CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ARV Therapies and Therapeutic Strategies

Report from the

51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC

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Studies in Antiretroviral Naïve Patients

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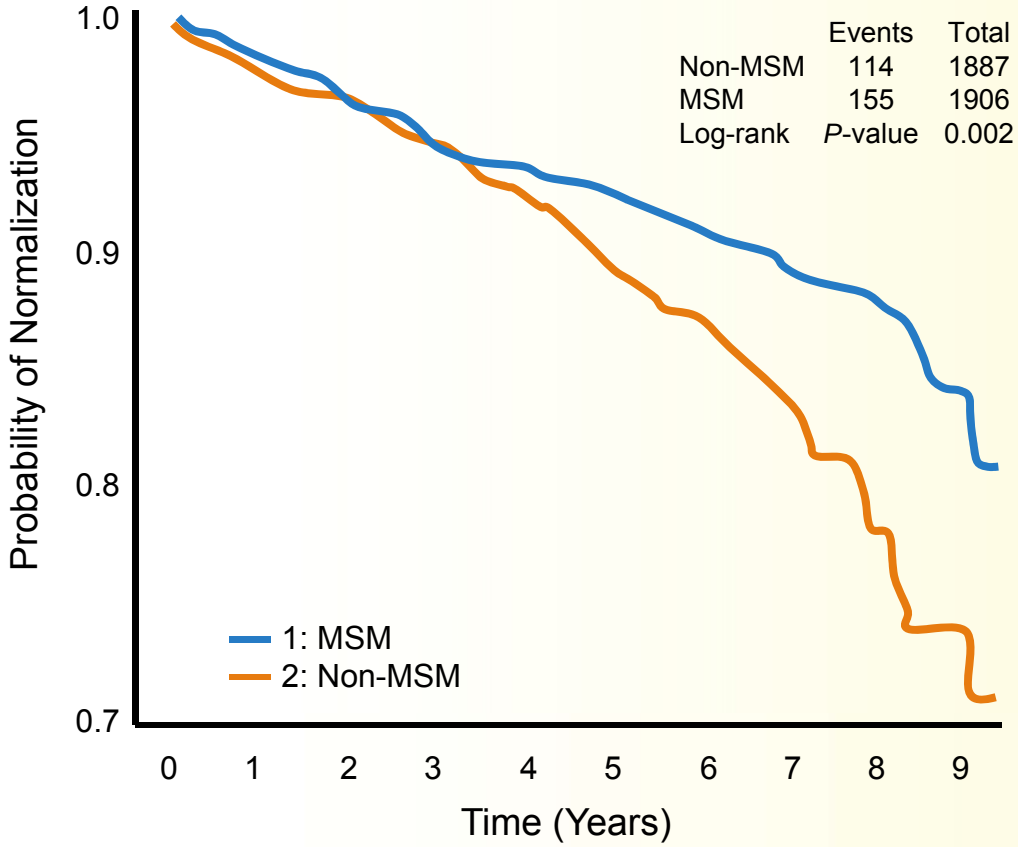
Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC Supported by an educational grant from Merck & Co., Inc.

Impact of CD4:CD8 Ratio Normalization

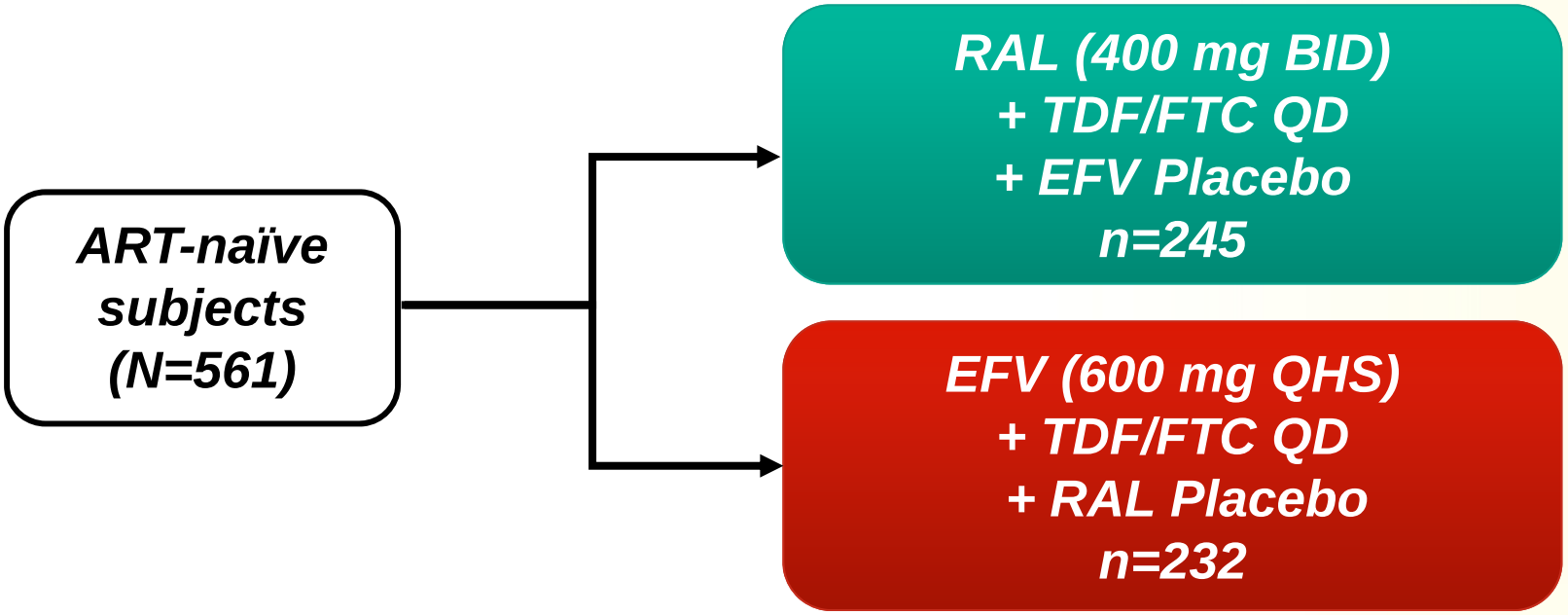
- Canadian Cohort Collaboration (CANOC)
- 4588 individuals (81% men) starting HAART followed 2.86 years (median). 321 (6.9%) normalized during follow-up
- Baseline CD4 <200, higher time-updated HIV VL and MSM significantly associated with failure to normalize



CD4:CD8 normalization NOT associated with lower risk of ADI or death

STARTMRK: RAL vs. EFV at 156 Weeks

Randomized (1:1), double blind



- **HIV RNA >5000 c/mL**
- **Susceptible to EFV, TDF and FTC**

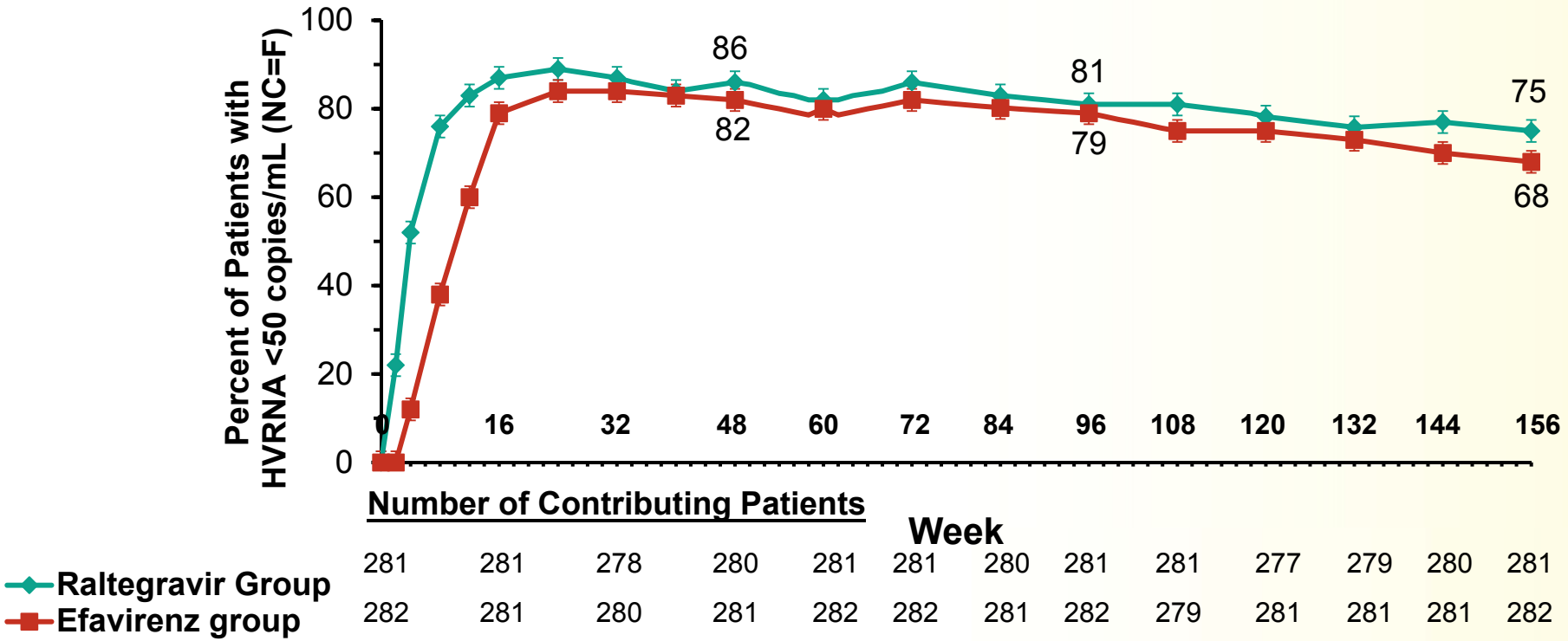
STARTMRK: Baseline Characteristics

	RAL	EFV
Patients Treated	281	282
Age (mean, years)	38	37
% Male	81	82
% Non-White	59	56
vRNA copies/mL (geometric mean)	103,205	106,215
% with vRNA >10^5 copies/mL	55	51
Mean CD4 count (cells/µl)	219	217
% with CD4 ≤200 cells/µl	47	48
% Hepatitis B or C	7	7
% Non-Clade B	21	17

Lazzarin A , et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. H2-790.

STARTMRK: Results through156 Weeks

- RAL provided potent and statistically non-inferior viral suppression compared to EFV, when counting non-completers as failures



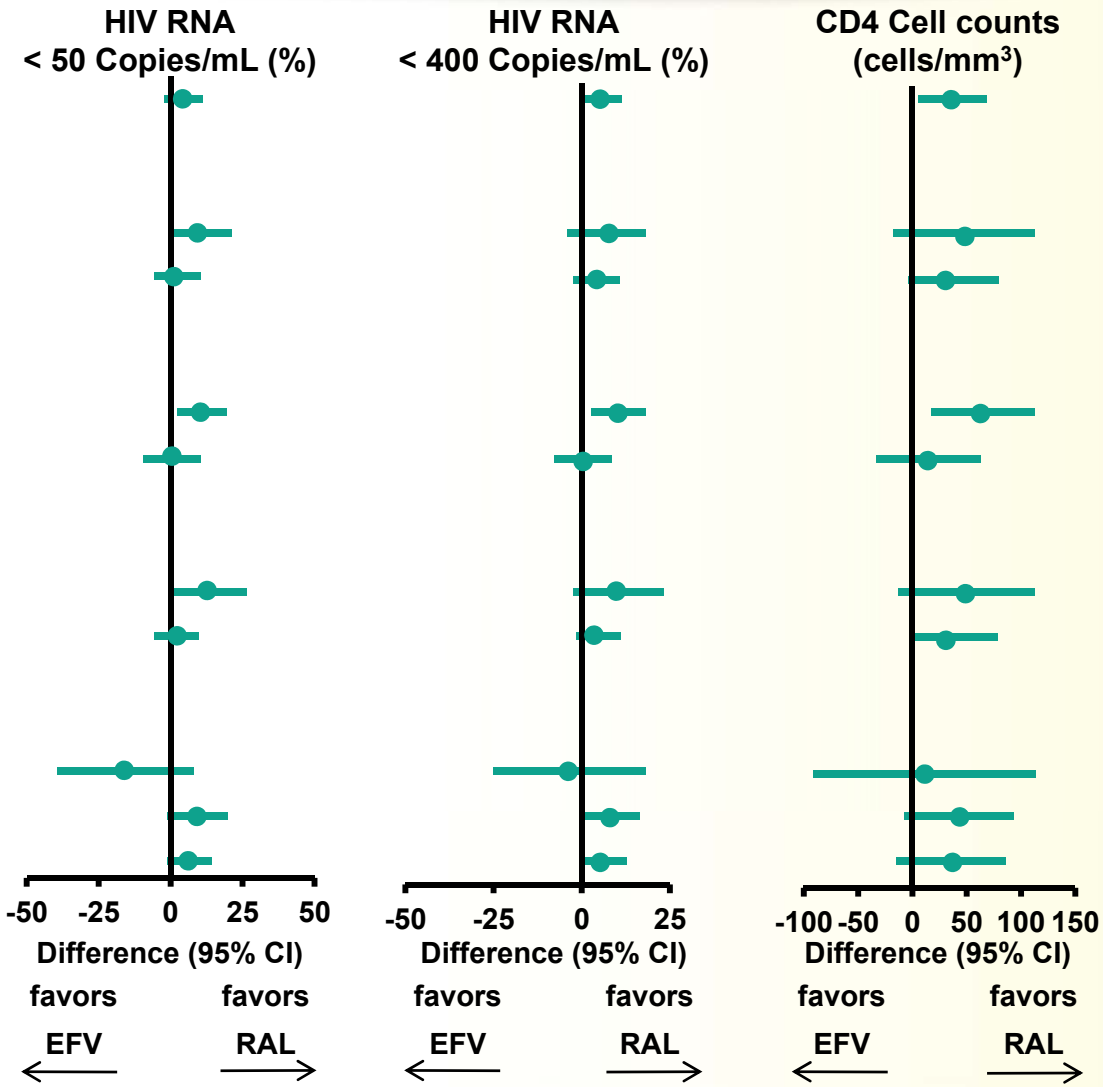
Immunologic: CD4 improvements RAL 332 vs. EFV 295 c/mm^3 (P<0.05)

Rockstroh J, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 542.

STARTMRK: Outcomes by Baseline Viral Load at Week 156

	Virologic Response Rates (vRNA <50 copies/mL) at Week 156		Percent Difference in Response Rates [95% CI]
	Raltegavir Group n/N (% [95% CI])	Efavirenz Group n/N (% [95% CI])	
OVERALL	**212/237 (89 [85, 93])**	**192/227 (85 [79, 89])**	**5 [-1, 11]**
Baseline Plasma vRNA Level [copies/mL]			
≤50, 000	61/65 (94 [85, 98])	55/66 (83 [72, 91])	11 [0, 22]
>50,000 to ≤ 100,000	38/40 (95 [83, 99])	38/45 (84 [71, 94])	11 [-3, 25]
>100,000 to ≤250,000	55/63 (87 [77, 94])	42/49 (86 [73, 94])	2 [-11, 16]
>250,000	58/69 (84 [73, 92])	57/67 (85 [74, 93])	-1 [-14, 12]

STARTMRK: Outcomes by Key Baseline Prognostic Factors at Week 156



Lazzarin A , et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. H2-790.

