

# HIV Highlights

## CCO Independent Conference Coverage

of the 2007 Interscience Conference on Antimicrobial Agents and  
Chemotherapy\*

September 17-20, 2007

Chicago, Illinois

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# About These Slides

- These slides accompany CCO's online Official Conference Coverage of the 2007 Interscience Conference on Antimicrobial Agents and Chemotherapy
- Our thanks to the presenters who gave permission to include their original data
- The full program is available on the Clinical Care Options HIV Web site: [clinicaloptions.com/hiv/ICAAC2007](http://clinicaloptions.com/hiv/ICAAC2007)
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# Faculty

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## Disclosure Information

**Joseph J. Eron, Jr., MD**, has disclosed that he has received grants or research support from Merck and Panacos; has served as a consultant for Avexa, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Panacos, Pfizer, Tibotec, Trimeris, and Virco; and has received fees for non-CME services from Bristol-Myers Squibb, Gilead Sciences, Merck, Roche, Tibotec and Virco.

**Edward King, MA**, has no significant financial interests to disclose.

**Taryn O'Loughlin Gross, PhD**, has no significant financial interests to disclose.

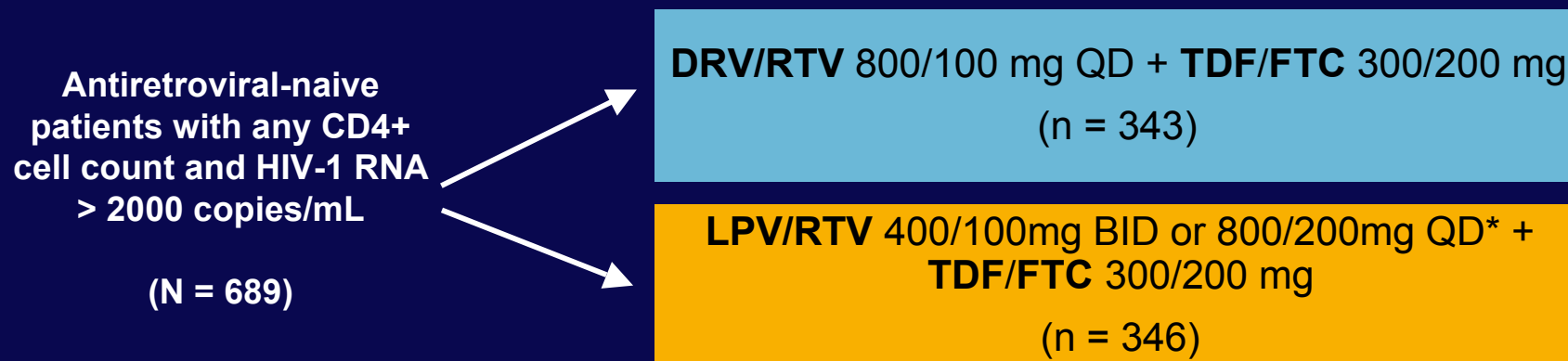
Dr. Eron discusses the investigational drugs elvitegravir, etravirine, interleukin-2, maraviroc, and raltegravir; he also discusses the unapproved use for the antiretroviral medication darunavir in treatment-naive patients.

# First-Line Therapy and Switch Strategies



# ARTEMIS: DRV/RTV vs LPV/RTV in Treatment-Naive Patients

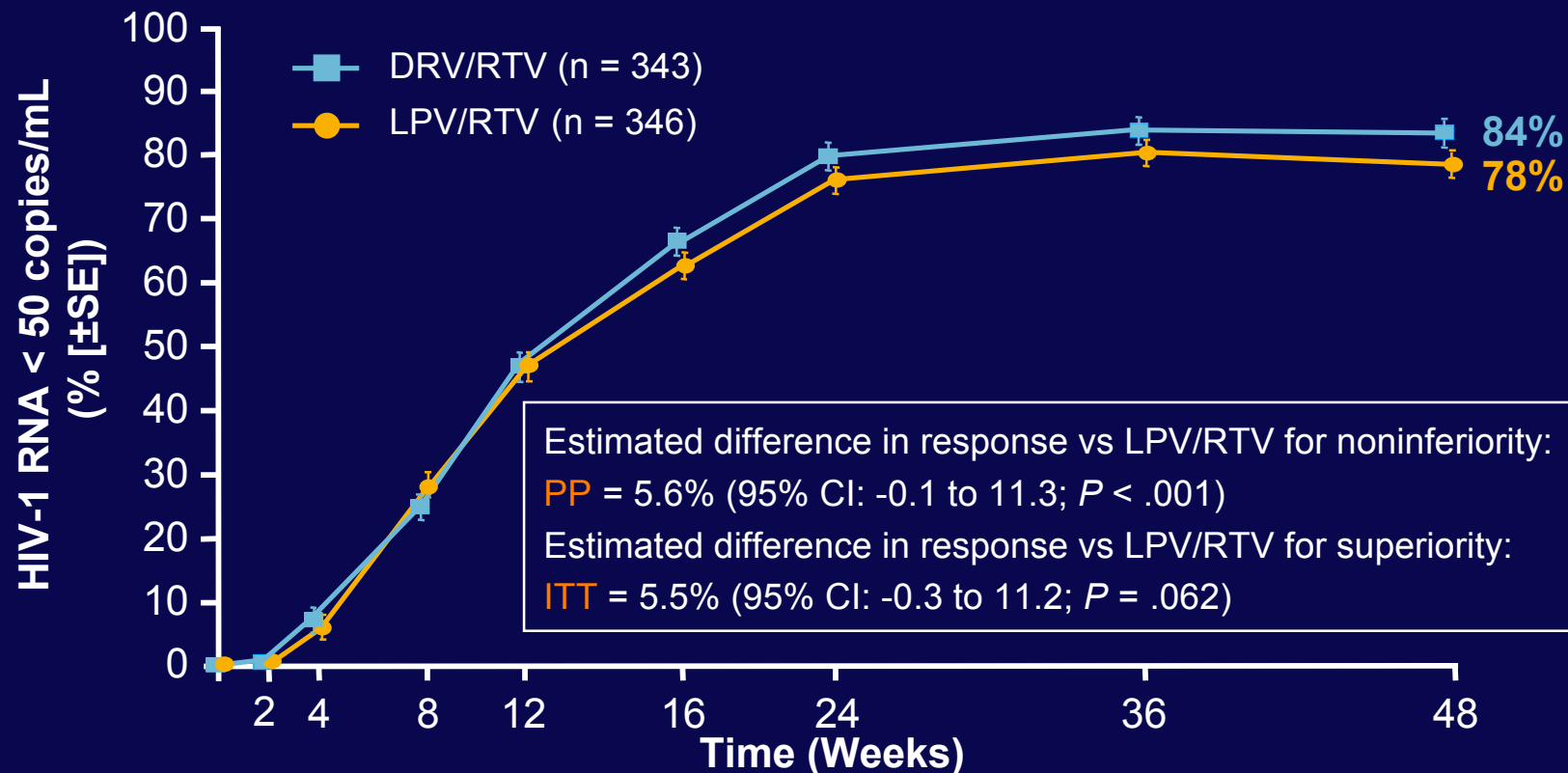
- Randomized, phase III, open-label study undertaken in 26 countries



- Baseline disease characteristics in DRV/RTV vs LPV/RTV arms
  - Median HIV-1 RNA: 70,800 copies/mL vs 62,100 copies/mL
  - Median CD4+ cell count: 228 cells/mm<sup>3</sup> vs 218 cells/mm<sup>3</sup>
- 83% of patients switched from capsule to tablet formulation of LPV/RTV during study; switch made according to local regulatory approval and drug availability

