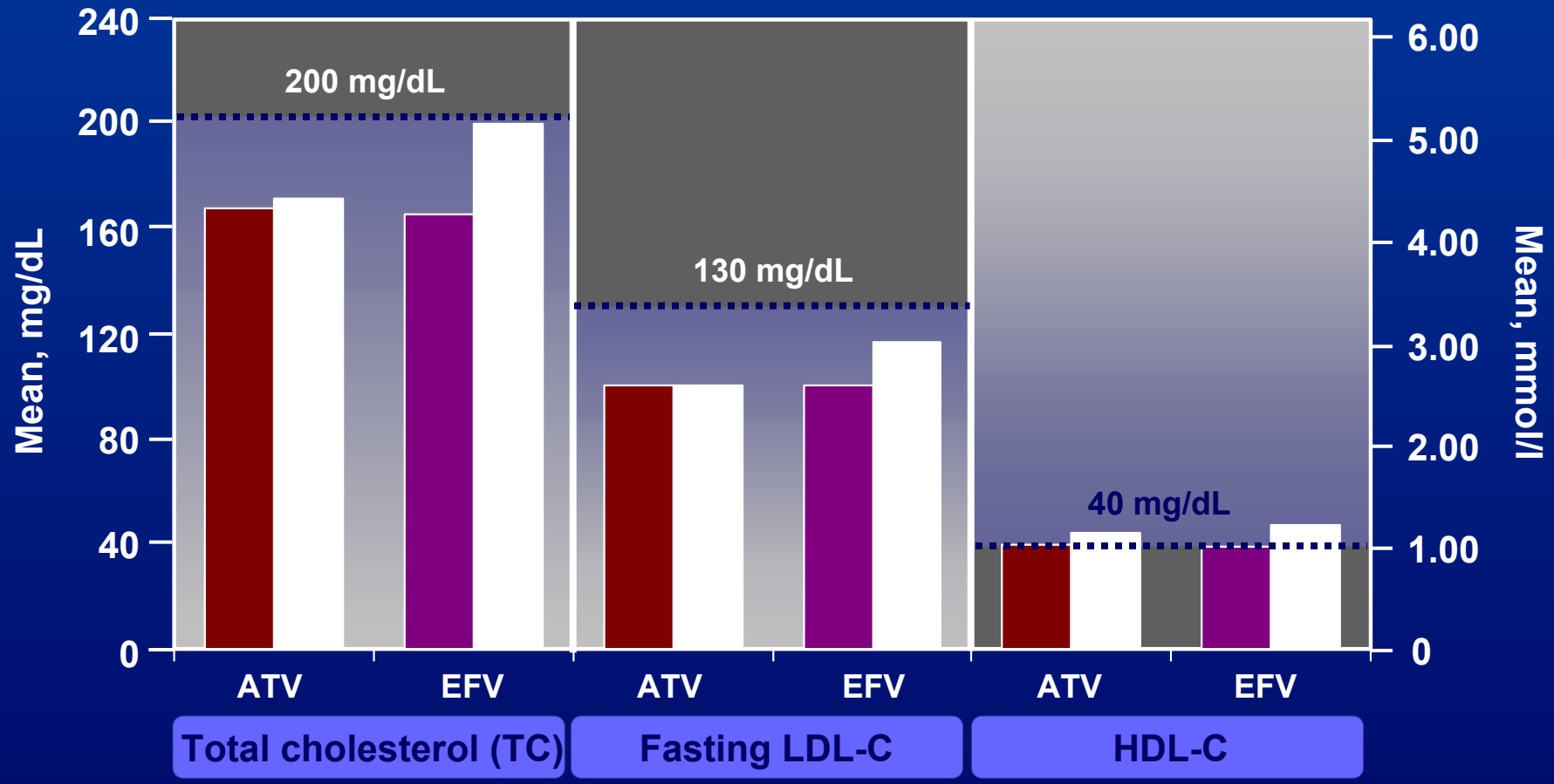
*P<0.0001, ATV vs EFV at 48 weeks

B/L

Week 48

Adapted from: Squires K *et al*. 42nd ICAAC, San Diego, Sep 2002. **Oral presentation H-1076**

