Continuing Medical Education Internet Symposium

ARV Therapies and Therapeutic Strategies

REPORTING FROM

The 19th Conference on Retroviruses and Opportunistic Infections (CROI)

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

HIV Prevention

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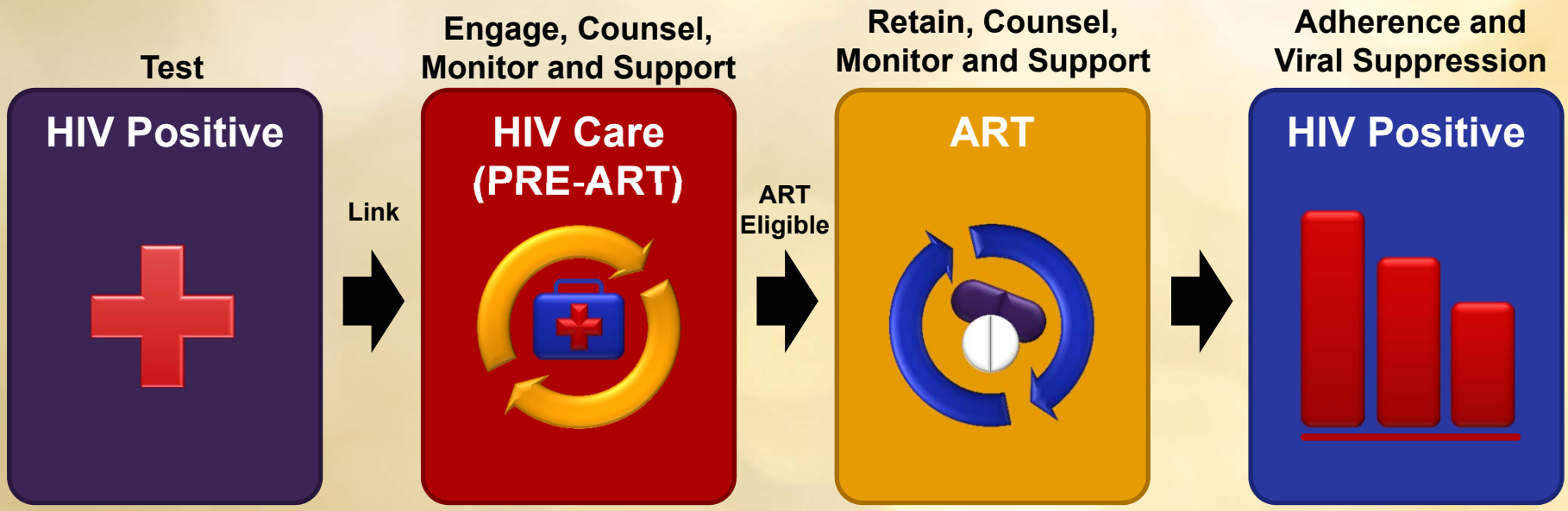
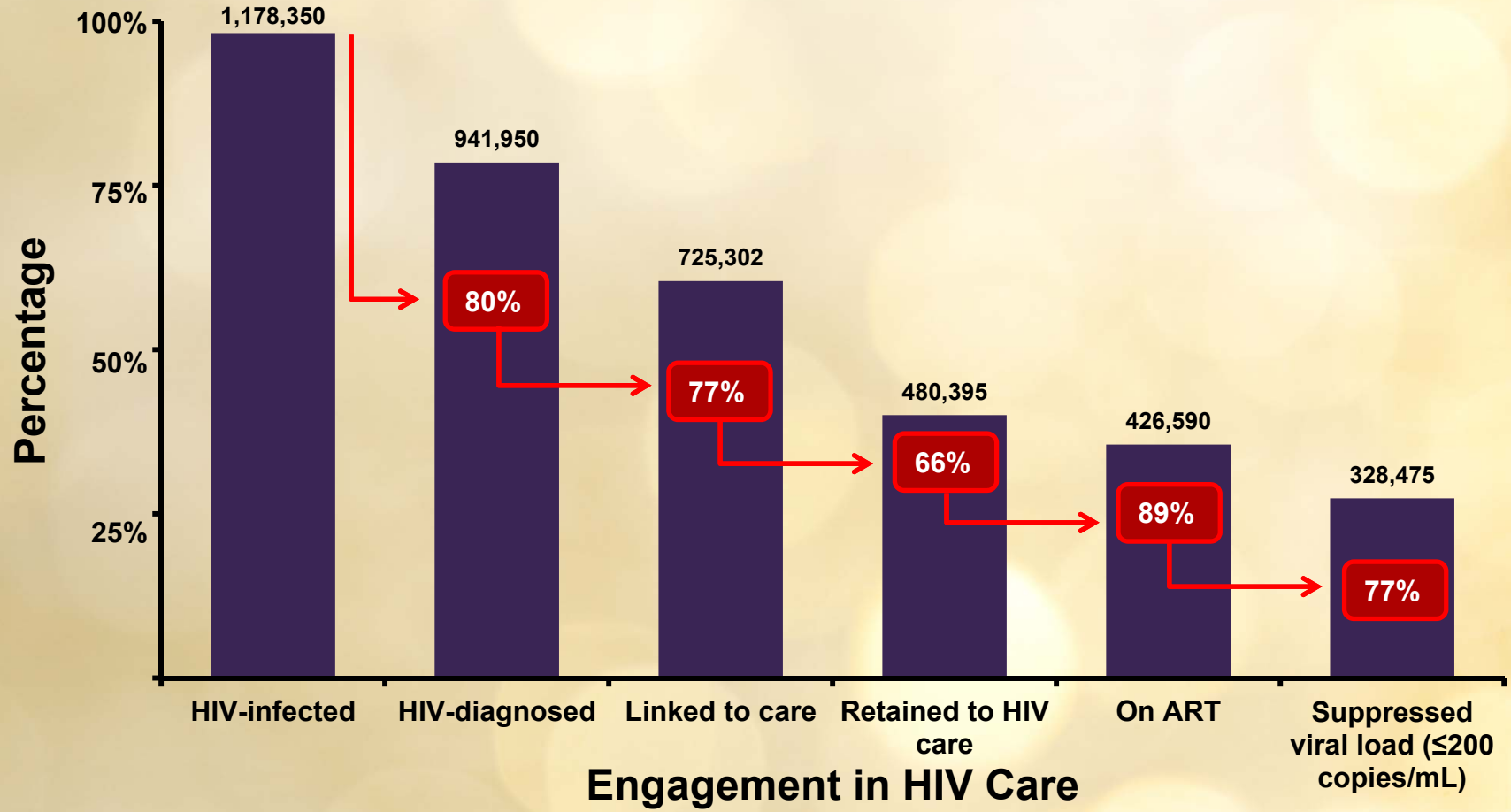
HIV Care/Prevention Continuum



El Sadr W, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 18.

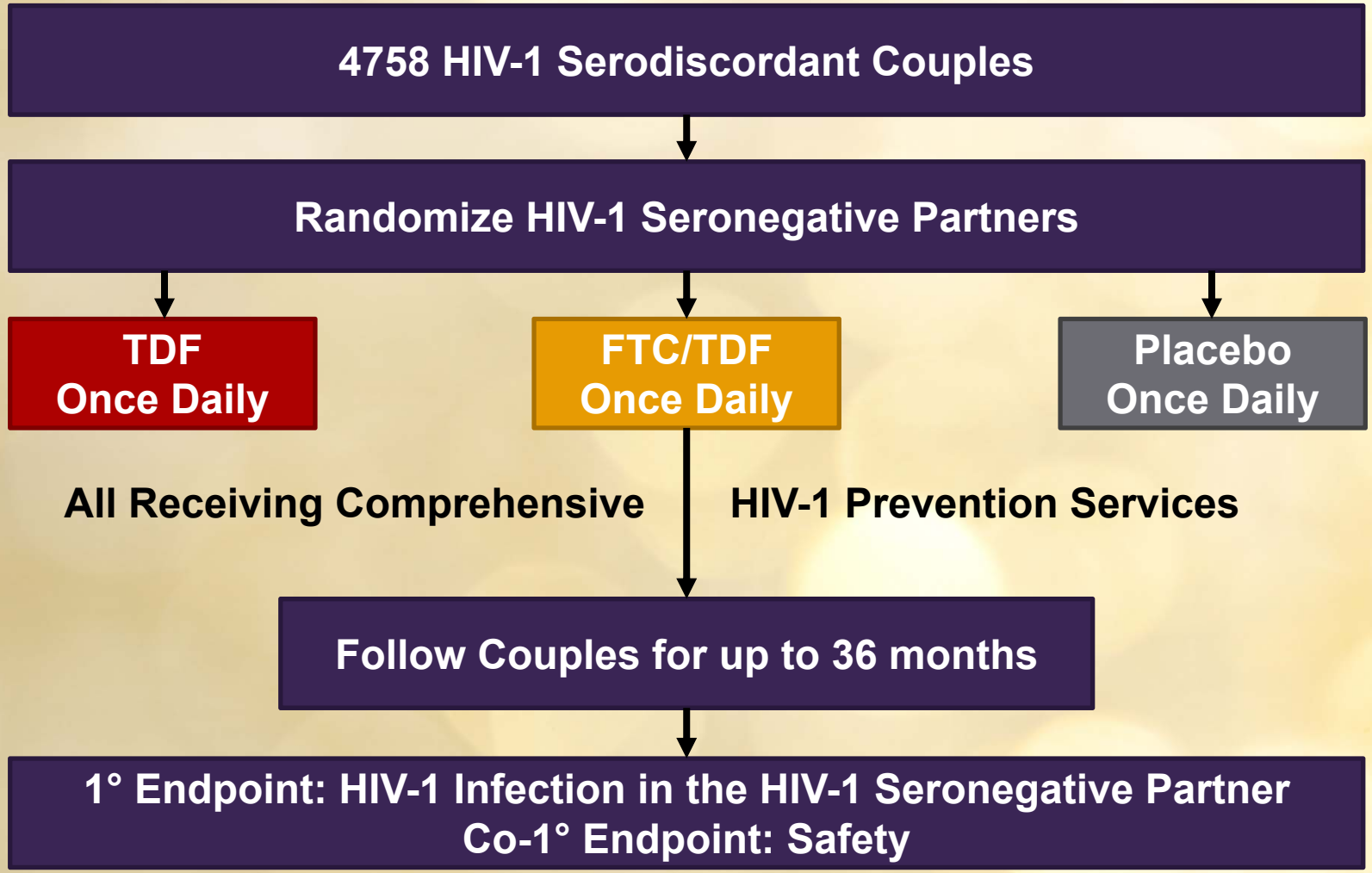
Continuum of HIV Care in United States



Of all with HIV infection, 850,000 individuals do not have suppressed HIV RNA (72%)

MMWR (60), 2011

Partners PrEP Study: HIV Prevention Among Heterosexual Men and Women



Baeten J, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 29.

Partners PrEP: Study Product Distribution and Estimated Adherence

	Total	TDF	FTC/TDF	Placebo
Study medication dispensed % of study visits	96%	95%	97%	96%
% of study time no medication dispensed due to pregnancy	2.0%	2.8%	1.4%	1.7%
% of study time no medication dispensed due to safety hold	0.6%	0.6%	0.7%	0.6%
Dispensed doses estimated to have been taken, based on monthly pill count of unused study product	**97%**	97%	97%	97%

Baeten J, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 29.

Partners PrEP: Primary Efficacy Results (mITT)

	TDF	FTC/TDF	Placebo
Number of HIV-1 infections	17	13	52
HIV-1 incidence, per 100 person-years	0.65	0.50	1.99
HIV-1 protection efficacy, vs. placebo	**67%**	**75%**	
95% CI	**(44.81%)**	**(55.87%)**	
P-value	**<0.0001**	**<0.0001**	

Both TDF and FTC/TDF ruled out <30% efficacy (test against H0=0.7): P=0.003 for TDF and P=0.0004 for FTC/TDF

Baeten J, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 29.

Partners PrEP: Tenofovir Levels Indicate PrEP Use Strongly Correlated with HIV Protective Effects

- Cases
  - 30 seroconverters in active arms (17 TDF, 13 FTC/TDF)
- Cohort
  - 200 uninfected subjects randomly selected from active arms (100 TDF, 100 FTC/TDF)
  - Random selection had no restrictions related to study drug hold, loss to follow up or risk
- Case-cohort design assesses drug levels throughout follow-up

Donnell D, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 30.

Partners PrEP: HIV Risk Reduction for Detectable Levels of Tenofovir

	Cases (TDF = 17, FTC/TDF = 12)				Cohort (N=198)	
	Visits Prior to Seroconversion		Seroconversion Visits		All Visits	
TDF Arm	35/63	**56%**	6/17	**31%**	363/437	**83%**
FTC/TDF Arm	20/36	**56%**	3/12	**25%**	375/465	**81%**

Relative Risk Associated with Detectable Tenofovir

TDF Arm: **86%** (95% CI: 57%, 95%)

FTC/TDF Arm: **90%** (95% CI: 56%, 98%)

Donnell D, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 30.

FEM-PrEP Trial: TDF/FTC as PrEP for HIV in African Women

- Randomized, placebo-controlled, blinded multi-center trial
- 52 weeks of once-daily TDF/FTC or placebo use
- Enroll up to 3900 women to observe 72 HIV infections
- Primary endpoints: incident HIV infection, liver and kidney abnormalities and other safety events
- Extensive behavioral research and community support activities

Van Damme L, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 32LB.

FEM-PrEP: Baseline Data

	TDF/FTC N=1062	Placebo N=1058
	%	%
Age < 25 yr	59	59
Sex for gifts/money with non-primary partners	13	12
Condom use	51	52
Little or no perceived chance of HIV	69	71
Gonorrhea	6	6
Chlamydia	15	13
Vaginal sex acts/week: mean (range)	3.7 (0-28)	3.7 (0-23)

Van Damme L, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 32LB.