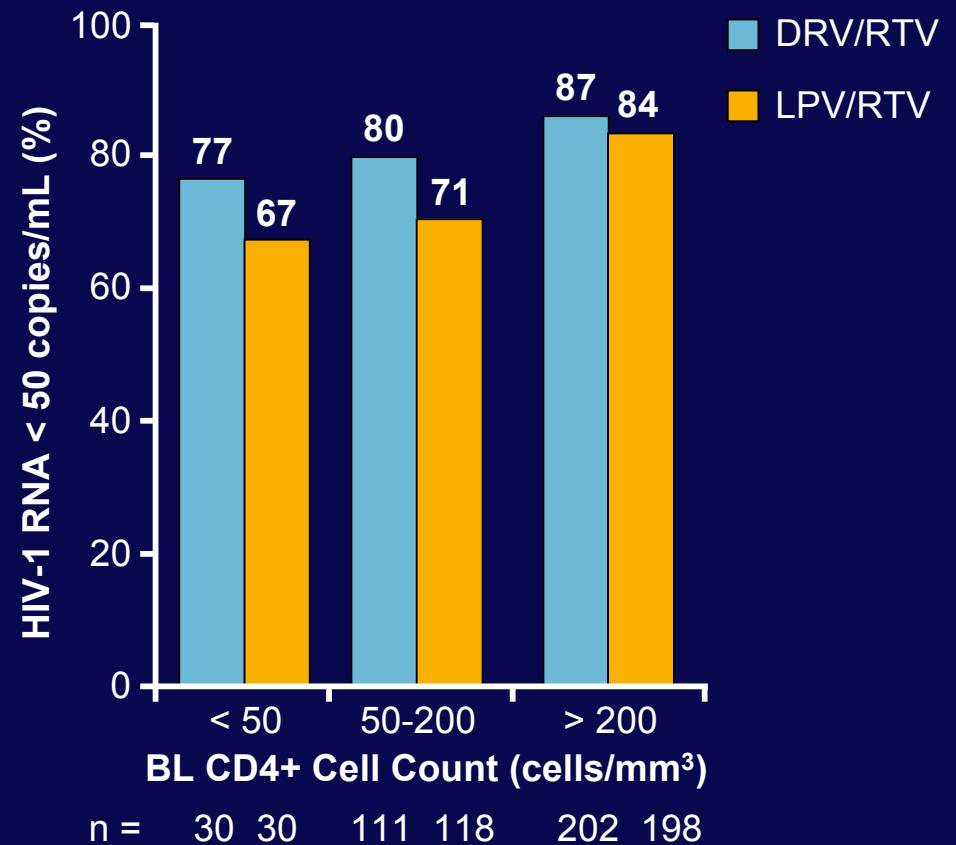
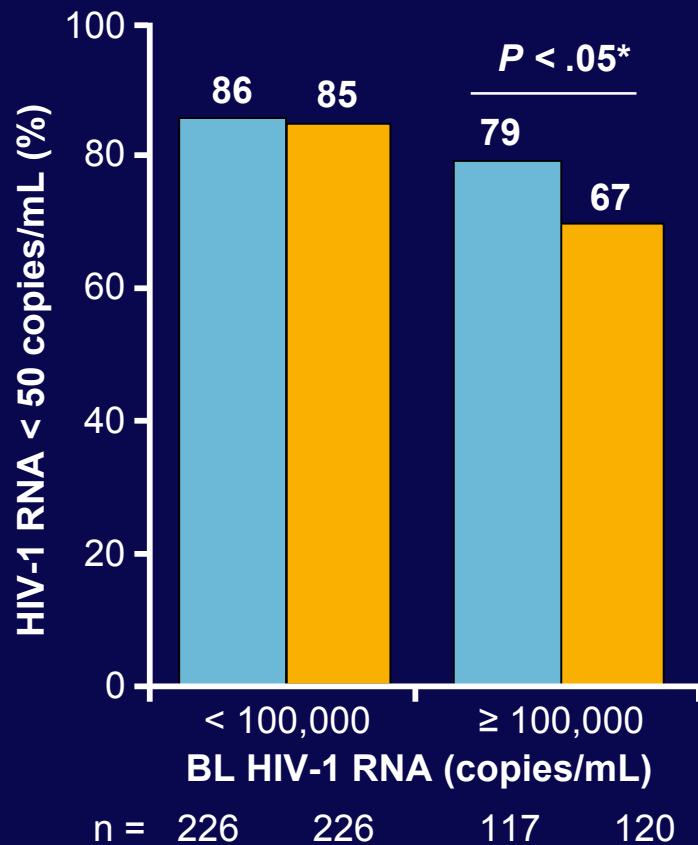
\*Dosing based on regulatory approval; 77% of patients received BID dosing.

# ARTEMIS: Noninferiority in HIV-1 RNA < 50 copies/mL at Week 48



- Median change in CD4+ cell count to Week 48 (ITT): 141 cells/mm<sup>3</sup> for DRV/RTV arm and 137 cells/mm<sup>3</sup> for LPV/RTV arm

# ARTEMIS: Virologic Response at Week 48 by BL VL and CD4+ Cell Count (ITT-TLOVR)



\*Chi square analysis.

De Jesus E, et al. ICAAC 2007. Abstract 718b.

[clinicaloptions.com/hiv](http://clinicaloptions.com/hiv)

# ARTEMIS: Treatment-Associated AEs and Resistance

	DRV/RTV QD (n = 343)	LPV/RTV QD or BID (n = 346)
<b>Grade 2-4 adverse events*, n (%)</b>		
All GI events†	23 (7)	47 (14)
▪ Diarrhea‡	14 (4)	34 (10)
▪ Nausea	6 (2)	10 (3)
Rash	9 (3)	4 (1)
<b>Virologic failure, n (%)</b>		
HIV-1 RNA > 50 copies/mL	34 (10)	49 (14)
HIV-1 RNA > 400 copies/mL	11 (3)	18 (5)
<b>Resistance, n</b>		
Paired BL and VF genotype available	10	18
IAS-USA PI RAMs	0	1

\*At least possibly related to study drug

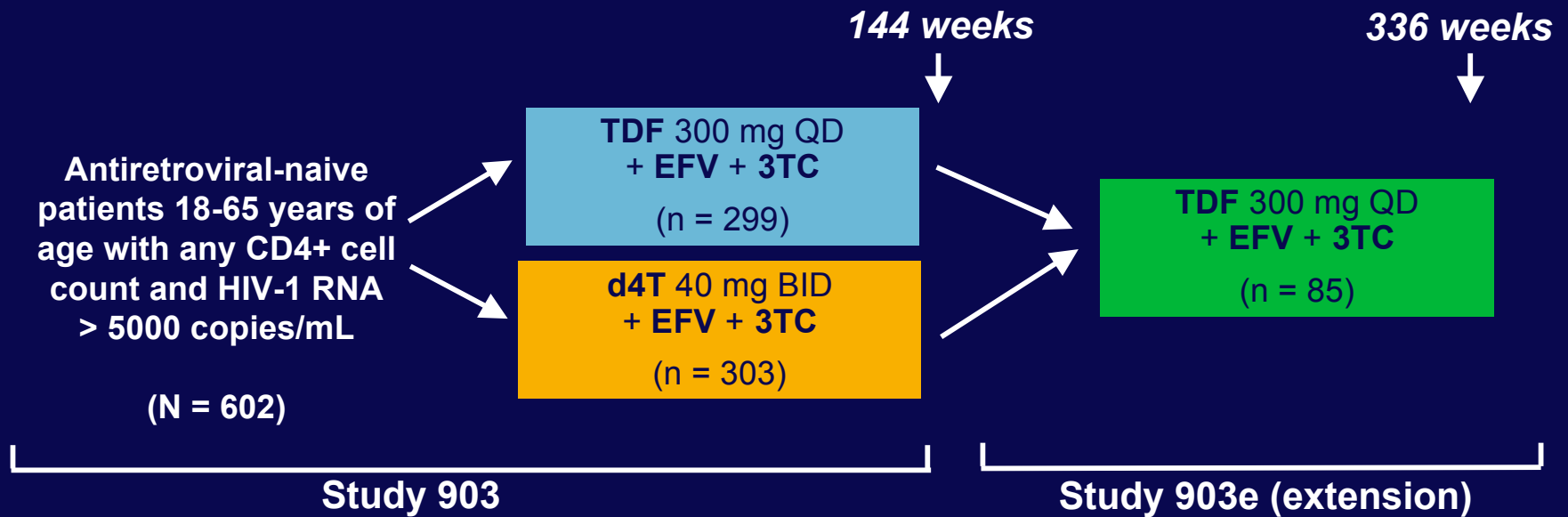
† $P < .01$

‡ $P < .05$



# GS903E: Safety and Efficacy 3 Years After Switch From d4T to TDF

- Non-random subset of patients from select sites (Argentina, Brazil, and Dominican Republic) rolled-over from long-term, open-label randomized, placebo-controlled, phase III Study 903 into a 336-week open-label extension phase (903E)



# GS903E: Virologic and Metabolic Outcomes After d4T to TDF Switch

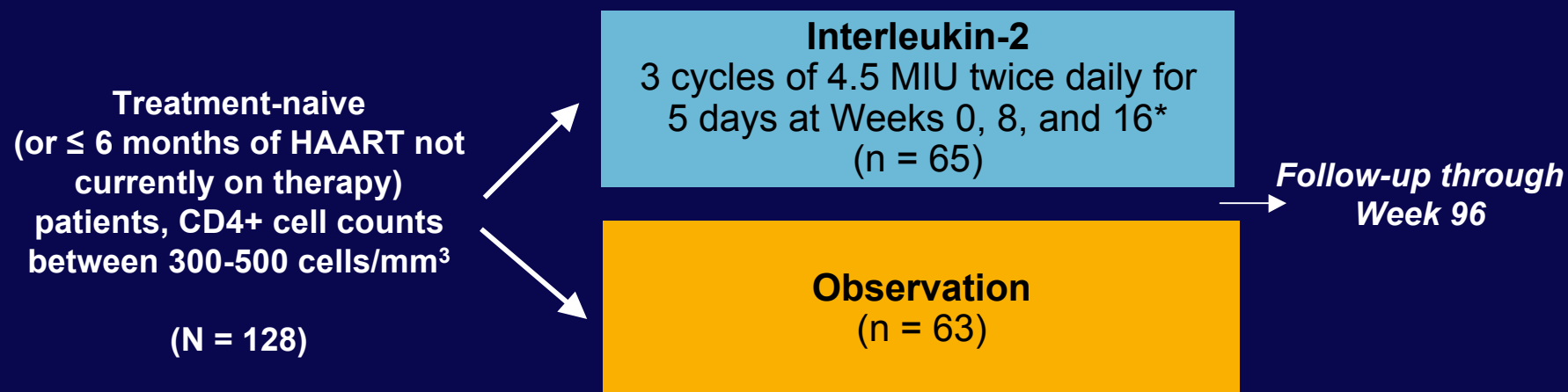
- Virologic outcomes in patients who switched from d4T to TDF
  - Patients maintaining HIV-1 RNA < 50 copies/mL: 87% (down from 99% at switch)
  - Mean change in CD4+ cell count from study 903e baseline: +155 cells/mm<sup>3</sup>

Metabolic Outcomes	Week 144 (From Study 903 BL)	Week 288 (From Study 903 BL)
Mean change in total cholesterol, mg/dL (mmol/L)	+59 (+0.67)	+38 (+0.43)*
Mean change in triglycerides, mg/dL (mmol/L)	+102 (+2.64)	+41 (+1.06)*
Mean change in hip BMD, %	-1.0	-3.4*
Mean change in spine BMD, %	-0.6	-1.3
Median limb fat, kg	3.8	4.8*

\* $P < .0001$  based on difference from Week 144 to Week 288.

