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CROI 2013 – Eindrücke aus der Ferne

Funktionelle Heilung

Paper #48LB
Functional HIV Cure after Very Early ART of an Infected Infant

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The Second Cure?

- Infant born at U. Miss Medical Center
- Mother HIV+ (EIA, WB); no prenatal care

- Maternal VL: 2423 c/mL, CD4 644/mm^3
  - Infant born 35 weeks; NSVD
  - Rapid test HIV+ in neonate

- Standard testing of exposed infants:

2 HIV+ tests from 2 samples

Sample	Age	Test	Result
Blood	30 hours	HIV DNA	positive
Blood	31 hours	HIV RNA	19,812 c/mL

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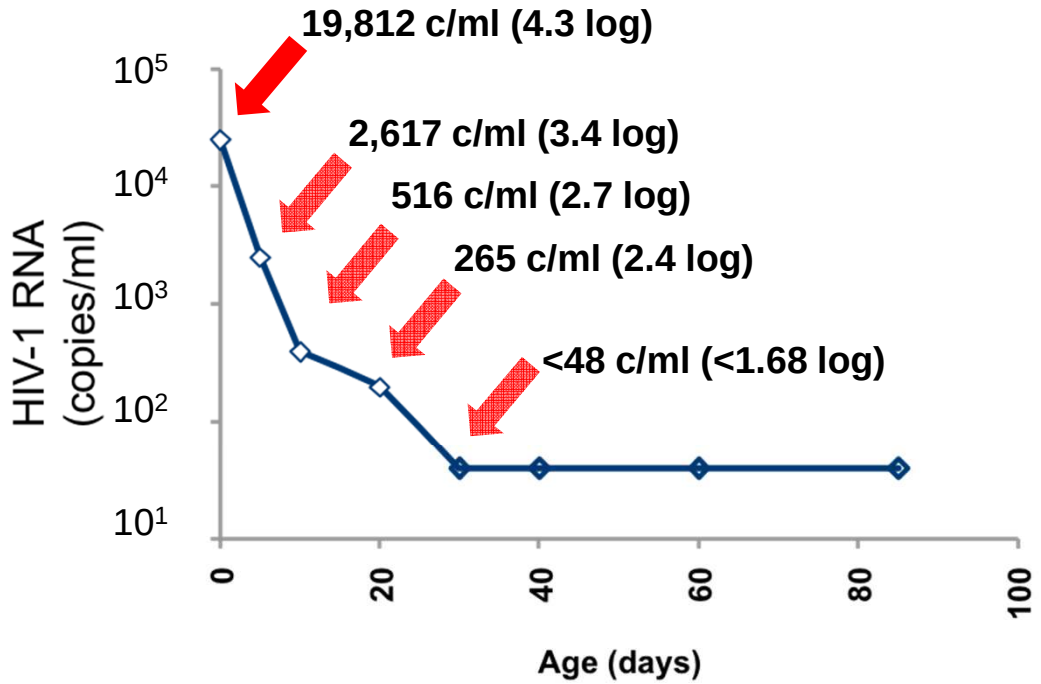
Virologic Response to HART Regimen



AZT/3TC/NVP
31 Hours – 7 days →

AZT/3TC/LPV/r
7 days – ~18 months

Mother stops ART about month 18 – LTFU until month 23
HIV testing of infant done before restarting ART

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Virologic Studies to Detect Residual HIV

Virologic Studies to Detect Residual HIV in this Very-Early Treated Child

Measurement	Sample Type (amount of sample)	Age at Testing	Quantity (per 1 x 10^6 cells)	Number Cells Tested per well/ (No. Replicates positive)
Total Proviral DNA				
	PBMC	24-months	<2.7 [0]	122,000 (0/2)
		26-months	4.2 [0]	113,000 (1/6)
	Resting CD4+ T cells	24-months	<3.5 [0]	96,500 (0/3)
		26-months	<2.5 [0]	134,000 (0/6)
	Enriched for activated CD4+ T cells	24-months	<2.2 [0]	154,000 (0/6)
		26-months	<2.6 [0]	130,000 (0/6)
	Monocyte-derived adherent cells	24-months	37.6 [0]	14,300 (1/3)
		26-months	<11.5 [0]	29,000 (0/6)
Residual Viremia				
	Plasma	24-months	1- copy/ml	NA
		26-months	<2- copies/ml	NA
Infectious Virus Recovery	Resting CD4+ T cells	24-months	<1/ 22x10^6 IUMP (No HIV recovered)	NA

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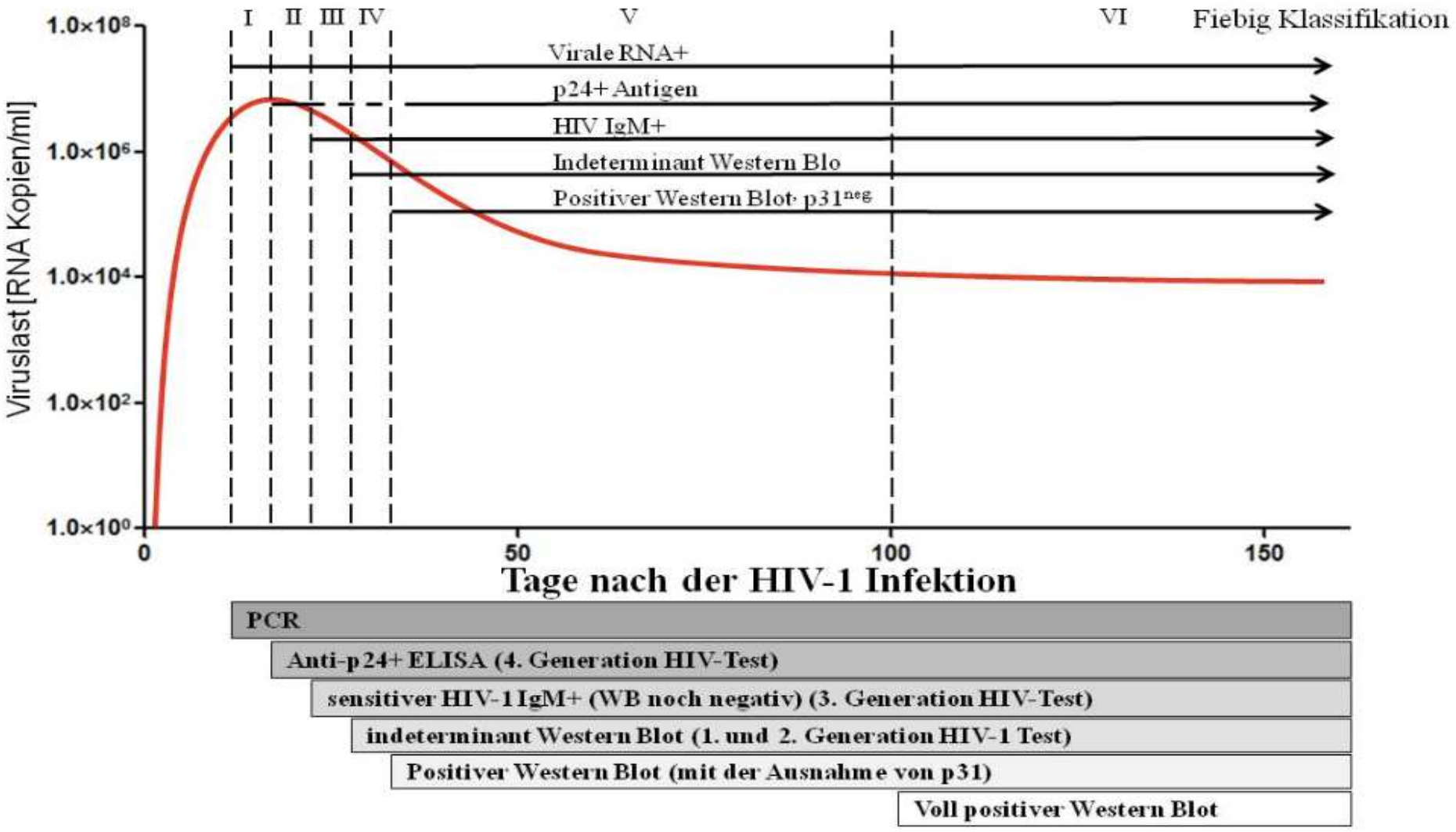
Die Fiebig Klassifikation für die akute HIV Infektion



adaptiert nach: (Fiebig 2009 und McMichael 2010)

Early ART: Reducing the Size of Initial Reservoir?

Screening NAT/EIA 52,767 samples → 89 AHI identified
3 days
75 enrolled into Main Protocol
Optional procedures: Sigmoid biopsy Leukapheresis
Within 2 days → optional ART

Fiebig Classification System of Early Infection:				% enrolled
Fiebig I	RNA +	p24-	3rd Gen EIA -	37%
Fiebig II	RNA+	p24+	3rd Gen EIA -	10%
Fiebig III	RNA+	p24+	3rd Gen EIA + WB neg	53%

Ananworanich J, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 47.

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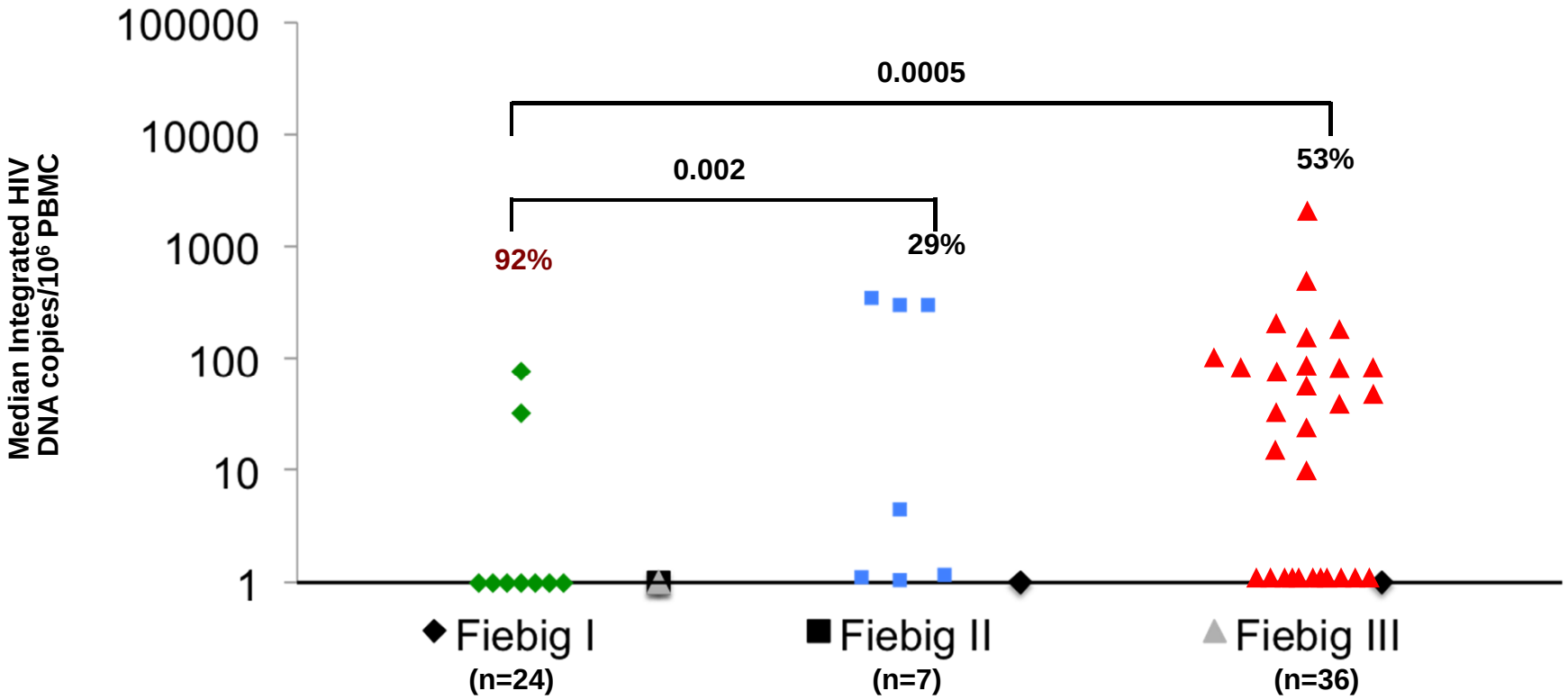
Early ART: Reducing the Size of Initial Reservoir? Week 24 Results on ART

Almost all Fiebig I Subjects had Undetectable Integrated HIV DNA in PBMC



Ananworanich J, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 47.