Metabolic Profile: Total, LDL, and HDL Cholesterol

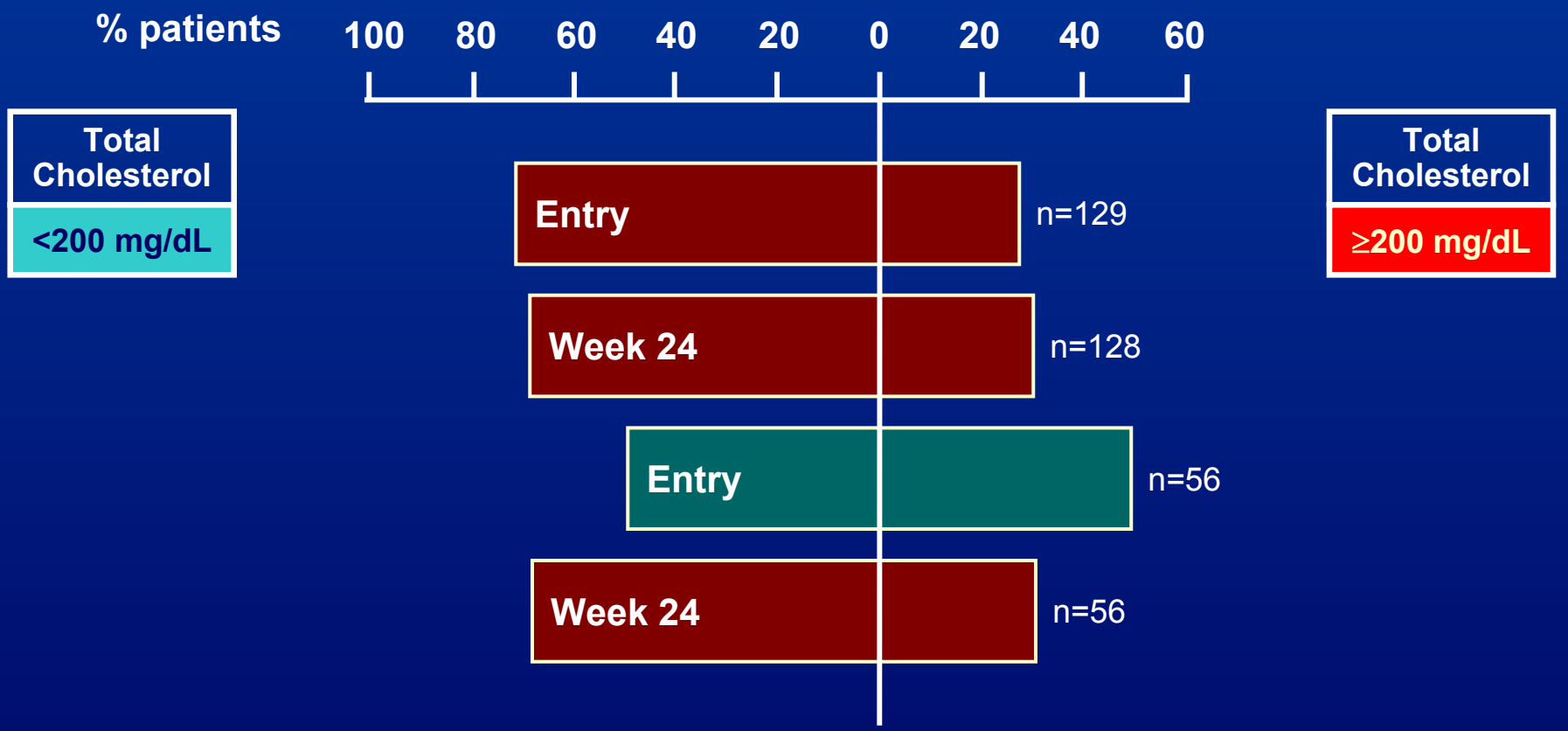


P<0.0001, ATV vs EFV at 48 weeks, all comparisons

B/L Week 48

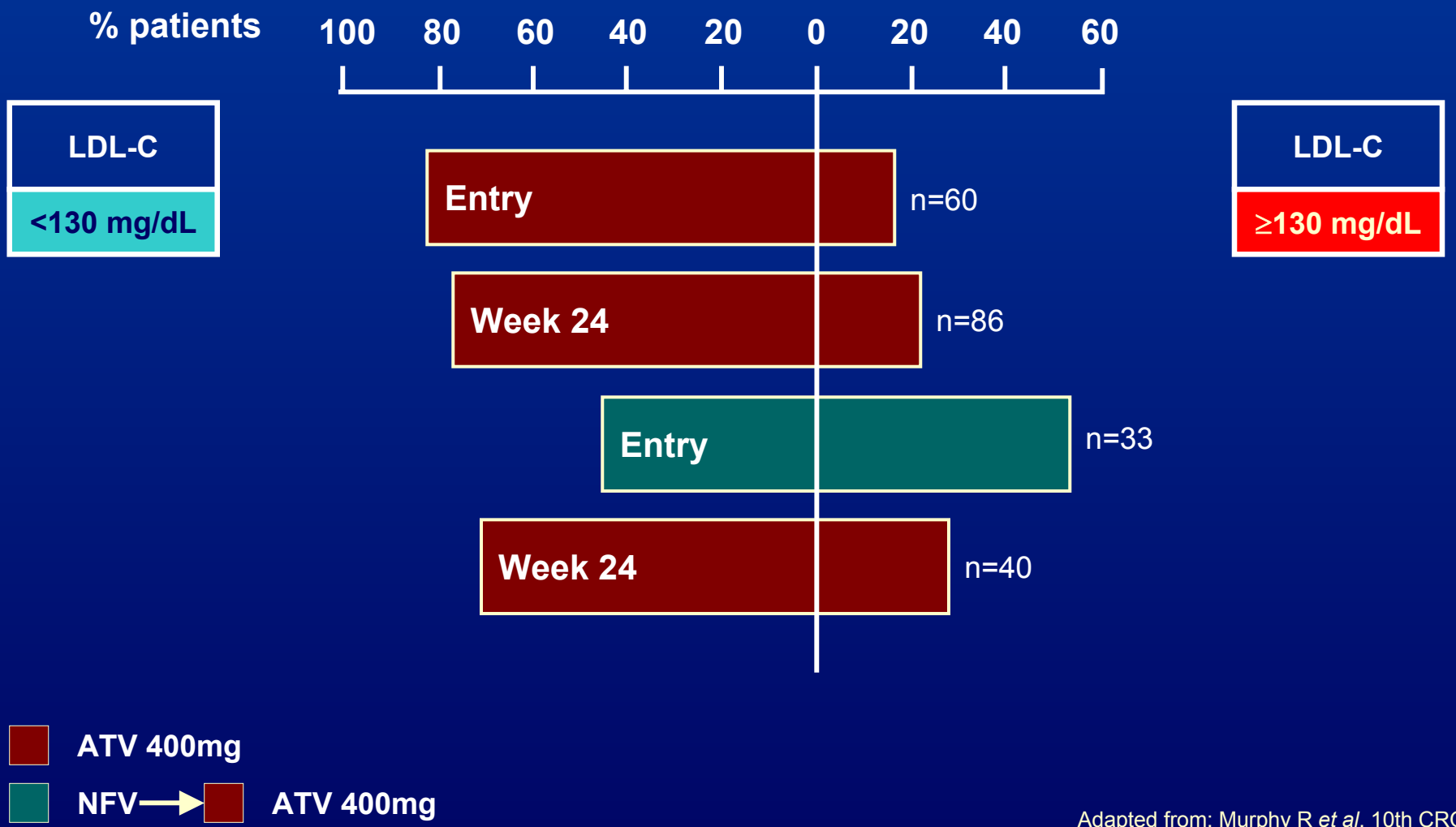
Adapted from: Squires K *et al*. 42nd ICAAC, San Diego, Sep 2002. **Oral presentation H-1076**

Total and LDL Cholesterol: NCEP Categories



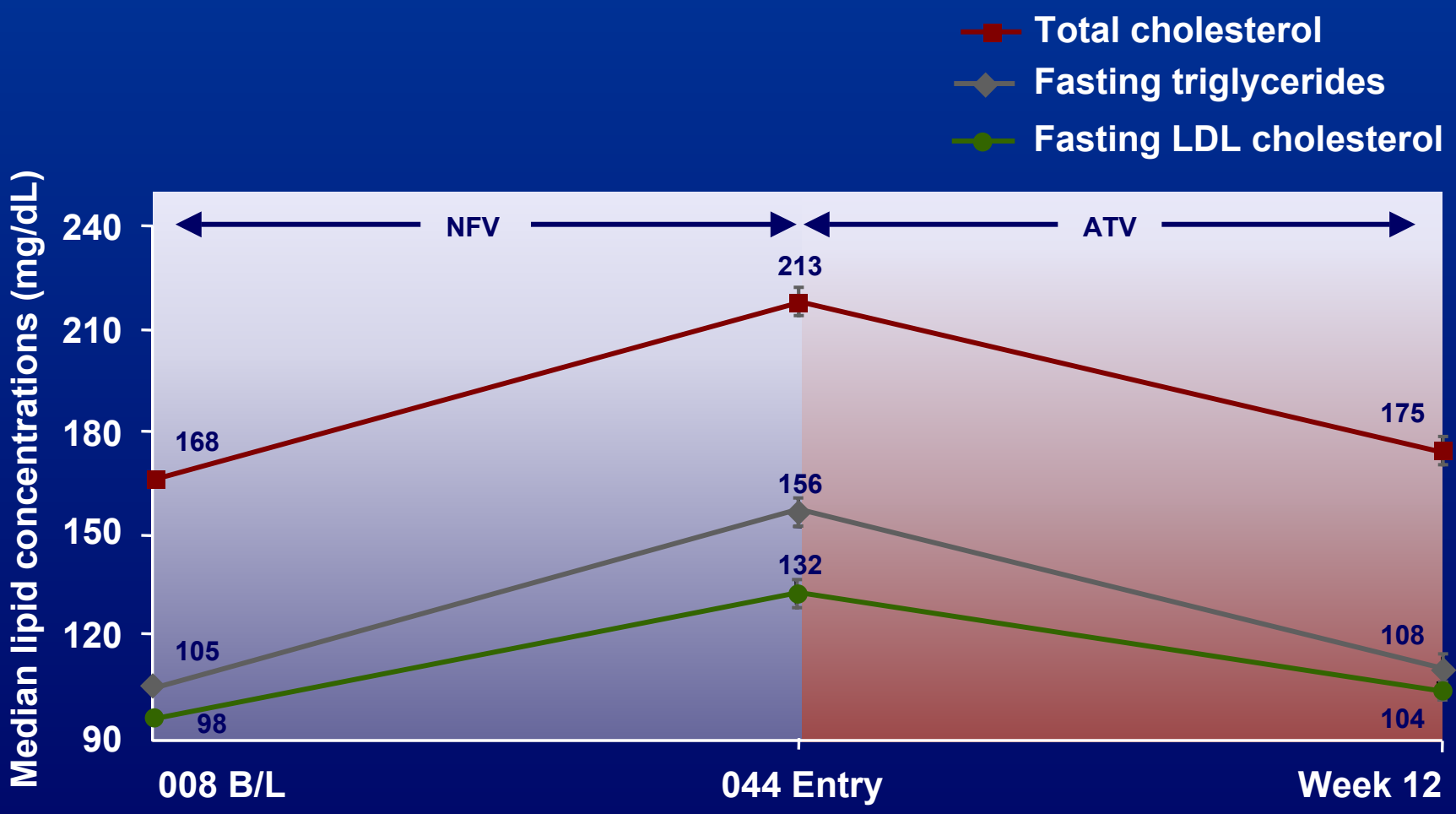
Adapted from: Murphy R *et al*. 10th CROI, Boston, Feb 2003. **Poster 555**

