

Using the New Antiretroviral Agents



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Recently Approved or Available Agents

- NNRTIs

- » Etravirine (ETR)

- PIs

- » Tipranavir (TPV)

- » Darunavir (DRV)

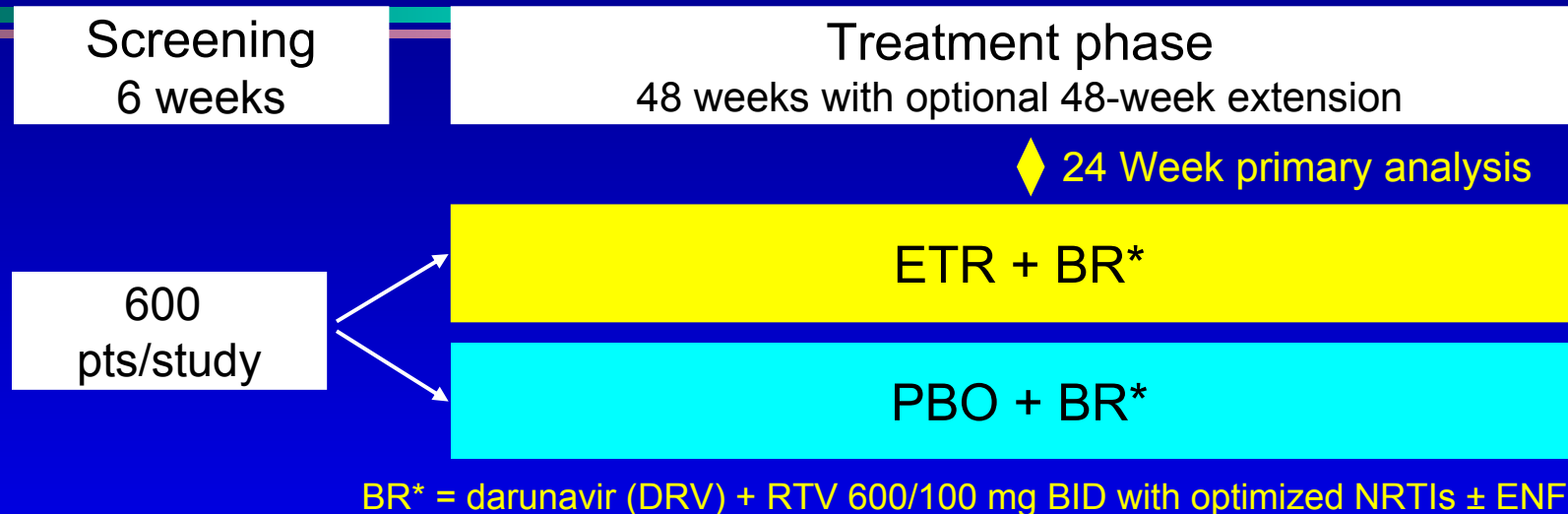
- CCR5 Inhibitors

- » Maraviroc (MVC)

- Integrase Inhibitors

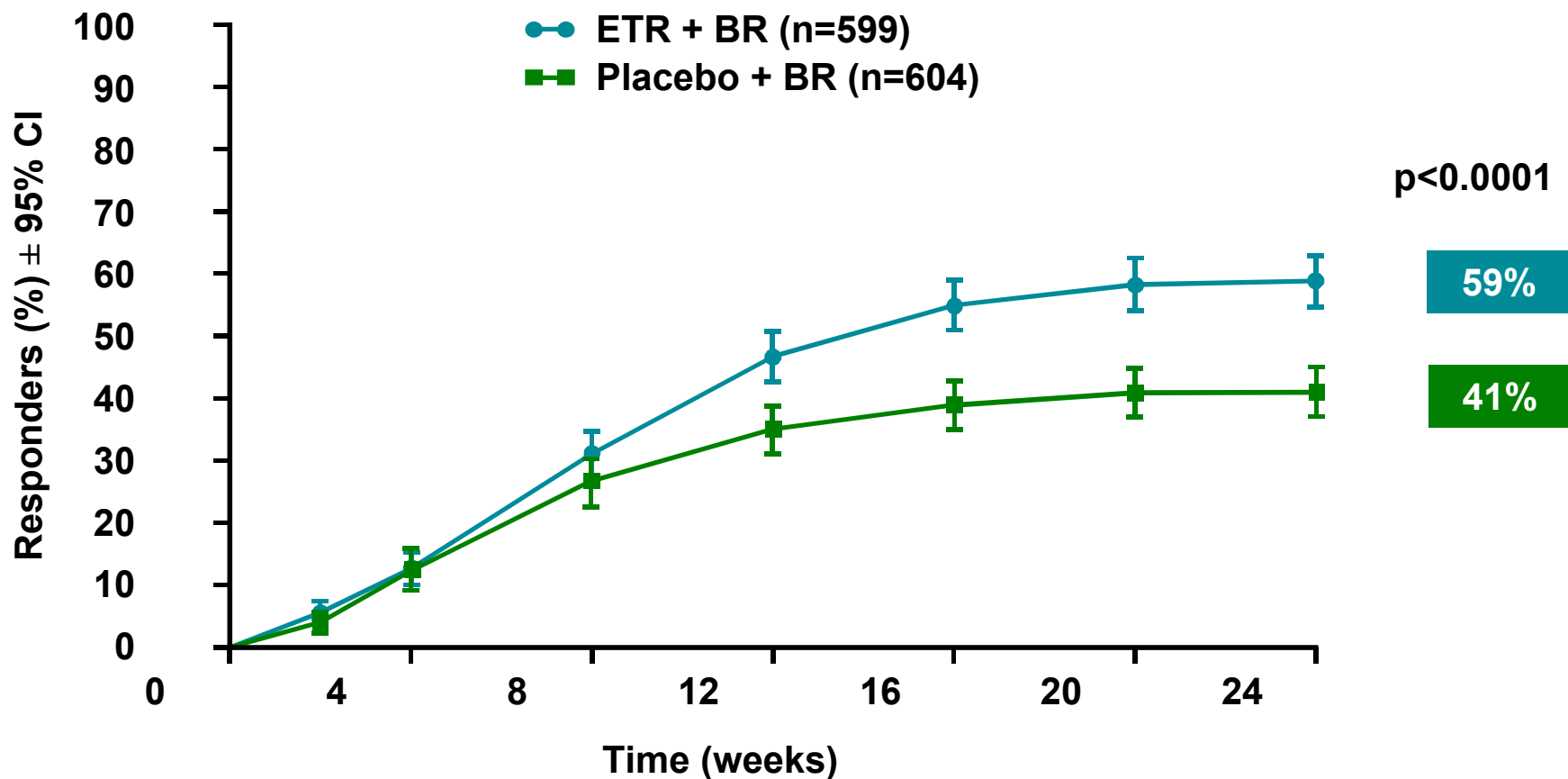
- » Raltegravir (RAL)

DUET 1 and 2: Phase III etravirine (ETR) trial



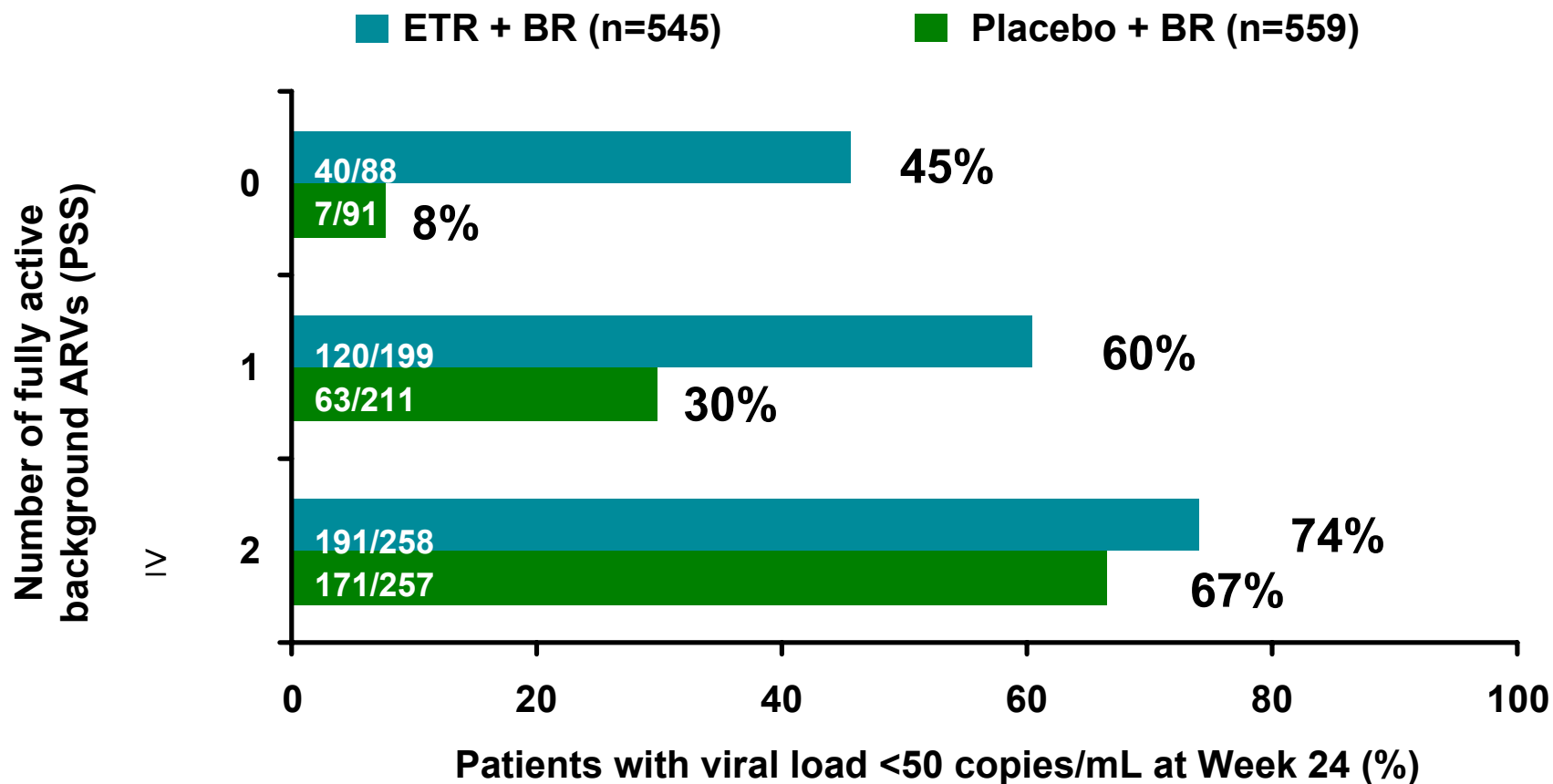
- Stratification: ENF use (none, 1st use, re-use), prior DRV, VL < or ≥30,000
- Inclusion criteria:
 - » Stable ART ≥ 8 wks with VL >5000
 - » ≥1 NNRTI mutation at screening or on prior GT
 - » ≥3 primary PI mutations at screening

Patients with viral load <50 c/mL at Week 24 (primary endpoint; ITT TLOVR)