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Was bedeutet Heilung von HIV, im Sinne von Eradikation?

- Eradikation von Virus Reservoirs

  - Resting memory CD4+ Zellen mit latent, replikationskompetentem Virus
  - ab welchem Alter werden diese aufgebaut?
  - Wie bald nach der Infektion?

- Wenn aufgebaut- Reaktivierung latenter HIV trotz cART mit Beschleunigung des Zelluntergangs?

- Wie kann eine Verschlechterung festgestellt werden?

  - Differenzierung von replizierendem und defekten Pro-Virus
  - Ist eine partielle Reduktion des Virusreservoirs mit einer „funktionellen“ Heilung gleichzusetzen? (Das Mädchen hatte 1-3 RNA/ 1Mio PBMC)

Siliciano R, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 16.

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PrEP: The VOICE Trial

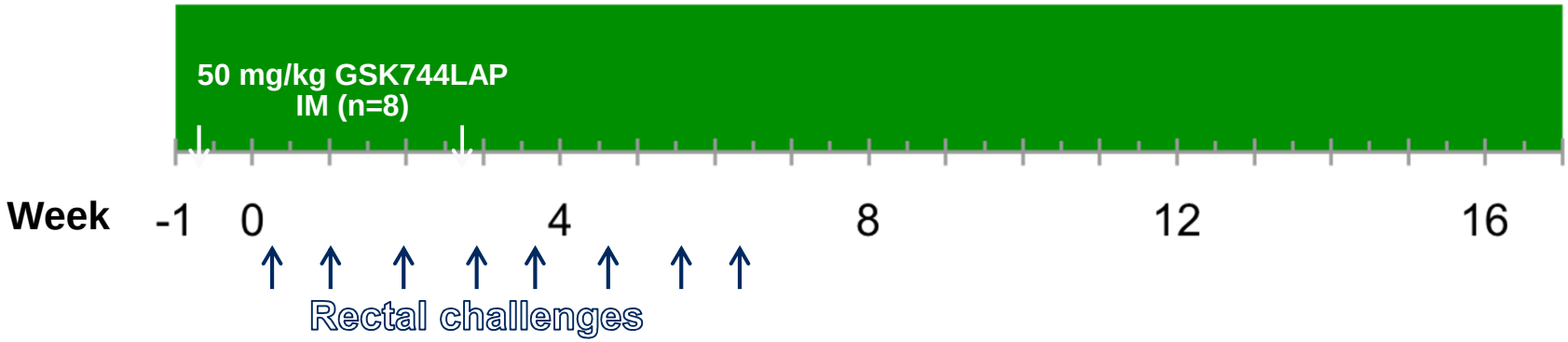
Final Results

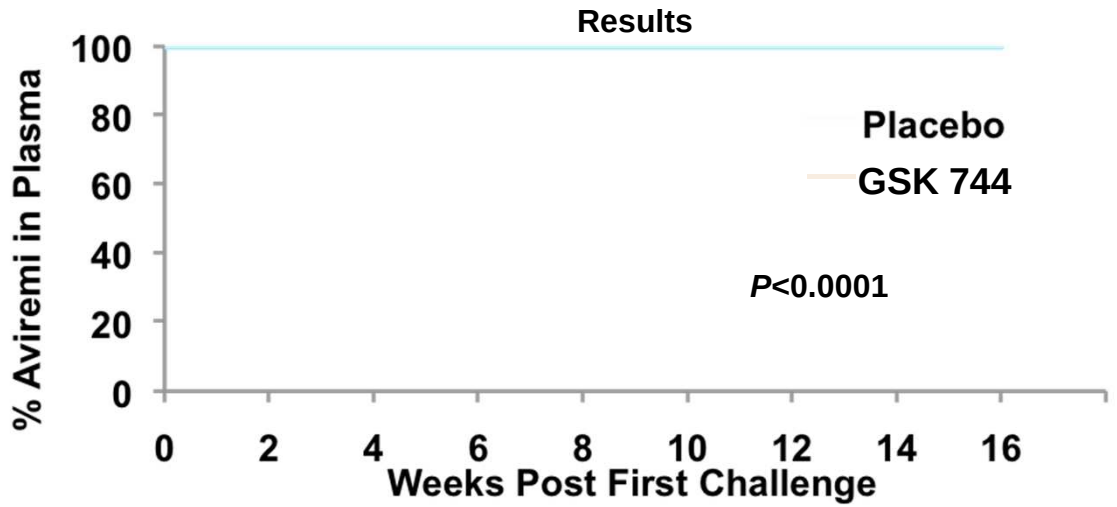
N=5029 HIV- Women: Primary Efficacy Results (mITT)

	TDF	Oral Placebo	FTC/TDF	Oral Placebo	TFV Gel	Gel Placebo
Person-years	823	837	1285	1306	1026	1030
No. of HIV Infections	52	35	61	60	61	70
HIV incidence per 100 p-y	6.3 (4.7, 8.3)	4.2 (2.9, 5.8)	4.7 (3.6, 6.1)	4.6 (3.5, 5.9)	5.9 (4.5, 7.6)	6.8 (5.3, 8.6)
% samples with TFV detected	30%		29%		25%	
% women with no TFV detected ever	58%		50%		55%	

Marrazzo J, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 26LB.

Long Acting Parenteral GSK1265744 (Dolutegravir): Macaque Model with SHIV





Based on very long parenteral (IM or IV) half life – protective effect of 744 will be assessed with q1-3 month dosing

Andrews C, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 24LB.

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Hepatitis

Protective Effect of HBV-active cART Against Primary HBV-Infection

- Does HBV-active cART protect against new HBV infection (HBV-PrEP)?

- all HBV-susceptible patients at entry, anti-HBc and anti-HBs negative (<10 IU/L) and 2nd sample available in time for follow-up HBV serology

- All patients n=2,924, msm n=2,280, HBV susceptible + 2 samples available n=349

Brinkman K, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 33.

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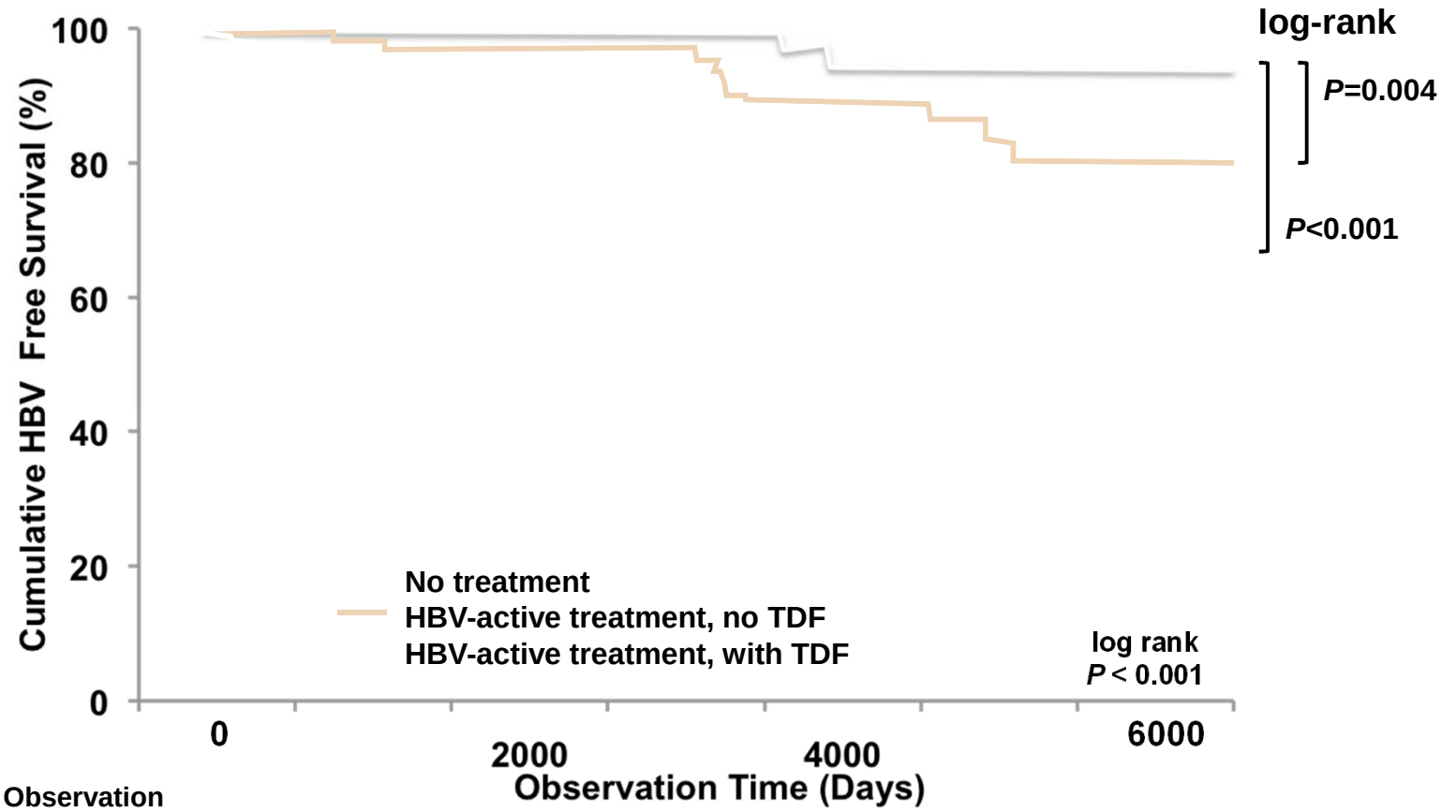
Kaplan Meier: HBV-Free Survival (MSM)



Numbers in Observation				
No Treatment	10	50	19	8
Treatment, No TDF	7	67	36	16
Treatment, with TDF	86	49	38	12
	18			
	9			

Brinkman K, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 33.