Total and LDL Cholesterol: NCEP Categories



Adapted from: Murphy R *et al*. 10th CROI, Boston, Feb 2003. **Poster 555**

Median Lipid Concentration Changes in Patients Switched from Nelfinavir to Atazanavir



Adapted from: Murphy R *et al*. 10th CROI, Boston, Feb 2003. **Poster 555**

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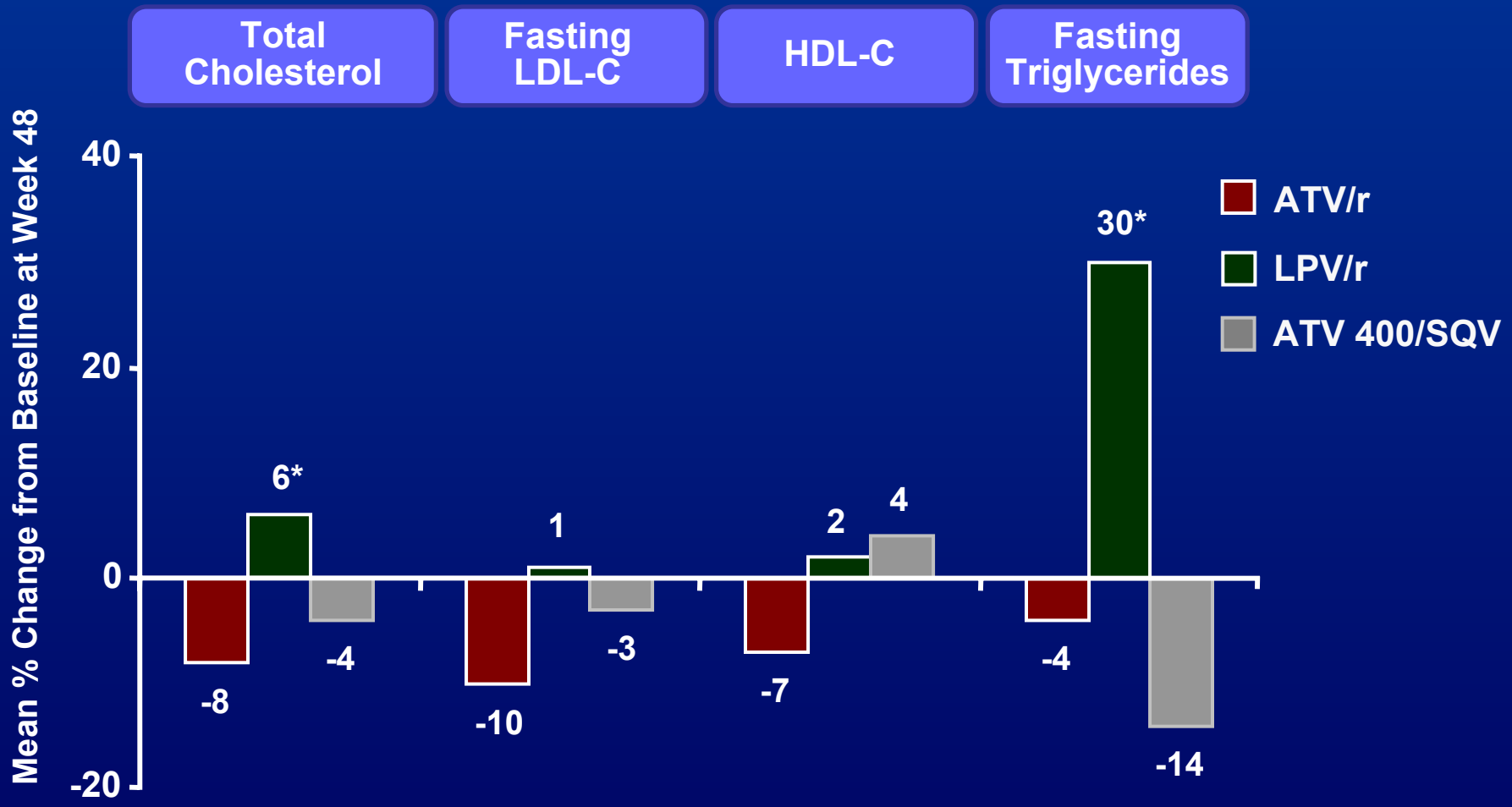
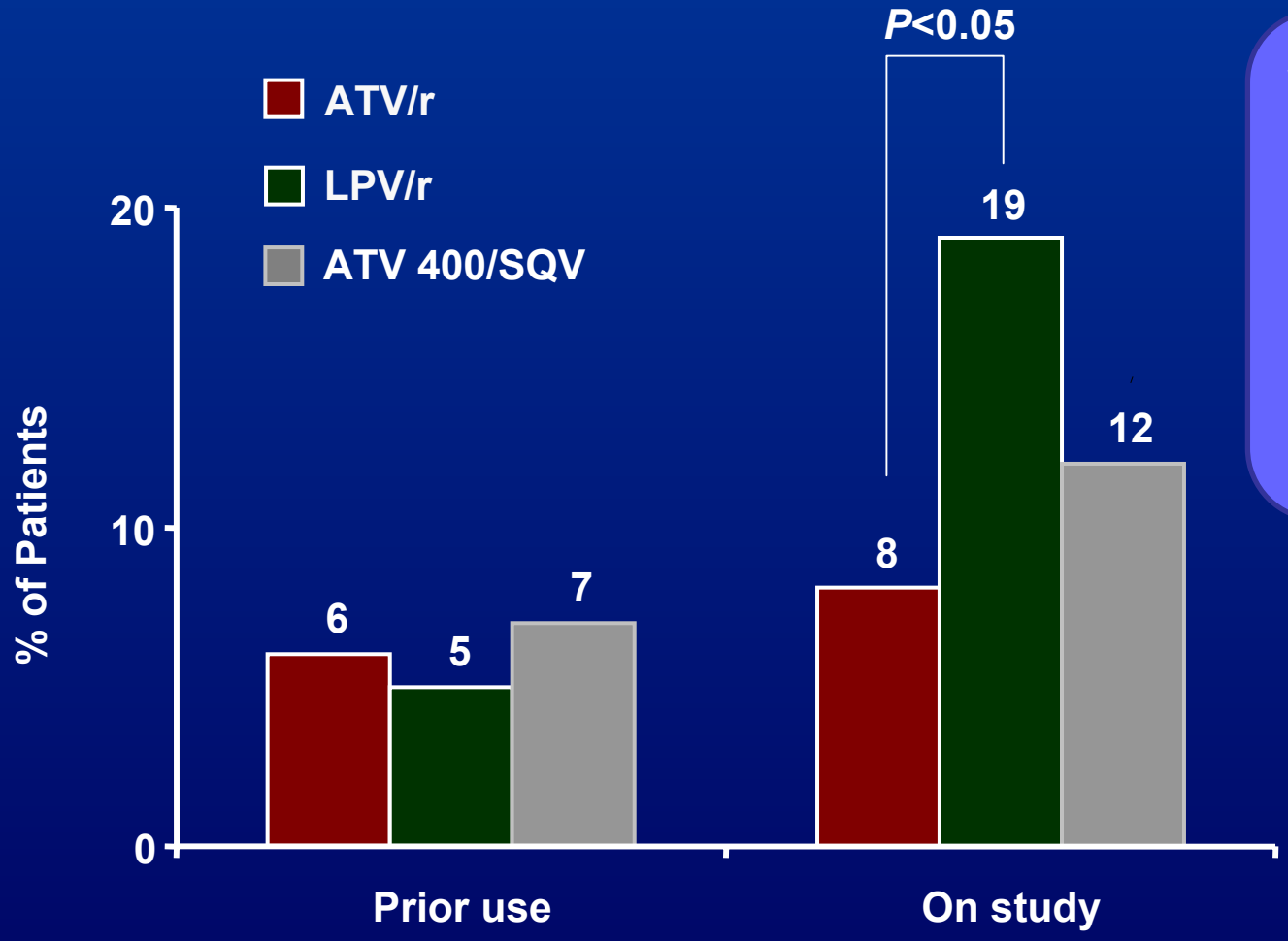
ATV/r vs LPV/r: Lipid Evaluation Through 48 Weeks