FEM-PrEP: Participant Disposition

Screened (N=4163)

Randomize (N=2120)

Arusha, Tanzania	Bondo, Kenya	Bloemfontein, SA	Pretoria, SA
N=63	N=739	N=554	N=764

FTC/TDF	Placebo
N=1024 with follow-up (702 women-years)	N=1032 with follow-up (706 women-years)
148 (13.9%) Lost to FU	118 (11.2%) Lost to FU
59 (5.6%) Discontinued	54 (5.1%) Discontinued
855 (80.5%) Completed	886 (83.7%) Completed

Van Damme L, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 32LB.

FEM-PrEP: Primary Effectiveness Analysis

	TDF/FTC N=1024	Placebo N=1032
HIV Infections	33	35
Incidence Rate	4.7 per 100 P-Y	5.0 per 100 P-Y

Estimated Effectiveness: 6% Reduction in Risk
Hazard Ratio = 0.94 (0.59, 1.52): *P*-value = 0.81

Van Damme L, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 32LB.

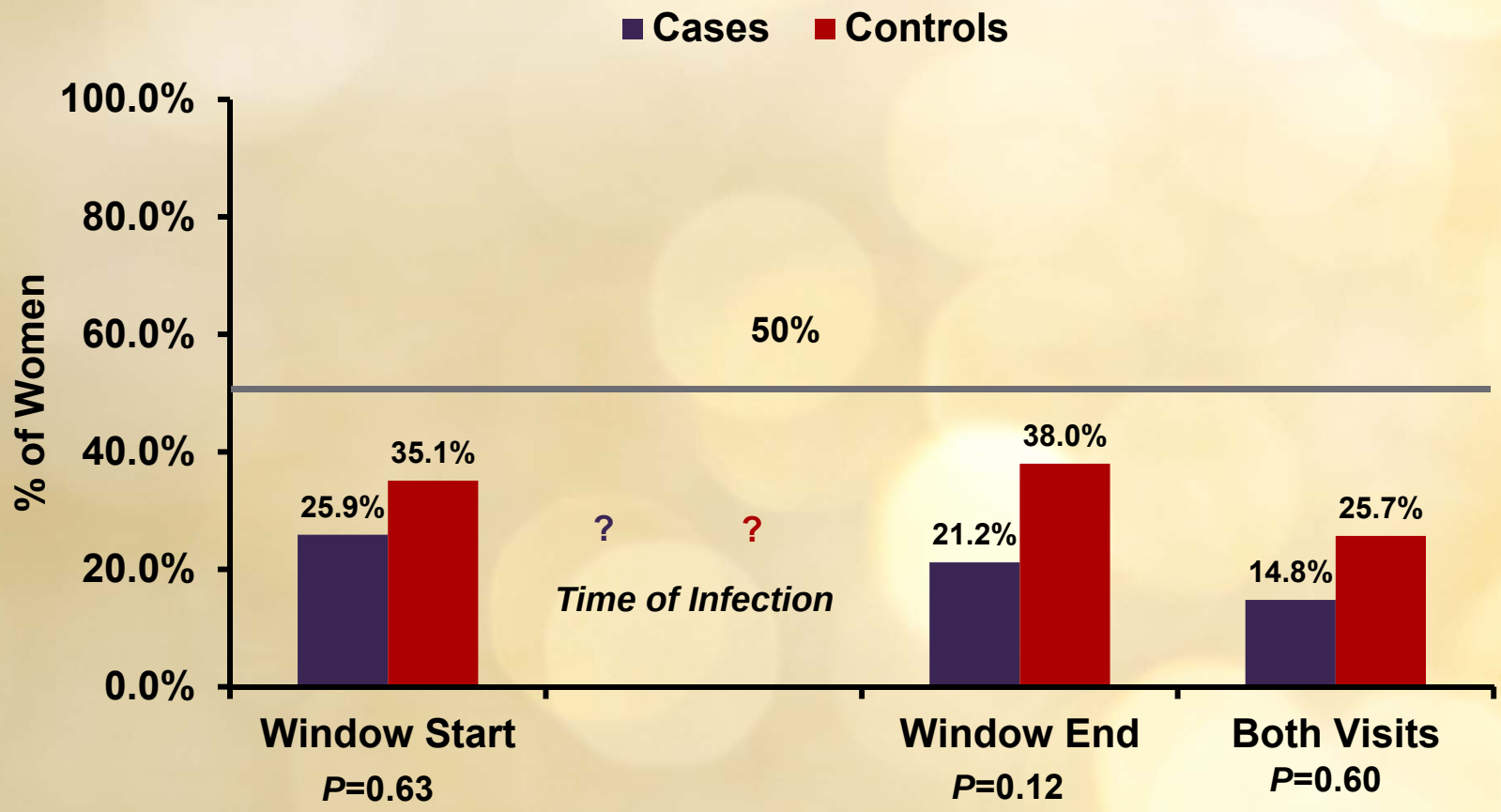
FEM-PrEP Adherence: Self-Report and Pill Counts

	TDF/FTC	Placebo
Usually/always took study pill	95%	95%
Easy/very easy to take pills	97%	96%
Days covered by pills (based on pill counts)	86%	89%

Van Damme L, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 32LB.

FEM-PrEP: Assessment of Tenofovir Drug Levels

Infected *Cases* and Matched *Controls* with ≥10 ng/ml Tenofovir in Plasma at Visits Defining Infection Windows



Van Damme L, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 32LB.

iPrEX: Intracellular Tenofovir Drug Levels and HIV Infection

- Drug levels measured for all active arm participants in iPrEX
- Estimate HIV incidence by time dependent covariates
- Drug levels compared to those in STRAND – PK study of oral TDF in 23 HIV- volunteers

Model estimates for HIV Risk Reduction (95% CI)

2 doses/wk	76% (56-96%)
4 doses/wk	96% (90->99%)
7 doses/wk	99% (96->99%)

Anderson PL, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 31LB.

Studies in Antiretroviral Naïve Patients

Jose R. Arribas, MD
Research Director
HIV & Infectious Diseases
Hospital La Paz
Madrid, Spain

SMART and ESPRIT: Mortality in Patients on ART with Well Controlled HIV and High CD4 Counts

3280 Non-IDU Patients from SMART and ESPRIT

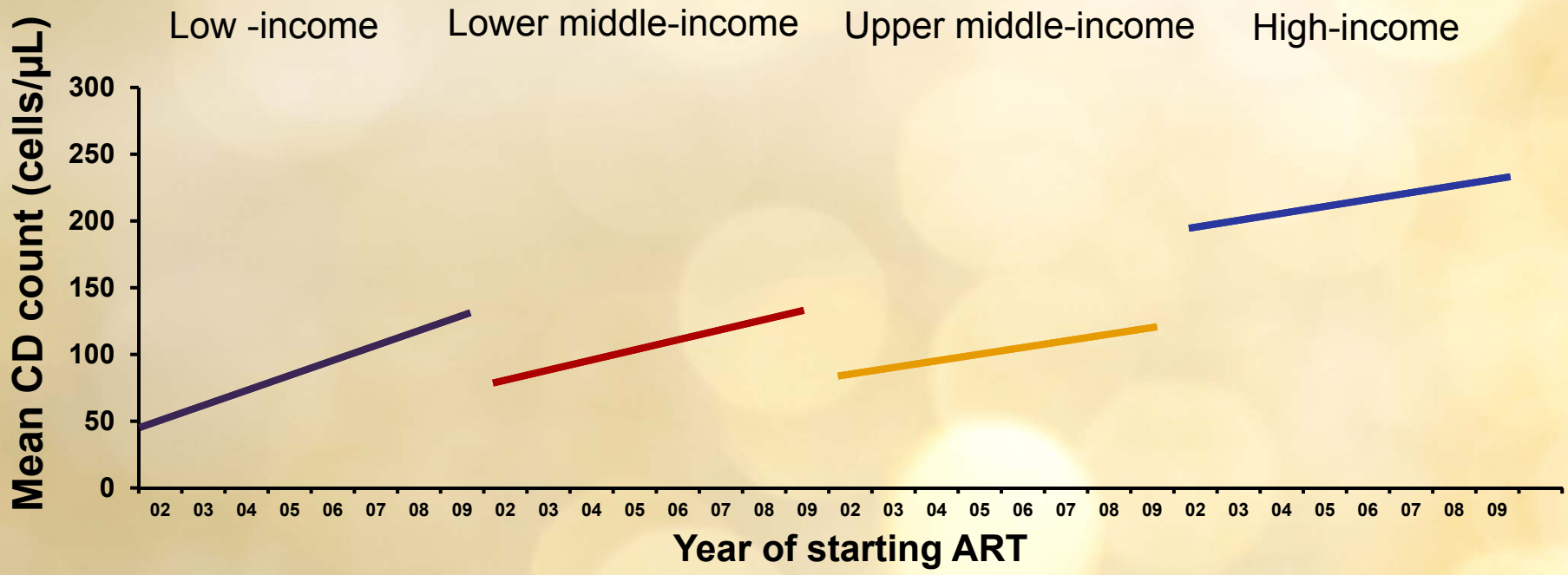
Observed Death Rates and SMRs Standardized by Age and Sex and Country

	Overall	Most Recent Eligible CD4 Count Cells/μL	
		350-499	**>500**
Person-years of follow-up *Proportion*	12357 *100%*	3729 *30%*	8628 *70%*
Observed deaths	62	28	34
Expected deaths	49.82	15.86	33.96
SMR *(95% CI)*	1.24 (*0.95-1.59*)	1.77 (*1.17-2.55*)	1.00 (*0.69-1.40*)

- Patients on ART, with an undetectable VL, with > 500 cells/μL no evidence for a raised risk of death compared to the general population
- Those with 350-500 cells/μL had evidence of higher mortality rates

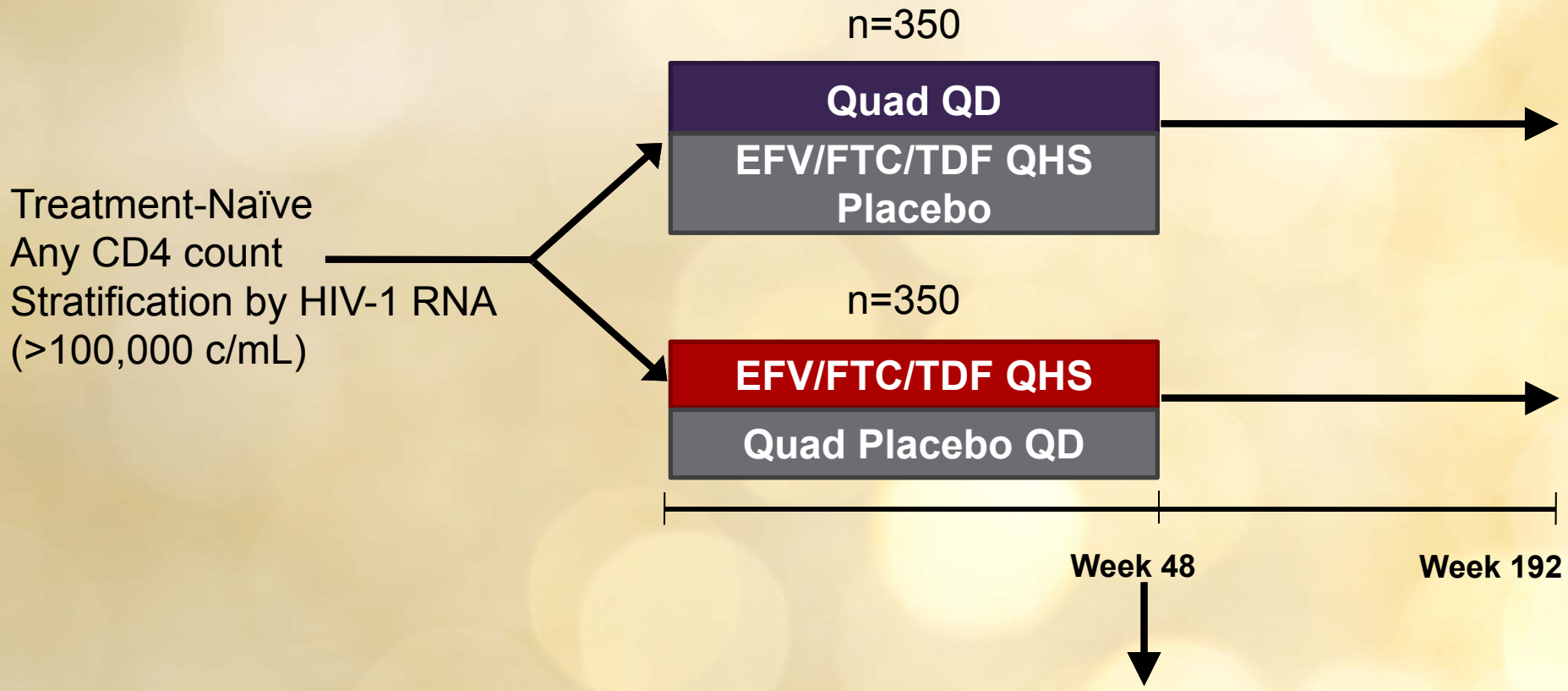
Rodger A, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 638.

CD4 at Start of ART according to country income 2002-2009



Mugglin C, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 100.

