FDA Antiviral Drugs Advisory Committee Meeting

Atazanavir (ATV, BMS-232632)

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Bristol-Myers Squibb Company

Introduction

Elliott Sigal, M.D., Ph.D.

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Global Clinical and Pharmaceutical Development
Bristol-Myers Squibb

Atazanavir: Profile of a Novel Protease Inhibitor

- Meets evolving medical need
  - Distinct resistance profile
  - Favorable cholesterol and triglyceride profile
  - Decreased pill burden – Two pills once daily
- Acceptable safety/tolerability profile with well-characterized and manageable risks
- Demonstrates antiviral efficacy

Atazanavir Development Program

- Substantial clinical program demonstrating efficacy and safety
  - ~ 1000 antiviral treatment-naïve subjects studied on ATV with over 500 subjects treated for over 2 years
  - ~ 500 antiviral treatment-experienced subjects studied on ATV
  - Pediatric program ongoing
- Nine Phase II / III studies conducted
- Early Access Program with ~3600 patients enrolled to date
- Extensive characterization of safety profile

Experts Available to Committee

Richard T. D'Aquila, M.D.	Director, Division of Infectious Diseases, Department of Medicine, The Addision B. Scoville Professor of Medicine, and Professor of Microbiology and Immunology, Vanderbilt University School of Medicine
Carl Grunfeld, M.D., Ph.D.	Professor of Medicine, University of California, San Francisco Metabolism and Endocrine Sections, Veterans Affairs Medical Center, San Francisco
Thomas Pearson, M.D., Ph.D.	Albert D. Kaiser Professor and Chair, Department of Community and Preventive Medicine and Senior Associate Dean for Clinical Research, University of Rochester School of Medicine
Craig Pratt, M.D.	Professor of Medicine and Director, Clinical Cardiology Research, Baylor College of Medicine Director Coronary Intensive Care Unit and Director, Non-Invasive Laboratories, The Methodist Hospital
Mark Ratain, M.D.	Leon O. Jacobson Professor of Medicine, Chairman, Committee on Clinical Pharmacology and Pharmacogenomics, and Associate Director for Clinical Science, Cancer Research Center, The University of Chicago

Experts Available to Committee (Cont'd)

Jeremy Ruskin, M.D.	Associate Professor of Medicine, Harvard University Medical School Director, Cardiac Arrhythmia Service, Massachusetts General Hospital
Richard Rutstein, M.D.	Associate Professor of Pediatrics, The University of Pennsylvania School of Medicine Medical Director, Special Immunology Service, Children's Hospital of Philadelphia
Kathleen Squires, M.D.	Associate Professor of Medicine, Keck School of Medicine, University of Southern California Medical Director, Rand Schrader Clinic
Mark Sulkowski, M.D.	Assistant Professor of Medicine, Johns Hopkins University School of Medicine
Lee-Jen Wei, Ph.D.	Professor of Biostatistics, Harvard University
Allan W. Wolkoff, M.D.	Professor of Medicine and Anatomy & Structural Biology and Director, Belfer Institute for Advanced Biomedical Studies, Albert Einstein College of Medicine

Atazanavir Proposed Indication

"Atazanavir is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection."

Bristol-Myers Squibb Presentation

- Steven M. Schnittman, M.D.
  - Clinical Development Program and Clinical Trial Results
- John H. Lawrence, M.D.
  - Cardiac Electrophysiology Evaluations
- Michael F. Giordano, M.D.
  - Characterization of Hyperbilirubinemia
  - Characterization of Lipid Profile
- Elliott Sigal, M.D., Ph.D.
  - Conclusion

Clinical Development Program and Clinical Trial Results

Steven M. Schnittman, M.D.

Vice President
Global Development
Bristol-Myers Squibb

Atazanavir Clinical Development and Results

- ADME, drug-drug interaction profile, and dose selection
- Clinical results in treatment-naïve patients
- Dosing strategies and clinical results in treatment-experienced patients

ATV ADME Summary

Absorption

- Rapidly absorbed (Tmax ~ 1-3 hours)
- Food: ↑ exposure and ↓ intersubject variability
  - ATV to be administered with food

Distribution

- Protein Binding ~ 86% (albumin & α_1-AG)

Metabolism

- Primarily metabolized by CYP3A4 like other PIs
- Inhibitor of CYP3A4 (Ki = 2.35 μM) like other PIs
  - NFV < ATV < LPV < RTV
- Inhibitor of UGT 1A1 (Ki = 1.9 μM, bilirubin glucuronidation) like indinavir

Elimination

- Primarily eliminated in feces
- Urinary excretion – 7% unchanged drug
- T½ ~ 7 hours (supportive of once-daily dosing)

Drug Interactions Recommendations

No changes to either ATV or coadministered drug

- Atenolol
- Stavudine
- Lamivudine
- Zidovudine
- Ketoconazole

Modify dose and/or schedule of coadministered drug

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

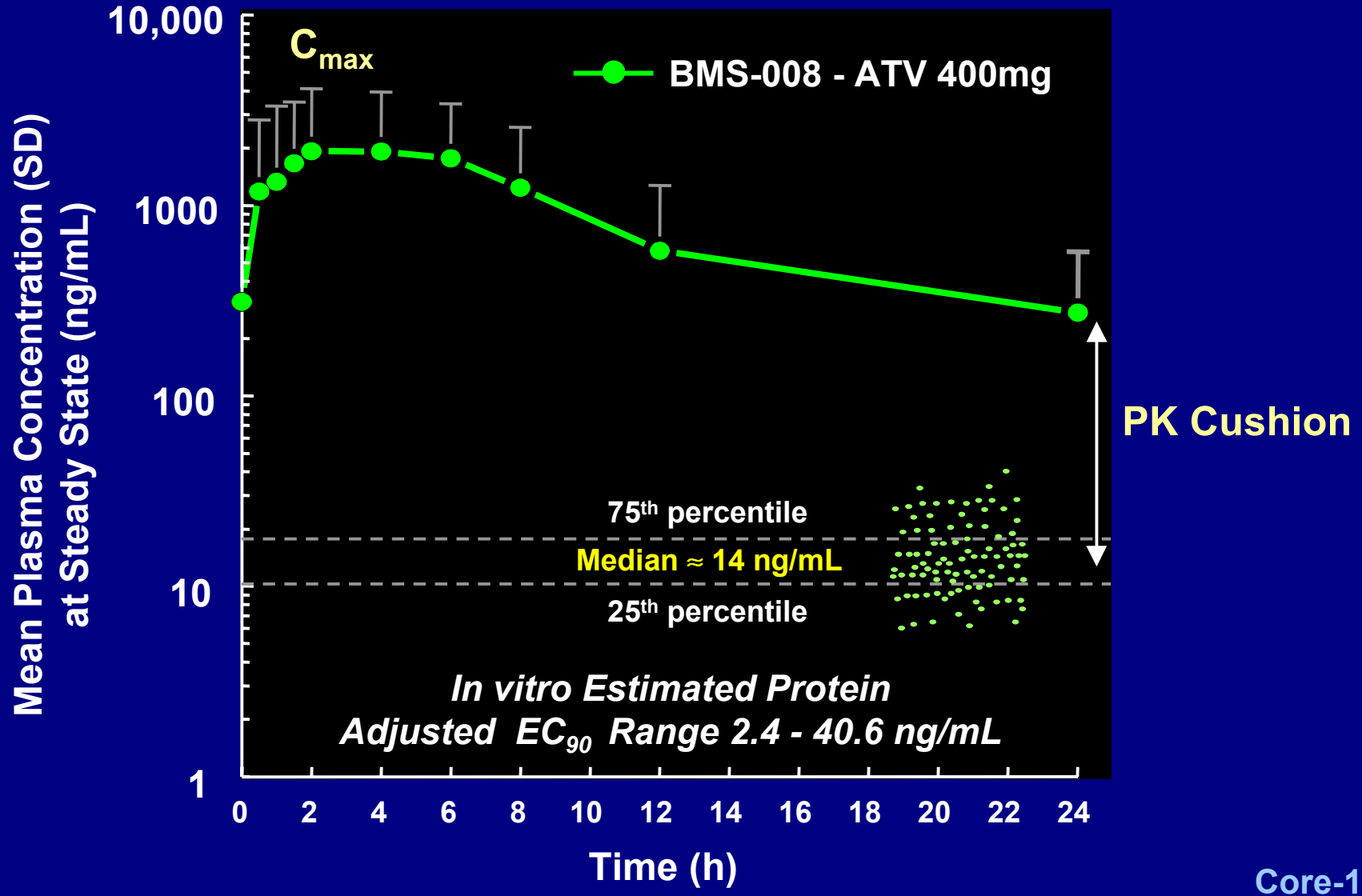
Modify ATV dose or regimens

- Efavirenz
- Ritonavir

Separation in dosing from ATV

- Didanosine – buffered formulation

Rationale for ATV 400 mg Once Daily Treatment-Naïve Patients



Rationale for ATV 400 mg Once Daily Treatment-Naïve Patients

	BMS-007				BMS-008		
	ATV 200	ATV 400	ATV 500	NFV	ATV 400	ATV 600	NFV
2-Week Mean RNA Decline (log_{10} c/mL)	-1.18	-1.27	-1.58	-1.36	—	—	—
Hollow Fiber Model (RNA Suppression)	poor	good	—	—	good	good	—
Mean Cmin (ng/mL)	24*	150*	148*	—	143**	306**	—
Grade 3 - 4 Total Bilirubin (> 2.5 x ULN)	20%	41%	49%	1%	41%	58%	4%
Grade 4 Total Bilirubin (> 5 x ULN)	< 1%	3%	14%	0%	8%	13%	3%

* Without regard to food

** With food

Summary of Efficacy in Phase II Treatment-Naïve Subjects Through Week 48

	BMS-007		BMS-008	
	ATV 400 mg N = 78	NFV N = 82	ATV 400 mg N = 181	NFV N = 91
TLOVR (< 400 c/mL)	62%	61%	68%	59%
Mean Change in HIV RNA (log_{10} c/mL)	- 2.42	- 2.33	- 2.51	- 2.31

Atazanavir Clinical Development and Results

- ADME, drug-drug interaction profile, and dose selection
- Clinical results in treatment-naïve patients
- Dosing strategies and clinical results in treatment-experienced patients

BMS-034 – Phase III Pivotal Study

Study Design

- **Randomized, double-blind, double-dummy, active-controlled**
- **Treatment-naïve subjects: HIV RNA ≥ 2000 c/mL, CD4 ≥ 100 cells/mm^3 (or > 75 cells/mm^3 if no prior AIDS events)**

1:1 Randomization, N = 810

ATV 400 mg QD EFV placebo QD	**EFV 600 mg QD** ATV placebo QD
ZDV + 3TC BID (fixed dose)	**ZDV + 3TC BID (fixed dose)**
Treated N = 404	N = 401

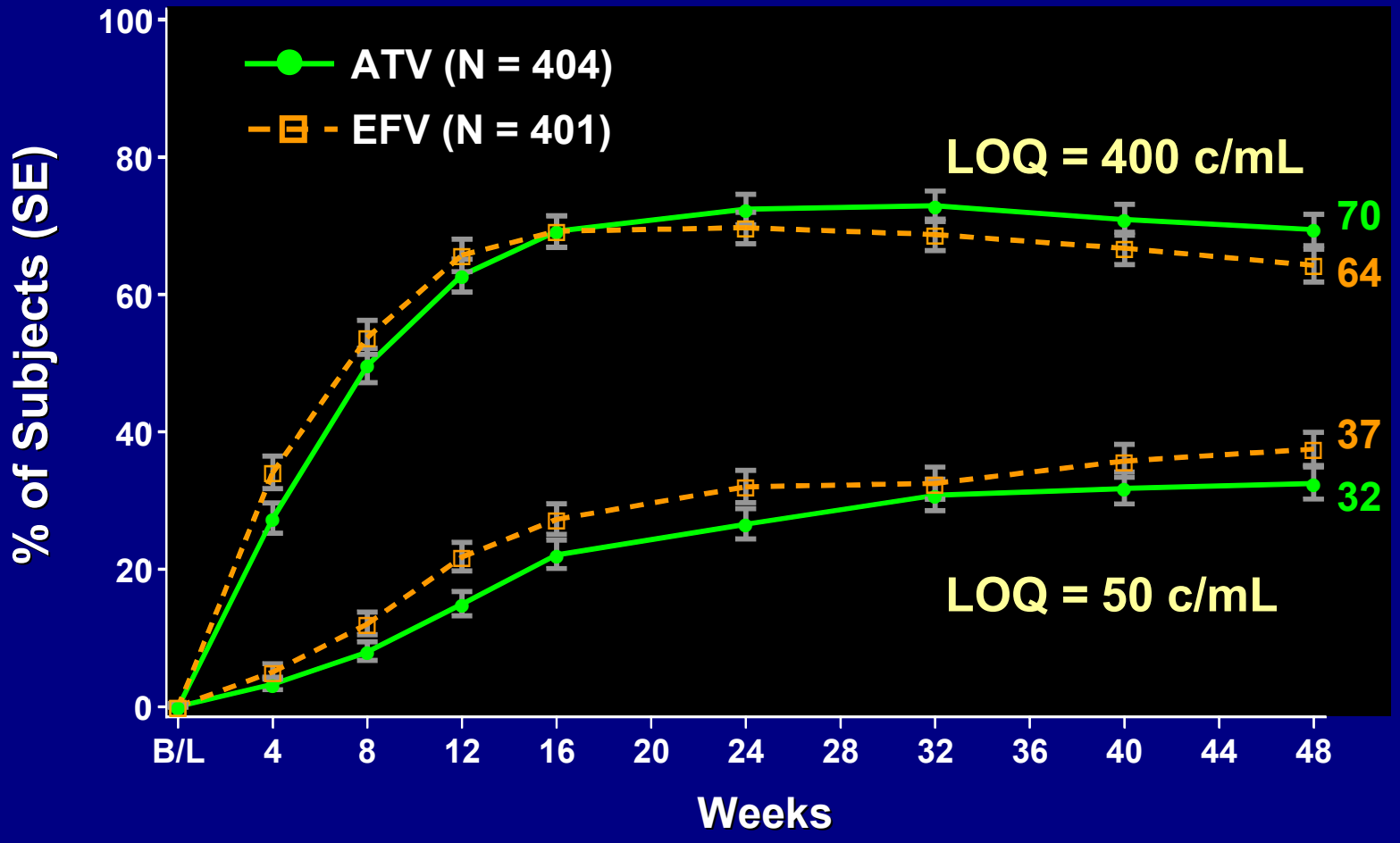
BMS-034

Subject Characteristics at Baseline

Characteristics	Treatment Regimen	
	ATV / ZDV + 3TC N = 404	EFV / ZDV + 3TC N = 401
Median Age (Years)	33	33
Gender (%)		
Male	64	66
Female	36	34
Race (%)		
Hispanic/Latino	38	35
White	34	32
Asian/Pacific Islanders	14	17
Black	13	13
Other	1	2
AIDS (%)	4	6
Median HIV RNA Level (log_{10} c/mL)	4.87	4.91
HIV RNA Distribution (%)		
< 30,000 c/mL	28	26
30,000 - < 100,000 c/mL	30	31
≥ 100,000 c/mL	42	43
Median CD4 Cell Count (cells/mm^3)	286	280
Hep B/C Co-Infected (%)	13	15

BMS-034

Virologic Response* Through Week 48
Intent to Treat (NC = F)