STARTMRK: Outcomes by Key Baseline Prognostic Factors at Week 156

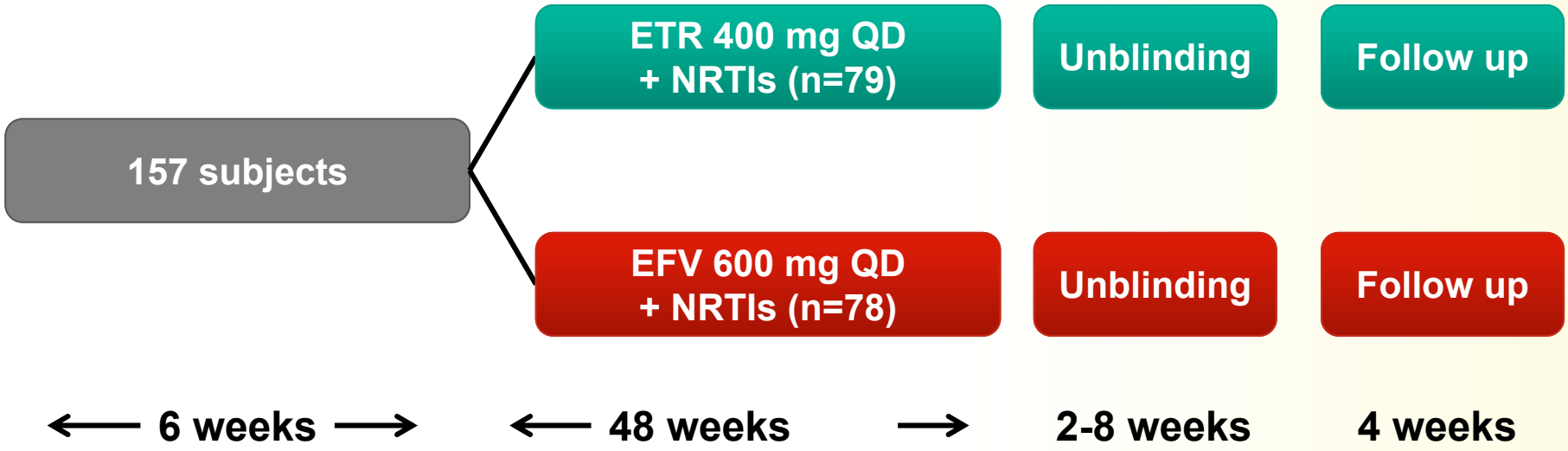
No differences (virological outcomes) by race, gender, age, region

	Virologic Response Rates at Week 156 (vRNA <50 copies/mL)		Percent Difference in Response Rates [95% CI]
	Raltegavir Group n/N (%)	Efavirenz Group n/N (%)	
OVERALL	212/237 (89)	192/227 (85)	5 [-1, 11]
HIV-1 Subtype			
Clade B	162/184 (88)	154/182 (85)	3 [-4, 11]
Non-clade B	47/50 (94)	34/40 (85)	9 [-4, 24]
Hepatitis Co-infection			
B and/or C	11/12 (92)	11/13 (85)	7 [-24, 37]
Neither B or C	201/225 (89)	181/214 (85)	5 [-2, 11]

SENSE: Detection of Baseline Resistance and HIV RNA Suppression to Week 48

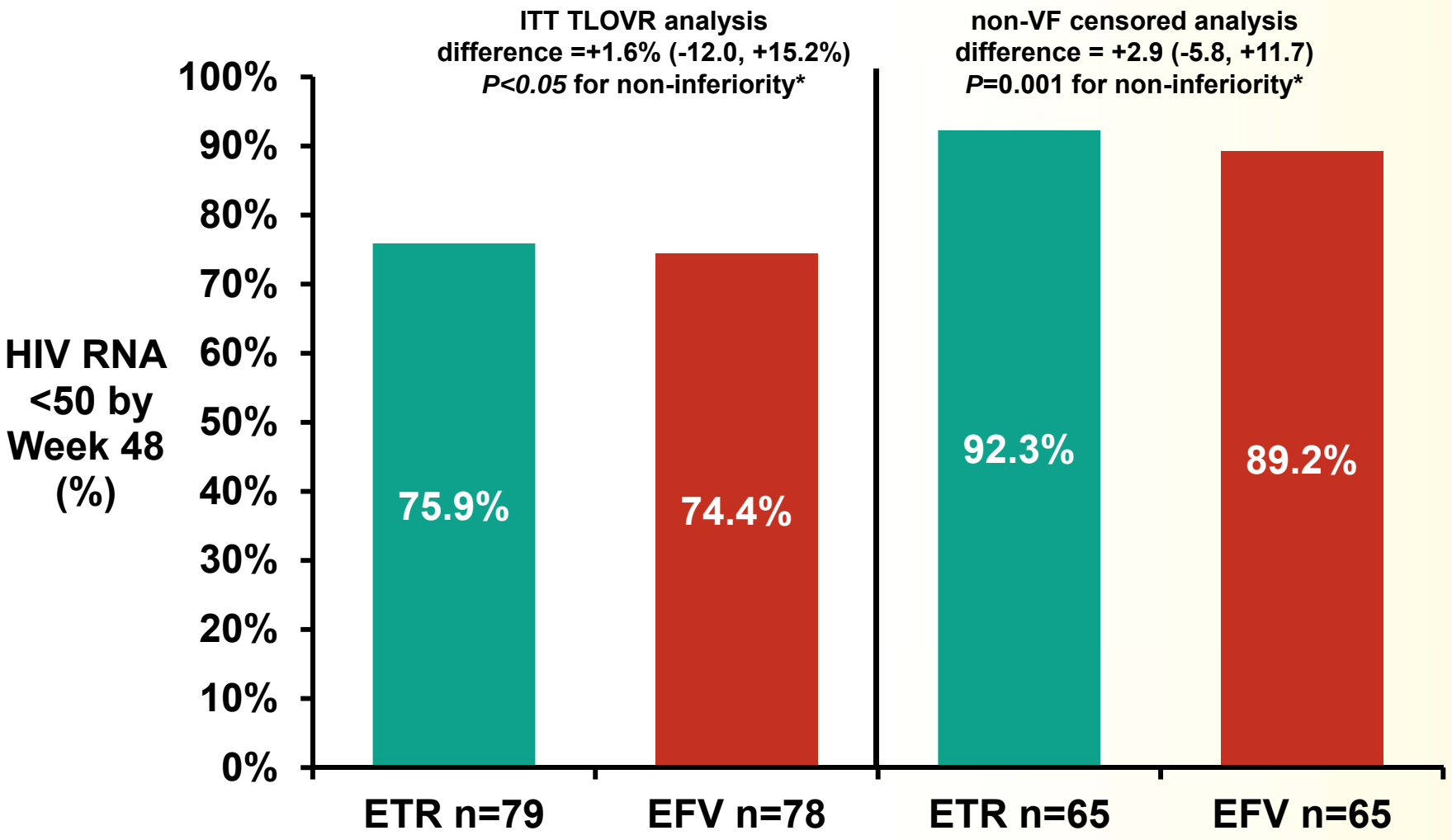
Inclusion: Treatment naïve, HIV RNA >5,000 copies/mL

No genotypic mutations to NRTIs, NNRTIs or PIs (Bennett lists)
Predicted Phenotypic sensitivity to NNRTIs and selected NRTIs (Virtual Phenotype)



Double-blinded, active controlled to Week 48
Two investigator-selected NRTIs (AZT+3TC; ABC+3TC; TDF+FTC)
Primary endpoint: neuropsychiatric adverse events up to Week 12

SENSE: Efficacy Results



SENSE: Baseline Resistance Mutations

	ETR arm (n=79)	EFV arm (n=78)
Patients with IAS-USA NNRTI mutations (2010)*	**12 (15.2%)**	**4 (5.1%)**
V90I (in ETR algorithm, score = 1)	5	1
V106I (in ETR algorithm, score = 1.5)	3	1
V108I (not in ETR algorithm)	1	0
E138A (in ETR algorithm, score = 1.5)	3	2
Patients with IAS-USA/WHO NRTI mutations (protocol violators)	**6 (5%)**	**0 (0%)**
M41L	2	0
A62V	3	0
L210W	1	0
T215C/D/E	3	0
K219R	1	0
Patients with IAS-USA/WHO NNRTI mutations	**1 (1.3%)**	**0 (0%)**
K103N*	1	0
Patients with IAS-USA/WHO NRTI mutations	**1 (1.3%)**	**1 (1.3%)**
M184V*	1	1

detected by allele-specific PCR at the assay cut-off [0.9% K103N; 0.5% M184V]

Garetti A , et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. H1-373.

SENSE: Outcomes for Patients with Baseline NNRTI Resistance Mutations

Patient (Subtype, NRTIs)	Mutations		LFMA	HIV RNA Copies/mL		
	NRTI	NNRTI		Baseline	Week 48	Outcome
EFV1 (B, ABC/3TC)	None	E138A/E	None	247,000	<50	Responder
EFV2 (F1, ABC/3TC)	None	E138A	None	22,100	<50	Responder
EFV3 (B, TDF/FTC)	None	V90I	None	136,000	<50	Responder
EFV4 (F, ABC/3TC)	None	V106I	None	5,080	No data	d/c day 2 AE
EFV5 (C, TDF/FTC)	None	None	M184V	251,000	<50	Responder

Patient (Subtype, NRTIs)	Mutations		LFMA	HIV RNA Copies/mL		
	NRTI	NNRTI		Baseline	Week 48	Outcome
ETR1 (B, TDF/FTC)	None	E138A/E	K103N	138,000	<50	Responder
ETR2 (B, ABC/3TC)	None	E138A	None	22,800	<50	Responder
ETR3 (B, TDF/FTC)	None	E138A	None	56,900	<50	Responder
ETR4 (F1, TDF/FTC)	None	V106I	None	2,050,000	<50	Responder
ETR5 (B, ABC/3TC)	None	V106I	None	21,900	<50	Responder
ETR6 (B, TDF/FTC)	None	V106I	None	67,400	<50	Responder
ETR7 (B, TDF/FTC)	None	V90I	None	11,100	<50	Responder
ETR8 (B, ABC/3TC)	None	V90I	None	219,000	<50	Responder
ETR9 (CRFAG, ZDV/3TC)	None	V90I	None	153,000	<50	Responder
ETR10 (B, ABC/3TC)	None	V108I	None	34,100	<50	Responder

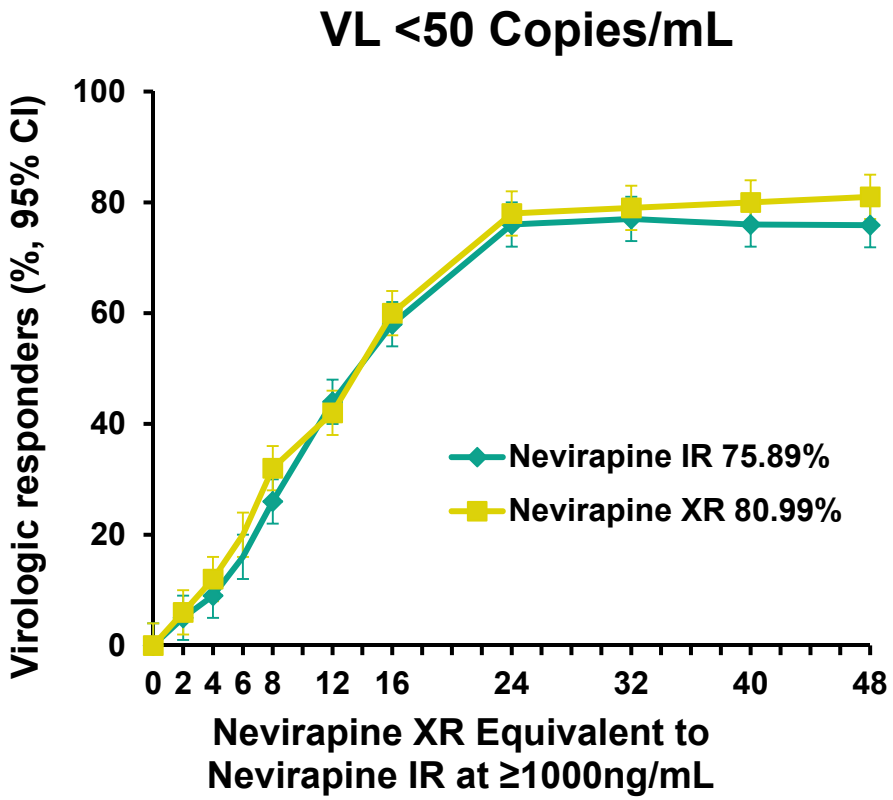
Garetti A , et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. H1-373.

SENSE: Outcomes for Patients with Baseline NRTI Resistance Mutations, Etravirine Arm

Patient (Subtype, NRTIs)	Mutations		LFMA*	HIV RNA		
	NRTI	NNRTI		Baseline	Week 48	Outcome
ETR11 (B,ABC/3TC)	M41L L210W T215C	None	None	45,400	<50	Responder
ETR12 (B, TDF/FTC)	M41L T215D K219R	None	None	787,000	<50	Responder
ETR13(A1,ABC/3TC)	A62V	V90I	None	13,100	<50	Responder
ETR14** (CRFAE, ZDV/3TC)	A62V	None	None	185,000	<50	Responder
ETR15 (CRFAE, ZDV/3TC)	A62V	V90I	None	554,000	d/c bl	Lost to follow up
ETR16 (B, TDF/FTC)	T215E	None	None	2,000,000	d/c wk2^	<50 on LPV/r
ETR17 (CRFAE, TDF/FTC)	None	None	**M184V**	30,800	<50	Responder

VERxVE: Nevirapine XR QD vs. Nevirapine BID IR

- Double-blind, double-dummy, non-inferiority study. 1:1 randomization to 400 mg XR QD vs. 200 mg IR BID after a 14-day IR lead-in 200 mg QD dose (given to all patients); FTC/TDF fixed-dose background



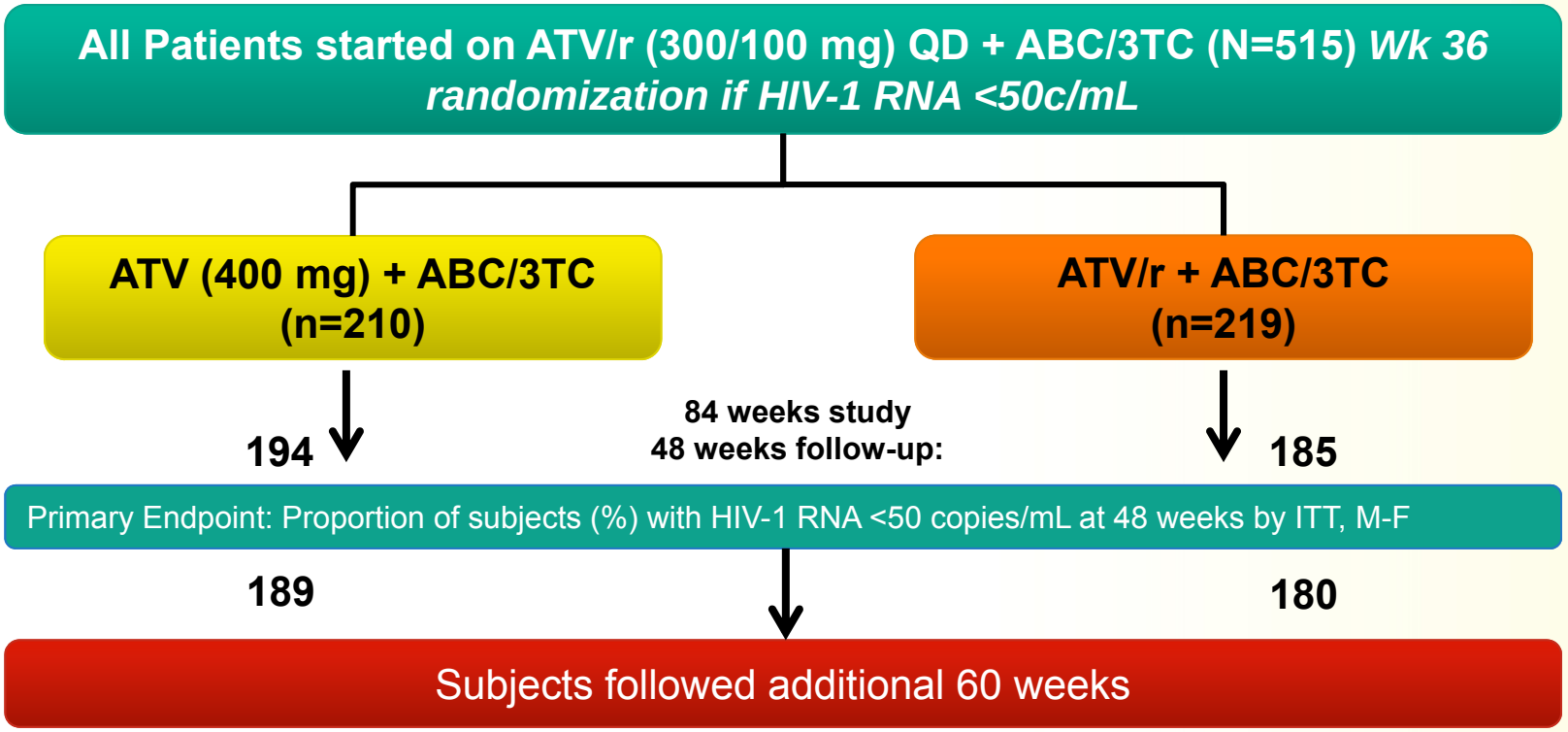
- Non-inferior efficacy for XR QD to IR BID
- Similar safety and tolerability for both formulations
- Similar efficacy noted across many PK strata indicating adequate trough drug exposure for VXR

Gathe J, et al. 18th IAC; Vienna, July 18-23, 2010; Abst. THLBB202.

