

*IAS Meeting Update: New and
Emerging Therapies in Existing
and Novel Classes*

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Honoraria: Tibotec, Virco, BIPI, GSK, Gilead, Roche, BMS, Vertex.

Discussion of unlabeled/unapproved use of drugs or products:

Yes No X

Learning Objectives

- **Develop individualized treatment protocols for patients with HIV that incorporate existing drugs and describe how emerging therapies fit into these protocols**
- **Explain the mechanisms of action and strengths and weaknesses of novel classes of drugs to treat patients with HIV**
- **Describe the clinical trial data regarding new drugs in development for treating patients with HIV**

Summary of AIDS Epidemic in United States

- Annual infection rate 40% higher than previously estimated due to new technology and new methodology, according to Centers for Disease Control^[1]
 - Estimates rose from 40,000 to 56,300 in 2006
- Blacks disproportionately infected with HIV in United States

HIV Prevalence, %		
United States	NHANES, ^[2] Ages 18-39	NHANES, ^[2] Ages 40-49
Whites	0.26	0.36
Blacks	1.42	3.58
Select Comparator Countries ^[3]		
Burkina Faso	1.6	
Ghana	1.9	
Rwanda	2.8	
Haiti	2.2	

According to a 2008 report from the Black AIDS Institute:

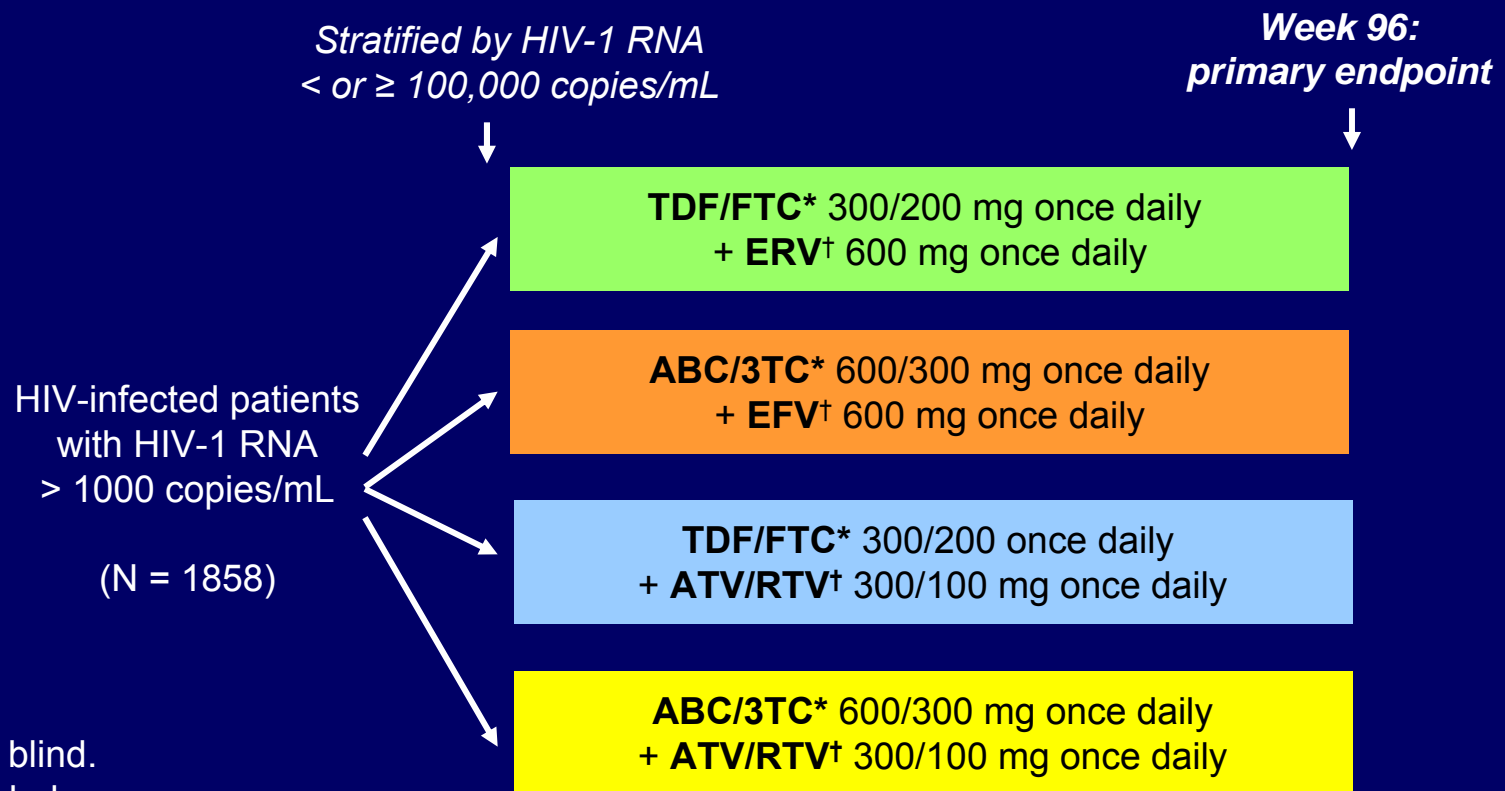
“A free-standing black America would rank 16th in the world in the number of people living with HIV”

“The number of black Americans living with HIV is greater than the HIV population of 7 of the 15 PEPFAR focus countries”

1. Hall HI, et al. JAMA. 2008;300:520-529. 2. McQuillan GM, et al. J Acquir Immune Defic Syndr. 2006;41:651-656. 3. UNAIDS, 2008. Available at: <http://www.unaids.org>.

ACTG 5202: ABC/3TC vs TDF/FTC + EFV or ATV/RTV

- Randomized, double-blind, open-label, phase IIIb study



*Double blind.

†Open label.

ACTG 5202: Comparison of ABC/3TC vs TDF/FTC in Pts With High VL

- **VF**
 - Early failure: confirmed HIV-1 RNA \geq 1000 copies/mL at Weeks 16-24
 - Late failure: confirmed HIV-1 RNA \geq 200 copies/mL at Week 24 or later
- **Initial efficacy review by DSMB in January 2008**
 - Excess VFs observed with ABC/3TC
 - DSMB recommended combining data to compare ABC/3TC vs TDF/FTC
 - Combined analysis indicated highly significant difference between arms, with excess failures with ABC/3TC in patients with HIV-1 RNA \geq 100,000 copies/mL
 - DSMB recommended unblinding of ABC/3TC and TDF/FTC regimens in this stratum
- **Current analysis: 2-arm comparison of ABC/3TC vs TDF/FTC in patients with BL HIV-1 RNA \geq 100,000 copies/mL**

ACTG 5202: BL Characteristics

Characteristic	ABC/3TC (n = 398)	TDF/FTC (n = 399)	All Subjects (n = 797)
Mean age, yrs (SD)	38.8 (9.9)	39.7 (10.1)	39.2 (10.0)
Males, n (%)	331 (83)	345 (86)	676 (85)
Race, n (%)			
▪ White, non-Hispanic	170 (43)	202 (51)	372 (47)
▪ Black, non-Hispanic	112 (28)	94 (24)	206 (26)
▪ Hispanic	103 (26)	93 (23)	196 (25)
Mean HIV-1 RNA, log ₁₀ copies/mL (SD)	5.1 (0.6)	5.1 (0.6)	5.1 (0.6)
Mean CD4+ cell count, cells/mm ³ (SD)	181 (173)	182 (153)	181 (163)
History of AIDS, n (%)	102 (26)	87 (22)	189 (24)
Genotype* at screening, n (%)	175 (44)	166 (42)	341 (43)

*Only *required* if HIV infection acquired in previous 12 months.

Sax PE, et al. IAC 2008. Abstract THAB0303.

ACTG 5202: Shorter Time to VF in Pts With High VL Receiving ABC/3TC

- Shorter time to virologic failure in patients receiving ABC/3TC
 - Proportion of patients with virologic failure receiving ABC/3TC vs TDF/FTC: 14% vs 7%
 - HR: 2.33 (95% confidence interval [CI]: 1.46-3.72; $P = .0003$)

Outcome, n	ABC/3TC (n = 398)	TDF/FTC (n = 399)
Virologic failure (VF), total	57	26
▪ Early VF with no previous suppression to HIV-1 RNA < 200 copies/mL	19	9
▪ Late VF with no previous suppression to HIV-1 RNA < 200 copies/mL	9	2
▪ Late VF with previous suppression to HIV-1 RNA < 200 copies/mL	29	15

- Similar proportions in each arm with VL < 50 c/mL at Wk 48 ($P = .20$) by ITT (prior regimen changes and virologic failures allowed)
- Post hoc analysis: for subjects achieving 2 VL < 50 c/mL on therapy, no significant difference in risk of viral rebound between arm ($P = .247$)

ACTG 5202: Immunologic Response and Adverse Events

- Similar increases in CD4+ cell count in both arms, reaching approximately 400 cells/mm³ by Week 96
- No association of suspected drug HSR and VF
 - Rates of suspected HSR similar between arms
 - Most patients with suspected HSR did not experience VF

Adverse Events, %	ABC/3TC (n = 398)	TDF/3TC (n = 399)
Any grade 3/4 adverse event*	33	19
▪ Lipid abnormalities	10	3
▪ Gastrointestinal	7	5
▪ Generalized symptoms	14	10
Suspected drug HSR	7	7

*Occurring in $\geq 5\%$ of patients reported.

Sax PE, et al. IAS 2008. Abstract THAB0303.

ABC/3TC Clinical Trials Reanalyzed Using ACTG 5202 Endpoints

- Data stratified by HIV-1 RNA $< 100,000$ and $\geq 100,000$ copies/mL
- Time to VF
 - Early: HIV-1 RNA ≥ 1000 copies/mL between Weeks 16-24
 - Late: HIV-1 RNA ≥ 200 copies/mL at Week 24 and beyond

NRTI-Based Regimens

CNA30021: ABC/3TC + EFV QD

CNA30024: ABC/3TC BID + EFV QD

ESS30009: fixed-dose ABC/3TC + EFV QD

PI-Based Regimens

KLEAN: fixed-dose ABC/3TC QD + either FPV/RTV or LPV/RTV

HEAT: fixed-dose ABC/3TC + LPV/RTV QD

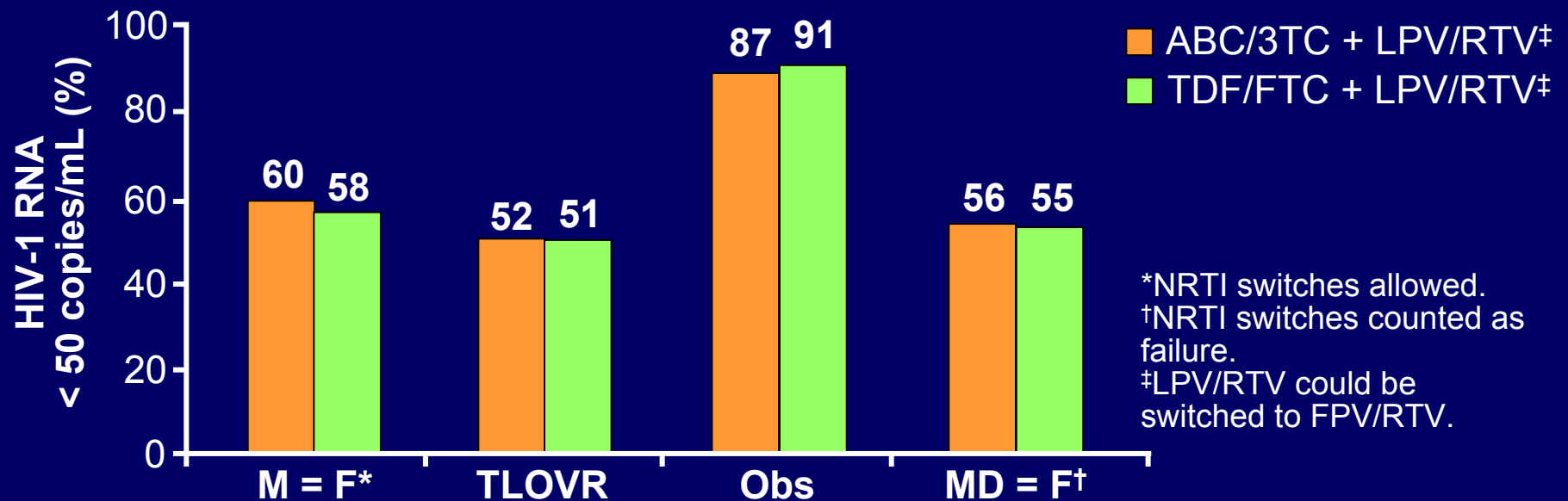
SHARE: fixed-dose ABC/3TC + ATV/RTV QD

No Difference in Virologic Response to ABC/3TC by BL HIV-1 RNA in 6 Trials

Virologic Survival at Week 48, % (n)	Third Drug	Baseline HIV-1 RNA < 100,000 copies/mL	Baseline HIV-1 RNA ≥ 100,000 copies/mL
CNA30021	Efavirenz	94 (218)	89 (166)
CNA30024	Efavirenz	95 (198)	93 (126)
ESS30009	Efavirenz	95 (123)	95 (46)
SHARE	Atazanavir/ritonavir	94 (49)	93 (62)
KLEAN	Fosamprenavir/ritonavir	94 (197)	92 (235)
	Lopinavir/ritonavir	95 (209)	92 (237)
HEAT			
▪ ABC/3TC	Lopinavir/ritonavir	90 (188)	87 (205)
▪ TDF/FTC	Lopinavir/ritonavir	87 (155)	90 (140)

- Safety data in patients with BL HIV-1 RNA ≥ 100,000 copies/mL show similar frequency of grade 3/4 adverse events between arms in HEAT

HEAT: ABC/3TC Noninferior to TDF/FTC at Week 96



- VF occurred in 14% of patients in each arm according to conservative definition (failure to achieve HIV-1 RNA \leq 200 copies/mL after achieving < 50 copies/mL; confirmed HIV-1 RNA \geq 200 copies/mL after Wk 24)
- Median CD4+ cell count increases similar in both ABC/3TC and TDF/FTC arms: +250 vs +247 cells/mm³ from BL to Week 96, respectively