# INTERSTART: Interleukin-2 Prior to HAART in Treatment-Naive Patients

- Phase II/III open-label randomised controlled trial with primary analysis at Week 96



\*4th optional cycle at Week 24 if CD4+ cell count  $< 2 \times$  baseline value; 1 or 2 additional cycles from Weeks 48-80 if CD4+ cell count  $< 1.2 \times$  baseline.

# INTERSTART: Failure Rate Lower in Interleukin-2 Arm

Outcome Through Week 96	Interleukin-2 (n = 65)	Observation (n = 63)
Failure,* %	36 <sup>†</sup>	61
Cause of failure, n		
▪ CD4+ cell count < 300 cells/mm <sup>3</sup>	18	28
▪ HAART initiation	4	6
▪ AIDS-defining event	0	2
▪ Death	1	1

- Interleukin-2 increased CD4+ cell counts (+51 vs -64 cells/mm<sup>3</sup>;  $P < .0001$ ) without affecting plasma HIV-1 RNA
- Interleukin-2 delayed significantly time to HAART initiation

\*Failure defined as confirmed CD4+ cell count < 300 cells/mm<sup>3</sup>, initiation of HAART, occurrence of an AIDS-defining event or death.

<sup>†</sup> $P = .006$  vs observation.

Molina J, et al. ICAAC 2007. Abstract H-718.

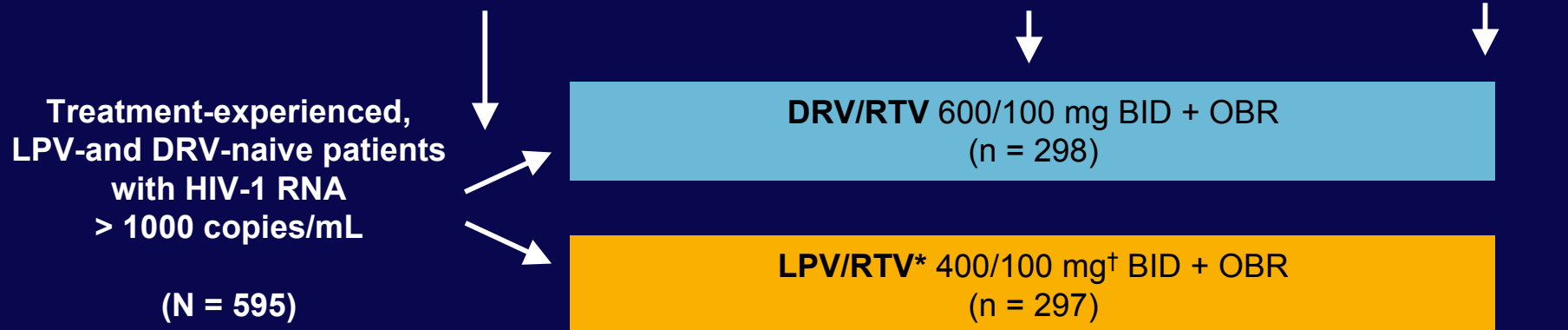
[clinicaloptions.com/hiv](http://clinicaloptions.com/hiv)

# Treatment-Experienced Patients



# TITAN: DRV/RTV vs LPV/RTV in Tx-Experienced, LPV-Naive Patients

Stratification by treatment site, use of NNRTI in OBR, and HIV-1 RNA > or < 50,000 copies/mL



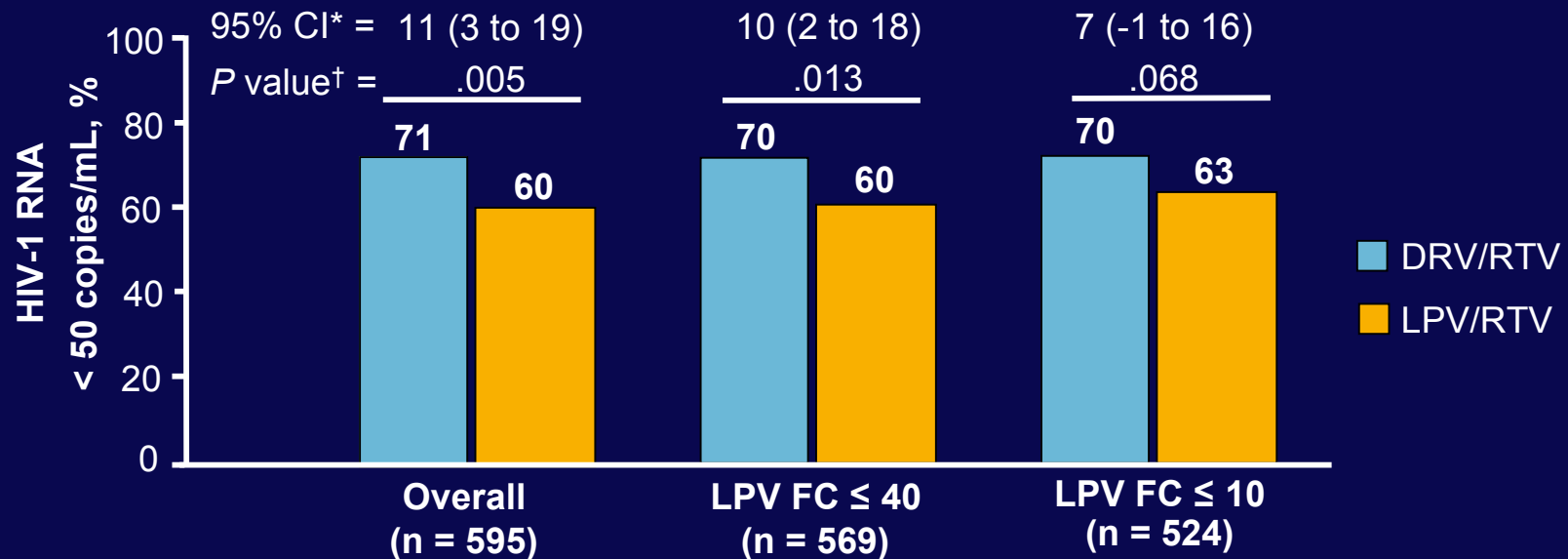
\*Patients started on LPV/RTV 133/33-mg capsules and then some (18%) were switched to 200/50-mg tablets.

†LPV/RTV increased to 533/133 mg BID (for capsules) or 600/150 mg BID (for tablets) if NNRTI included in OBR.

Valdez-Madruga J, et al. IAS 2007. Abstract TUAB101.  
Madruga JV, et al. Lancet. 2007;370:49-58.

# TITAN: Week 48 Outcomes, Overall and by BL LPV Fold Change

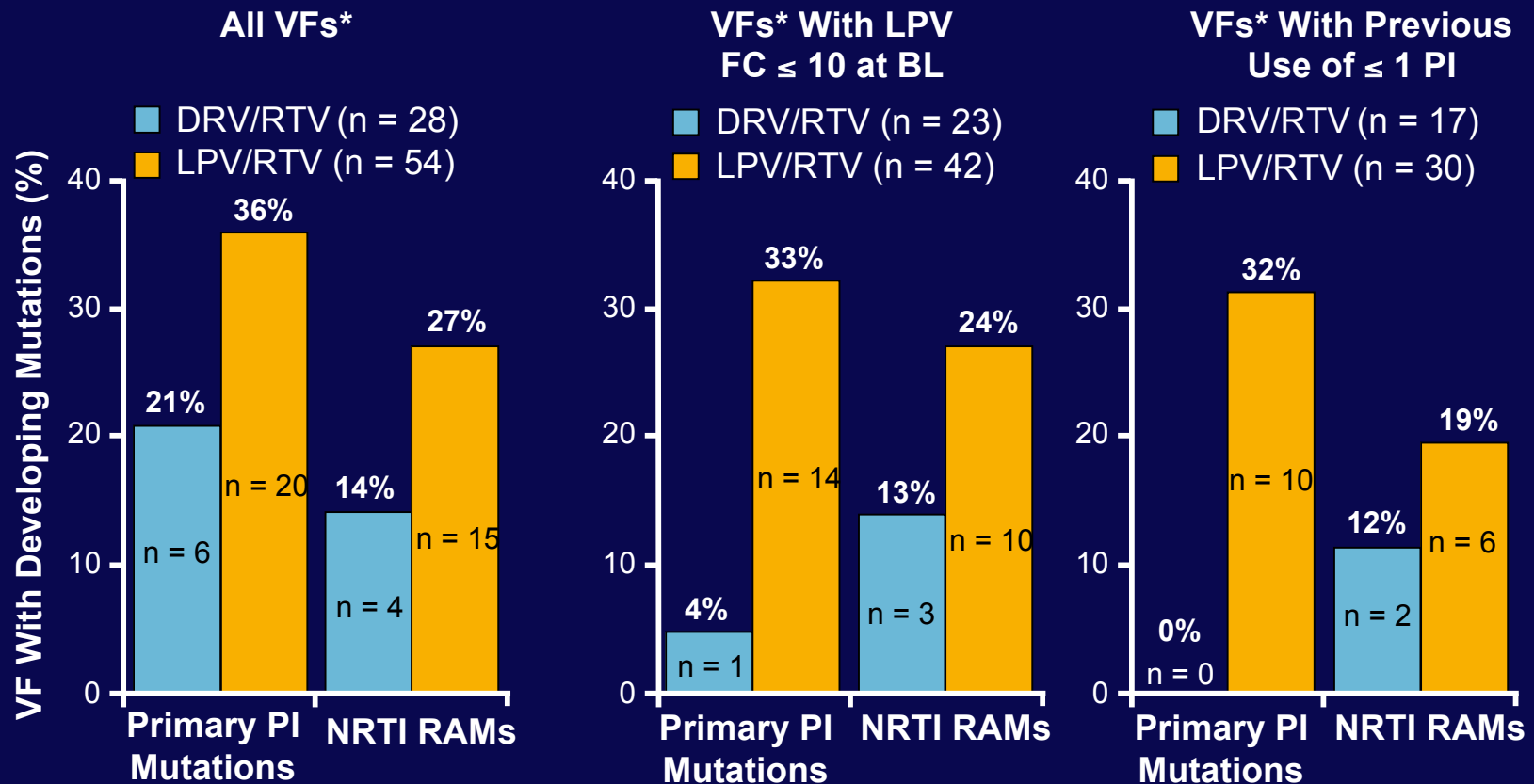
- DRV/RTV met criteria for superiority to LPV/RTV in proportion of patients with VL < 50 copies/mL in overall study population ( $P < .0001$  for noninferiority)
- Mean CD4+ cell count change from BL: 88 cells/mm<sup>3</sup> vs 81 cells/mm<sup>3</sup> in DRV/RTV and LPV/RTV arms, respectively ( $P = .33$ )



\*DRV/RTV-LPV/RTV; estimated from logistic regression model including treatment and stratification factors: baseline log<sub>10</sub> HIV-1 RNA and use of NNRTIs in the OBR.