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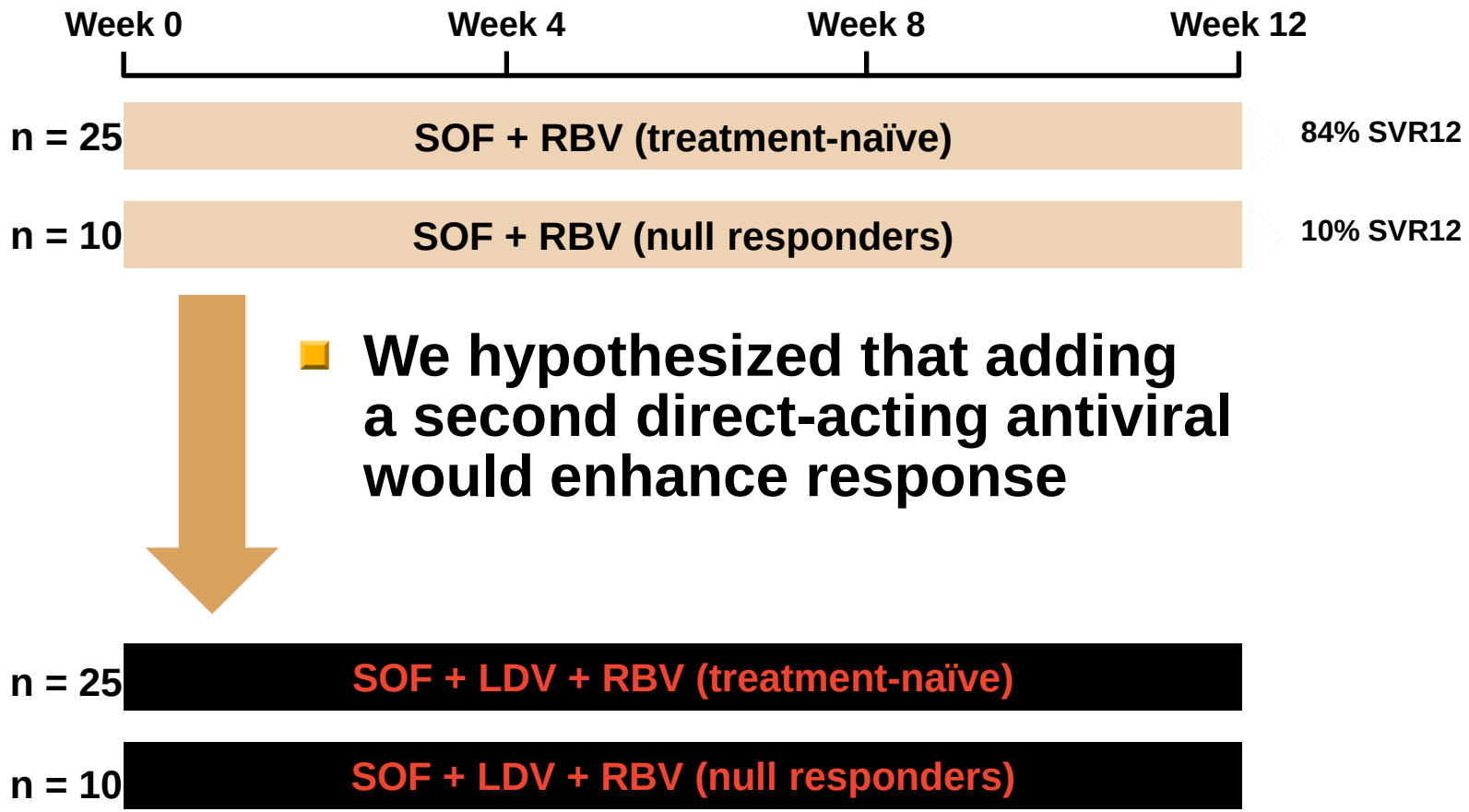
ELECTRON Study Design:
Genotype 1 Cohorts (SOF=Sofosbuvir, Nucleotide; LDV=Ledispavir, NS5A, GS5885)



Gane E, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 41LB.

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ELECTRON Results: Efficacy
(SOF=Sofosbuvir, Nucleotide; LDV=Ledispavir, NS5A, GS5885)

Patients with HCV RNA <LOD* Over Time, n/N (%)

	SOF + RBV		SOF + LDV + RBV	
	Treatment-naïve (n=25)	Null responder (n=10)	Treatment-naïve (n=25)	Null responder (n=9)
Week 1	8/25 (32)	1/10 (10)	11/25 (44)	0/9 (0)
Week 2	17/25 (68)	7/10 (70)	22/25 (88)	4/9 (44)
Week 4	25/25 (100)	10/10 (100)	25/25 (100)	8/9 (89)
EOT	25/25 (100)	10/10 (100)	25/25 (100)	9/9 (100)
SVR4	22/25 (88)	1/10 (10)	25/25 (100)†	9/9 (100)
SVR12	21/25 (84)	1/10 (10)	25/25 (100)	9/9 (100)

Further studies RBV free and duration are planed

Gane E, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 41LB.

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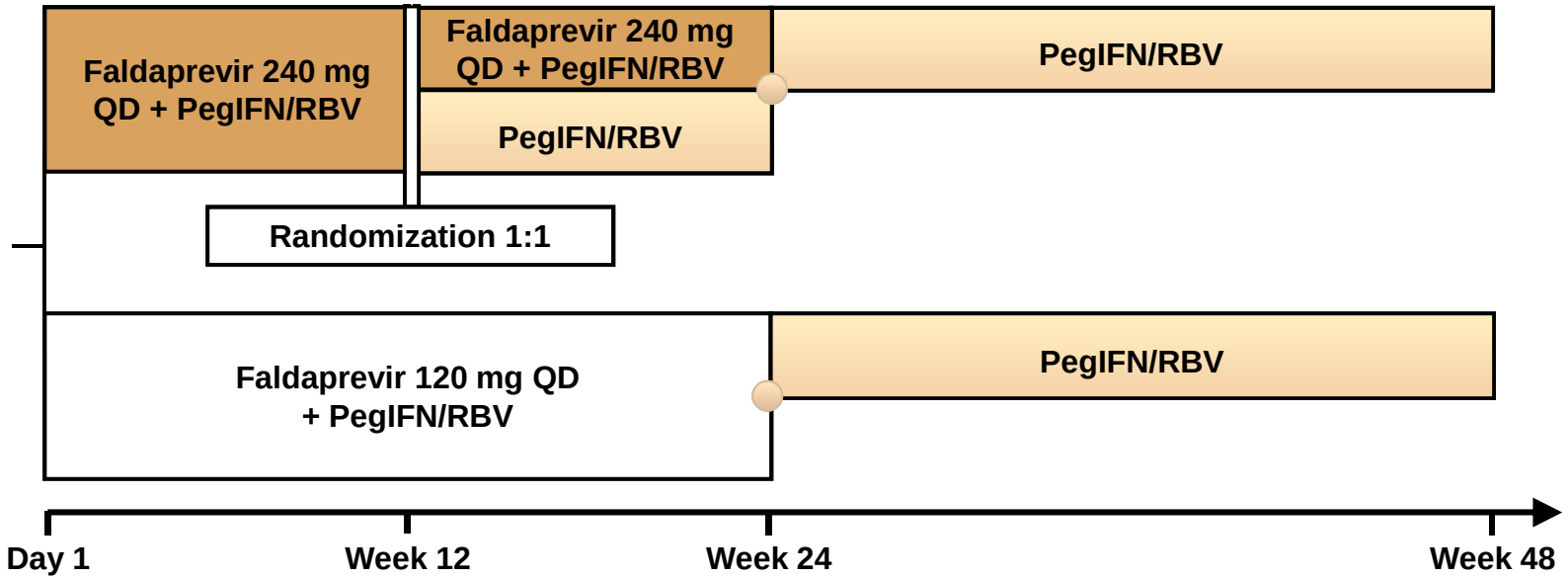
STARTVerso 4: Study Design

Phase III Open-label, Sponsor-blinded Study in Treatment-naïve and Relapser Patients with Chronic HCV GT-1 and HIV Infection



- Patients with HCV RNA below LLoQ, at Week 4, and HCV RNA below LLoQ target not detected at Week 8 (=ETS) will be re-randomized 1:1 at week 24 to stop treatment or continue pegIFN/RBV through week 48
  Patients who did not achieve ETS will continue pegIFN/RBV through week 48

Dieterich D, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 40LB.

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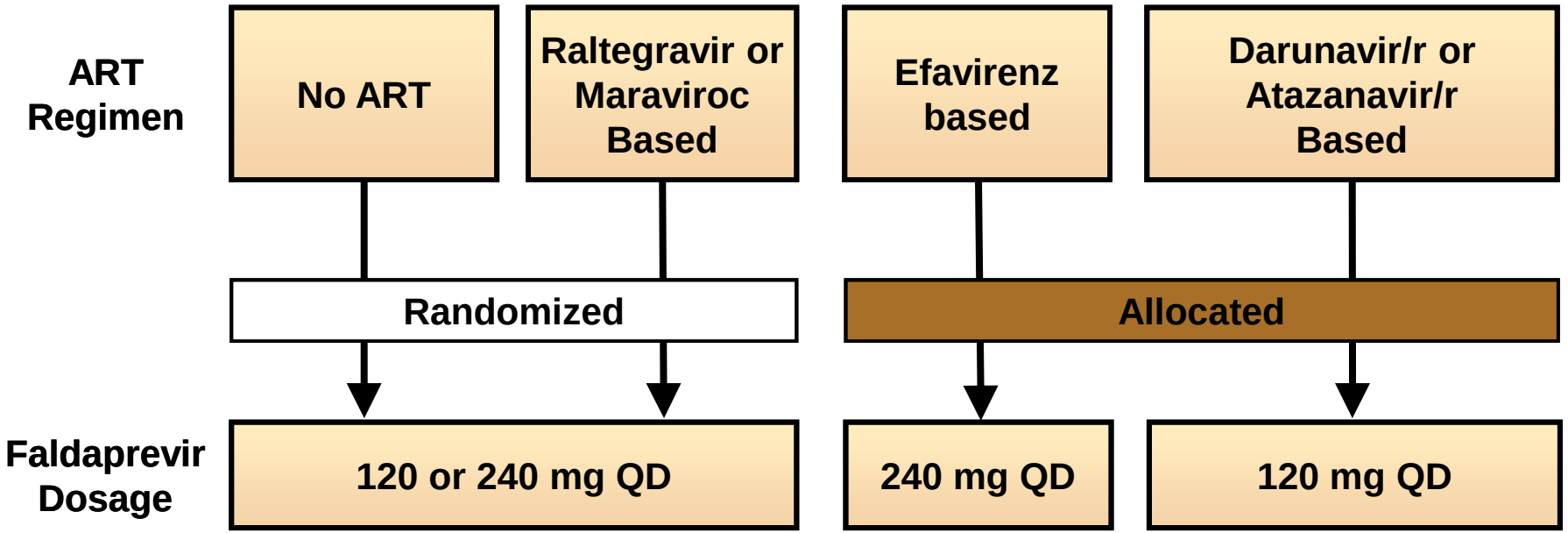
STARTVerso 4: Study Design

HCV GT-1 infection, including compensated cirrhosis
- HCV treatment-naive or relapsers
- Cirrhosis F4 or FibroScan >13 kPa 17%; GT1a 78%



Dieterich D, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 40LB.