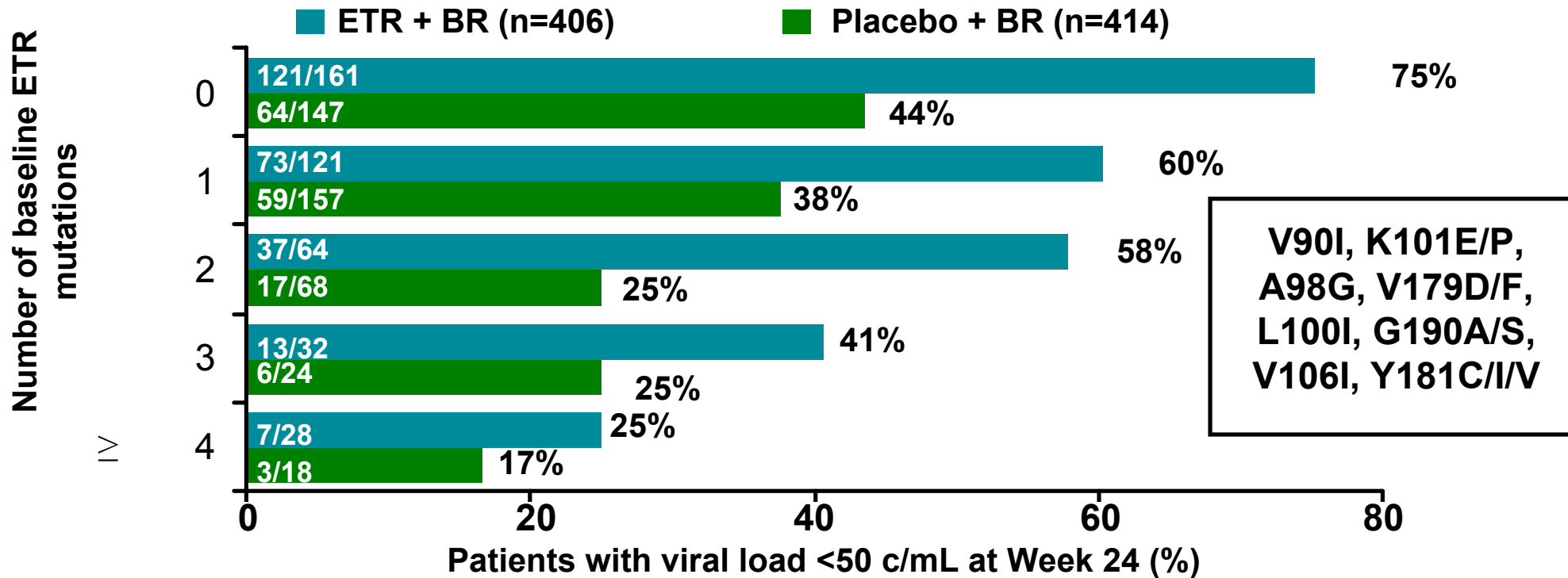
BR = background regimen; CI = confidence interval;
ITT = intent-to-treat population; TLOVR = time to loss of virologic response imputation algorithm

Response (<50 c/mL) according to number of active background ARVs



Analysis excludes patients who discontinued except for virological failure; PSS = phenotypic sensitivity score; darunavir and enfuvirtide are counted as fully active if FC<10 or used *de novo*, respectively

Response (<50 c/mL) according to number of ETR mutations



- Greatest added benefit in the ETR vs. placebo group seen in patients with <3 ETR mutations
- 86% of patients had <3 ETR mutations

Analysis excludes patients who used de-novo enfuvirtide or discontinued except for virological failure
BR = background regimen; RAM = resistance-associated mutation;

Overview of adverse events (AEs; regardless of causality)

Parameter, %		ETR + BR (n=599)	PBO + BR (n=604)
Any AE (any cause)		93	93
Grade 3/4 AE		25	27
Discontinuation due to AE		5.8	4.5
Serious AE		13	19
Death (any cause), % (n)		1.3 (8)*	2.5 (15)
Most common AEs‡	Rash (any type)	17§	9
	Diarrhea	15	20
	Nausea	14	11
	Headache	9	12
AEs of interest	Nervous system disorders	15	19
	Psychiatric disorders	13	15
	Hepatic AEs	5	5

- No consistent or clinically relevant trends in laboratory, vital signs or ECG data
- Profile of lab abnormalities, including hepatic and lipid parameters, generally similar between the ETR and PBO groups

*no deaths in the ETR group were considered at least possibly related to trial medication;

‡ in >10% patients in either group, excluding injection site reactions; §p=0.0001 vs placebo

NNRTIs:

The Use of Etravirine in Clinical Practice

- Effective against many NNRTI-resistant strains
 - » K103N has no effect on susceptibility
 - » No single NNRTI mutation reduces activity
- Efficacy decreases with increasing NNRTI mutations
 - » Don't continue EFV or NVP in a non-suppressive regimen
- Cross-resistance:
 - » Genotype:
 - Not all ETR mutations included in past commercial genotypes
 - » Phenotype: Not available until drug approved. Can't use old phenotypes to assess ETR susceptibility

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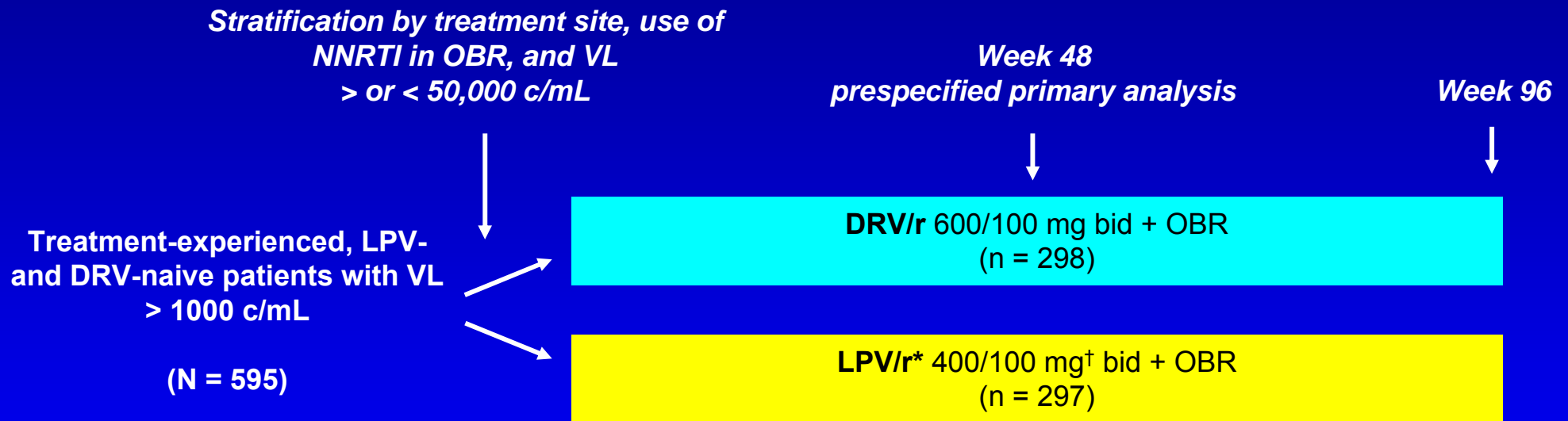
- CCR5 Inhibitors

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- » Raltegravir (RAL)

TITAN: DRV/r vs LPV/r in Experienced, LPV/r-Naive Patients



Arms well balanced at baseline except for proportion with ≥ 2 active drugs in OBR: 65% DRV/r vs. 51% LPV/r

[†]LPV/r increased to 533/133 mg bid (caps) or 600/150 mg bid (for tabs) if NNRTI included in OBR.

TITAN: VL < 50 c/mL at Week 48 by Baseline LPV Fold Change

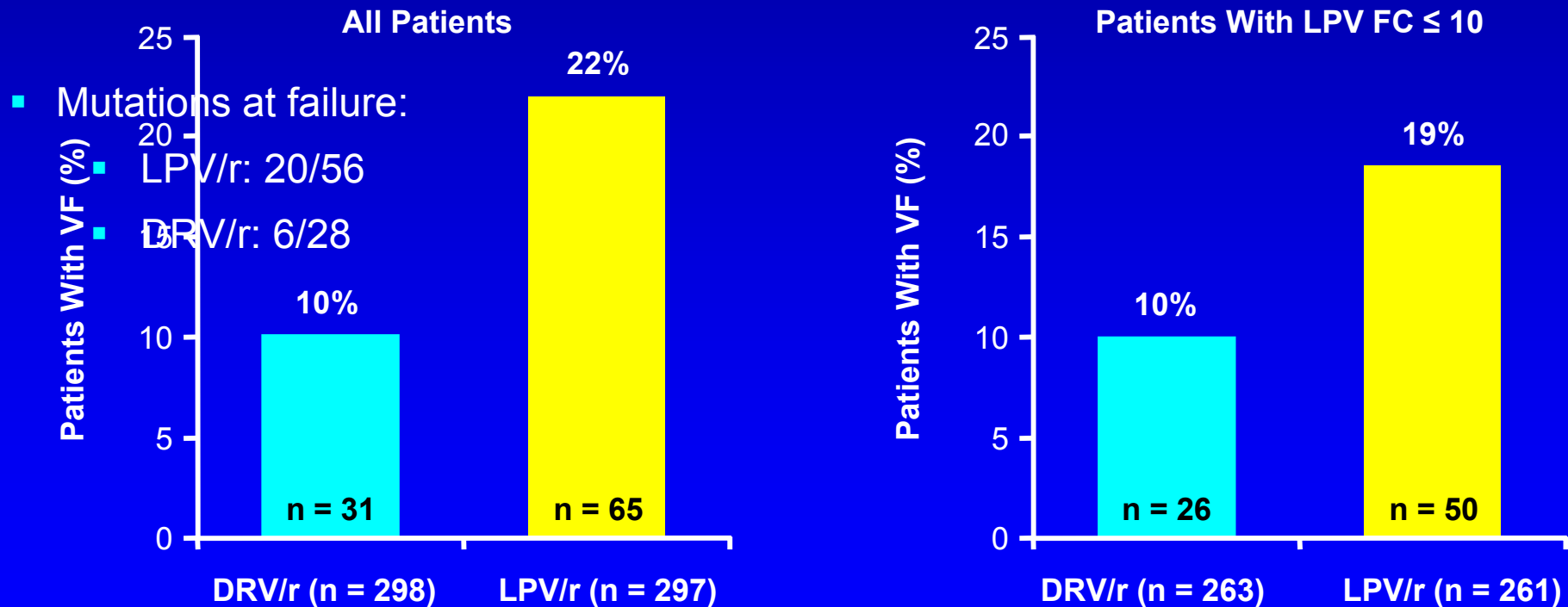
- DRV/r met criteria for superiority to LPV/r in proportion of pts with VL < 50 c/mL in overall study population
 - DRV/r noninferior but not superior in patients with baseline LPV FC ≤ 10

Patient Response, %	DRV/r	LPV/r	DRV/r-LPV/r, % (95% CI)*	Noninferiority P Value*	Superiority P Value*
Overall (n = 595)	71	60	11 (3 to 19)	< .0001	.005
LPV FC ≤ 40 (n = 569)	70	60	10 (2 to 18)	< .0001	.013
LPV FC ≤ 10 (n = 524)	70	63	7 (-1 to 16)	< .0001	.068

*Estimated from logistic regression model including treatment and stratification factors: baseline VL and use of NNRTIs in OBR.