Censoring: Patients on Lipid Lowering Therapy Excluded



*Both ATV regimens vs LPV/RTV: *P*-value <0.005

Reduced Use of Lipid Lowering Agents with ATV/r



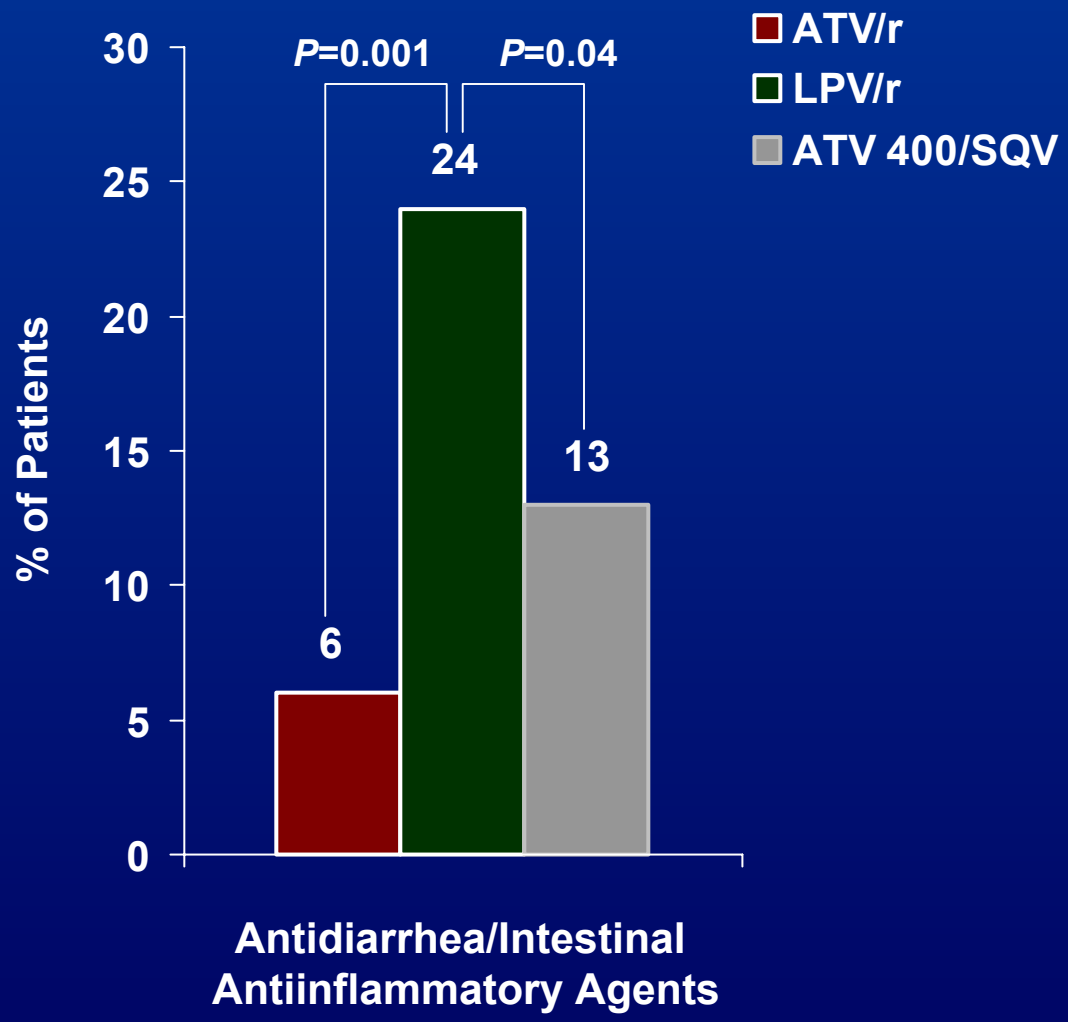
Serum Lipid Reducing Agents:

- Atorvastatin
- Bezafibrate
- Fenofibrate
- Gemfibrozil
- Lovastatin
- Pravastatin

Conclusions: Metabolics

- ATV has a superior lipid profile compared to other members of the protease inhibitor class
- Switching from NFV to ATV led to an improvement in TC, LDL-C and TG levels. These metabolic abnormalities have been associated with increased cardiovascular risk and often require lipid-lowering therapy
- Even when boosted with ritonavir, ATV was associated with a superior lipid profile compared to LPV/r
- ATV has not been associated with body shape changes, hyperglycemia or hyperinsulinemia

ATV/r vs LPV/r: Use of Antidiarrheal Agents



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Tolerability and Safety

- *adverse event profiles*
  - *–unboosted ATV*
  - *–boosted ATV*
- *laboratory measurements*
  - *–bilirubin*

ATV vs NFV: Adverse Event Profile*

Grade 1-4 Related adverse events in %	ATV 400 mg QD n=178	NFV 1250 mg BID n=91	ATV 600 mg QD n=195
Any adverse event	93	92	91
Diarrhea	20	56**	15
Infection	42	48	55
Headache	25	26	27
Pain (abdomen)	19	13	22
Perip neuro symptoms	18	21	22
Rash	22	19	17
Nausea	21	18	18

*Reported with a frequency of >20% in any treatment group
***P*>0.0001

Panteleo G et al. 8th ECCATHI, Athens, October 2001. Oral Presentation O-11.

ATV vs EFV: Adverse Events

Grade 2-4 related adverse events in %	ATV n=404	EFV n=401
Total	41	45
Nausea	14	13
Rash*	6	10
Headache	6	6
Jaundice*	5	0
Vomiting	4	7
Dizziness	2	6
Scleral icterus*	1	0
Diarrhea	1	2
LAS/SHL	0	<1

*$P<0.05$, ATV vs. EFV

Adapted from: Squires K *et al*. 42nd ICAAC, San Diego, Sep 2002. **Oral presentation H-1076**

ATV/r vs LPV/r: Adverse Events*

Grade 2-4 related adverse events in %	ATV 300 mg QD + RTV 100 mg	LPV 400 mg BID + RTV 100 mg	ATV 400/SQV
	n=119	n=118	n=110
Total	29	25	26
Diarrhea	3	11	6
Jaundice	6	0	2
Nausea	3	2	8
Vomiting	0	<1	4
Scleral icterus	3	0	0
Withdrawal due to AE **	5	4	7

*≥5% of patients, **No patients withdrew treatment due to jaundice

ATV vs EFV: Laboratory Changes

Lab abnormalities, grade 3-4 in %	ATV n=404	EFV n=401
ALT/SGPT	4	3
AST/SGOT	2	2
Total Bilirubin	33*	<1
↓ Neutrophils	6	9
↓Hemoglobin	4	3

*Dose reductions, n (%): 20 (5); discontinuations: 2 (<1)

Adapted from: Squires K *et al*. 42nd ICAAC, San Diego, Sep 2002. **Oral presentation H-1076**