†P values for superiority

# TITAN: Proportion of Treatment-Emergent Resistance Mutations with VF

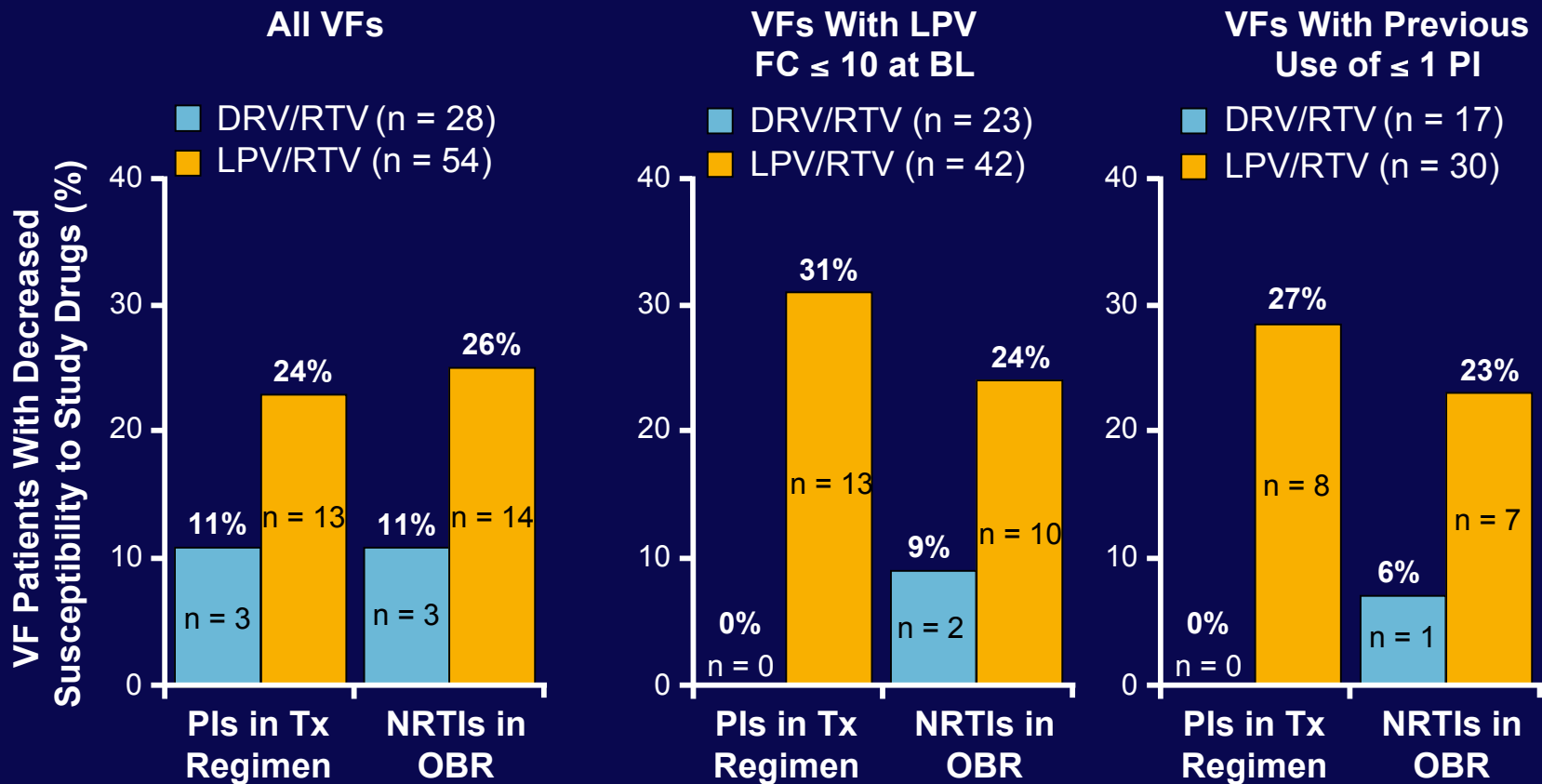


\*Virologic failure = never having achieved HIV-1 RNA < 400 copies/mL or rebounding to ≥ 400 copies/mL.

De Meyer S, et al. ICAAC 2007. Abstract H-1020.

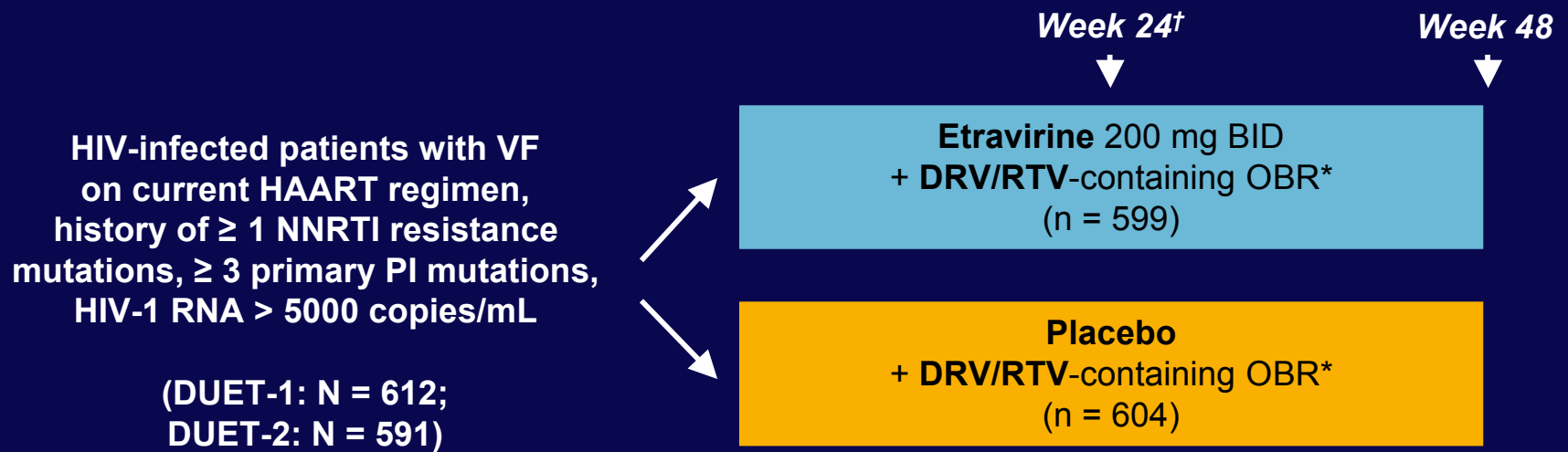
[clinicaloptions.com/hiv](http://clinicaloptions.com/hiv)

# TITAN: Virologic Failure and ARV Susceptibility



■ ARV susceptibility measured by Antivirogram test.

# DUET-1 and -2: Etravirine + DRV/RTV-Containing OBR Phase III Trials



\*Investigator-selected OBR to consist of DRV/RTV (600/100 mg/mL) +  $\geq 2$  NRTIs  $\pm$  enfuvirtide.

<sup>†</sup>Planned Week 24 analysis: primary endpoint HIV-1 RNA < 50 copies/mL (TLOVR).