TITAN: Virologic Failure Rates (ITT-TLOVR)

- Virologic failure = nonresponders and rebounders with VL > 400 c/ml



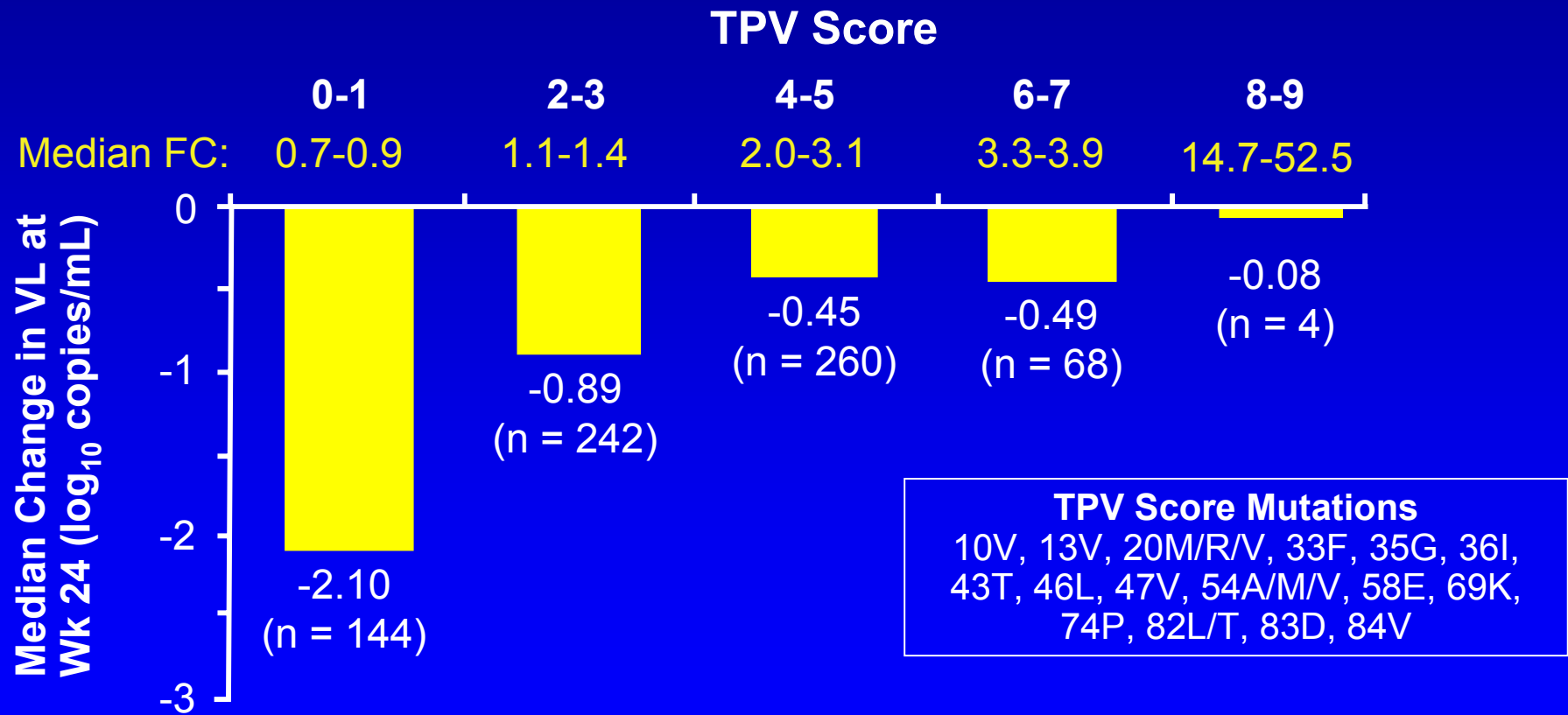
TITAN: Safety and Tolerability

- Safety and tolerability of DRV/r and LPV/r similar
 - Less diarrhea in DRV/r arm (32% vs 42%)
 - LPV/r soft gel caps used in study
 - 18% had switched to tablets by week 48
 - Less rash in LPV/r arm (8% vs 16%)
- Rates of AE- or HIV-related discontinuations comparable
 - 6.7% DRV/r vs 7.1% LPV/r

Using PIs in Treatment-Experienced Patients

- The choice of PIs should be based on resistance testing
 - » Genotype: Scoring systems in evolution, especially for new agents (TPV and DRV)
 - » Phenotype: May be most useful in assessing and comparing susceptibility to PIs

Relationship of TPV Score to TPV Phenotype Results and Response

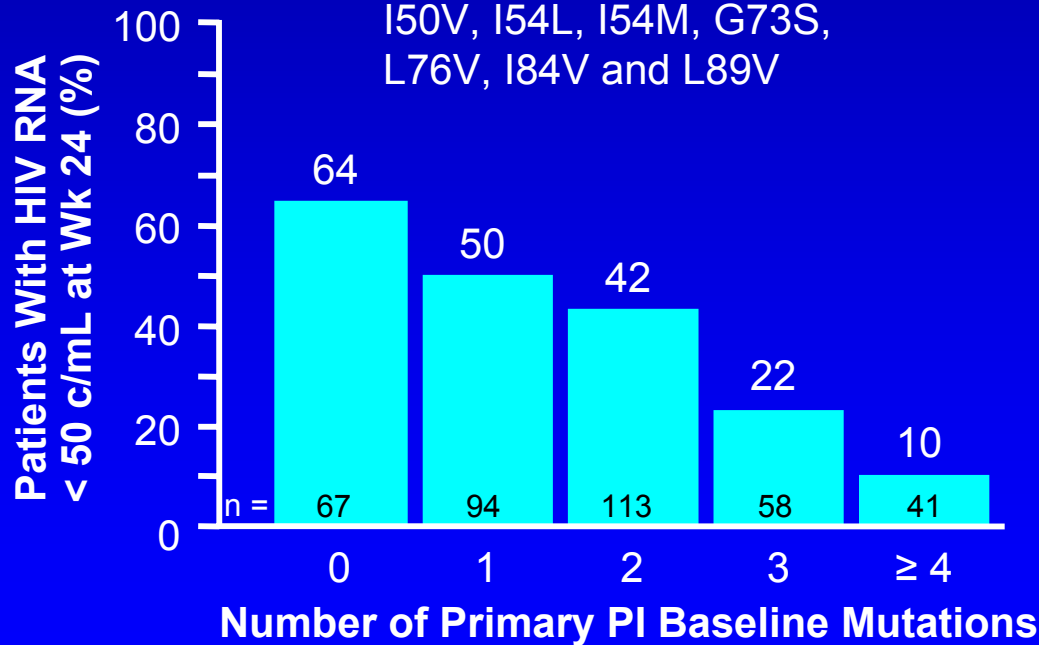


*24-week data from patients in RESIST-1 and -2 given TPV/r.

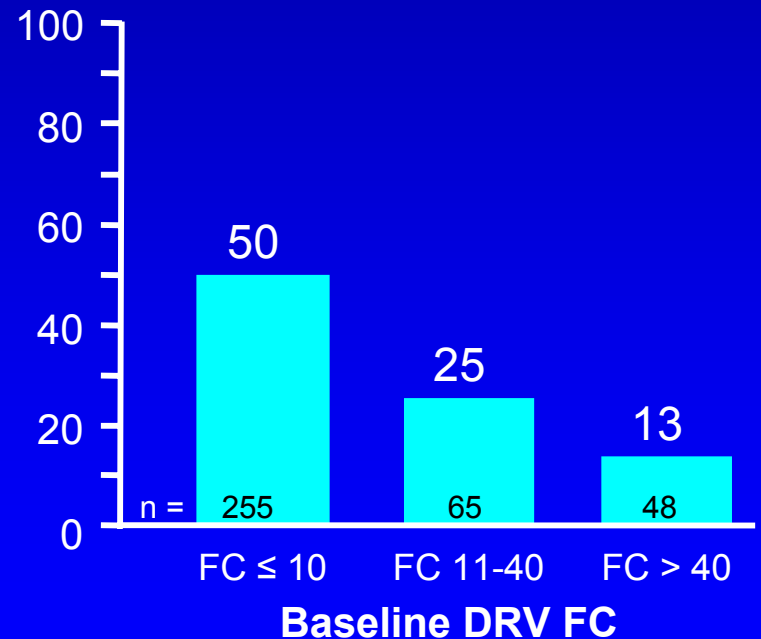
Effect of Baseline Resistance on Response to DRV

- 11 mutations associated with reduced response

– V11I, V32I, L33F, I47V, I50V, I54L, I54M, G73S, L76V, I84V and L89V



- Baseline fold-change strongest predictor of Week 24 response (Antivirogram)



TPV and DRV Mutations and Phenotypic Cut-offs

Similarities and Differences in Key Mutations

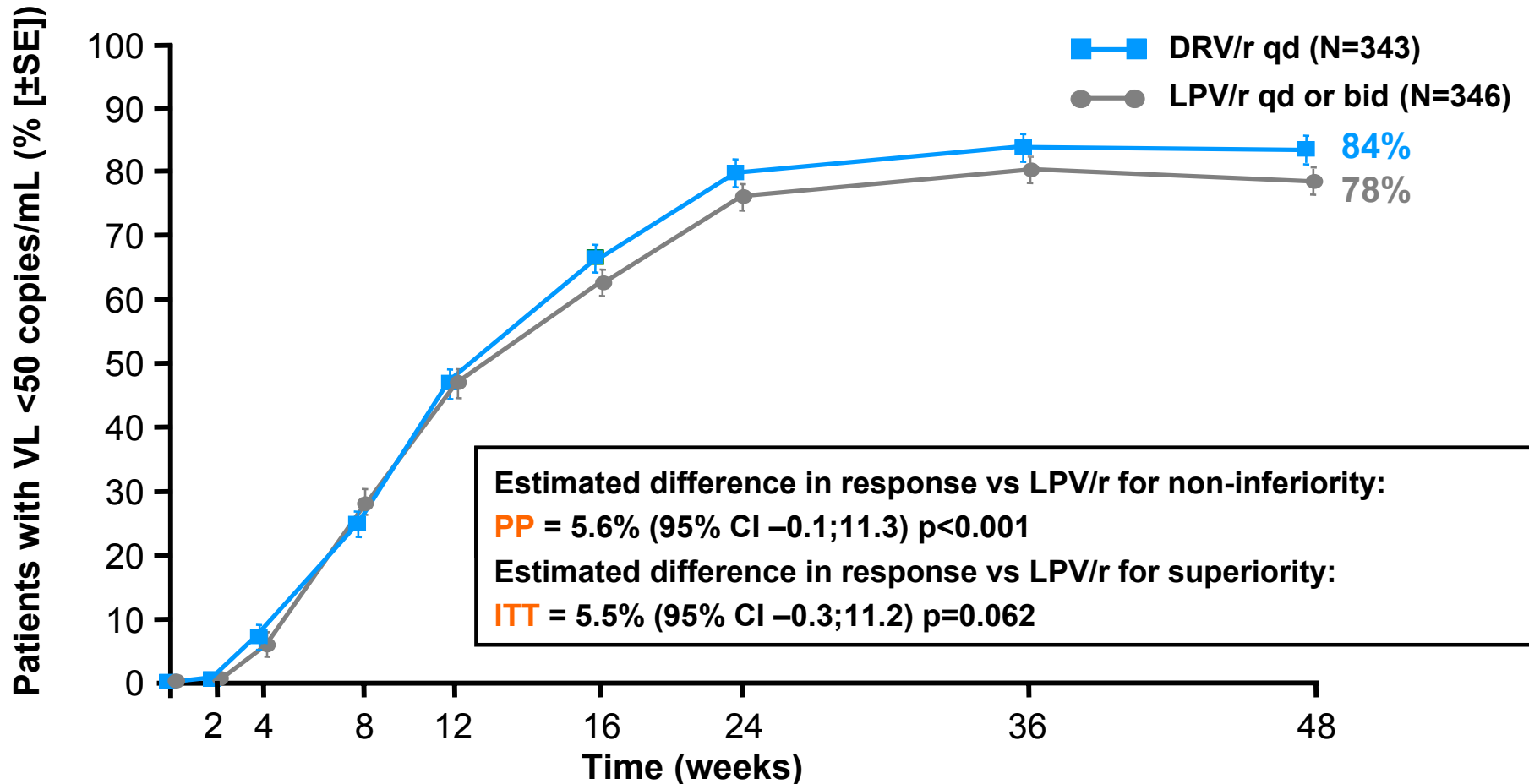
TPV	10V		13V	20M/R/V		33F	35G	36I	43T	46L	47V
DRV		11I			32I	33F					47V
TPV		54A/M/V	58E	69K		74P		82L/T	83D	84V	
DRV	50V	54L/M			73S		76V			84V	89V