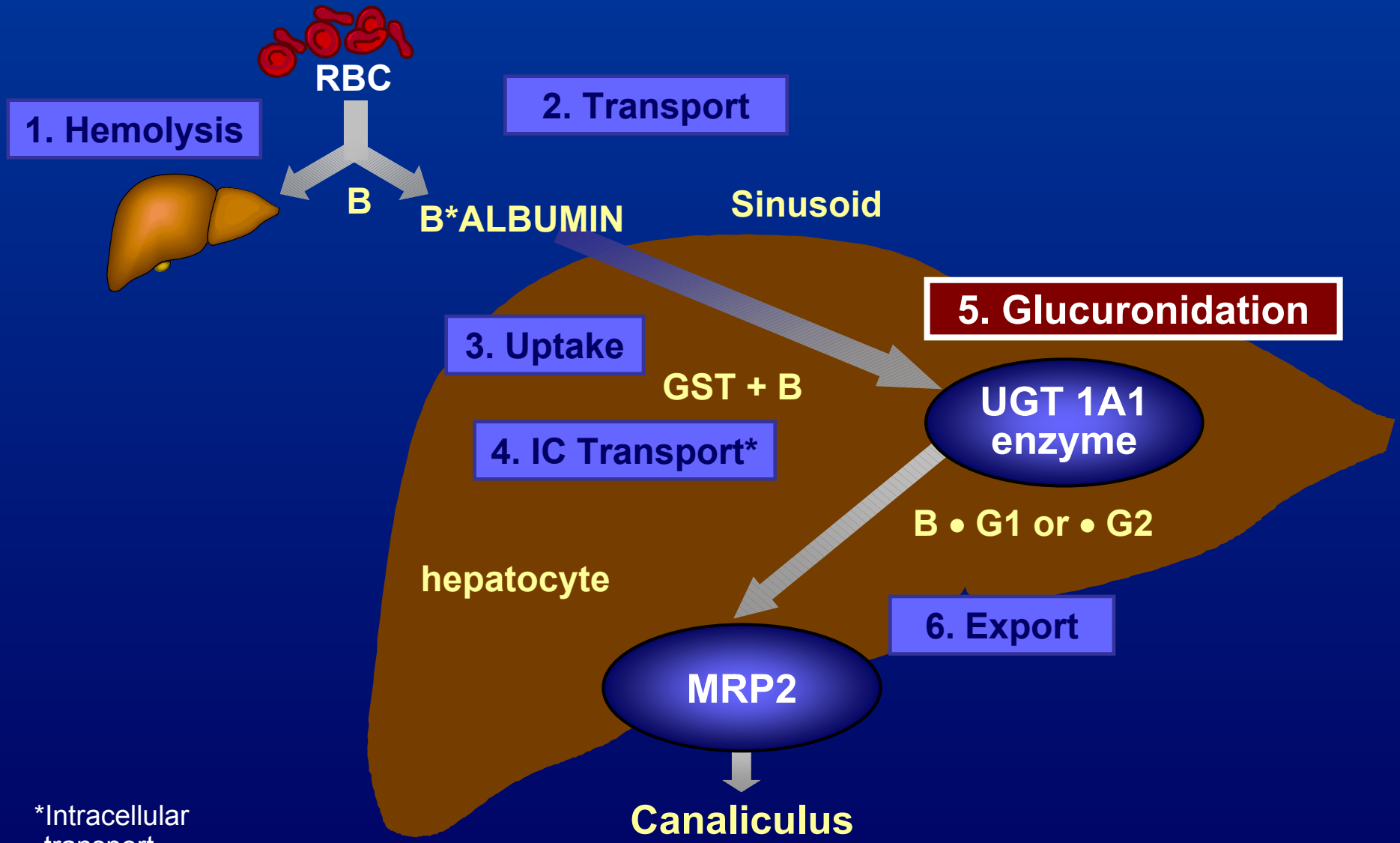
ATV/r vs LPV/r: Laboratory Changes

Grade 3-4 Laboratory parameter in %	ATV 300 mg QD + RTV 100 mg n=119	LPV 400 mg BID + RTV 100 mg n=118	ATV 400/SQV n=110
Total bilirubin*	49	<1	20
ALT/SGPT	4	3	4
AST/SGOT	3	3	2

*No patients withdrew treatment due to bilirubin elevations

*Grade 3 hyperbilirubinemia : 2.6 - 5 UNL (> 62 mmol/L)
*Grade 4 hyperbilirubinemia: > 5 UNL (> 120 mmol/L)

Steps at which bilirubin metabolism is effected



*Intracellular transport

Indirect Bilirubin Elevations With ATV:

Mechanism

- Elevated indirect (unconjugated) bilirubin
- Atazanavir inhibits UGT
- Decreased UGT activity similar to the effect observed with Gilbert's syndrome and mechanistically similar to that seen with IDV

Meaning

- No evidence of a hepatotoxic process: Grade 3-4 elevations in total bilirubin were rarely associated with grade 3-4 elevations in ALT/AST
- Readily reversible upon discontinuation of ATV
- No difference in frequency of bilirubin elevations or virologic suppression in HBV/HCV co-infected patients
- <1% discontinuation in clinical trials due to bilirubin increases in studies 034 and 043

ATV vs LPV/r: Laboratory Changes

Lab abnormalities, grade 3-4 in %	ATV n=144	LPV/r n=146
Total bilirubin*	22	0
ALT/SGPT	6	1
AST/SGOT	3	1
Neutrophils <750 cells/mm^3	5	3
Lipase	4	3

*Discontinuations: 1 (<1)

Adapted from: Cohen C *et al*. 2nd IAS, Paris, July 2003. **Oral presentation 117**

Grade 3-4 ALT Elevations in HBV/HCV Co-Infected Subjects: ATV Versus Comparators*

Overall Frequency of ALT >5 x ULN
n (%)

	ATV	Comparator
Hep B/C +	13/131 (10)	10/88 (11)
Hep B/C –	20/777 (3)	8/542 (1)

*Data from Study 008, 034, and 043; comparators are NFV for study 008, EFV for Study 034, and LPV/r for study 043.