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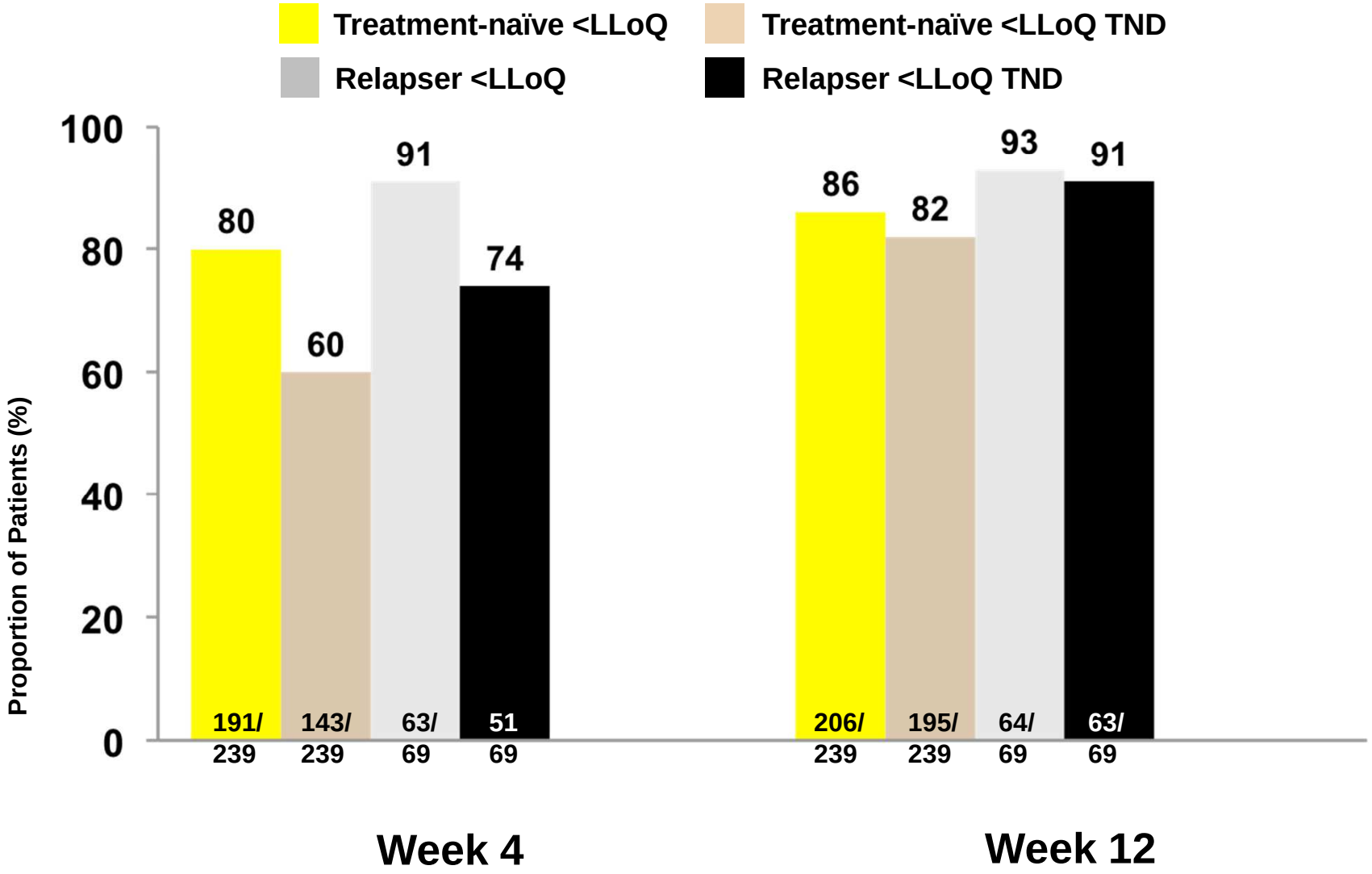
Early Virologic Response in HIV/HCV Co-infected Patients: HCV Treatment-naïve and Relapsers



Dieterich D, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 40LB.

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HIV Therapie

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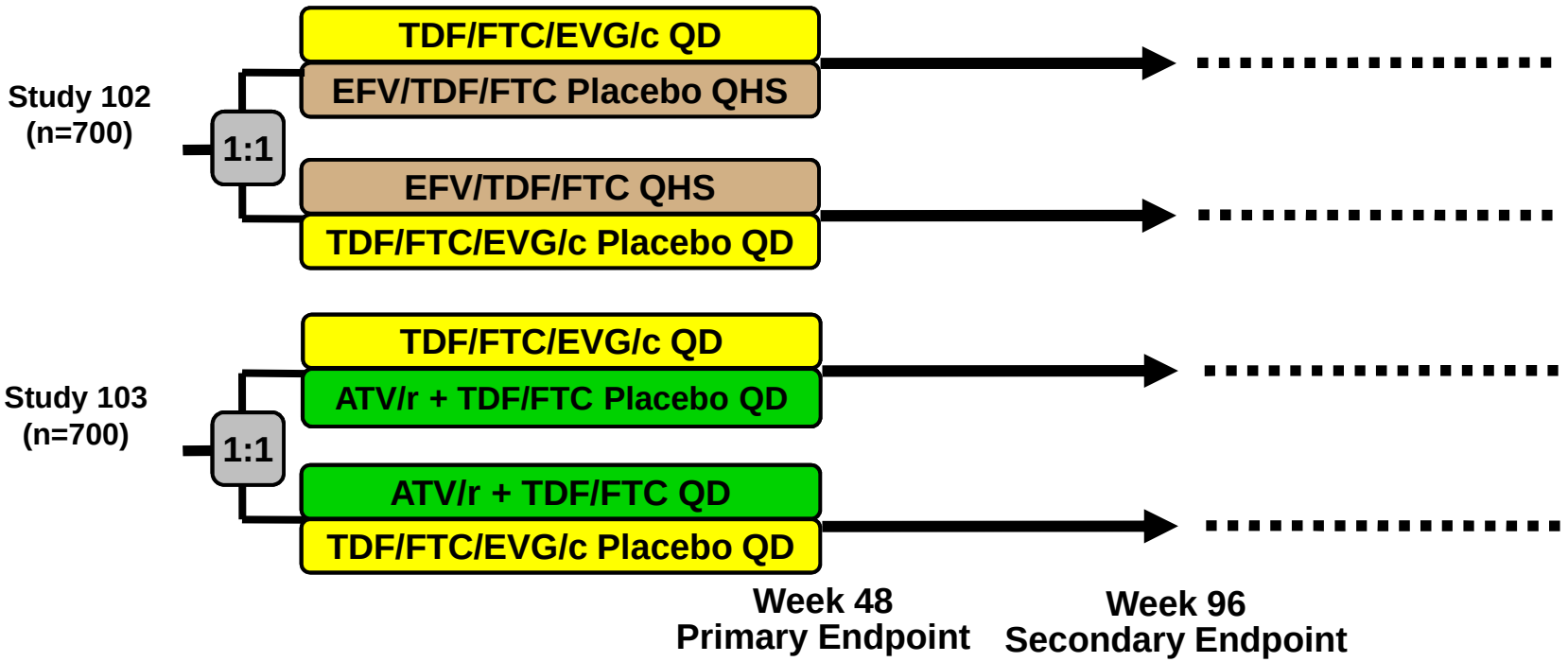
Study 102 and 103: Study Design (Elvitegravir)

Randomized, double-blind, double dummy, active-controlled study
Treatment Naïve Patients with HIV-1 RNA ≥5,000 c/mL
Any CD4 cell count, eGFR ≥70 mL/min



Zolopa A, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 553.

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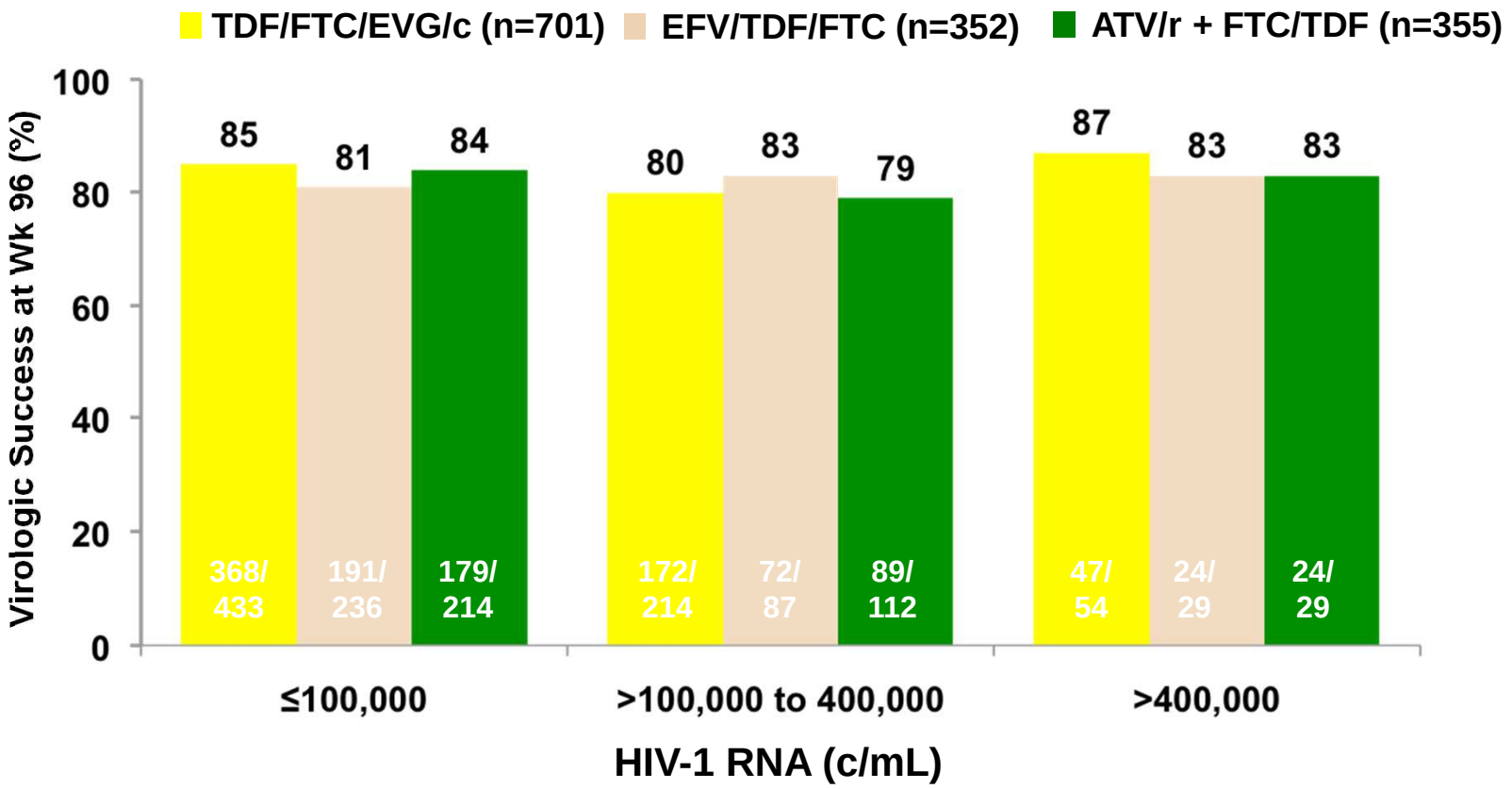
Combined Study 102 and 103: Efficacy by Baseline HIV-1 RNA Subgroups – Week 96



Zolopa A, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 553.