VERxVE: Resistance outcomes

Type/No. of mutations	NVP XR N (%)	NVP IR N (%)	Total N (%)
Total number genotyped	32 (100.0)	54 (100.0)	86 (100.0)
No resistance to NNRTIs	11 (34.4)	20 (37.0)	31 (36.0)
NVP only	0 (0.0)	0 (0.0)	0 (0.0)
Efavirenz (EFV) only	0 (0.0)	0 (0.0)	0 (0.0)
Etravirine (ETR) only	2 (6.3)	3 (5.6)	5 (5.8)
NVP and EFV only	4 (12.5)	7 (13.0)	11 (12.8)
NVP and ETR only	8 (25.0)	14 (25.9)	22 (25.6)
EFV and ETR only	0 (0.0)	0 (0.0)	0 (0.0)
NVP and EFV and ETR	7 (21.9)	10 (18.5)	17 (19.8)
NRTI mutations			
M184 I/V	14 (43.8)	24 (44.4)	38 (44.2)
K65 R	6 (18.8)	7 (13.0)	13 (15.1)
K65 N	1 (3.1)	0 (0)	1 (1.2)
No resistance to NNRTIs or NRTIs	13 (40.6)	23 (42.6)	36 (41.9)

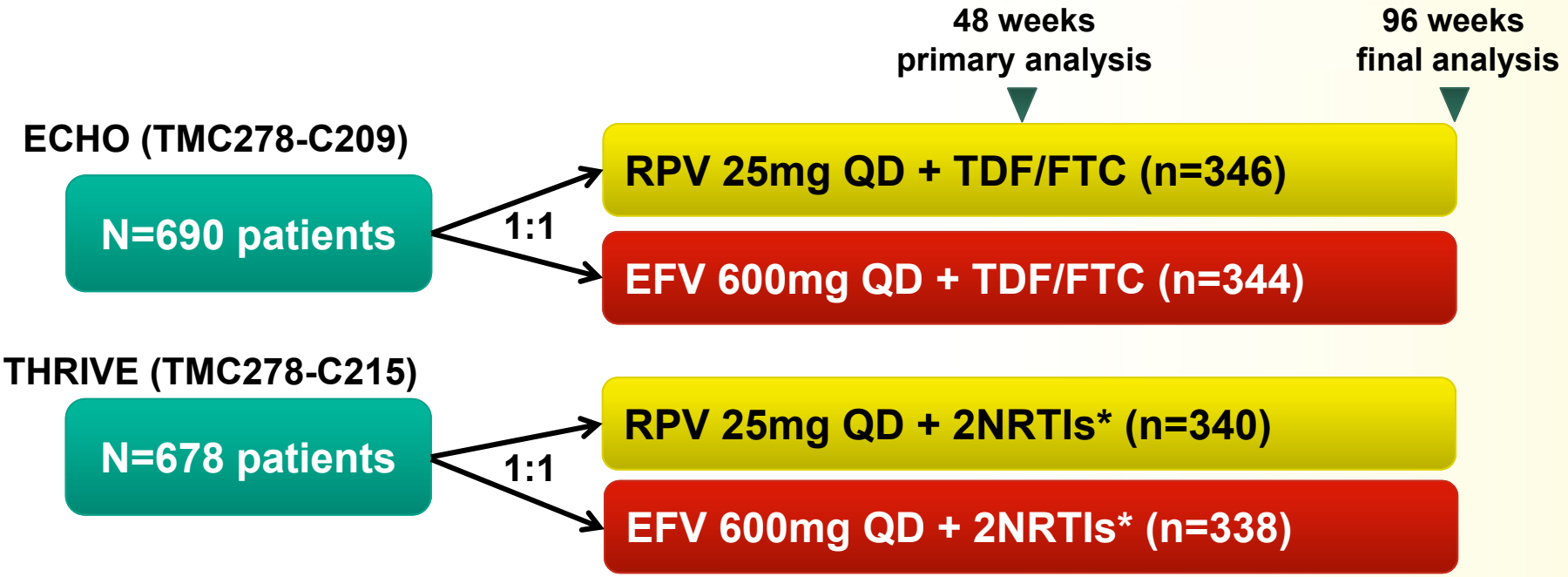
ARIES: Minority Resistant Variants and Response



- A randomly selected, pre-therapy subset of 250/515 samples from the enrolled subjects were analyzed by UDS for mutations in HIV RT and Protease
- Only 5/20 subjects who experienced CVF during the study also met UDS genotypic exclusion criteria.

Ross L, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. H2-796.

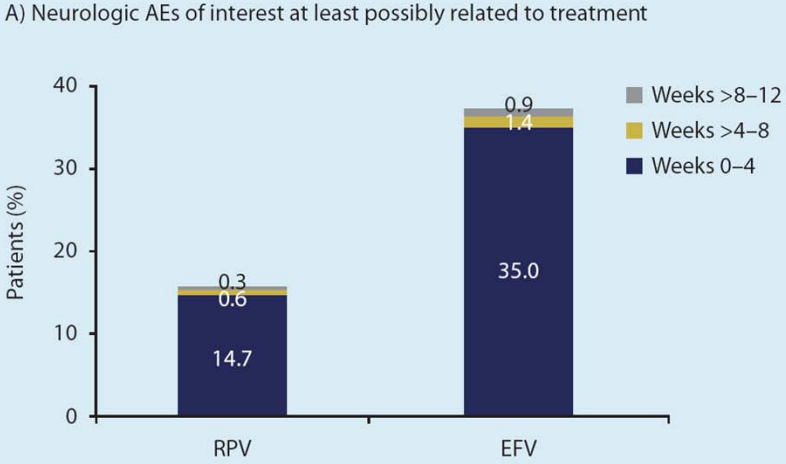
ECHO and THRIVE: Rilpivirine Tolerability Over the First 12 Weeks of Treatment

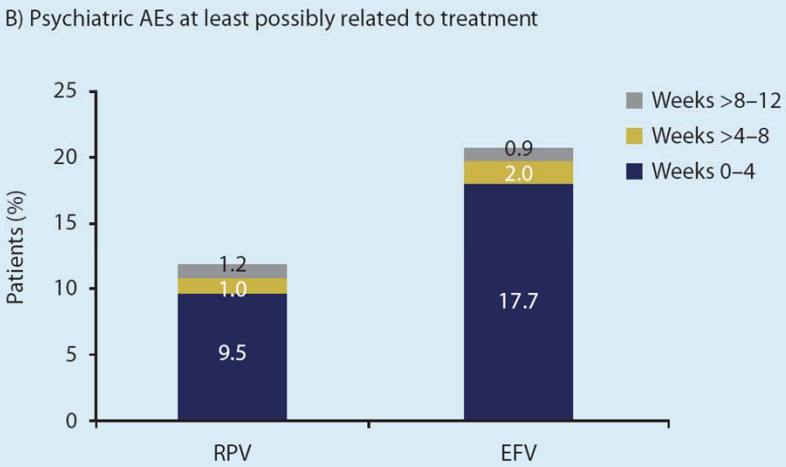


- Inclusion criteria: viral load (VL) ≥5K: no NNRTI RAMs; sensitivity to the NRTIs
- Primary objective: demonstrate non-inferiority (12% margin) vs. EFV in confirmed virologic response (VL <50 copies/mL ITT-TLOVR) at Week 48
- Stratification factors by screening VL (both) and NRTI background (THRIVE only)

Rashbaum B, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. H2-805.

ECHO and THRIVE: Rilpivirine Tolerability Over the First 12 Weeks of Treatment





- Increased rates of G 2-4 AE with EFV(4.5%) compared to RPV (1.3%) with an OR of 0.4 and an increased chance of discontinuation (OR 0.3)
- Lower incidence of rash in the RPV arm
- Lipid elevations (triglycerides, total cholesterol and LDL-cholesterol) occurred in the EFV group but not in the RPV group over the first 12 weeks of treatment. There was no difference between groups in total cholesterol/HDL-cholesterol ratio

Rashbaum B, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. H2-805.

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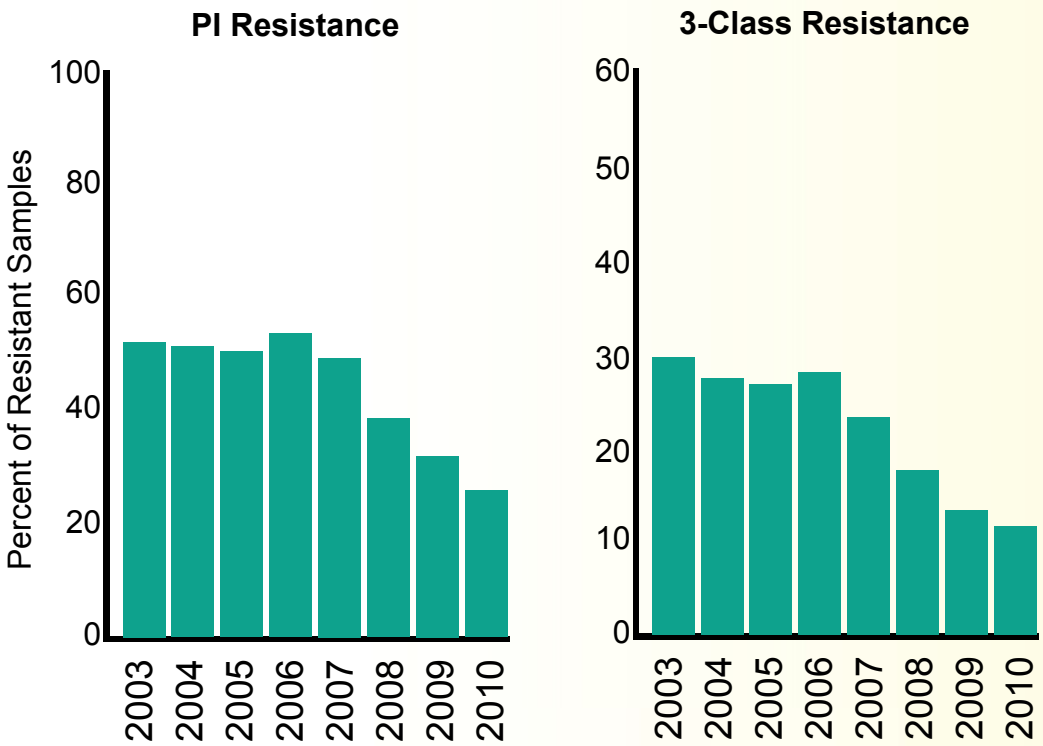
Studies in Antiretroviral Experienced Patients

Andrew Zolopa, MD
Associate Professor
Stanford University
Palo Alto, CA

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC Supported by an educational grant from Merck & Co., Inc.

Resistance Continues to Decline in Treated Patients

- Review of 68,587 samples submitted to Monogram which had phenotypic resistance to at least one drug between 2003-2010
- Decreases in rates of 3 drug-class resistance after 2007 driven by declines in resistance to PIs
- NNRTI and nRTI resistance was stable



Veritas Study: Effect of Discontinuation of an Inactive NRTI in a Salvage Regimen

- 31 patients with 3-class ART experience on 4 or 5-drug salvage ART with suppressed HIV RNA stopped one "inactive NRTI"
- 29/31 stopped 3TC or FTC (one ZDV; one TDF)
- All patients sustained virologic suppression
- Mean gain of +10 CD4+ cells/mm^3
- Conclusions: Discontinuing one NRTI from a suppressive 4 or 5-drug salvage regimen is safe and is not associated with loss of virologic suppression or declines in CD4 cells over 24 weeks
- Roll of nRTIs remains undefined

Trottier, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011. Abst. H2-787.

Impact of Genotypic Mutations on Phenotypic Susceptibility to Rilpivirine

- Data from Monogram Database (assessed regarding the phenotypic impact of single genotypic mutations in reverse transcriptase)
- Viruses with NRTI and PI mutations specifically excluded
- RPV RAMs: K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, H221Y, F227C and M230I/L

- Y181 C/I/V – 77% of isolates > BCO
- H221Y – 13% of isolates > BCO
- K103N – 7% of isolates > BCO

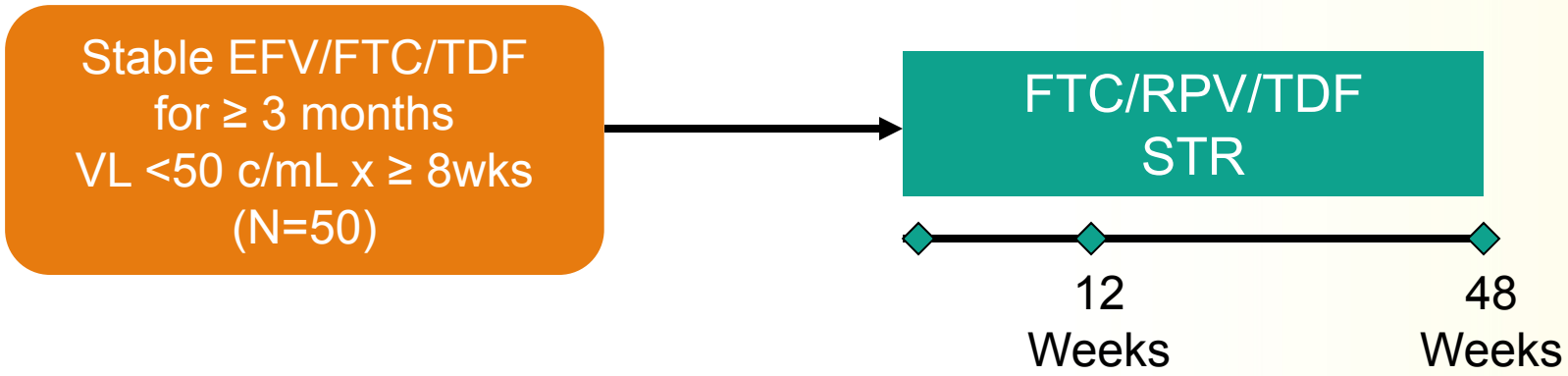
Impact of Genotypic Mutations on Phenotypic Susceptibility to Rilpivirine

Mutation	Median FC	Percent ≥ BCO	N	OR*	FET *P*-value
K101E	1.68	40	15	22.38	0
K101P	25.5	100	13	All above BCO	0
E138A	1	47.9	188	26.08	0
E138G	.94	33.53	10	50	0.00011
E138K	2.25	40	10	22.38	0.00022
E138Q	1.65	75	8	100.78	0
Y181C/1/V	3.04	77	56	114.25	0
Y181C	3.82	76.9	52	112.17	0
Y181I	3.79	100	2	All above BCO	0.00061
Y181V	217.5	100	2	All above BCO	0.00061
H221H/Y AND H221Y	1.05	13.3	30	5.17	0.00012
M230L	2.66	50	2	39.7	0.04854
K103N	0.96	7.5	818	2.52	0

Napolitano LA, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011. Abst. H1-371.

Switching EFV/TDF/FTC to RPV/TDF/FTC

Switching from EFV to RPV resulted in reduced RPV C_{min} up to 25% for approximately 4 weeks in a healthy volunteer PK study[4]



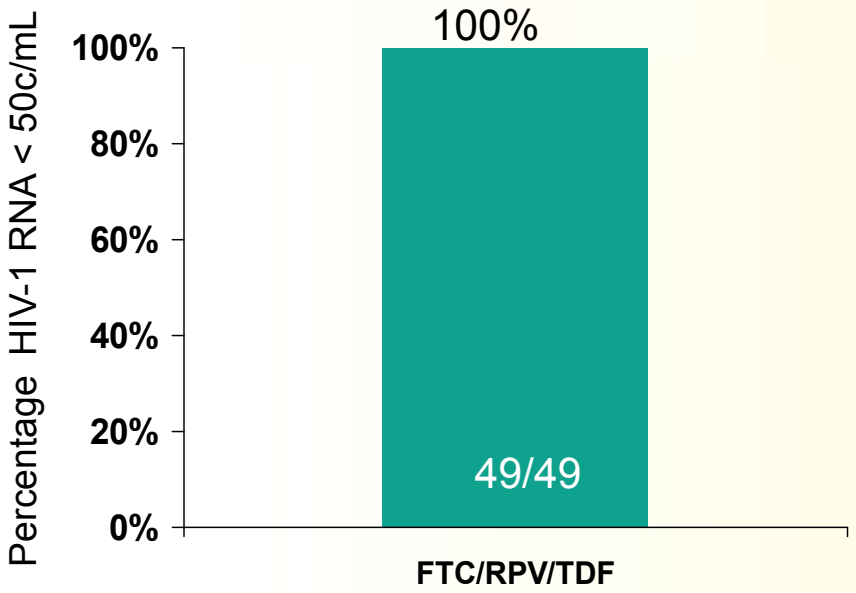
Primary endpoint:	Percentage of subjects with HIV-1 RNA <50 c/mL at week 12 after switching - ITT population Snapshot analysis
Secondary endpoints:	Safety and tolerability of FTC/RPV/TDF over 24 & 48 weeks HIV-1 RNA <50 c/mL at Week 24 and Week 48 after switching Pharmacokinetics of RPV after switching from EFV

ITT = intent to treat

Mills A, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011. Abst. H2-974c.