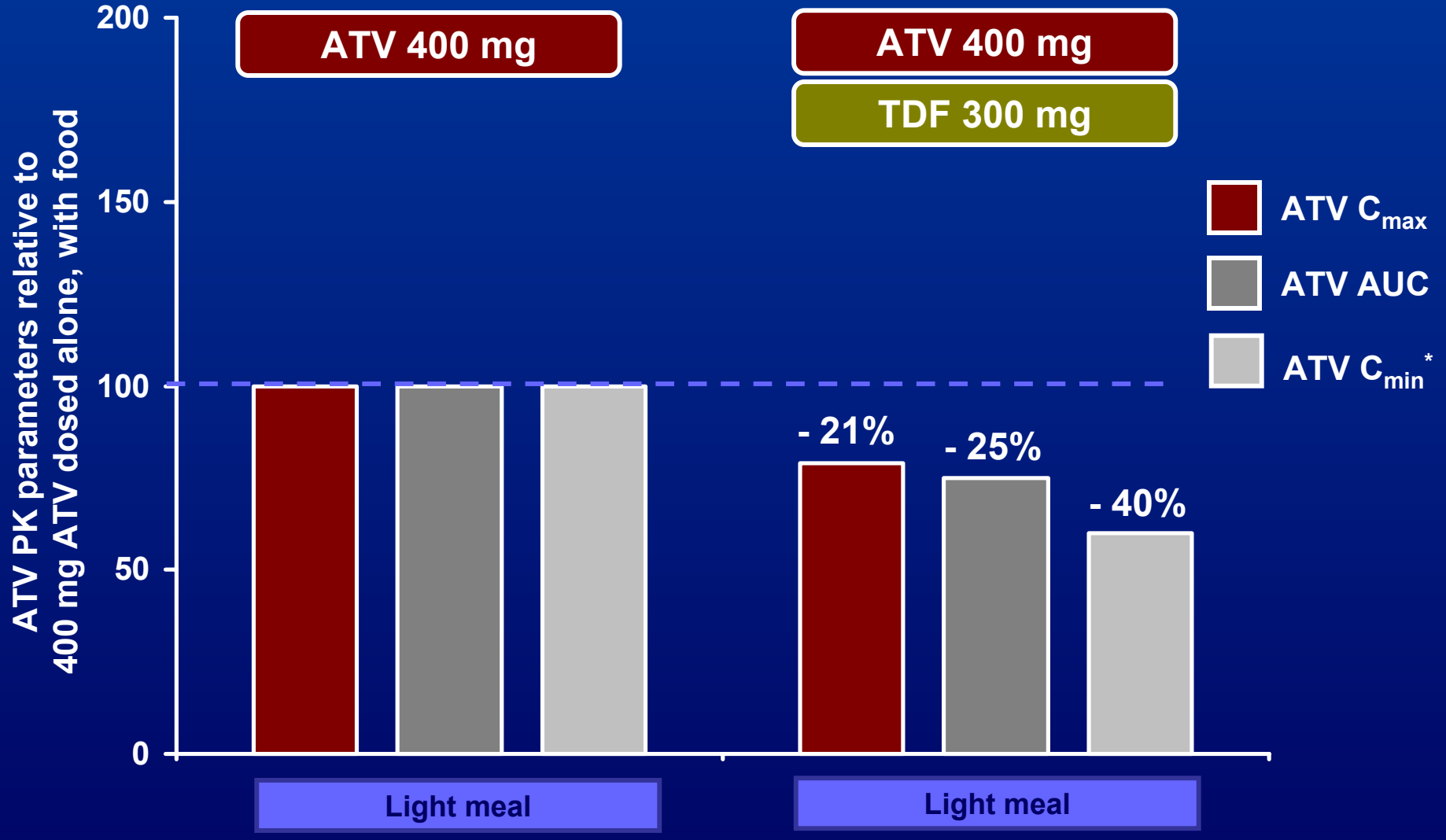
atazanavir

Important Pharmacokinetic Considerations for Atazanavir

ATV Pharmacokinetics

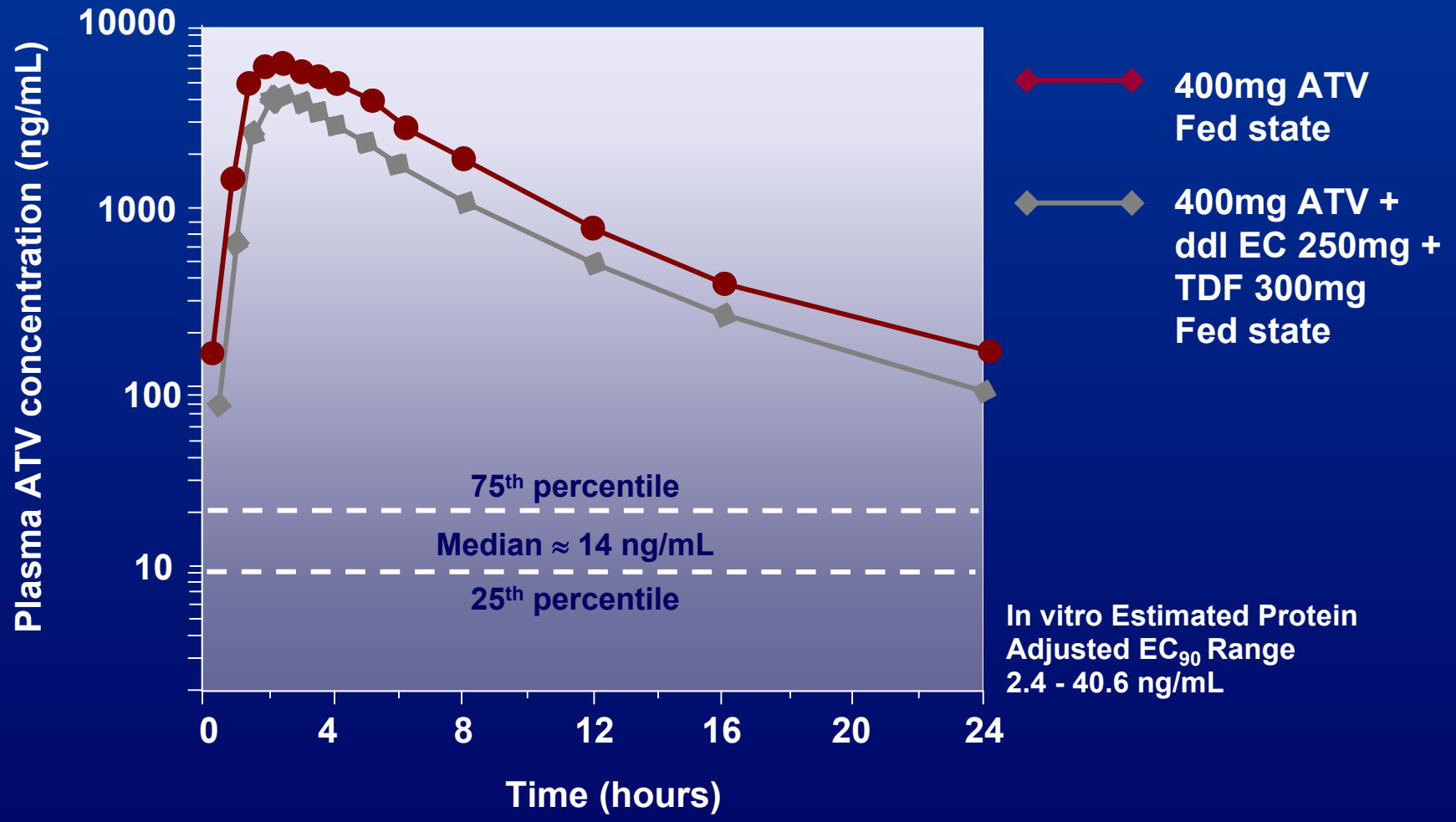
- **Absorption**
  - Acidic environment
  - Rapidly absorbed (T_{max} ~1-4 hours)
  - Food: ↑ exposure, ↓ intersubject variability
- **Distribution**
  - Measurable concentrations in CSF and semen
  - Protein binding ~86% (albumin and α1-AG)
- **Metabolism**
  - Primarily metabolized by CYP3A4
  - Inhibitor of CYP3A4 (Ki = 2.35 μM) and UGT 1A1 (Ki = 1.9) [not 2B7]
- **Elimination**
  - Primarily eliminated in bile
  - Urinary excretion—7% unchanged drug
  - $T_{½}$ ~7 hours