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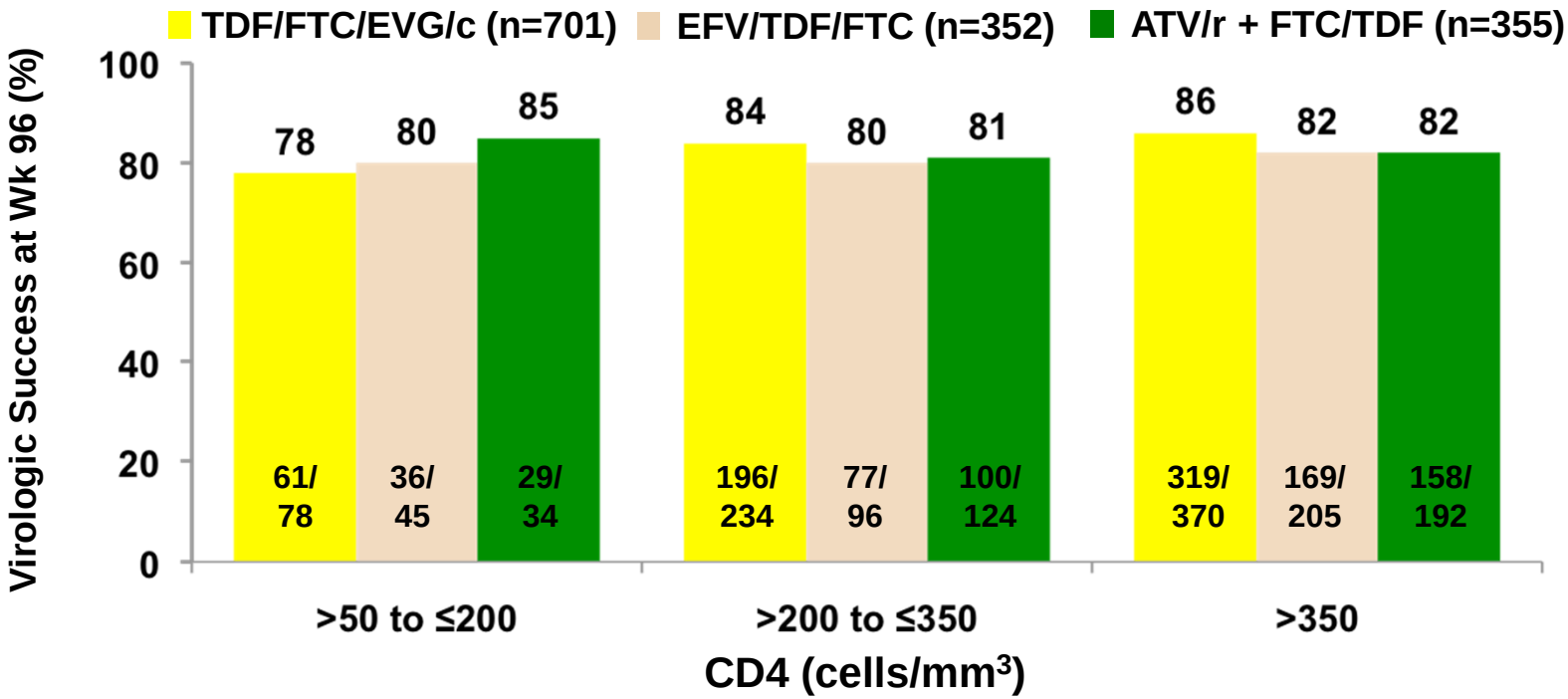
Combined Study 102 and 103: Efficacy by Baseline CD4 Subgroups - Week 96



- Subgroup of CD4 <50 (n=30)
- 11/19 STB with virologic success. 8 were non-success (all with VL > 100 K c/mL, 4 with suboptimal adherence)
- 5/6 ATR with virologic success. 1 was non-success (VL > 100 K c/mL, suboptimal adherence)
- 5/5 ATV/r + TDF/FTC with virologic success

Zolopa A, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 553.

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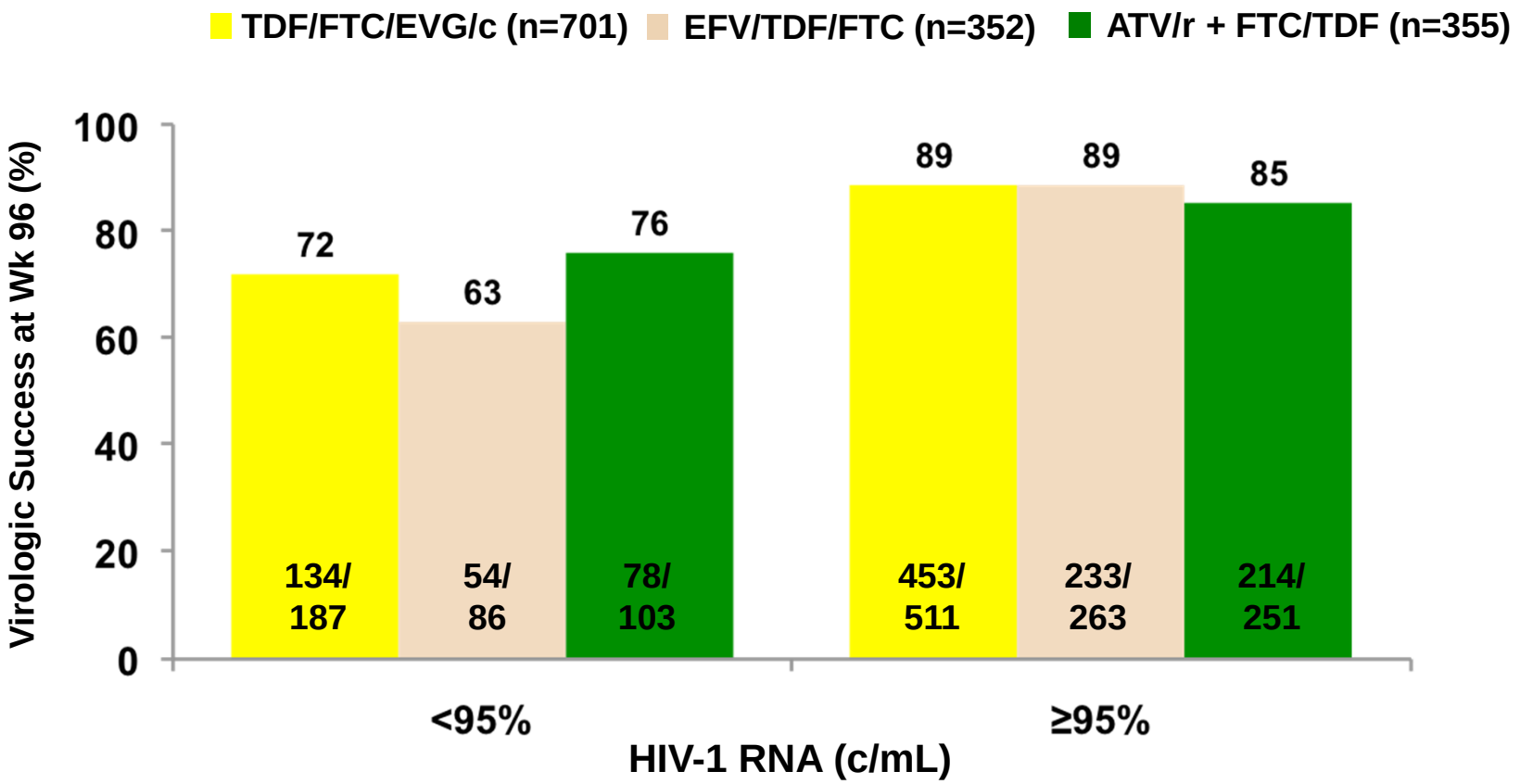
Combined Study 102 and 103: Efficacy by Adherence – Week 96



Zolopa A, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 553.

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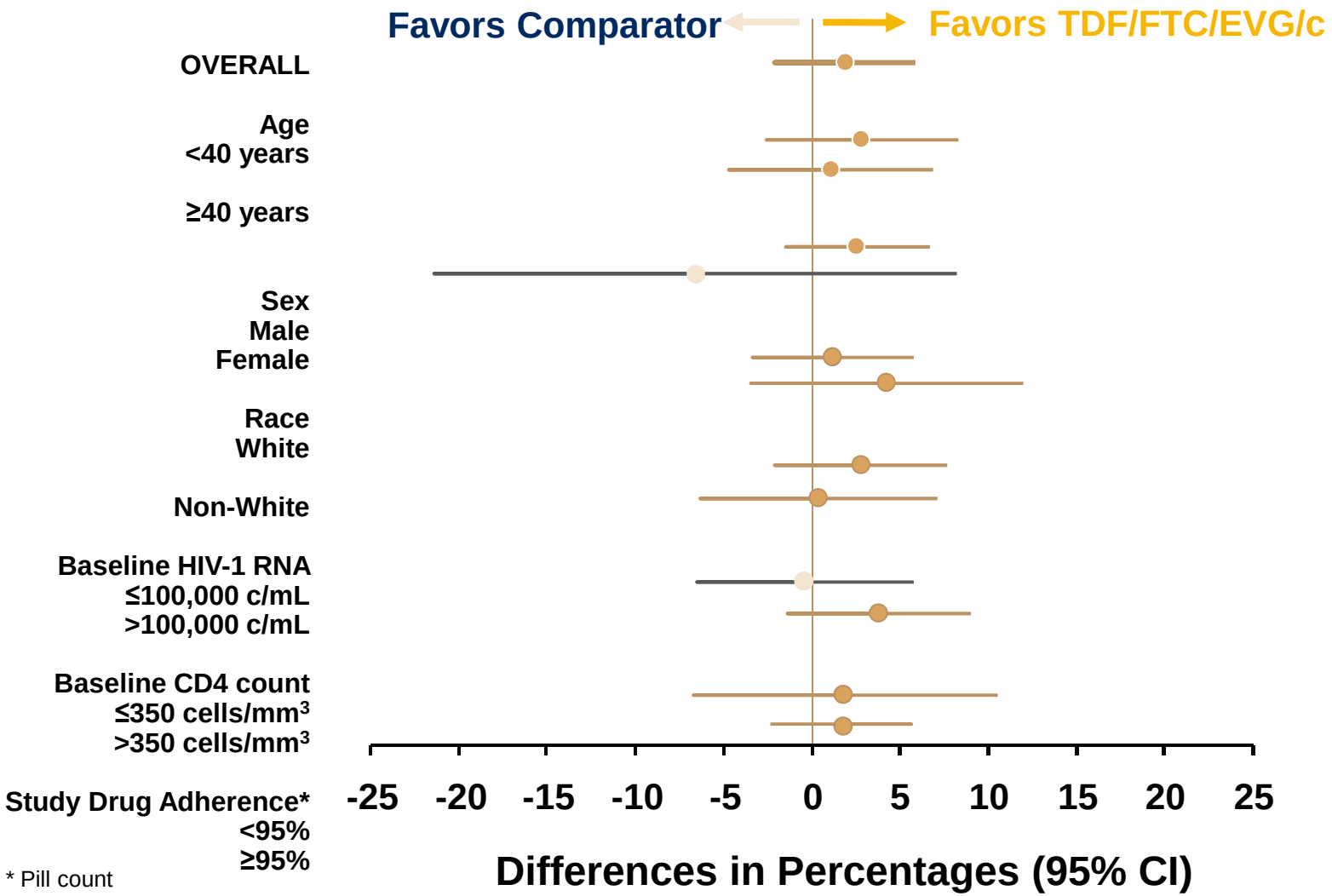
Combined Study 102 and 103: Difference in Efficacy by Subgroup – Week 96



* Pill count

Zolopa A, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 553.