Possible Explanations for Differing Results in Similar Trials

- Differing study designs
 - Longer vs shorter duration of follow-up
 - Endpoints: different definitions/time points for VF; TLOVR vs proportion of patients with HIV-1 RNA < 50 copies/mL
 - Larger vs smaller sample size
 - ABC/3TC compared with different NRTI strategies: ZDV/3TC, TDF/FTC
 - Different third drug used: ATV/RTV, EFV, LPV/RTV, FPV/RTV

Background: Previous D:A:D Findings on CV Risk Associated With ABC, ddI

- **D:A:D — a collaboration of 11 prospective cohorts at 212 clinics in the United States, Europe, and Australia with data on 33,347 HIV-infected patients receiving antiretroviral therapy**
 - 517 (1.6%) of patients developed MI over 5 years
- **Impact of cumulative, recent, and past use of select NRTIs on risk of MI in HIV-infected individuals**
 - Recent use of ABC and ddI associated with 90% and 47% increased risk of MI, respectively
 - Risk most prominent in individuals with underlying CV risk factors
 - Increased risk not seen in those who had previously used these drugs

Observational Analysis of SMART Study to Confirm/Refute D:A:D Results

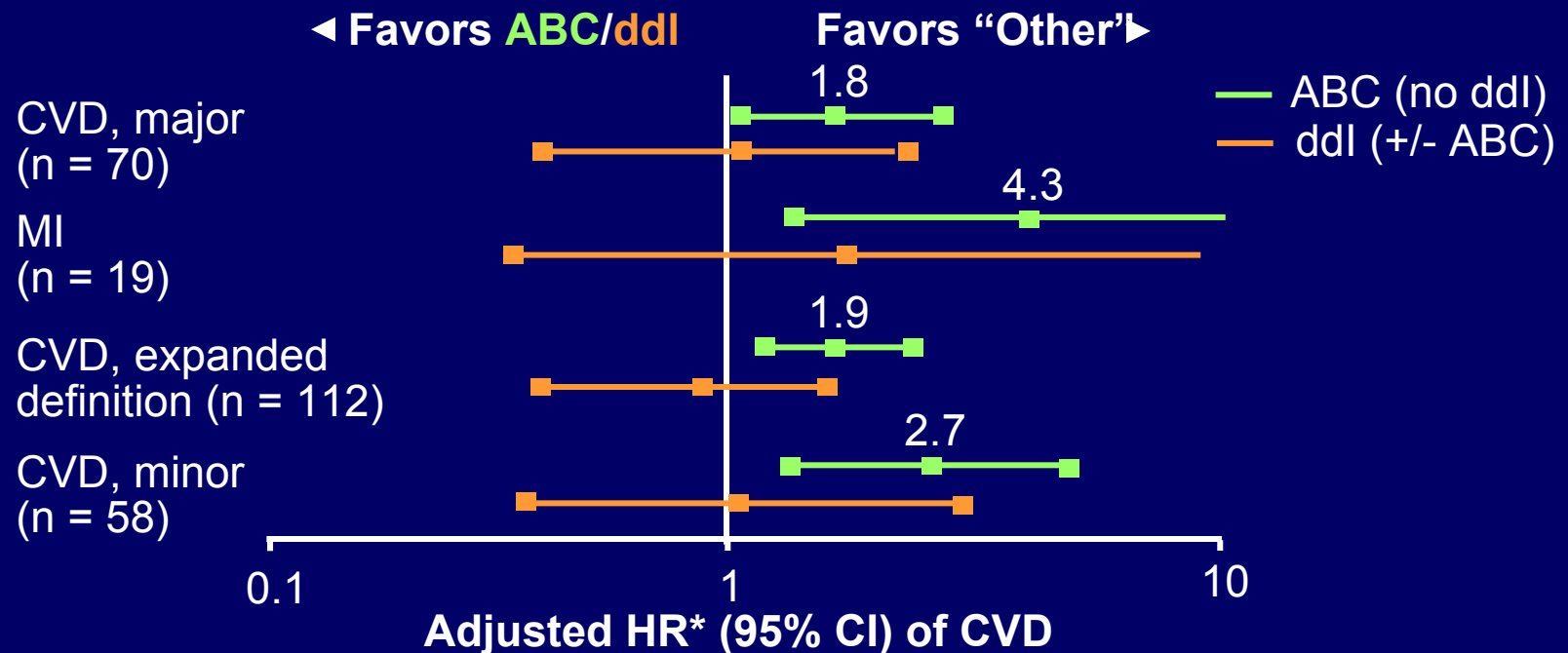
- **Analysis of SMART participants in 3 post hoc subgroups by NRTI use**
 - Patients receiving ABC and not ddl
 - Patients receiving ddl, with ABC or other NRTIs
 - Patients receiving NRTIs other than ABC and ddl
- **CV endpoints**
 - MI
 - Major CVD events: clinical and silent MI, stroke, surgery for CAD, and CVD death
 - Expanded major CVD events: major CVD events plus peripheral vascular disease, CHF, pharmacotherapy for CAD, and unwitnessed deaths
 - Minor CVD events: CHF, peripheral vascular disease, or CAD requiring pharmacotherapy

SMART: BL Characteristics

	ABC, no ddl (n = 1019)	ddl ± ABC (n = 643)	Other NRTIs (n = 2882)	Total (N = 4554)
Median age, yrs (IQR)	45 (39-51)	44 (38-49)	44 (38-50)	44 (38-50)
Female, %	23	23	28	27
HIV-1 RNA ≤ 400 copies/mL, %	82	78	84	83
Median CD4+ cell count, cells/mm ³ (IQR)	639 (495-836)	596 (475-794)	630 (486-814)	630 (487-819)
Previous CV disease, %	4	5	3	4
Current smoker, %	38	41	39	39
Ischemic abnormalities, %	36	35	36	36
Diabetes, %	7	6	7	7
BP lowering drugs, %	21	20	18	19
Lipid lowering drugs, %	21	21	15	18
Median total/HDL ratio (IQR)	4.6 (3.6-5.9)	4.7 (3.6-5.9)	4.6 (3.6-5.9)	4.6 (3.6-5.9)
Past/current ABC use, %	100	28	7	31
NRTI only, %	39	28	7	31
TDF use, %	17	25	22	21
≥ 5 CV risk factors, %	18	17	14	15

Lundgren J, et al. IAC 2008. Abstract THAB0305.

SMART: Current Use of ABC but Not ddl Associated With Increased CV Risk



- Increased risk of CVD events with use of ABC detected only among patients with ≥ 5 CV risk factors at BL (adjusted HR: 3.1)
 - However, difference in risk between patients with vs without these factors failed to reach statistical significance

Inflammatory Biomarkers at BL and on Treatment With ABC

- **SMART^[1]**
 - BL levels of high-sensitivity C-reactive protein and IL-6 27% ($P = .02$) and 16% ($P = .02$) higher, respectively, for patients receiving ABC without ddl vs those receiving other NRTIs
- **HEAT^[2]**
 - IL-6 and high-sensitivity C-reactive protein decreased from BL at Week 48 and 96 in patients receiving ABC/3TC and TDF/FTC

Inflammatory Marker	Study Arm	BL, Geometric Mean in pg/mL	Week 48, Fold Δ in Geometric Mean vs BL	Week 96, Fold Δ in Geometric Mean vs BL
IL-6	ABC/3TC	1.91	0.74	0.81
	TDF/FTC	1.97	0.77	0.75
High-sensitivity C-reactive protein	ABC/3TC	1.88	0.88	0.95
	TDF/FTC	1.72	0.80	0.83

1. Lundgren J, et al. IAC 2008. Abstract THAB0305.
 2. Smith KY, et al. IAC 2008. Abstract LBPE1138.

Retrospective Analysis of ABC and CV Risk in Clinical Trials Database

- Retrospective analysis of 54 clinical trials (N = 14,683 treatment-naive and -experienced patients) with ≥ 24 weeks of follow-up (1995 - 2006)
 - 13 trials randomized adults to ABC vs control
 - 33 trials included ABC in background regimen
 - 8 trials did not include ABC
- Performed MedDRA database query for events coded as “coronary artery disorders” or “ischemic coronary artery disorders”
 - Specific preferred terms: coronary artery atherosclerosis, coronary artery disease, coronary artery occlusion, acute myocardial infarction, angina pectoris, angina unstable, myocardial infarction, myocardial ischemia
- Fatal cases due to any cause externally reviewed
- Incomplete BL data precluded calculation of Framingham risk

ABC Not Associated With CV Risk in Clinical Trials Database, HOPS

- No difference in incidence of CV events with ABC exposure in 54-trial analysis with 24-48 weeks of follow-up^[1]
 - RR of any or acute MI with ABC: 0.863 (95% CI: 0.40-1.86)
 - RR of any ischemic CAD or disorder with ABC: 0.593 (95% CI: 0.35-1.01)

Outcome	ABC-Treated Patients (n = 1570)		No ABC Treatment (n = 1692)	
	Frequency, %	Rate/1000 Person-Yrs	Frequency, %	Rate/1000 Person-Yrs
MI (any or acute)	0.127	2.15	0.355	4.1
Any ischemic CAD or disorder	0.318	4.3	0.768	7.64

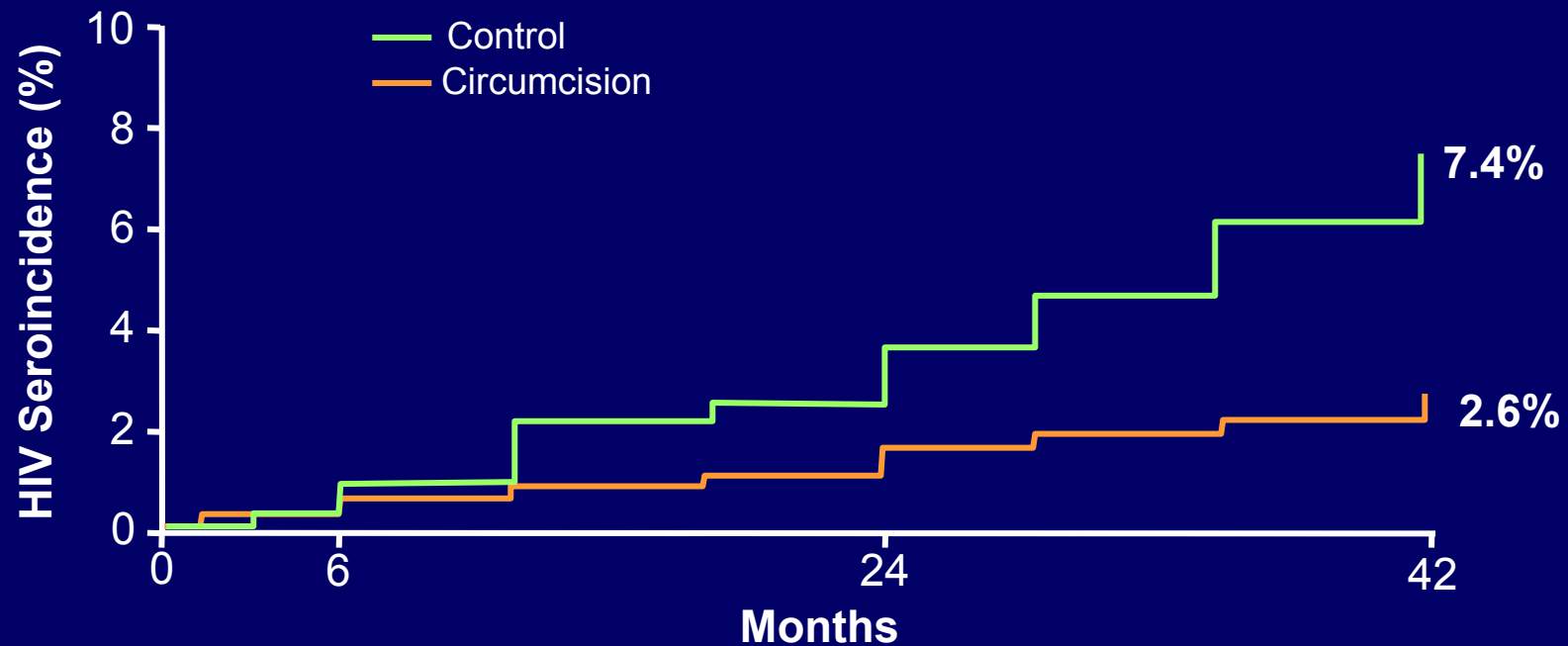
- **Of 119 CV events in HOPS cohort, no association with ABC use^[2]**