Elvitegravir/Cobicistat/FTC/TDF (QUAD) vs. TDF/FTC/EFV (Study 236-102)



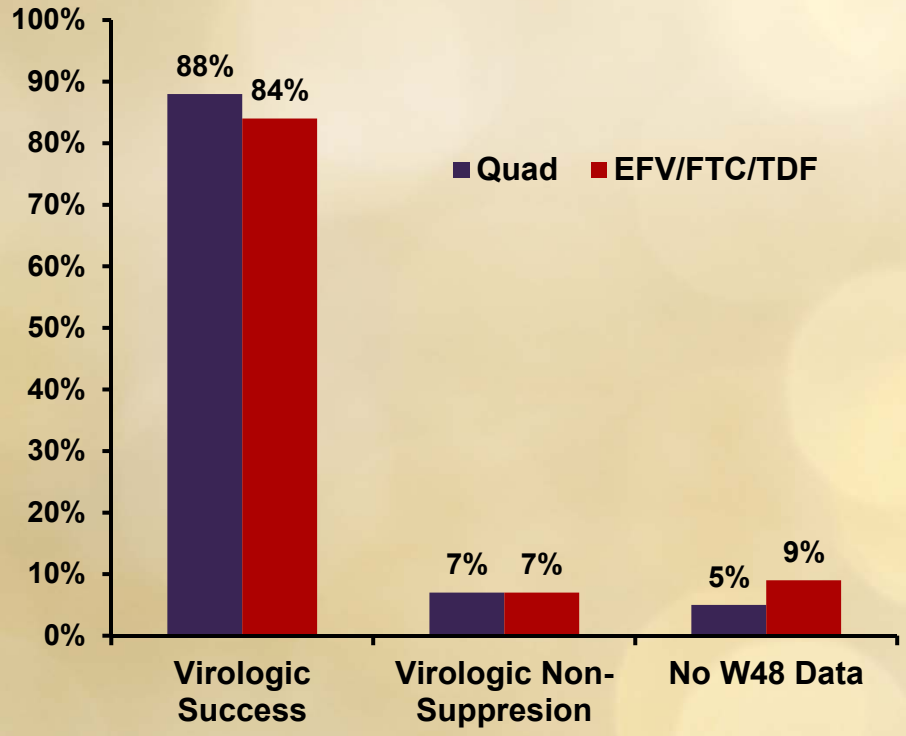
Sax P, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 101.

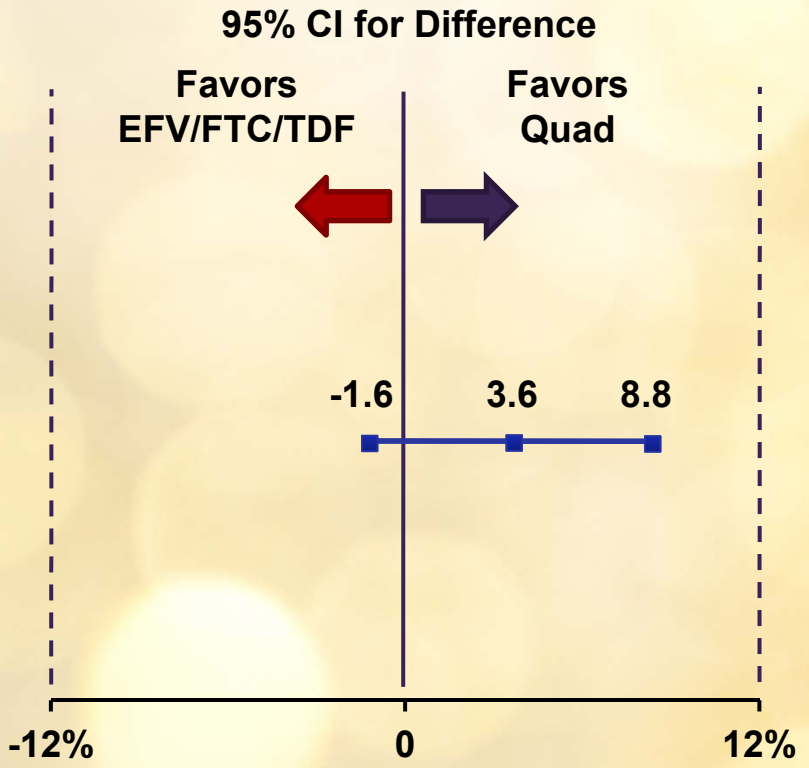
Study 102: Baseline Characteristics

Characteristic	Quad (n=348)	EFV/FTC/TDF (n=352)
Age (years)	38	38
Male	88%	90%
Non-white	39%	36%
Black or African descent	31%	26%
Asymptomatic HIV Infection	83%	84%
HBV – HCV seropositive	1% - 5%	3% - 4%
HIV-1 RNA (log_{10} copies/mL), Median	4.75	4.78
>100,000	34%	33%
CD4 count (cells/mm^3), Mean	391	382
≤200 cells/mm^3	12%	14%
200 to ≤350	32%	27%
351 to ≤500	32%	39%
>500	23%	20%

Sax P, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 101.

Study 102: Efficacy at 48 Weeks

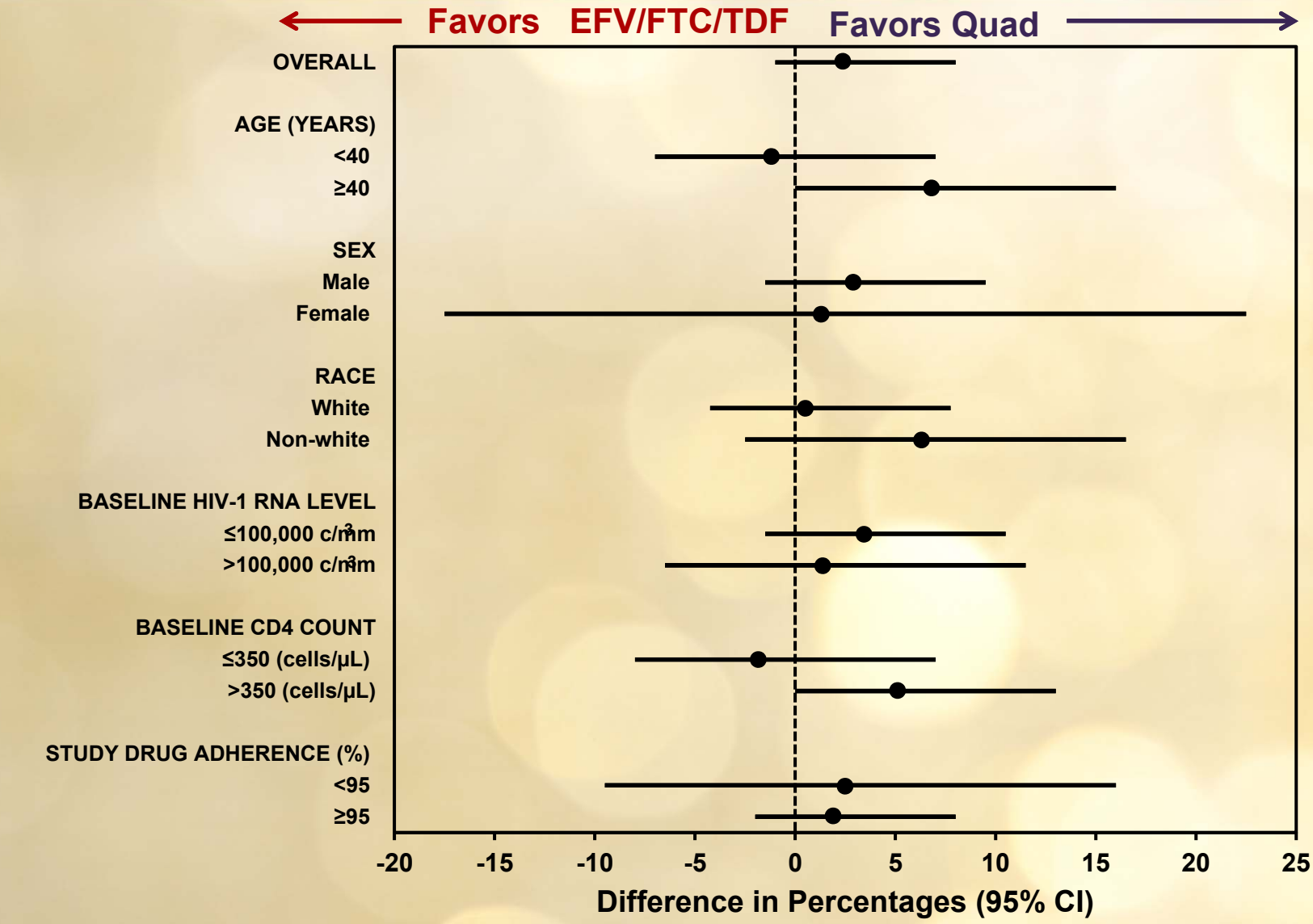




CD4 Change: QUAD +239 vs. EFV +206 Cells/μL (*P*=.009)

Sax P, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 101.

Study 102: Subgroup Analysis



Sax P, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 101.

Study 102: Resistance

	Quad (n=348)	EFV/FTC/TDF (n=352)
Subjects Analyzed for Resistance, n (%)	**14 (4%)**	**17 (5%)**
Subjects with Resistance to ARV Regimen, n (%)	**8 (2%)**	**8 (2%)**
Any Primary Integrase-R, n	**7**	
E92Q	7	
T66I	1	
Q148R	1	
N155H	1	
Any Primary NNRTI-R n		**8**
K103N		7
V108I		2
Y188Y/F/H/L		1
G190A		1
Any Primary NRTI-R, n	**8**	**2**
M184V/I	8	2
K65R	3	2

Sax P, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 101.

Study 102: Adverse Events

	Quad (n=348)	EFV/FTC/TDF (n=352)
Treatment Emergent Adverse Events in ≥ 10% of subjects		
Diarrhea	23%	19%
Nausea*	21%	14%
Abnormal Dreams^	15%	27%
Upper Respiratory Infection	14%	11%
Headache	14%	9%
Fatigue	12%	13%
Insomnla*	9%	14%
Depression	9%	11%
Dizziness^	7%	24%
Rash#	6%	12%

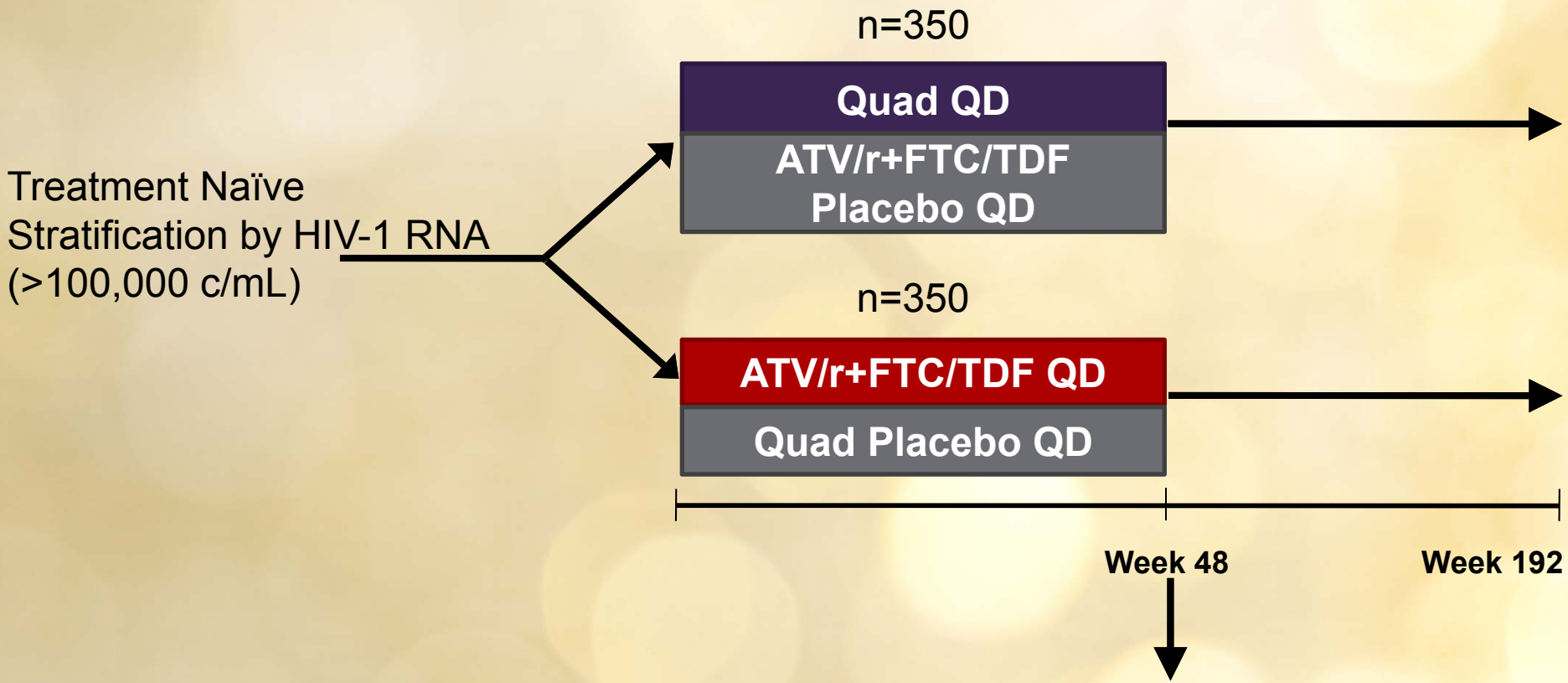
	Quad (n=348)	EFV/FTC/TDF (n=352)
Discontinuations Due to AE	4%	5%
AE leading to discontinuation in >1 subject (%)		
Rash and Drug Hypersensitivity	0	1.4%
Renal Abnormalities	1.4%	0
Depression	0.3%	0.9%
Abnormal Dreams	0	0.6%
Fatigue	0.3%	0.3%
Paranoia	0.3%	0.3%

Change from baseline is serum creatinine 0.14 mg/dL vs. 0.01 mg/dL (Quad vs. EFV/FTC/TDF group, p<0.001).
Smaller increases in total cholesterol and LDL in QUAD

*P<0.05
^P<0.001
#P=0.009

Sax P, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 101.