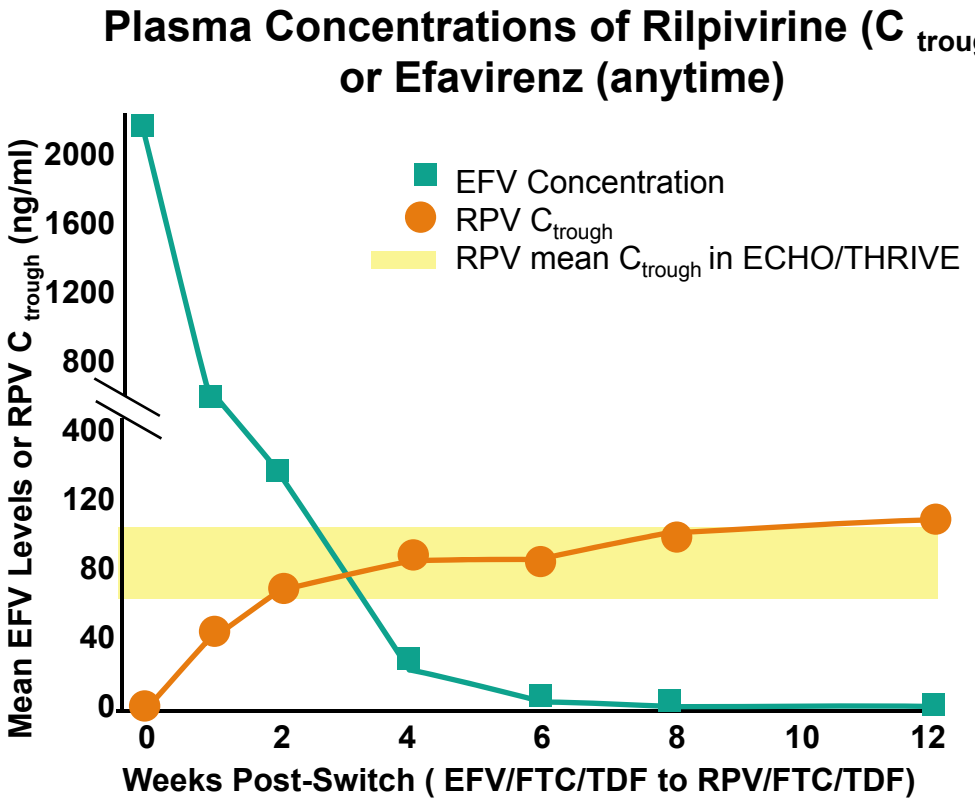
Baseline Characteristics and Virologic Results

Baseline parameter	FTC/RPV/TDF N=49
Male, percentage	92
Median age, years	39
Race, percentage Caucasian	80
Median treatment duration prior to switch, years	2.5
Median CD4 cell count, cells/mm^3	653



- 50 subjects enrolled in the study
- 49 subjects dosed and completed the study through 12 weeks
  - One subject withdrew consent before dosing
- All subjects were virologically suppressed at the week 16 visit
- No subjects had events leading to study drug discontinuation

Secondary Endpoint: RPV PK after Switching from EFV

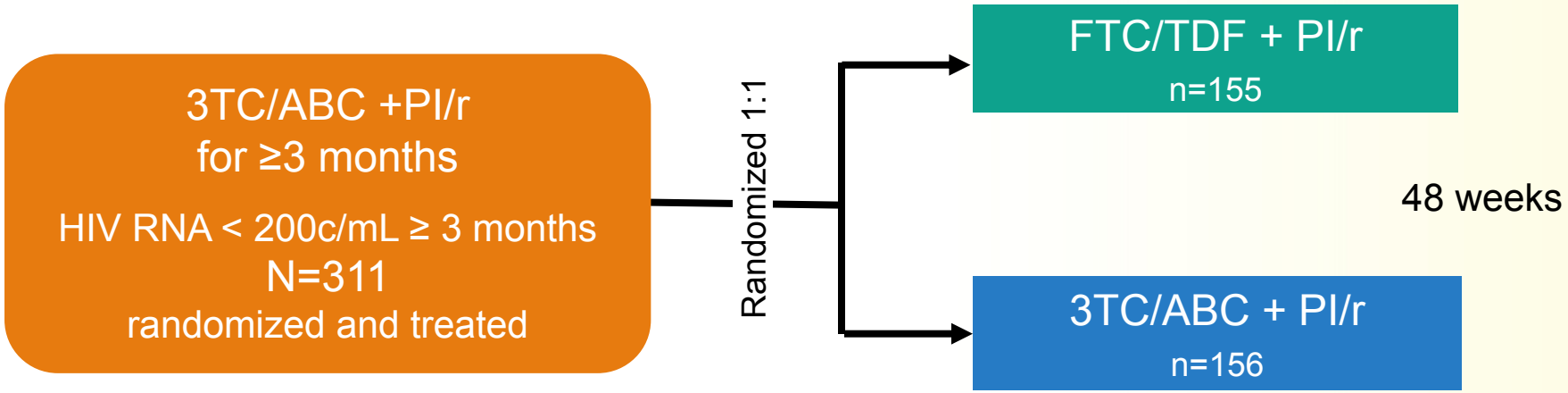


- Phase 3 (ECHO and THRIVE) mean RPV C_{trough} ~ 50-80 ng/ml (PK substudy and overall data; %CV ~ 46)
- Mean (%CV) RPV C_{trough}
  - Week 2 post-switch: 52 (47) ng/ml
  - Week 4-12: 66 (51) – 84 (76) ng/ml
- No subject had RPV below quantifiable levels at any visit

- RPV mean C_{trough} within target range by 2 weeks
- EFV mean C_{trough} above IC_{90} (~10 ng/ml*) for ~4 weeks

*protein-binding adjusted; Corbett JW, et al. J Med. Chem 2000:43;2019-2030

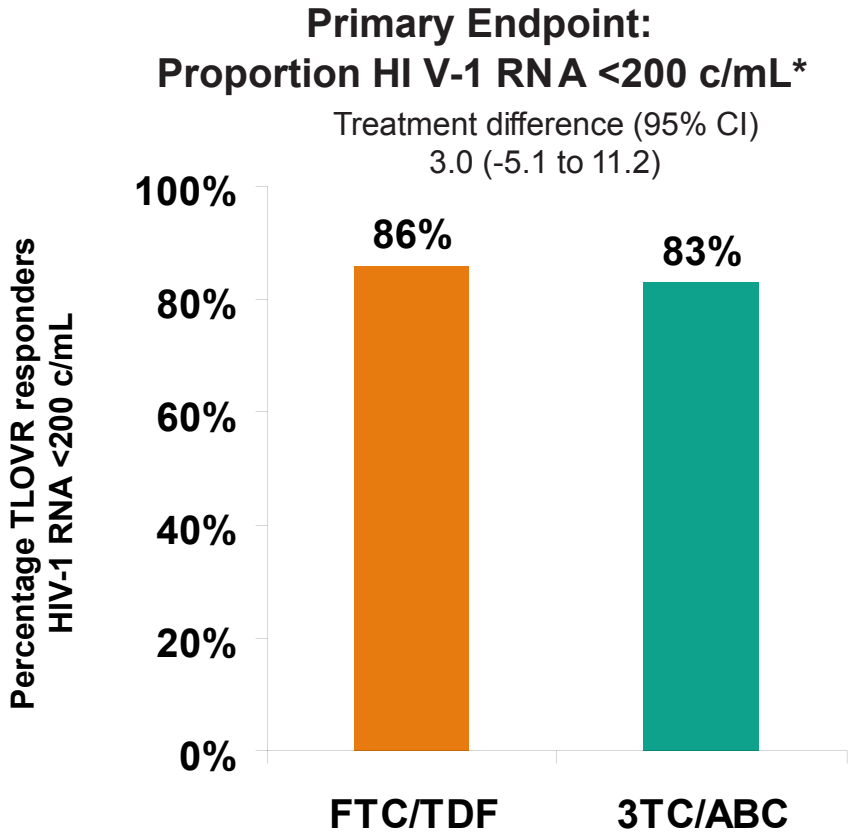
SWIFT: Switching from 3TC/ABC to FTC/TDF

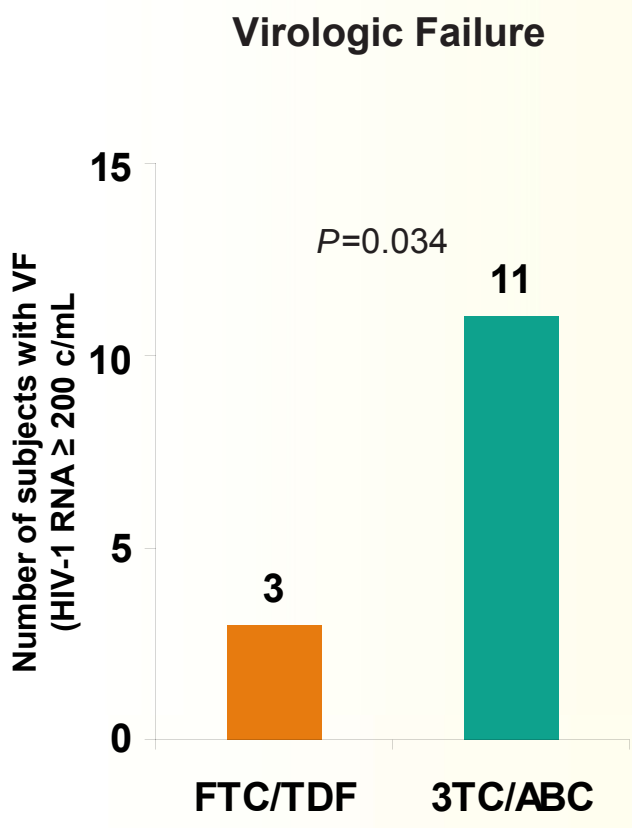


No prior history of resistance to study drugs
No CD4 restriction
Stratified by PI: 32% LPV/r vs. 68% Non-LPV/r

	LPV/r	ATV+RTV	FPV+RTV 100mg	FPV+RTV 200mg	DRV+RTV
FTC/TDF	48/155 (31%)	62/155 (40%)	22/155 (14%)	12/155 (8%)	9/155 (6%)
3TC/ABC	53/156 (34%)	60/156 (38%)	12/156 (8%)	19/156 (12%)	11/156 (7%)

SWIFT: Virologic Response through Week 48

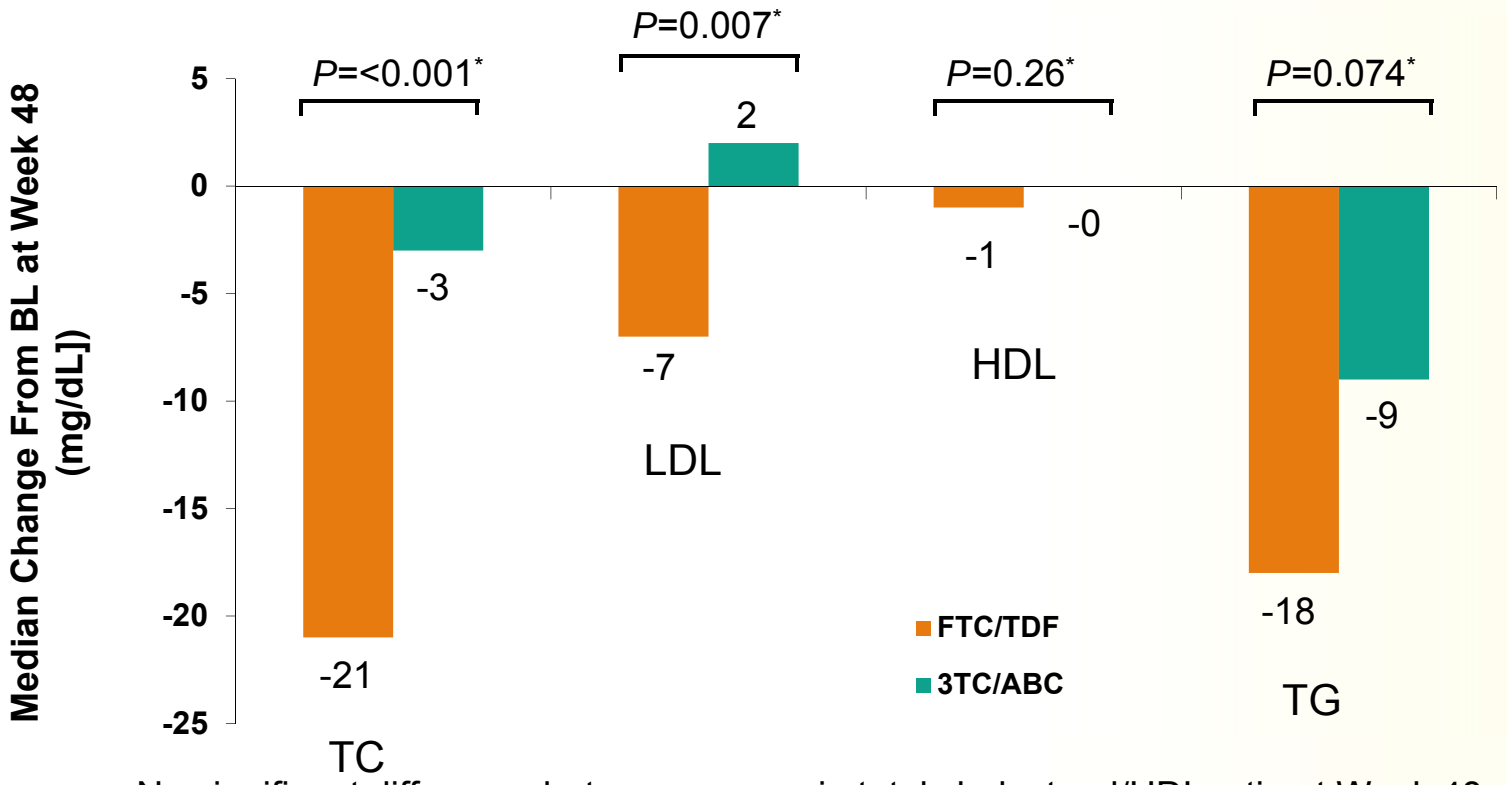




*TLOVR failure includes: virologic failure, premature discontinuation for any reason, ARV modifications

Campo R, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011. Abst. H2-786.

SWIFT: Change from Baseline in Fasting Lipids and eGFR at Week 48



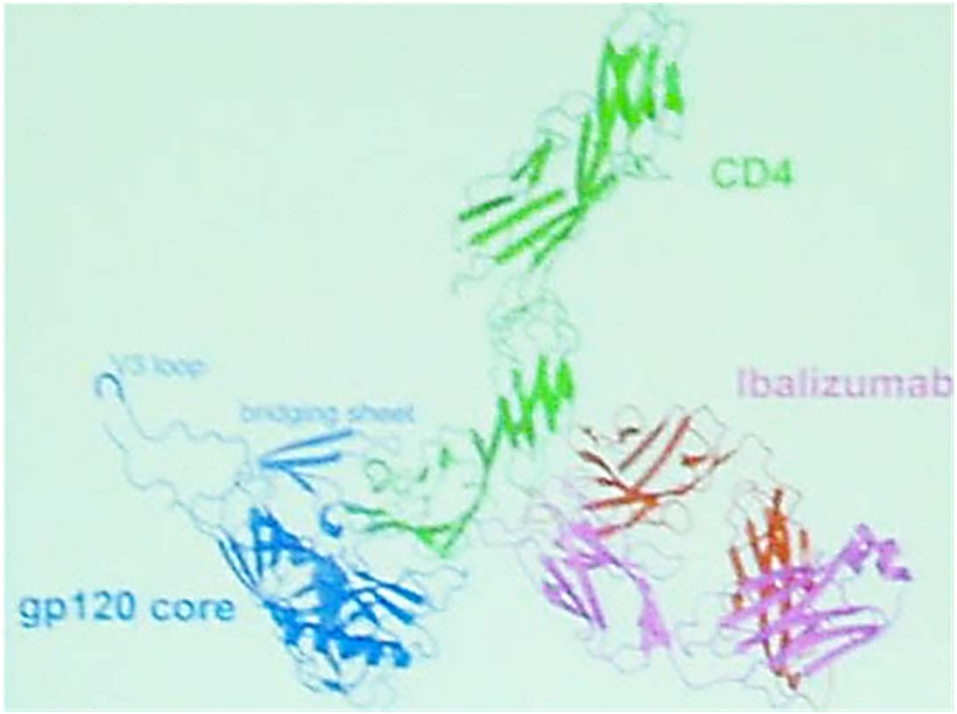
No significant difference between groups in total cholesterol/HDL ratio at Week 48

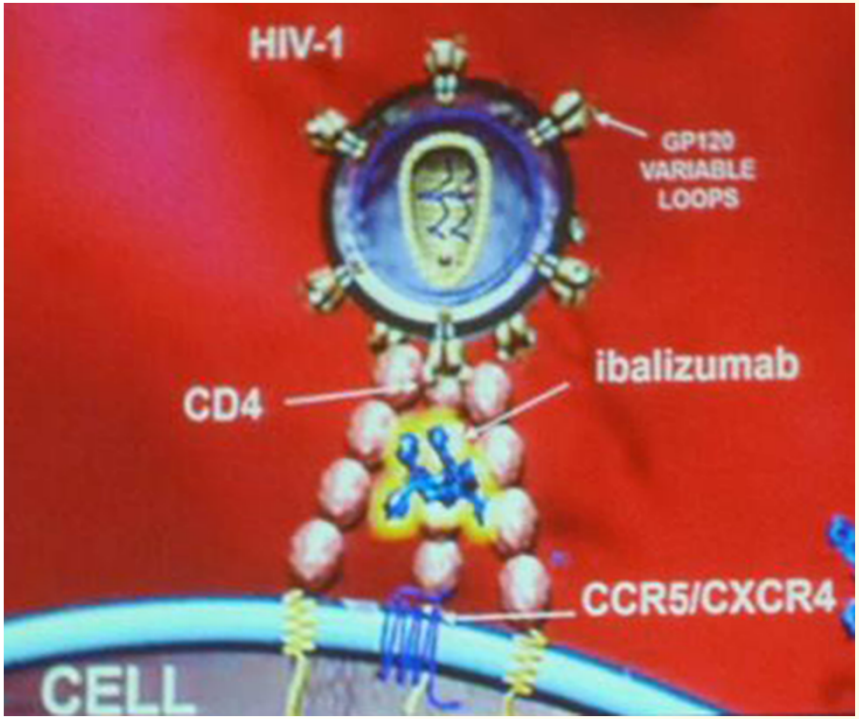
eGFR decreased in both arms TDF -8.3 ml/min vs. ABC -4.5 ml/min (*P*=0.012)

**P* values for between arm differences from Wilcoxon rank-sum test
TC = Total Cholesterol, LDL = Low-Density Lipoprotein, HDL = High-Density Lipoprotein, TG = Triglycerides
Campo R, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011. Abst. H2-786.