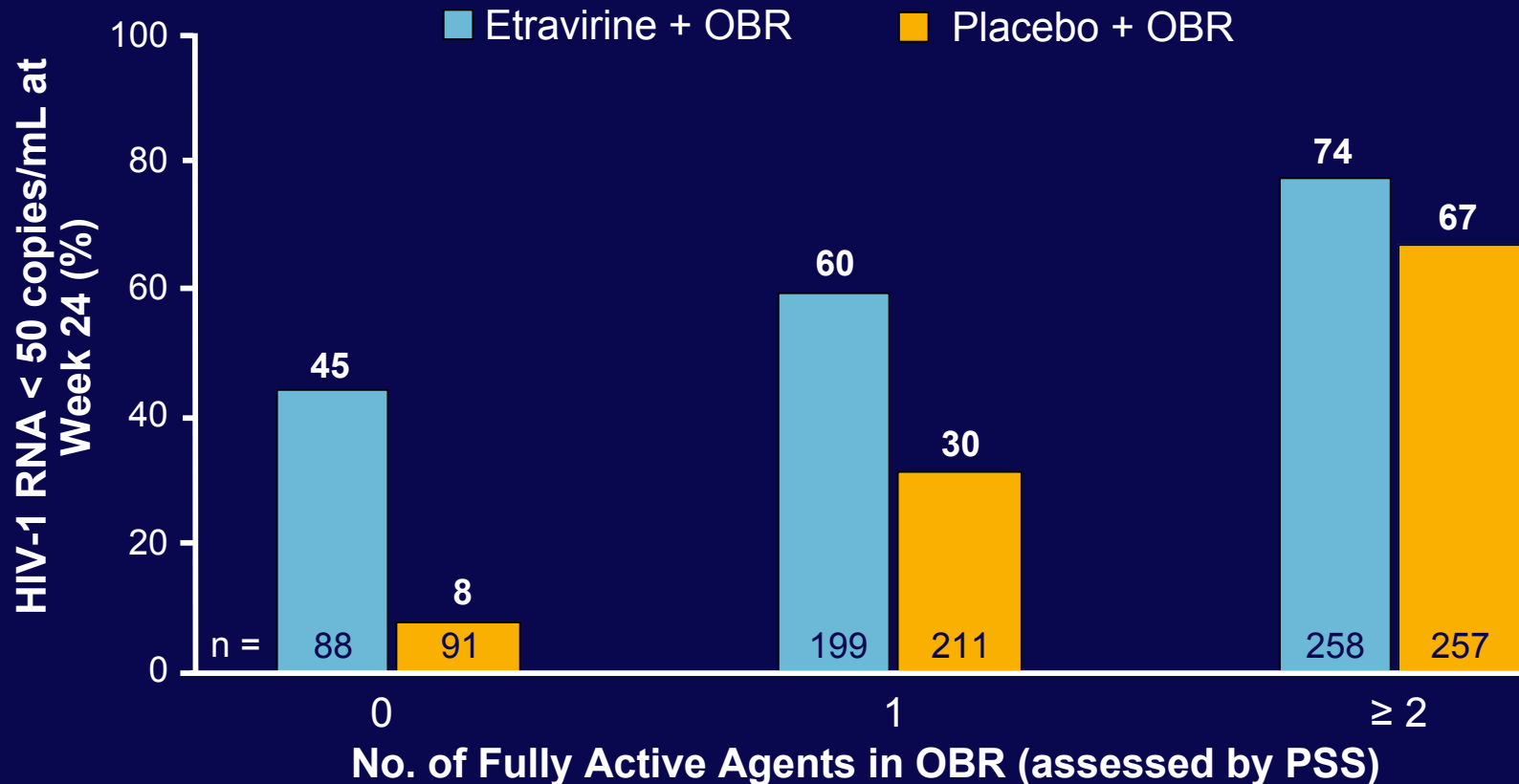
Madrugá JV, et al. Lancet. 2007;370:29-38. Lazzarin A, et al. Lancet. 2007;370:39-48. Mills A, et al. IAS 2007. Abstract WESS204.1. Katlama C, et al. IAS 2007. Abstract WESS204.2. Cahn P, et al. ICAAC 2007. Abstract H-717.

# DUET-1 and -2: Pooled Virologic and Immunologic Responses

Outcome at Week 24	Etravirine (n = 599)	Placebo (n = 604)	P Value
HIV-1 RNA < 50 copies/mL, %	59	41	< .0001
Mean change in HIV-1 RNA from baseline, log <sub>10</sub> copies/mL	-2.4	-1.7	< .0001
Mean change in CD4+ cell count from baseline, cells/mm <sup>3</sup>	+86	+67	< .0001

- In patients using enfuvirtide for the first time (n = 201), the difference between treatment arms (67% and 62% for etravirine vs placebo, respectively) was not significant ( $P = .427$ )

# DUET-1 and -2: Response Based on Active Agents in OBR



# BLQ Study: DRV/RTV + ENF in Triple-Class Experienced Patients

- 142 triple-class-experienced, DRV/RTV-naive and ENF-naive patients with HIV-1 RNA > 2000 copies/mL
- Switched from failing regimen to DRV/RTV (600/100 mg BID), ENF (90 mg SC BID), and other investigator-selected antiretrovirals
  - Single arm, nonrandomized design
- Overall, 60% achieved HIV-1 RNA < 50 copies/mL at Week 24
- No difference in response according to baseline DRV susceptibility

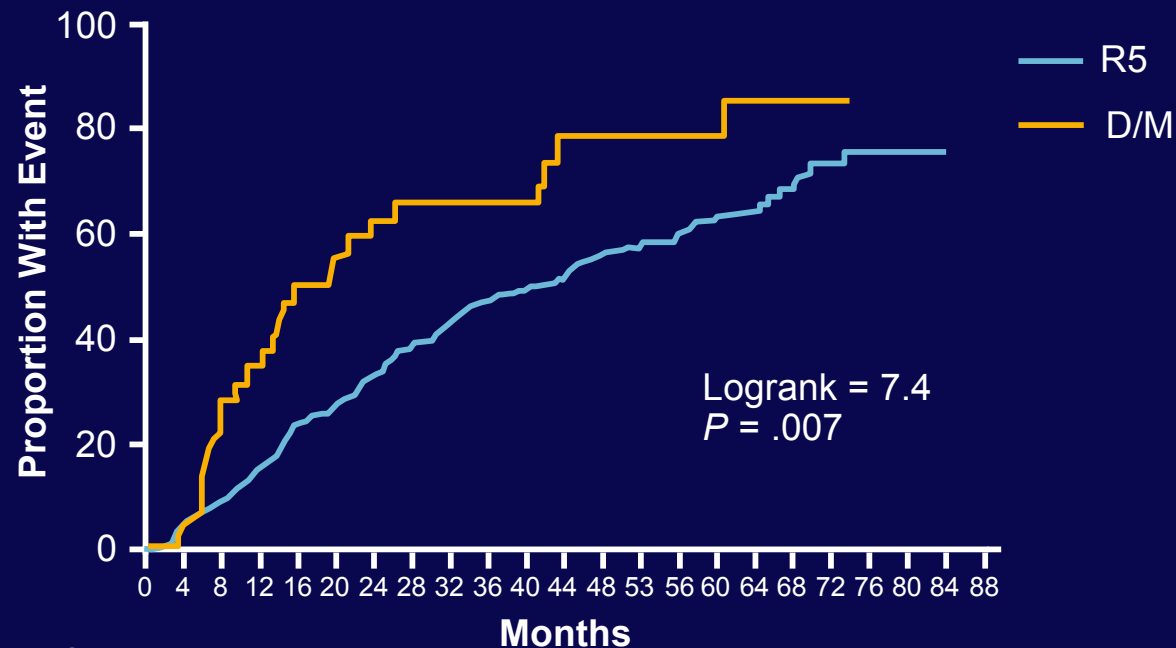
Baseline Phenotypic Susceptibility to Darunavir	HIV-1 RNA < 50 copies/mL at Week 24, %
<b>Categorical cutoffs</b>	
▪ FC < 10 (n = 87)	64.4
▪ FC 10-40 (n = 19)	57.9
▪ FC > 40 (n = 8)	62.5

# Viral Tropism and Entry Inhibitors



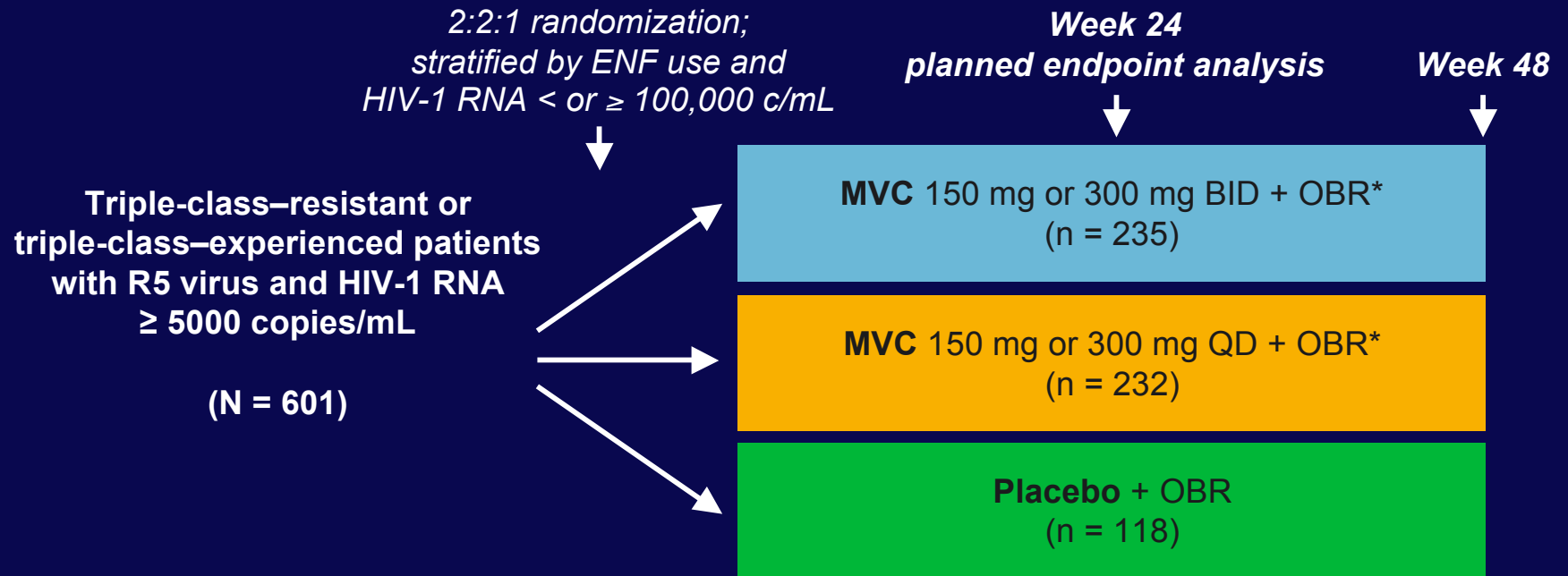
# Baseline Viral Tropism and Disease Progression

- Tropism assessed in 313 treatment-naive patients in CPCRA cohort
  - 90% had R5-only virus; 10% had D/M virus
- Significantly shorter time to combined endpoint of CD4+ cell count < 350 cells/mm<sup>3</sup>, treatment initiation, or death among patients with D/M virus