1. Cutrell A, et al. IAC 2008. Abstract WEAB0106.

2. Lichtenstein K, et al. IAC 2008. Abstract THPE0236.

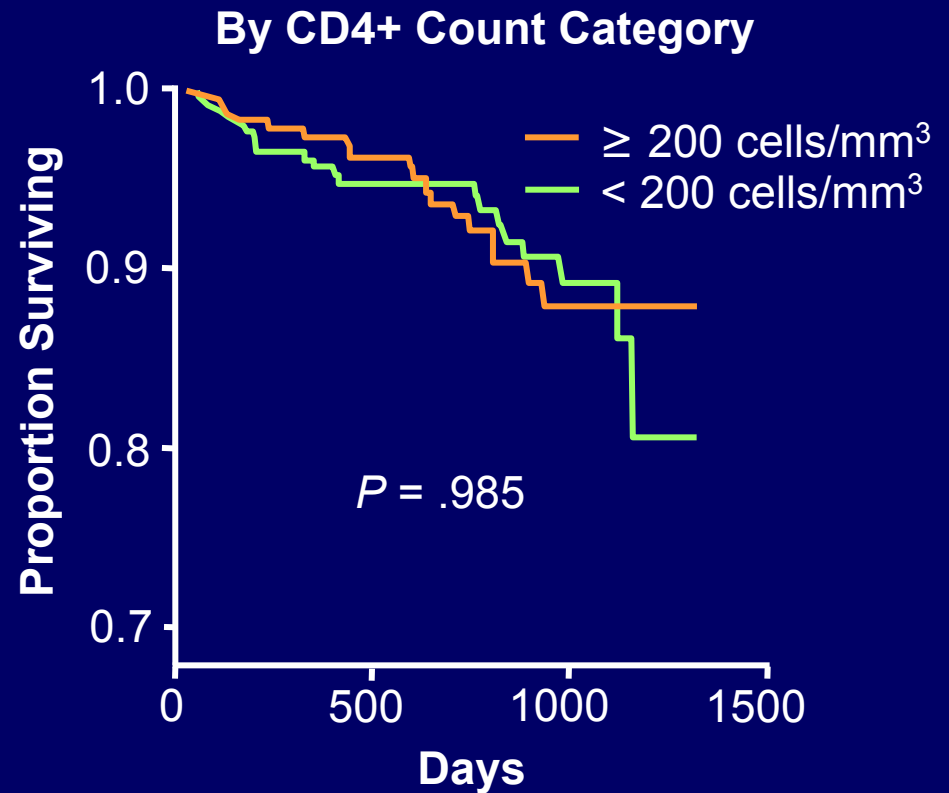
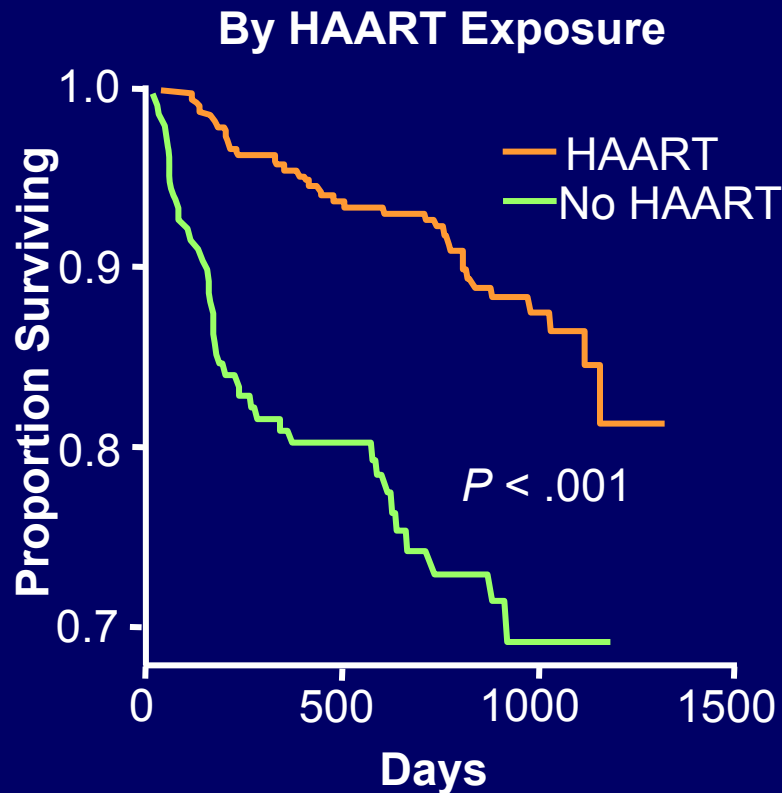
Kisumu Study: Circumcision Remains Protective Against HIV Acquisition

- Kisumu, Kenya trial: extended follow-up of prospective, randomized, controlled trial (N = 1491)
 - Cumulative risk of HIV infection 64% lower in circumcision vs control at 42 months



THRio Cohort: HAART Initiation After TB Diagnosis Improves Survival

- Retrospective, observational cohort of 662 HAART-naïve patients diagnosed with TB in Rio de Janeiro, Brazil



Updated IAS-USA Guidelines: When to Start

Year	Recommendation to Begin Immediate Therapy	Recommendation to Consider Immediate Therapy	Recommendation to Delay Therapy
2006	<ul style="list-style-type: none"> Active AIDS No history of active AIDS, but CD4+ cell count ≤ 200 cells/mm³ 	<ul style="list-style-type: none"> No history of active AIDS, but CD4+ cell count from 200-350 cells/mm³ CD4+ cell count > 350 cells/mm³ but rapid CD4+ cell count decline, HIV-1 RNA $> 100,000$ copies/mL, CVD risk factors, other non-AIDS risk factors* 	<ul style="list-style-type: none"> CD4+ cell count > 350 cells/mm³
2008	<ul style="list-style-type: none"> Active AIDS No history of active AIDS, but CD4+ cell count ≤ 350 cells/mm³ 	<ul style="list-style-type: none"> CD4+ cell count > 350 cells/mm³ but rapid CD4+ cell count decline, HIV-1 RNA $> 100,000$ copies/mL, CVD risk factors, other non-AIDS risk factors* 	<ul style="list-style-type: none"> CD4+ cell count > 350 cells/mm³

*Non-AIDS risk factors include HIV-associated neuropathy, hepatitis C, hepatitis B

Hammer SM, et al. JAMA. 2008;300:555-570.

IAS-USA Recommended Regimens for ARV-Naive Patients, 2008

IAS-USA Guidelines “Recommended”			
NNRTI-based regimen	EFV*	+	TDF/FTC [†] ABC [‡] /3TC [§]
PI-based regimen	LPV/RTV ATV/RTV FPV/RTV DRV/RTV SQV/RTV		

*Except during first trimester of pregnancy or in women with high pregnancy potential.

[†]Or 3TC.

[‡]Possible increased risk of CVD; possible increased risk of failure with high HIV-1 RNA.

[§]Or FTC.

Putting Together New Regimens: Antiretrovirals 2008 and Beyond

NRTIs

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

NNRTIs

- Delavirdine
- Efavirenz
- Nevirapine
- Etravirine
- Rilpivirine*

Protease Inhibitors (PIs)

- Atazanavir
- **Darunavir[†]**
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- **Tipranavir[†]**

Entry Inhibitors

- Enfuvirtide
- Maraviroc
- Vicriviroc*

Integrase Inhibitors

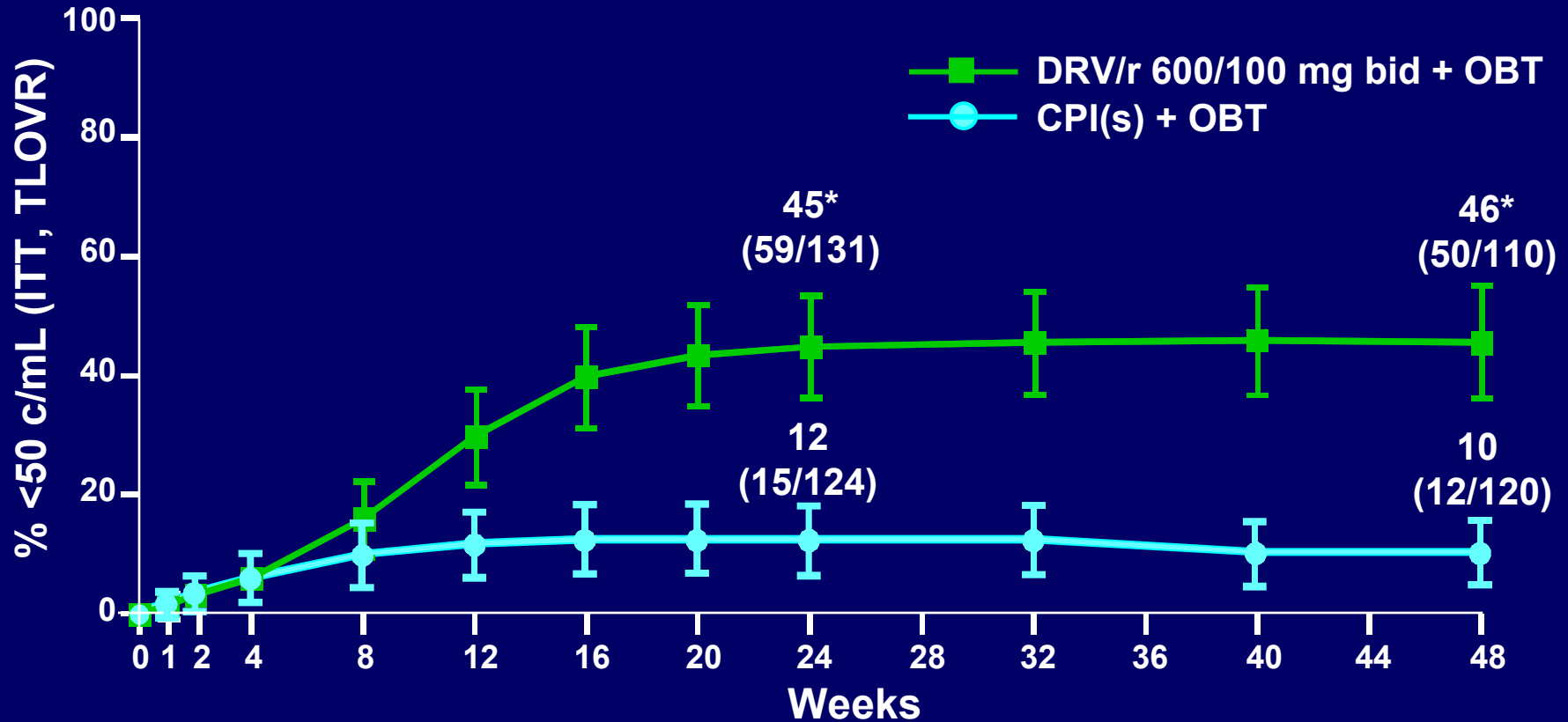
- Raltegravir
- Elvitegravir*

*In development and not yet approved for use; †Second-generation agent.

Newer PIs: The Role of Darunavir (DRV)

- **Initially targeted for patients with multiple PI-resistance mutations resulting from prior use of PIs**
- **Subsequent studies assessed**
 - **Differences in patients with fewer baseline resistance mutations and fewer prior PIs (LPV/r naïve)**
 - **Results using a lower dose in treatment-naïve patients**

POWER 1 & 2: DRV/r vs Comparator PI in Heavily Treatment-Experienced Patients

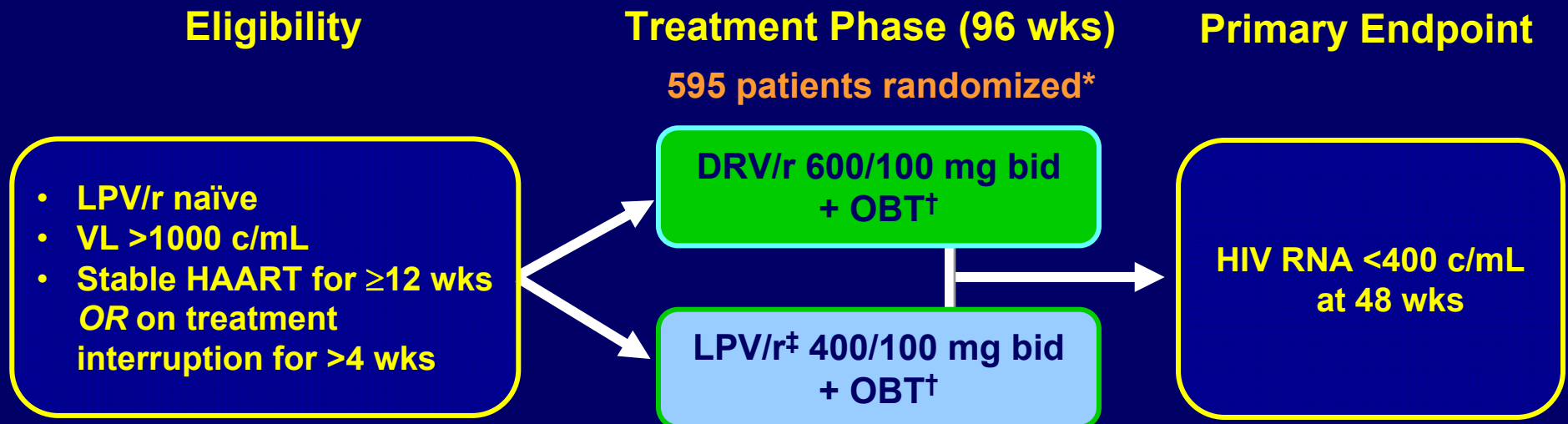


*OBT: RTIs ± ENF; dual PI use allowed in CPI arm; $P < .001$ vs CPI(s).

POWER = Performance of TMC114/ritonavir When Evaluated in Treatment-experienced Patients with PI Resistance; /r = ritonavir; ITT = intent to treat; TLOVR = time to loss of virologic response; RTI = reverse-transcriptase inhibitor.

Clotet B et al. *Lancet*. 2007;369(9568):1169-1178.

TITAN: DRV/r vs LPV/r in Treatment-Experienced Adults

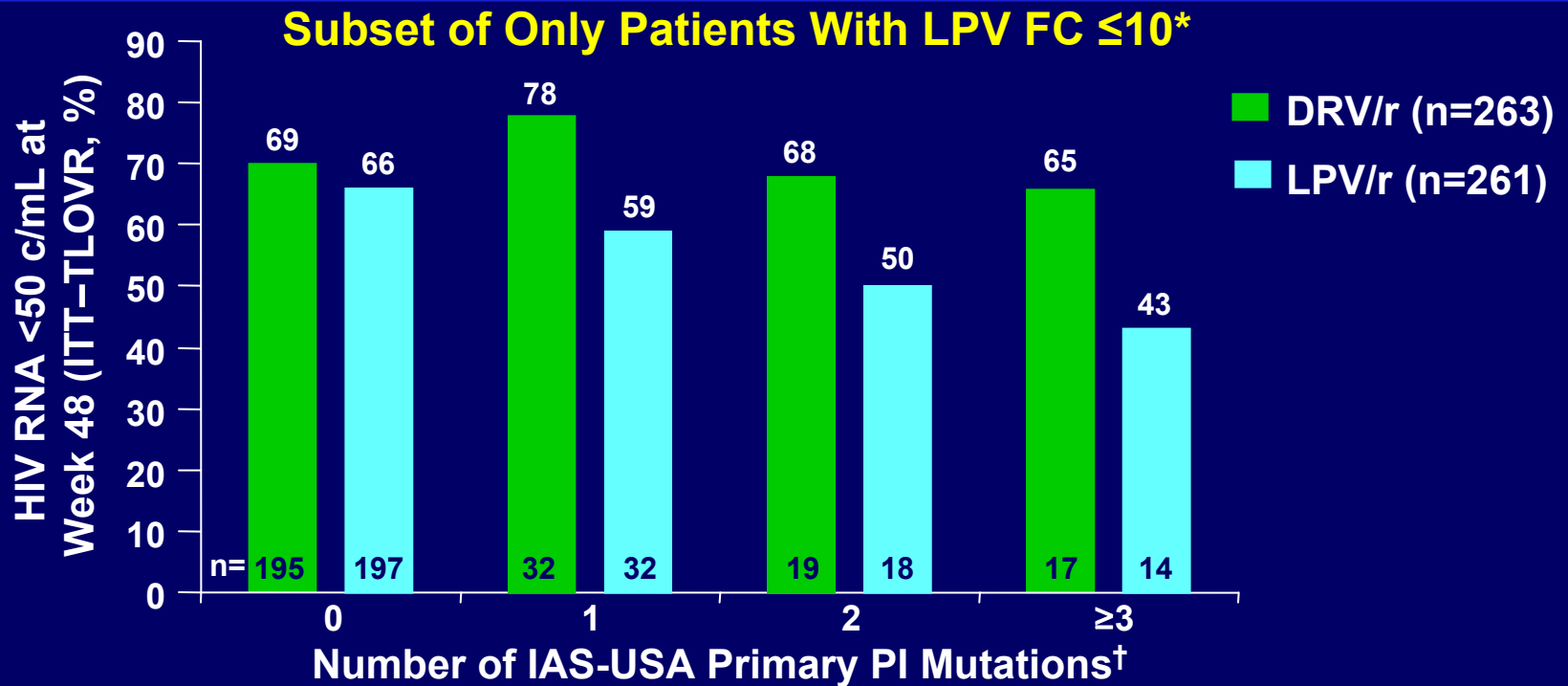


*ENF and TPV use excluded; [†]OBT = 2–3 ARVs from approved NRTI/NNRTIs; [‡]Tablet formulation LPV/r use allowed if approved within country.

