

HIV resistance and the role of novel therapies

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Introduction

- HIV can develop resistance to antiretroviral agents
- This limits the use of these agents in the long term
- New agents and new classes are required for treatment experienced patients in order to suppress the virus
- The last 9 months has seen the approval of new classes and new agents offering effective suppressive regimens for treatment experienced failing patients

Clinical case

- 46 year old man
- In a long term male male relationship
- Working as a cook
- Diagnosed with HIV in 1988 in Melbourne

Antiretroviral treatment history

Date	CD4	%	VL	ART	ART	ART
Dec 98	185	15	23 000	AZT	3TC	SQV
Aug 99	94	14	21 000	d4T	ddl	NFV
Jun 00	166	12	200 000	3TC	ABC	EFV
Aug 01	72	8	135 000	CBV	Kaletra	
Nov 07	57	4	75 293	CBV	Kaletra	

PI Major Resistance Mutations: M46I, I54V, V82A, I84V, L90M

PI Minor Resistance Mutations: L10I, L33F, K43T, T74P

Other Mutations: None

Protease Inhibitors

atazanavir (ATV)

High-level resistance

darunavir (DRV)

Intermediate resistance

fosamprenavir (FPV)

High-level resistance

indinavir (IDV)

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lopinavir (LPV)

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nelfinavir (NFV)

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saquinavir (SQV)

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tipranavir (TPV)

High-level resistance

NRTI Resistance Mutations: M41L, E44D, D67N, L74V, V118I, M184V, L210W, T215Y

NNRTI Resistance Mutations: G190Q

Other Mutations: None

Nucleoside RTI

lamivudine (3TC) High-level resistance

abacavir (ABC) High-level resistance

zidovudine (AZT) High-level resistance

stavudine (D4T) High-level resistance

didanosine (DDI) High-level resistance

emtricitabine (FTC) High-level resistance

tenofovir (TDF) Intermediate resistance

Non-Nucleoside RTI

delavirdine (DLV) Low-level resistance

efavirenz (EFV) High-level resistance

etravirine (ETR) Low-level resistance

nevirapine (NVP) High-level resistance

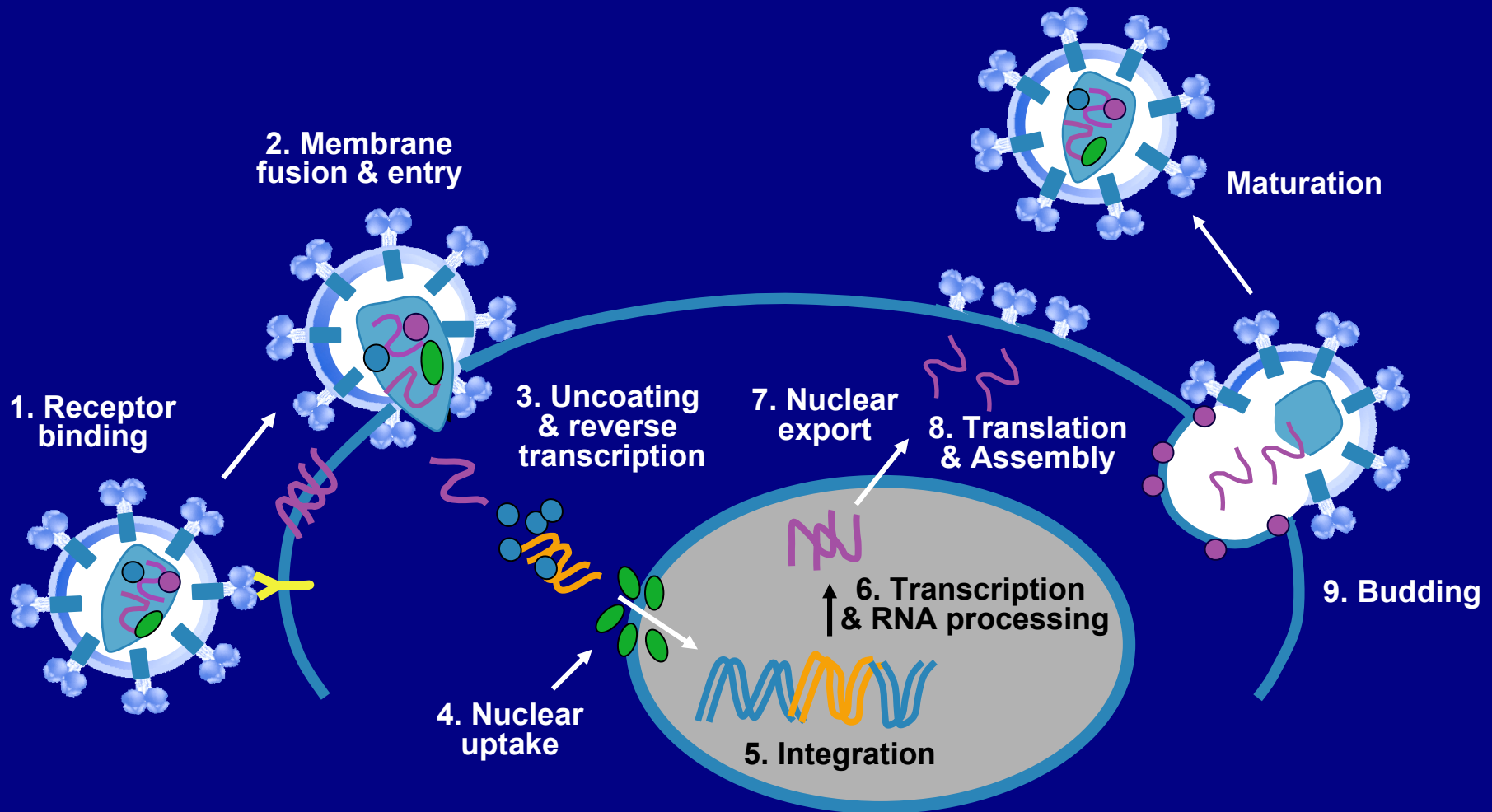
Aims for this patient

- Treatment to achieve viral load <40 copies/ml
- At least two fully active agents plus OBT
- Prevent further mutations
- Improve immune status
- Improve general health and condition
- Maintain ability to work
- Long term success
- Minimise toxicities