# MOTIVATE 1: Maraviroc in Treatment-Experienced Patients With R5 Virus

- Randomized, double-blind, placebo-controlled, phase IIb/III studies

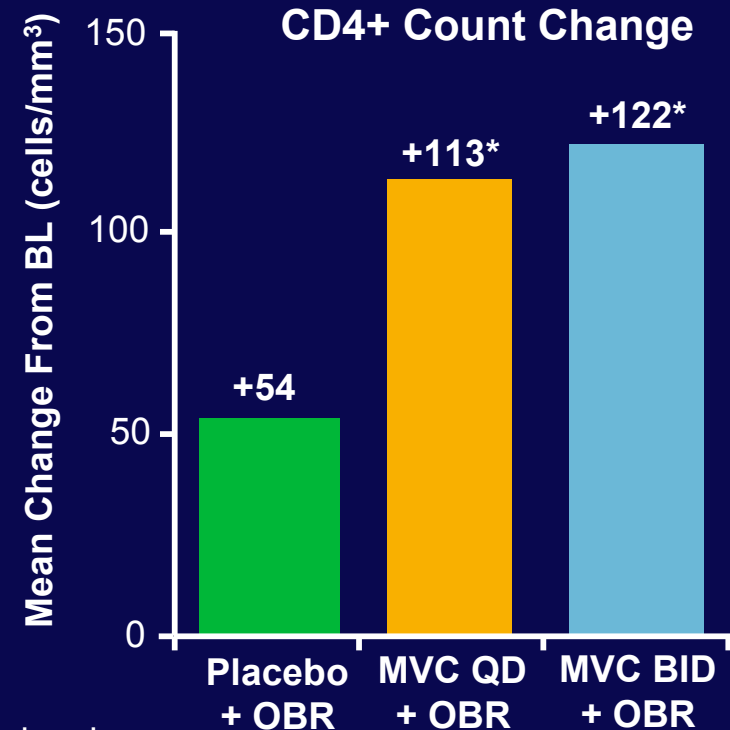
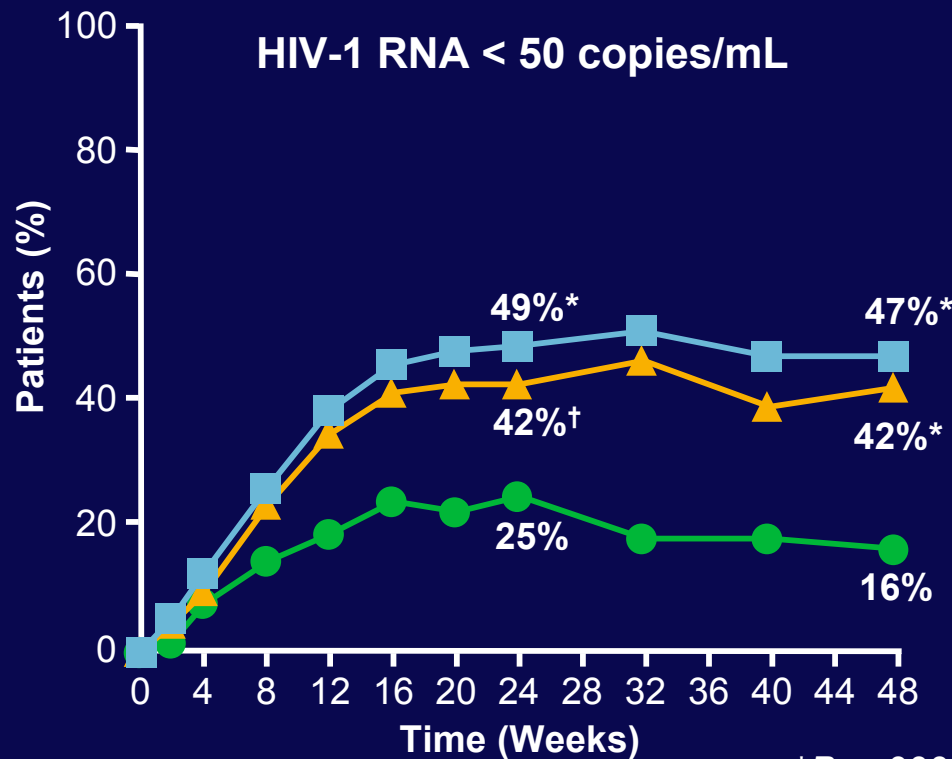


\*Patients receiving PI (except TPV) or delavirdine received 150 mg; all others received 300 mg.

- 48-week results of MOTIVATE-2 to be presented at EACS

# MOTIVATE 1: Virologic and Immunologic Outcomes at Week 48

● Placebo + OBR (n = 118)    ▲ MVC QD + OBR (n = 232)    ■ MVC BID + OBR (n = 235)



\*P < .0001 vs placebo.  
†P = .0006 vs placebo.

# MOTIVATE 1: Adverse Events Similar to Placebo

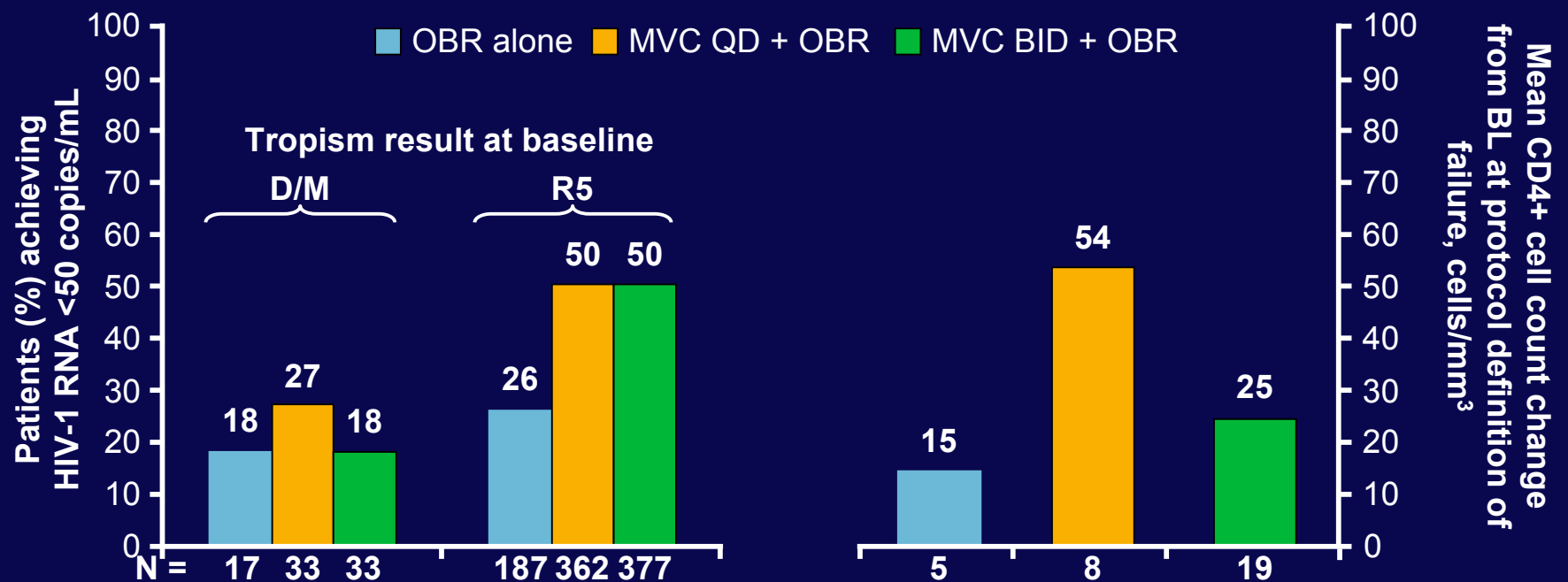
Adverse Event	MCV QD + OBR (n = 232)	MVC BID + OBR (n = 235)	OBR Alone (n = 118)
Total exposure, patient-yrs	168	169	64
Discontinuation due to adverse events, %	6	5	6
Adverse events,* %	90	92	86
▪ Grade 3	17	23	25
▪ Grade 4	9	10	7
▪ Serious adverse events	14	17	16
CDC category C events,* n (%)	11 (5)	12 (5)	6 (5)
Deaths,† %	1	2	1

\*Unadjusted for duration of exposure; includes all patients who received  $\geq 1$  dose of study drug.

†No deaths deemed associated with use of study drug.

# MOTIVATE 1/2: Week 24 Outcomes Based on Tropism

- Of 1042 pts with R5 virus at screening, 83 (8%) had D/M virus detected at study entry
  - Correlated with lower CD4+ cell count and slightly higher viral loads at screening
- Patients with D/M virus at baseline had inferior virologic outcomes at Week 24
  - Protocol definition of failure: HIV-1 RNA > 500 copies/mL.



Van der Ryst, et al. ICAAC 2007 Abstract H-715.