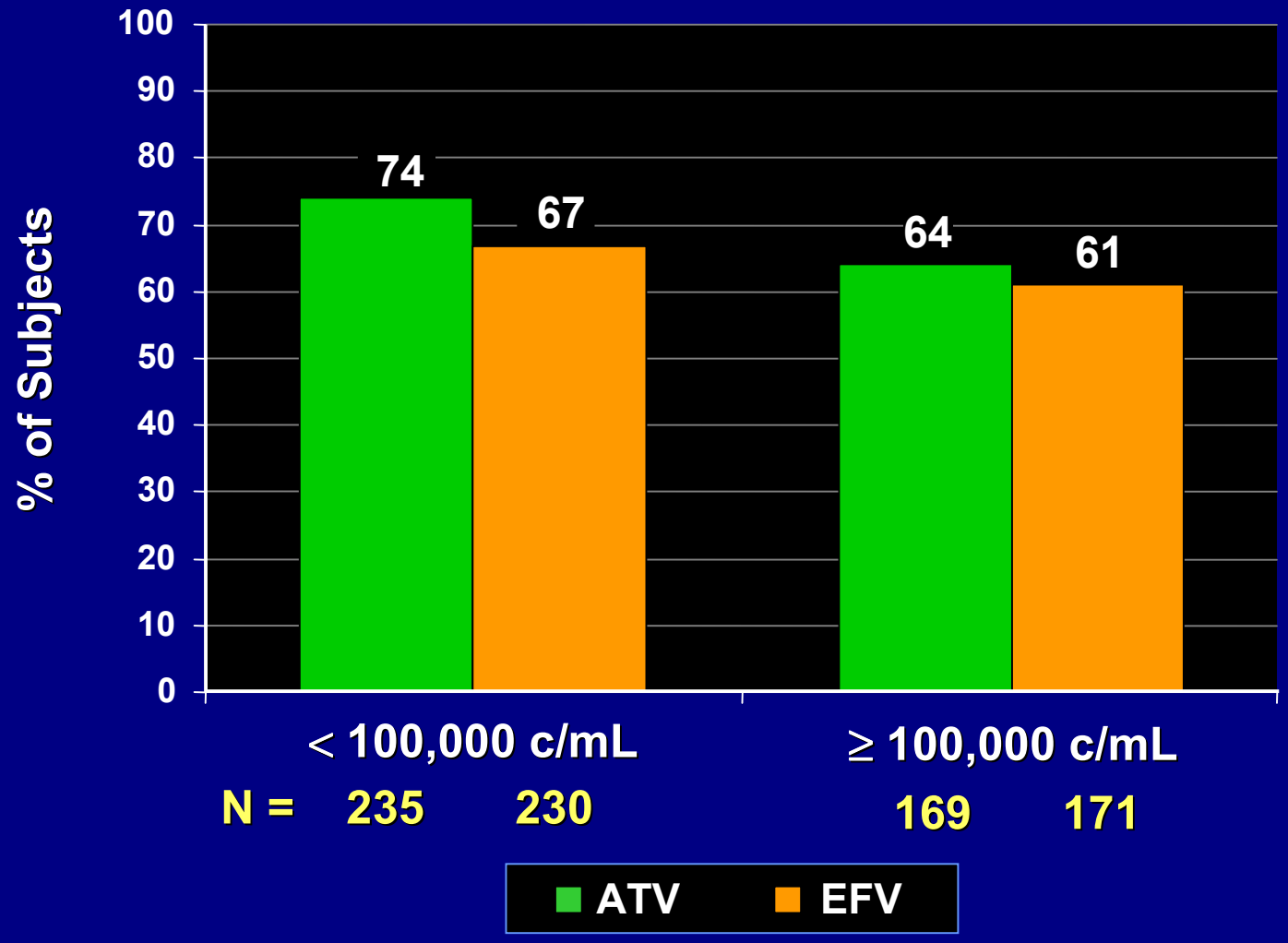


ATV-EFV Difference Estimate (95% CI): LOQ = 400 c/mL: 5.2 (-1.2, 11.7)
LOQ = 50 c/mL: -4.9 (-11.4, 1.5)

*TLOVR

BMS-034

Virologic Response* Through Week 48 (ITT) by Baseline HIV RNA (LOQ = 400 c/mL)



*TLOVR

BMS-034

I50L Identified in All ATV-Resistant Isolates

	ATV N = 404
Virologic failure through 48 weeks*	69
Phenotypeable/Genotypeable, N	26
Phenotype > 2.5 x IC_{50} of control, N	6
I50L or I50I/L, N	6

Reasons for no result include: HIV RNA level ≤ 1000 c/mL (n = 44), isolate non-typeable (n = 23) or sample unavailable (n = 25)

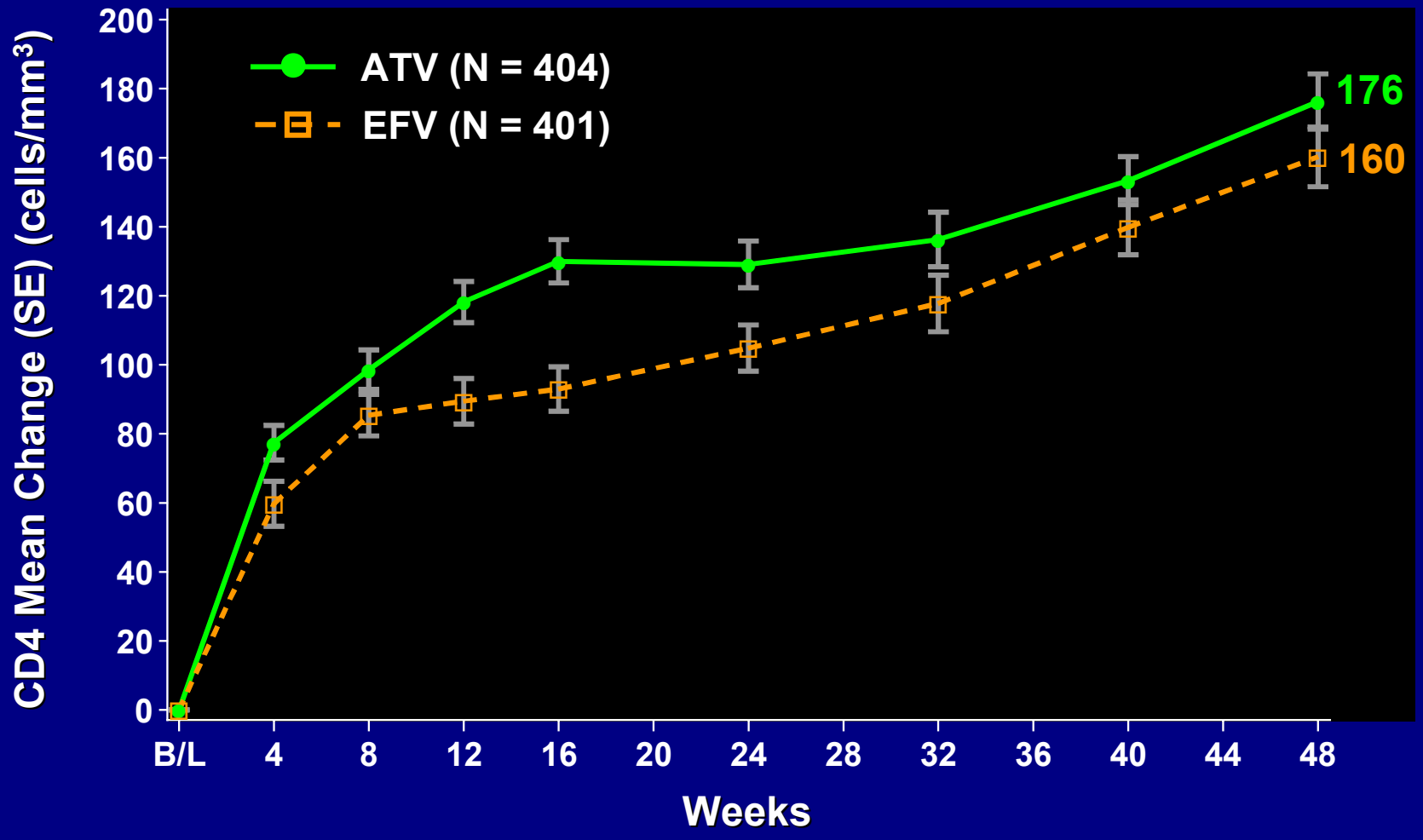
*TLOVR (LOQ = 400 c/mL)

Summary of ATV Resistance Treatment-Naïve Subjects

- 23 on-study resistant isolates tested from Phase II and III studies
  - All have I50L signature mutation
  - I50L associated with
    - ATV-specific resistance
    - Decreased viral fitness
    - Phenotypic susceptibility maintained to other PIs

BMS-034

CD4 Cell Count Mean Increase From Baseline Treated Subjects



ATV-EFV TAD Estimate (95% CI) = 23.1 (9.7, 36.5)

BMS-034

Grade 2 – 4 Related Adverse Events

Grade 2 – 4 Related AEs (≥ 5% of Subjects) and AEs of Interest	Subjects, N (%)	
	ATV N = 404	EFV N = 401
Total	165 (41)	182 (45)
Nausea	57 (14)	51 (13)
Rash	25 (6)	41 (10)
Headache	23 (6)	25 (6)
Jaundice	21 (5)	0
Vomiting	17 (4)	27 (7)
Dizziness	8 (2)	24 (6)
Scleral Icterus	6 (1)	0
Diarrhea	5 (1)	10 (2)

BMS-008/044
Study Design

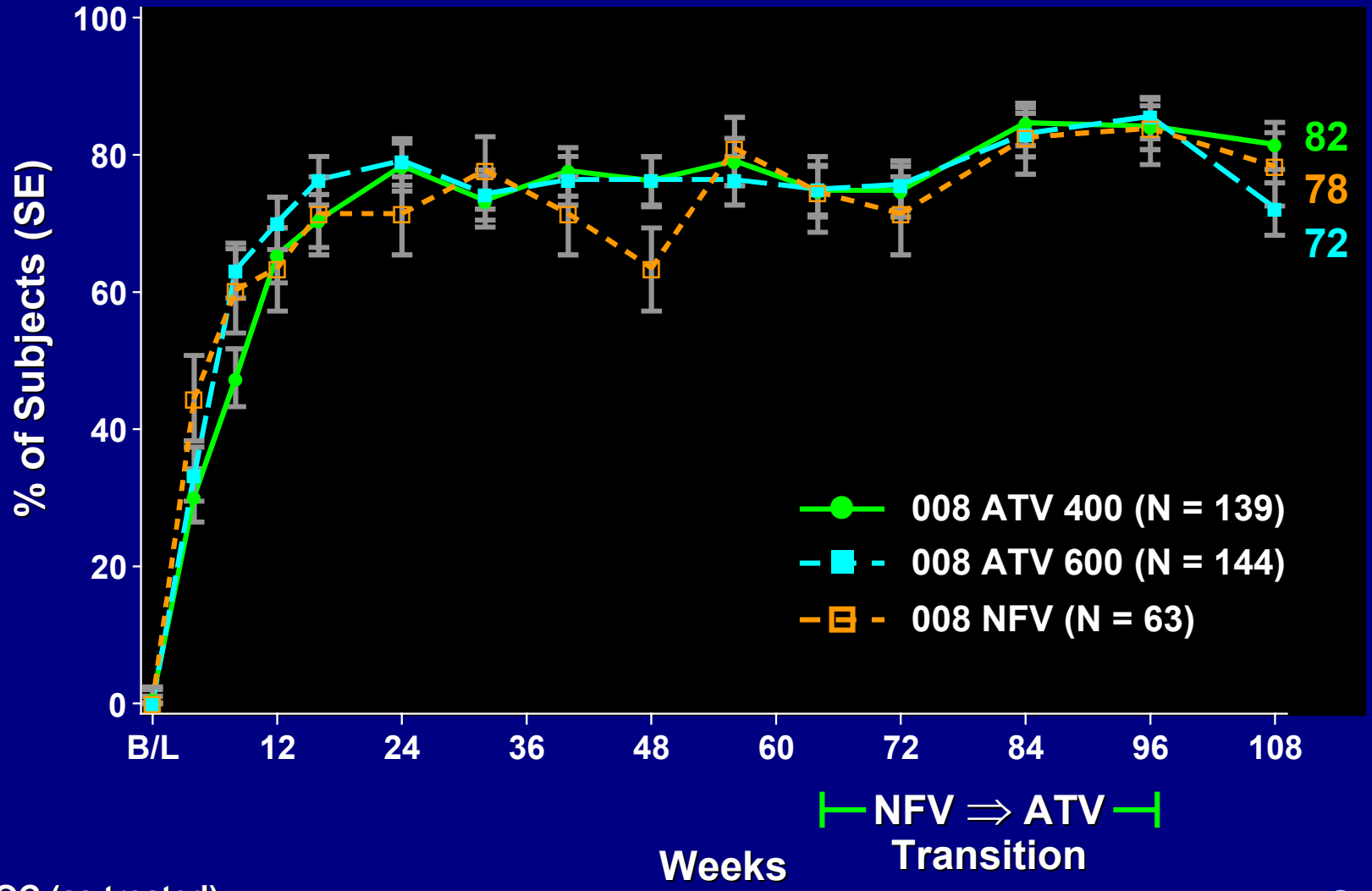
BMS-008: 467 Randomized in 2:2:1 ratio
(Blinded to ATV Dose)

Group I	Group II	Group III
48 Wks Triple Therapy: ATV 400 mg QD d4T / 3TC	48 Wks Triple Therapy: ATV 600 mg QD d4T / 3TC	48 Wks Triple Therapy: NFV 1250 mg BID d4T / 3TC
ATV 400 mg QD d4T / 3TC	ATV 600 mg QD d4T / 3TC	Open-label ATV 400 mg QD d4T / 3TC

BMS-044: 346 Treated

BMS-008/044

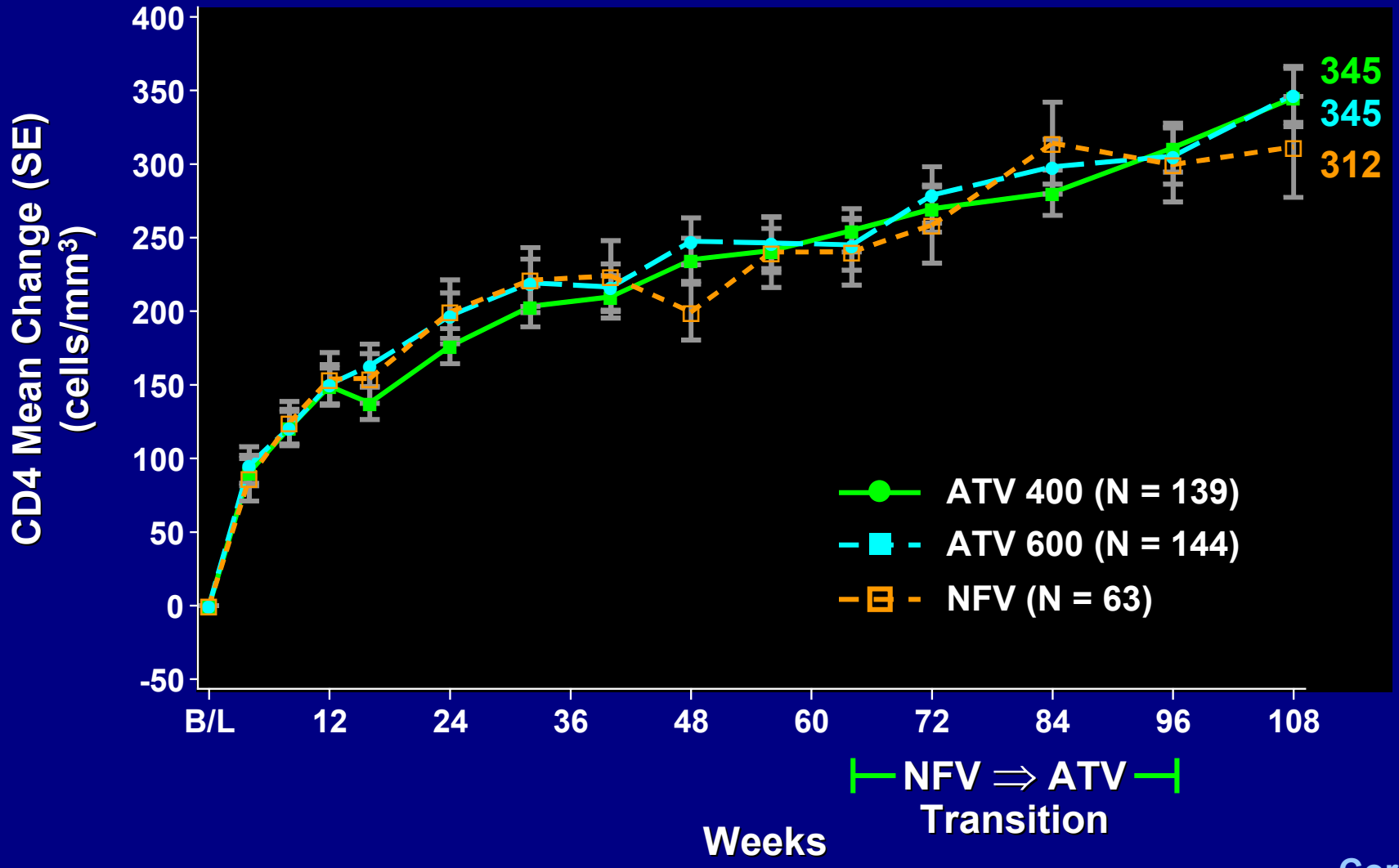
Virologic Response (AT)* Through Week 108 (LOQ = 400 c/mL)
Treated Subjects in BMS-044