Phase II Study of Ibalizumab in Art-experienced Patients

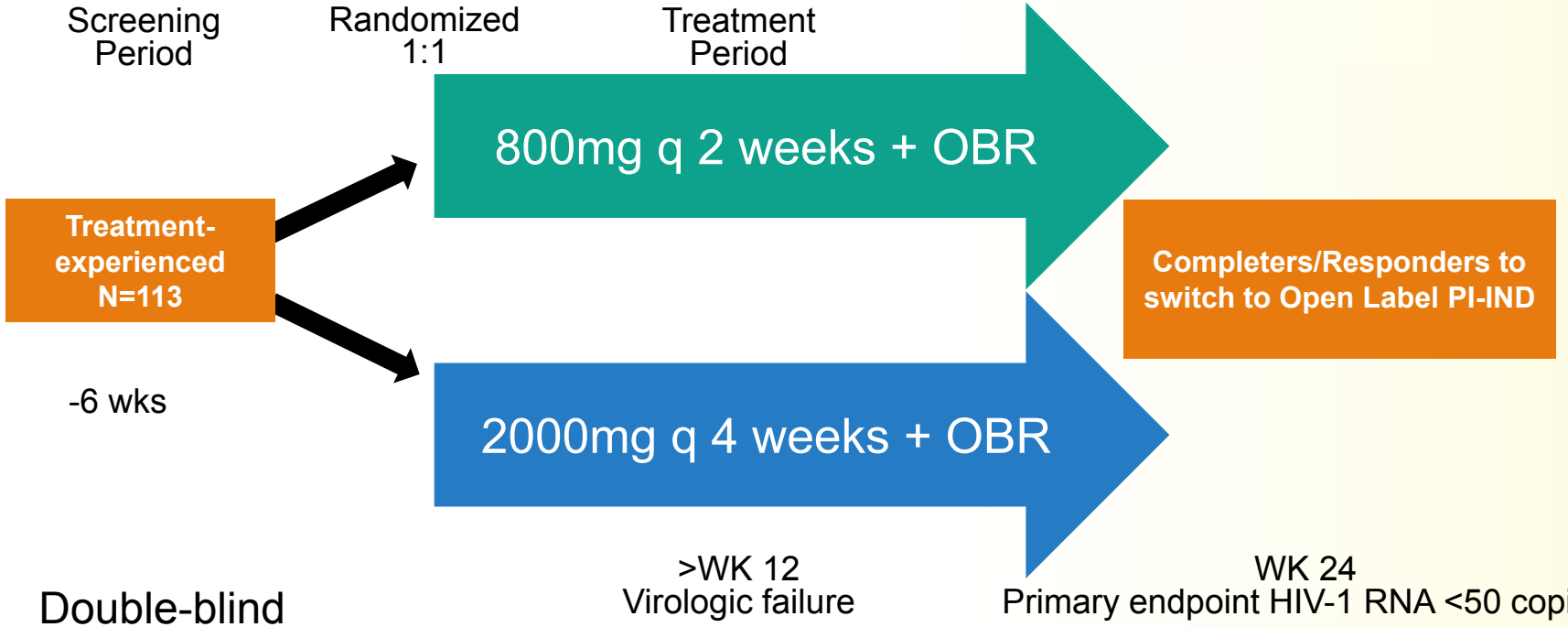
- Ibalizumab is a novel humanized MAb binding to a conformational epitope on CD4, blocking entry of HIV-1. A 24-week randomized, double-blind, Phase 2b study was conducted to optimize dosing regimens





Khanlou H, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011. Abst. H1-376a.

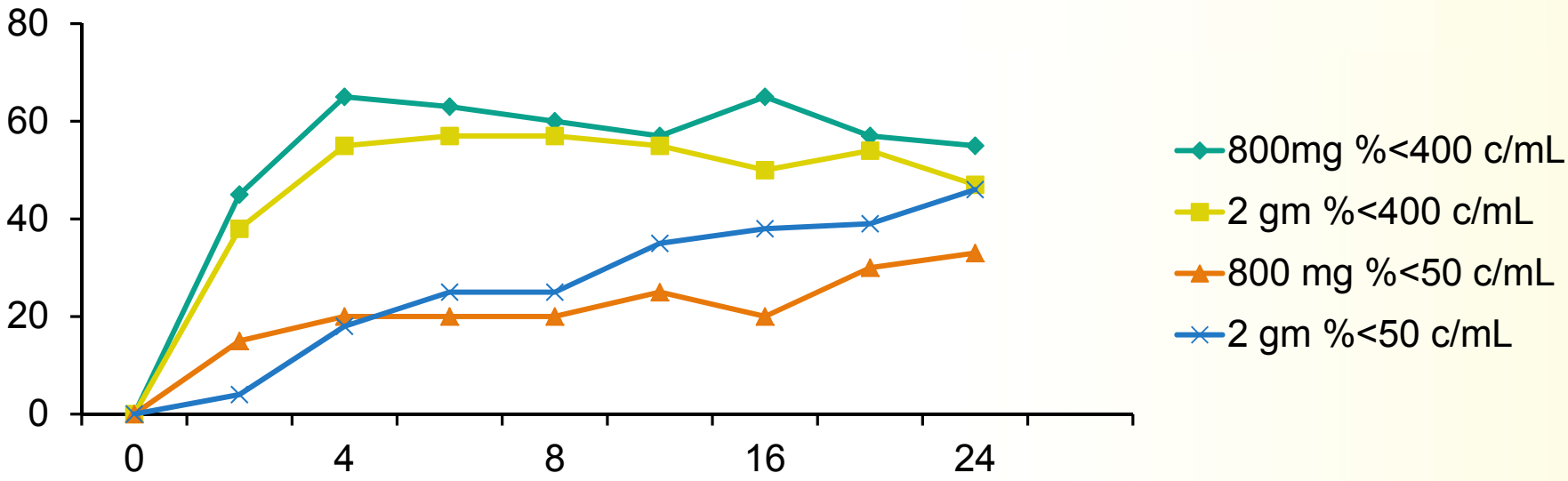
IV Ibalizumab Phase 2b Study Design



- Double-blind
- NRTI, NNRTI, PI resistance
- Failing regimen
- OBR contains 1 Sensitive Agent
- Viral Load 1,000
- No CD4 restriction
- Prospectively stratify by use of integrase and EIs

Khanlou H, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011. Abst. H1-376a.

TMB-202: Primary Endpoint, ITT-MEF



- Percent of patients with <50 copies/mL at Week 24 were 44% and 28% for the 800 mg q2wk arm and the 2000 mg q4wk arm respectively (*P*=0.160)
- Percent of patients with <400 copies/mL were 58% and 46% for the 800 mg q2wk arm and the 2000 mg q4wk arm respectively (*P*=0.321)
- Differenced between arms the were not statistically significant

Zinc Fingers: A Gene Therapy approach to controlling HIV without ART

- ZINC FINGERS – "Designer restriction Endonucleases"
  - Cleave DNA in CD4 binding domains rendering the CD4 Cell resistant to HIV binding (analogous to delta 32 deletion)
  - Delivered to Cells ex-vivo with a adenoviral vector
  - Modified Cells are then re-infused (autologous CD4 infusion)
- Open label Single Arm proof of concept trial
  - N=6 HIV infected on ART with CD4 >450
  - Received 10 billion modified CD4 cells
- ART interrupted for 12 weeks , 4 weeks after infusion
- CCR5 Modified CD4 cells persisted in peripheral blood >1yr
- CD4 cell counts increased
- Inverse correlation of viral load during TI and number of CCR5 modified cells circulating
- Phase 1 and 2 studies ongoing/planned

Ando D, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011. Abst. H2-794a.

CONTINUING MEDICAL EDUCATION INTERNET SYMPOSIUM

ARV Therapies and Therapeutic Strategies

Report from the

51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC

ARV Therapies and Therapeutic Strategies

Report from the

51st Interscience Conference on
Antimicrobial Agents and Chemotherapy (ICAAC)

Management Issues

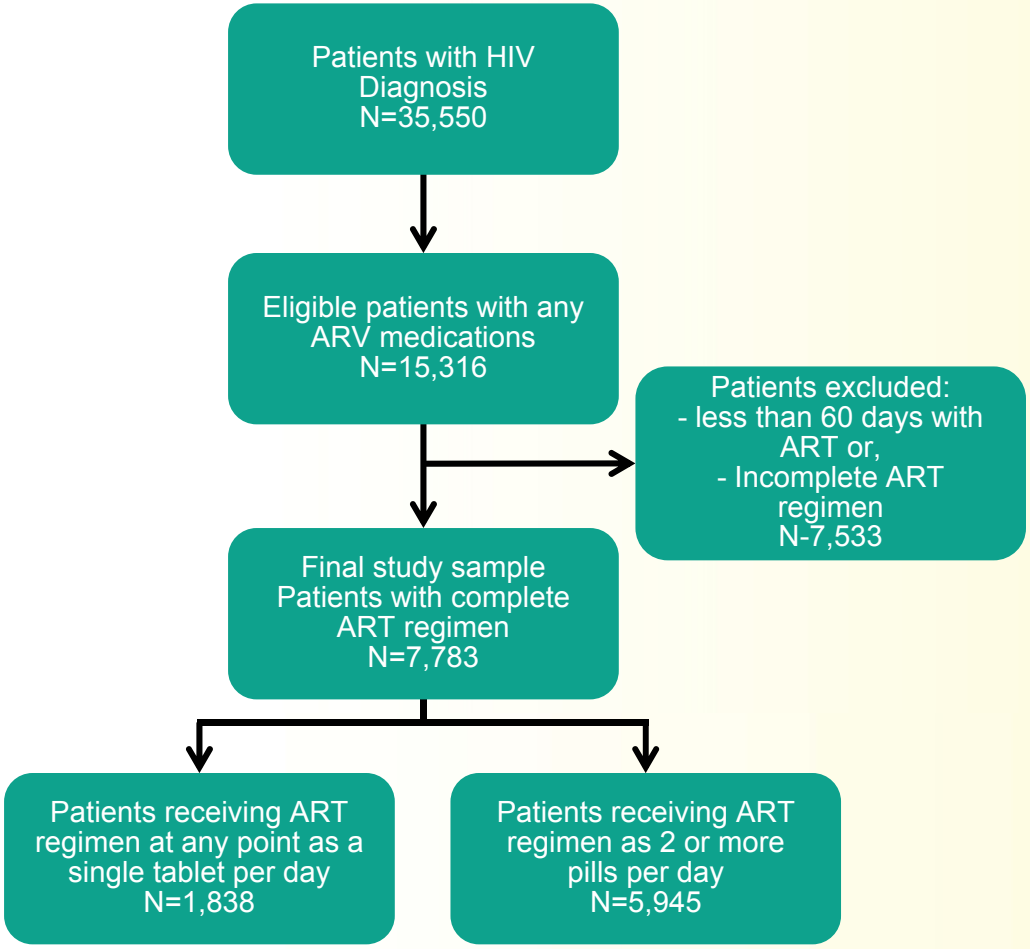
Calvin Cohen, MD
CRI New England
Harvard Vanguard Medical Associates
Boston MA

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC Supported by an educational grant from Merck & Co., Inc.

Association of Regimen Pill Burden and Risk of Hospitalization

- Study analysis of a large US Multistate Medicaid database
- Outcome: to explore the relationship between number of pills in an HIV regimen vs. risk for hospitalization outside of study populations
- Adherence data from pharmacy refill records
- Note:
  - Lab data not available

Time Period:1/1/05-12/31/09



Cohen C, et al. 51st ICAAC; Chicago , IL; Sept 17-20, 2011. Abst. H2-791.

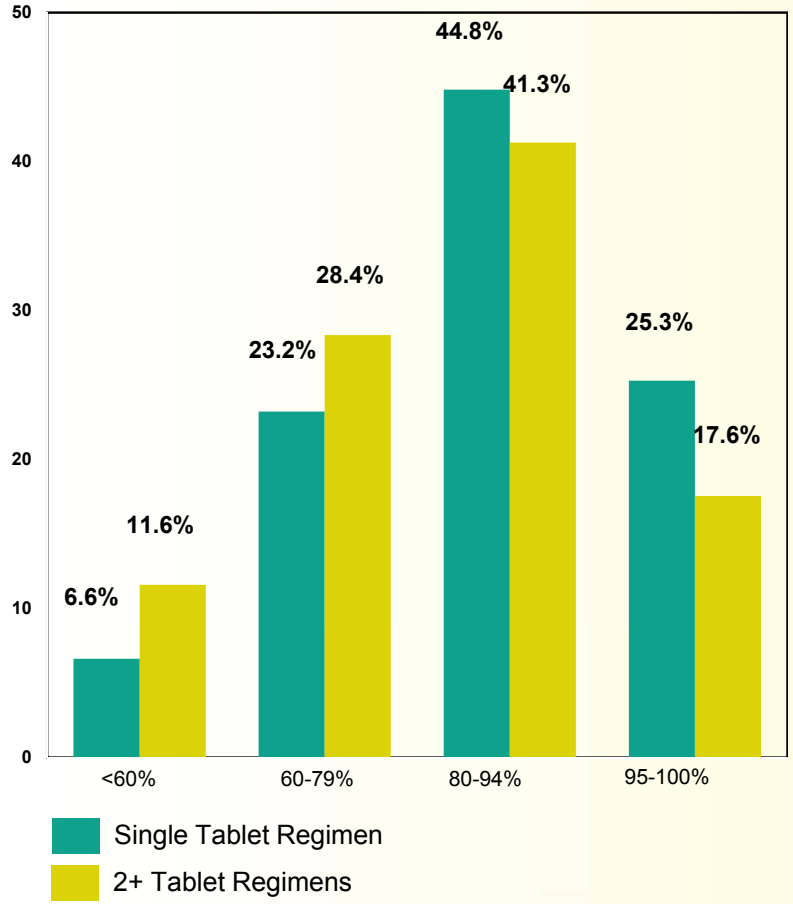
Pill Burden and Risk of Hospitalization: Demographics and Adherence Outcomes

Groups similar in characteristics for risk of hospitalization

Characteristic	Single Tablet Per Day Regimen	2+ Tablet Per Day Regimen
N	1,838	5,945
Female	48.6%	48.7%
Mean Age (SE)	41.4 (0.3)	41.5 (0.2)
Age 55+ years	9.8%	11.1%
Mean (SE) Charlson Comorbidity Index	0.7 (0.03)	0.6 (0.02)
Concomitant Mental Health/Substance Abuse		
Mental disorders	21.3%	23.7%
Illicit drug or alcohol abuse	18.8%	14.9%
Treatment naïve patients	47.0%	25.9%
ART Classes Received		
NRTIs	100.0%	100.0%
NNRTIs	100.0%	26.1%
Protease Inhibitors	---	73.6%
Received a boosted Protease Inhibitor	6.3%	64.1%
Mean (SE) treatment and follow-up duration (days)	347 (6.46)	428 (4.84)

Adherence significantly higher with STR
***P*<0.01 for each stratum**

Adherence to Antiretroviral Therapy



Cohen C, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. H2-791

Association of Regimen Pill Burden and Risk of Hospitalization: Primary Outcome

	Multiple-Event Cox Model	
	Hazard Ratio	P-Value
Received a Single Tablet Per Day Regimen (vs. a 2+ TPD)	0.753	<0.0001
Charlson comorbidity index - Between 1 and 2 vs. less than 1	2.381	<0.0001
Had a mental disorder diagnosis (vs. no mental disorder diagnosis)	1.301	<0.0001
Had a drug or alcohol abuse diagnosis (vs. no drug or alcohol abuse diagnosis)	2.052	<0.0001

Number of Hospitalizations per 100 pts. in specific subsets: (p all <0.001 in Poisson count model)			
	STR	2+ PPD	Difference
ARV Naïve pre-study	39.2	53.3	-14.1
ARV Experienced pre-study	39.7	53.9	-14.3
ARV Naïve Female, <35 yrs, no prior MH illness	28.4	47.3	-18.9
ARV Naïve Male, 35-44 yrs, prior MH illness	30.8	51.3	-20.5

Summary: Consistently lower hospitalization risk for those on STR vs. other regimens

How often do Clinicians stop EFV/TDF/FTC?