QUAD vs. ATV/r + TDF/FTC (Study 236-103)



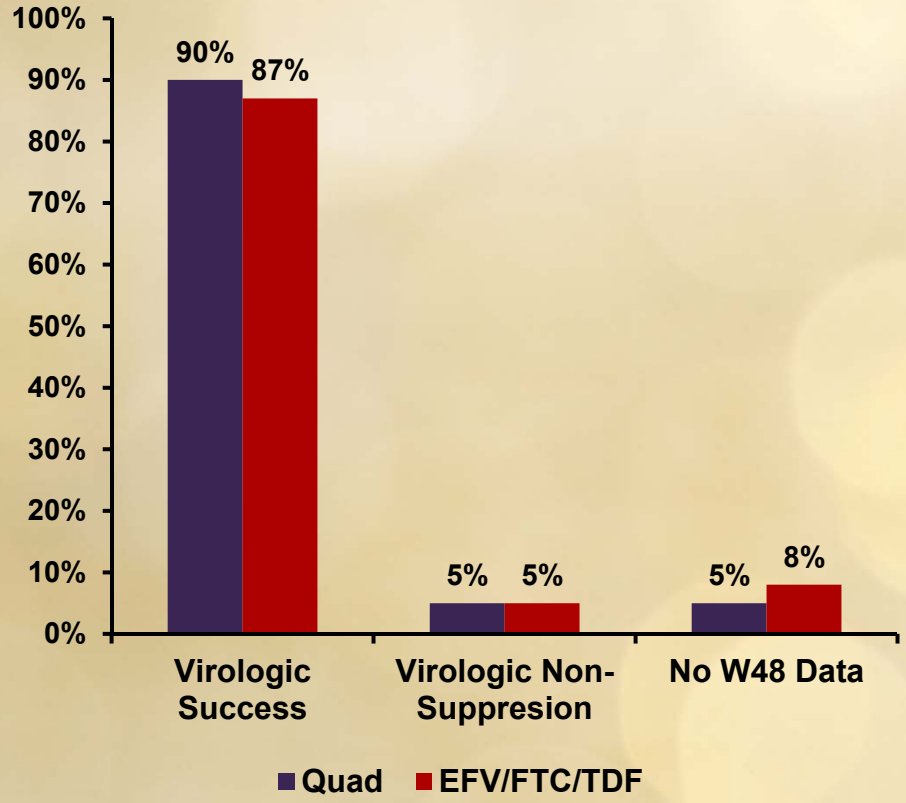
DeJesus E, et al. 19th CROI; Seattle, WA; **March** 5-8, 2012. Abst. 627.

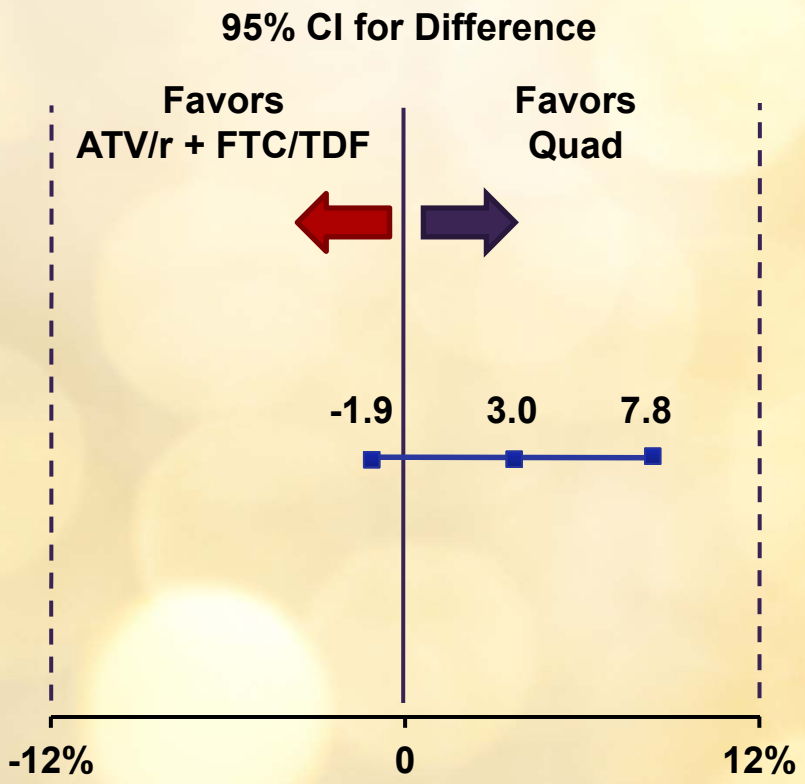
Study 103: Baseline Characteristics

Characteristic	Quad (n=353)	ATV/r + FTC/TDF (n=355)
Age (years)	38	39
Male	92%	89%
Non-White	29%	22%
Black or African Heritage	20%	13%
Asymptomatic HIV Infection	81%	83%
HBV – HCV Seropositive	1% - 5%	2% - 3%
HIV-1 RNA (log_{10} copies mL), Median	4.88	4.86
HIV RNA > 100,000 c/mL	43%	40%
CD4 count (cells/mm^3), Mean	364	375
<200	15%	11%
201 to ≤ 350	35%	35%
351 to ≤ 500	35%	34%
>500	16%	20%

DeJesus E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 627.

Study 103: Efficacy

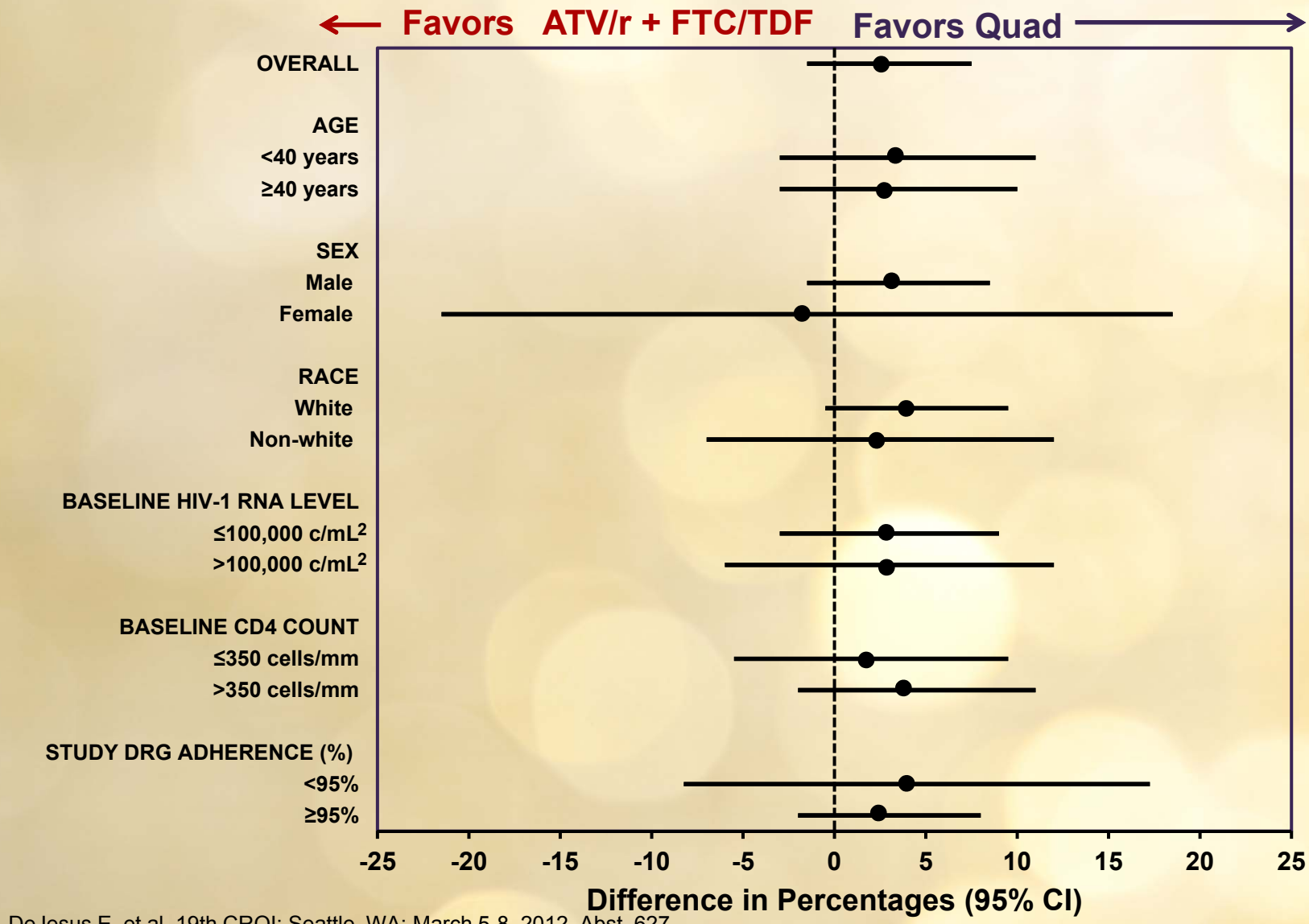




No difference in CD4 cell recovery

DeJesus E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 627.

Study 103: Subgroup Analysis



DeJesus E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 627.

Study 103: Resistance

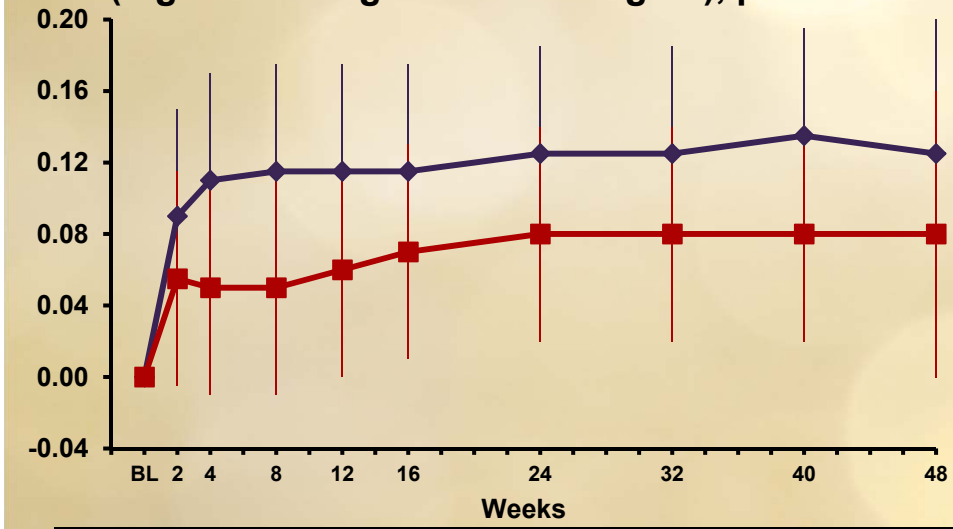
	Quad (n=353)	ATV/r + FTC/TDF (n=355)
Subjects Analyzed for Resistance[a], n (%)	12 (3%)	8 (2%)
Subjects with Resistance to ARV Regimen, n (%)	5 (1%)	0
Any Primary Integrase-R, n	4	-
E92Q	1	-
T66I	1	-
Q148R	2	-
N155H	2	-
Any Primary PI-R, n	-	0
Any Primary NRTI-R, n	4	0
M184V/I	4	
K65R	1	

a. Subjects who experienced either suboptimal virologic response (two consecutive visits with HIV-1 RNA $\geq$ 50 c/mL and <1 log10 below baseline after Week 8), virologic rebound (two consecutive visits with HIV-1 RNA either $\geq$400 c/mL after achieving HIV-1 RNA <50, or >1 log10 increase from nadir), or had HIV-1 RNA $\geq$400 c/mL at their last visit

DeJesus E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 627.

Study 103: Adverse Events

Change from baseline in serum creatinine (mg/dL 0.12 mg/dL vs. 0.08 mg/dL), p<0.001



Adverse Event leading to D/C	Quad (n=353)	ATV/r+FTC/TDF (n=355)
Overall	4%	5%
Diarrhea	1%	<1%
Pyrexia	1%	0%
Nausea	<1%	1%
Vomiting	<1%	1%
Fatigue	<1%	1%
Ocular Icterus	0%	1%
Jaundice	0%	1%
Dizziness	0%	1%
Drug eruption	0%	1%

Grade 3 or 4 labs[a]	Quad (N=353)	ATV/r + FTC/TDF (n=355)
Creatinine Kinase	6%	7%
Hematuria	4%	2%
AST	2%	3%
Amylase	2%	3%
ALT	2%	2%
Hyperbilirubinemia	1%	58%

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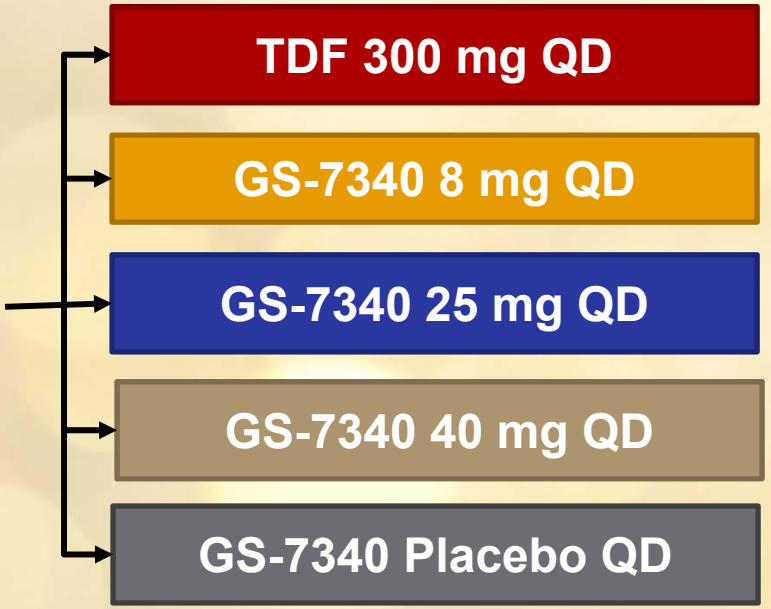
New Antivirals, Newer Biomarkers

Calvin Cohen, MD
Research Director, CRI New England
Clinical Instructor, Harvard Medical School
Boston, Massachusetts

GS 7340 vs. Tenofovir (Study GS-US-120-0104)