*VR-OC (as treated)

BMS-008/044

CD4 Cell Count Mean Increase Through Week 108
Treated Subjects in BMS-044



ATV Conclusions – Treatment-Naïve Subjects

- ATV 400 mg safe and effective
  - vs EFV in pivotal Phase III study
  - vs NFV in two Phase II studies
- Durable antiviral efficacy and safety
  - Dosing > 3 years
- Distinct resistance profile in treatment-naïve (I50L signature mutation)
- No increase in cholesterol, triglycerides

Atazanavir Clinical Development and Results

- ADME, drug-drug interaction profile, and dose selection
- Clinical results in treatment-naïve patients
- Dosing strategies and clinical results in treatment-experienced patients

Dose Selection Strategies Treatment-Experienced Patients

- Treatment-experienced patients heterogeneous
  - Prior ARV therapies and duration variable
  - Generally ↓ phenotypic susceptibility, varied mutations
- Several dosing strategies evaluated
  - ATV 400 mg alone
  - ATV boosted with ritonavir
  - ATV combined with another PI (e.g., SQV)

Rationale for ATV 400 Unboosted Treatment-Experienced Patients

Selection of ATV 400 QD supported for Phase III study in subjects who failed a single PI (BMS-043)

- 551 clinical PI-resistant isolates: ATV susceptibility maintained vs 86% of isolates resistant to 1-2 approved PIs
- 400 mg QD dose provides mean Cmin ~150 ng/mL; Estimated median protein adjusted EC_{90} 31.2 ng/mL (25 – 75 %-ile: 17.8 – 59.9 ng/ml)

BMS-043 - Phase III Pivotal Study

Study Design

Screening: Prior PI Failure

1:1 Randomization (N = 300)

Group I	Group II
ATV 400 mg QD + 2 NRTIs	LPV / RTV 400/100 BID + 2 NRTIs
Treated 144	146
Efficacy Cohort* 114	115

*Protocol-planned analysis which includes all subjects randomized through April 2, 2002 (≥ 24 weeks of therapy)

BMS-043

Subject Characteristics at Baseline Efficacy Cohort

Characteristics	Treatment Regimen	
	ATV N = 114	LPV / RTV N = 115
Median Age (Years)	36	38
Gender (%)		
Male	77	84
Female	23	16
Race (%)		
Hispanic/Latino	53	53
White	40	41
Black	6	6
Asian/Pacific Islanders	< 1	0
AIDS (%)	26	30
Median HIV RNA Level (log_{10} c/mL)	4.19	4.30
Median CD4 Cell Count (cells/mm^3)	279	249
Hep B/C Co-Infected (%)*	20	12

*All treated subjects

BMS-043

Mean Duration Prior ARV Use Efficacy Cohort

- Prior duration of antiretroviral drugs by class included:
  - PIs 140 weeks
  - NRTIs 180 weeks
  - NNRTIs 85 weeks

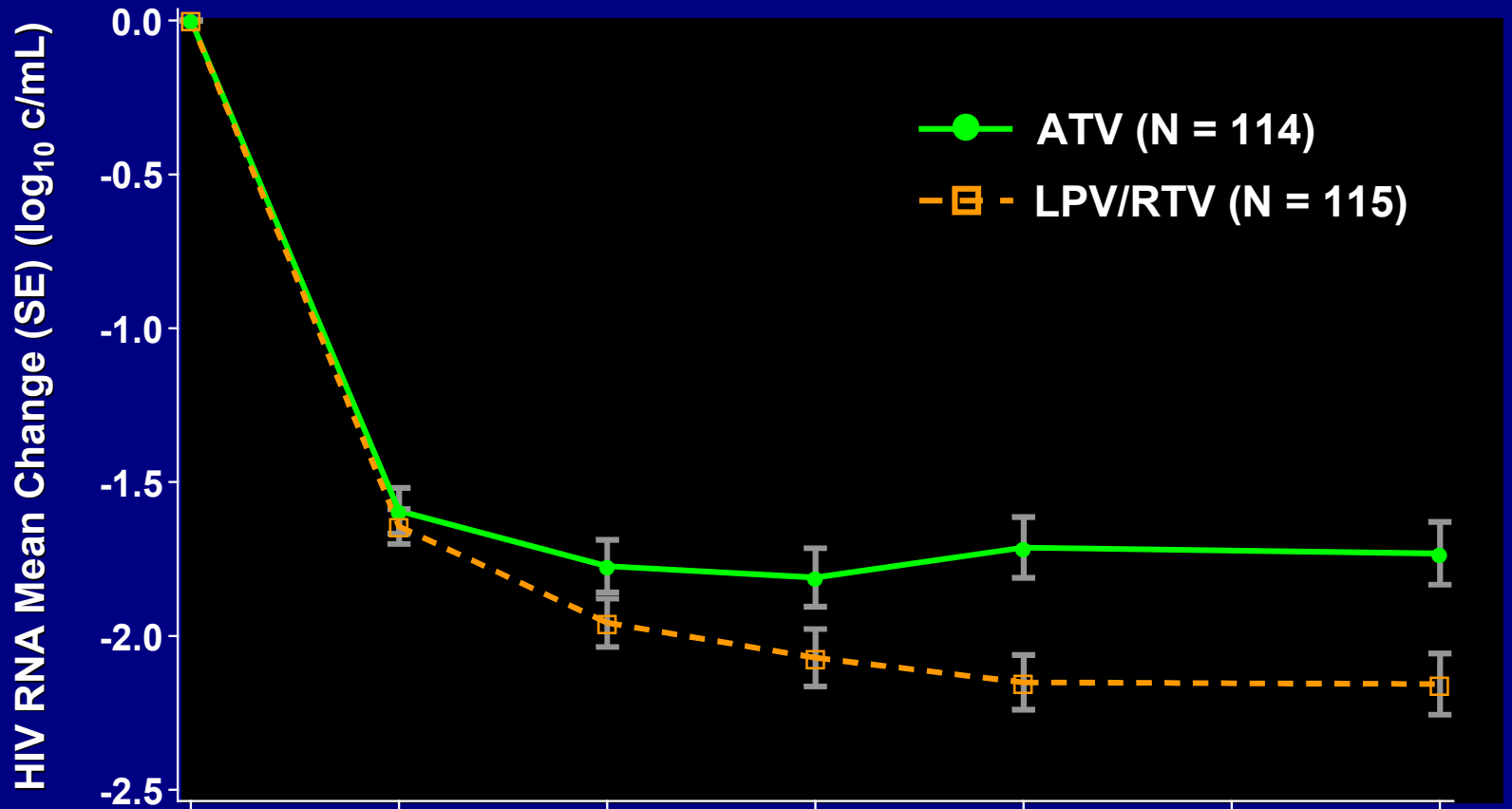
BMS-043

PI Phenotypic Sensitivity at Baseline Efficacy Cohort

PI	$IC_{50} \leq 2.5$ x CTL Subjects, N (%)	
	ATV N = 114	LPV / RTV N = 115
APV	104 (91)	104 (90)
ATV	84 (74)	89 (77)
LPV	94 (82)	101 (88)
NFV	55 (48)	51 (44)
RTV	80 (70)	84 (73)
SQV	87 (76)	93 (81)

BMS-043

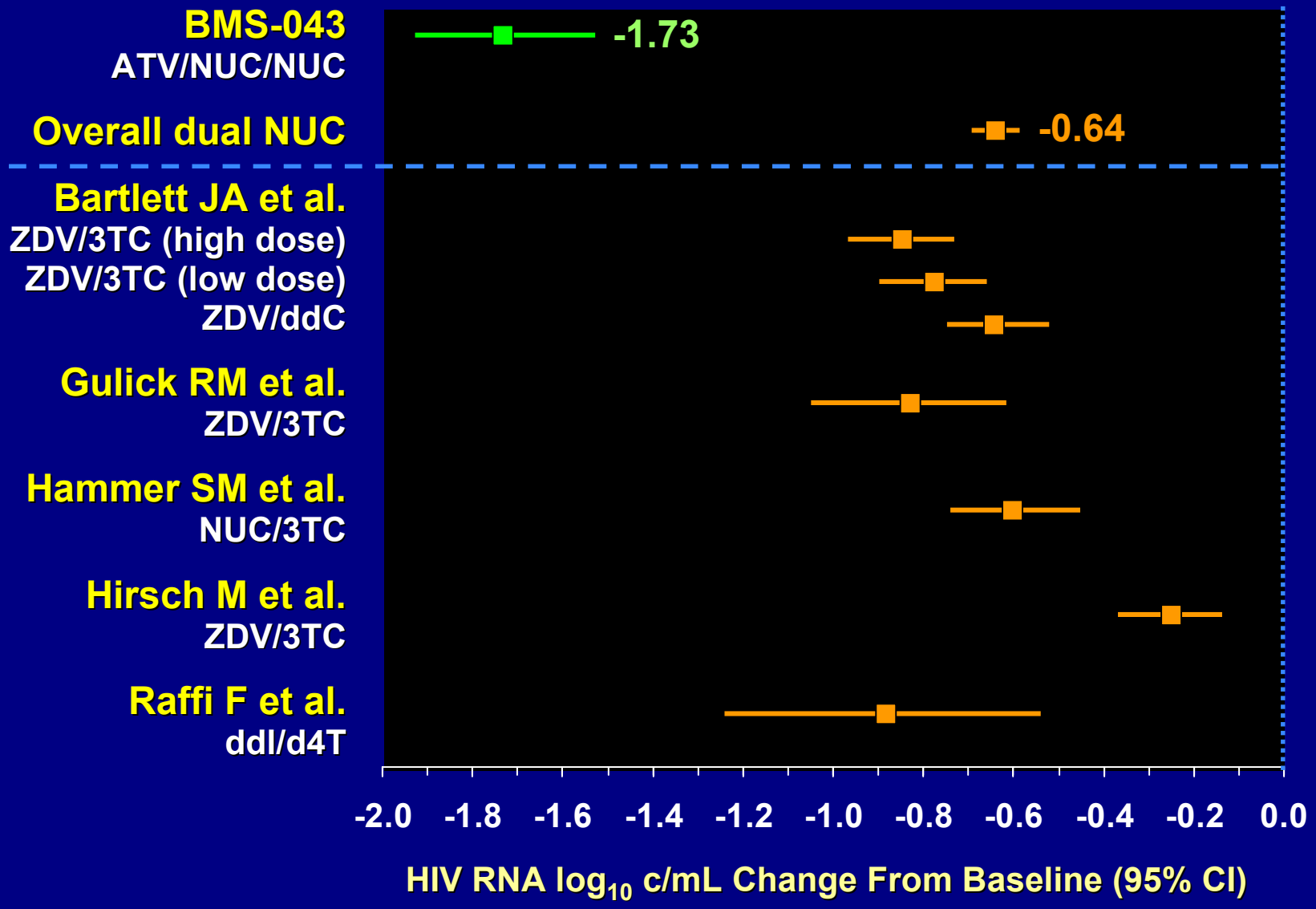
HIV RNA Mean Change – Co-Primary Endpoint 1 Efficacy Cohort



ATV	114	106	105	103	102	95
LPV / RTV	115	112	112	109	108	102

ATV - LPV/RTV TAD Estimate (97.5% CI) = 0.31 (0.06, 0.55)

ATV Contribution to Efficacy: Meta-analysis



ATV/NUC/NUC - NUC/NUC Difference Estimate (95 CI) = -1.09 (-1.30, -0.88)

BMS-043

Virologic Response (ITT)* Through Week 24 Efficacy Cohort

	% Undetectable	
	ATV N = 114	LPV / RTV N = 115
LOQ = 400 c/mL	61	81
LOQ = 50 c/mL	41	52

* TLOVR

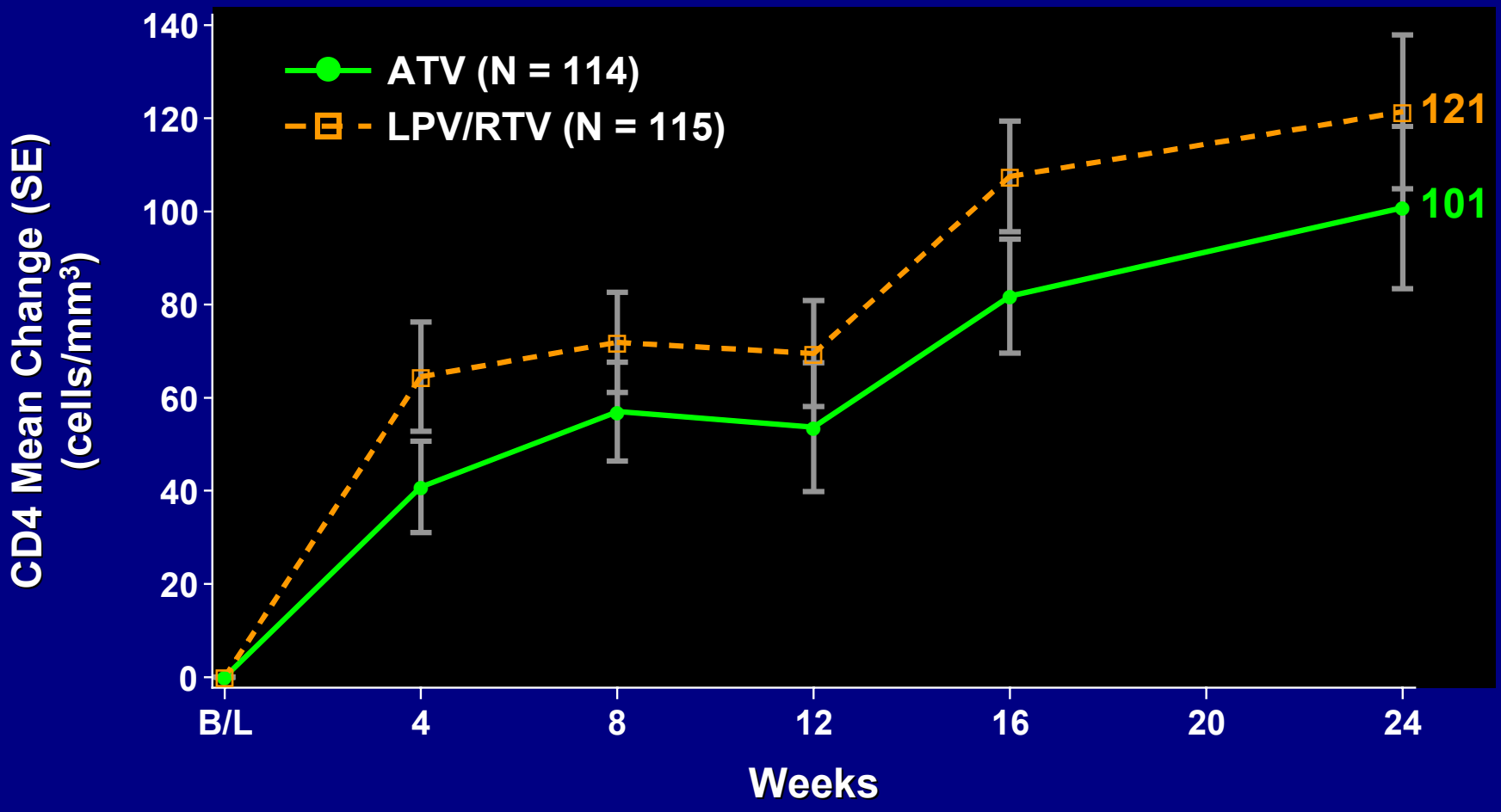
BMS-043

Pheno / Genotypic Baseline Predictors of ATV Virologic Response (Exploratory Analyses) Efficacy Cohort

Baseline Characteristic	TLOVR (LOQ = 400 c/mL)
PI Phenotype $\leq$ 2.5 x IC_{50} of control	68%
PI Phenotype $>$ 2.5 x IC_{50} of control	42%
One Prior PI	68%
$\geq$ 2 Prior PIs	39%
No NRTI Mutations	59%
$\geq$ 1 NRTI Mutation	61%