TITAN = TMC114/r in Treatment-Experienced Patients Naïve to Lopinavir; VL = viral load; HAART = highly active–antiretroviral therapy; ARV = antiretroviral therapy; TPV = tipranavir.

Madrugá JV et al. *Lancet*. 2007;370(9581):49-58.

TITAN: Outcome by PI Mutations at Baseline



	n=	195	197	32	32	19	18	17	14
DRV Median FC		0.50	0.50	0.40	0.50	0.70	0.65	0.90	0.85
LPV Median FC		0.70	0.70	0.80	1.10	1.80	2.60	3.60	5.35
Med LPV mutations		1.00	1.00	2.00	2.50	4.00	4.00	5.00	6.50

*Plus OBT: >2 RTIs only (excludes missing LPV FC at BL); [†]D30N, V32I, L33F, M46I/L, I47A/V, G48V, I50V/L, I54L/M, L76V, V82A/F/L/S/T, I84V, N88S, or L90M.
FC = fold change.

Johnson VA et al. *Top HIV Med.* 2006;14(3):125-130; Berger DS et al. 11th European AIDS Conference/EACS 2007; October 24-27, 2007; Madrid, Spain. Poster P7.3/27.

ARTEMIS: DRV/r vs LPV/r in ARV-Naïve Patients

689 ARV-naïve patients
VL>5000; no CD4 entry

DRV/r 800/100 mg qd
+ TDF 300 mg and FTC 200 mg
(n=343)

LPV/r* 400/100 mg bid or
800/200 mg qd
+ TDF 300 mg and FTC 200 mg
(n=346)

Primary endpoint: Proportion of patients with an HIV RNA <50 c/mL at Week 48

Primary objective: Demonstrate noninferiority of DRV/r qd vs LPV/r based on primary endpoint

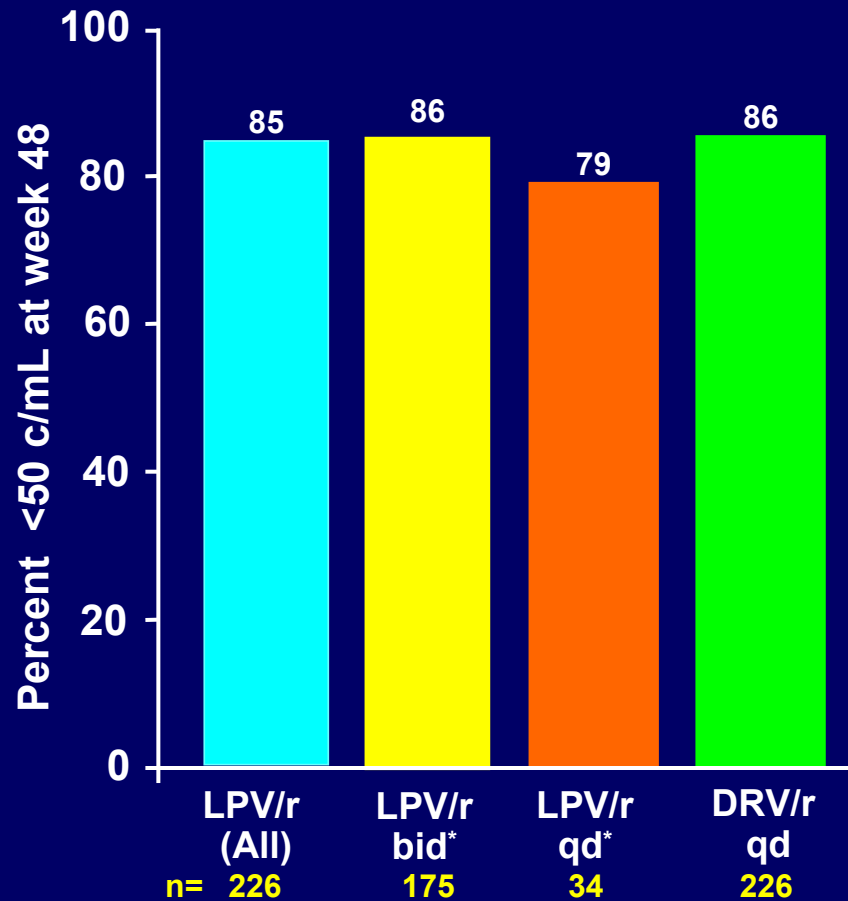
*Dosing was based on regulatory approval; switch was made according to local regulatory approval and drug availability. LPV/r bid, 77%; qd, 15%; bid/qd, 8%; capsule/tablet switch, 83%.

ARTEMIS = Antiretroviral Therapy With TMC114 Examined In Naïve Subjects; FTC = emtricitabine; TDF = tenofovir.

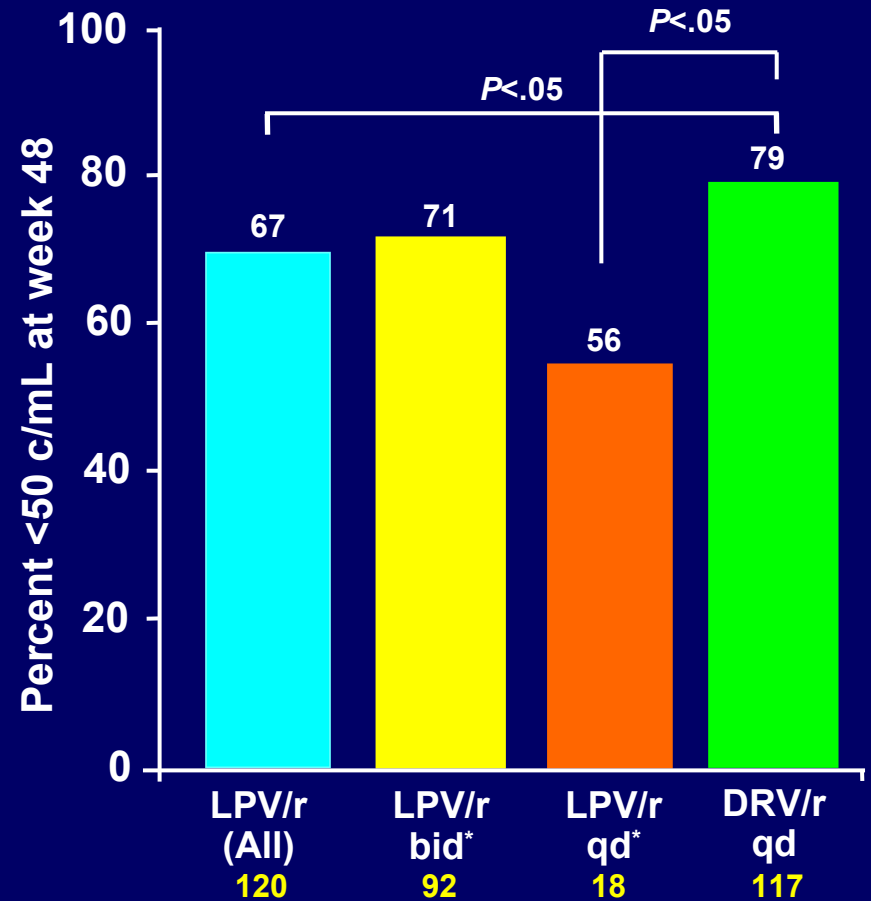
Clumeck N et al. 11th European Aids Conference/EACS; October 24, 2007; Madrid, Spain. Abstract LBPS7/5.

ARTEMIS: Virologic Response by Baseline Viral Load and Schedule

Baseline Viral Load <100,000 c/mL



Baseline Viral Load ≥100,000 c/mL



*27 patients receiving LPV/r bid and qd during the study were excluded from this analysis.

Clumeck N et al. 11th European Aids Conference/EACS; October 24, 2007; Madrid, Spain. Abstract LBPS7/5.

Putting Together New Regimens: Antiretrovirals 2008 and Beyond

NRTIs

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- Tenofovir
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Protease Inhibitors (PIs)

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Entry Inhibitors

- Enfuvirtide
- Maraviroc
- Vicriviroc*

Integrase Inhibitors

- Raltegravir
- Elvitegravir*

*In development and not yet approved for use; [†]Second-generation agent.

BENCHMARK 1 & 2: Trial Design

**2 Identical, Ongoing, Phase III Studies (in different countries)
Randomized (2:1), Double-blind, Placebo-controlled**

ART-experienced adult patients

Genotypic/phenotypic resistance to ≥ 1 drug in each of 3 classes
(NNRTI + NRTI + PI)
HIV RNA >1000 c/mL

RAL (400 mg bid) + OBT
(n=462)

PBO + OBT
(n=237)

Primary endpoints (Week 16): HIV RNA and CD4 counts
and adverse experiences

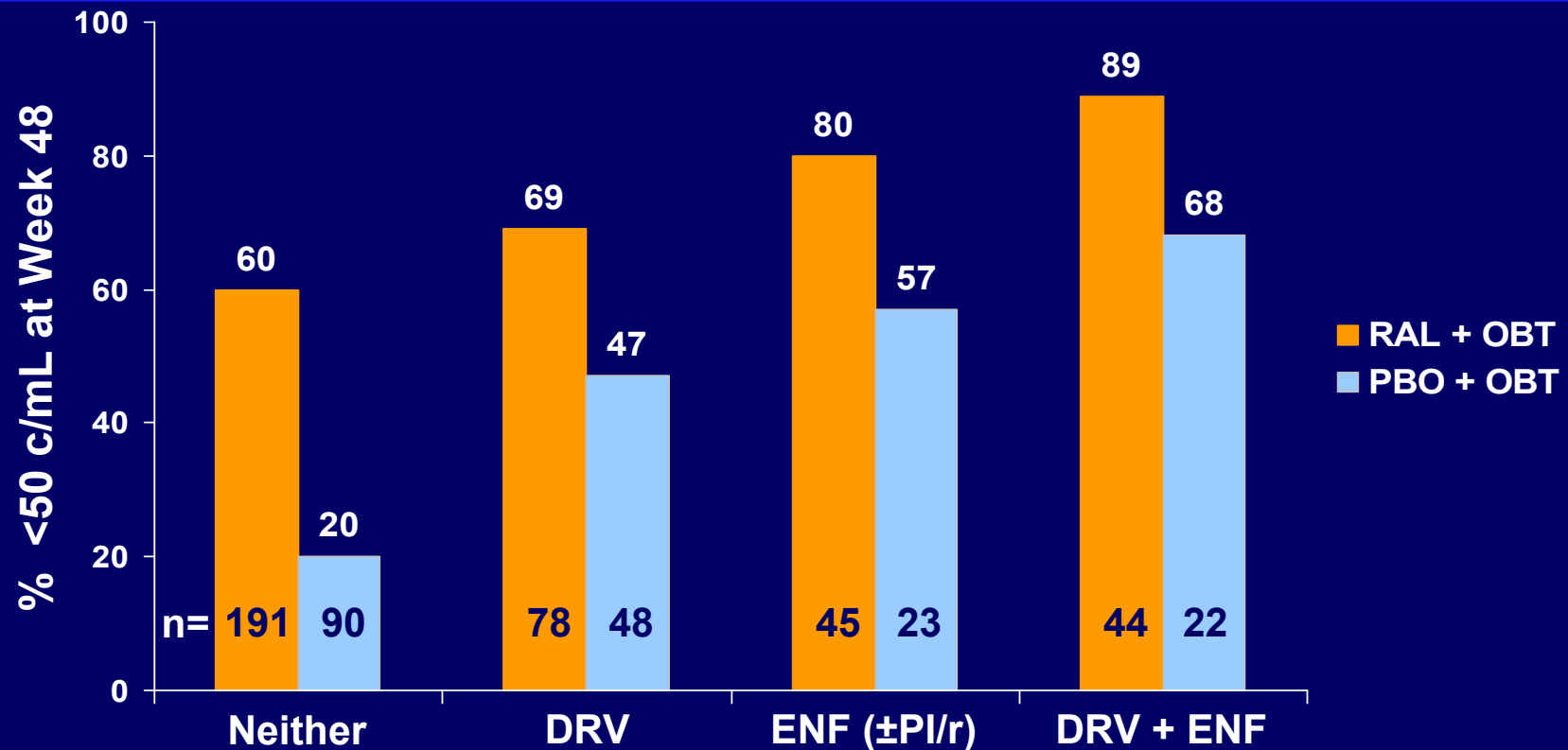
Patients with virologic treatment failure after ≥ 16 weeks could enter open-label RAL arm.

PBO = placebo.

Kumar P et al. 11th European AIDS Clinical Conference/EACS; October 24-27, 2007; Madrid, Spain. Abstract P7.2/06.