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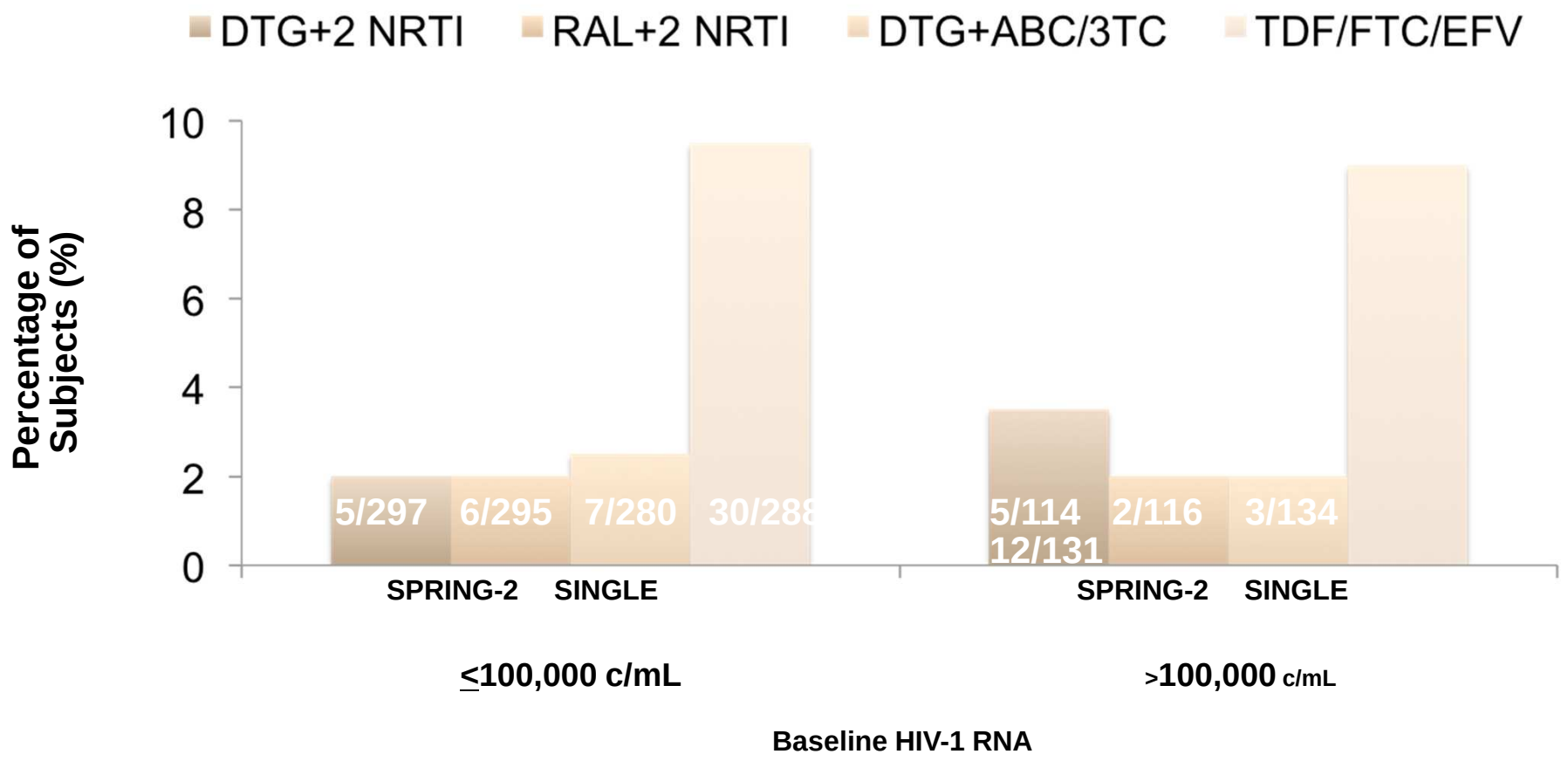
Dolutegravir: Combined Virologic Efficacy in Phase 3 Studies

Proportion with Plasma HIV-1 RNA <50 c/mL at Week 48 (1˚ Endpoint by FDA Snapshot)

	SPRING-2		SINGLE	
	DTG + 2 NRTI	RAL + 2 NRTI	DTG + ABC/3TC	TDF/FTC/EFV
Overall (Primary analysis)	361/411 (88%)	351/411 (85%)*	364/414 (88%)	338/419 (81%)
BL HIV-1 RNA ≤100,000 c mL	267/297 (90%)	264/295 (89%)	253/280 (90%)	238/288 (83%)
BL HIV-1 RNA >100,000 c/mL	94/114 (82%)	87/116 (75%)	111/134 (83%)	100/131 (76%)
CD4<350 cells/mm^3	171/199 (86%)	152/189 (80%)	188/220 (85%)	174/221 (79%)
CD4≥350 cells/mm^3	190/212 (90%)	190/222 (90%)	176/194 (91%)	164/198 (83%)

Brinson C, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 554.

Dolutegravir: AEs Leading to Withdrawal



Brinson C, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 554.

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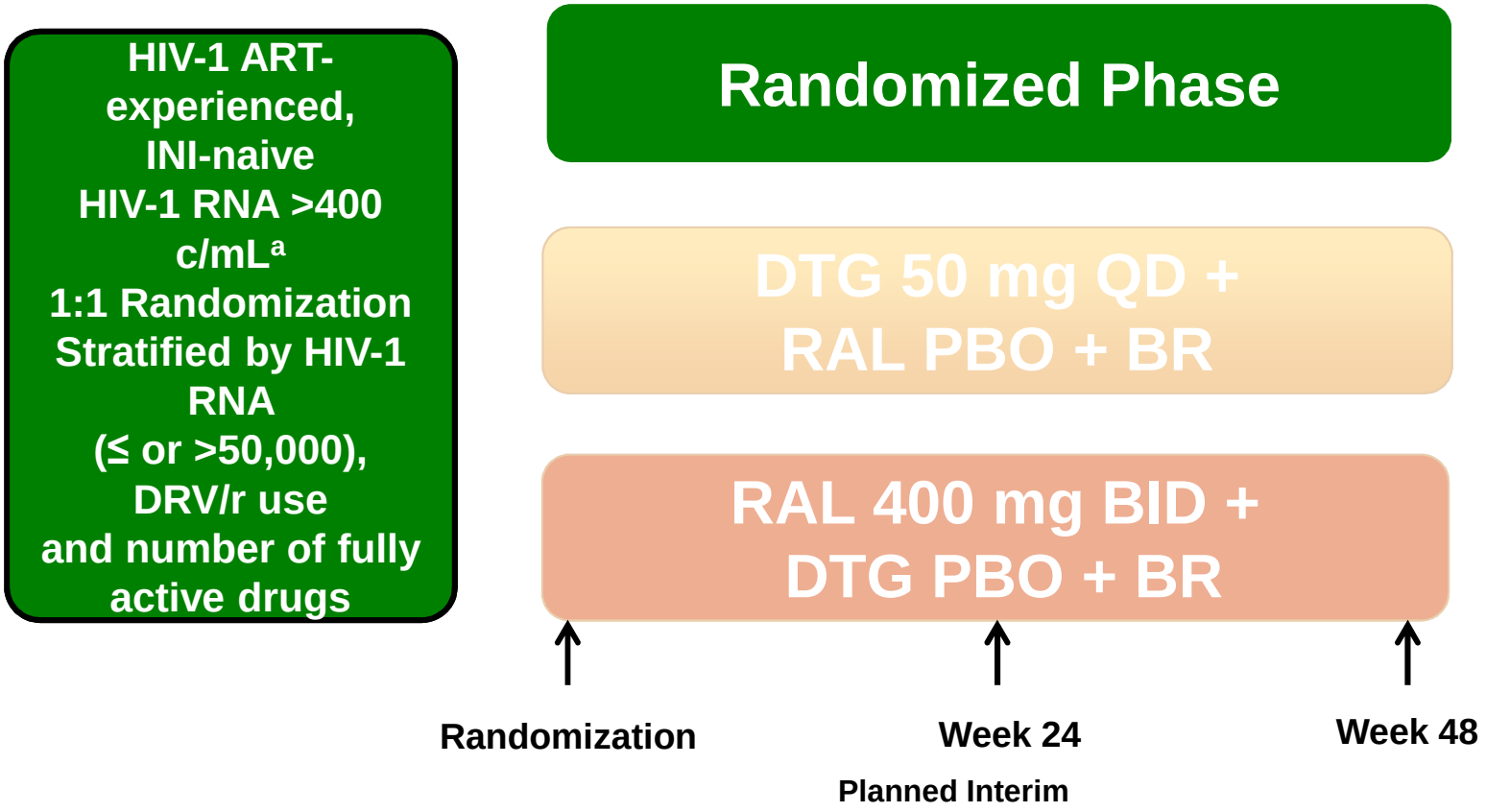
SAILING: Study Design



a At Screening and a second consecutive test >400 c/mL within 4 months prior to Screening (if Screening HIV-1 RNA >1,000 c/mL, no additional HIV-1 RNA assessment was needed). PBO, placebo; BR, background regimen.

Pozniak A, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 179LB.

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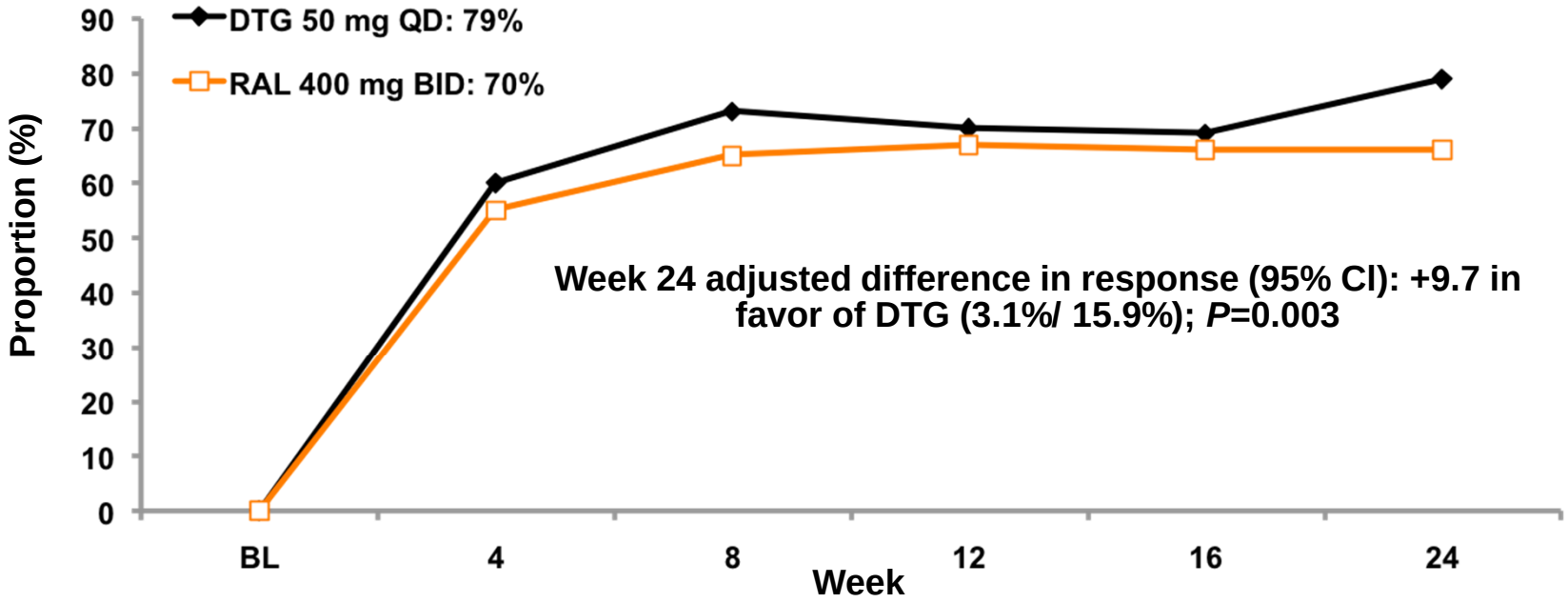
Proportion of Subjects With HIV-1 RNA <50 c/mL (Snapshot, mITT-E)

DTG 50 mg QD was statistically superior to RAL 400 mg BID at Week 24



- Median CD4+ (interquartile range [IQR]) change from Baseline (observed case) was similar between arms: DTG: +99 cells/mm^3 (n=325; IQR: 34, 184); RAL: +93 cells/mm^3 (n=326; IQR: 46, 166)

Pozniak A, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 179LB.