BMS-043

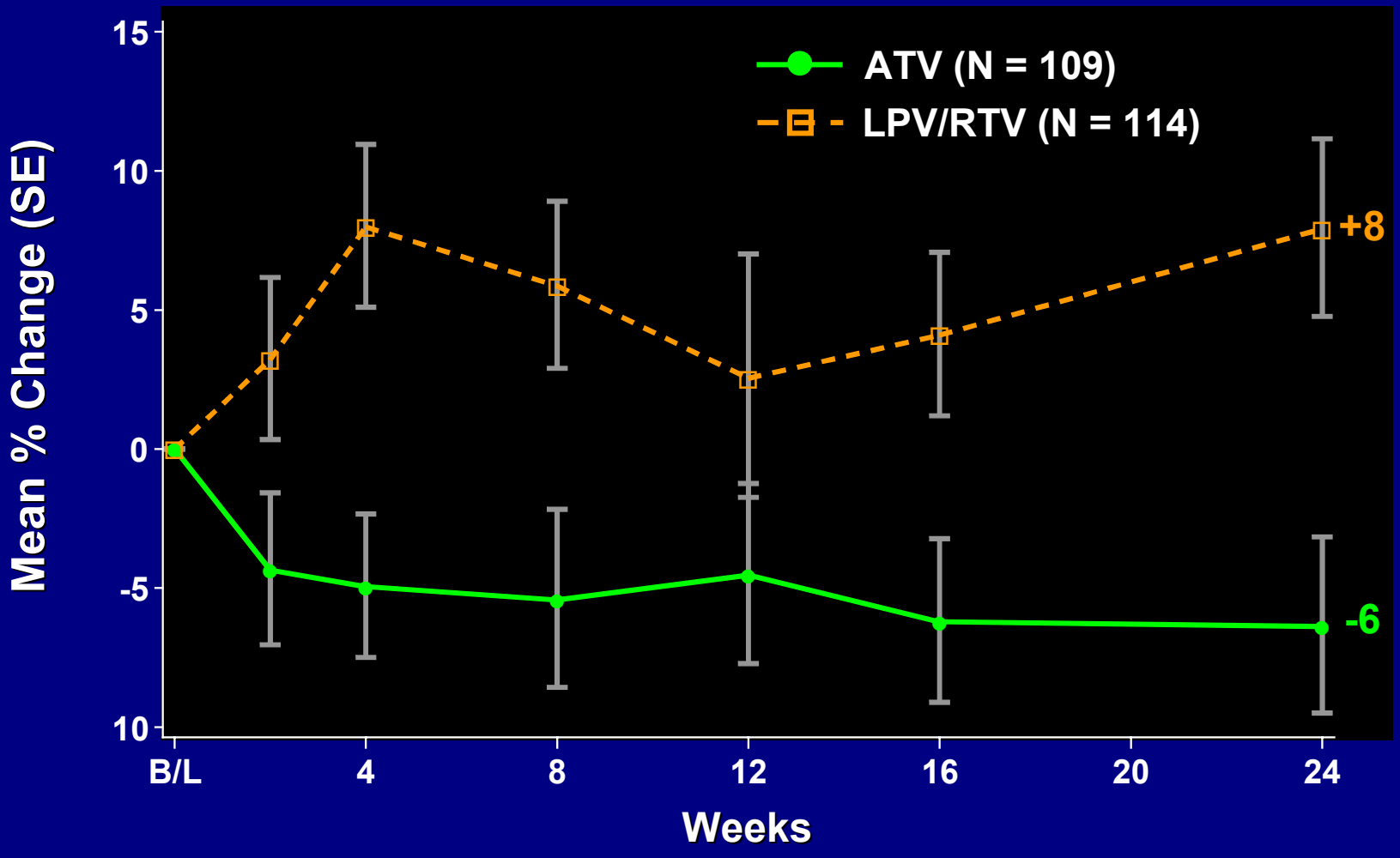
CD4 Cell Count Mean Increase From Baseline Efficacy Cohort



ATV-LPV/RTV TAD Estimate (95% CI) = -25.3 (-49.8, -0.8)

BMS-043

Fasting LDL-Cholesterol Change From Baseline Co-Primary Endpoint 2 – Efficacy Cohort



ATV - LPV/RTV Difference Estimate (97.5% CI) = -14.2 (-23.0, -5.4)

BMS-043

Grade 2 – 4 Related Adverse Events

Grade 2 – 4 Related AEs (≥ 5% of Subjects) and AEs of Interest	Subjects, N (%)	
	ATV N = 144	LPV / RTV N = 146
Total	26 (18)	32 (22)
Headache	6 (4)	5 (3)
Jaundice	5 (3)	0
Diarrhea	2 (1)	5 (3)
Nausea	1 (< 1)	4 (3)

BMS-043

Conclusions

- ATV 400 mg safe and effective
  - Majority of subjects achieve virologic response (< 400 c/mL)
  - Efficacy appears enhanced when subjects have ATV susceptibility ≤ 2.5 x IC_{50} of control, exposure to only one prior PI, irrespective of NRTI mutations
- Superior lipid profile demonstrated

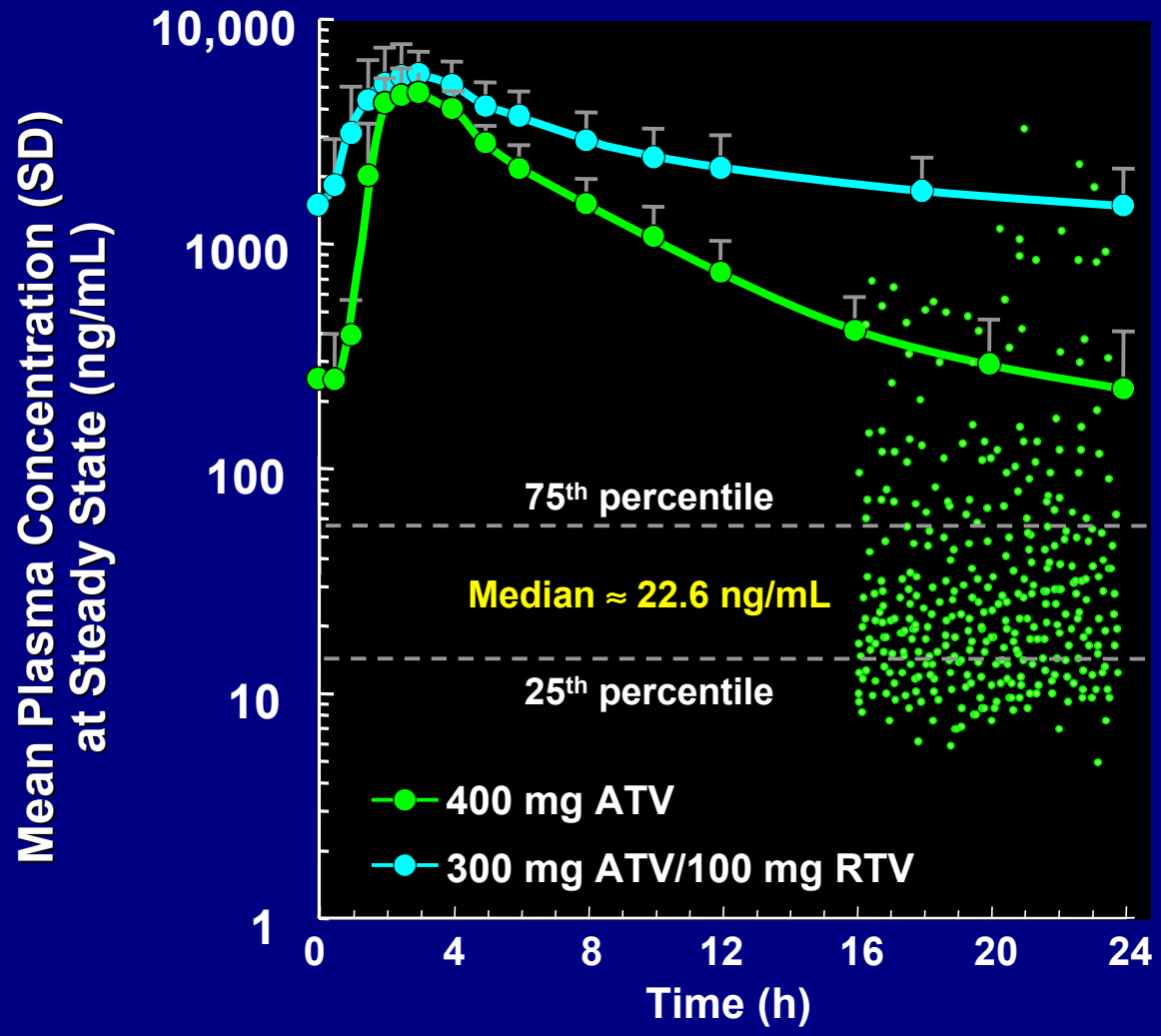
Efficacy with substantial lipid benefit

Dose-Selection Strategies Highly Treatment-Experienced Patients

- Highly treatment-experienced patients
  - Extensive use of ARVs across all drug classes
  - Significant pheno- and genotypic resistance
- Two dosing strategies evaluated
  - ATV boosted with ritonavir
  - ATV combined with another PI, SQV

BMS-045

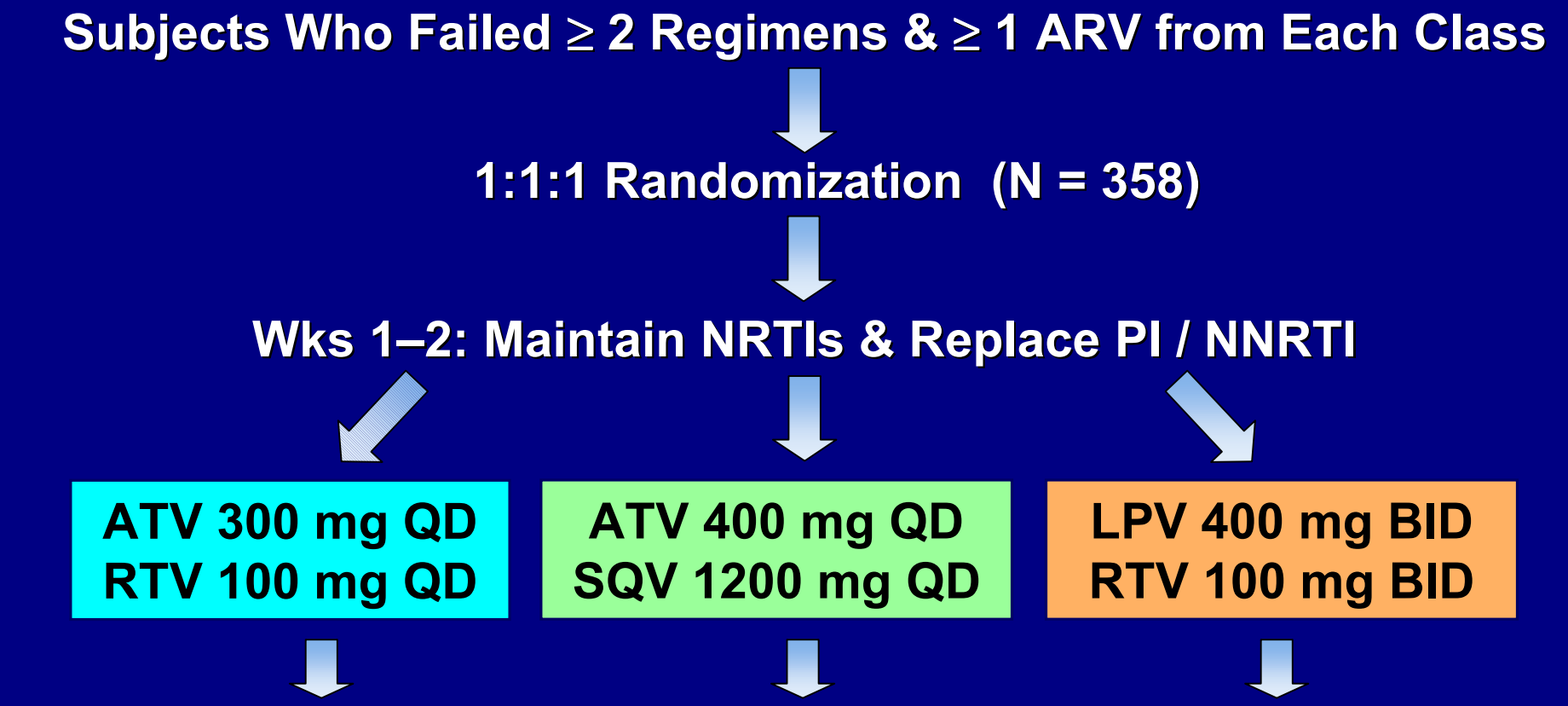
Rationale for ATV 300 Boosted with RTV 100 Treatment-Experienced Patients



In vitro Estimated Protein Adjusted EC_{90} Range
4.8 - 3132.3 ng/mL

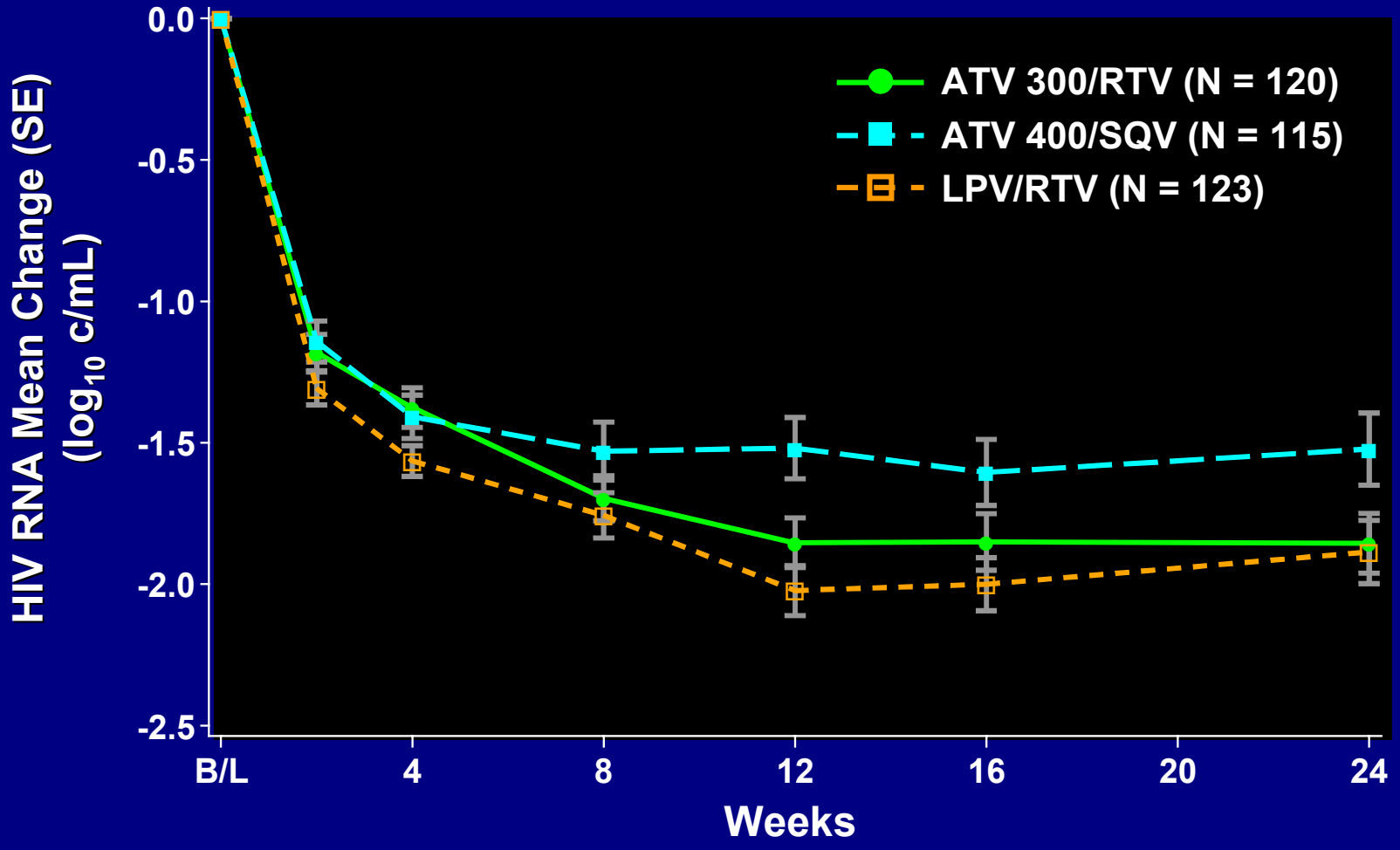
Supports selection of ATV 300 / RTV QD dose for Phase III study in patients who failed multiple HAART regimens (BMS-045)

BMS-045 - Phase III Study
Study Design



BMS-045: Antiviral Efficacy

HIV RNA Mean Change From Baseline Through Week 24
Randomized Subjects



ATV 300/RTV – LPV/RTV TAD Estimate (97.5% CI) = 0.14 (-0.09, 0.37)

ATV 400/SQV – LPV/RTV TAD Estimate (97.5% CI) = 0.31 (0.07, 0.55)