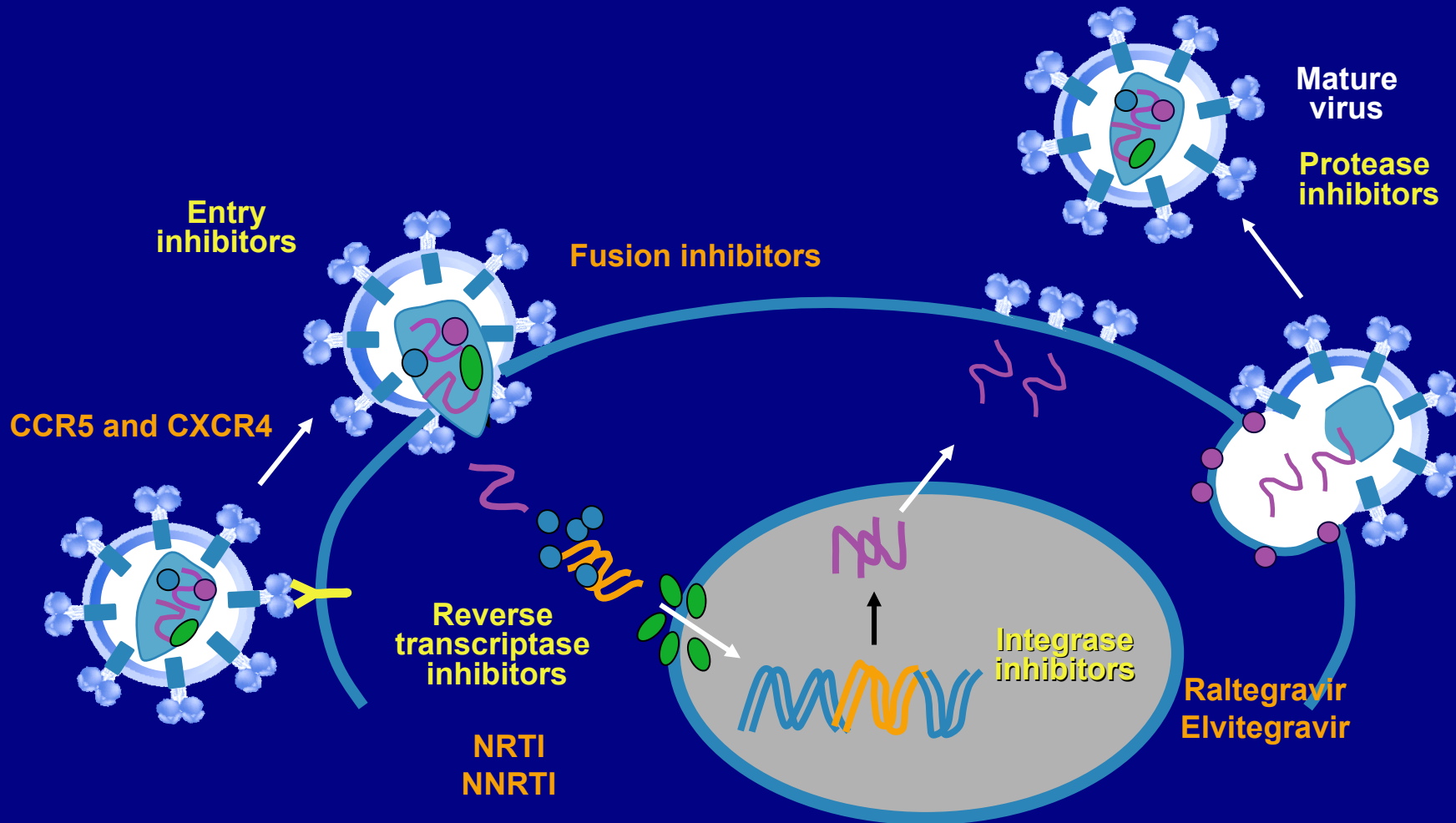
Antiretroviral options

- Protease inhibitors with superior resistance profile
- New classes such as entry inhibitors, integrase inhibitors
- New agents such as next generation NNRTIs
- Agents accessible through trials, compassionate access or the PBS

HIV Life Cycle



HIV Inhibition



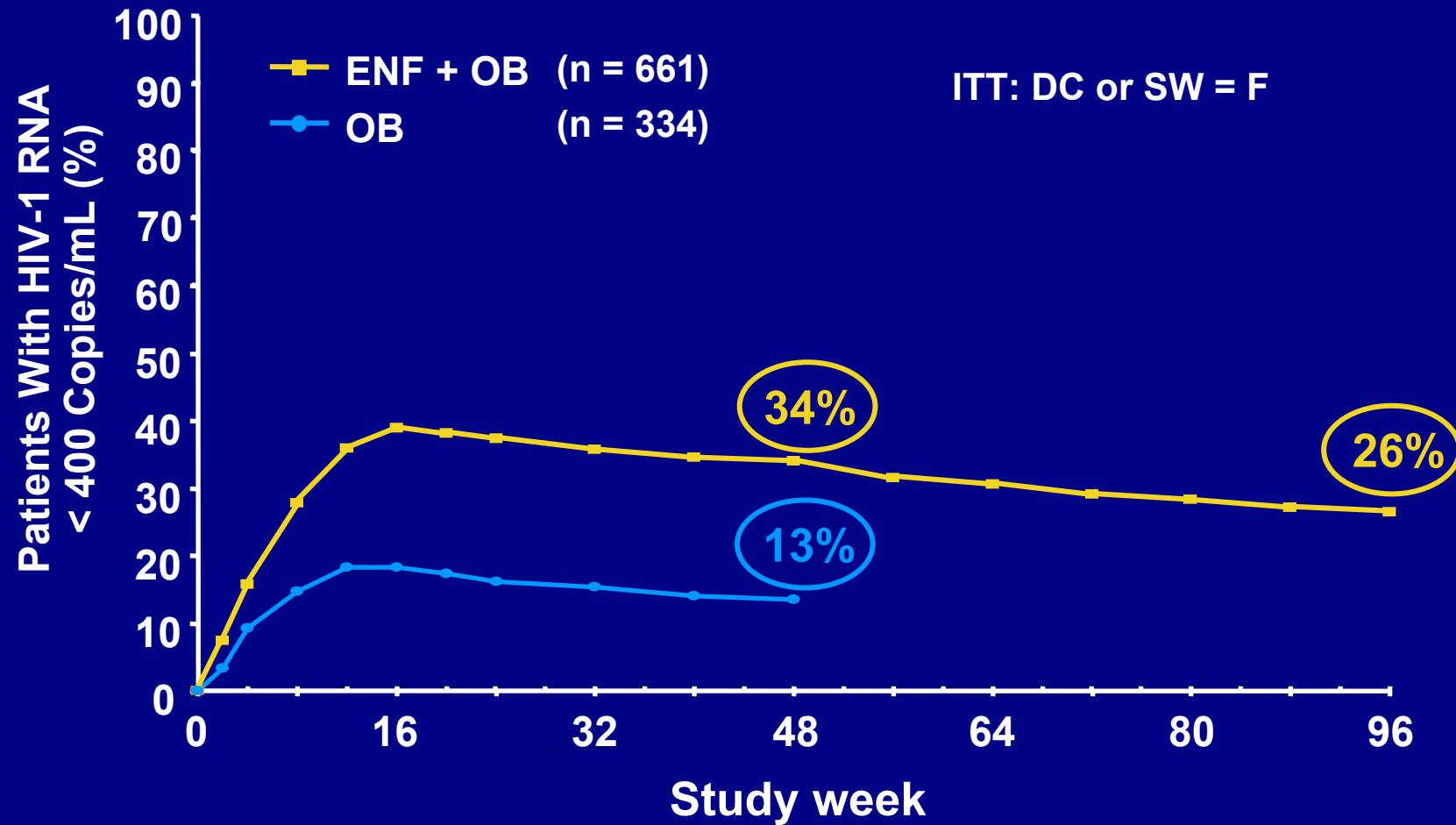
Novel therapies for treatment experienced patients

- Protease inhibitor
 - Darunavir
 - Tipranavir
- Fusion Inhibitor
 - T20 (Enfuvirtide)
- Next generation NNRTI
 - **Etravirine**
- Integrase inhibitor
 - **Raltegravir**
- CCR5 Antagonist
 - **Maraviroc**
 - **Vicriviroc**