# MOTIVATE: Time to Failure and Tropism Reversion

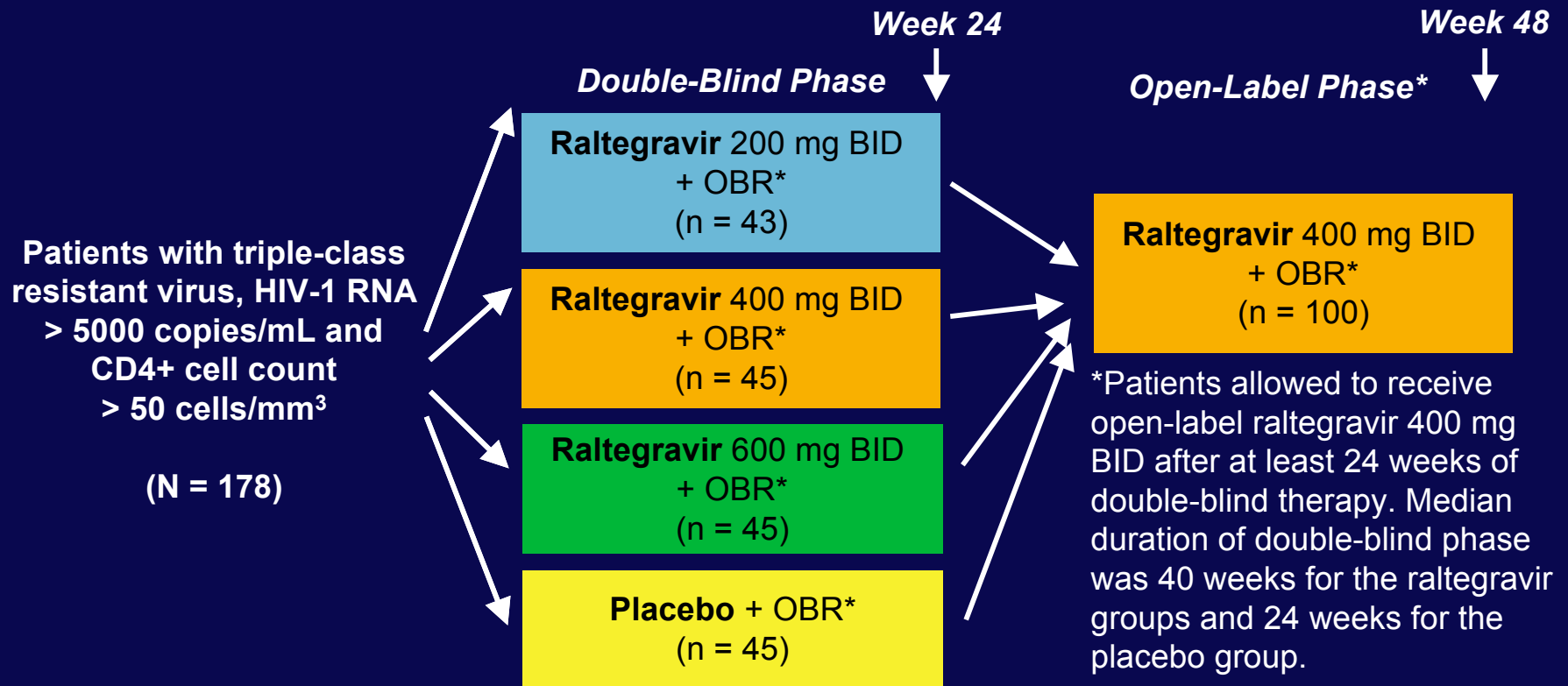
- Two thirds of patients failing MVC had detectable X4 virus at failure
- Time to MVC failure shorter (by ~ 30 days) in patients failing with D/M or X4 virus vs those failing with R5 virus
- After MVC discontinuation, R5 virus typically re-emerged
  - In the 44 MVC recipients with D/M or X4 virus at failure and follow-up data obtained off drug, 30 (68%) had R5 virus re-emerge
  - In those with D/M or X4 virus at last visit, duration of follow-up off-drug was shorter than in those with reversion to R5 (median: 16 vs 203 days)
  - 30 (97%) of 31 MVC recipients with follow-up data obtained > 1 month after failure reverted to R5 virus

# Integrase Inhibitors



# Protocol 005: Raltegravir + OBR in Patients With Triple Class-Resistant Virus

- Randomized, double-blind, placebo-controlled, dose-ranging, phase IIb study

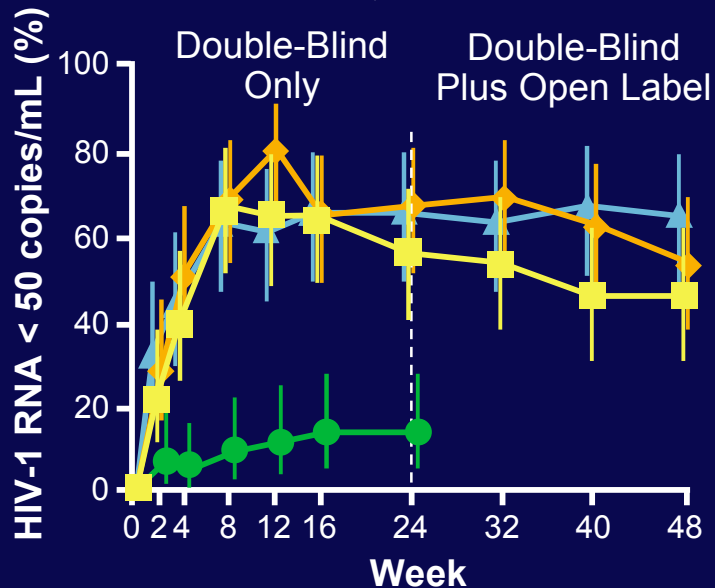


\*DRV/RTV was not available for use in OBR  
Grinsztejn B, et al. ICAAC 2007. Abstract H-713.

# Protocol 005: 48-Week Results

▲ Raltegravir 200 mg BID   ■ Raltegravir 400 mg BID   ◆ Raltegravir 600 mg BID   ● Placebo

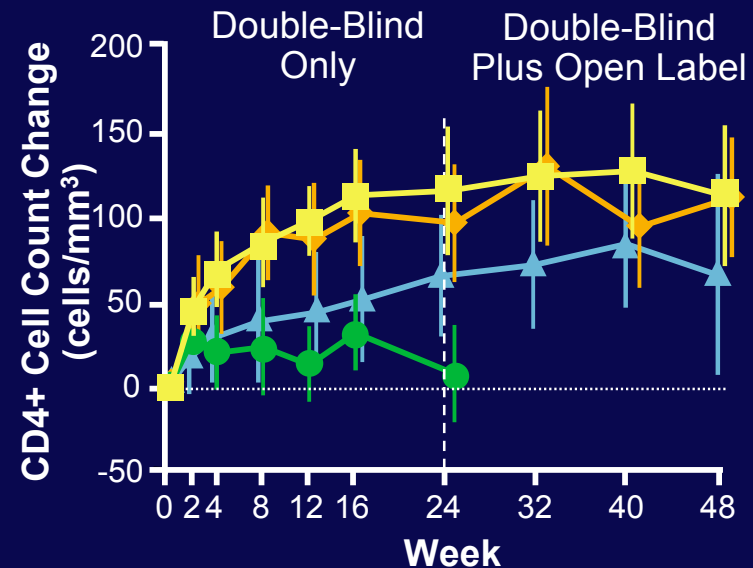
ITT, NC = F



No. of Contributing Patients

▲	43	43	42
■	45	45	44
◆	45	45	45
●	45	45	

Baseline Carried Forward for VFs



No. of Contributing Patients

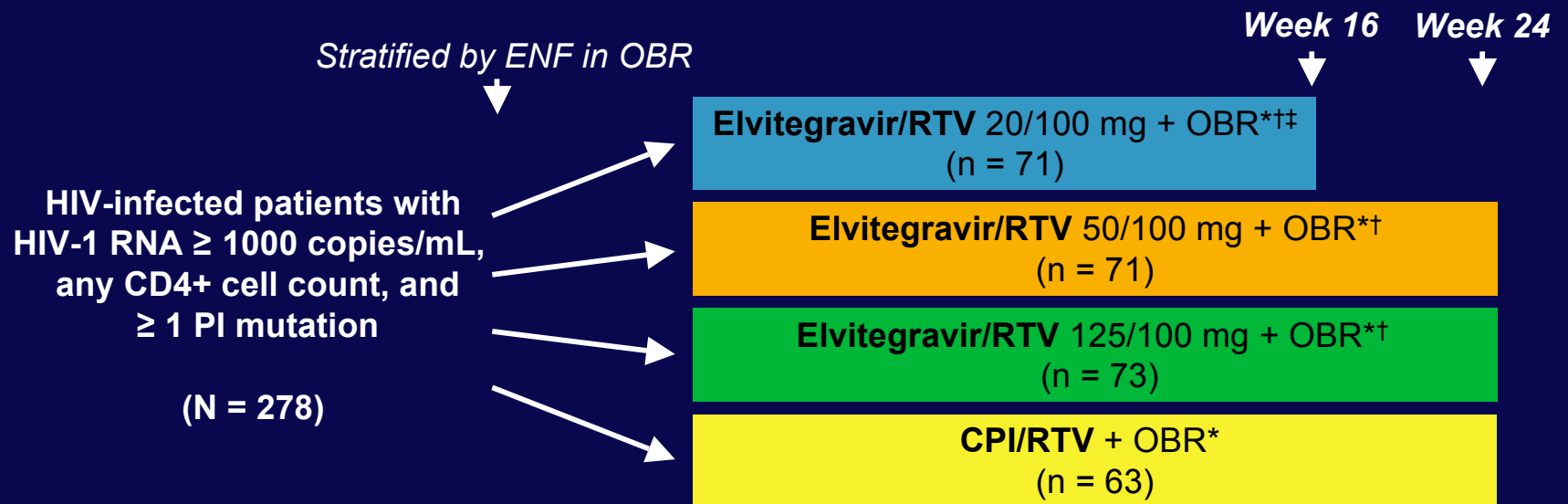
▲	43	41	37
■	45	43	44
◆	45	42	43
●	45	43	

## Protocol 005: Raltegravir Resistance

- 38 (29%) of 133 RAL recipients in double-blind phase experienced VF (rebound or failure to achieve HIV-1 RNA < 400 copies/mL)
- Genotypic data available for all 38 failures
- Majority (35/38) had integrase mutations conferring raltegravir resistance
  - N155 or Q148 mutational pathway present in 34/35
  - $\geq 2$  mutations present in 31/35 patients
    - Q148H/G140S most common combination (n = 13)
- Factors associated with reduced likelihood of mutations at failure
  - HIV-1 RNA  $\leq$  100,000 copies/mL
  - First-time use of ENF in OBR
  - Phenotypic susceptibility score > 0