BMS-045

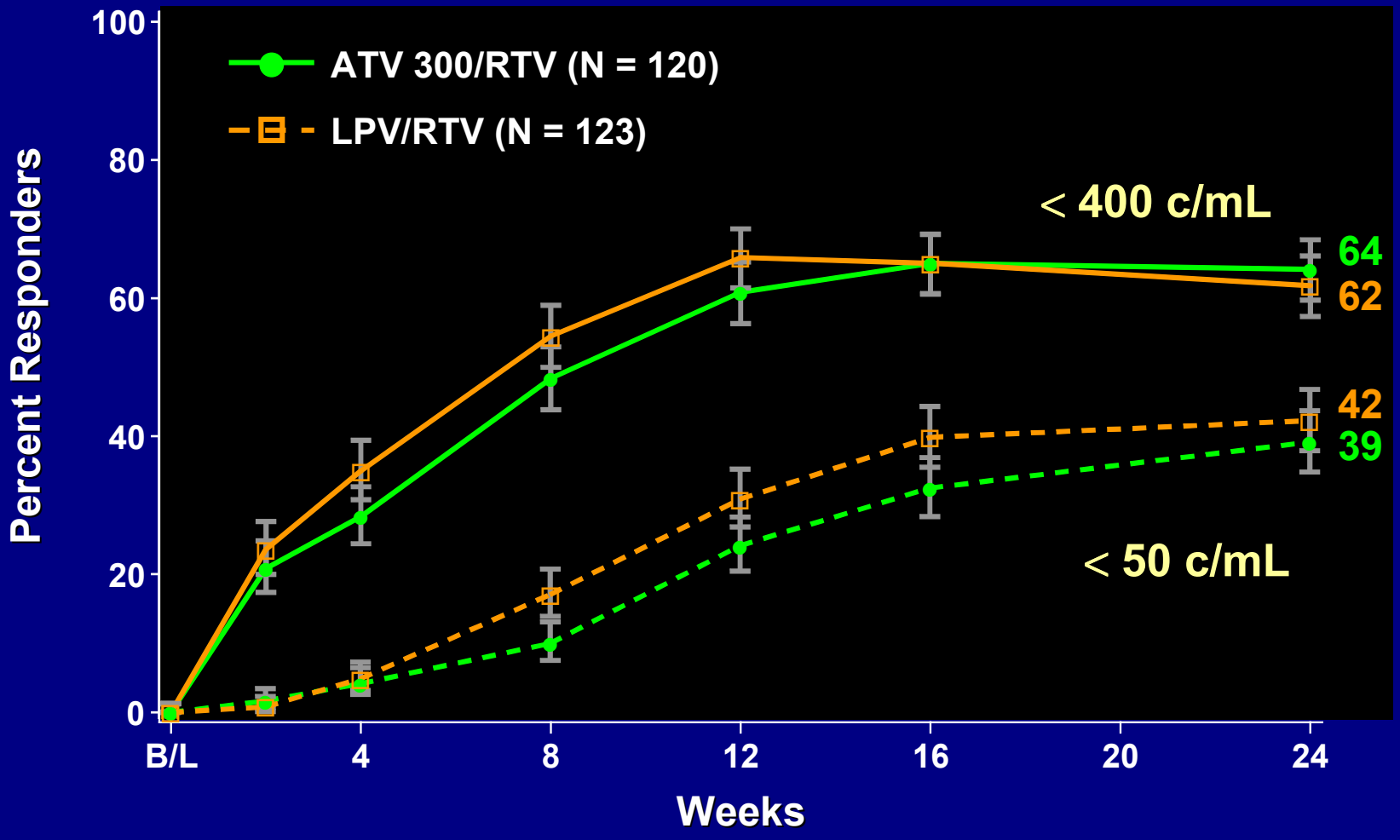
Virologic Response (ITT)* Through Week 24 Randomized Subjects

	% Undetectable		
	ATV 300 / RTV N = 120	ATV 400 / SQV N = 115	LPV / RTV N = 123
LOQ = 400 c/mL	64	44	62
LOQ = 50 c/mL	39	23	42

*TLOVR

BMS-045

Virologic Response (ITT)* Through Week 24 Randomized Subjects – ATV/RTV vs LPV/RTV

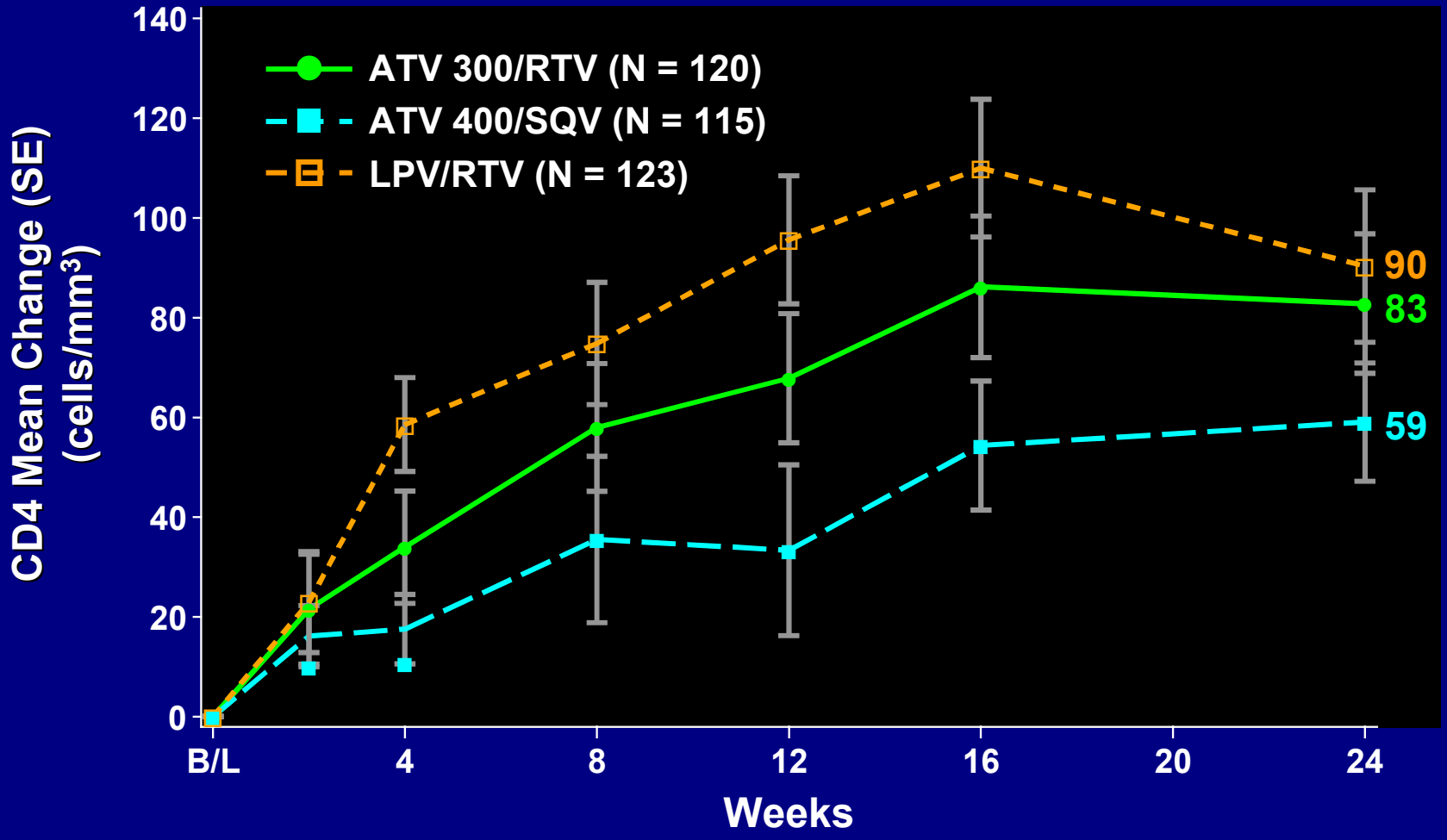


For LOQ = 400 c/mL:
ATV 300/RTV – LPV/RTV Difference Estimate (95% CI) = 2.4 (-9.8, 14.5)

*TLOVR

BMS-045

CD4 Cell Count Mean Increase From Baseline Randomized Subjects



ATV 300/RTV – LPV/RTV TAD Estimate (95% CI) -18.4 (-44.3, 7.5)

ATV 400/SQV – LPV/RTV TAD Estimate (95% CI) -44.9 (-74.5, 15.3)

BMS-045
Grade 2 – 4 Related Adverse Events Week 24

Grade 2 – 4 Related AEs (≥ 5% of Subjects) and AEs of Interest	Subjects, N (%)		
	ATV 300 / RTV N = 119	ATV 400 / SQV N = 110	LPV / RTV N = 118
Total	26 (22)	29 (26)	26 (22)
Diarrhea	3 (3)	5 (5)	13 (11)
Jaundice	7 (6)	2 (2)	0
Nausea	2 (2)	8 (7)	2 (2)
Vomiting	0	4 (4)	1 (< 1)
Scleral Icterus	4 (3)	0	0

BMS-045

Conclusions

- Safety and efficacy for ATV 300 / RTV 100 similar to LPV / RTV through 24 weeks (unreviewed)

Overall Clinical Conclusions of Efficacy and General Safety

- Durable efficacy in treatment-naïve patients vs EFV, NFV
- Efficacy of ATV 400 QD demonstrated in treatment-experienced patients
- Distinct resistance profile (I50L) in treatment-naïve and susceptible experienced patients
- Safe and well-tolerated at 400 QD
  - Hyperbilirubinemia / jaundice are dose-related and manageable
  - Consistent, durable lipid profile may provide reduced CV risk
- Drug-drug interactions well characterized
- Early data indicate safety and efficacy of ATV 300 QD boosted with RTV

Cardiac Electrophysiology Evaluations

John H. Lawrence, M.D.

Executive Director
Clinical Design and Evaluation
Bristol-Myers Squibb

Introduction
Electrophysiology Evaluations

- Preclinical assessments
  - *In vitro* and *in vivo* studies
- QTc and PR intervals and changes from baseline
  - 8 studies in healthy volunteers (N = 254 ATV; 28% females)
  - 5 studies in HIV-infected subjects (N = 1037 ATV, 31% females; N = 629 comparator, 28% females)

Electrophysiologic Effects of ATV in Preclinical Studies

Ion Channel Assay IC_{50}			Purkinje Fiber Action Potential
Na Block	Ca Block	HERG Block	↑ Duration (APD_{90}) at 30 μM
> 30 μM (16% @ 30 μM)	10.4 μM	> 30 μM (15% @ 30 μM)	13%

- All PIs tested blocked HERG channels or prolonged action potential duration with *in vitro* potency similar to or greater than ATV
- No ECG changes in 9 month dog toxicology study

BMS-076

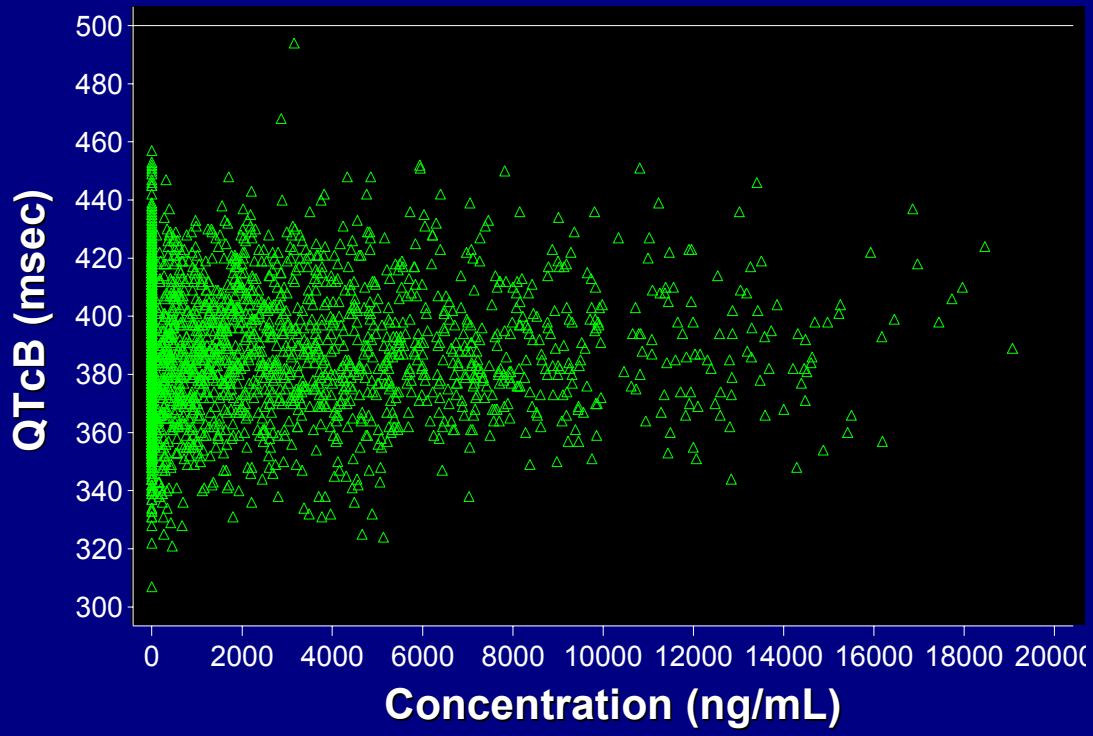
Study Design

- Double-blind, placebo-controlled, three-treatment crossover study
- Randomized treatment sequence (N = 72 subjects)
  - Placebo, 400 mg ATV, 800 mg ATV
- 6 day treatment period with ≥ 14 day washout period
- Serial ECGs and PK samples
- Primary endpoints:
  - QTc and PR intervals and changes from baseline on Day 6 of each treatment period

QTc Introduction

- Heart rate correction of QT
  - Bazett formula: $QTcB = QT / RR^{1/2}$
  - Fridericia formula: $QTcF = QT / RR^{1/3}$
- Mean ΔHR ↑ 3.5 beats/min at 400 mg ATV
  ↑ 8.2 beats/min at 800 mg ATV
- QTc assessments
  - Mean change from baseline
  - Individual subjects with prolonged QTc
  - Concentration-dependence of QTc changes

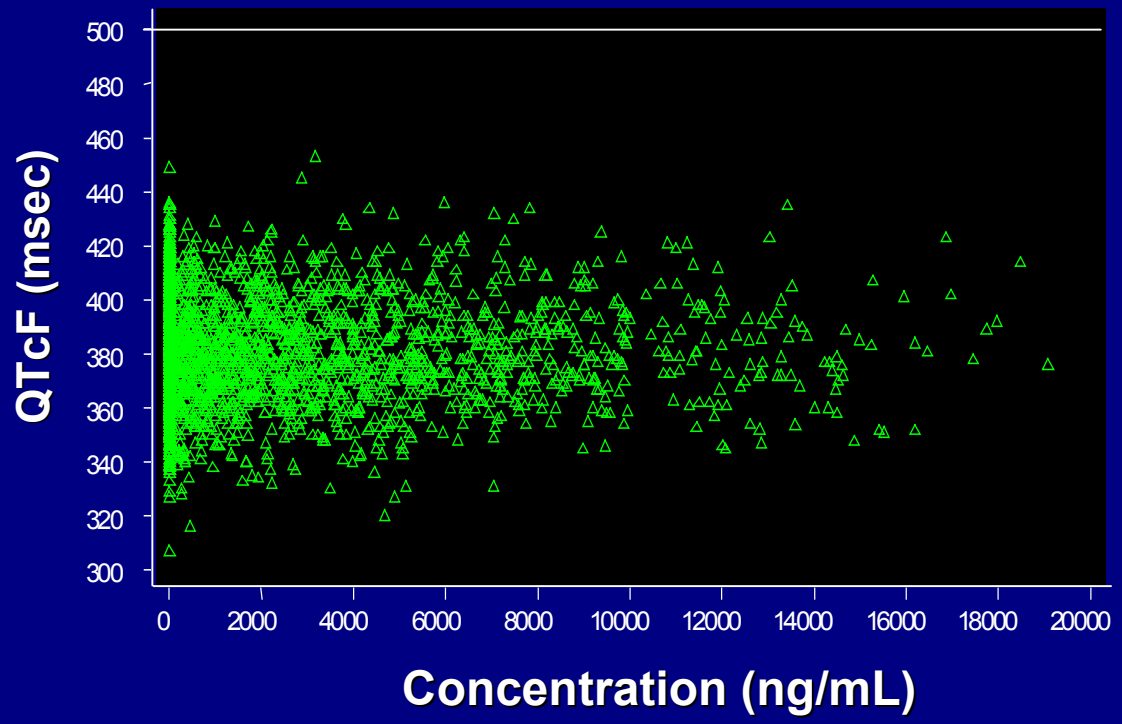
BMS-076
QTc Data (using Bazett's Formula)