- N=472 patients who started treatment with EFV/FTC/TDF
  - Started using the co-formulated tablet, not separate components
- Retrospective chart review
  - Patients at Chelsea and Westminster Hospital
  - 94% male, median age 37, 52% MSM, 75% Caucasian
  - Median CD4 285, median viral load 16,000
  - 92% had undetectable viral load by 6 months
  - N=6 stop for virologic reasons

Most common Reasons

Number (%) stopping	**89 (19%)**
CNS toxicity*	63
Hepatotoxicity	7
Rash	6

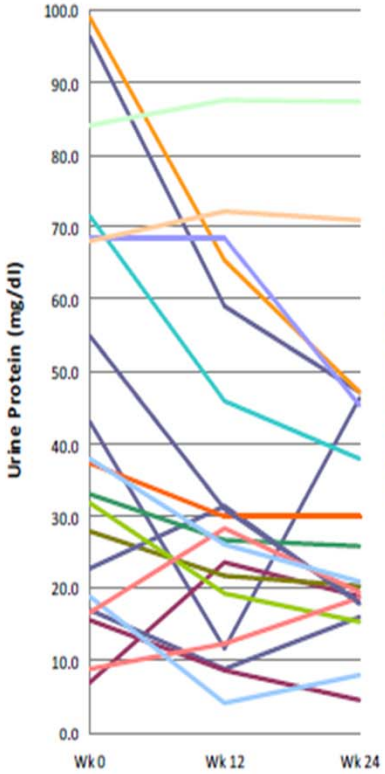
Week of Stopping EFV/TDF/FTC	n (%)
0-4	6 (10%)
4-12	4 (6%)
12-52	30 (48%)
52-96	23 (36%)

*insomnia, nightmares, depression, dizziness

Switch from TDF/FTC + PI/r to RAL + PI/r in Patients with Proteinuria

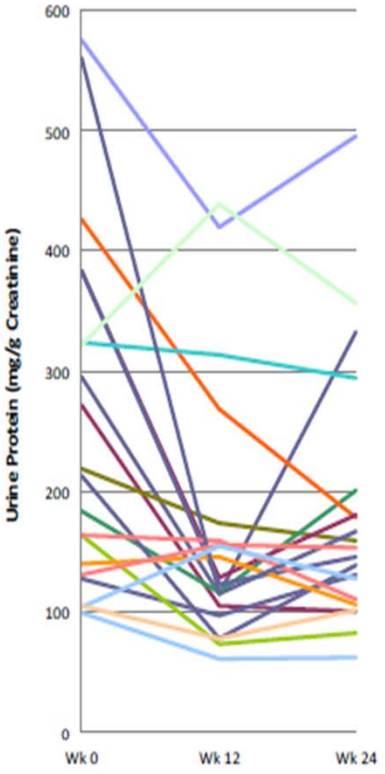
- N=21, VL<200c/mL on TDF/FTC and PI/r based regimen
  - ATV, LPV, f-APV
- All had proteinuria
  - No other known etiology ex. possible role of TDF
  - On TDF mean 45 mos. (6-85)
- Study: Stop TDF/FTC, start raltegravir
  - No change in PI/r
- Results: Majority show decline in proteinuria
  - Some increase
  - n=1 ARF week 4 – resolved after d/c RAL + LPV/r
- n=1 VF with INSTI resistance

Urine Protein Over Time



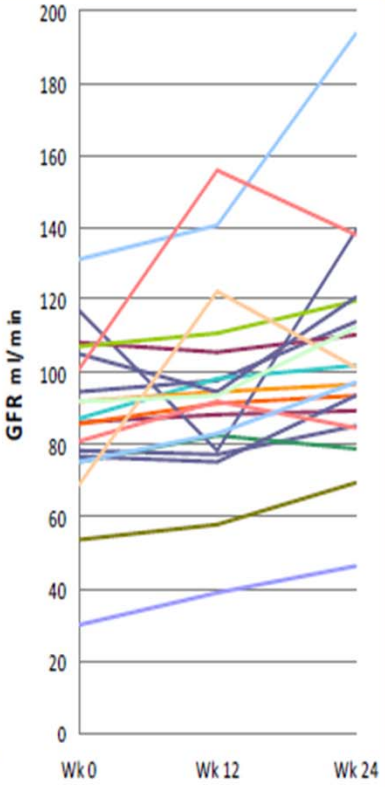
N=14/21 decreased Ur Protein -20 mg% (-1 to -52mg%);
N=6 incr. ur protein +6 (3-12)

Urine Protein Clearance Over Time



N=14/21 decreased Ur Pr Cl -122 (-4, -394)
N=6 incr. Ur Pr Cl +21 (3, 37)

GFR Over Time



GFR by C-G 20/21 increase +17.5(2-63)
N=1; creat of 1.2 at BL → 2.6 at week 4

Bredeek UF, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. H-1399b.

Effect of Drugs on Creatinine Secretion

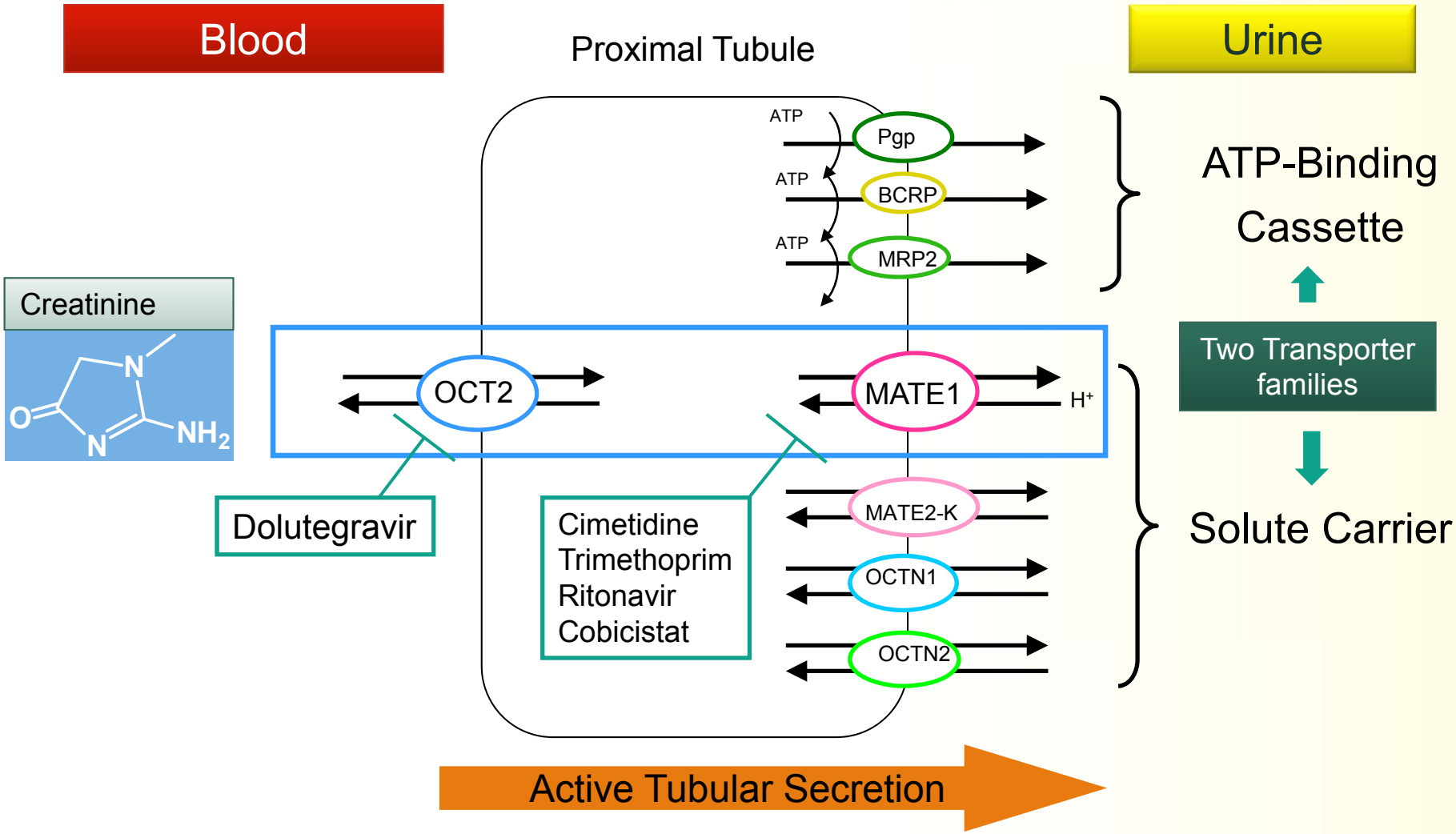
- Creatinine elimination: both glomerular filtration and active tubular secretion
- Some drugs result in increased serum creatinine (Cr) with lower estimated glomerular filtration rate (eGFR) but no change in actual GFR (aGFR)
  - Noted in several HIV-related medications
- Study done to define mechanism of this laboratory phenomenon

Examples of Drugs Reported to Inhibit CrCl and eGFR Without Affecting aGFR

Class	Examples
Antacid	Cimetidine
Antibiotic	Trimethoprim
Antiviral	Dolutegravir Rilpivirine
Antiparasitic	Pyrimethamine
Pharmacoenhancer	Cobicistat Ritonavir
Cardiovascular	Ranolazine Dronedarone Amiodarone

Lepist E, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. A1-1724.

Model for the Effect of Drugs on Creatinine Secretion



MATE: multidrug and toxin extrusion protein; OCT: organic cation transport

REALMRK: Use of Raltegravir in Diverse Patient Populations

- Studies that led to FDA approval of raltegravir had:
  - <20% Female
  - <15% Black
  - FDA request for additional data in these populations

Treatment experienced – intolerance

Treatment experienced – Viremic

Treatment Naïve (<20% of enrollment)

→ New Regimen containing RAL 400 BID

	Previously Treated		Treatment Naïve	Total
	Failure (N=97)	Intolerant† (N=88)	(N=21)	(N=206)
Emtricitabine + tenofovir	55.7	44.3	81.0	53.4
Ritonavir	52.6	34.1	19.0	41.3
Darunavir	37.1	17.0	9.5	25.7
Lopinavir + ritonavir	30.9	14.8	4.8	21.4
Tenofovir	23.7	11.4	4.8	16.5
Atazanavir	13.4	17.0	9.5	14.6
Lamivudine	20.6	8.0	4.8	13.6
Zidovudine	16.5	5.7	0	10.2

Squires K, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. H2-789.

REALMRK: Baseline Characteristics

Baseline Patient Characteristics

	Previously Treated		Treatment Naïve (N=21)	Total (N=206)
	Failure (N=97)	Intolerant† (N=88)		
Mean age (SD)	44.0 (9.2)	46.9 (9.0)	38.5 (10.1)	**44.7 (9.5)**
Gender, % Female	47.4	50.0	33.3	**47.1**
Race, % Black	72.2	78.4	66.7	**74.3**
Region, % North America	78.4	96.6	95.2	**87.9**
% Southern Africa	10.3	2.3	4.8	**6.3**
vRNA copies/mL (median)	15100	<50*	85700	**6440**
% with vRNA > 10^5 copies/mL	20.6	10.2	42.9	**18.4**
Median CD4 count (cells/μl)	190	375	168	**236**
% Hepatitis B or C	13.4	13.6	9.5	**13.1**

*Among patients intolerant to prior therapy, 62.5% had HIV RNA < 50 copies/mL at baseline.

REALMRK: Virologic Results and AEs

% of Patients with HIV RNA < 50 copies/mL† at Week 48

	Previously Treated							
	Failure		Intolerant†		Treatment Naïve		Total	
	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)
Male	33/50	66.0 (51.2, 78.8)	33/41	80.5 (65.1, 91.2)	10/14	71.4 (41.9, 91.6)	76/105	72.4 (62.8, 80.7)
Female	27/44	61.4 (45.5, 75.6)	28/39	71.8 (55.1, 85.0)	6/7	85.7 (42.1, 99.6)	61/90	67.8 (57.1, 77.2)
Black	44/69	63.8 (51.3, 75.0)	43/62	69.4 (56.3, 80.4)	11/14	78.6 (49.2, 95.3)	98/145	67.6 (59.3, 75.1)
Non-black	16/25	64.0 (42.5, 82.0)	18/18	100 (81.5, 100)	5/7	71.4 (29.0, 96.3)	39/50	78.0 (64.0, 88.5)
Total	60/94	63.8 (53.3, 73.5)	61/80	76.3 (65.4, 85.1)	16/21	76.2 (52.8, 91.8)	137/195	70.3 (63.3, 76.6)

Most Common* Drug Related† Clinical Adverse Events

	Male (N=109)		Female (N=97)	
% of patients with:	Black (N=70)	Non-Black (N=39)	Black (N=83)	Non-Black (N=14)
Abdominal discomfort	0	0	2.4	0
Diarrhea	1.4	2.6	2.4	0
Nausea	2.9	5.1	4.8	0
Vomiting	1.4	2.6	2.4	0
Myalgia	0	0	2.4	0
Headache	1.4	0	2.4	0

* Present in ≥2% of any group

†Determined by Investigator to be possibly, probably, or definitely related to raltegravir alone or in combination with background ART.

Squires K, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. H2-789.

REALMRK: PK outcomes and conclusions

Summary of PK Parameters

	Female	Male	Ratio (Female/Male)	
	N	N	GMR (90% CI)	*P*-value
C_{all} (nM)	91	105	0.89 (0.69, 1.13)	0.422
GM C_{12hr} (nM)	60	58	1.17 (0.84, 1.64)	0.423
C_{min} (nM)	91	105	1.20 (0.89, 1.61)	0.322
	Black	**Non-Black**	**Ratio (Black/Non-Black)**	
	N	N	GMR (90% CI)	*P*-value
C_{all} (nM)	146	50	0.92 (0.69, 1.22)	0.613
GM C_{12hr} (nM)	90	28	0.74 (0.50, 1.09)	0.199
C_{min} (nM)	146	50	1.17 (0.83, 1.64)	0.457

Conclusions:

- Raltegravir containing regimens were similarly safe and effective without major differences by race or gender
  - Similar adverse events, and similar discontinuations rates
- PK parameters were similar by gender or race

Interest in PrEP among HIV Negative Patients seen in a Chicago STI Clinic

- Survey of 359 high risk heterosexuals
  - Survey done just before iPrex trial results available
  - 65% Male, 75% Black, 72% single
  - 79% education high school or less
  - 21% report anal sex
  - >84% report inconsistent condom use for any sexual activity
- Results:

Would you take a pill for PrEP?	**83%**
One hour before sex?	77%
Once a week?	76%
One day before?	75%
Once a day?	63%

  - Lower education level had 5 fold greater report of no interest in taking PrEP

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ARV Therapies and Therapeutic Strategies

Report from the

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Antimicrobial Agents and Chemotherapy (ICAAC)

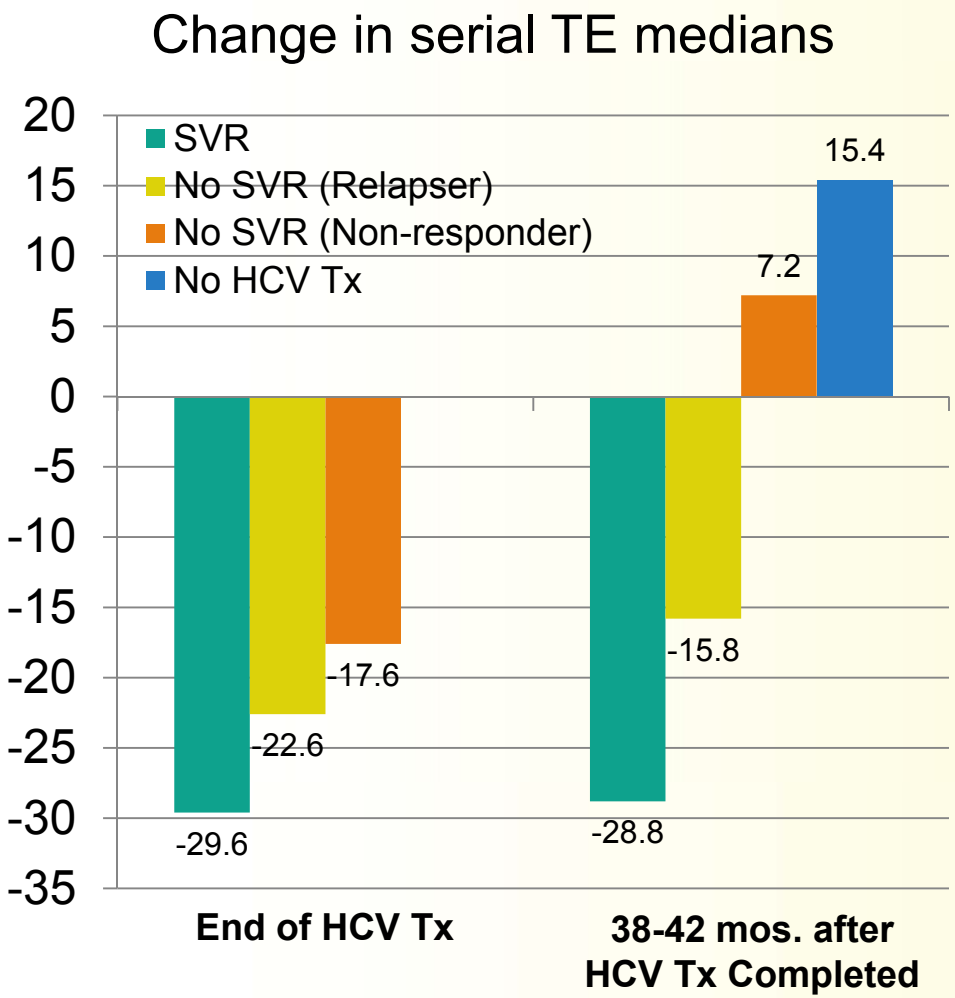
Hepatitis Co-infection Issues

Jürgen Rockstroh, MD
Professor, University of Bonn
Bonn, Germany

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC Supported by an educational grant from Merck & Co., Inc.