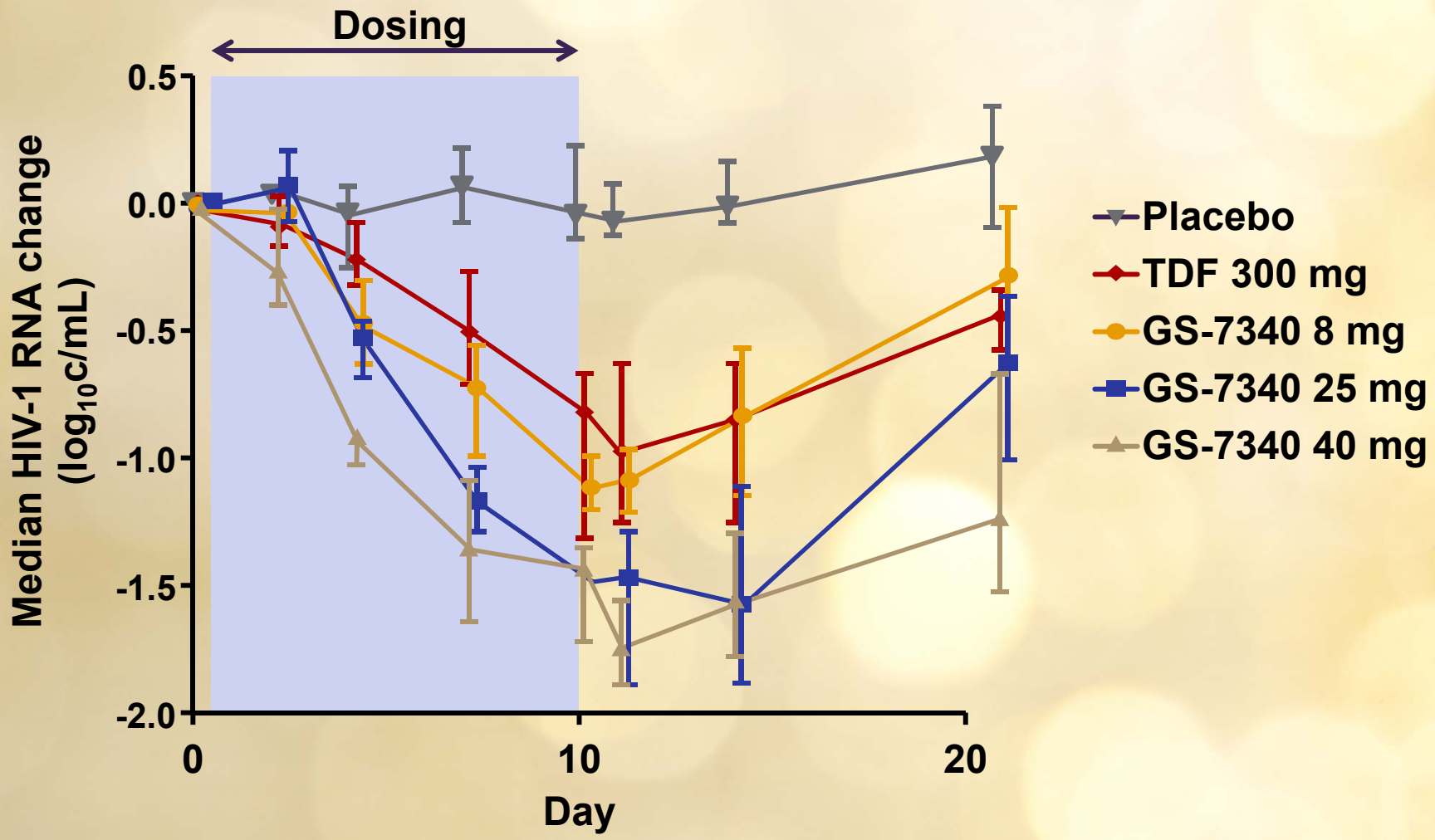
Randomized, Partially-blinded, Placebo and Active Controlled 10-day Monotherapy Study

Treatment-naïve adults
HIV-1 RNA ≥ 2,000 c/mL
CD4 ≥ 200 cells/mm^3
(N = 36)



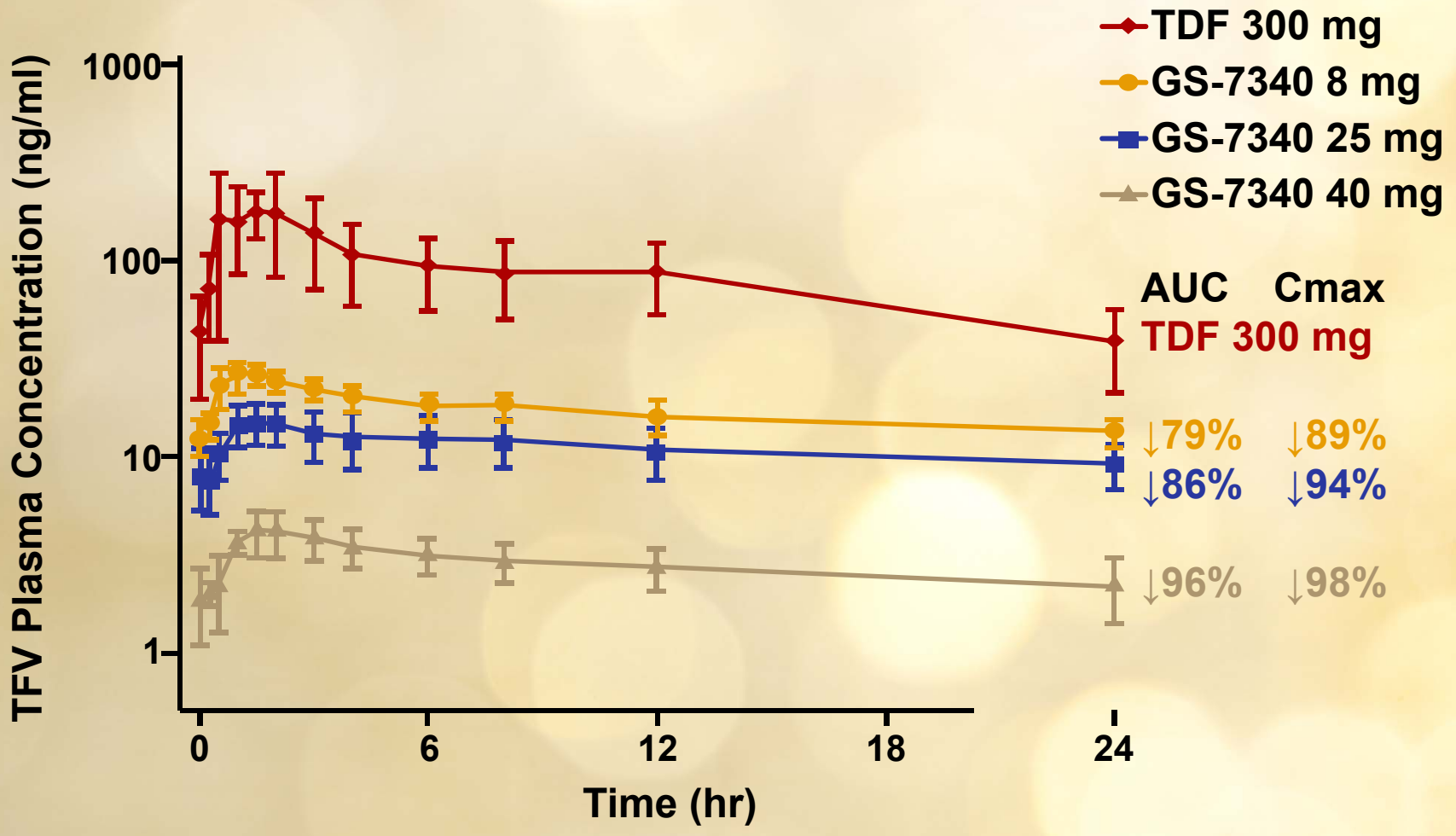
Ruane P, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 100.

GS 7340: Change in Viral Load



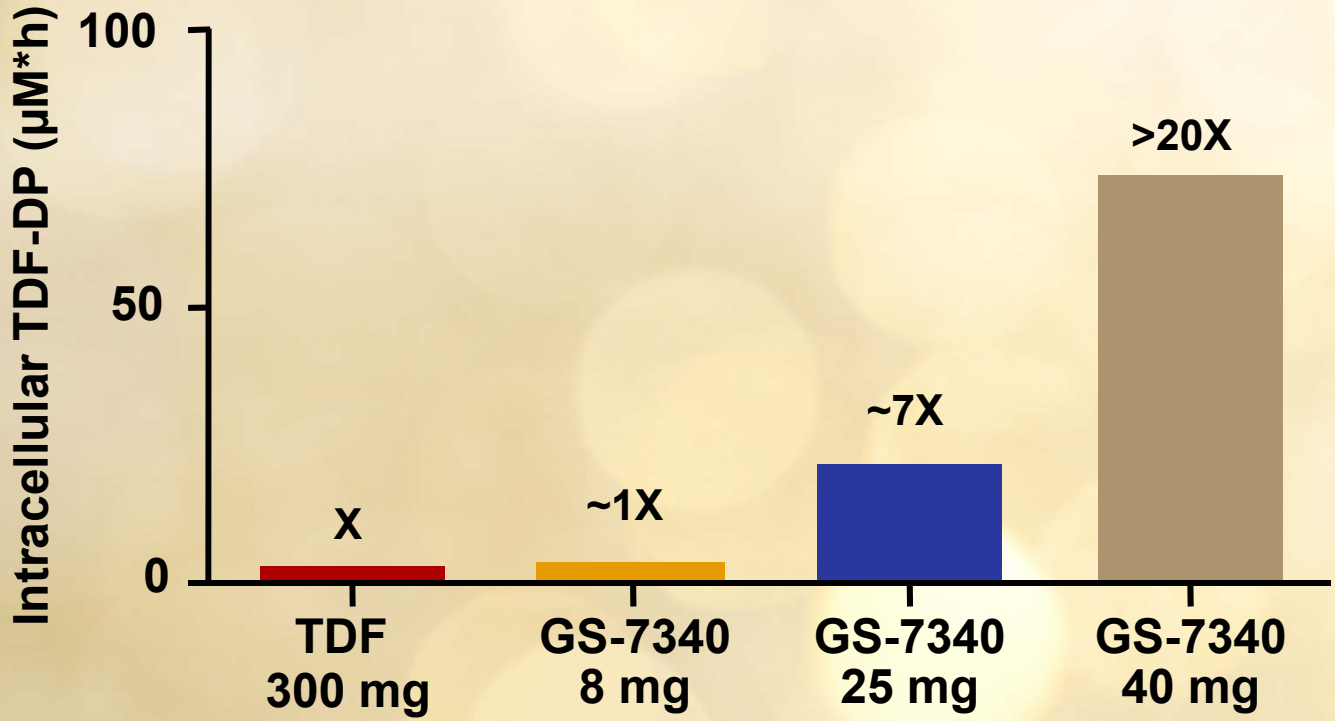
Ruane P, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 100.

GS-7340: Lower Plasma TDF exposure



Ruane P, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 100.

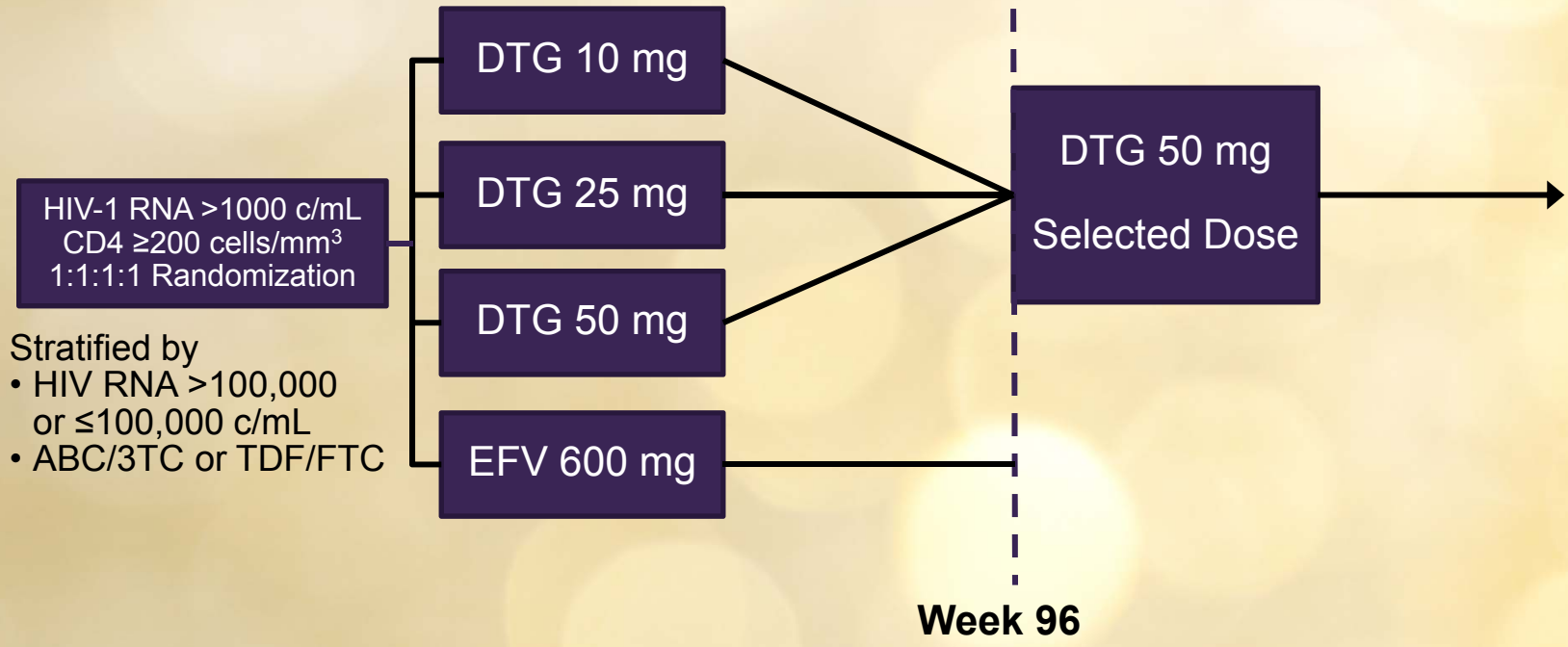
GS-7340: Higher Intracellular TDF-DP concentration in PBMCs



25 mg dose selected for co-formulation with DRV/cobi/FTC for phase II treatment naïve studies

Ruane P, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 100.