ECG Parameter	Treatment		
	Placebo N = 67	ATV 400 N = 65	ATV 800 N = 66
ΔQTcB Avg (msec), Mean (SD)	-3 (10)	-3 (10)	3 (13)
ΔQTcB Max (msec), Mean (SD)	17 (18)	14 (17)	21 (22)
ΔQTcB Tmax (msec), Mean (SD)	-15 (20)	-17 (18)	-4 (22)
QTcB > 500 msec, N	0	0	0
ΔQTcB > 60 msec, N	1	0	3

BMS-076

QTc Data (using Fridericia's Formula)



ECG Parameter	Treatment		
	Placebo N = 67	ATV 400 N = 65	ATV 800 N = 66
ΔQTcF Avg (msec), Mean (SD)	-4 (8)	-6 (8)	-5 (11)
ΔQTcF Max (msec), Mean (SD)	11 (13)	6 (13)	9 (17)
ΔQTcF Tmax (msec), Mean (SD)	-9 (17)	-15 (13)	-8 (17)
QTcF > 500 msec, N	0	0	0
ΔQTcF > 60 msec, N	0	0	0

Comparator Studies of QTc Data in HIV-infected Subjects

QTcF (msec)	QTc Intervals[a]	
	ATV[b] N = 864	Comparators[c] N = 629
Males	N = 609	N = 454
451 - 500	2	2
> 500	0	0
Females	N = 255	N = 175
471 - 500	0	0
> 500	0	0

[a]Includes data from BMS-041, BMS-034, BMS-043, BMS-045
[b]In study BMS-045, ATV is co-administered with either ritonavir or saquinavir
[c]Comparators included nelfinavir, lopinavir/ritonavir, ritonavir, and efavirenz

Summary QTc Interval

QTc Interval

- No concentration-dependent effect of ATV on QTcF
- No QTcF $>$ 500 msec or ΔQTcF $>$ 60 msec
- QTc results comparable to comparator drugs

PR Introduction

- Clinical significance of AV block
  - 1° AVB (PR > 200 msec)
    - Asymptomatic, no change in heart rate
  - 2° AVB or 3° AVB
    - Symptoms related to ventricular rate
- PR assessments
  - Mean change from baseline
  - Individual subjects with prolonged PR
  - Dose-dependence of PR prolongation

BMS-076

Maximum PR Interval Data

ECG Parameter	Treatment		
	Placebo N = 67	ATV 400 N = 65	ATV 800 N = 66
Δ PR Max (msec), Mean (SD)	13 (11)	24 (15)	60 (25)
1° AV Block, N (%)	1 (1)	9 (14)	39 (59)
2° or 3° AV Block, N (%)	0	0	0

PR Interval Prolongation Similar for ATV and Comparators

PR Interval (msec)	Number with AV Block (%)[a]			
	ATV[b] N = 864	NFV[c] N = 48	EFV[d] N = 329	LPV / RTV[e] N = 252
1° AV Block, N (%)	44 (5)	5 (10)	10 (3)	13 (5)
2° or 3° AV Block, N (%)	0	0	0	0

[a]Includes data from BMS-041, BMS-034, BMS-043, BMS-045
[b]In study BMS-045, ATV is co-administered with either ritonavir or saquinavir
[c]Comparator for study BMS-041
[d]Comparator for study BMS-034
[e]Comparator for studies BMS-043 and BMS-045

Summary PR Interval

PR Interval

- Dose-related PR prolongation
- PR prolongation limited to 1st-degree AV block (with rare exceptions)
- Incidence of PR prolongations comparable between ATV and comparators

Conclusions
Cardiac Electrophysiology

- ATV has no effect on the QTc interval
- ATV has manageable effects on the PR interval that are comparable to several other HIV drugs
- As with other PIs, caution advised when ATV is co-administered with drugs known to prolong the QTc or PR intervals that are metabolized by CYP3A4

Characterization of Hyperbilirubinemia

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Laboratory Bilirubin Elevations

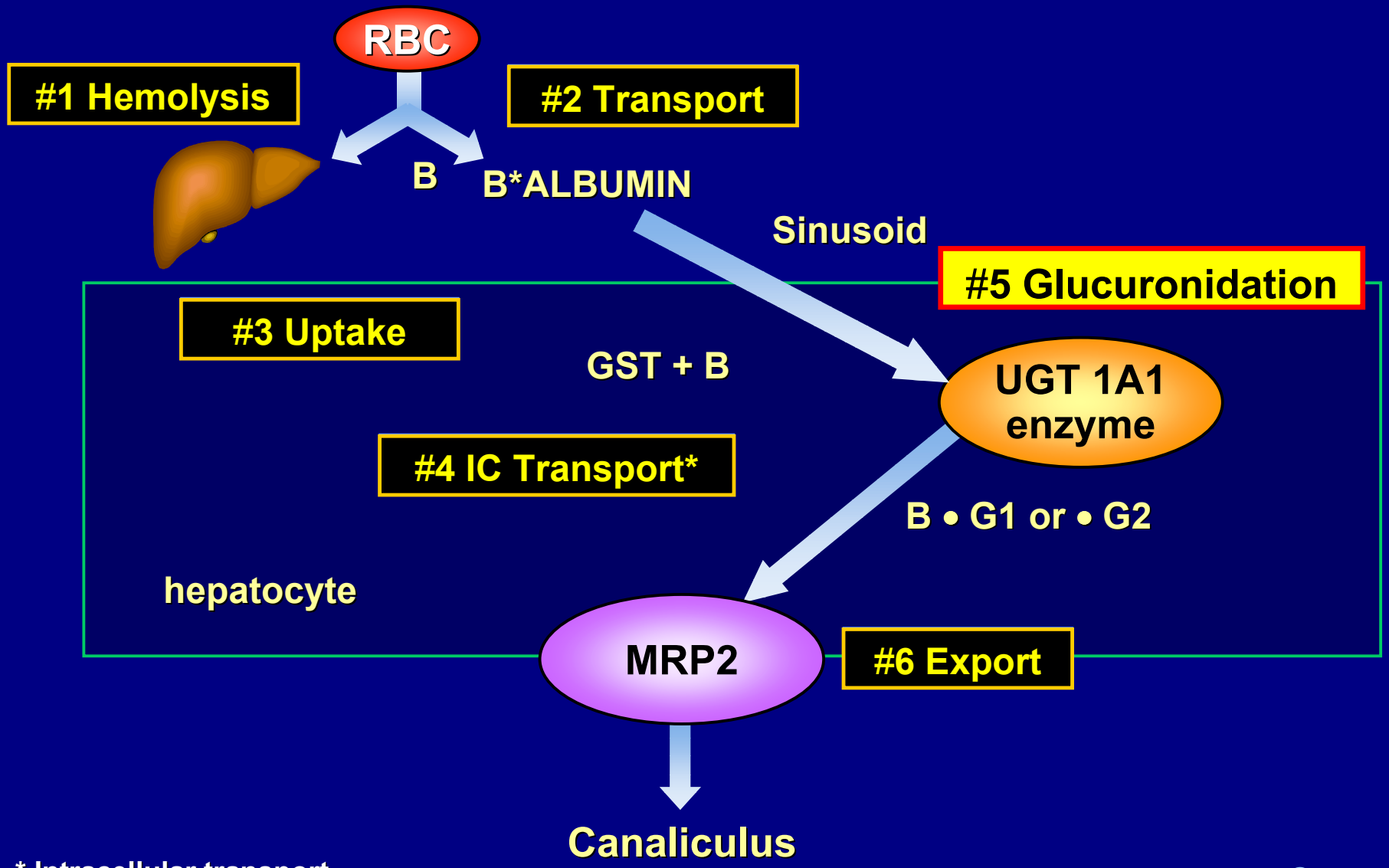
Total bilirubin elevations identified early in ATV clinical development

- Principally unconjugated bilirubin
  - Using HPLC – entirely unconjugated
- ~ 50% Grade 1-2 ($\leq$ 2.5 x ULN)
- ~ 25% Grade 3 (2.6 – 5 x ULN)
- ~ 5% Grade 4 ($>$ 5 x ULN)
- Reversible within days

Atazanavir Bilirubin Elevations

- Review mechanisms of bilirubin production
  - UGT 1A1 enzyme inhibition as seen with PI indinavir
  - Related to benign inherited condition, Gilbert's Syndrome
- Description of clinical manifestation
  - No relationship to hepatic toxicity
    - Includes large number of hepatitis co-infection
  - Clinical signs and symptoms infrequent
- Patient Management plan

Bilirubin Production and Metabolism



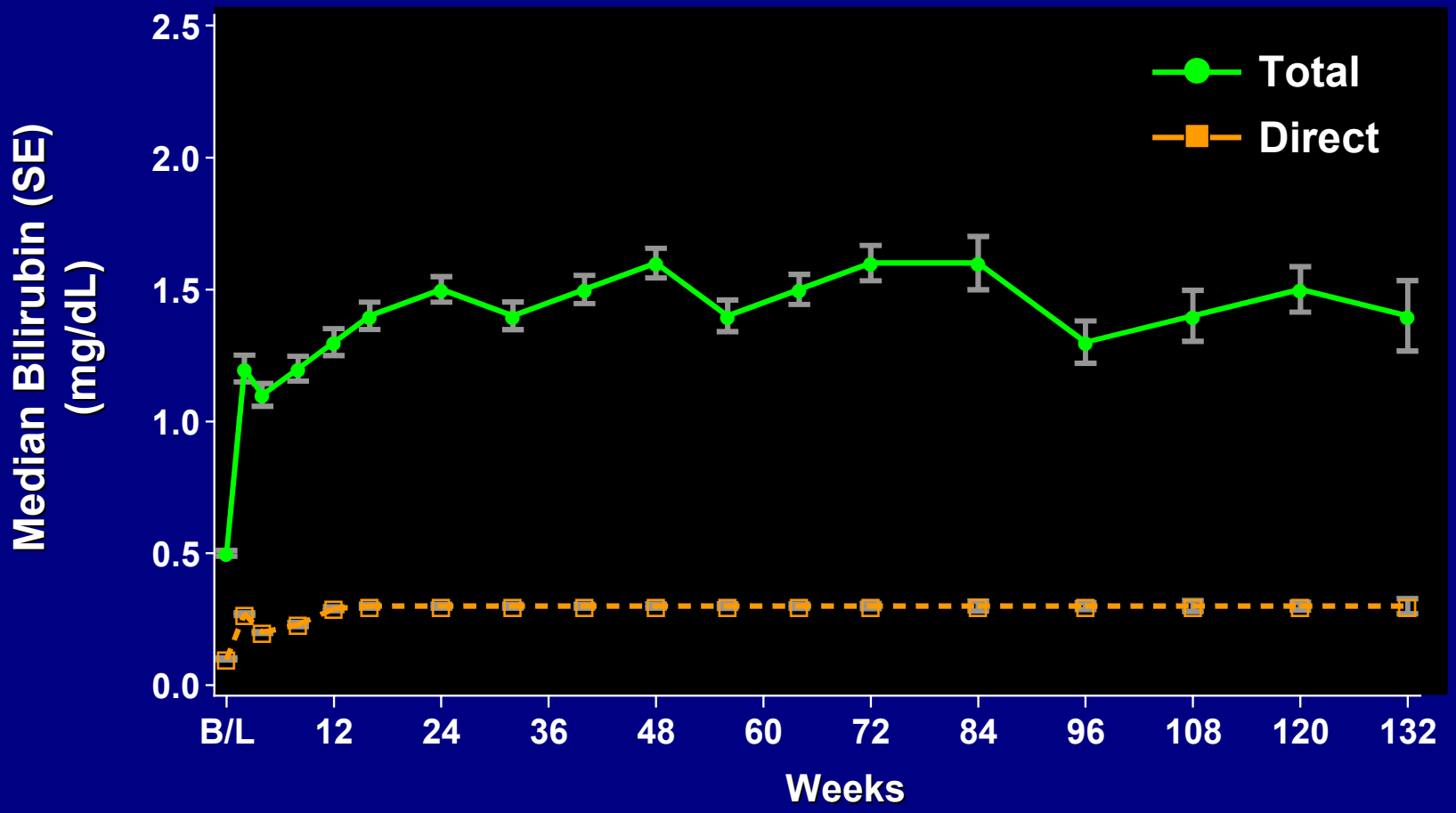
* Intracellular transport

UGT 1A1 Inhibition Mechanism for Bilirubin Elevations

- Common UGT 1A1 polymorphism is responsible for Gilbert's Syndrome
- ATV inhibition of UGT 1A1 – same mechanism as indinavir*
- UGT 1A1 genotype predicts bilirubin level in patients on ATV

*Zucker S.D., Qin X, et. al. Mechanism of indinavir-induced hyperbilirubinemia. *Proc. Natl. Acad. Sci. USA*, Vol. 98, Issue 22, 12671-12676, October 23, 2001.

Total and Direct Bilirubin
ATV 400 mg Treatment-Naïve Subjects (N = 683)

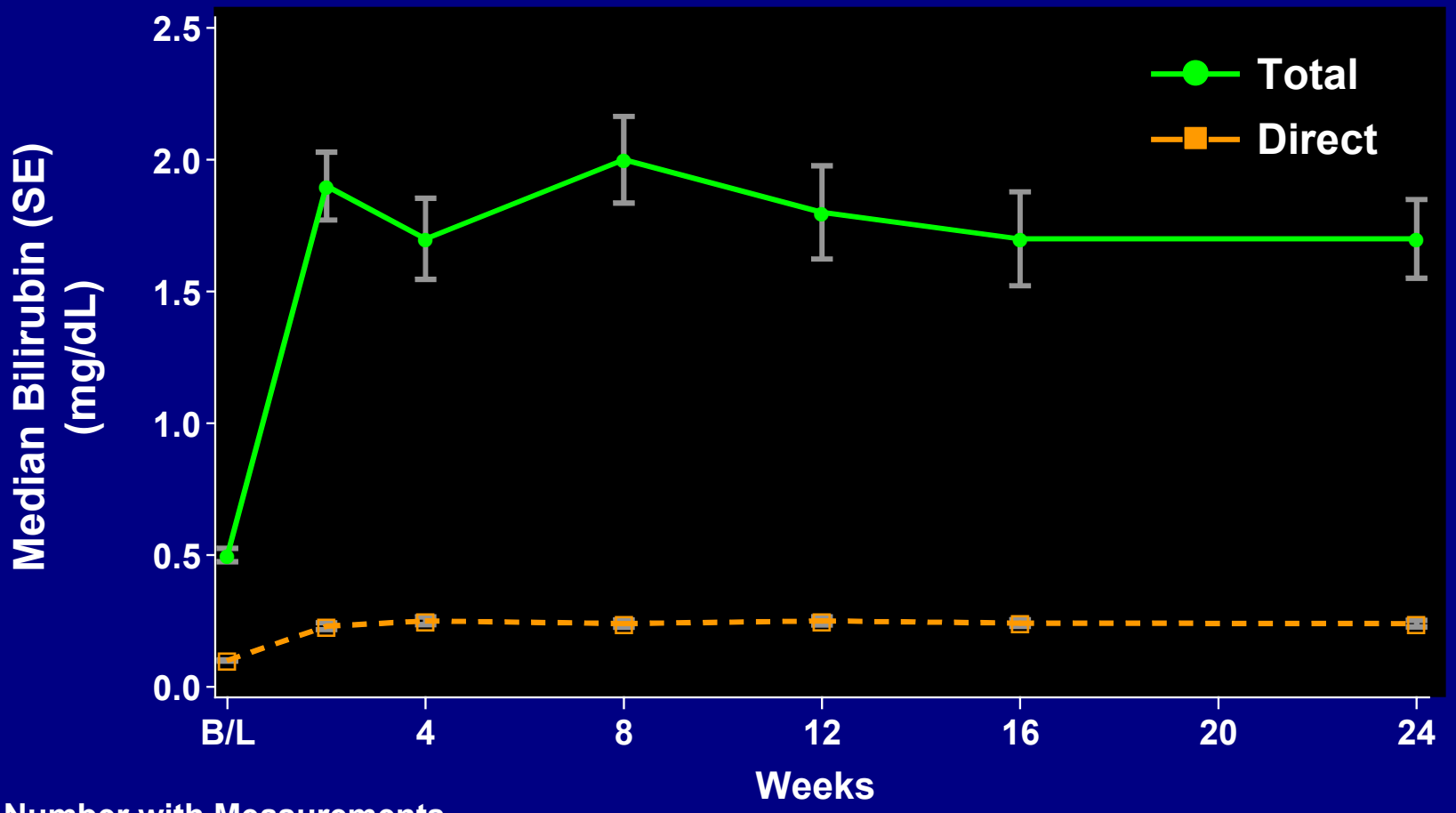


Number with Measurements												
Total:	683	650	628	615	572	471	376	217	194	182	167	76
Direct:	679	649	627	615	572	470	376	217	194	183	167	76