BENCHMARK 1 & 2: Week 48

Outcomes by Use of DRV \pm ENF*



- First use of ENF in OBT only included here
- No baseline resistance testing to DRV done

*Virologic failures carried forward.

Cooper D et al. 15th Conference on Retroviruses and Opportunistic Infections; February 3-8, 2008; Boston, MA. Abstract 788; Steigbigel R et al. 15th Conference on Retroviruses and Opportunistic Infections; February 3-8, 2008; Boston, MA. Abstract 789.

BENCHMARK 1 & 2: Resistance and Adverse Events

	BENCHMARK 1	BENCHMARK 2
	Virologic Failure (n=50) Baseline and Follow-up Sequence (n=49)	Virologic Failure (n=48) Baseline and Follow-up Sequence (n=45)
With mutation at amino acid 148 or 155	28 (57)	29 (64)
With other known RAL resistance mutations	5 (10)	2 (4)
With no significant amino acid changes from baseline	9 (18)	13 (29)

- Virologic failure is generally associated with mutations at 1 of 2 primary residues, Q148 or N155, in combination with at least 1 other mutation
- Adverse events were similar between RAL and PBO; no increased risk of malignancy with RAL in these studies or when additional data from phase II studies were included

Cooper D et al. 15th Conference on Retroviruses and Opportunistic Infections; February 3-8, 2008; Boston, MA. Abstract 788; Steigbigel R et al. 15th Conference on Retroviruses and Opportunistic Infections; February 3-8, 2008; Boston, MA. Abstract 789.

Merck 004: Comparison of Efavirenz (EFV) and RAL in ARV-Naïve Patients

- Phase II multicenter, double-blind, randomized 2-part study
- Part I—monotherapy with RAL vs PBO
- Part II—dose escalation with 4 doses of RAL vs EFV
 - Late (failure to suppress to <200 c/mL or rebound)

198 Subjects (~150 Part II only)

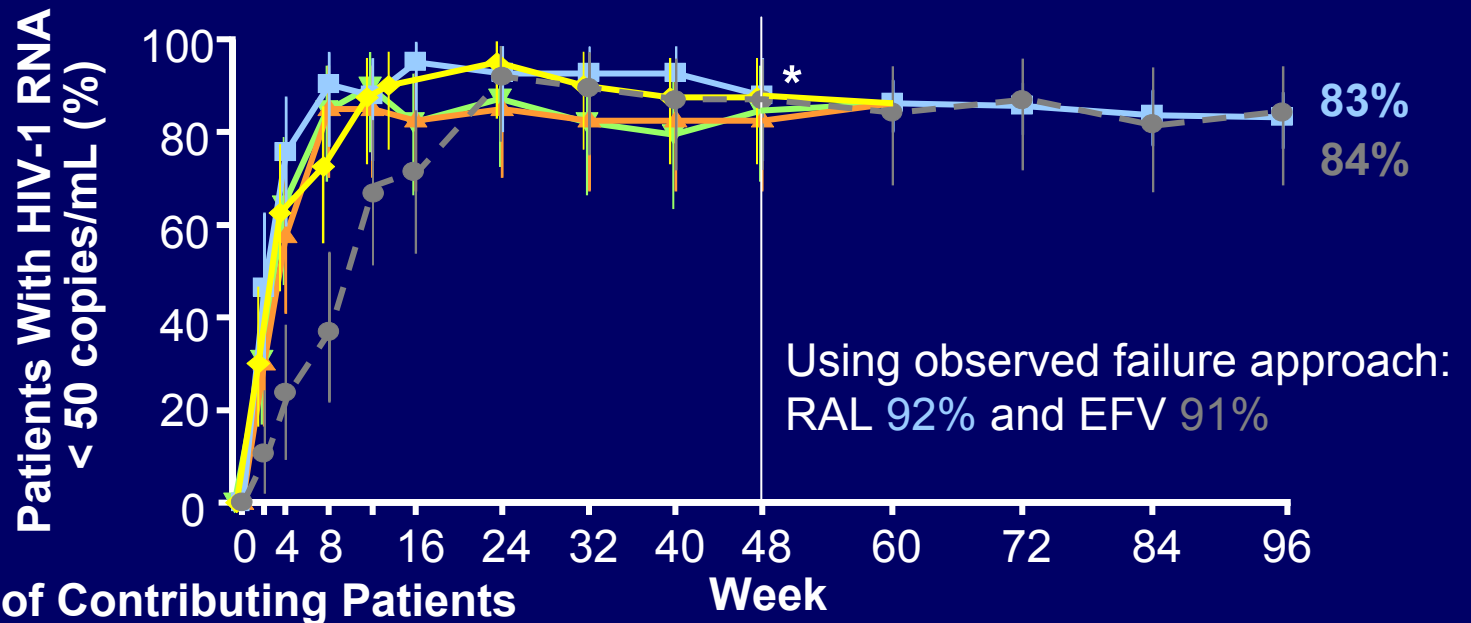
- Susceptible to EFV, 3TC, TDF (by genotype)
- No prior ART (<7 days allowed)
- HIV RNA ≥ 5000 c/mL (stratification for HIV RNA \leq or $> 50,000$ c/mL)
- CD4 ≥ 100 cells/mm³



3TC = lamivudine.

Markowitz M et al. *J Acquir Immune Defic Syndr.* 2006;43(5):509-515; Markowitz M et al. *J Acquir Immune Defic Syndr.* 2007;46(2):125-133.

Protocol 004: 96-Week Results of RAL vs EFV in Treatment-Naive Pts (NC = F)



Number of Contributing Patients

—▲—	RAL 100 mg BID.	39	39	39				
—▲—	RAL 200 mg BID.	40	40	40				
—■—	RAL 400 mg BID.	41	41	41	160	160	159	160
—◆—	RAL 600 mg BID.	40	40	40				
-●-	EFV 600 mg QD	38	37	38	38	38	38	38

*After Week 48, patients in all RAL groups continued at 400 mg BID.

All patients received TDF/3TC

Markowitz M, et al. IAC 2008. Abstract TUAB0102.

Resistance Data and Adverse Events With RAL

- **Protocol 004^[1]**
 - 6 patients in RAL arm and 2 patients in EFV arm failed during study through Week 96
 - 2 failures in RAL arm not associated with resistance mutations
 - **Adverse events similar in both study arms**
 - **Grade 3/4 creatinine kinase elevations greater with RAL vs EFV: 6.3% vs 2.6%**
 - **Neuropsychiatric symptoms more common with EFV vs RAL: 29% vs 13% by Week 48 and 32% vs 16% by Week 96**
- **Response rates and resistance mutations developing at failure similar in clade B and non-clade B viruses^[2]**

1. Markowitz M, et al. IAC 2008. Abstract TUAB0102.

2. Danovich R, et al. IAC 2008. Abstract TUAA0302.

Putting Together New Regimens: Antiretrovirals 2008 and Beyond

NRTIs

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

NNRTIs

- Delavirdine
- Efavirenz
- Nevirapine
- Etravirine
- Rilpivirine*

Protease Inhibitors (PIs)

- Atazanavir
- Darunavir[†]
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir[†]

Entry Inhibitors

- Enfuvirtide
- **Maraviroc**
- **Vicriviroc***

Integrase Inhibitors

- Raltegravir
- Elvitegravir*

*In development and not yet approved for use; [†]Second-generation agent.

CCR5 Inhibitors and Tropism Testing

- **CCR5 inhibitors**
 - Maraviroc (MVC) approved 2007
 - Others in phase I/II
 - Vicriviroc (VCV) furthest along
 - Active in treatment naïve patients
- **Role for testing tropism essential to successful use**
 - Future potential use of testing
 - If rebound viremia on MVC-containing regimen
 - Does the patient have R5, X4, or D/M virus?
 - Experimental use: In a patient off therapy to estimate risk of progression?

CCR5 = chemokine (C-C motif) receptor 5, (a chemokine receptor); D/M virus = dual/mixed strain (both R5 and X4).

van Lunzen J. *Eur J Med Res.* 2007;12(9):435-140; US Department of Health and Human Services Guidelines. January 29, 2008. <http://aidsinfo.nih.gov/contentfiles/adultandadolescentGL.pdf>. Accessed March 13, 2008.

MOTIVATE 1 & 2: Trial Design

**2 Identical Ongoing Phase IIb/III Studies
Randomized (1:2:2), Double-blind, Placebo Controlled**

1076 ARV-experienced patients

**R5 HIV-1 infection (44% screen failures); HIV-1-RNA $\geq 5,000$ c/mL
Stable prestudy ARV regimen or no ARVs for ≥ 4 weeks
Resistance to and/or ≥ 6 months' experience with ≥ 1 ARV from 3 classes (≥ 2 for PIs)**

**All received OBT*
Stratified by ENF use and HIV-1 RNA $<$ and $\geq 100,000$ c/mL**

**PBO
(n=209)**

**MVC 150 mg[†] qd
(n=414)**

**MVC 150 mg[†] bid
(n=426)**

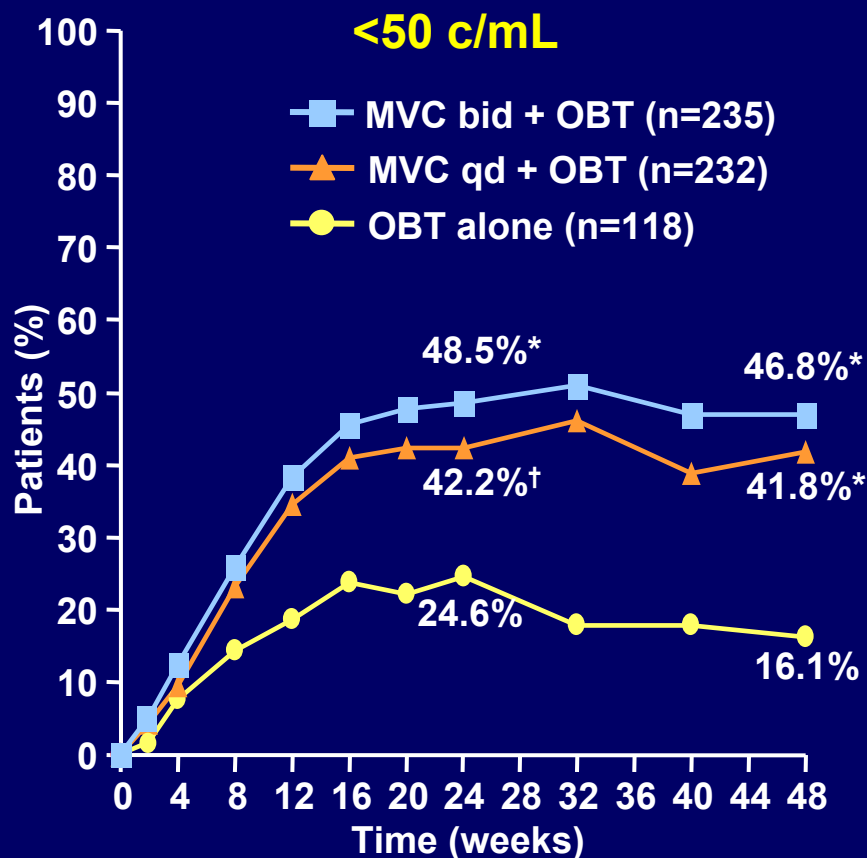
Primary endpoint at 24 weeks: mean Δ from baseline in HIV-1 RNA

*OBT of 3–6 ARVs (PK-boosting doses of RTV not counted as an ARV); [†]Pts receiving a PI (except TPV) and/or DVR in their OBT received 150 mg of MVC, all others received 300 mg of MVC.
MOTIVATE = Maraviroc Plus Optimized Background Therapy (OBT) In Viraemic, Antiretroviral Treatment-Experienced Patients.

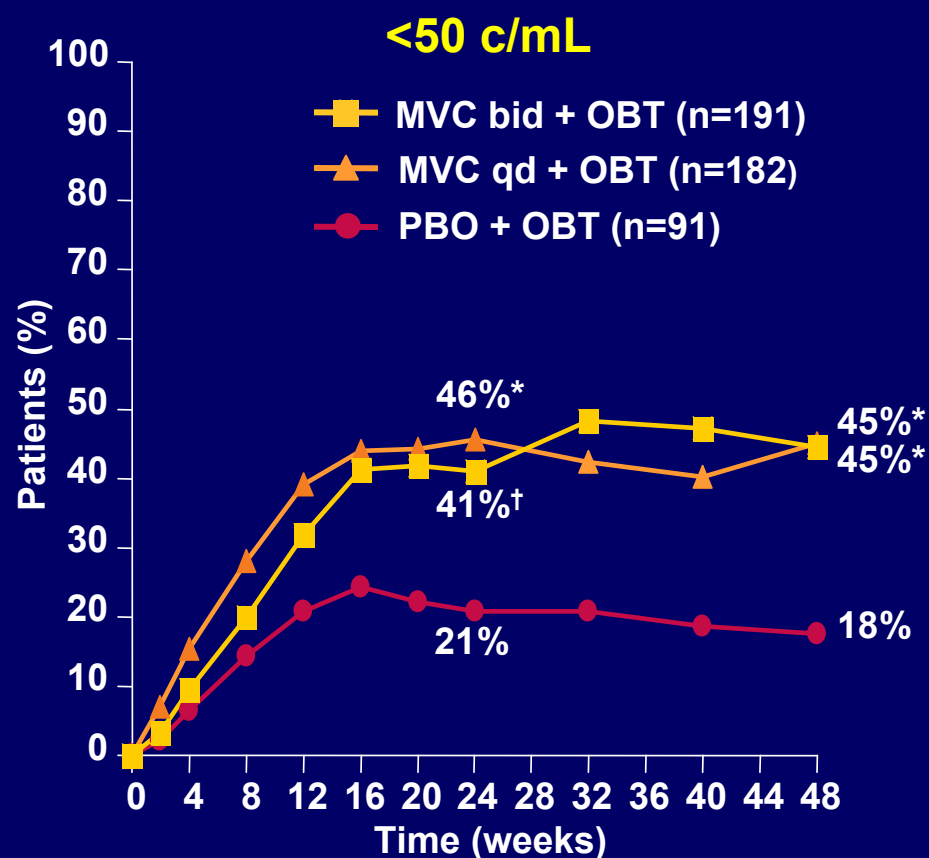
Nelson M, Lalezari J, et al. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 200; Los Angeles, California. Abstracts 104aLB and 104bLB.