Phenotypic Cutoffs

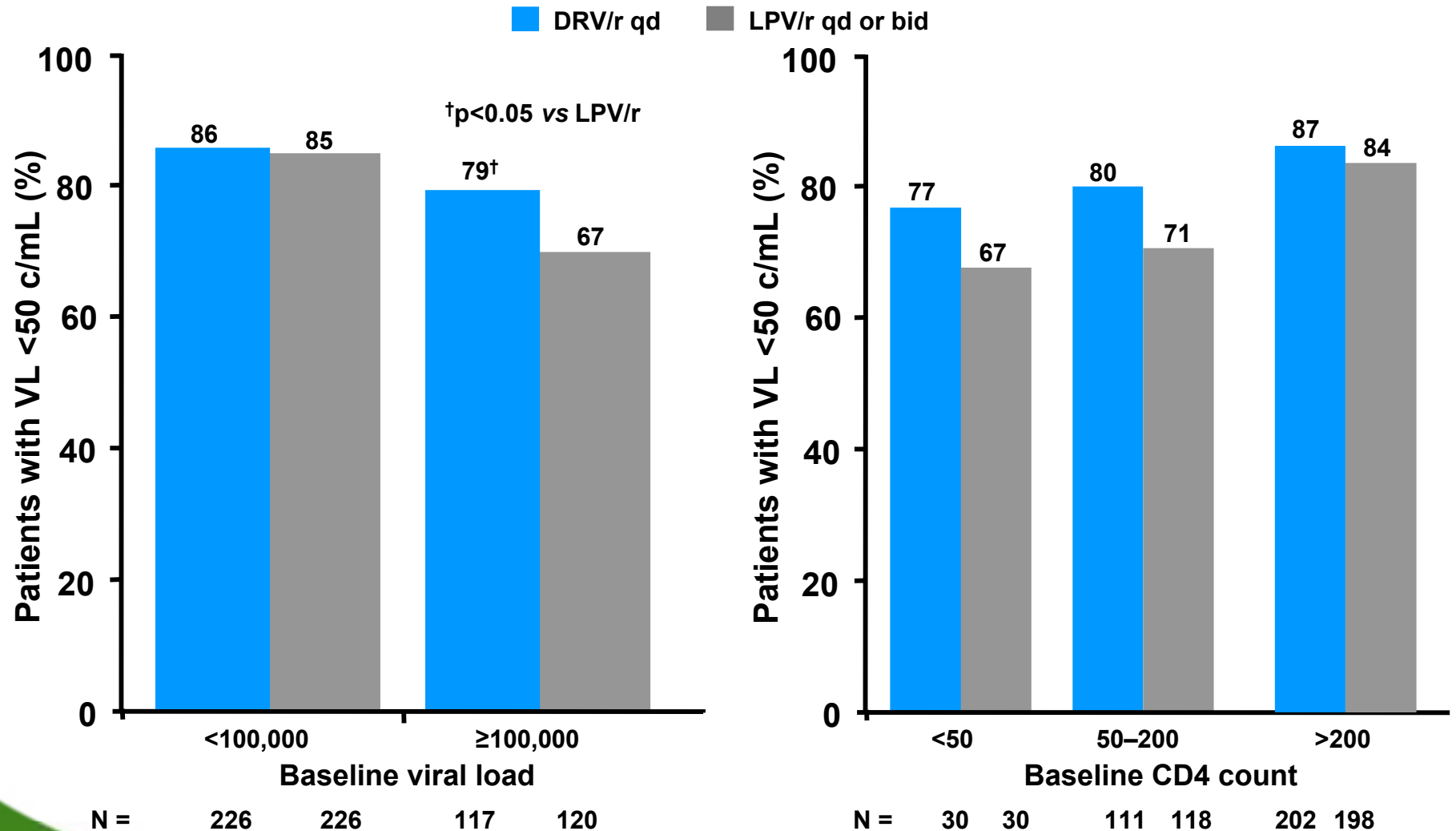
Assay/ Cutoff	Monogram: FC for Reduced Activity	Monogram: FC for No Response	Virco: FC for Maximal Response	Virco: FC for Minimal Response
TPV^[1,2]	≥ 2	≥ 8	< 1.2	≥ 5.4
DRV^[3,4]	≥ 10	≥ 40	< 3.4	≥ 96.9

1. Coakley E, et al. Antivir Ther. 2006;11:S81.
2. Bachelier L, et al. Euro Resistance Wkshp 2006. Abstract 40.
3. De Meyer S, et al. Antivir Ther. 2006;11:S83.
4. Winters B, et al. Antivir Ther. 2006; 11:S180.

ARTEMIS: Viral load <50 copies/mL to Week 48 (ITT-TLOVR)



ARTEMIS: Confirmed response by baseline VL or CD4 at Week 48 (ITT-TLOVR)



[†]Chi square analysis

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R5 Viruses

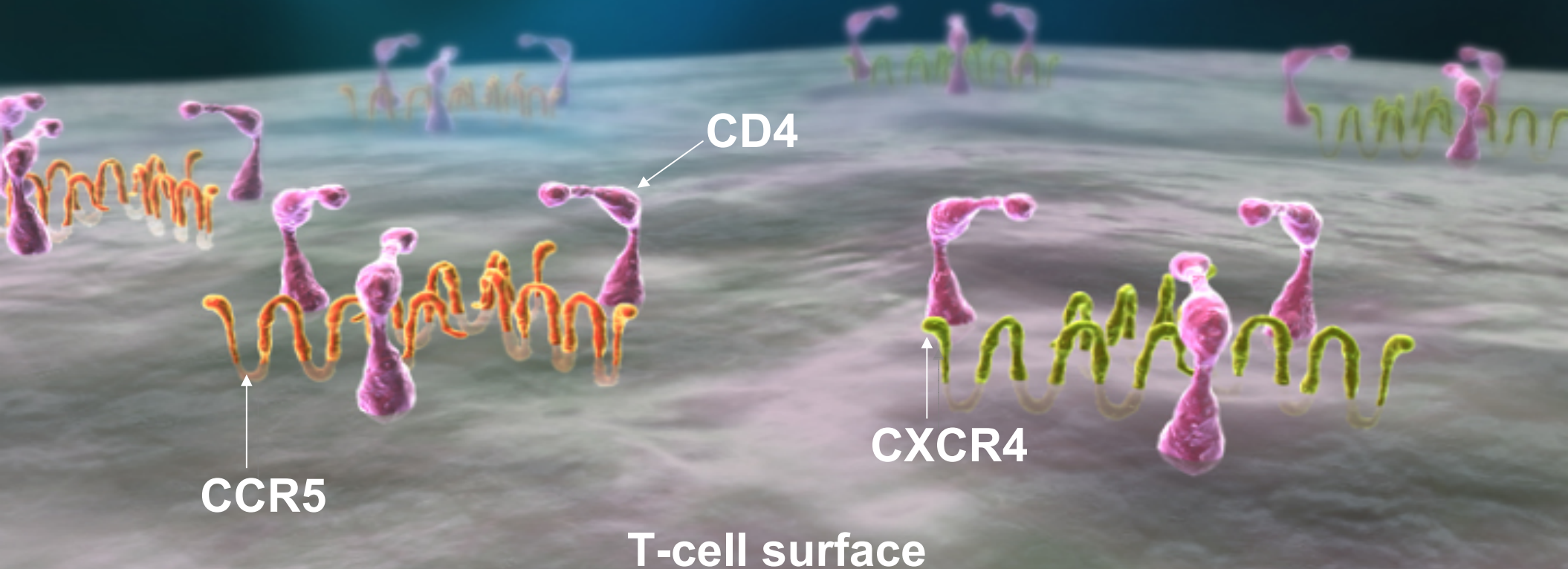
- Utilize the CCR5 co-receptor
- Also known as M-tropic or nonsyncytium inducing (NSI)
- Transmitted variants
- Prevalent in early disease

Dual Viruses

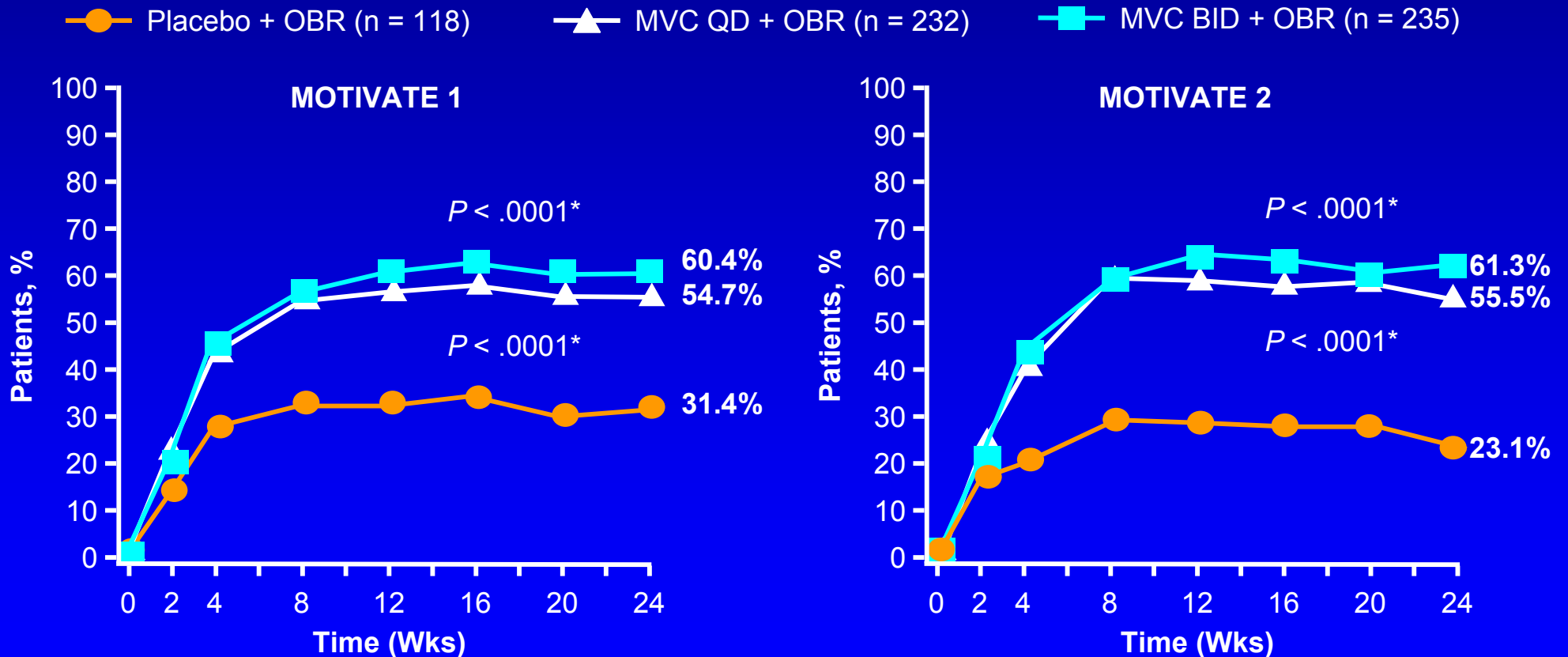
Can utilize either co-receptor

X4 Viruses

- Utilize the CXCR4 co-receptor
- Also known as T-tropic or syncytium inducing (SI)
- Emerge in later disease
- Associated with accelerated CD4 T-cell decline and disease progression