Studies BMS-034, BMS-007 and BMS-008

BMS-045

Total and Direct Bilirubin
ATV 300 / RTV 100 Subjects (N = 119)



Number with Measurements							
Total:	119	117	118	115	110	114	112
Direct:	119	117	118	115	110	114	112

Total Bilirubin Elevations and Clinical Events

- Naïve subjects BMS-034
  - 6% bilirubin > 5 x ULN
  - 11% jaundice
  - 11% scleral icterus
  - < 1% D/C due to hyperbilirubinemia
- Experienced subjects ATV 300/RTV
  - 9% bilirubin > 5 x ULN
  - 15% jaundice
  - 10% scleral icterus
  - 0 D/C due to hyperbilirubinemia

BMS-034
Treatment-Naïve Subjects
Transaminase and Bilirubin Elevations Not Associated
ATV + ZDV / 3TC

ALT (SGPT)	Bilirubin Grade 0 - 2 (≤ 2.5 X ULN) N = 271	Bilirubin Grade 3 - 4 (> 2.5 X ULN) N = 131
Grade 0 - 2 (≤ 5 X ULN)	262 (96%)	125 (95%)
Grade 3 - 4 (> 5 X ULN)	9 (4%)	6 (5%)

Median follow-up: 52 weeks

Grade 3 – 4 ALT Elevations In Phase III ATV Studies

	Naïve Subjects		Experienced Subjects				
	BMS-034		BMS-043		BMS-045		
	ATV 400 N = 404	EFV N = 401	ATV 400 N = 144	LPV / RTV N = 146	ATV 300 / RTV 100 N = 119	ATV 400 / SQV N = 110	LPV / RTV N = 118
ALT (SGPT)	4%	3%	6%	1%	3%	4%	3%

Median Time on Therapy: BMS-034 (52 weeks); BMS-043 (24 weeks); BMS-045 (24 weeks)

Grade 3 – 4 ALT Elevations in Co-Infected Subjects ATV vs 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)

BMS-008, BMS-034, and BMS-043

Unconjugated Hyperbilirubinemia Conclusions

- Frequency and magnitude thoroughly described
  - Not associated with hepatotoxicity based on mechanism and clinical ALT data
  - Benign and manageable
  - Frequency of dose-limiting hyperbilirubinemia / jaundice not different from AE profile for other ARVs
  - No evidence for long-term sequelae

Hyperbilirubinemia Management

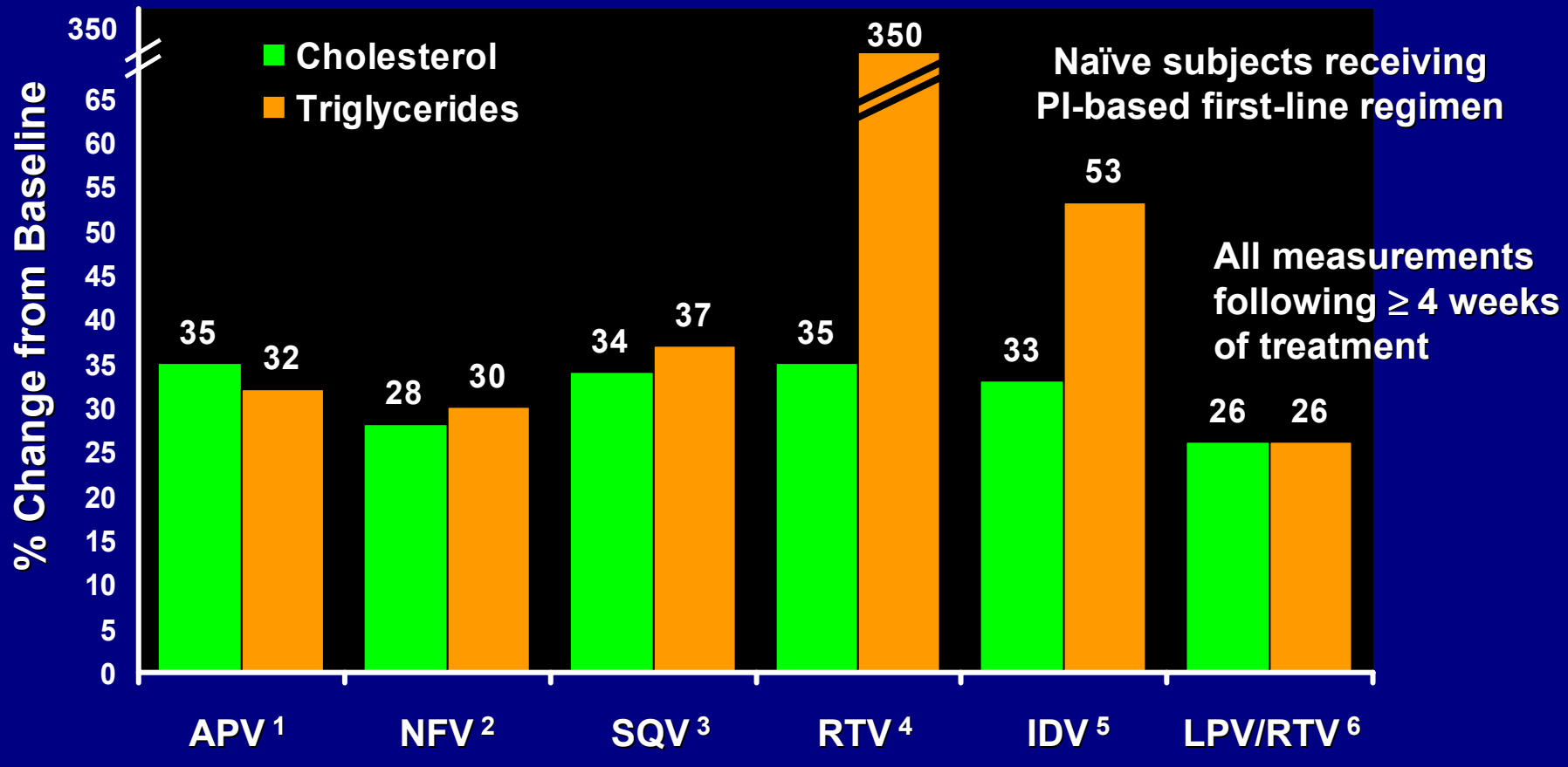
- Physician and Patient Education
  - What to expect
  - Extend upon the indinavir experience
- LFT monitoring above standard of care not anticipated
- Recommendation
  - Alternative therapy should be considered if patients experience total serum bilirubin concentrations > 5 x ULN

Characterization of Lipid Profile

Introduction
Atazanavir Lipid and Metabolic Profile

- Lipid and metabolic problem with current PIs
- Lower cholesterol and triglycerides for ATV
  - Magnitude, durability assessed
  - Consistent data in treated and naïve subjects and ARV combinations
- Reduced need for lipid lowering therapy
- CV risk related to cholesterol and metabolic effects
  - Established for general population
  - Data in HIV and HAART evolving
  - NCEP recommended for HIV

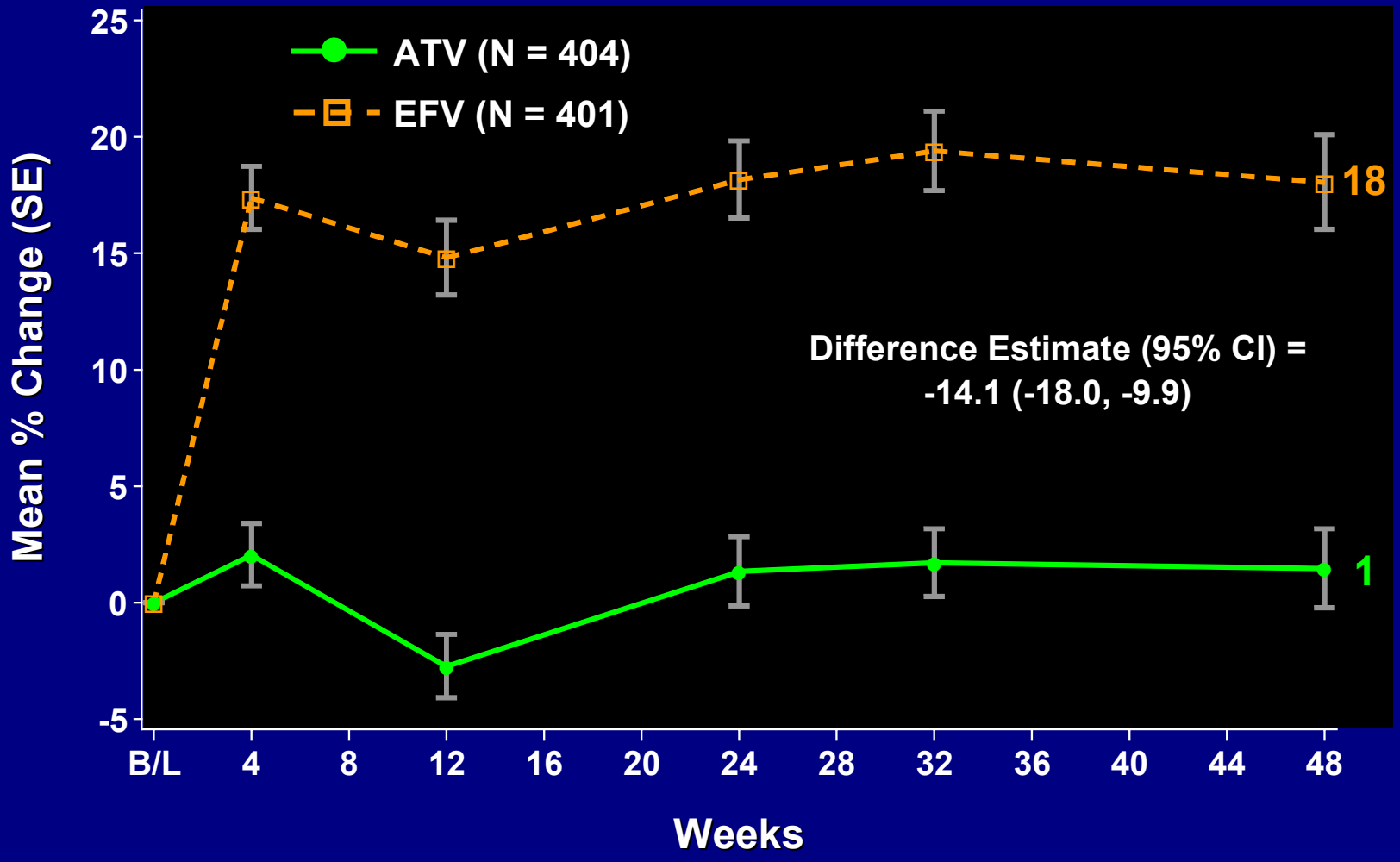
Other PI Regimens Increase Cholesterol and Triglyceride



[1] Drug Facts and Comparisons, April 2001; [2] Cahn P *et al*. IAS July 2001; [3] Moyle, Baldwin 1999; [4] Danner *et al*. 1995; [5] Rockstroh *et al*. 2000; [6] MicroMedEx-DrugDex