MOTIVATE 1 & 2: Week 48 Responses

MOTIVATE 1



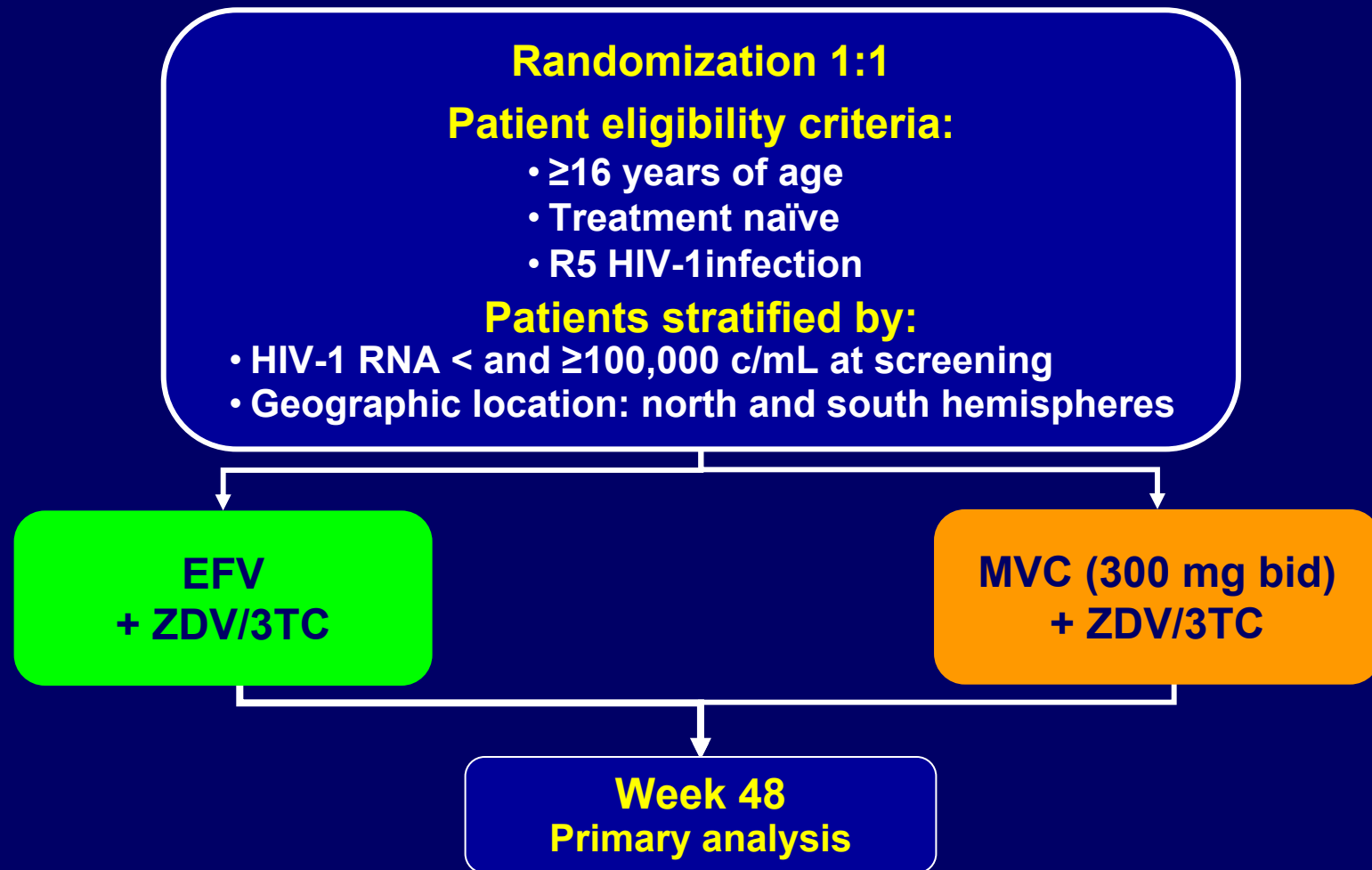
MOTIVATE 2



* $P < .0001$ vs OBT; † $P < .0006$ vs OBT; HIV-1 RNA value imputed as BL if patient discontinued before 48 wks.

Nelson M, Lalezari J, et al. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17-20, 2007; Chicago, Illinois. Abstract H-370.

MERIT: Comparison of EFV and MVC in ARV-Naïve Patients

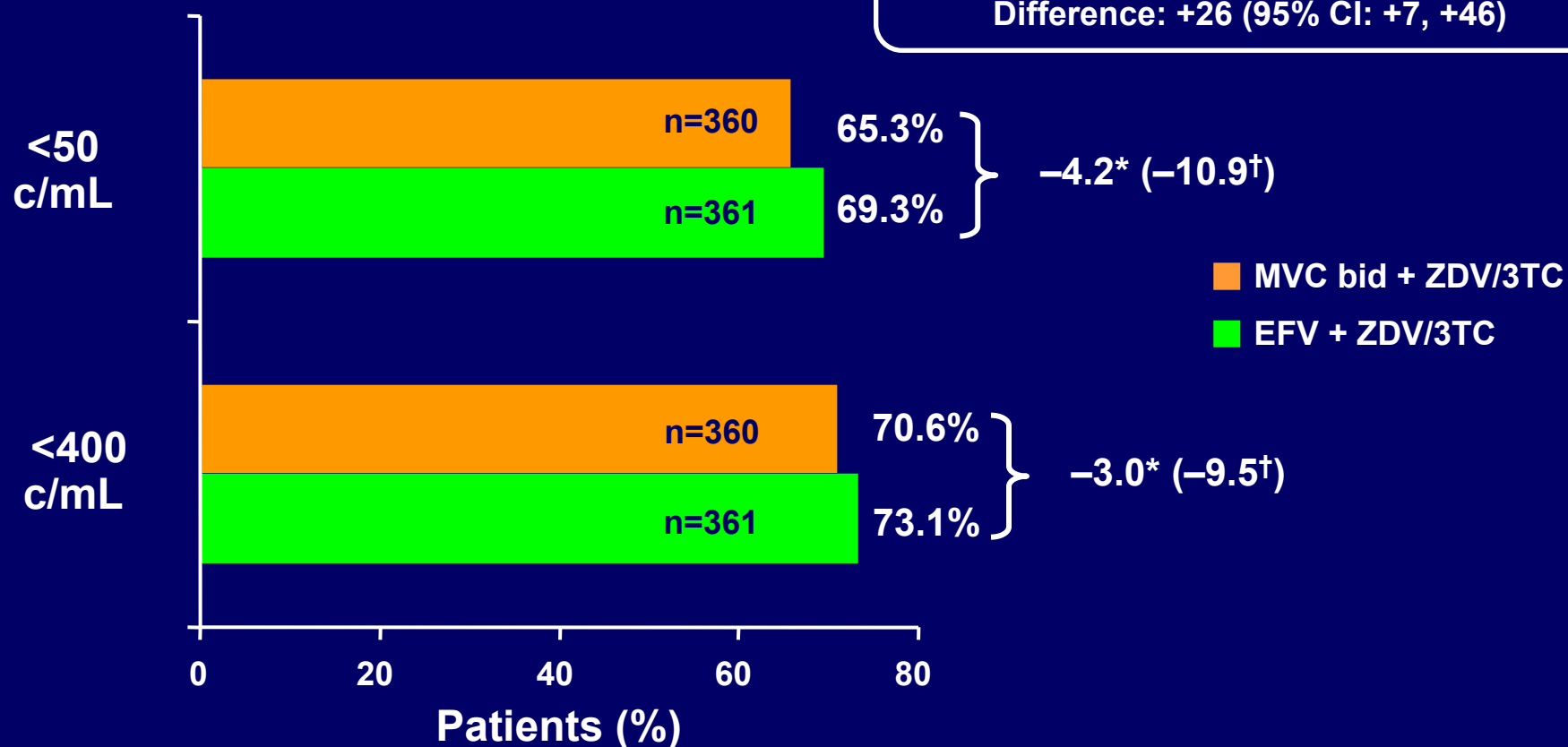


MERIT = Maraviroc Versus Efavirenz Regimens as Initial Therapy; ZDV = zidovudine.

Saag M et al. 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 22-25, 2007; Sydney, Australia. Abstract WESS104.

MERIT: Virologic Efficacy at 48 Weeks

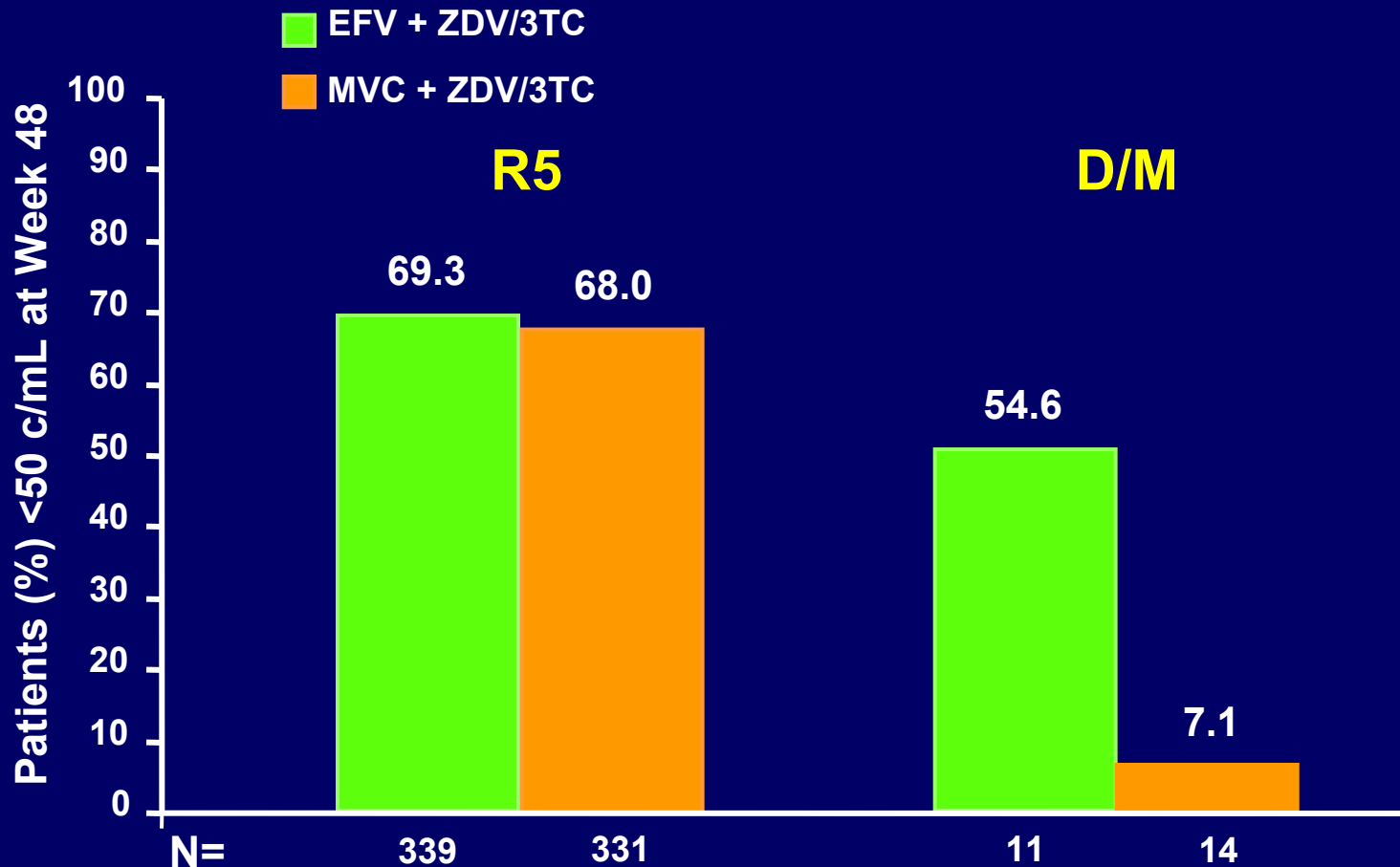
Mean Δ CD4+ from baseline:
EFV +144 vs MVC +170 cells/mm³
Difference: +26 (95% CI: +7, +46)



*Difference; †Lower bound of 1-sided 97.5% confidence interval; noninferiority margin = -10%.

Saag M et al. 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention; July 22-25, 200; Sydney, Australia. Abstract WESS104.

Virologic Efficacy by Tropism Result at Baseline



Putting Together New Regimens: Antiretrovirals 2008 and Beyond

NRTIs

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

NNRTIs

- Delavirdine
- Efavirenz
- Nevirapine
- **Etravirine**
- **Rilpivirine***

Protease Inhibitors (PIs)

- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

Entry Inhibitors

- Enfuvirtide
- Maraviroc
- Vicriviroc*

Integrase Inhibitors

- Raltegravir
- Elvitegravir*

*In development and not yet approved for use; †second-generation agent.