SPRING-1: Dolutegravir vs. Efavirenz



Stellbrink JH, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 102LB.

Spring-1: <50 c/mL at Week 96 (TLOVR)

Outcome	DTG 10 mg (N=53)	DTG 25 mg (N=51)	DTG 50 mg (N=51)	EFV 600 mg (N=50)
Responder	79%	78%	88%	72%
Virologic nonresponders				
Rebound by TLOVR	13%	8%	4%	8%
Re-suppressed by Week 96	3	2	1	3
Other nonresponders				
Adverse event	0	2%	2%	10%
Protocol deviation	2%	4%	2%	0
Subject reached protocol-defined stopping criteria	0	0	0	2%
Lost to follow-up/decision by subject	4%	6%	4%	4%
Death	2%	0	0	0
Not discontinued but no data at Week 96 and beyond	0	2%	0	4%

Stellbrink JH, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 102LB.

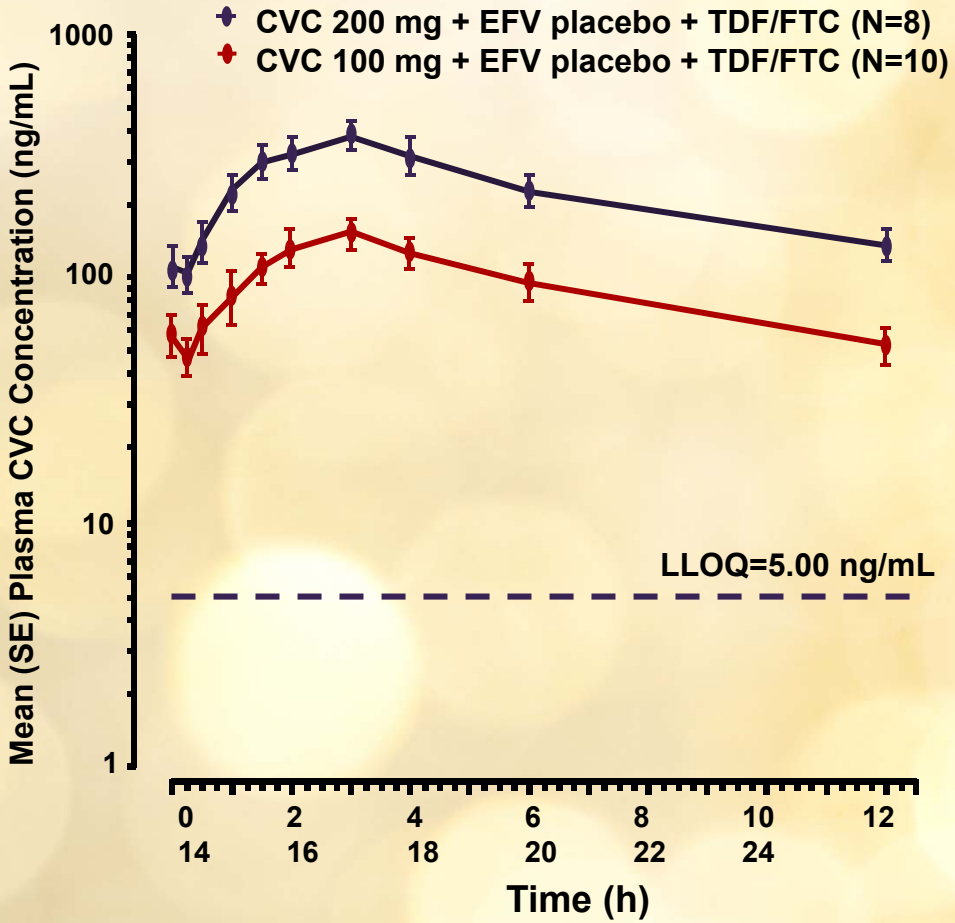
Spring-1: Adverse Events

	DTG 10 mg (N=53)	DTG 25 mg (N=51)	DTG 50 mg (N=51)	DTG Subtotal (N=155)	EFV 600 mg (N=50)
Number of Subjects with any Grade 2-4 Drug-Related Event	8%	10%	16%	11%	24%
Gastrointestinal	2%	4%	2%	3%	4%
Psychiatric disorders	0	0	0	0	6%
Metabolic disorders	0	6%	2%	3%	0
Skin disorders	0	0	0	0	6%
Infections	4%	0	0	1%	0
General disorders	2%	2%	2%	2%	2%
Laboratory Abnormalities	0	2%	2%	1%	2%
Nervous system disorders	0	0	2%	<1%	2%
Serious Adverse Events (all)	9%	10%	14%	11%	14%
AEs Leading to WD/IP Discontinuation	2%	2%	4%	3%	10%

Stellbrink JH, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 102LB.

Cenicriviroc: PK from phase II Study

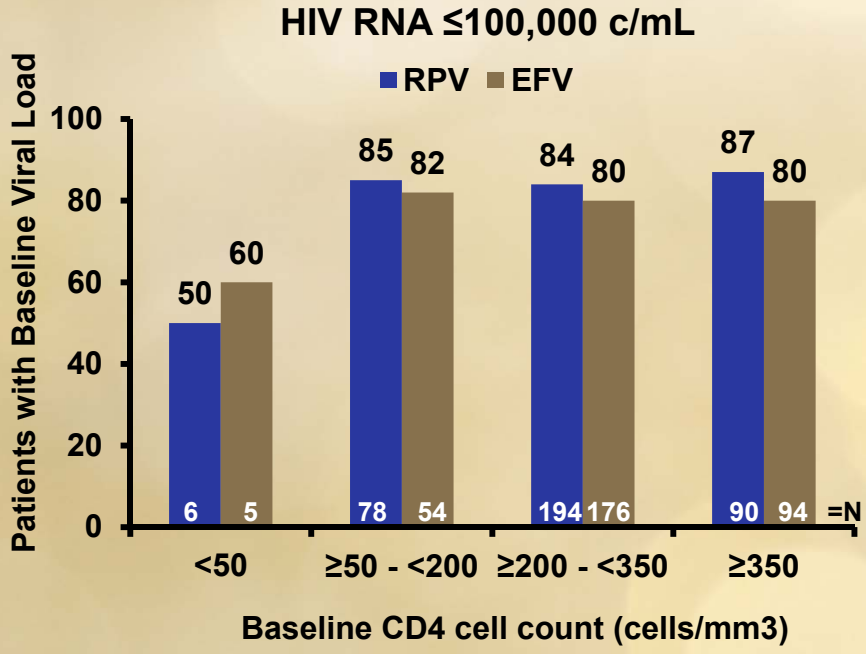
- Cenicriviroc (CVC): Novel CCR5 and CCR2 inhibitor
- Study assessing CVC drug levels in combination with TDF/FTC (N=25)
- Intensive PK done on Day 14 after drug initiated
  - 100 mg QD
  - 200 mg QD
- Conclusion: Adequate exposures seen with both doses
- Phase II study ongoing

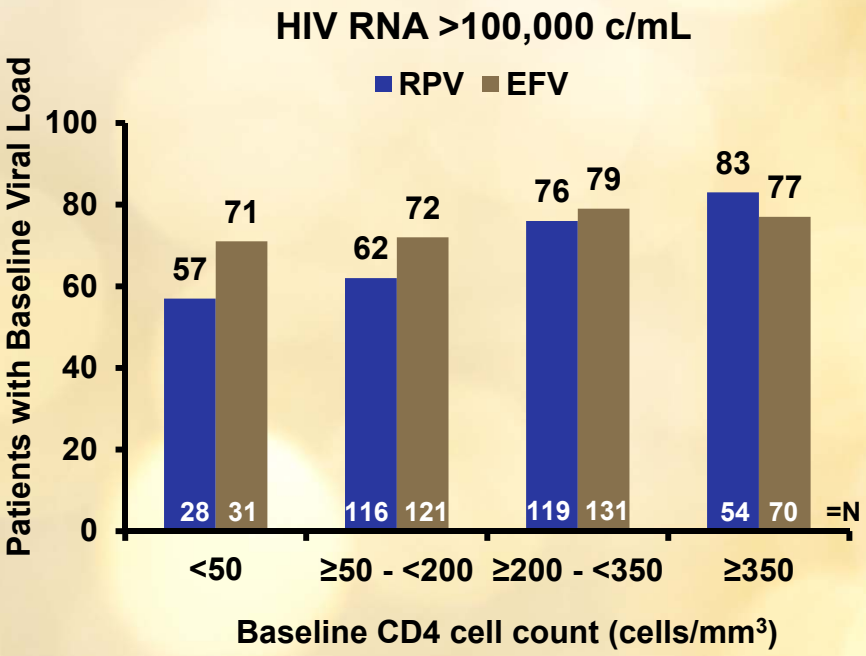


Martin D, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 600.

Pooled ECHO & THRIVE: Response by Baseline CD4 and HIV RNA

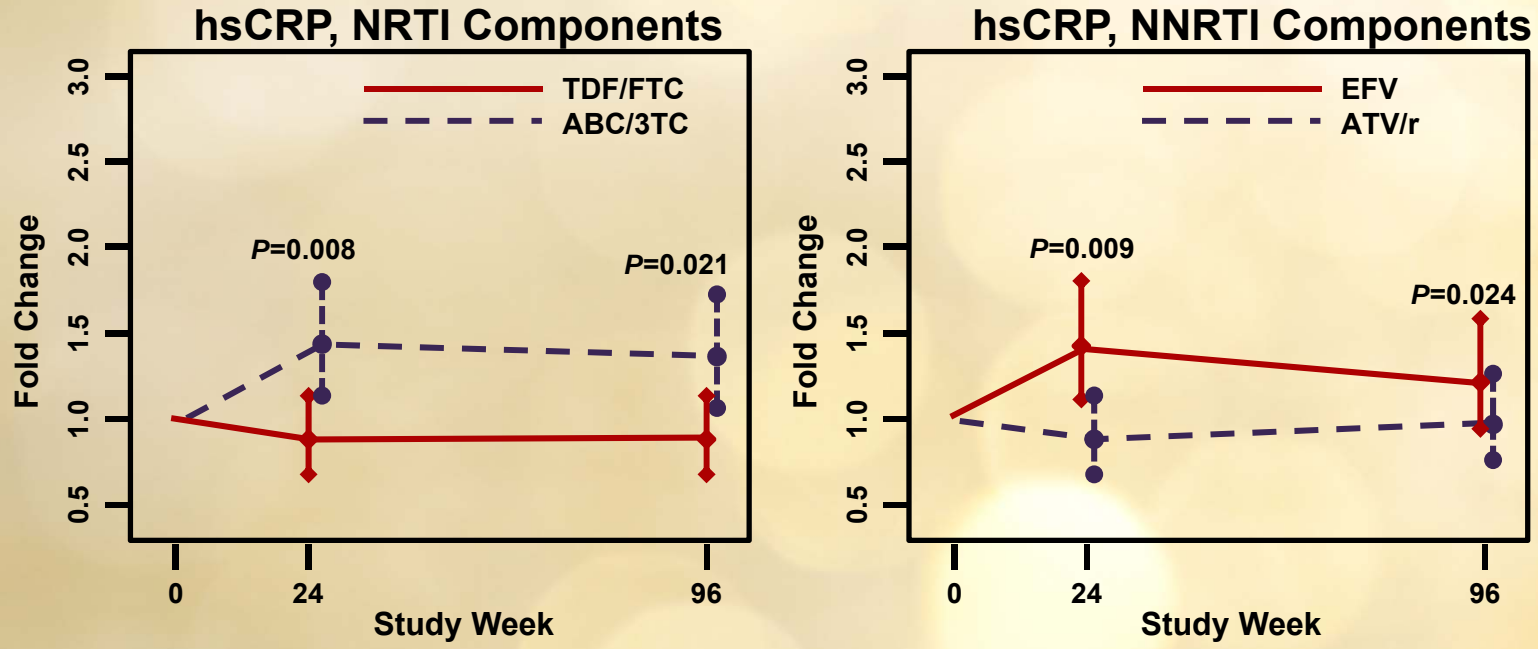
Randomized, double-blind, double-dummy, multicenter, 96-week study
Objective: virologic outcomes; univariate





Cohen C, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 626.