# Elvitegravir in Treatment-Experienced Patients

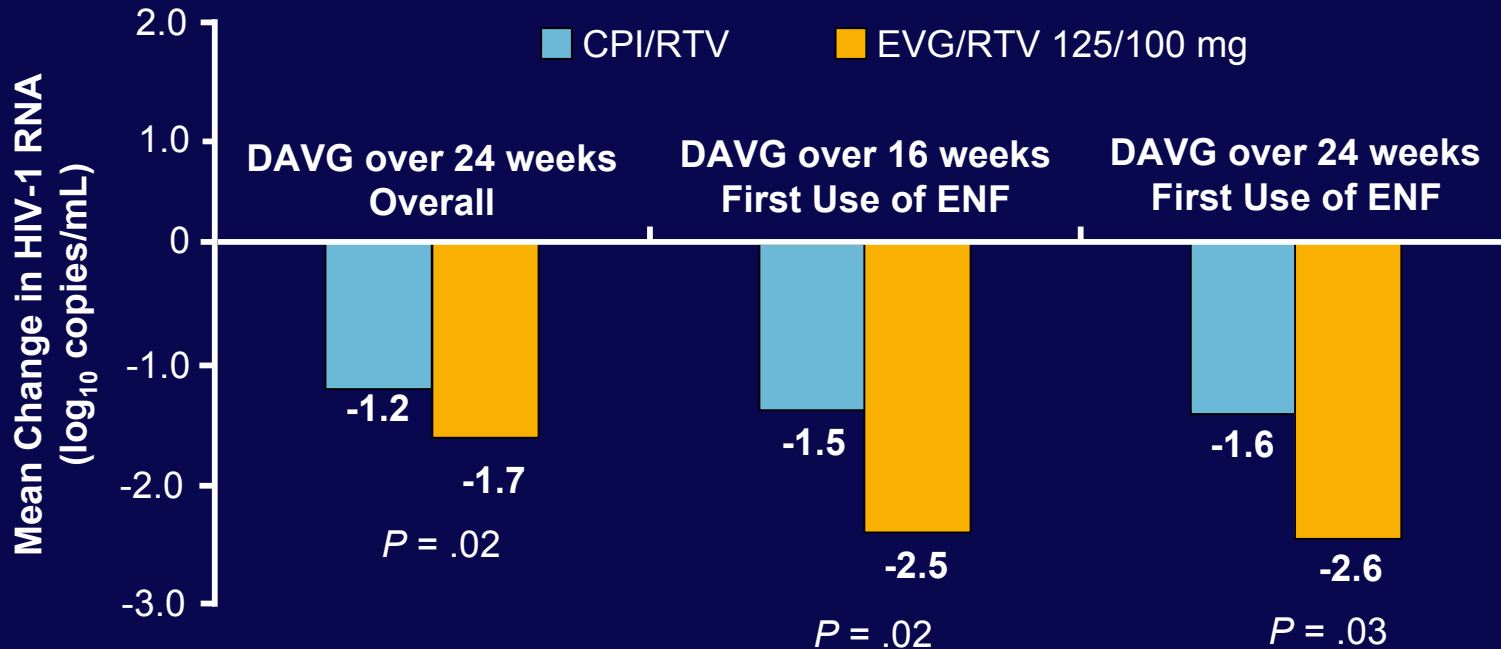
- Randomized, active-control, partially-blinded (dose of elvitegravir), phase II dose-finding study
  - Primary endpoint: time-weighted average change from baseline in HIV RNA through 24 weeks (DAVG<sub>24</sub>)



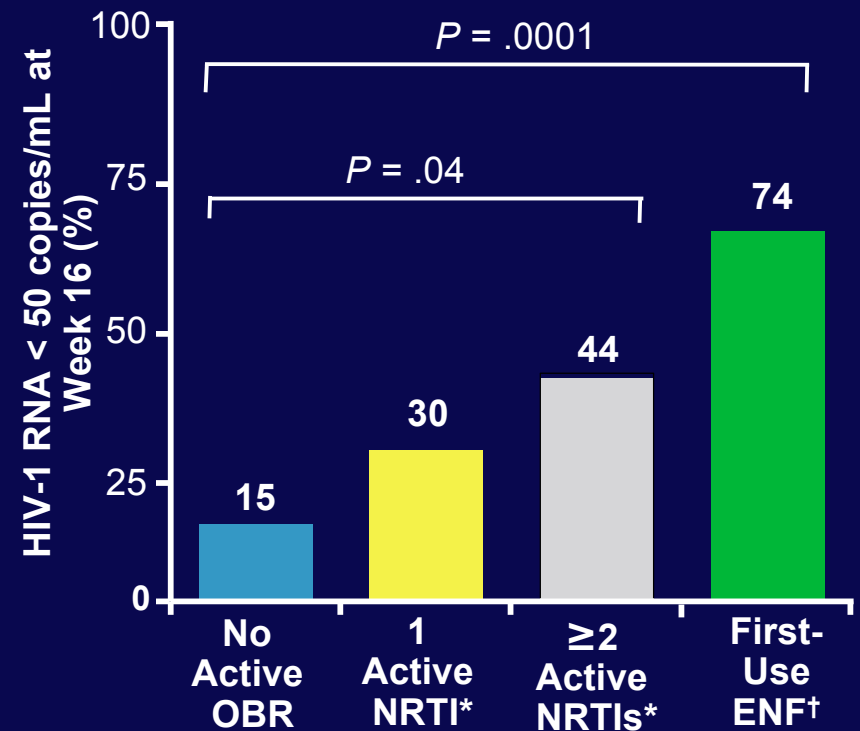
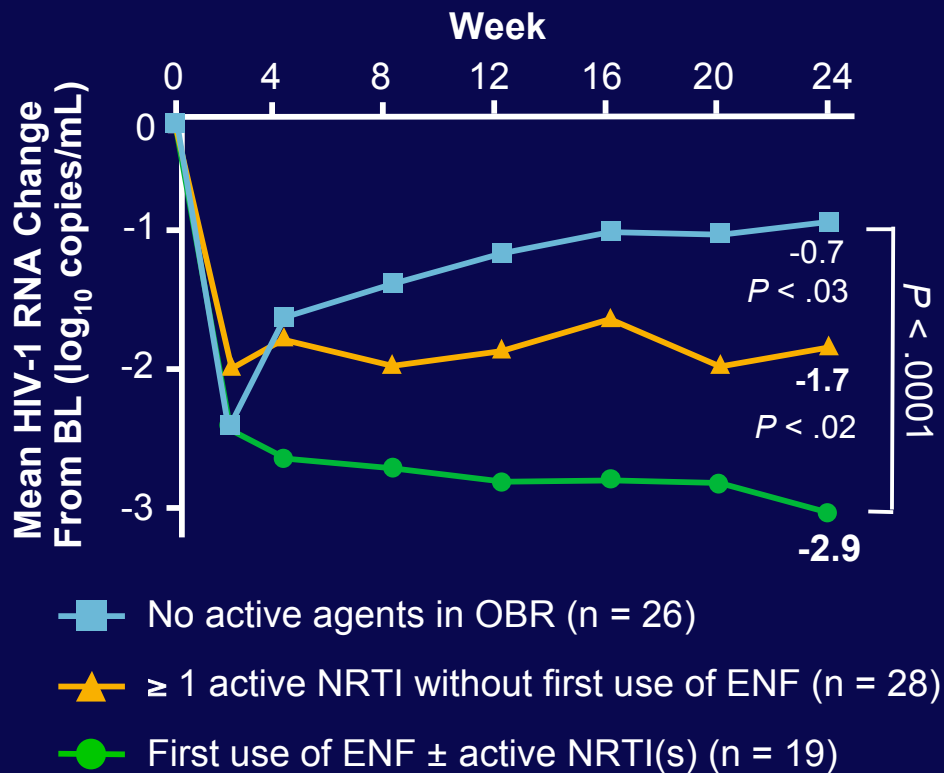
\*OBR = NRTIs ± ENF (NNRTIs excluded). <sup>†</sup>TPV and DRV permitted after Week 16.

<sup>‡‡</sup>Discontinued at Week 16 by DMSB.

# Elvitegravir 125/100 mg: DAVG Overall and With First-time Use of Enfuvirtide



# Elvitegravir 125/100 mg: Virologic Response by Active Agents in OBR



Data from patients after addition of PI were excluded

\*Without first use of ENF.

†With or without active NRTI(s).

# Clinical Complications



# Non-AIDS–Defining Adverse Events

- APROCO-COPILOTE cohort (N = 1231): high incidence of non-AIDS–defining, non-HAART–related events in HAART-treated patients<sup>[1]</sup>
  - 10.5/100 patient-years (vs 2.7/100 patient-years for AIDS-related events)
  - Independent risk factors: HIV-1 RNA > 10,000; lower CD4+ count strata; age > 60 years; HCV coinfection; smoking
  - Bacterial infections most common events (23.4% of events)
- VA records review: higher incidence of non-AIDS–defining malignancies in HIV+ (n = 33,420) vs HIV- (n = 66,840) veterans<sup>[2]</sup>
  - Incidence rate ratio: 1.6
  - Highest incidence rate ratios: anal (14.9), Hodgkin’s (4.6), liver (2.8), lung (2.0) cancers
  - Possible association with lower CD4+ count

1. Ferry T, et al. ICAAC 2007. Abstract H-1722.

2. Bedimo RF, et al. ICAAC 2007. Abstract H-1721.

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