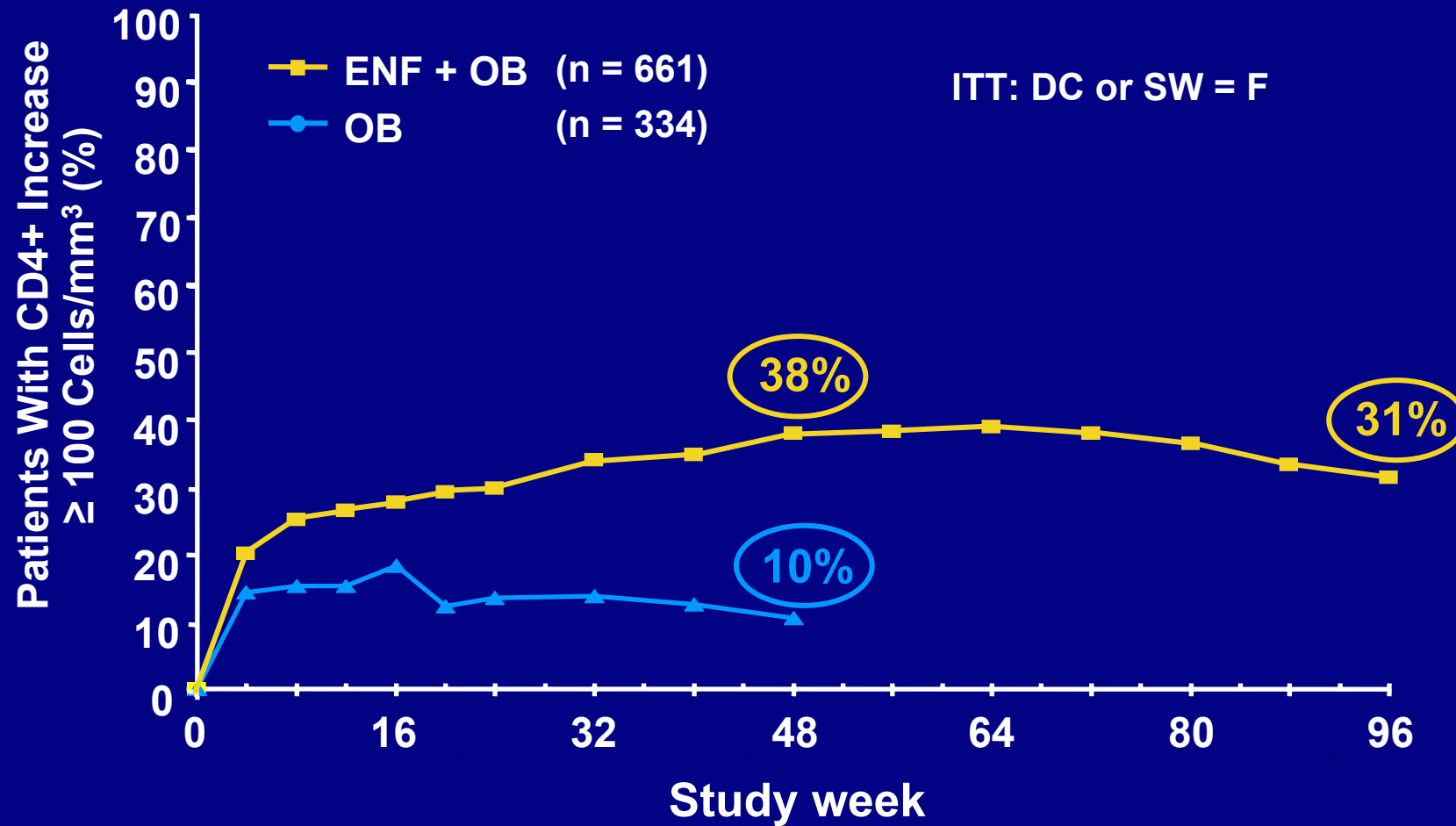
Enfuvirtide in treatment experienced patients

- TORO 1 and 2
- 96 week data presented at 15th International AIDS Conference 2004
- Enfuvirtide plus OBR superior to OBR alone with durable virologic and immunologic response