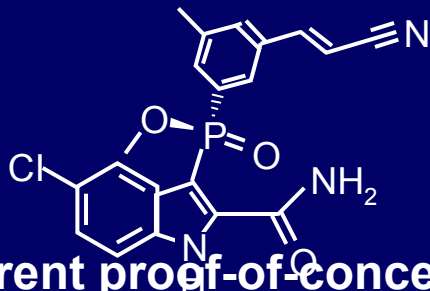
Newer NNRTIs

- RDEA806, an investigational NNRTI with in vitro activity against NNRTI-resistant mutants, including K103N
- Etravirine (ETR) recently FDA approved
 - 2nd-generation NNRTI
 - Higher resistance barrier
 - Not affected by K103N
- Rilpivirine (RPV, TMC 278) in phase II for treatment-naïve patients

Novel NNRTI IDX899 Safe, Effective In HIV-Infected, Treatment-Naive Patients

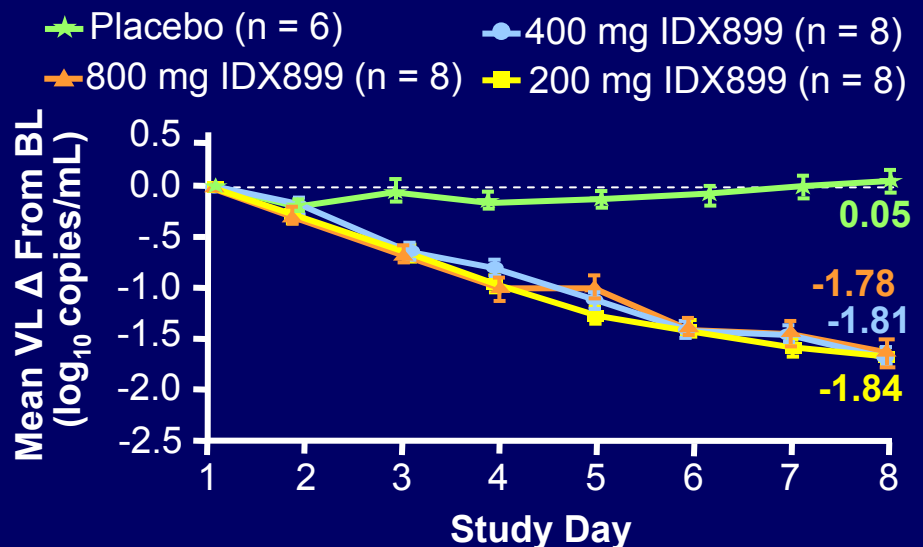
- **New and Emerging Therapies in Existing and Novel Classes: Clinical Trial Update**

- High genetic barrier to resistance in vitro
- QD dosing feasible



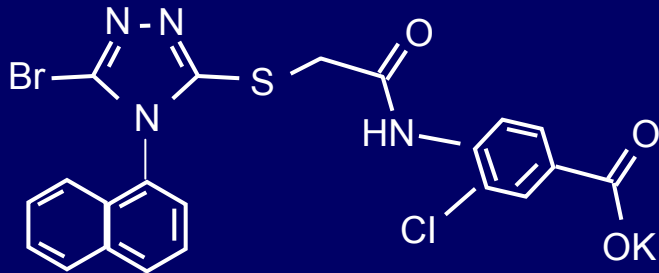
- **Current proof-of-concept study assessed safety, activity, and PK of IDX899 monotherapy vs placebo for 7 days in treatment-naive HIV-infected patients**

- Adverse events mild and similar to placebo-treated group
- Mean HIV-1 RNA level declined by ~ 1.8 log₁₀ copies/mL from BL to Day 8 with all 3 doses tested



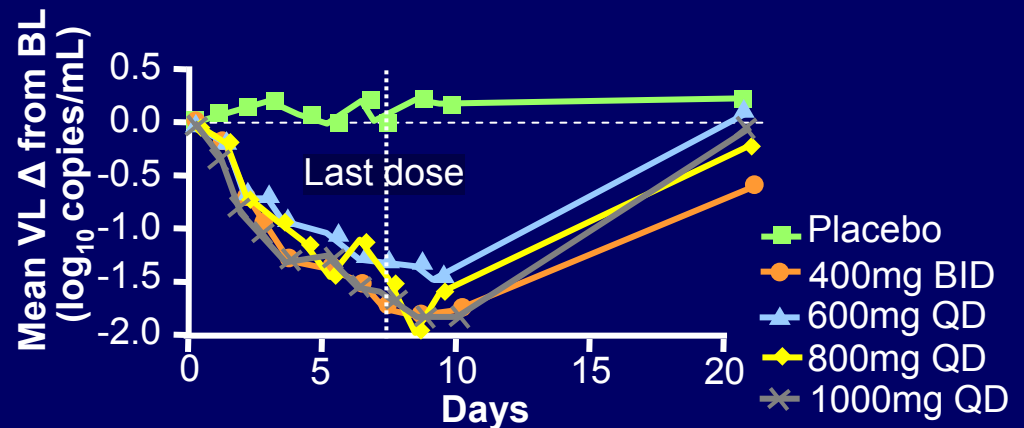
Novel NNRTI RDEA806 Safe, Effective in Pilot Study in HIV-Infected Patients

- RDEA806, an investigational NNRTI with in vitro activity against NNRTI-resistant mutants, including K103N
 - Preclinical studies show high barrier to resistance
 - No reproductive toxicity in animals
 - Does not inhibit/induce of CYP450

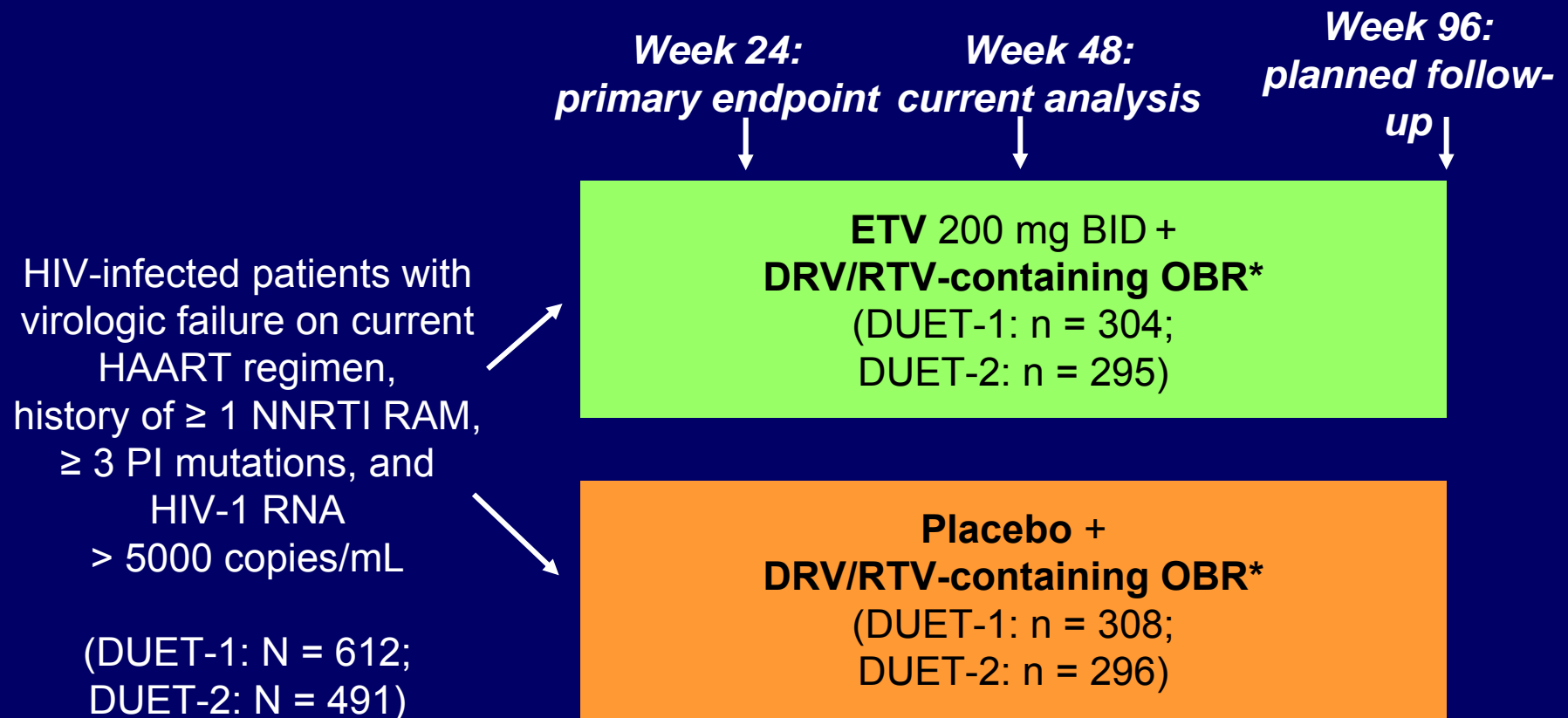


- Current study explored safety, efficacy, and PK of RDEA806 monotherapy vs placebo in treatment-naive HIV-infected pts

- **No serious, grade 3/4 adverse events, significant laboratory toxicities or discontinuations**
 - Potentially drug related AEs of moderate severity reported in 6 of 36 pts receiving RDEA806 vs 1 of 12 receiving placebo
- **Median -1.3 to -1.8 log₁₀ copies/mL VL reduction at Day 8**



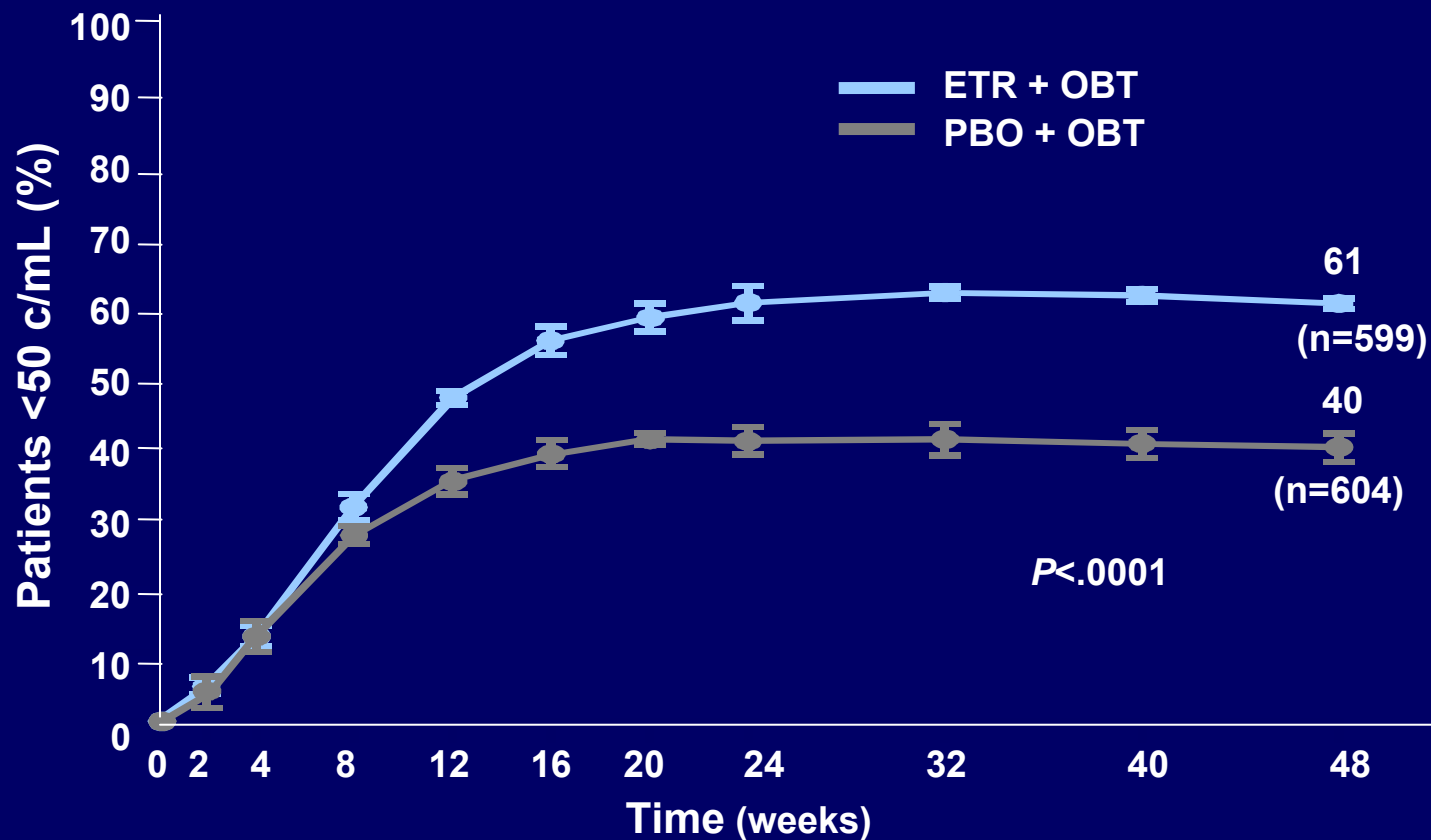
DUET-1 and -2: ETV + DRV/RTV-Containing OBR, Phase III Trials



*Investigator-selected OBR comprising DRV/RTV 600/100 mg BID + ≥ 2 NRTIs \pm ENF.

DUET 1 and 2: Results at Week 48 (ITT-TLOVR)

Pooled DUET-1 and DUET-2



Haubrich R et al. 15th Conference on Retroviruses and Opportunistic Infections; February 3-8, 2008; Boston, MA. Abstract 790; Johnson M et al. 15th Conference on Retroviruses and Opportunistic Infections; February 3-8, 2008; Boston, MA. Abstract 791.