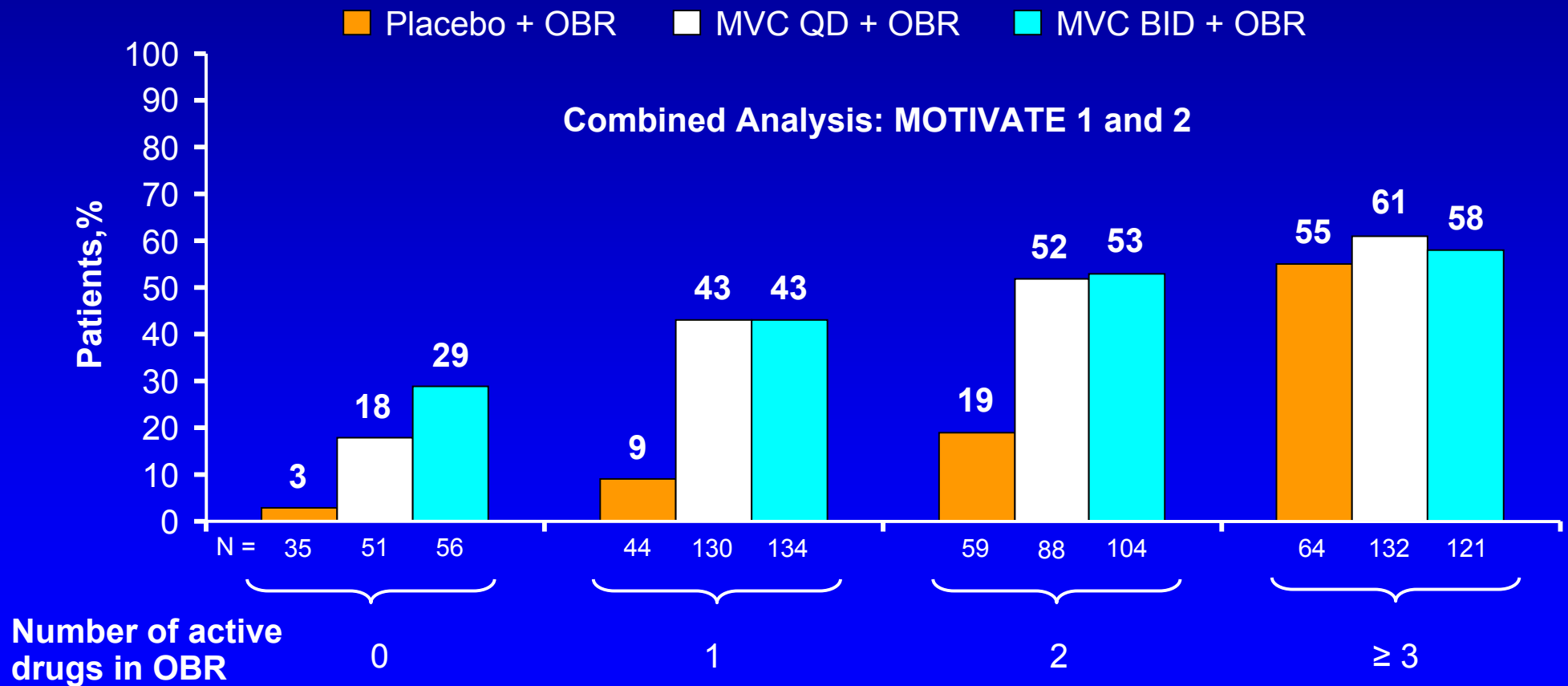
MOTIVATE 1 & 2: VL <400 (ITT, NC = F)



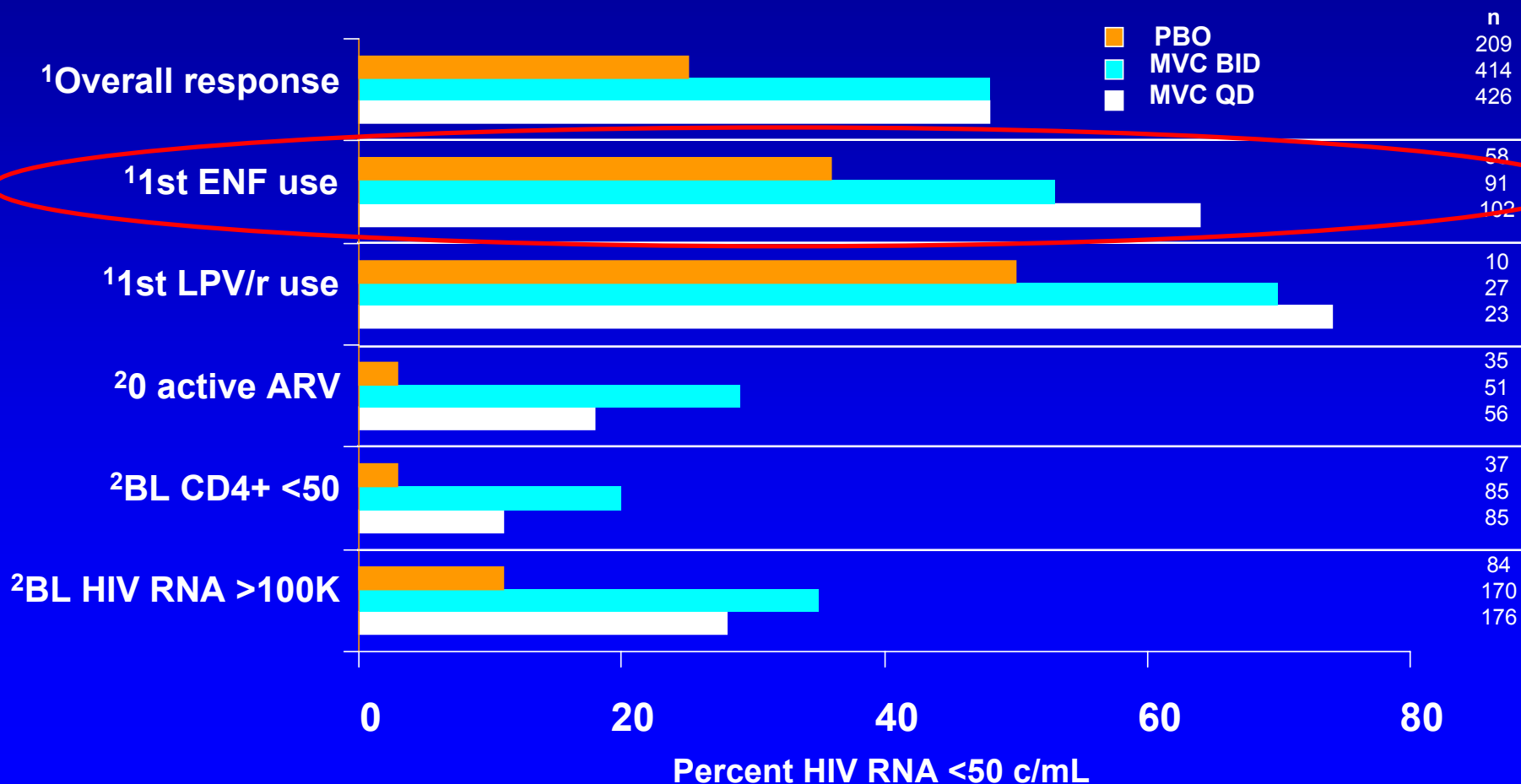
* *P* values vs placebo at Week 24

Nelson M, et al. CROI 2007. Abstract 104aLB. Lalezari J, et al. CROI 2007. Abstract 104bLB.

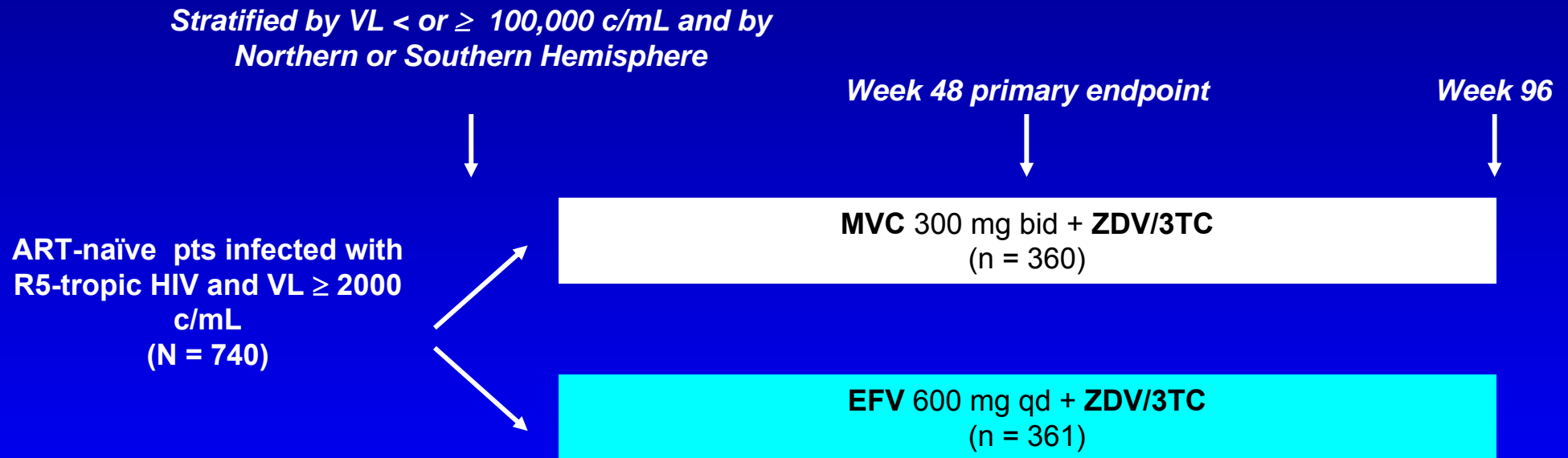
Patients With VL < 50 at Wk 24 by Number of Active Drugs in OBR