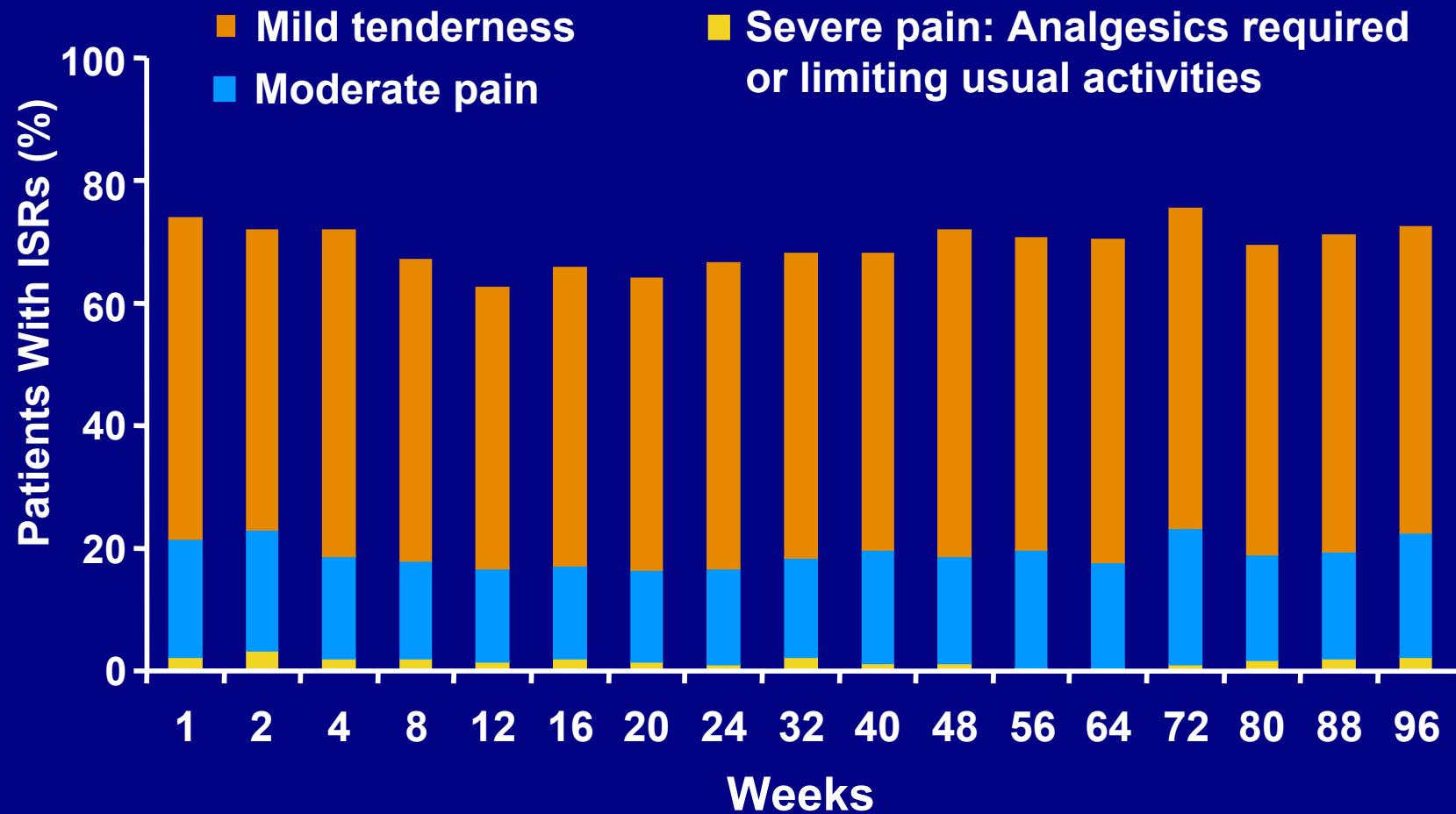
Durability of Virologic Response



Durability of Immunologic Response



Injection Site Reactions With Enfuvirtide



Darunavir in treatment experienced patients

- **POWER 1 and 2**
 - Presented at 2006 16th International AIDS Conference
 - Efficacy of DRV/Rit plus OBR superior to comparator PIs plus OBR in multiclass experienced patients at week 48
 - 46% of DRV/Rit patients achieved VL <50 copies/ml
- **POWER 3**
 - Molina et al. J AIDS. 2007;46:24-31
 - Pooled analysis of 327 patients from 2 open label phase IIb trials of DRV/Rit plus OBR
 - Primary endpoint week 24
 - Similar results to POWER 1 and 2
- **TITAN**
 - Presented at 2007 IAS
 - Compared DRV/Rit to LPV/Rit in treatment experience LPV naïve patients
 - DRV non inferior at week 48 for VL <400 copies/ml
 - DRV superior for VL<400 and VL < 50 copies/ml

Tipranavir in treatment experienced patients

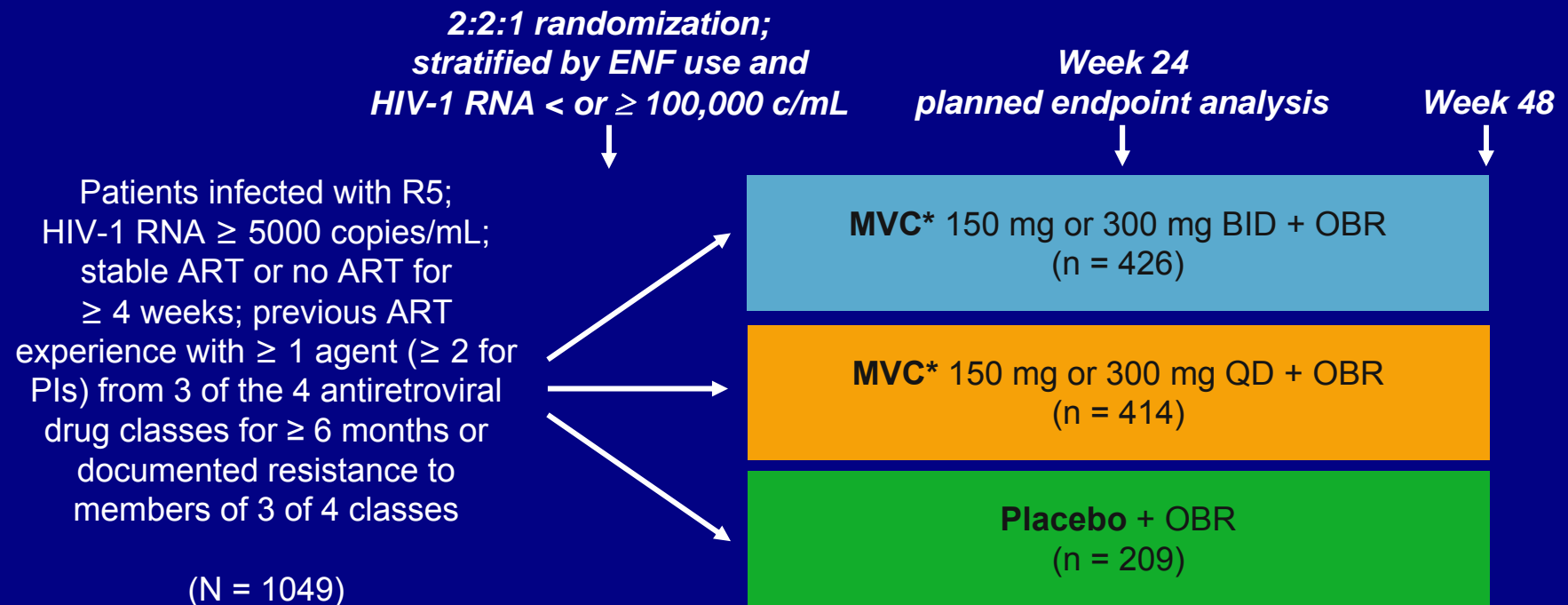
- RESIST 1 and 2
- 96 week data presented at ICAAC 2006
- TPV/Rit plus OBR superior to comparator PI plus OBR in highly treatment experienced patients
- Use of TPV/Rit plus OBR produced significantly superior treatment outcomes vs comparator PI plus OBR out to 96 weeks follow up

Tipranavir vs Darunavir

- Choice is dependent upon activity based on presence of mutations
- Tipranavir mutation score
 - 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, 84V
 - Score 0-1 good activity, 2-7 partial, 8+ no activity
- Darunavir
 - 11I, 32I, 33F, 47V, 50V, 54L/M, 73S, 76V, 84V, 89V
 - 3 or more associated with diminished response
- Interaction with other agents, side effect profile, toxicities

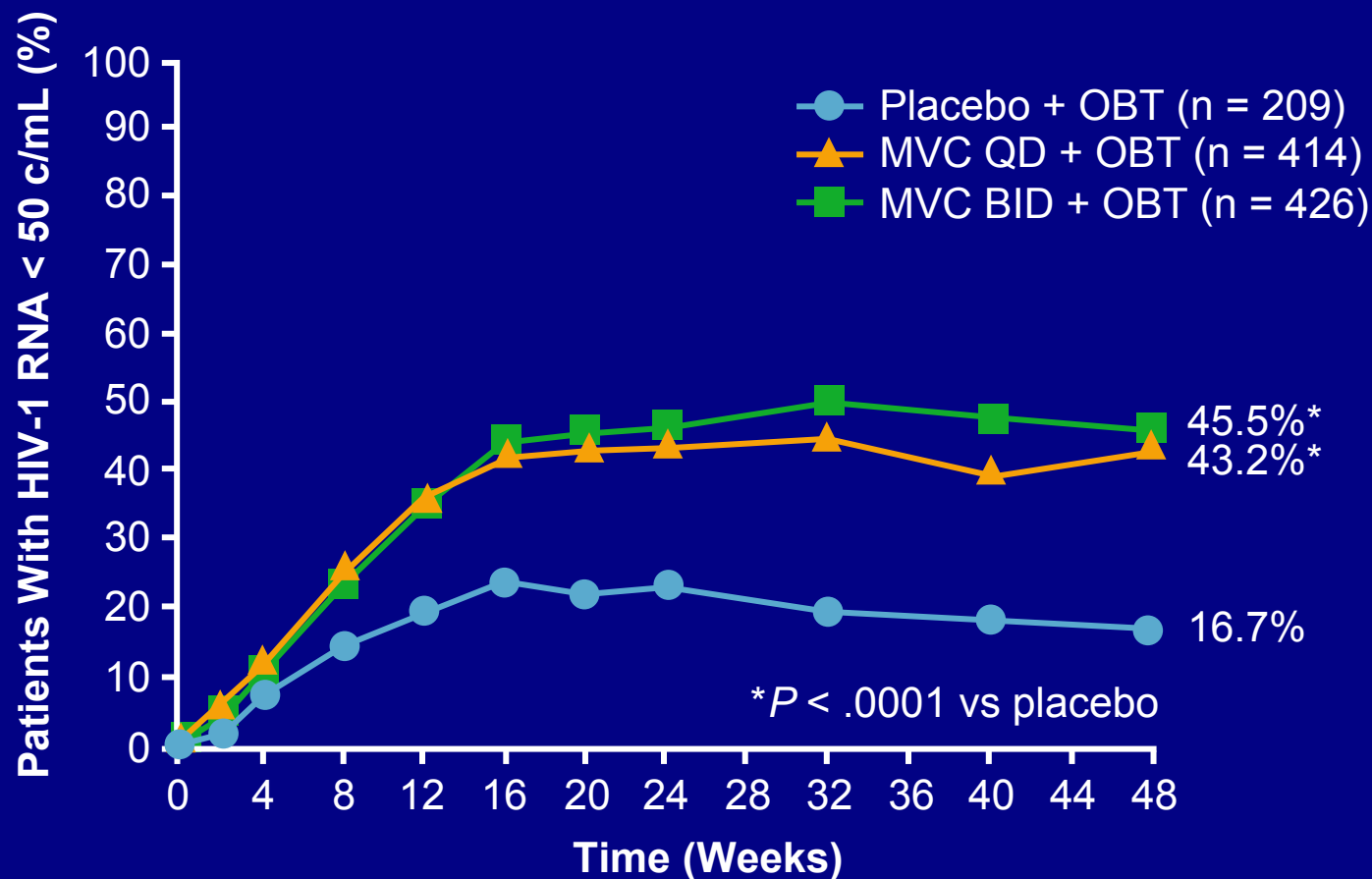
MOTIVATE 1 and 2: MVC in Treatment-Experienced Patients With R5 Virus