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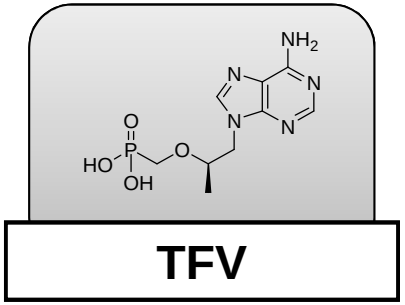
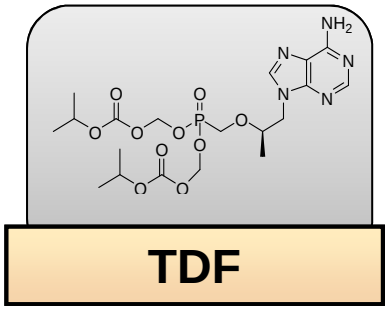
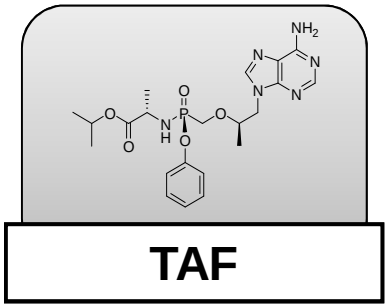
Tenofovir Alafenamide (TAF)
Next Generation Prodrug of Tenofovir



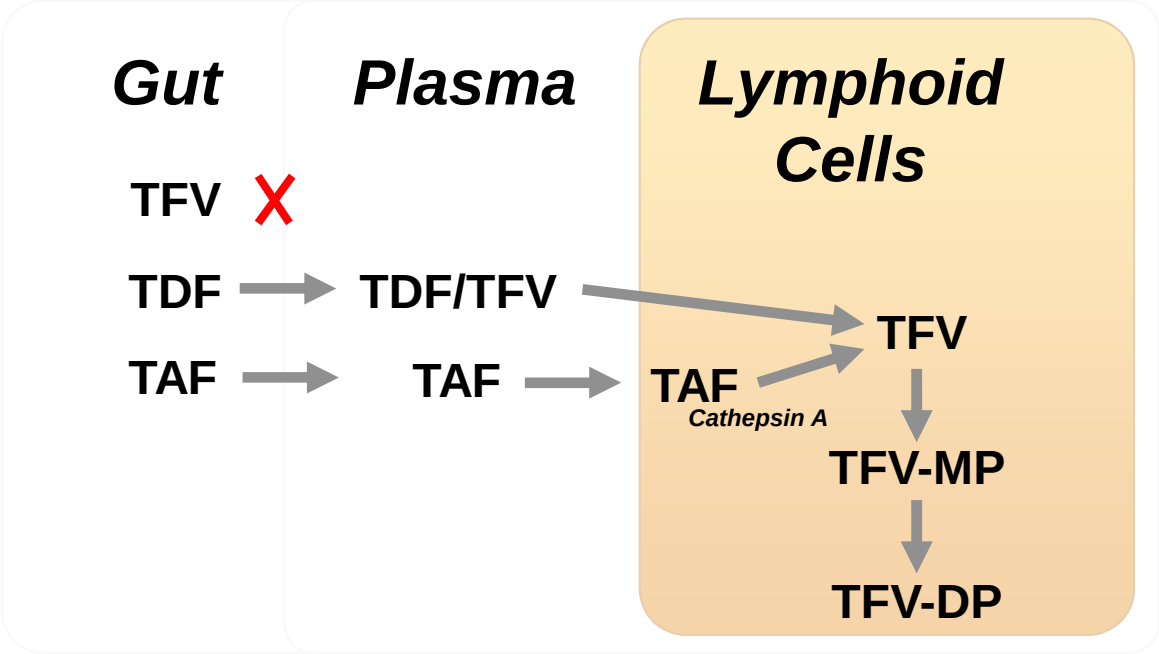
Tenofovir



Tenofovir Disoproxil Fumarate



Tenofovir Alafenamide



Zolopa A, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 99LB.

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Tenofovir Alafenamide (TAF): Background (Formerly GS-7340)

- TAF is a prodrug of tenofovir (TFV) with increased delivery to lymphoid cells and hepatocytes

- Relative to TDF 300 mg, TAF 25 mg has[1]:
  - Increased anti-HIV-1 activity in Phase 1
  - Increased intracellular TFV-DP levels by ~7-fold
  - Decreased circulating plasma TFV levels by ~90%
  - Lower levels of TFV in kidney and bone tissue expected

- TAF formulated into a single tablet regimen as TAF/FTC/EVG/c
  - Elvitegravir 150 mg
  - Cobicistat 150 mg
  - FTC (emtricitabine) 200 mg
  - TAF 10 mg

- TAF 10 mg in TAF/FTC/EVG/c has PK comparable to TAF 25 mg alone[2]
  - COBI ↑ TAF levels ~2.2-fold

1. P Ruane, et al. CROI 2012; Paper # 103.
2. S Ramanathan, et al. IWCPHT 2012; Abstract O_13.

Zolopa A, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 99LB.

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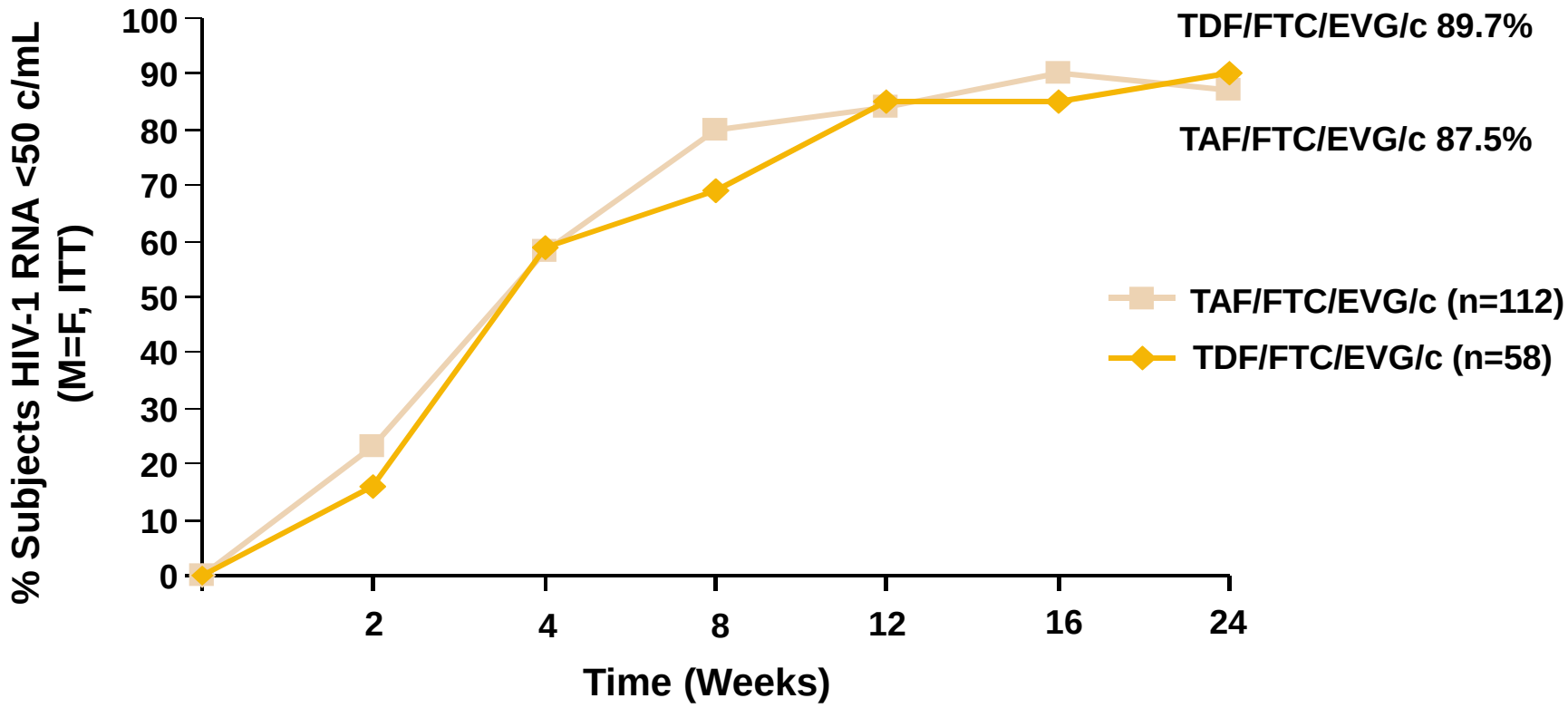
GS-US-292-0102: Virologic Response (M=F, ITT) – Week 24 Analysis



- Mean change from baseline CD4+ cell count:
  - TAF/FTC/EVG/c, +163 cells/μL
  - TDF/FTC/EVG/c, +177 cells/μL (*P*=0.76)

Zolopa A, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 99LB.