Liver Fibrosis in HIV/HCV After HCV Treatment

- Study assessing liver fibrosis (LF) over time in 328 HIV/HCV patients on ART
  - 210 received HCV Tx: 80 SVR, 130 No SVR (49 Relapse, 81 non-responders)
- LF assessments
  - Baseline: Liver Bx or elastometry (TE)
  - Over time: TE, biochemical indices
- Results:
  - Decreased LF during HCV Tx in all patients receiving Tx
    - 28.5% improved > than 1 stage
  - Sustained decrease in LF only in patients with SVR and relapsers

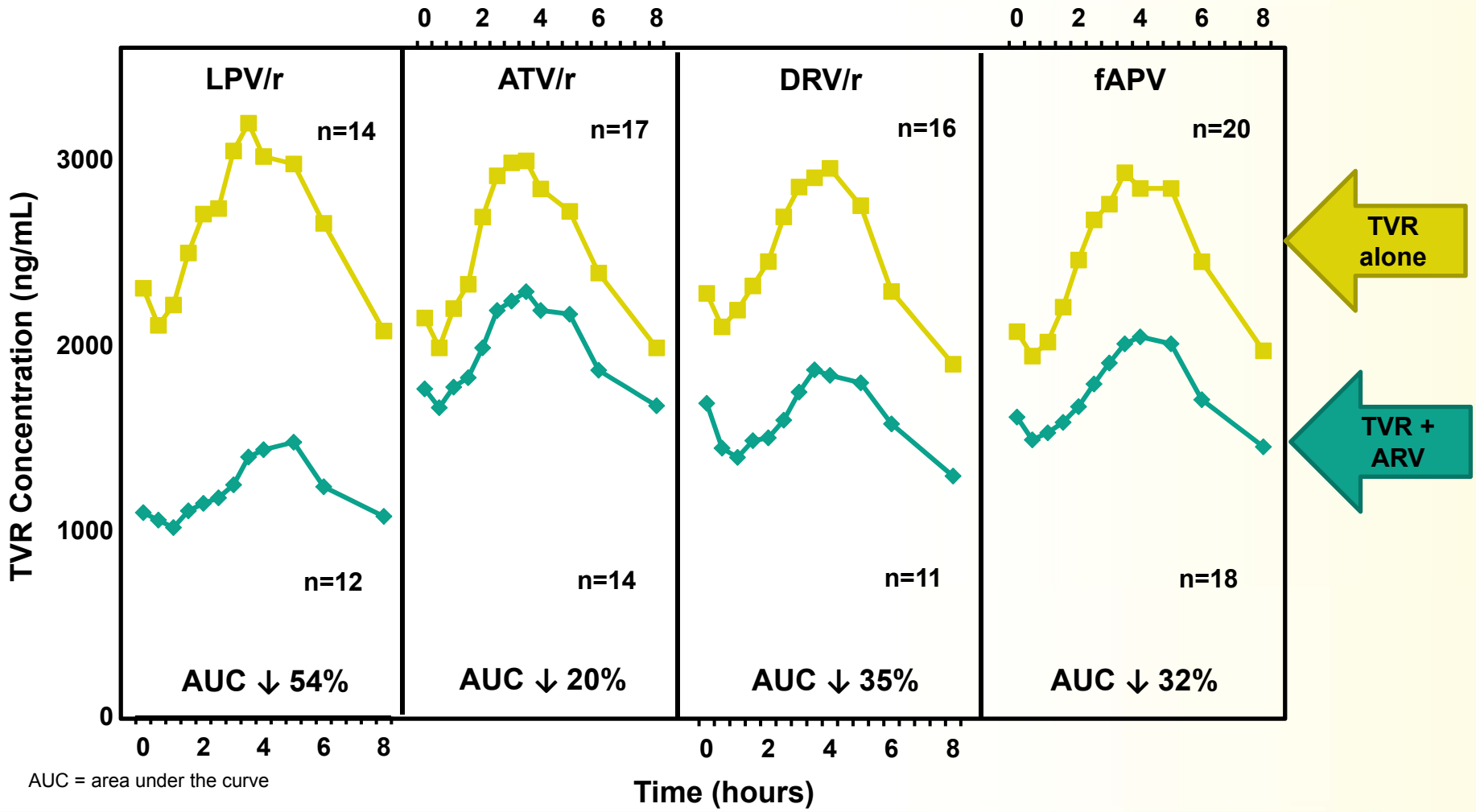


TVR Drug Interactions with ARVs

TVR Dose	ARV	TVR AUC	TVR Cmin	ARV AUC	ARVCmin
TVR 750mg TID	Raltegravir	1.07 (1.00-1.15)	1.14 (1.04-1.26)	1.31 (1.03-1.67)	1.78 (1.26-2.53)
TVR 1250 mg TID	EFV	0.82 (0.73-0.92)	0.75 (0.66-0.86)	0.82 (0.74-0.90)	0.90 (0.81-1.01)
	TDF			1.10 (1.03-1.18)	1.17 (1.06-1.28)
TVR 1500 mg BID	EFV	0.80 (0.73-0.88)	0.52 (0.42-0.64)	0.85 (0.79-0.91)	0.89 (0.82-0.96)
	TDF			1.10 (1.03-1.17)	1.06 (0.98-1.15)

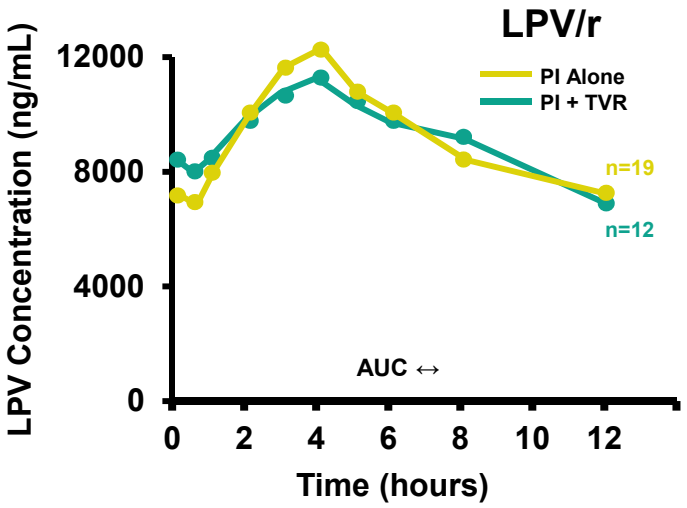
Van Heeswijk R, et al. 18th CROI; Boston, MA;; February 27-March 2, 2011. Abst. 119.
Van Heeswijk R, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. A1-1738a.

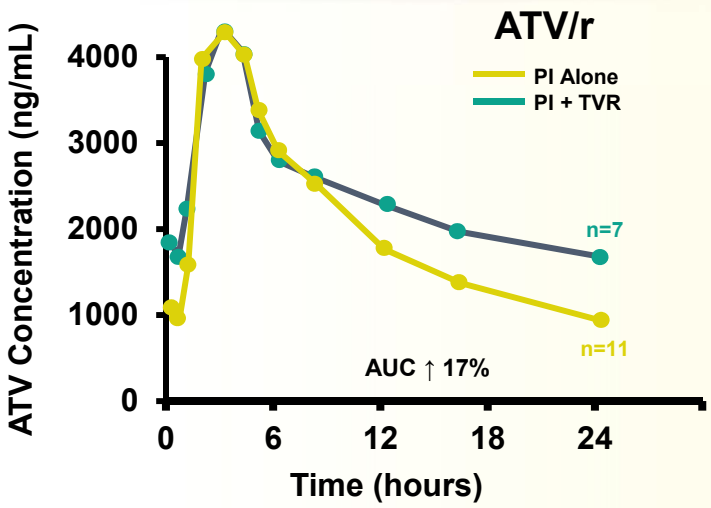
Mean Telaprevir PK-Profile

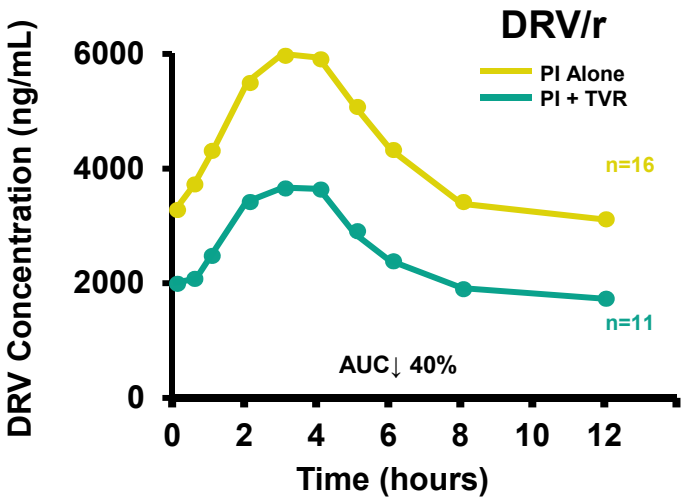


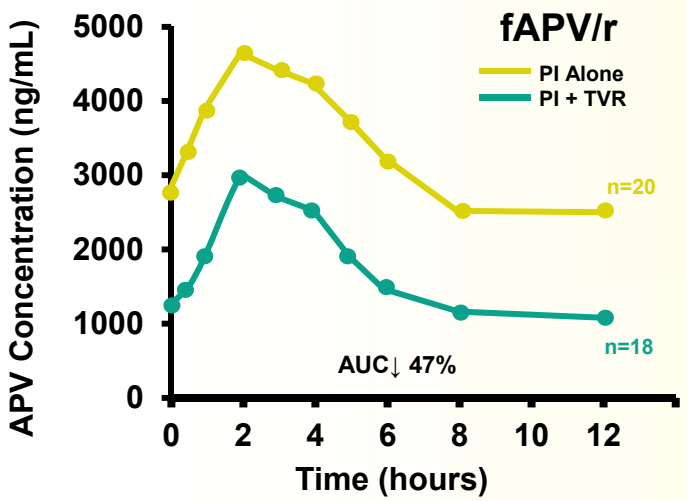
AUC = area under the curve

Mean HIV-Protease Inhibitor PK-Profile







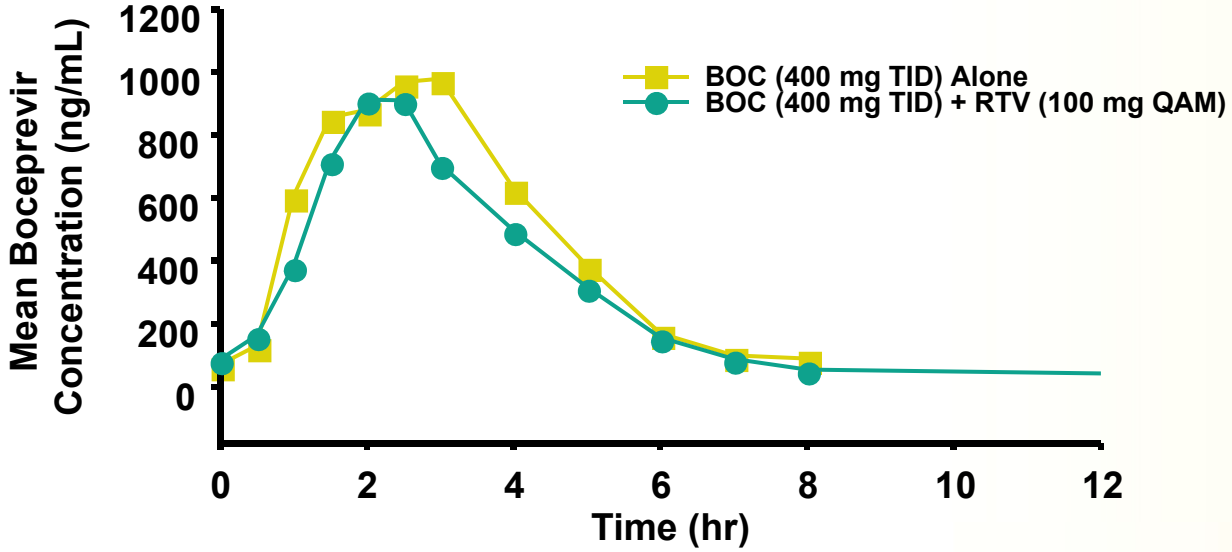


APV = amprenavir

Boceprevir and Ritonavir

Effect of Ritonavir on Boceprevir†

- Mean ratio estimate C_{max}=0.73 (↓)
- Mean ratio estimate $AUC_{(\tau)}$=0.81 (↔)
- Mean ratio estimate C_{min}=1.04 (↔)



Mean Plasma Concentration-Time Data of SCH 503034 and SCH 629144 Following Multiple Oral Administrations of SCH 503034 Alone (Treatment A, Period 1, Day 5) or SCH 503034 in Combination With Ritonavir (Treatment B and C, Period 2, Day 15) to Healthy Adult Volunteers (Protocol No. P04624)

† Ratio estimate (in combination vs. alone). ↓=<0.8; ↔=≥0.8 and ≤1.25. Data from P04624.
AUC=area under the concentration-time curve; BOC=boceprevir; Cmax=maximum observed plasma concentration; Cmin=minimum observed plasma concentration; QAM=once in morning; RTV=ritonavir; TID=three times daily.

Boceprevir and Efavirenz

Days 1-5: BOC 800 mg TID
Day 6: BOC 800 mg single dose

Washout ≥7 days

Days 1-10:
- **EFV 600 mg QD**

Days 11-15: BOC 800 mg TID
Day 16: BOC 800 mg single dose
Days 11-16: EFV 600 mg QD

N = 12 healthy volunteers

	Treatment	LS Mean[a]	Ratio Estimate, % (90% CI)
Effect of EFV (600 mg QD) on BOC (800 mg TID)			
Cmax (ng/mL)	BOC BOC + EFV	2038 1871	92 (78-108)
$AUC_{(0\text{-}8hr)}$ (ng·hr/mL)	BOC BOC + EFV	6913 5630	81 (75-89)
Cmin (ng/mL)	BOC BOC + EFV	94.4 52.5	56 (42-74)
Effect of BOC (800 mg TID) on EFV (600 mg QD)			
Cmax (ng/mL)	EFV EFV + BOC	4573 5077	111 (102-120)
$AUC_{(0\text{-}24hr)}$ (ng·hr/mL)	EFV EFV + BOC	78667 94655	120 (115-126)

Management of Newly Diagnosed HIV-HCV Coinfected Genotype-1 Patients

Newly diagnosed chronic HCV GT 1 infection

Perform Fibroscan® and/or serum marker and/or liver biopsy

F0F1[a]	F2F3[a]	F4[a]
In general, treatment can be deferred. Consider treatment with Peg/RBV and an HCV protease inhibitor or Peg/RBV alone if low HCV viral load, IL28B CC genotype, absence of insulin resistance and high CD4 count.	Treatment with Peg/RBV and an HCV protease inhibitor. Consider treatment with Peg/RBV if low HCV viral load, IL28B CC genotype, absence of insulin resistance and high CD4 count.	Treatment with Peg/RBV and an HCV protease inhibitor if compensated disease. Treatment should be undergone in specialized centers.

aMetavir fibrosis score: F0=no fibrosis; F1= portal fibrosis, no septae; F2= portal fibrosis, few septae, F3=bridging fibrosis, F4=cirrhosis; Peg, pegylated interferon; RBV, ribavirin

Ingilz & Rockstroh personal communication;
Rockstroh J; 51st ICAAC,;Chicago IL; September 17-20, 2011. Symposium 155.

Management of HIV-HCV GT1-coinfected Patients (Chronic) According to Prior Treatment Outcome

	Naive	Relapser	Nonresponder
F0F1	Individual decision	Individual decision/triple therapy	defer
F2F3	Triple therapy	Triple therapy	defer*
F4	Triple therapy	Triple therapy	Triple therapy

*monitor fibrosis stage annually, preferably with two established methods. Treat with triple therapy, if rapid progression.