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



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

MOTIVATE 1 and 2: Combined Virologic Efficacy at Week 48



MOTIVATE 1 and 2: Combined Virologic and Immunologic Efficacy

- MVC + OBR associated with significantly greater viral suppression than placebo + OBR in treatment-experienced patients^[1]

Patient Outcome at Week 48	Placebo + OBR (n = 209)	MVC QD + OBR (n = 414)	MVC BID + OBR (n = 426)
Median HIV-1 RNA change from BL, log ₁₀ copies/mL*	-0.78	-1.68*	-1.84 [†]
HIV-1 RNA < 50 copies/mL by BL HIV-1 RNA, %			
▪ < 100,000 copies/mL	26 (n = 123)	59 (n = 238)	58 (n = 243)
▪ ≥ 100,000 copies/mL	10 (n = 84)	32 (n = 170)	35 (n = 176)
Mean CD4+ cell count change from baseline, cells/mm ³	61	116	124

*Difference vs placebo: -0.89 (95% CI: -1.17 to -0.62).

[†]Difference vs placebo: -1.05 (95% CI: -1.33 to -0.78).

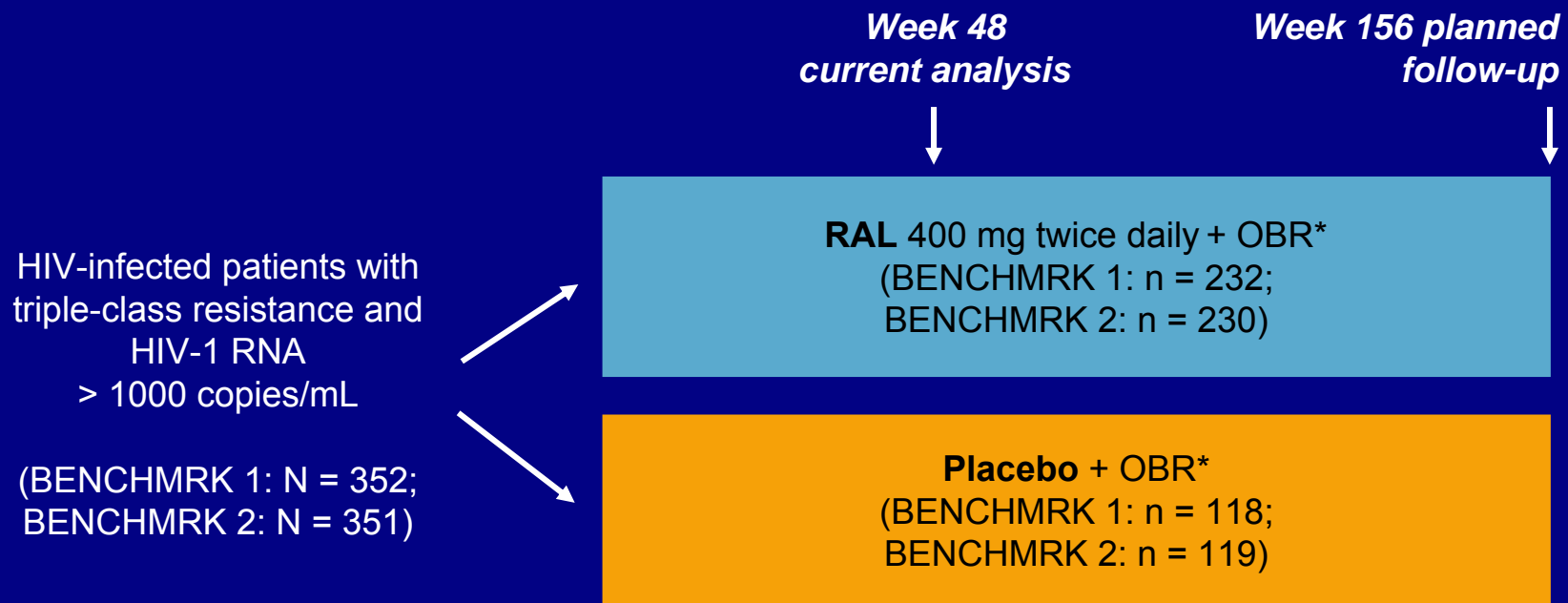
- In meta-analysis of 16 clinical trials in treatment-experienced patients, use of CCR5 inhibitor associated with greater increase in CD4+ cell count, after controlling for baseline HIV-1 RNA and virologic response (+32 cells/mm³; 95% CI: 19-54)^[2]

1. Hardy D, et al. CROI 2008. Abstract 792. 2. Wilkin T, et al. CROI 2008. Abstract 800.

MOTIVATE 1 and 2: Maraviroc Safe and Well Tolerated at Week 48

- No unexpected AEs through Week 48^[1]
- Similar frequency of serious all-grade AEs, toxicity-driven discontinuations, laboratory abnormalities, AIDS-defining infections, and AIDS- or non-AIDS–defining malignancies among MVC vs placebo arms at Week 48
- Most common AEs across study arms: diarrhea, nausea, fatigue, headache
- Analysis of MVC resistance^[2]
 - gp120 V3 loop mutations important in conferring genotypic resistance to MVC in some patients who fail with R5 virus
 - Amino acid substitutions detected in stem and tip of V3 loop in MVC-treated pts
 - Clinical implications of mutations not fully understood