MOTIVATE 1+2 Subanalyses



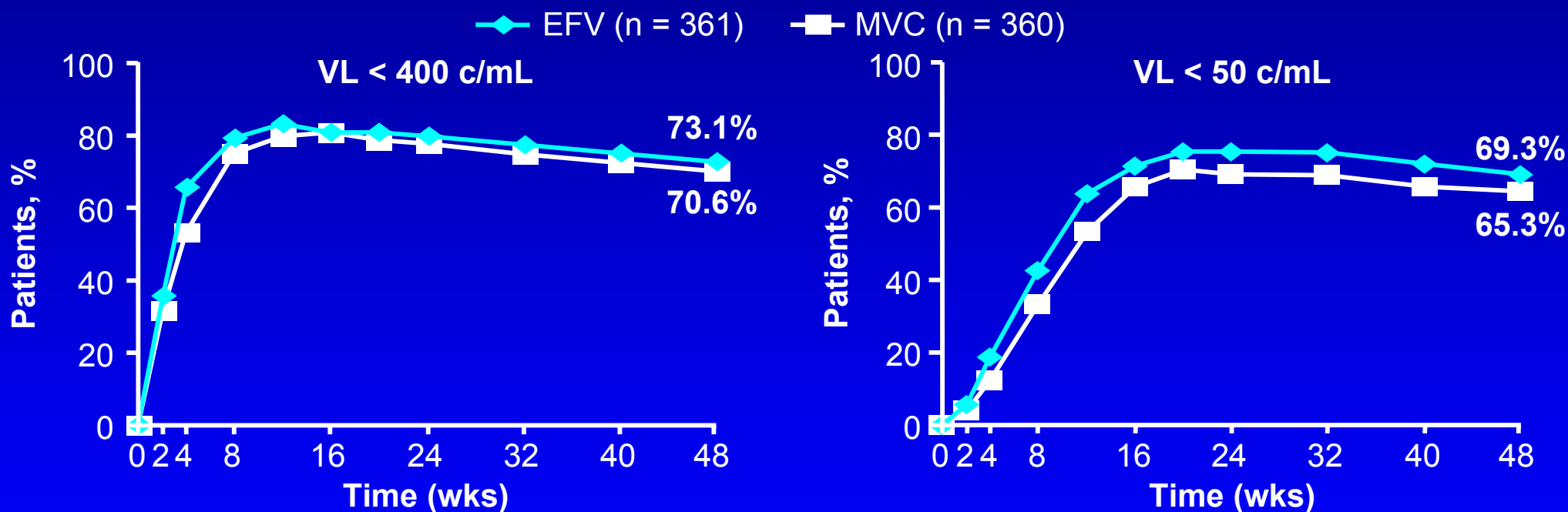
MERIT: Maraviroc vs Efavirenz in Treatment-Naive Patients



MVC 300-mg qd arm discontinued early due to failure to demonstrate noninferiority to efavirenz (Week 16)

- Stringent noninferiority margin: -10% for lower bound of 1-sided 97.5% CI

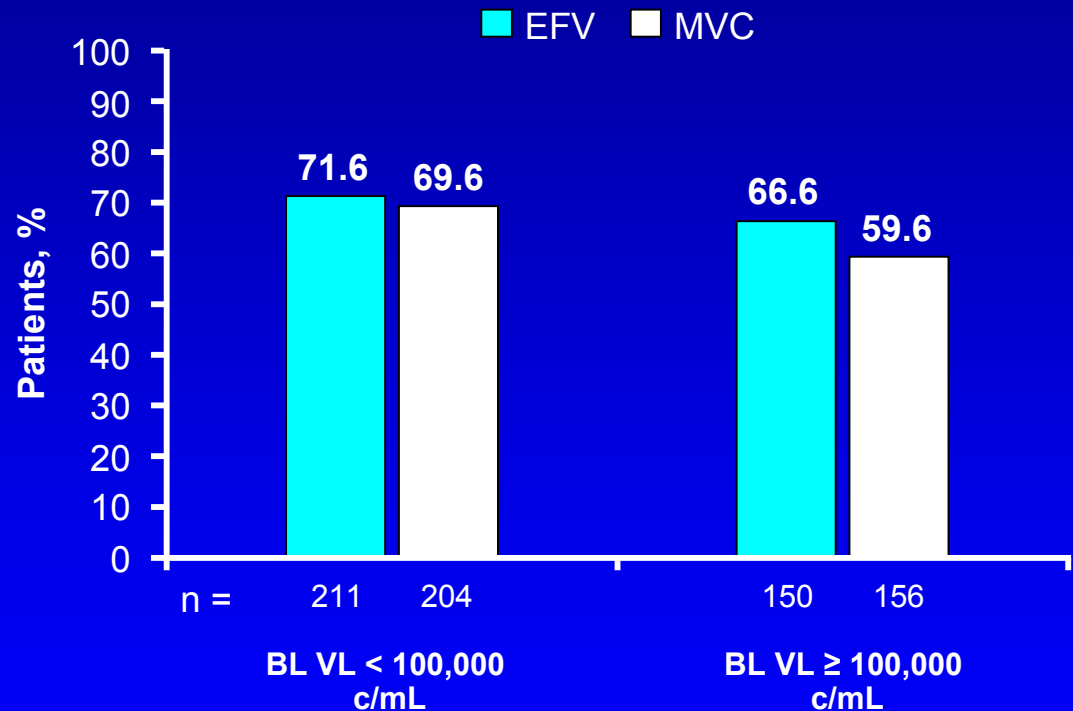
MERIT: Patients With VL < 400 and <50 c/mL by Week 48 (ITT)



- MVC noninferior to EFV for < 400 c/mL but not < 50 c/mL endpoint
- Greater CD4 count increase with MVC vs EFV (+170 vs +144)

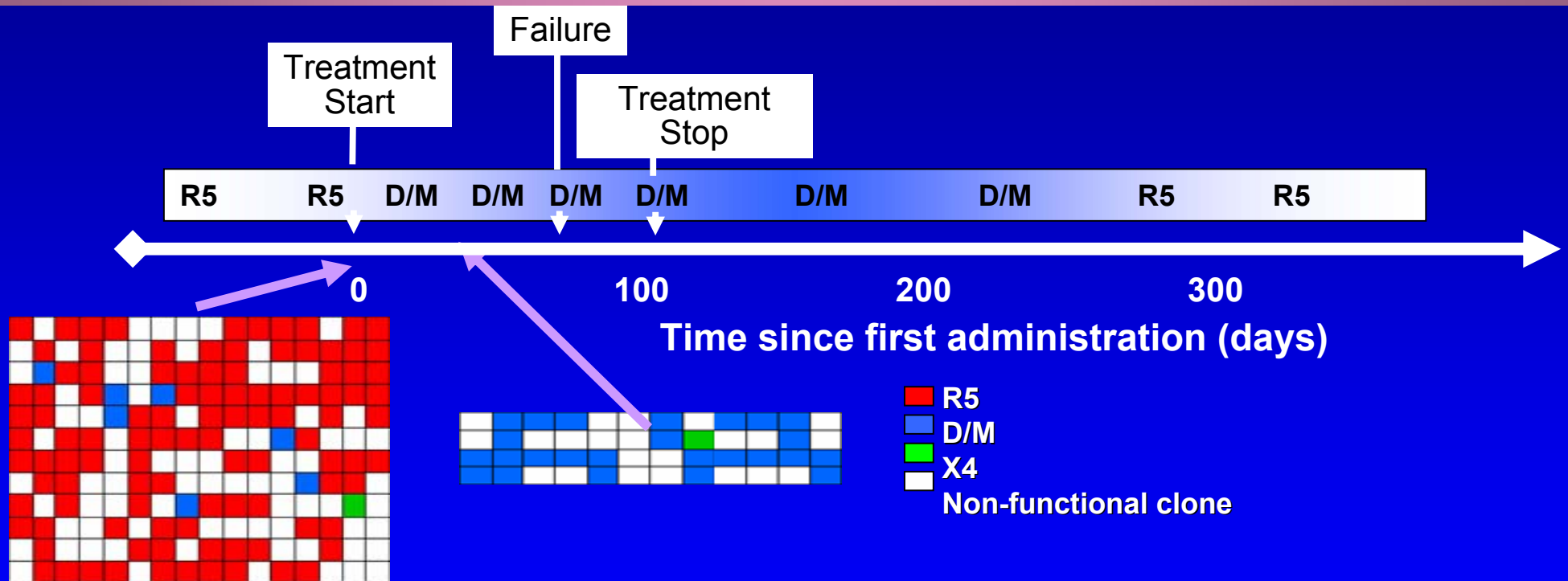
MERIT: Discontinuation, Safety and Patients With VL < 50 c/mL by BL VL

- MVC pts less likely to discontinue due to AEs and more likely to discontinue due to lack of efficacy vs EFV
 - Overall : 26.9 % vs 25.2 %
 - AE: 11.9% vs 13.6%
 - Efficacy: 11.9% vs 4.2%



- Overall rates of AEs and serious AEs similar in both arms
 - Fewer grade 3/4 AEs and fewer Category C AIDS-defining events in MVC arm

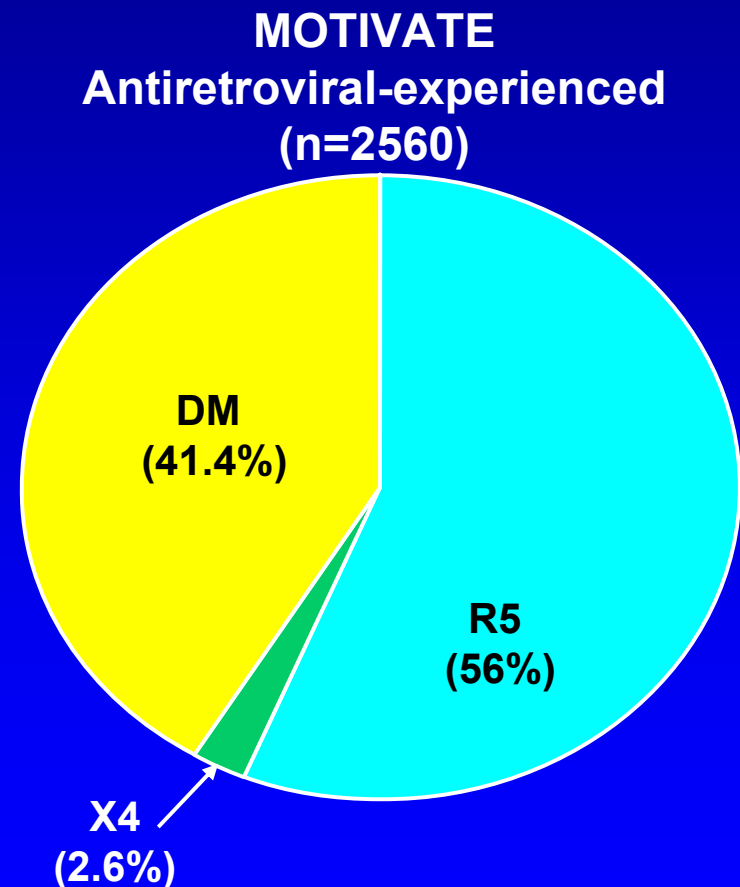
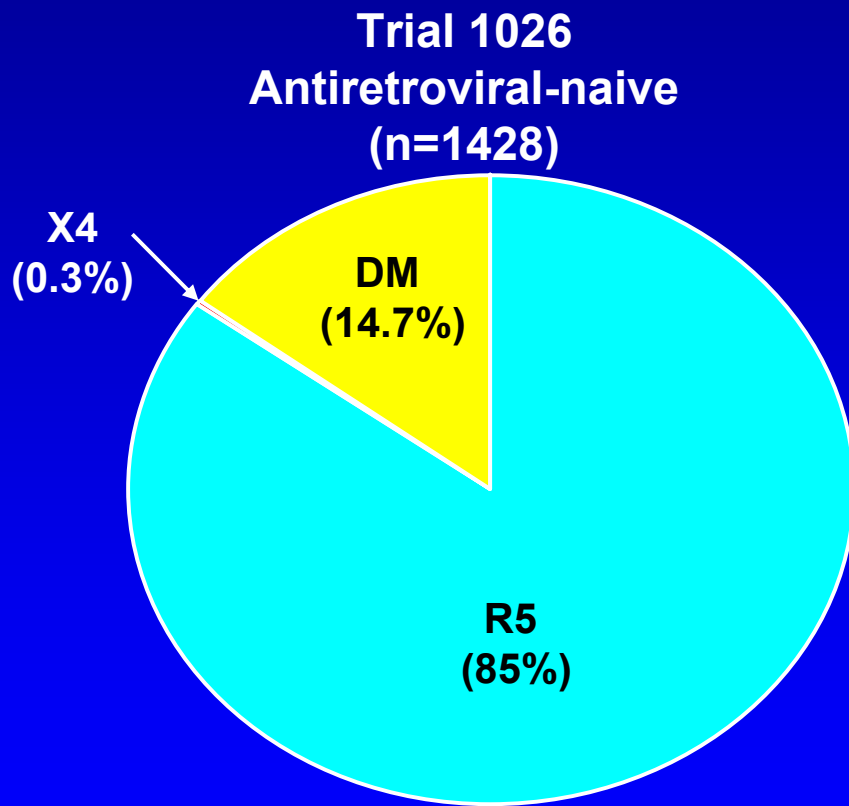
Emergence of D/M tropic virus on CCR5 antagonist therapy