Ingilz & Rockstroh personal communication;
Rockstroh J; 51st ICAAC,;Chicago IL; September 17-20, 2011. Symposium 155.

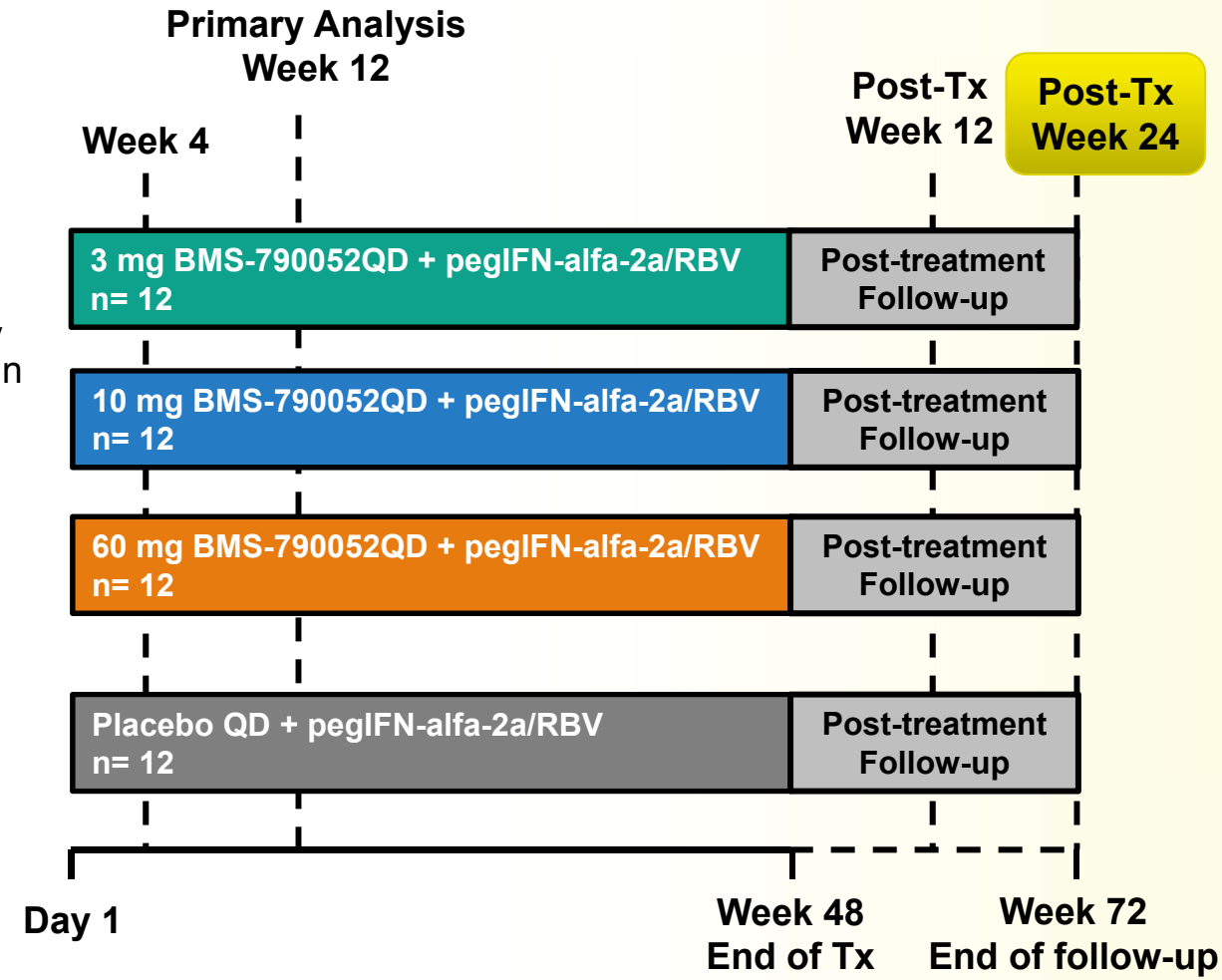
BMS-790052 + PEG-IFN + RBV Combination Therapy in Treatment-naïve HCV GT1 Subjects: Study Design

BMS-790052

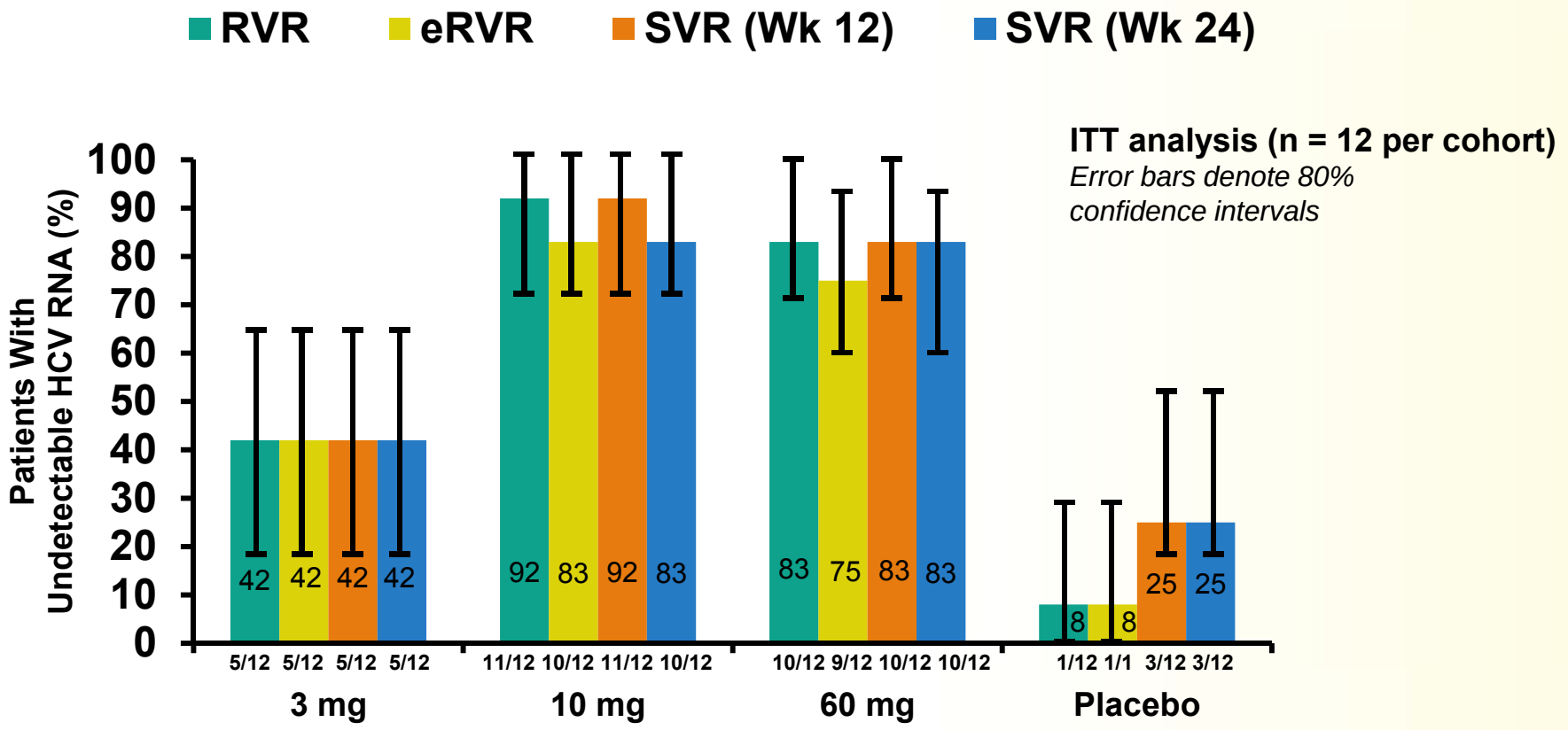
- first-in-class, highly selective HCV NS5A replication complex inhibitor with picomolar potency and broad genotypic coverage in vitro

Double blind, dose finding:

- Peg-IFN/RBV + BMS-072
- 3, 10, 60 mg) vs PCB x 48 wk
- 48 naïve, GT1, non-cirrhotic
- IL28B distribution similar



Virologic Responses During and After Treatment



BMS-790052 (QD)

Virologic failures: 75% in placebo, 17% in BMS-572 10 and 60mg and 58% in 3mg arm (all with resistance mutations)

On-Treatment Safety

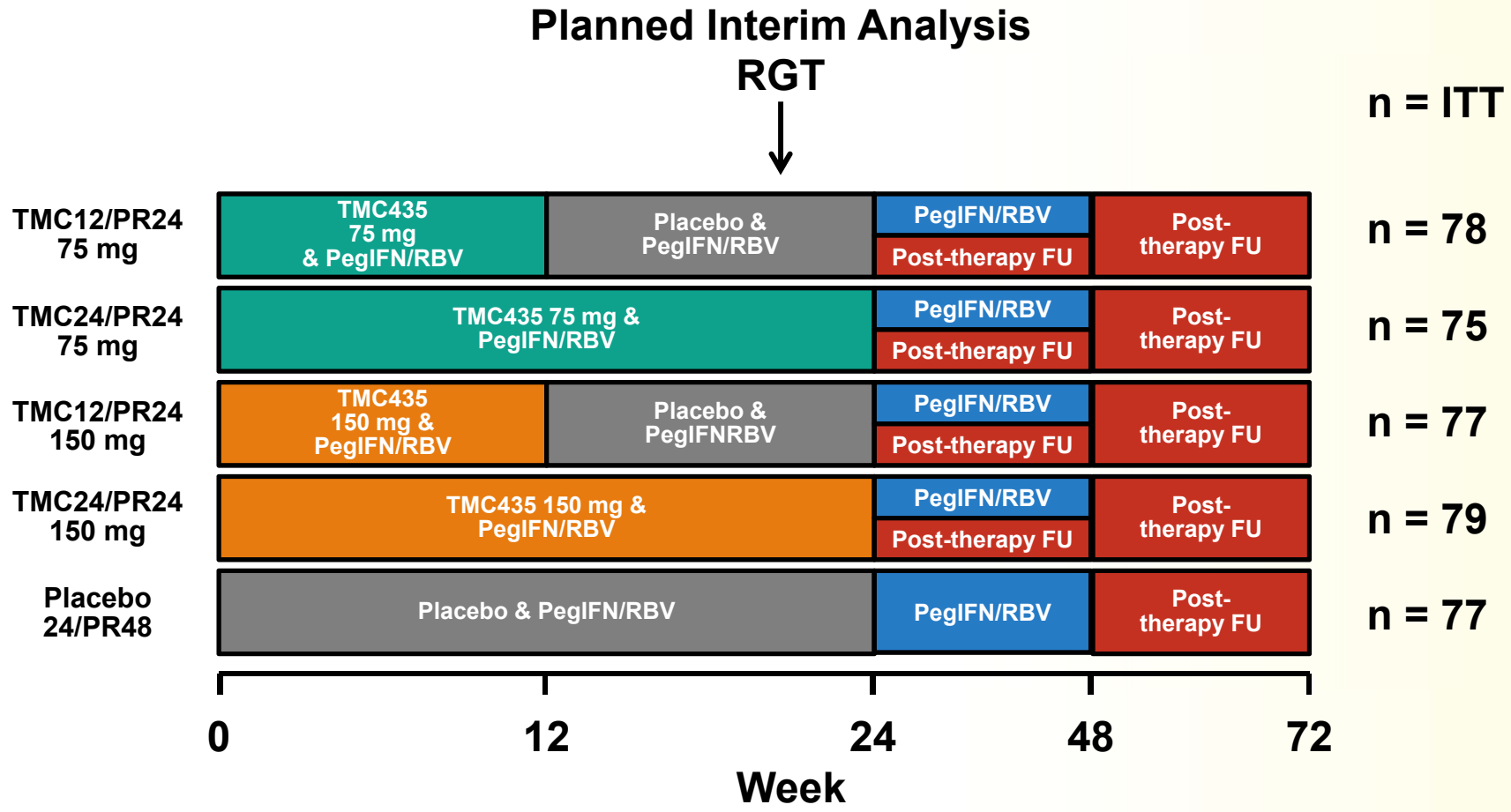
n (%)	BMS-790052 3 mg QD (n = 12)	BMS-790052 10 mg QD (n = 12)	BMS-790052 60 mg QD (n = 12)	Placebo (n = 12)
Grade 3-4 AEs	1 (8.3)	3 (25.0)	4 (33.3)	5 (41.7)
Discontinuations due to AEs	1 (8.3)	1 (8.3)	4 (33.3)	2 (16.7)
SAEs	1 (8.3)	1 (8.3)	1 (8.3)	0
Deaths	0	0	0	0
Treatment interruptions due to AEs				
BMS-790052 (> 3 days)	1 (8.3)	1 (8.3)	2 (16.7)	0
RBV (> 3 days)	1 (8.3)	1 (8.3)	1 (8.3)	0
PegIFN-alfa-2a (> 14 days)	0	0	0	0
Dose reductions				
PegIFN –alfa-2a	2 (16.7)	3 (25.0)	3 (25.0)	6 (50.0)
RBV	5 (41.7)	6 (50.0)	7 (58.3)	7 (58.3)
Filgrastim use	2 (16.7)	3 (25.0)	0	2 (16.7)
Erythropoietin use	1 (8.3)	3 (25.0)	3 (25.0)	2 (16.7)

PILLAR: TMC435 + PegIFN/RBV

- Phase 2b study of TMC435 a once daily HCV protease inhibitor
  - 386 HCV genotype 1 infected patients
  - Treatment-naive
- 5 study arms
  - TMC435 75 mg or 150 mg QD for 12 week + PegIFN/RBV for 24 weeks with response guided therapy with eRVR
  - TMC435 75 mg or 150 mg QD for 24 week + PegIFN/RBV for 24 weeks with response guided therapy with eRVR
  - Placebo +PegIFN + Ribavirin for 48 weeks
- No additional adverse effects compared to PR
- Discontinuation rate due to AE
  - TMC groups, 7.1%
  - Placebo, 7.8%

Fried MW, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. H1-815a.

TMC435 in Combination with PEG-IFN/RBV for Treatment of HCV GT1 Infection: The PILLAR Study

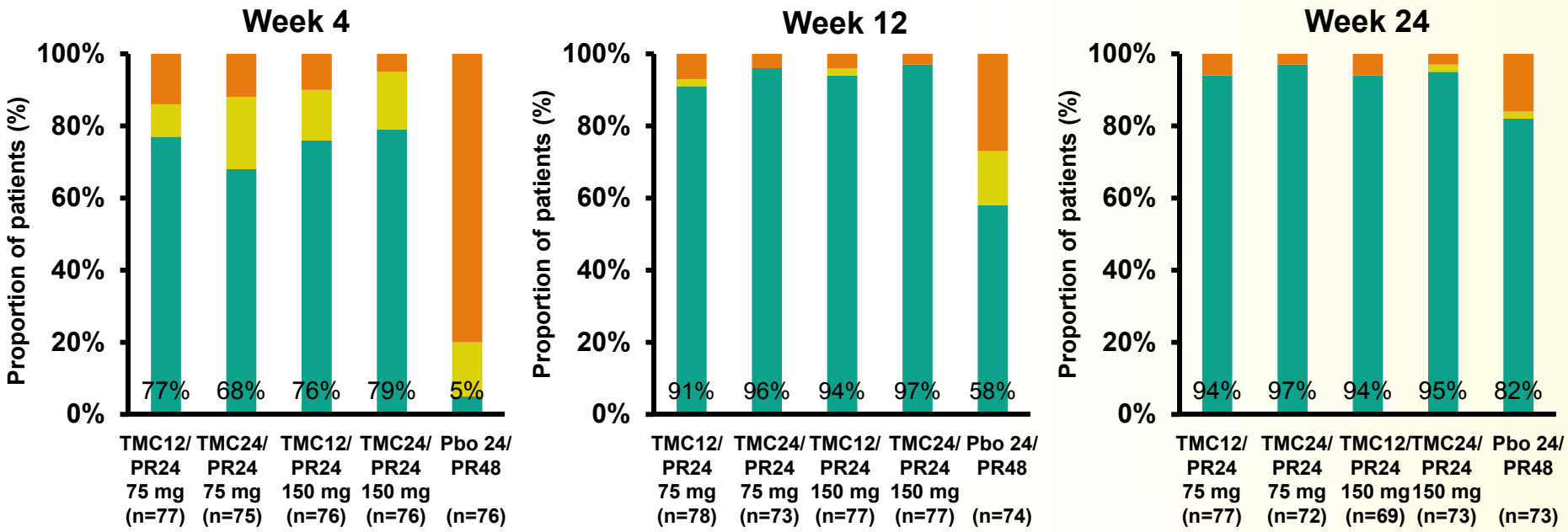


Fried MW, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. H1-815a.

Observed Virologic Response Rates

HCV RNA <25 IU/mL undetectable | HCV RNA <25 IU/mL detectable | HCV RNA ≥25 IU/mL

PILLAR (treatment naïve subjects)



Fried MW, et al. 51st ICAAC; Chicago, IL; September 17-20, 2011; Abst. H1-815a.

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