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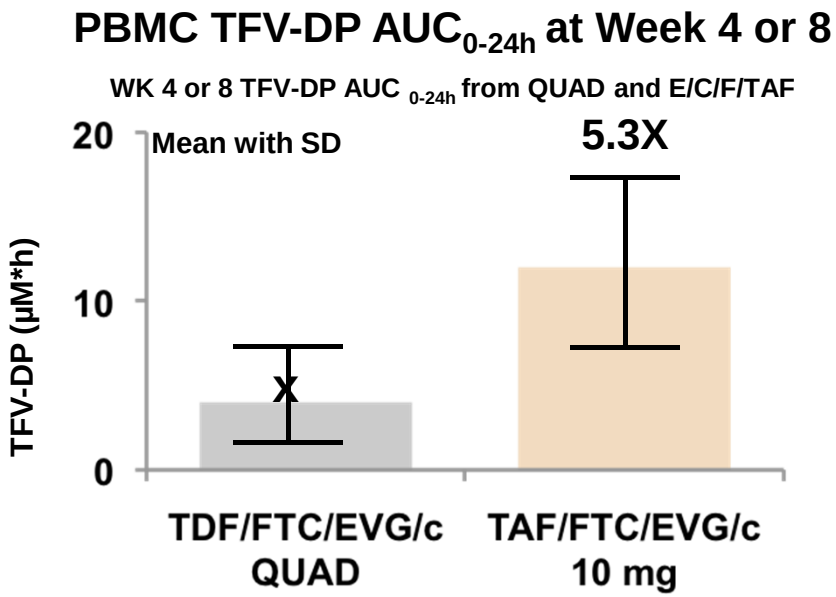
TFV Plasma and TFV-DP Intracellular Levels GS-US-292-0102 – Week 24 Analysis

- E/C/F/TAF
- PBMC TFV-DP exposure was 5.3-fold higher (90% CI: 2.9 to 9.6)
- Plasma TFV exposure (AUCtau) was 91% lower



Plasma TFV PK Mean (%CV)	TAF/FTC/EVG/c (n=19)	TDF/FTC/EVG/c (n=7)
C_{trough} (ng/mL)	11.4 (17.9)	82.8 (26.6)
AUC_{tau} (ng*hr/mL)	326.2 (14.8)	3795.2 (21.9)

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Cenicriviroc (CVC) Characteristics (Tobira)

- Oral CCR5/CCR2 receptor antagonist
- *In vitro* protein-adjusted IC_{90} against HIV clinical isolates = 0.25 nM
- Inhibits binding of MCP-1 to CCR2 at 5.9 nM (IC_{50})

- Once-daily dosing
- Long plasma $t_{½}$ = 30–40 hours

- Low drug–drug interaction potential
- Metabolized via CYP3A4 and CYP2C8
- Not a known CYP inducer or inhibitor

- Additive to synergistic antiviral activity *in vitro* with
- NRTIs, NNRTIs and Pis

Gathe J, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 106LB.

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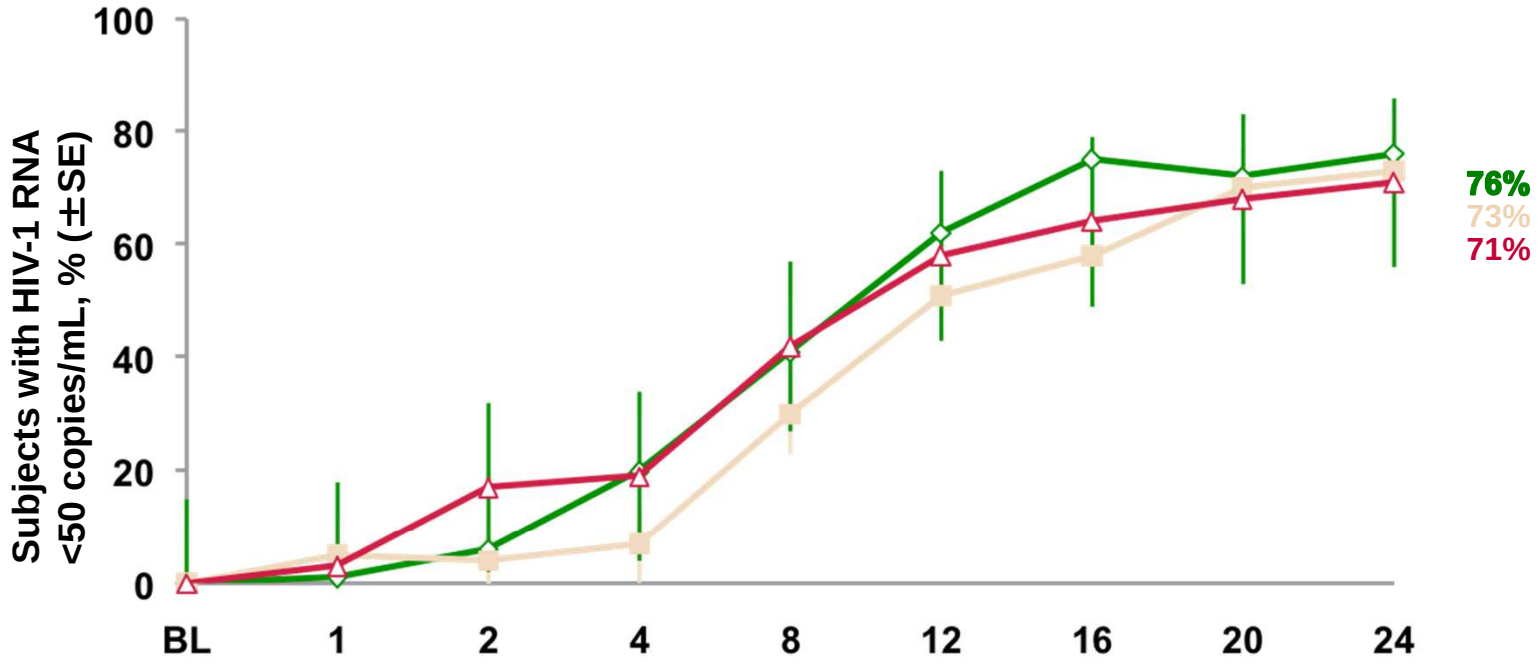
HIV-1 RNA <50 copies/mL (ITT-FDA Snapshot)



CVC 100 mg	0	3	11	25	37	44	42	45
CVC 200 mg	2	2	4	17	28	33	40	41
EFV	0	4	5	12	16	18	19	20

Gathe J, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 106LB.

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Zusammenfassung

- Die Prep ist als Konzept in jeder Hinsicht noch nicht entwickelt

- funktionelle Heilung ist noch sehr umstritten, die Parameter sind unklar

- Die Hepatitis C Therapie wird einfacher werden, Interferon kann wahrscheinlich bald weggelassen werden

- Die HIV Koinfektion ist für die HCV Therapie auch nach Studienergebnissen kein Hindernis

- Neue Substanzen die in der HIV Therapie werden entwickelt, werden hoffentlich auch zur Marktreife gebracht

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Danksagung

Jürgen Rockstroh und BMS für die Überlassung von Dateien und Informationen

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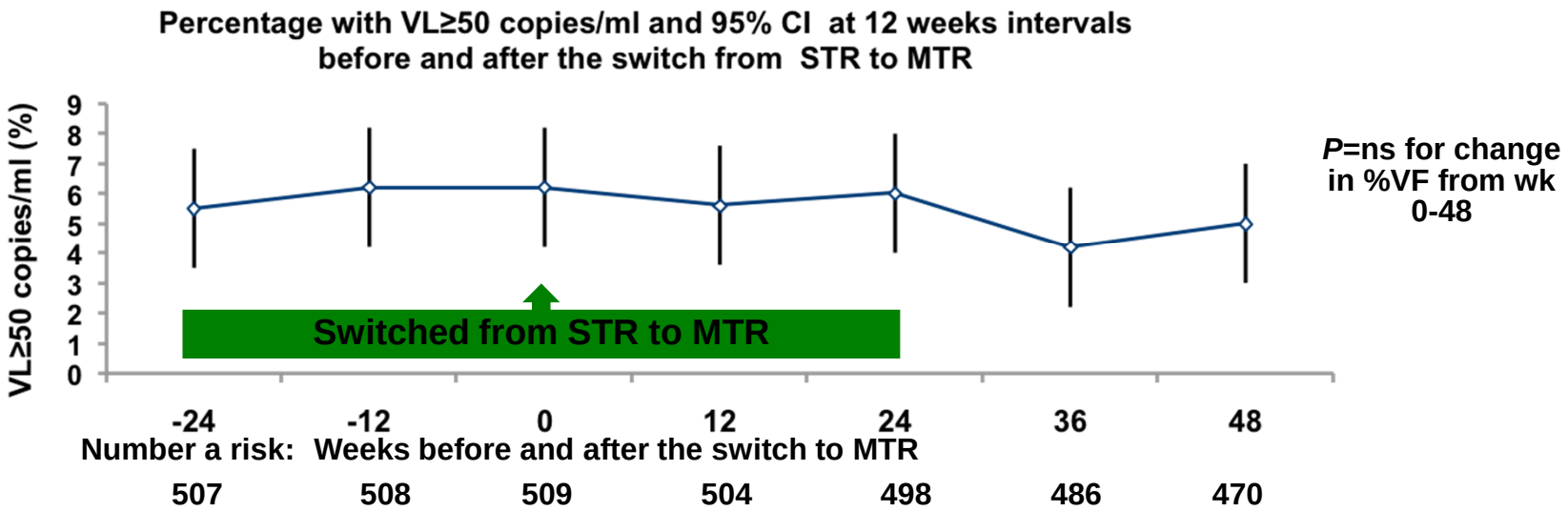
Change from STR to Multi-tablet Regimen (MTR) After Virologic Suppression

509 patients on STR (TDF/FTC/EFV); 478 (94%) switched to TDF + 3TC + EFV (MTR)

Eligibility
STR - first cART regimen in 215 (42%)
On TDF/FTC/EFV ≥ 1 year prior to the change to MTR
No known compliance problems



Conclusion:

- **In a well organized health care setting (free access to ART), switch from TDF/FTC/EFV to a MTR did not change virologic response**
- **Caveats: Generalizability may be limited by single population, observation time**

K. Arasteh

Engsig F, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 579.

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Combined Study 102 and 103: Emergent Resistance Through Week 96 – Week 96

	TDF/FTC/EVG/c (n=701)			EFV/TDF/FTC (n=352)			ATV/r + TDF/FTC (n=355)	
		Wk48	Wk96 (Δ)		Wk48	Wk96 (Δ)	Wk48	Wk96 (Δ)
Emergent Resistance, n		13 (1.9%)	+3 (+0.4%)		8 (2.3%)	+2 (+0.6%)	0	0
Primary INSTI-R		11 (1.6%)	+3 (+0.4%)		8 (2.3%)	+2 (+0.6%)	0	0
or NNRTI-R	E92Q	8	+1	K103N	7	+2		
or PI-R, n	N155H	3	+2	K101E	0	+3		
	Q148R	3	0	V108I	2	0		
	T66I	2	0	Y188F/H/L	1	+1		
				M230L	0	+2		
				V90I	0	+1		
				G190A	1	0		
				P225H	0	+1		
Primary NRTI-R, n		12 (1.7%)	+3 (+0.4%)		2 (0.6%)	+1 (+0.3%)	0	0
	M184V/I	12	+3	M184V/I	2	+1		
	K65R	4	+1	K65R	2	+1		

Zolopa A, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 553.

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Baseline Characteristics

	DTG 50 mg QD (n=354)	RAL 400 mg BID (n=361)
Age, median (y)	42	43
Gender, female	30%	34%
Race, white	50%	48%
African American heritage	40%	44%
HIV-1 RNA, median (log_{10} c/mL)	4.17	4.21
>50,000 c/mL	30%	30%
CD4+ count, median (cells/mm^3)	205	193
<200 cells/mm^3	49%	51%
HBV/HCV coinfection	14%	18%
Duration prior ART, median (y)	6.62	5.93
≥3 Class resistance	48%	50%
Most common background regimens, n (%)		
Darunavir/ritonavir, tenofovir	62 (18%)	73 (20%)
Lopinavir/ritonavir, tenofovir	40 (11%)	40 (11%)
Darunavir/ritonavir, etravirine	33 (9%)	40 (11%)
Lopinavir/ritonavir	36 (10%)	35 (10%)
Atazanavir/ritonavir, tenofovir	36 (10%)	33 (9%)
Darunavir/ritonavir, maraviroc	23 (6%)	19 (5%)

Pozniak A, et al. 20th CROI; Atlanta, GA; March 3-6, 2013. Abst. 179LB.

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