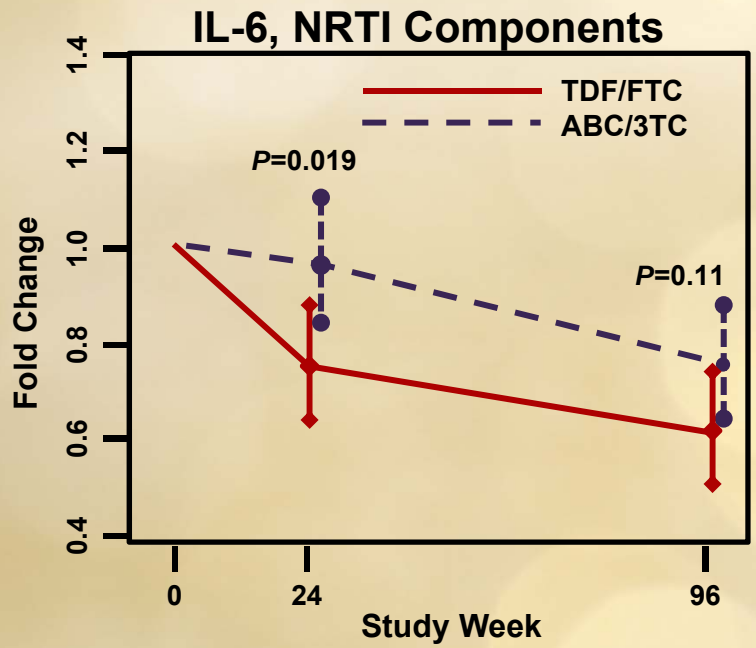
ACTG 5224s: High Sensitivity CRP

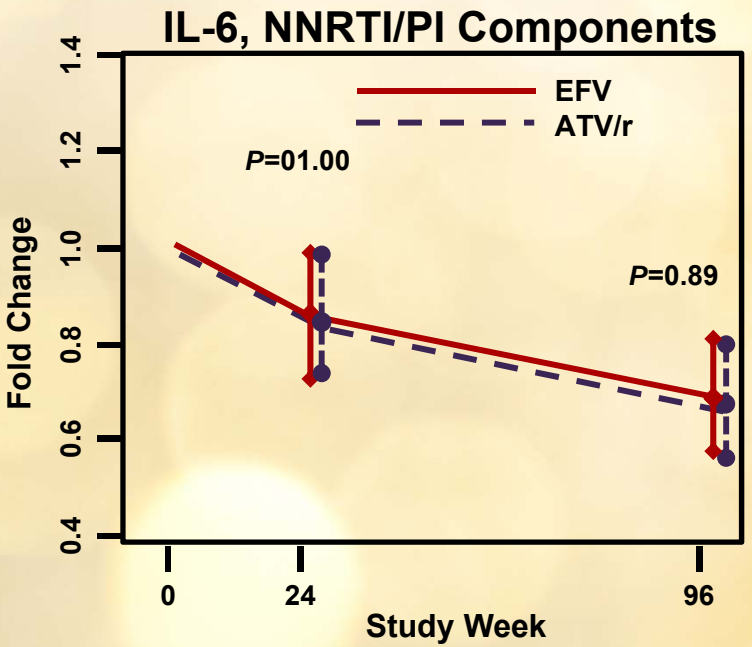


- Sensitivity analyses excluding subjects with suspected hypersensitivity reaction & those with HIV-1 RNA ≥50 copies/mL yielded similar results

McComsey G, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 835.

ACTG 5224s: IL-6 Levels





McComsey G, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 835.

SPIRAL Study: Impact of Switch on Biomarkers

Spiral Study Design: 223 virologically suppressed pts on PI/r

Randomized: Switch PI/r to RAL (n=119) vs. no change (n=114)

	hsCRP	IL-6	Insulin	D-Dimer
Change after switch from PI/r to RAL	-40%	-46%	-26%	-8%
***P* value**	<0.0001	<0.0001	<0.0001	0.018

Conclusions:

- Switch PI/r to RAL decreased biomarkers associated with inflammation, insulin resistance, hypercoagulability
  - No impact on markers of endothelial dysfunction
  - Marker change unrelated to lipid changes
- Similar decreases in hsCRP, IL-6 and D-dimer when switching from ENF to RAL

Martinez E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 840.

Continuing Medical Education Internet Symposium

ARV Therapies and Therapeutic Strategies

REPORTING FROM

The 19th Conference on Retroviruses and Opportunistic Infections (CROI)

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

Hepatitis

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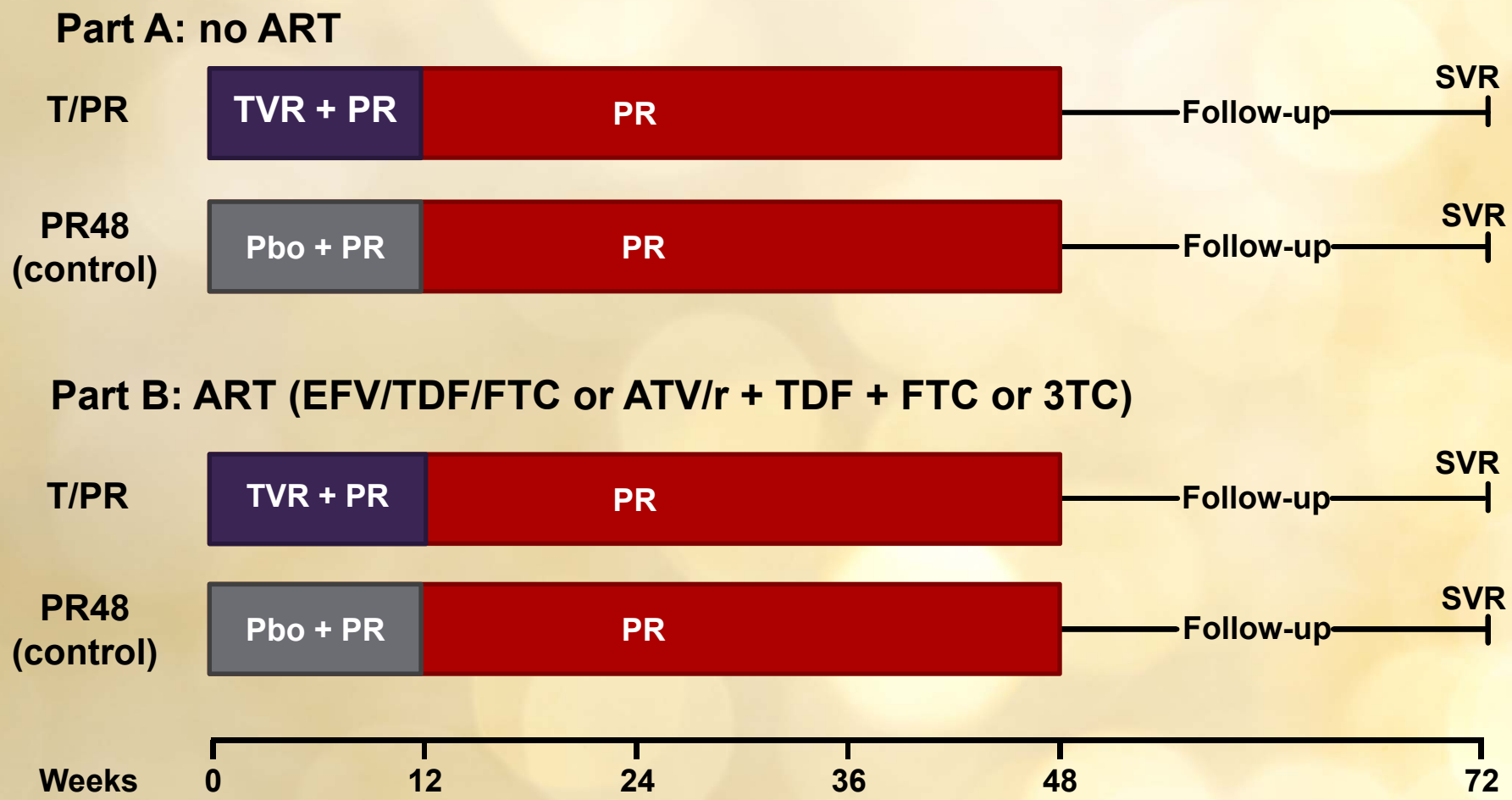
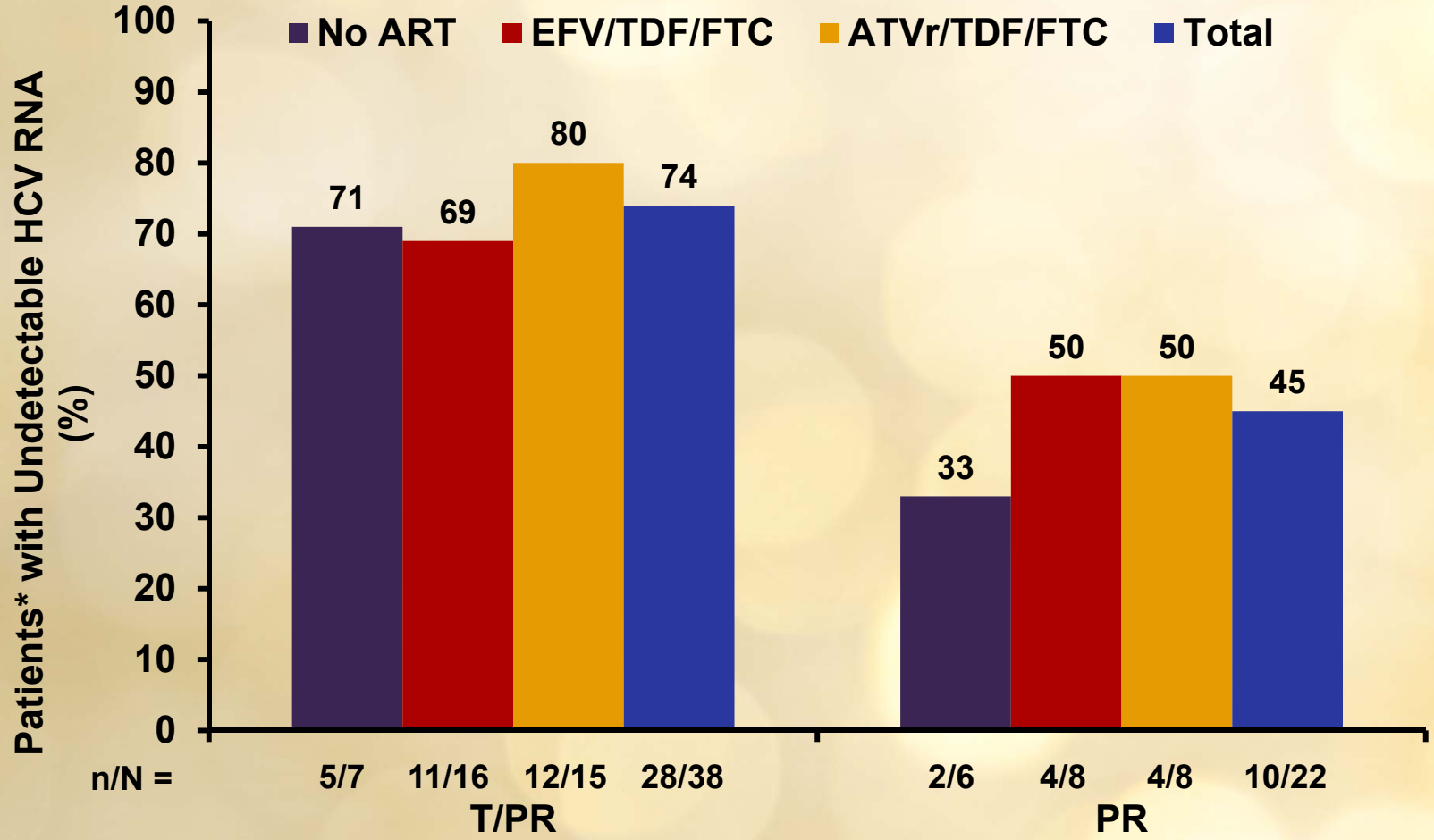
Study 110: Telaprevir in HIV/HCV Co-infected Patients



Dieterich D, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 46.

Study 110: SVR Rates 12 Weeks Post-Treatment (SVR12)



Dieterich D, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 46.

Study 110: Most Common Adverse Events: Overall Treatment Phase

N, (%)	T/PR (N=38), %	PR (N=22), %
Fatigue	16 (42)	9 (41)
Pruritus	**15 (39)**	**2 (9)**
Headache	**14 (37)**	**6 (27)**
Nausea	**13 (34)**	**5 (23)**
Rash‡	**13 (34)**	**5 (23)**
Diarrhea	9 (24)	4 (18)
Dizziness	8 (21)	3 (14)
Pyrexia	**8 (21)**	**2 (9)**
Depression	**8 (21)**	**2 (9)**
Neutropenia	9 (24)	5 (23)
Anemia‡	7 (18)	4 (18)
Vomiting	7 (18)	2 (9)
Myalgia	6 (16)	5 (23)
Chills	6 (16)	4 (18)
Insomnia	**5 (13)**	**5 (23)**
Decreased Appetite	4 (11)	4 (18)
Weight Decreased	**5 (13)**	**5 (23)**

Dieterich D, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 46.