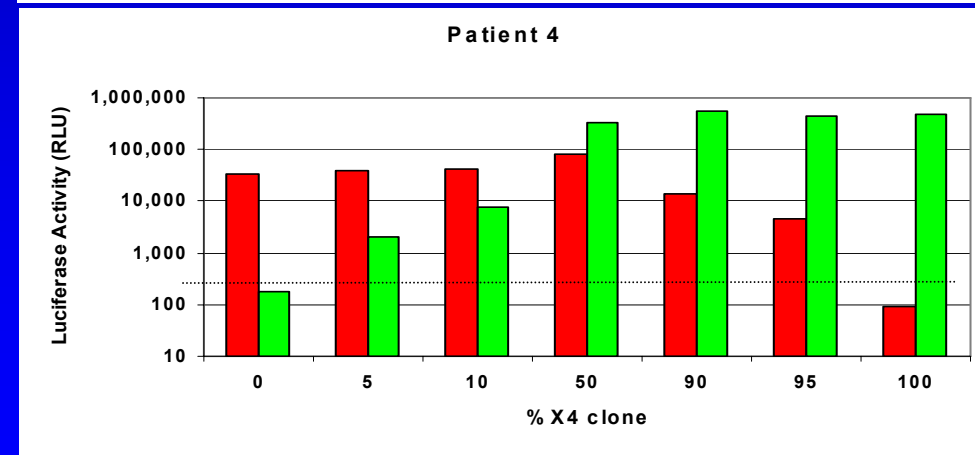
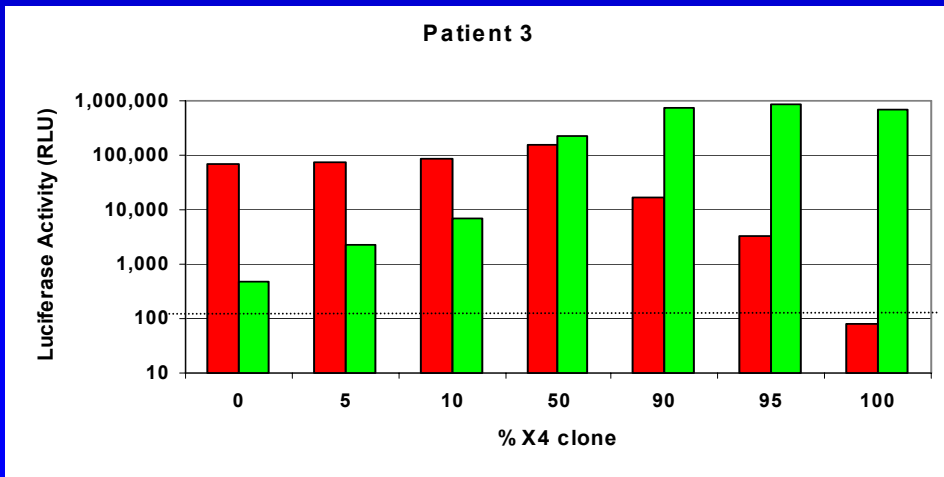
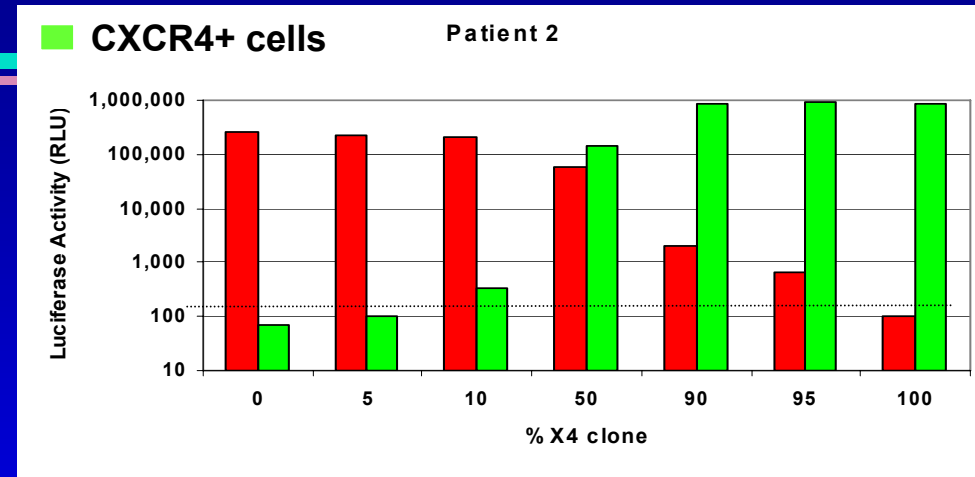
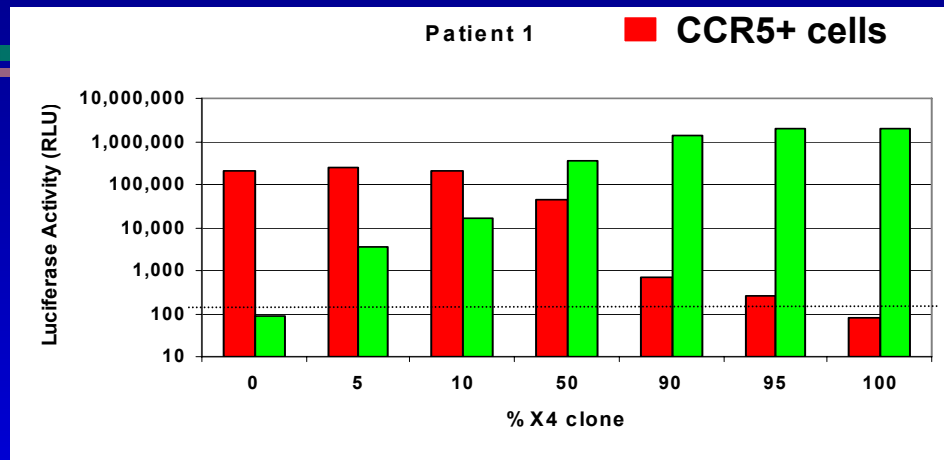
- Clonal and phylogenetic analyses suggest emergent D/M tropic virus on CCR5 antagonists predominantly from pre-existing population
- Clinical implications of emerging D/M virus remain to be fully defined

Tropism at Screening in MVC Trials

MOTIVATE 1, 2, and A4001026

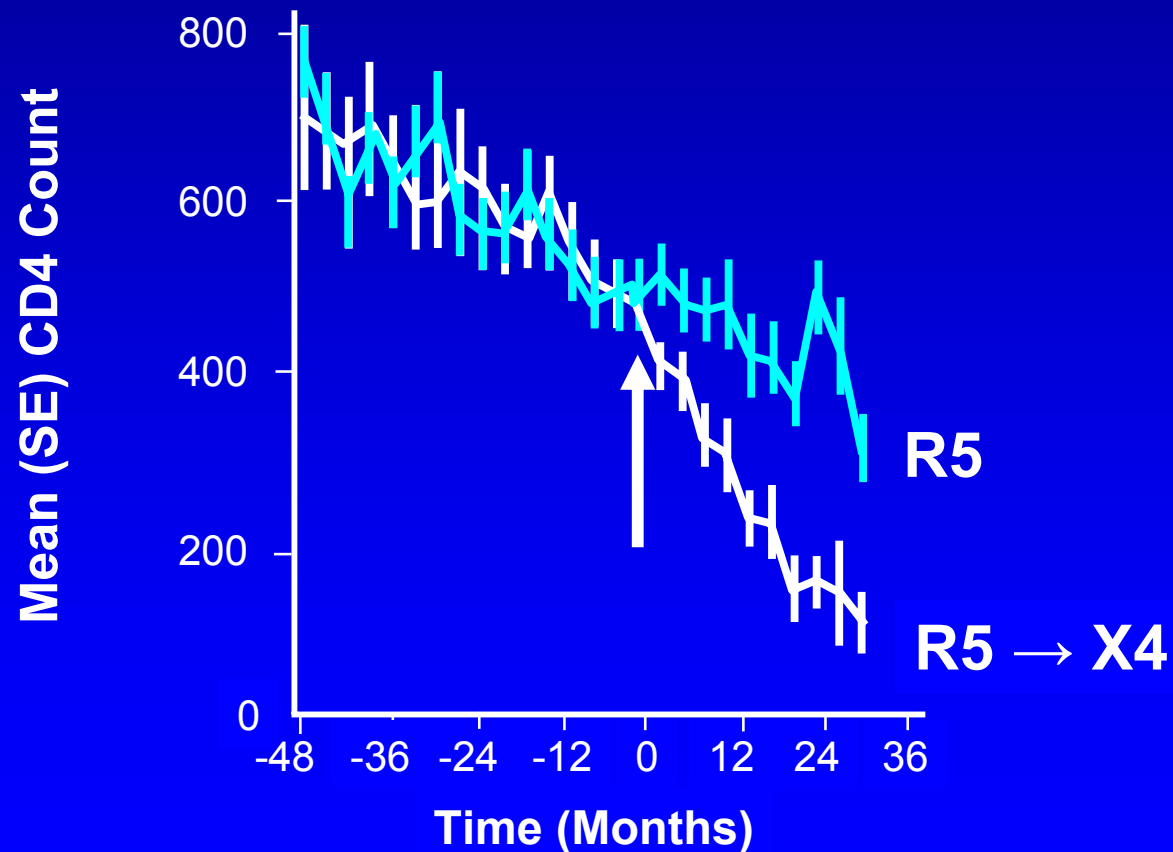


Phenotypic Tropism Assay: Minor Variant Sensitivity



100% sensitivity at 10% mixtures; 83% sensitivity at 5% mixtures

Effect of Emergence of SI (X4) Virus on CD4 Count



MOTIVATE 1 and 2: Change in CD4 Count at Time of Failure

Mean Change in CD4 in Patients with Treatment Failure			
	Placebo + OBR	MVC QD + OBR	MVC BID + OBR
All treatment failures	+14 (n = 97)	+49 (n = 68)	+71 (n = 77)
Patients with Tropism Results at Baseline and Failure			
R5 → R5	+15 (n = 80)	+61 (n = 18)	+138 (n = 17)
R5 → D/M or X4	+67 (n = 4)	+37 (n = 31)	+56 (n = 32)

- ~ 8% experienced shift in detected tropism between screening and baseline
- Among pts with treatment failure, shift in detected tropism more common among MVC vs PBO recipients
- Among MVC recipients with tropism results at failure, ~ 2/3 had D/M or X4 virus detected

The Role of Maraviroc

- Highly effective in experienced patients with R5 virus (MOTIVATE trials)
- Requires screening with tropism (*Trofile*) assay
- ~50% of experienced patients not candidates for MVC due to presence of D/M or X4 virus
- D/M or X4 virus can be missed if present at <10% (sensitivity 83% if present at 5%)
- Should not be used as a substitute for other agents (e.g. ENF) in a suppressive regimen