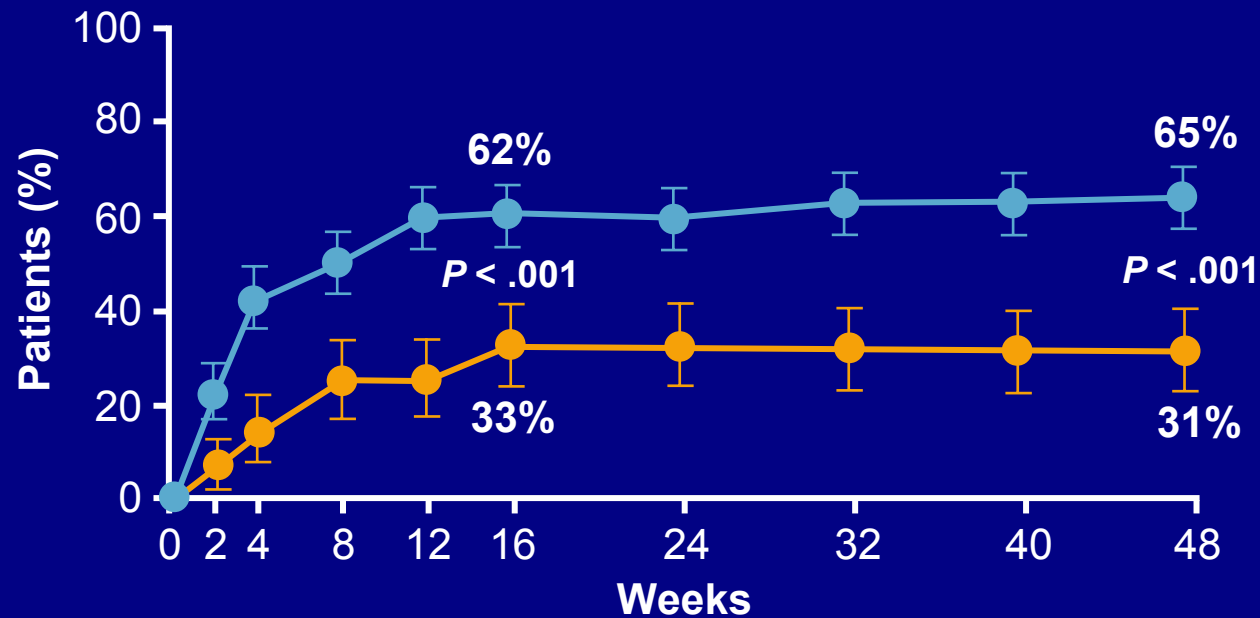
BENCHMRK 1 & 2: Raltegravir in Treatment-Experienced Patients



*Investigator-selected OBR based on baseline resistance data and history; inclusion of DRV and TPV permitted.

1. Cooper DA, et al. CROI 2008. Abstract 788.
2. Steigbigel R, et al. CROI 2008. Abstract 789.

BENCHMARK 1: Patients With HIV-1 RNA < 50 c/mL at Week 48

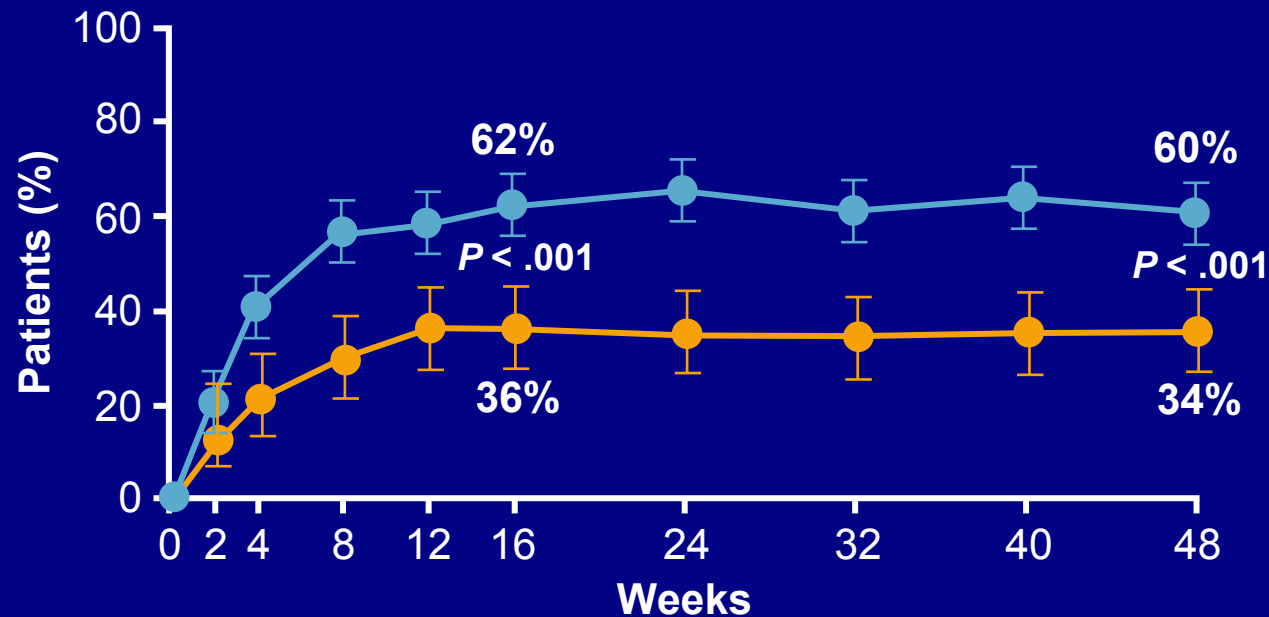


● Raltegravir* n = 232 231 231 230 229 232 229 230 231
 ● Placebo* n = 118 118 118 118 117 118 118 118 118

* Each + OBT; P-value was derived from a logistic regression model adjusted for BL HIV-1 RNA level (\log_{10}), first ENF use in OBT, first DRV use in OBT, active PI in OBT.

Cooper DA, et al. CROI 2008. Abstract 788.