Study 110: Pharmacokinetics of ART After and Before HCV Treatment in HIV/HCV Co-infected Patients

ART Medication	In HIV/HCV Co-infected Patients			
	Median C_{min} Before HCV Treatment (ng/mL)		Median Ratio of C_{min} After: Before HCV Treatment	
	+T/PR	+PR	+T/PR	+PR
Atazanavir (ATV)	962	1280	118%	97%
Efavirenz (EFV)	1320	1700	89%	84%
Tenofovir (+EFV)	51.2	73.9	103%	65%
Tenofovir (-EFV)	128	124	96%	86%

- Week 4 intensive telaprevir pharmacokinetic data were comparable across ART regimens
- Pharmacokinetics of ART medications when co-administered with T/PR resulted in modest changes, consistent with the values obtained in DDI studies in healthy volunteers

Dieterich D, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 461.
van Heeswijk et al. CROI 2011; Boston, MA; Feb 27 – Mar 2, 2011. Abstract 146LB

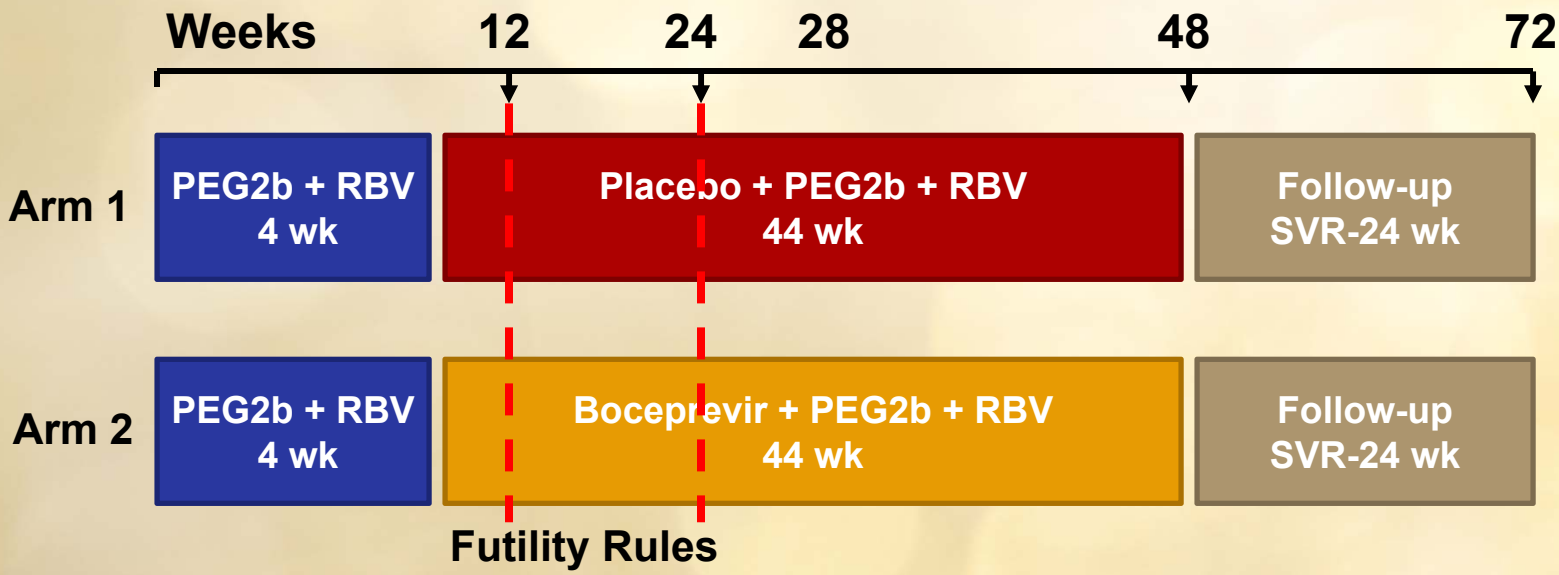
Telaprevir: DDIs with HIV Antiretrovirals

HIV Antiretroviral	Recommendation
Studies Completed	
Atazanavir/r	Clinical and laboratory monitoring for hyperbilirubinaemia is recommended
Darunavir/r **Fosamprenavir/r** **Lopinavir/r**	Not recommended
Efavirenz	TVR dose increase necessary (1125 mg q8h)
Raltegravir	No dose adjustment required
Tenofovir	Increased clinical and laboratory monitoring is warranted

DDI –Drug-drug interactions

Rockstroh J, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Invited Symposium.

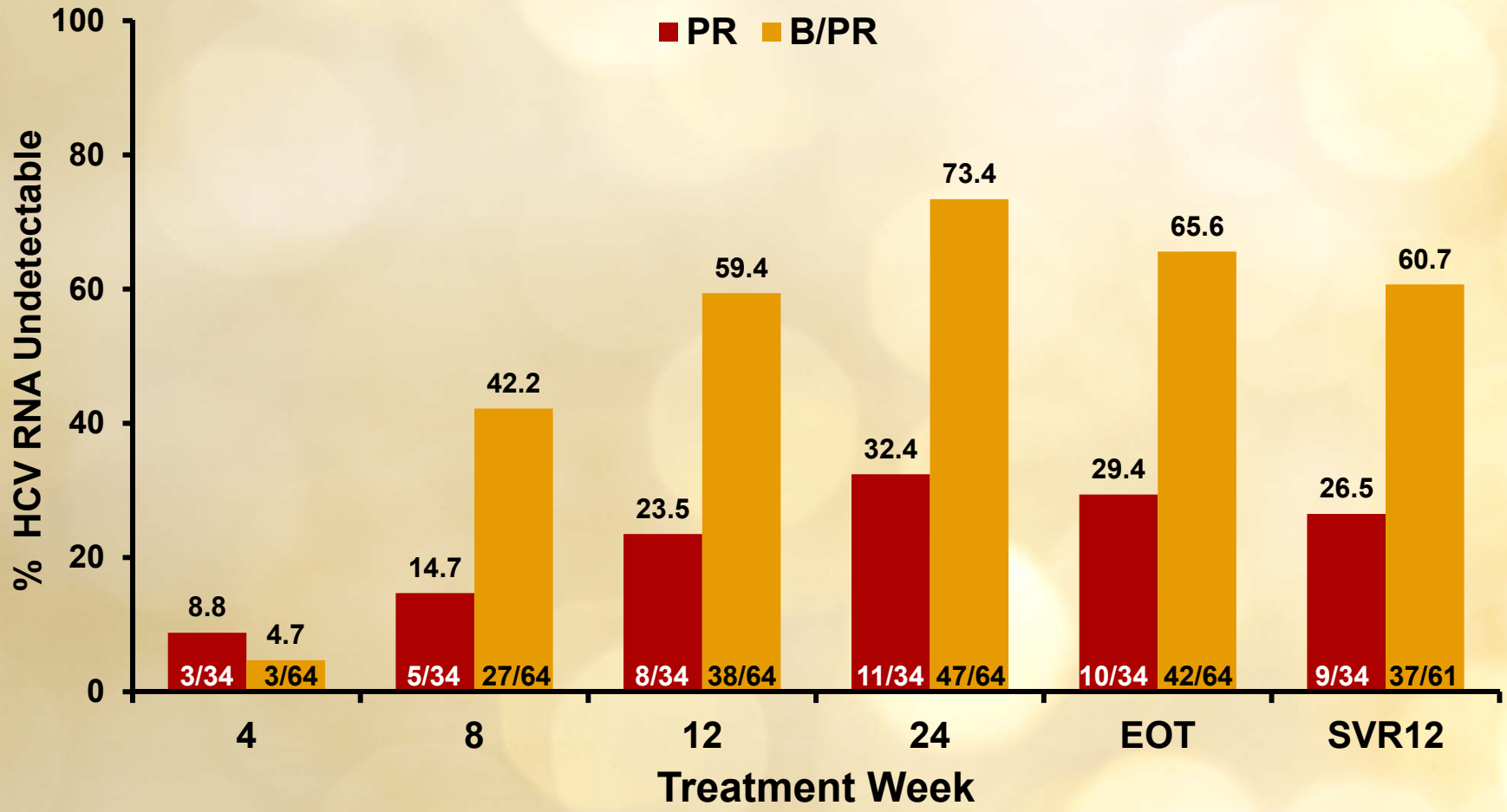
BOC + PEG/RBV for HCV/HIV Co-infection



- Two-arm study, double-blinded for BOC, open-label for PEG2b/RBV
  - 2:1 randomization (experimental: control)
  - Boceprevir dose 800 mg TID
- 4-week lead-in with PEG2b/RBV for all patients
  - PEG-2b 1.5 µg/kg QW; RBV 600-1400 mg/day divided BID
- Control arm patients with HCV-RNA ≥ LLOQ at TW 24 were offered open-label PEG2b/RBV+BOC via a crossover arm

Sulkowski M, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 47.

BOC: Virologic Response Over Time



Sulkowski M, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 47.

BOC: Most Common Adverse Events With a Difference of ≥10% Between Groups

	PR (N=34)	B/PR (N=64)
Anemia	26%	41%
Pyrexia	21%	36%
Asthenia	24%	34%
Decreased appetite	18%	34%
Diarrhea	18%	28%
Dysgeusia	15%	28%
Vomiting	15%	28%
Flu-like illness	38%	25%
Neutropenia	6%	19%

Sulkowski M, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 47.

Effect of ATV/r, LPV/r and DRV/r Co-administration on PK of Boceprevir

Co-administered Drug	Ratio Estimate of co-administered drug (in combination vs. boceprevir alone) GMR (90% CI)		
	AUC_{τ}	C_{max}	C_{min}
Atazanavir	0.95 (0.87, 1.05)	0.93 (0.80, 1.08)	0.82 (0.68, 0.98)
Lopinavir	0.55 (0.49, 0.61)	0.50 (0.45, 0.55)	0.43 (0.36, 0.53)
Darunavir	0.68 (0.65, 0.72)	0.75 (0.67, 0.85)	0.65 (0.56, 0.76)

- Co-administration with ATV/r does not alter boceprevir AUCτ, but coadministration with LPV/r and DRV/r decreases boceprevir AUCτ 45% and 32%, respectively

Hulskotte E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 771LB.

Effect of Boceprevir Co-administration on PK of Ritonavir-boosted ATV, LPV and DRV

Co-administered Drug	Ratio Estimate of Co-administered Drug (in Combination vs. Alone) GMR (90% CI)		
	$AUC_{0\text{-last}}$	C_{max}	C_{min}
Atazanavir (ATV)	0.65 (0.55, 0.78)	0.75 (0.64, 0.88)	0.51 (0.44, 0.61)
Lopinavir (LPV)	0.66 (0.60, 0.72)	0.70 (0.65, 0.77)	0.57 (0.49, 0.65)
Darunavir (DRV)	0.56 (0.51, 0.61)	0.64 (0.58, 0.71)	0.41 (0.38, 0.45)

- Boceprevir coadministration reduces the exposure of ATV, LPV, and DRV 35%, 34%, and 44%, respectively, and reduces trough concentrations 49%, 43%, and 59%, respectively
- Mean ATV C_{min} decreased from 693 ng/mL to 357 ng/mL; mean LPV C_{min} decreased from 6,730 ng/mL to 3,805 ng/mL; mean DRV C_{min} decreased from 3,220 ng/mL to 1,321 ng/mL

Hulskotte E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 771LB.

Boceprevir: DDIs with HIV Antiretrovirals

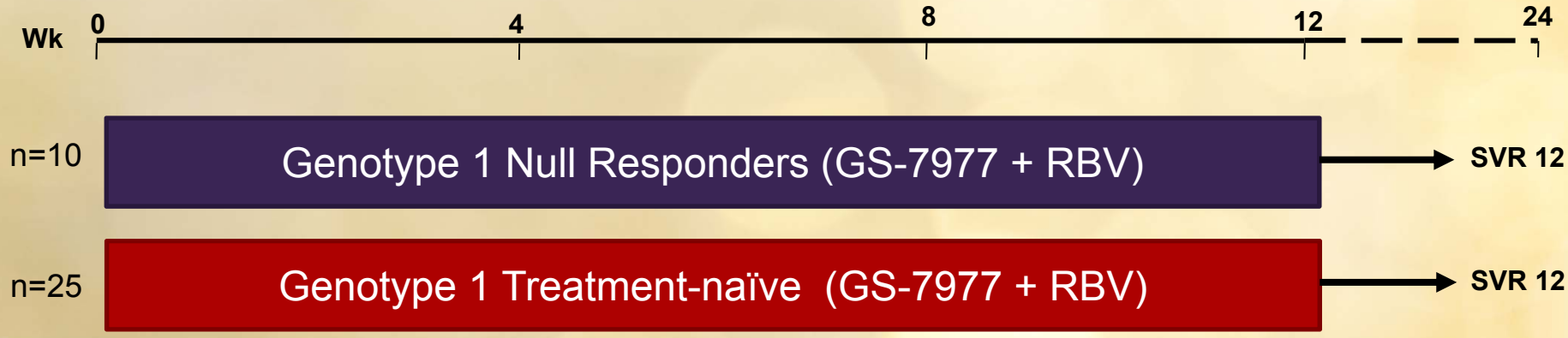
HIV Antiretroviral	Recommendation
Studies Completed	
Atazanavir/r	In general not recommended; EMEA says can be considered on a case-by-case basis if patient has no prior HIV drug resistance and is suppressed
Darunavir/r Fosamprenavir/r Lopinavir/r	Not recommended
Efavirenz	Not recommended
Raltegravir	No dose adjustment required

DDI –Drug-drug interactions

Hulskotte E et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 771LB.
De Kanter C et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 772LB.
FDA Safety Announcement, dated 08 Feb 2012
EMA press release, dated 17 Feb 2012
Merck "Dear Health Care Provider" letter, dated 06 Feb 2012

ELECTRON Study Design for HCV Genotype 1

- To evaluate the antiviral activity of 12 weeks GS-7977 + RBV in genotype 1 patients who were either:
  - Prior null responders (<2 $\log_{10}$ reduction in HCV RNA at Week 12 of a Peg/RBV regimen)
  - Treatment-naïve



- RBV dosing in all arms, independent of HCV genotype, was 1000 mg for patients <75 kg and 1200 mg for those ≥75 kg

Gane E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 54LB.

One Genotype 1 Prior Null Responder Achieved SVR4

	Genotype 1 Null Responders (N=10)		Genotype 1 Treatment-naive (N=25)		Genotype 2/3 Treatment-naive (N=10)	
	n/N	%<LOD	n/N	%<LOD	n/N	%<LOD
Week 1	1/10	10	7/25	28	2/10	20
Week 2	7/10	70	17/24	71	10/10	80
Week 4	10/10	100	25/25	100	10/10	100
Week 10	9/9	100	25/25	100	10/10	100
Week 11	9/9	100	16/16	100	10/10	100
Week 12	9/9	100	6/6	100	10/10	100
SVR 4	1/9	11	-	-	10/10	100

Gane E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 54LB.

GS-7977 + RBV was Generally Safe and Well Tolerated in Genotype 1 Patients

- No discontinuations
- No grade 3 or 4 adverse events
- No grade 2 adverse events in >1 patient
  - 1 null responder experienced 3 AEs: anxiety, depression, and sprained ankle
  - In the treatment-naïve arm, 1 patient each experienced headache, nerve pain, chest pain, and vomiting
- Low rates of laboratory abnormalities
  - In null responder arm, 1 patient had hemoglobin 7.0-8.9 g/dL and 1 patient (on concomitant warfarin) had INR 3 × ULN
  - In the treatment-naïve arm, 1 patient had WBC <1000/mm^3

Gane E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 54LB.

Roundtable Discussion

- Choosing Initial ARV Regimens
- HCV-HIV Co-infection
- HIV Prevention

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