TDF Pharmacokinetic Effects on Atazanavir



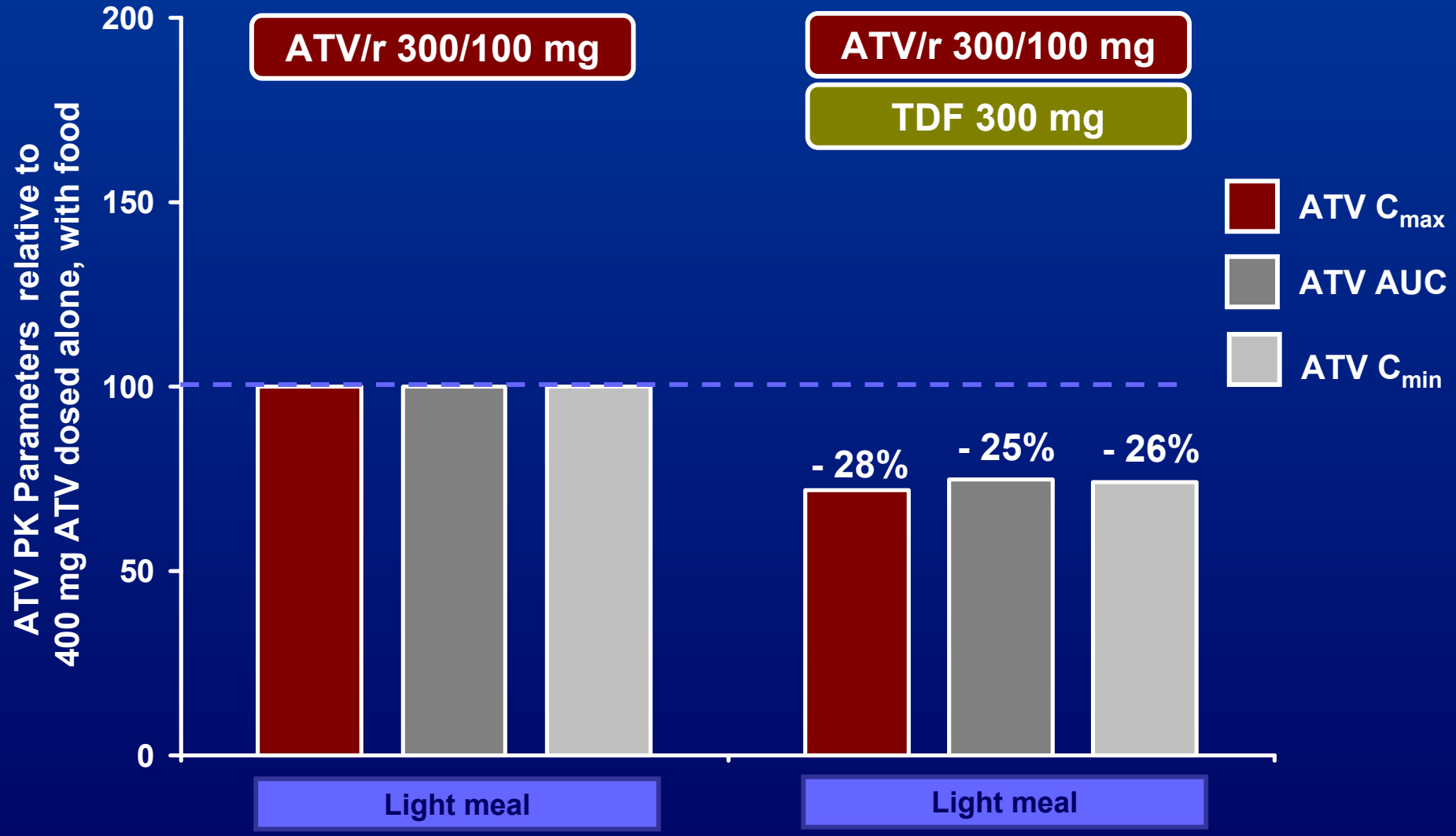
*Study not powered to discern difference in C_{min}

Pharmacokinetics of ATV in Combination With ddI EC 250mg + TDF 300mg



Data on file, Bristol-Myers-Squibb Co., 2003.

TDF Pharmacokinetic Effects on Boosted Atazanavir



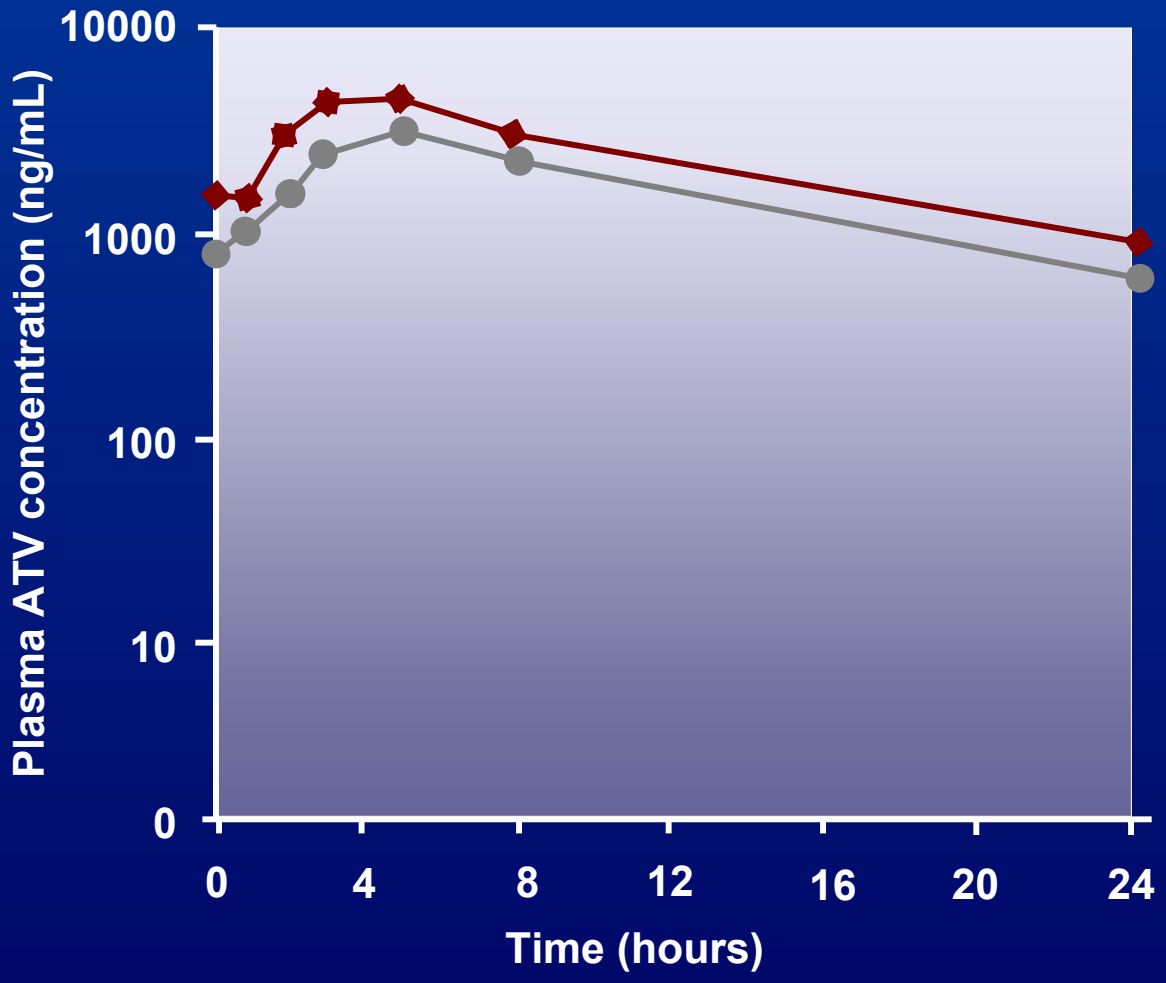
Adapted from: Taburet A et al. Poster 537, 10th CROI 2003.

Statistics for ATV Pharmacokinetic Parameters

	Week 2 ATV/r	Week 6 ATV/r + TDF	Percent difference*	*P*-value
C_{max} (ng/mL)	4422	3190	-28%	0.06
AUC_{24} (ng h/mL)	46073	34459	-25%	0.05
C_{min} (ng/mL)	696	513	-26%	NA
T_{max} (hours)	3 (2-5)	5 (1-5)	+67%	0.05

ATV = atazanavir, AUC_{24} = area-under-curve over 24 hours,
C_{max} = Maximum concentration within dosing interval, C_{min} = minimum concentration with dosing interval,
NS = not significant, TDF = tenofovir disoproxil fumarate, $T\text{-}_{max}$ = time to maximum concentration.
* Approximation.