BENCHMARK 2: Patients With HIV-1 RNA < 50 c/mL at Week 48

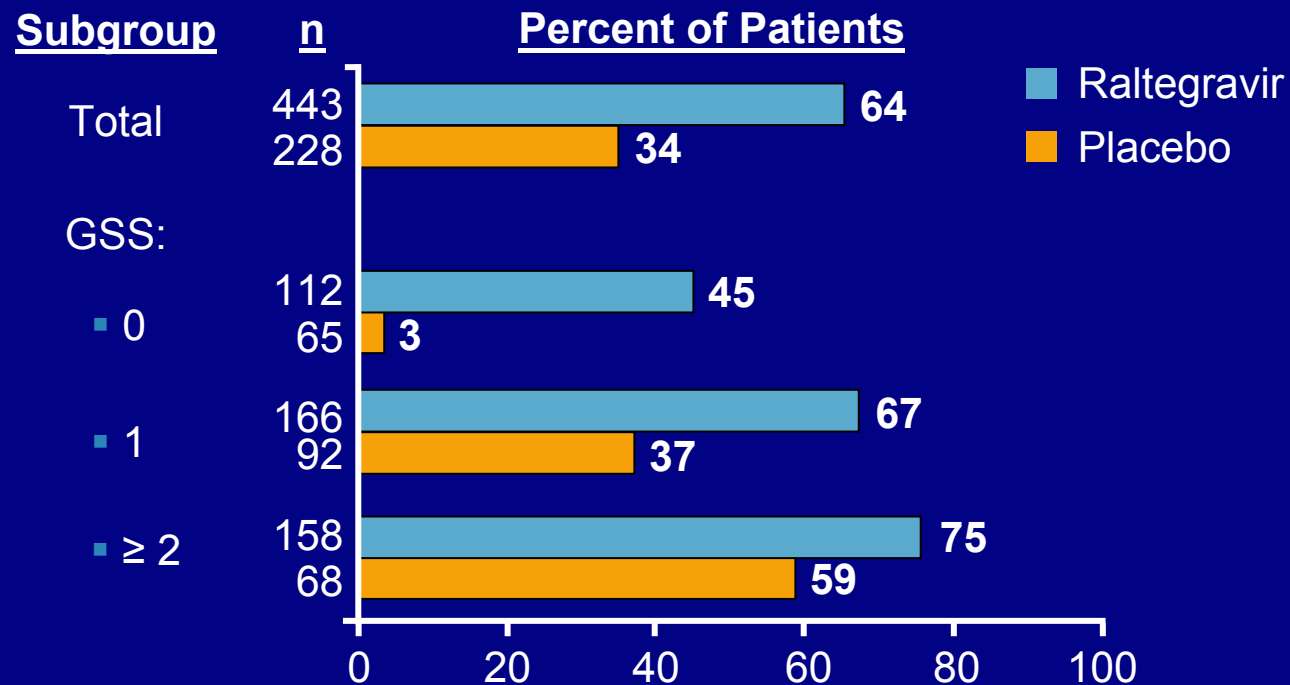


● Raltegravir* n = 230 228 227 230 229 229 224 228 228
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Steigbigel R, et al. CROI 2008. Abstract 789.

BENCHMARK 1 & 2: HIV-1 RNA < 50 c/mL at Week 48, Overall and by GSS



1. Cooper DA, et al. CROI 2008. Abstract 788.
2. Steigbigel R, et al. CROI 2008. Abstract 789.

DUET-1 and -2: Phase III Trials of ETR Plus DRV + RTV-Containing OBR

HIV-infected patients with VF on current HAART regimen, history of ≥ 1 NNRTI resistance mutations, ≥ 3 primary PI mutations, HIV-1 RNA > 5000 copies/mL

(DUET-1: N = 612;
DUET-2: N = 591)



**ETR 200 mg BID +
DRV + RTV-containing OBR***
(n = 599)

**Placebo +
DRV + RTV-containing OBR***
(n = 604)

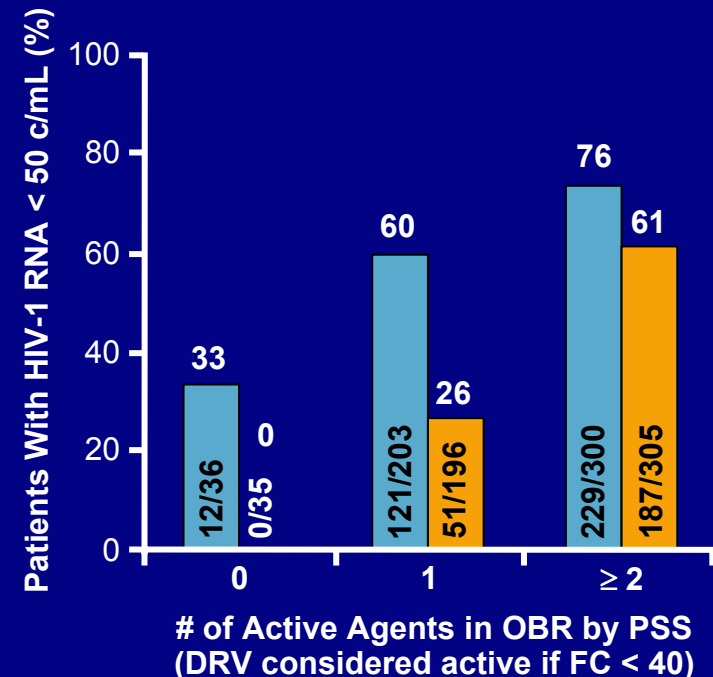
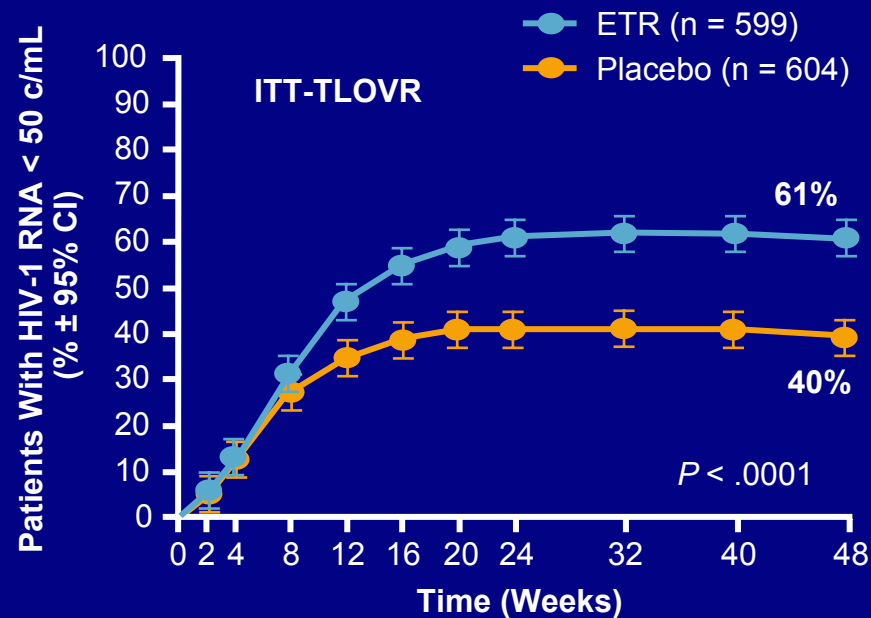
Week 48



*Investigator-selected OBR consisting of DRV + RTV (600/100 mg/mL BID) + ≥ 2 NRTIs \pm ENF.

DUET-1 and -2: VL < 50 c/mL at Wk 48, Overall, and by Active Agents in OBR

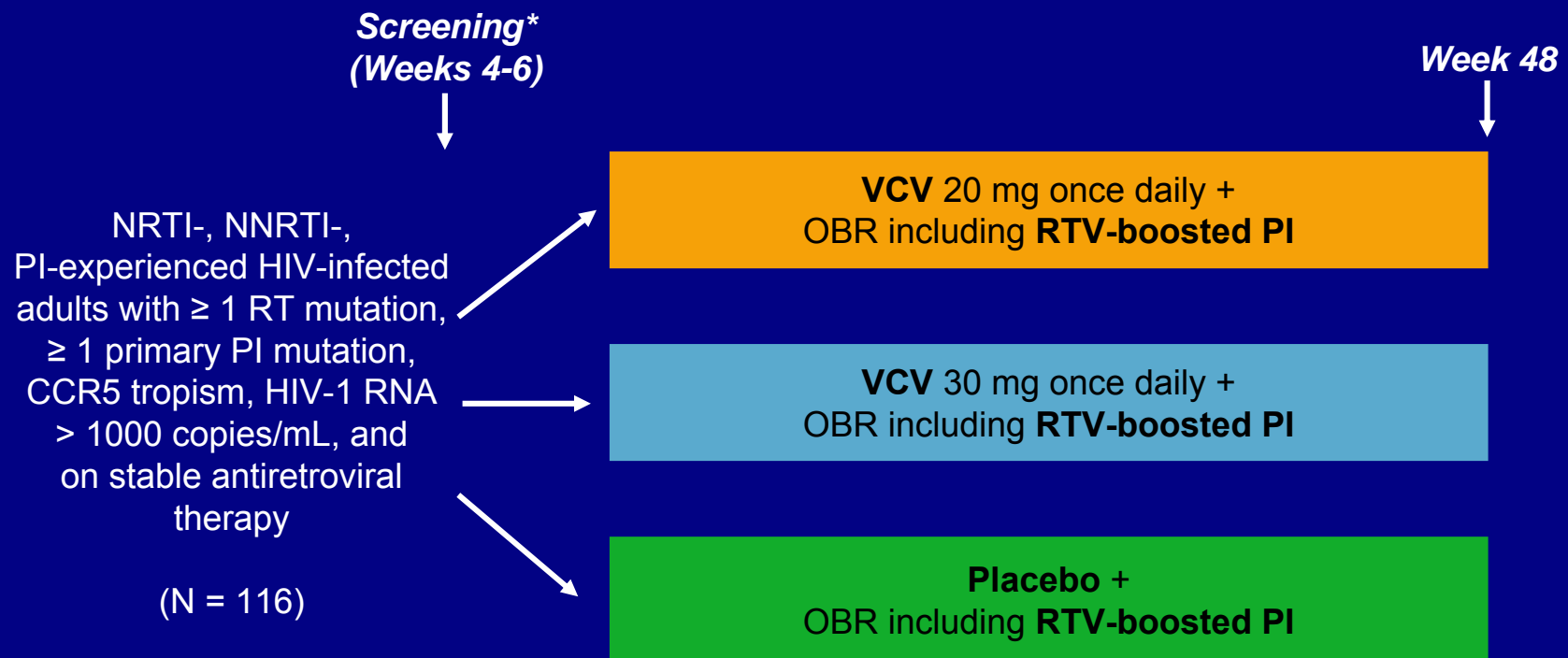
- Mean changes in CD4+ cell count response at Week 48 significantly greater in ETR arm: +98 cells/mm³ vs +73 cells/mm³ in placebo^[1,2]