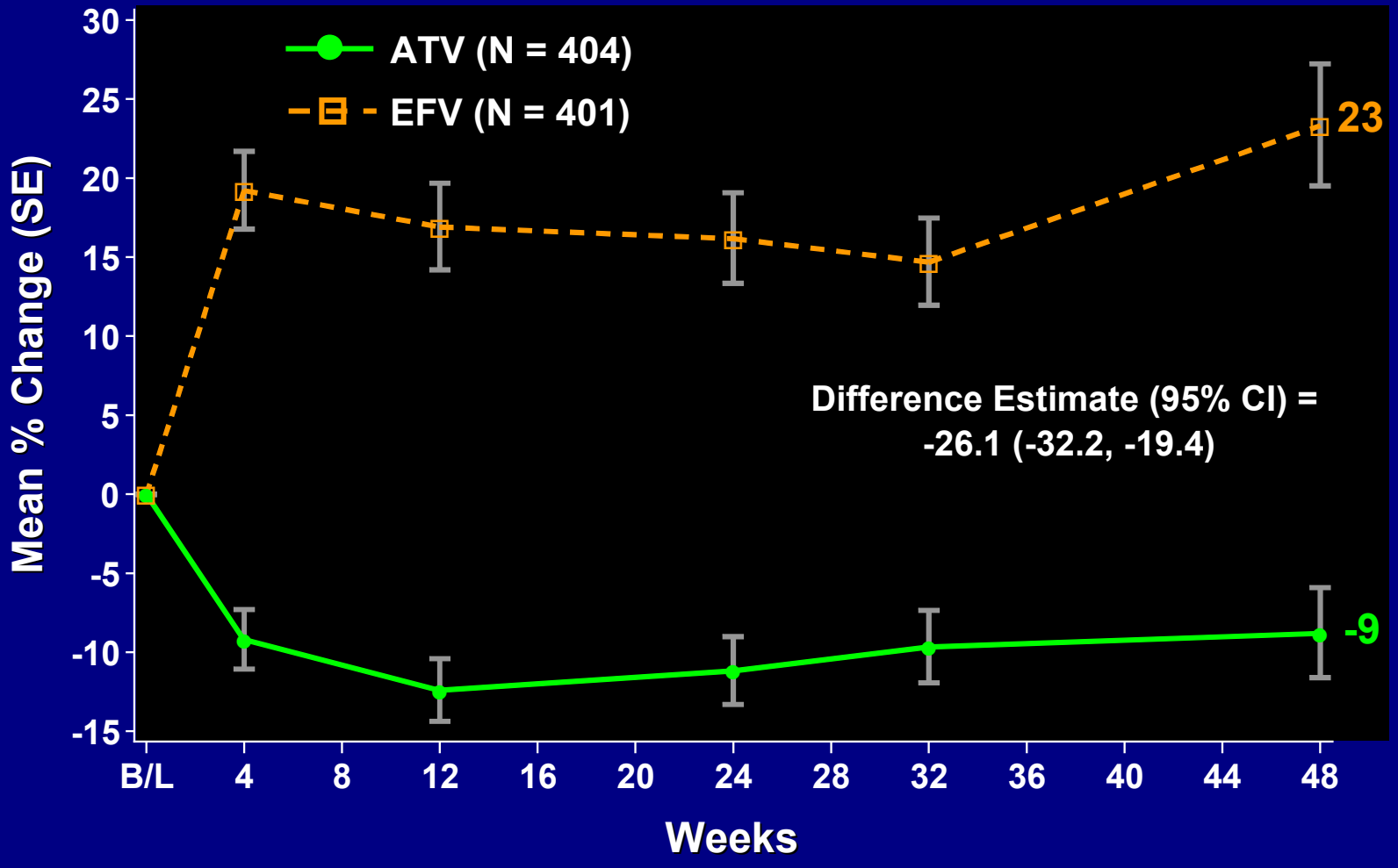
BMS-034

No Effect on LDL-C for ATV: Treatment-Naïve Subjects



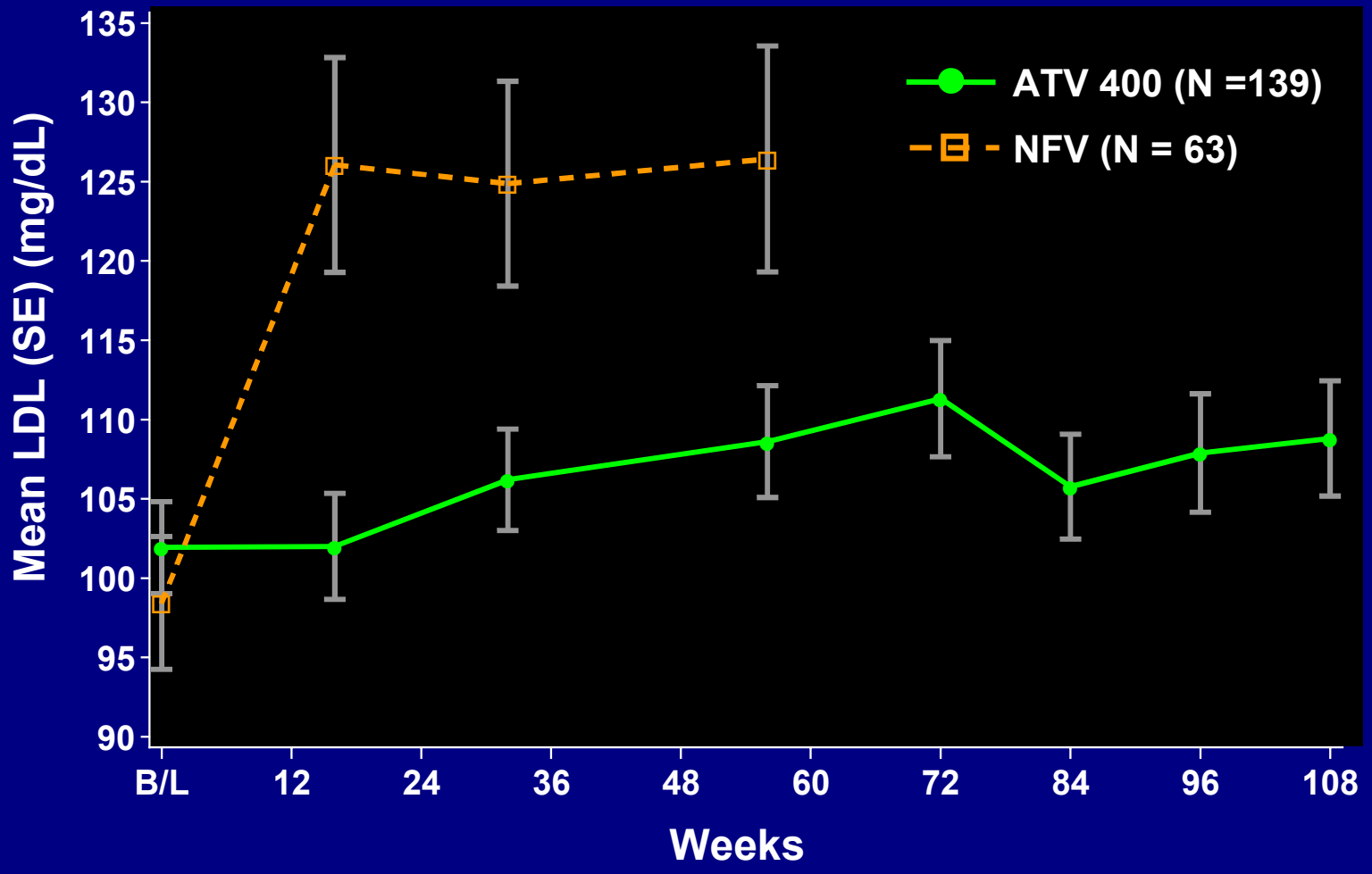
BMS-034

No Effect on Triglycerides for ATV: Treatment-Naïve Subjects



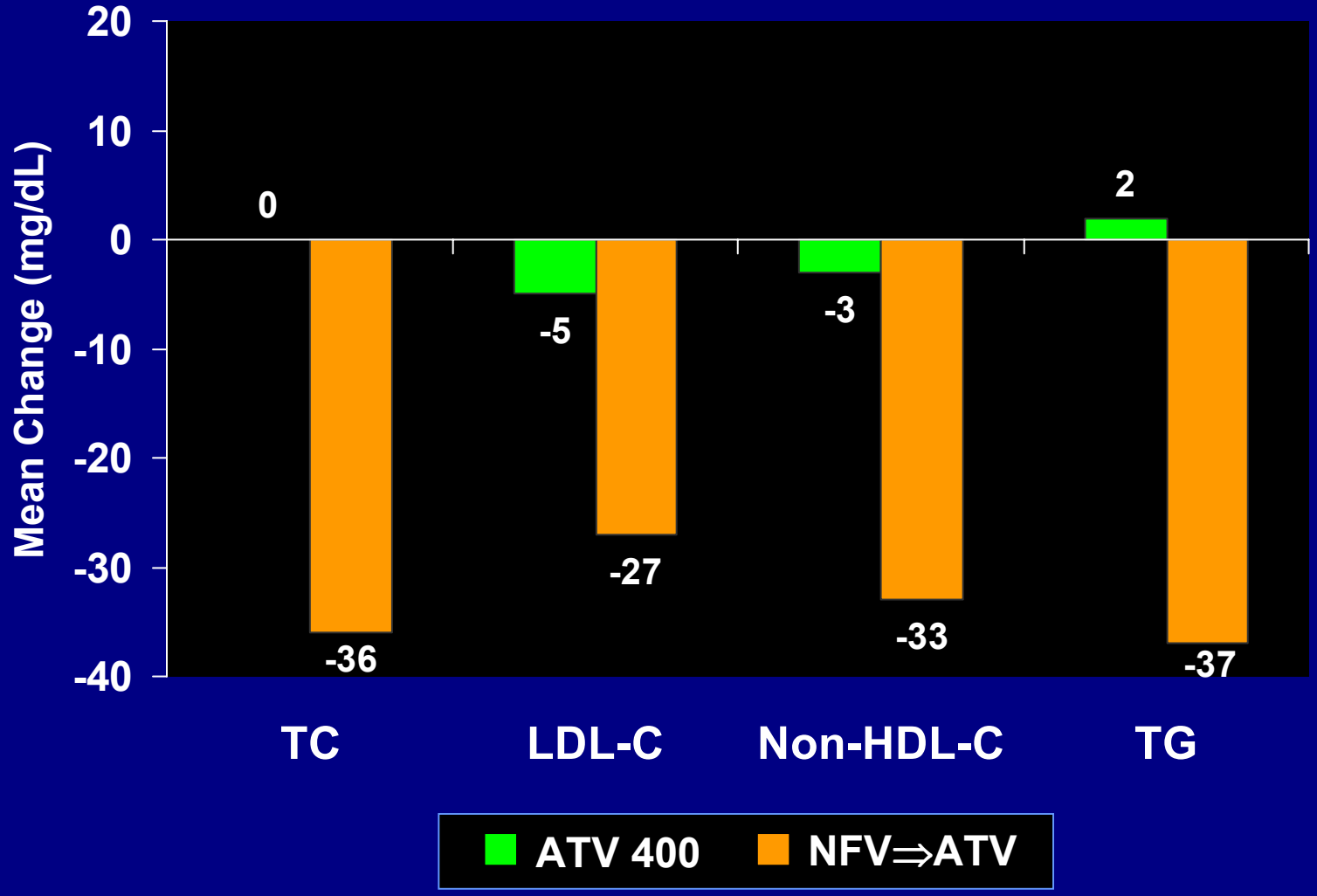
BMS-044

Durability of Lipid-Neutral Effects for ATV: LDL-Cholesterol Results Through 2 Years



BMS-044

Improvement in Lipids After Switch to ATV: Mean Change From Entry to Week 24



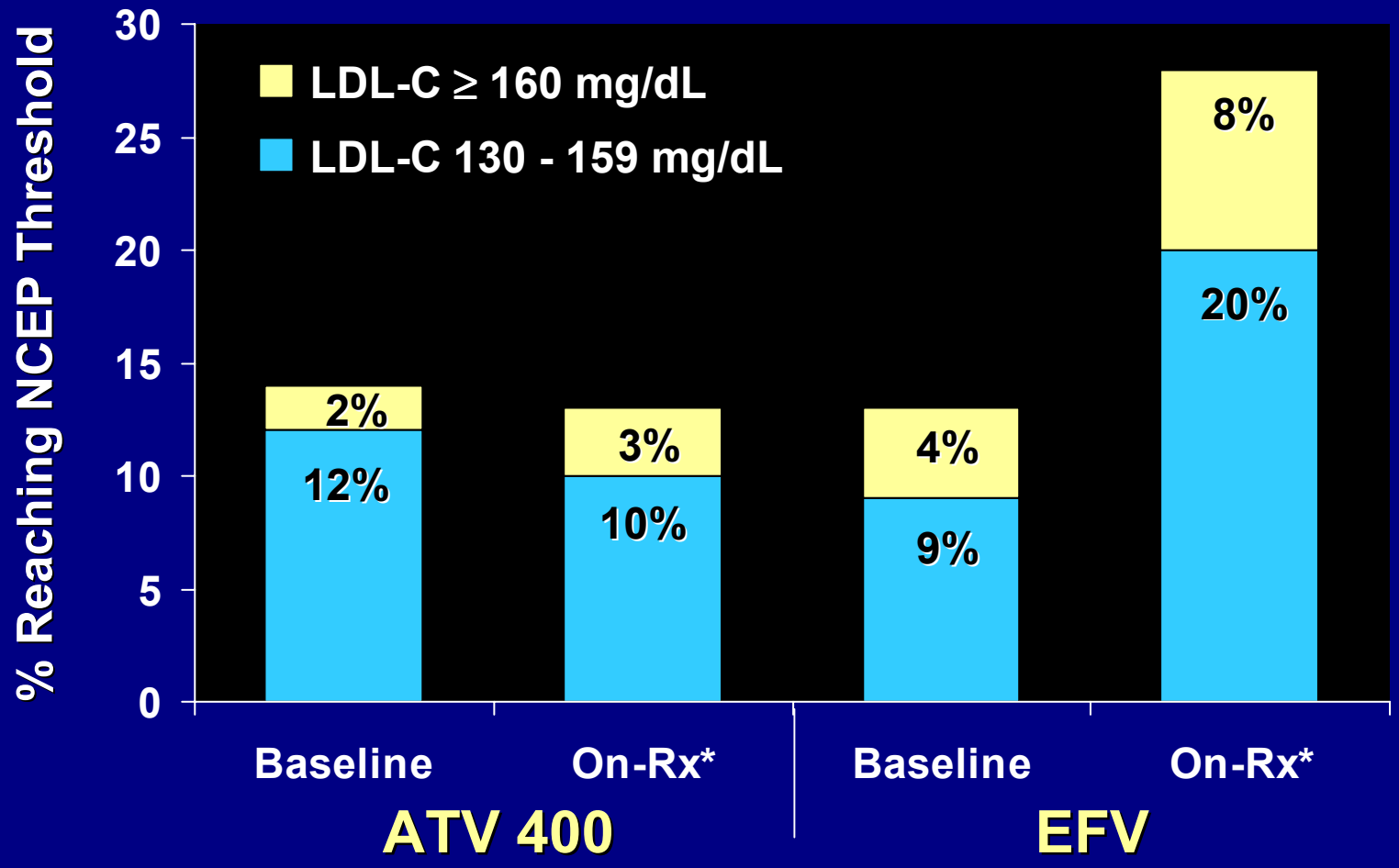
Hyperlipidemia Management for HIV-Infected Individuals

Use NCEP (National Cholesterol Education Program) Adult Treatment Panel III Guidelines

Risk Group	LDL-Cholesterol (mg/dL)	Non-HDL-Cholesterol (mg/dL)
CHD *or* risk equivalent	< 100	< 130
≥ 2 risk factors *and* 10-year risk ≤ 20%	< 130	< 160
0-1 risk factors	< 160	< 190

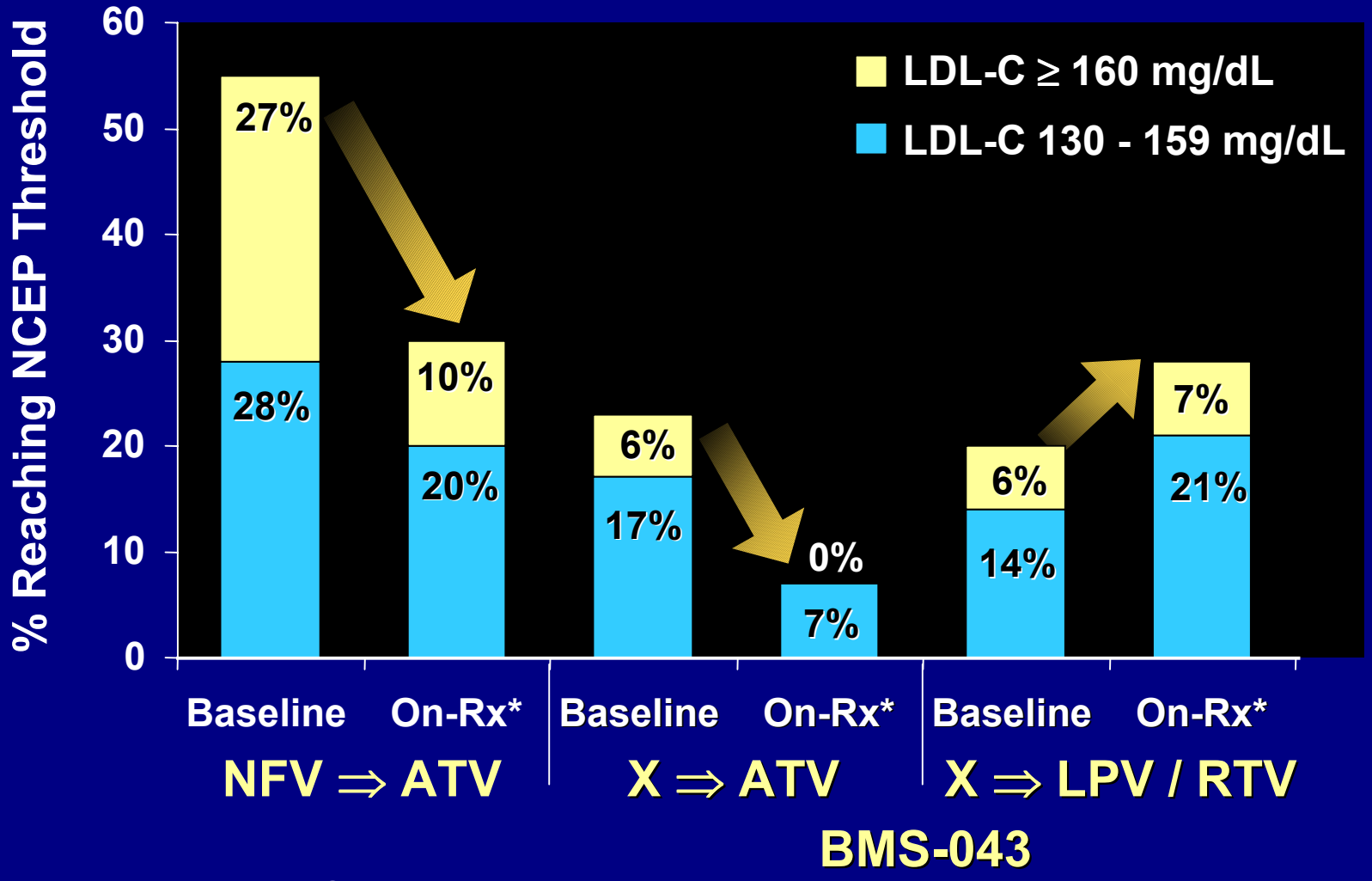
Management of Metabolic Complications Associated with Antiretroviral Therapy for HIV-1 Infection: Recommendations of an International AIDS Society-USA Panel, JAIDS 2002, 31:257-275.

Lipid Lowering Thresholds Based on NCEP Categories for ATV and Comparator – ARV Naïve



* BMS-034 (Week 48)

Lipid Lowering Thresholds Based on NCEP Categories for ATV and Comparator ARV Switch and Experienced Subjects



* BMS-044 (Week 24), BMS-043 (Week 24)

Importance of ATV Metabolic Profile Summary

- Maintaining favorable metabolic profile in HIV is important and challenging
- Problems with other PIs and statins / lipid lowering drugs
  - Statins complicate already complex regimens
  - Introduce potential toxicity and intolerance
  - Introduce potential drug-drug interactions
  - NCEP treatment goals frequently not achieved
    - for triglycerides in particular

Importance of ATV Metabolic Profile Summary

- ATV results in little or no detrimental effects
  - Cholesterol and triglycerides
  - Durable (108 weeks) and consistent results
  - Naïve and experienced, gender, race
  - Variety of companion ARVs
  - Improved lipids achieved after switch to ATV
- Unique benefit of ATV
  - Avoid lipid lowering therapy
  - May avoid unnecessary additional CV risk factor

Conclusion

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Risk-Benefit Assessment: Risks

- Adverse events generally mild
- Hyperbilirubinemia
  - Mild, manageable, and reversible
- Cardiac electrophysiology changes minimal
  - PR prolongation manageable

Risk-Benefit Assessment: Benefits

- Demonstrated antiviral efficacy
- Durable treatment effect
- Favorable lipid profile
- Unique resistance profile
- Once daily 2-pill regimen