Pharmacokinetics of ATV/r + TDF



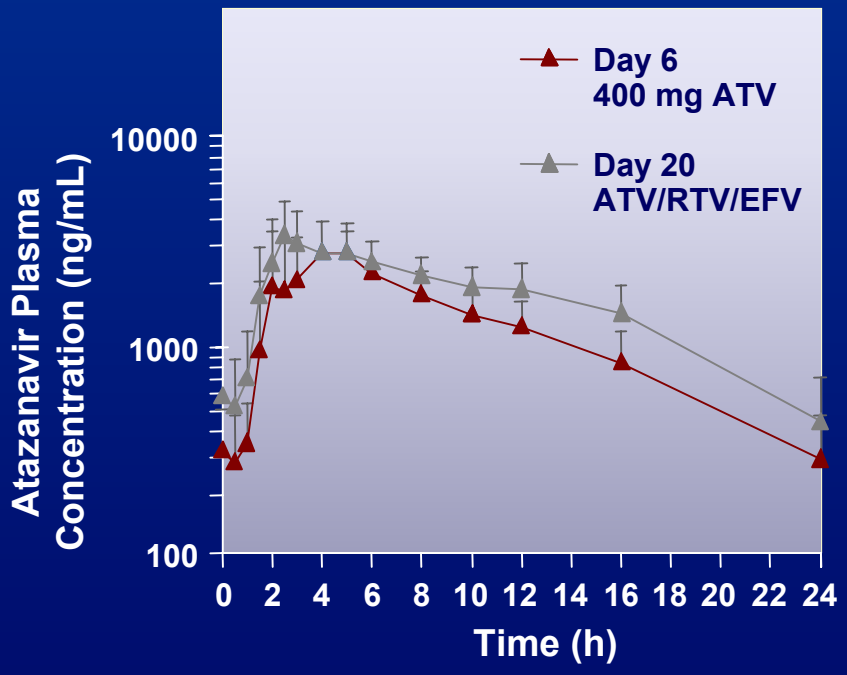
Summary of Results

- TDF decreased the concentrations of both ATV and RTV

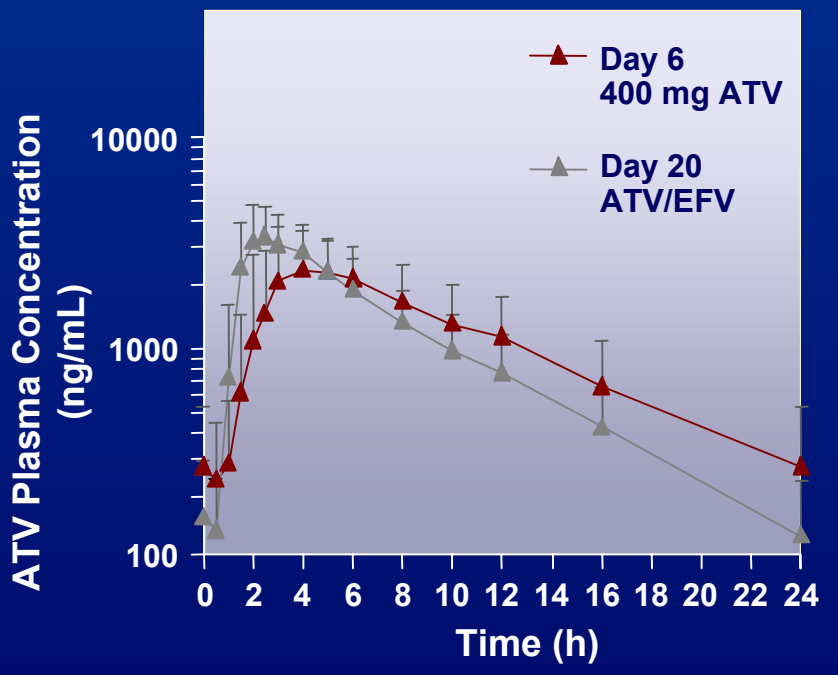
Adapted from: Taburet A et al. Poster 537, 10th CROI 2003.

Interaction Between ATV and EFV

Mean (SD) Plasma Concentration-Time Profiles of ATV +/– (RTV and EFV)



Mean (SD) Plasma Concentration-Time Profiles of 400 mg ATV +/– EFV



Interactions with RTV, EFV, and SQV

Atazanavir Dose	Coadministered Drug (Dose)	Results		Recommendations
300 mg QD	RTV (100 mg QD)	RTV	No change in AUC	Recommended that ATV 300 mg/ RTV 100 mg be administered QD with food
		ATV	Ratio of ATV AUC: 3.38	
400 mg QD	EFV (600 mg QD)	EFV	No change in AUC	Recommended that ATV 300 mg/ RTV 100 mg be administered with EFV 600 mg as single daily dose with food
		ATV	Ratio of ATV AUC: 0.26	
400 mg QD days 1 to 6 or 300 mg QD days 7 to 20	EFV (600 mg QD) RTV (100 mg QD)	EFV	No change in AUC	Recommended that ATV 300 mg/ RTV 100 mg be administered with EFV 600 mg as single daily dose with food
		RTV	No change in AUC	
		ATV	Ratio of ATV AUC: 1.39	
400 mg QD	SQV (1200 mg QD)	SQV	Ratio of SQV AUC: 5.49	Appropriate dosing recommendations have not been established for this combination
		ATV	No change in AUC	

Interactions With NRTIs

Atazanavir Dose	Coadministered NRTI (Dose)	Results		Recommendations
400 mg x 1 dose	ddI buffered tablets (200 mg) plus d4T (40 mg) X 1 dose	ddI	Ratio of ddI AUC: 0.98 when taken with ATV	Recommended that ATV is given with food 2 hours before or 1 hour after buffered ddI. No interaction is expected with ddI EC capsules, but ddI EC and ATV should be administered at different times because ddI EC is to be given without food and ATV is to be given with food.
		ATV	Ratio of ATV AUC: 0.13 when taken with ddI/d4T; 1.03 when taken after ddI/d4T	
		d4T	No change in AUC	
400 mg QD	3TC (150 mg) + AZT (300 mg)	3TC	Ratio of 3TC AUC: 1.03	No modifications needed
		AZT	Ratio of AZT AUC: 1.05	
		ATV	No change in AUC	

ddI = didanosine; d4T= stavudine; 3TC= lamivudine; AZT= zidovudine.

Other Relevant Interactions

Atazanavir Dose	Coadministered Drug (Dose)	Results		Recommendations
400 mg QD	rifabutin (150 mg QD)	RIF	Ratio of RIF AUC: 2.10	Dose reduction of rifabutin of up to 75% recommended
		ATV	Ratio of ATV AUC: 1.15	
400 mg QD	ketoconazole (200 mg QD)	KET	No change in AUC	No dosing adjustments required
		ATV	Ratio of ATV AUC: 1.10	
400 mg QD	atenolol (50 mg QD)	ALOL	Ratio of RIF AUC: 1.25	No dosing adjustments required
		ATV	Ratio of ATV AUC: 0.93	
400 mg QD	diltiazem (180 mg QD)	DIL	Ratio of DIL AUC: 2.25	Dose reduction of diltiazem by 50% should be considered
		ATV	No change in AUC	
400 mg QD	clarithromycin (500 mg QD)	CLA	Ratio of CLA AUC: 1.94	Dose reduction of clarithromycin by 50% should be considered
		ATV	Ratio of ATV AUC: 1.28	
400 mg QD	ethinyl estradiol norethindrone	EE/NE	Ratio of EE AUC: 1.48 Ratio of NE AUC: 2.10	Recommended that the lowest dose of each oral contraceptive component be used
		ATV	No change in AUC	

Summary of Drug Interactions Recommendations

No changes to either ATV or co-administered drug

- Atenolol
- Stavudine
- Lamivudine
- Zidovudine
- Ketoconazole

Modify dose and/or schedule of co-administered drug

- Saquinavir
- Clarithromycin
- Ethinyl estradiol / Norethindrone
- Rifabutin
- Diltiazem

Modify ATV dose or regimens

- Efavirenz
- Ritonavir

Separation in dosing from ATV

- Didanosine

Planned Drug-Drug Interaction Studies

- Methadone
- Fosamprenavir (908)
- Saquinavir
- PPI and H_2 blockers
- Nevirapine
- Interferon and ribavirin in patients with Hepatitis C virus (HCV)
- Possible in vivo inhibition of CYP2C9 with Warfarin
- Rifampin