DUET-1 and -2: Association of BL Variables and Response to ETR

- Rate of HIV-1 RNA < 50 copies/mL at Wk 48 significantly greater with ETR vs placebo (61% vs 40%, $P < .0001$)^[1]
 - ENF use, number of concomitant active agents, HIV-1 RNA, CD4+ cell count significantly predicted virologic response in both ETV and placebo-treated pts
 - Receipt of ≥ 2 previous NNRTIs predicted poorer response to ETR
- High response rates in pts with ≤ 3 combined ETR + DRV RAMs at Wk 24^[2]

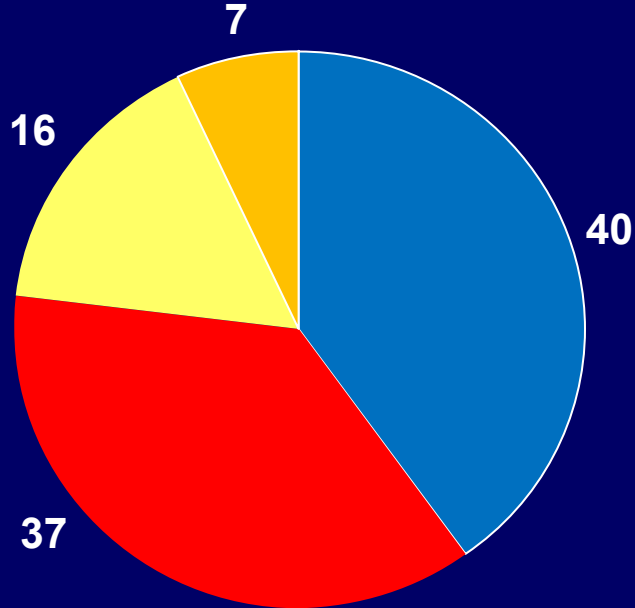
		ETR RAMs, n				
HIV-1 RNA < 50 copies/mL, % (n/N)		0	1	2	3	> 3
DRV RAMs, n	0	78 (7/9)	67 (8/12)	100 (3/3)	67 (2/3)	0 (0/1)
	1	83 (36/44)	71 (27/38)	93 (13/14)	57 (4/7)	40 (2/5)
	2	73 (30/41)	75 (18/24)	56 (9/16)	29 (2/7)	17 (1/6)
	3	78 (31/40)	50 (12/24)	45 (9/20)	60 (3/5)	30 (3/10)
	> 3	63 (17/27)	35 (8/23)	27 (3/11)	27 (3/11)	0 (0/5)

1. Cahn P, et al. IAC 2008. Abstract TUPE0047.
2. Haubrich R, et al. IAC 2008. Abstract TUPE0048.

Proportion of Isolates With ETR Mutations Among NNRTI-Resistant Samples

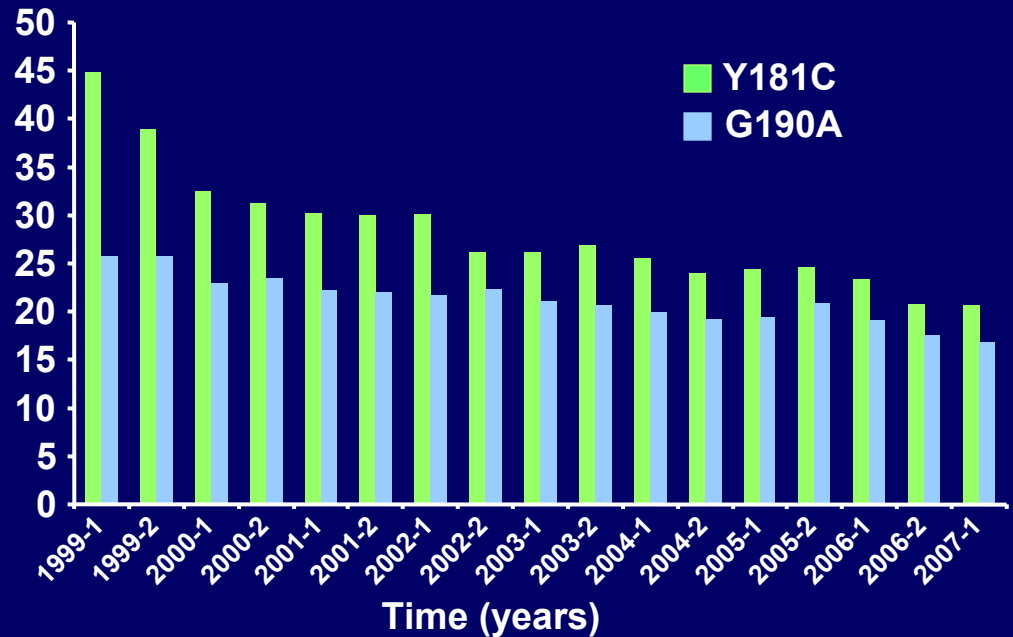
IAS-USA Resistance Isolates (n=89,113)

- 0 ETR mutations
- 1 ETR mutation
- 2 ETR mutations
- ≥3 ETR mutations



N=226,491 samples (1/99–6/07)

% With Y181C or G190A Among NNRTI-Resistant Samples



High Response Rates With ETR-Based Regimens in US Early Access Program

Outcome, Week 24	ETR + DRV/RTV + RAL + BR (n = 486)	ETR + DRV/RTV + BR (n = 338)	ETR + RAL + BR (n = 234)	ETR + BR (n = 140)
HIV-1 RNA < 75 copies/mL, %	66	62	65	66
HIV-1 RNA < 400 copies/mL, %	84	79	83	86
Mean change in HIV-1 RNA from BL, log ₁₀ copies/mL (SD)	-2.3 (1.14)	-1.9 (1.28)	-2.3 (1.18)	-1.8 (1.43)
Median change in CD4+ cell count from BL, cells/mm ³ (IQR)	91 (39-154)	82 (18-148)	98 (31-175)	88 (17-188)

- **Similar low rates of serious adverse events, discontinuations due to adverse events in all arms**

Towner W, et al. IAC 2008. Abstract TUPE0066.

Updated Safety Data on ETR

- In DUET studies, neuropsychiatric adverse events similar with ETR vs placebo, regardless of previous psychiatric history^[1]
 - Any event: 30% vs 34% ($P = .1745$)
 - Nervous system event: 17% vs 20% ($P = .2660$)
 - Psychiatric event: 17% vs 20% ($P = .2042$)
- No effects of ETR on fetal development in rats and rabbits^[2]

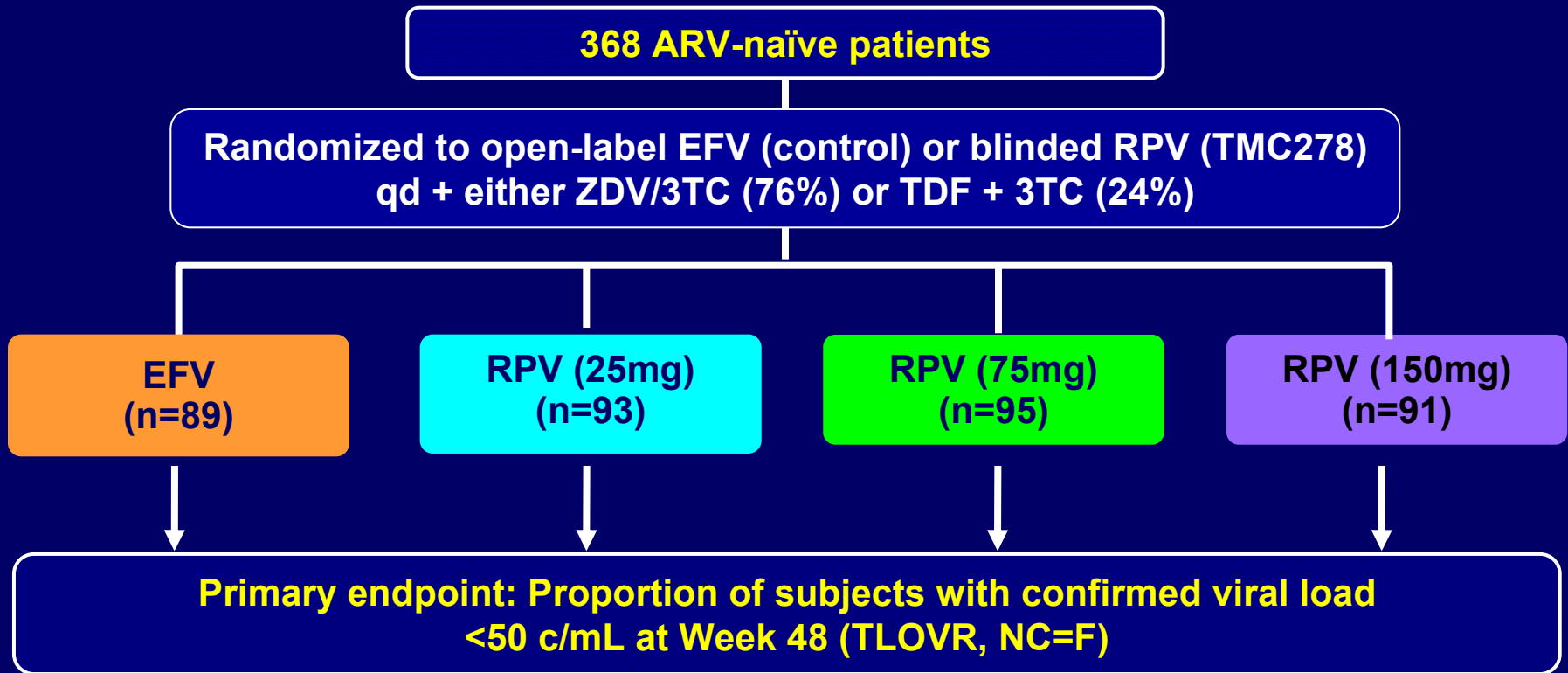
1. Katlama C, et al. IAC 2008. Abstract TUPE0056.

2. Raaof A, et al. IAC 2008. Abstract TUPE0013.

TRIO Study: RAL + ETR + DRV/RTV Highly Effective as 3 Active Agents

- **Multicenter, phase II study of DRV/RTV plus ETR plus RAL (N = 103); addition of NRTIs, ENF at discretion of physician**
 - Inclusion criteria included susceptibility to DRV and ETR based on ≤ 3 DRV and ≤ 3 ETR RAMs, respectively
 - 59% of patients had < 1 active agent in OBR, as assessed by GSS
- **90% of patients attained HIV-1 RNA < 50 copies/mL at Week 24 (95% CI: 85% to 96%)**
- **Median increase in CD4+ cell count from BL to Week 24: 99 cells/mm³ (IQR: 32-147)**
- **Of 10 patients with detectable HIV-1 RNA at Week 24, only 3 had confirmed HIV-1 RNA > 400 copies/mL**
- **2 possibly drug-related clinical grade 4 adverse events; only 1 led to treatment discontinuation**

Rilpivirine vs EFV: Study Design

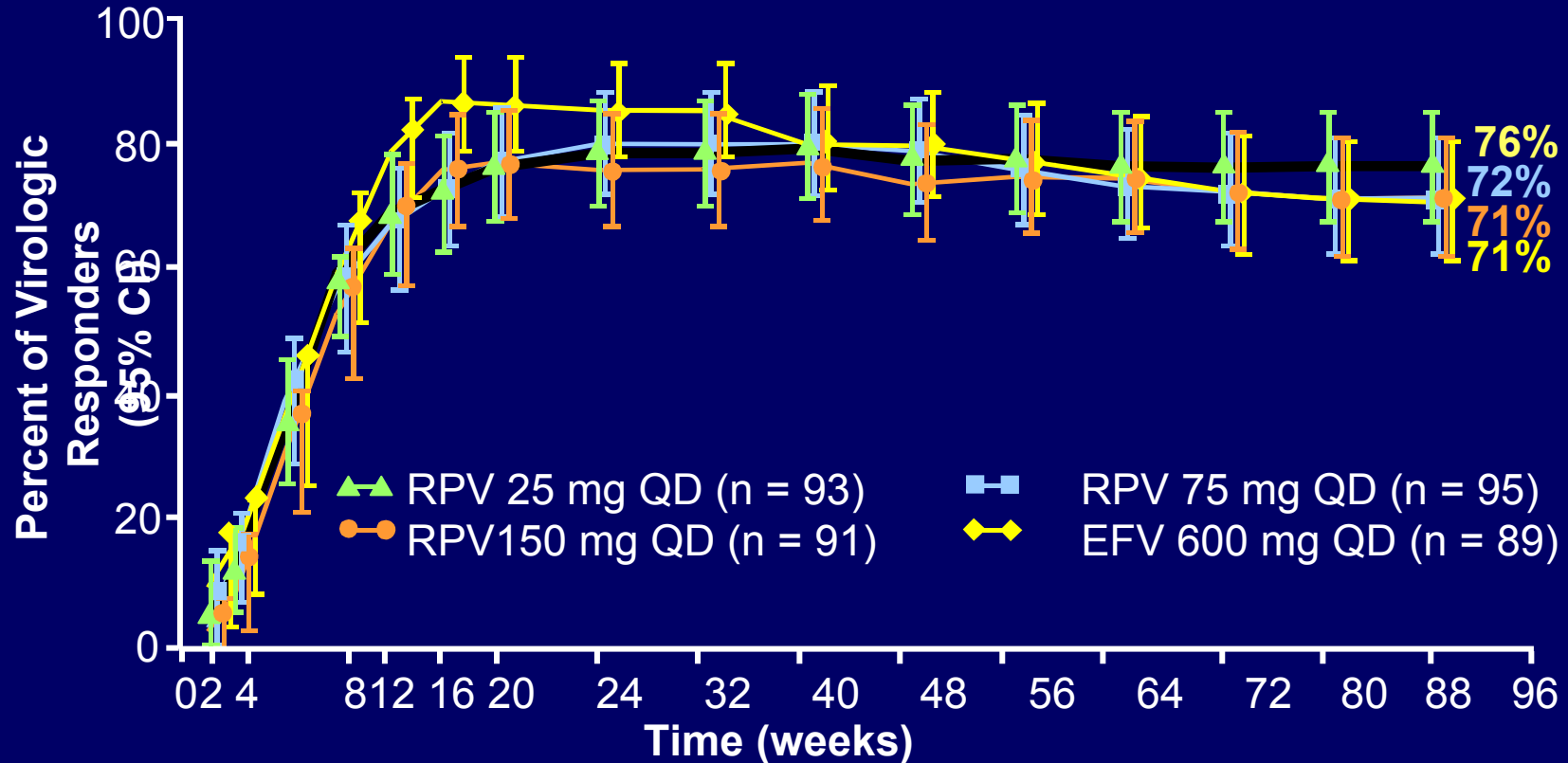


RPV = rilpivirine; NC=F = noncompleter=failure.

Pozniak A et al. 14th Conference on Retroviruses and Opportunistic Infections; February 25-28, 2007; Los Angeles, California. Abstract 144LB.

RPV (TMC278) vs EFV: HIV-1 RNA < 50 copies/mL at Week 96

- Treatment-naive patients with HIV-1 RNA ≥ 5000 copies/mL randomized to RPV or EFV, both plus 2 NRTIs (ITT-TLOVR)



Adverse Events and Resistance Similar With RPV vs EFV

- **Incidence of any adverse events similar in RPV and EFV arms**
 - More rash with EFV vs RPV: 21% vs 9% ($P < .01$)
 - More nervous system disorders with EFV vs RPV: 48% vs 31% ($P < .01$)
 - More neuropsychiatric adverse events with EFV vs RPV: 21% vs 16%
- **NNRTI RAMs emerged at a similar rate with RPV vs EFV**
- **QTc interval increased in all study arms through Week 48, then plateaued**
 - QTc prolongation lowest with 25 mg/day dose which has been selected for ongoing phase III trial

Thank You

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University of Miami School of Medicine