- VircoType* assay clinical cutoffs for ETR susceptibility defined: lower clinical cutoff (1.6), upper clinical cutoff (27.6)^[3]

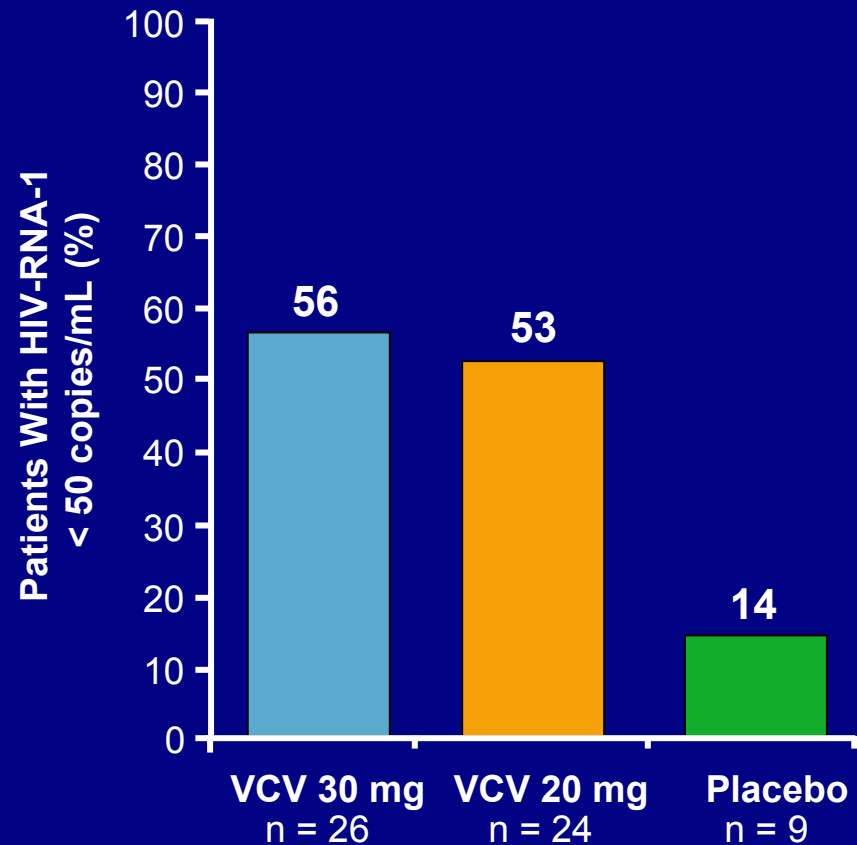
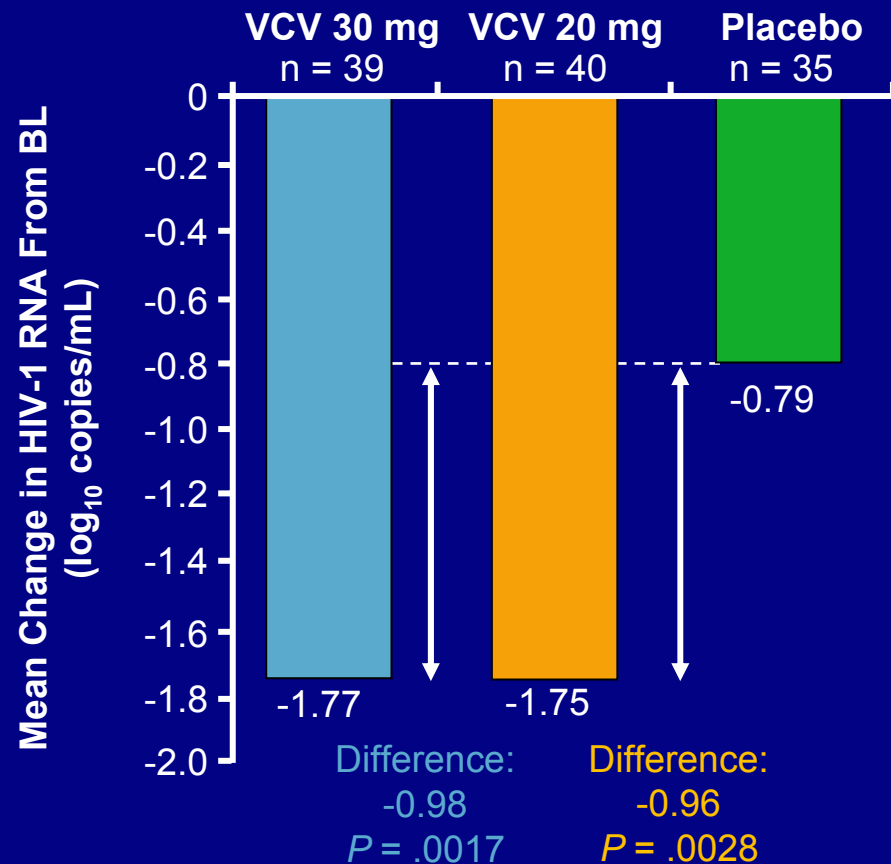
1. Haubrich R, et al. CROI 2008. Abstract 790. 2. Johnson M, et al. CROI 2008. Abstract 791.
3. Winters B, et al. CROI 2008. Abstract 873.

VICTOR-E1: Phase IIb Trial of Vicriviroc in Treatment-Experienced Patients



*Confirmation of tropism required before randomization.

VICTOR-E1: Superior Outcomes With Vicriviroc vs Placebo at Week 48



- No clinically significant differences in adverse events between VCV arms and placebo

Zingman B, et al. CROI 2008. Abstract 39LB.

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Conclusion

- New classes and new agents recently approved have opened the options for treatment experienced patients
- Aim for treatment should be to achieve undetectable viral loads
- Concern for the future still remains as currently there are no further classes or agents available for patients who fail these new regimens