When to Use a Tropism Assay

- Before using MVC?
 - » Definitely! Avoid MVC in patients with D/M or X4-tropic virus
- Before starting any ART regimen?
 - » Only if money is no object. Could allow switch to MVC in virologically suppressed pts with drug toxicity
- At baseline in patients not starting therapy?
 - » No! Would not influence management and tropism could change before ART initiation

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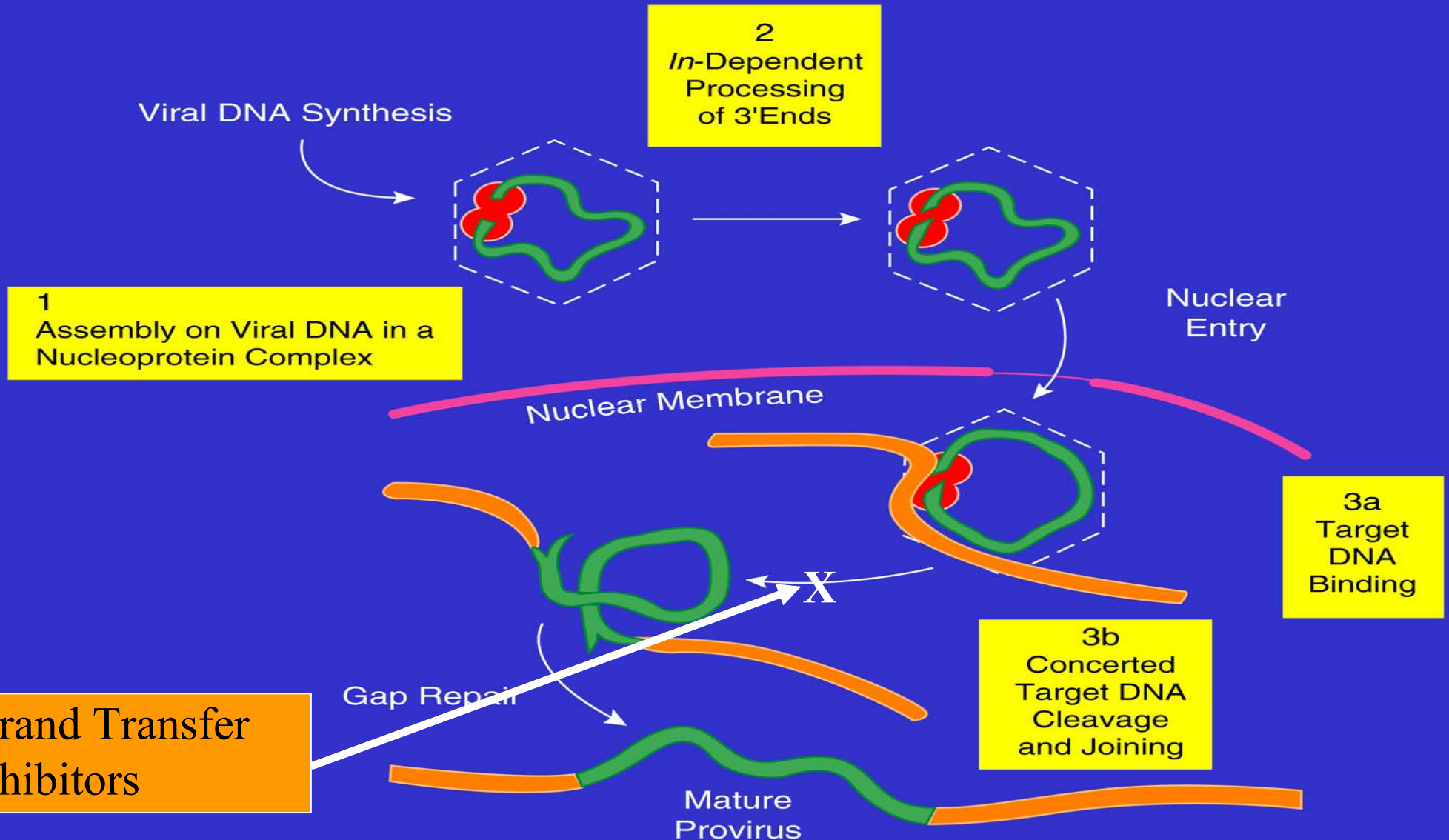
- CCR5 Inhibitors

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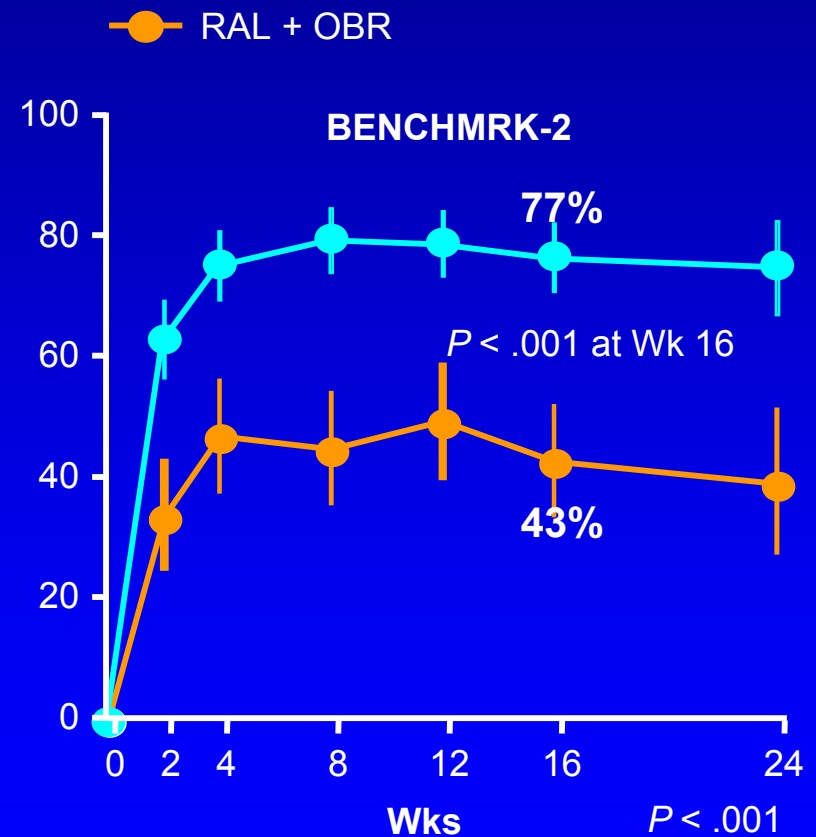
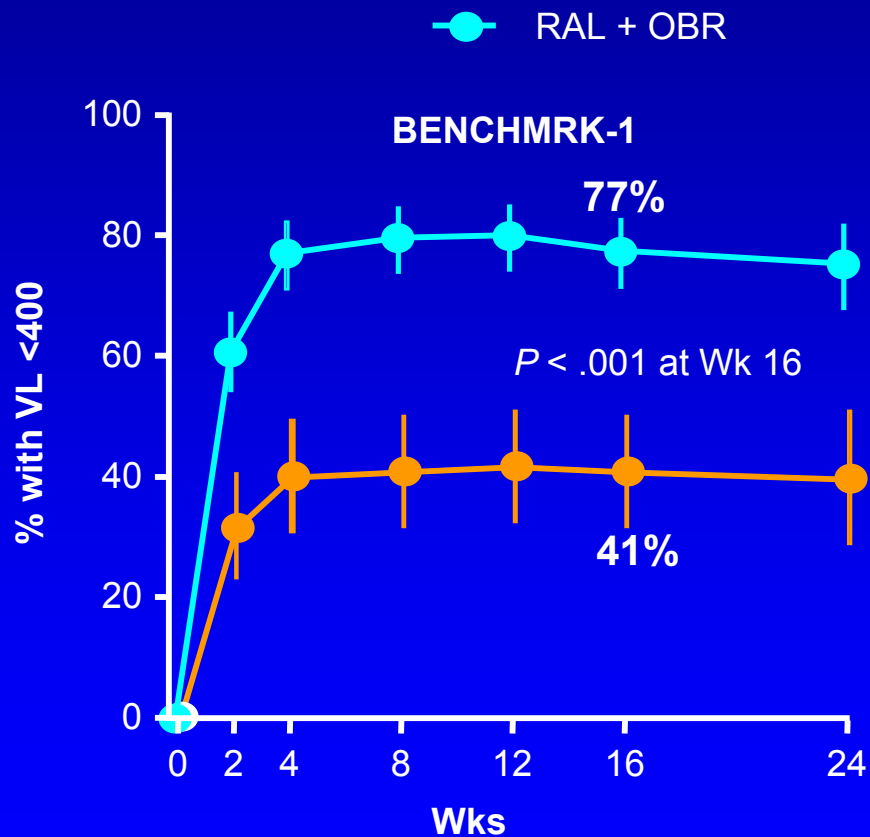
- Integrase Inhibitors

- » Raltegravir (RAL)

HIV Integrase Mechanism



BENCHMARK 1 & 2: VL <400 (ITT, NC = F)



BENCHMARK 1 & 2: VL < 400 at Wk 16 by Agents in OBR

■ RAL + OBR ■ Placebo + OBR

Overall Efficacy Data

Efficacy by Agents in OBR

Enfuvirtide

Darunavir

+

+

+

-

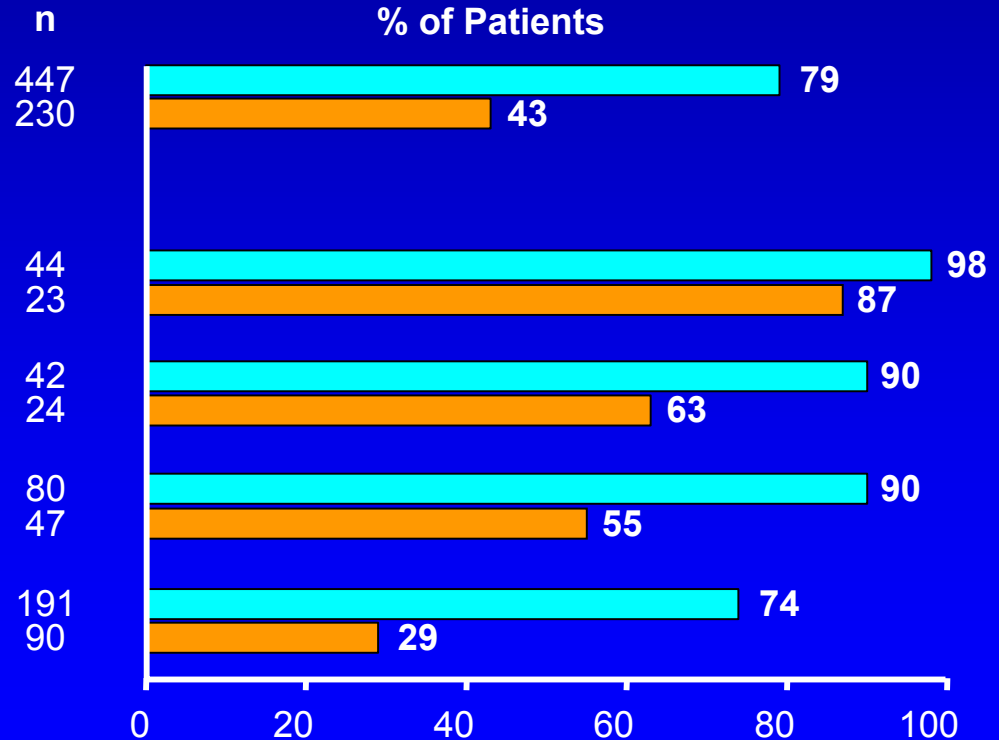
-

+

-

-

+ : First use in OBR
- : No use in OBR



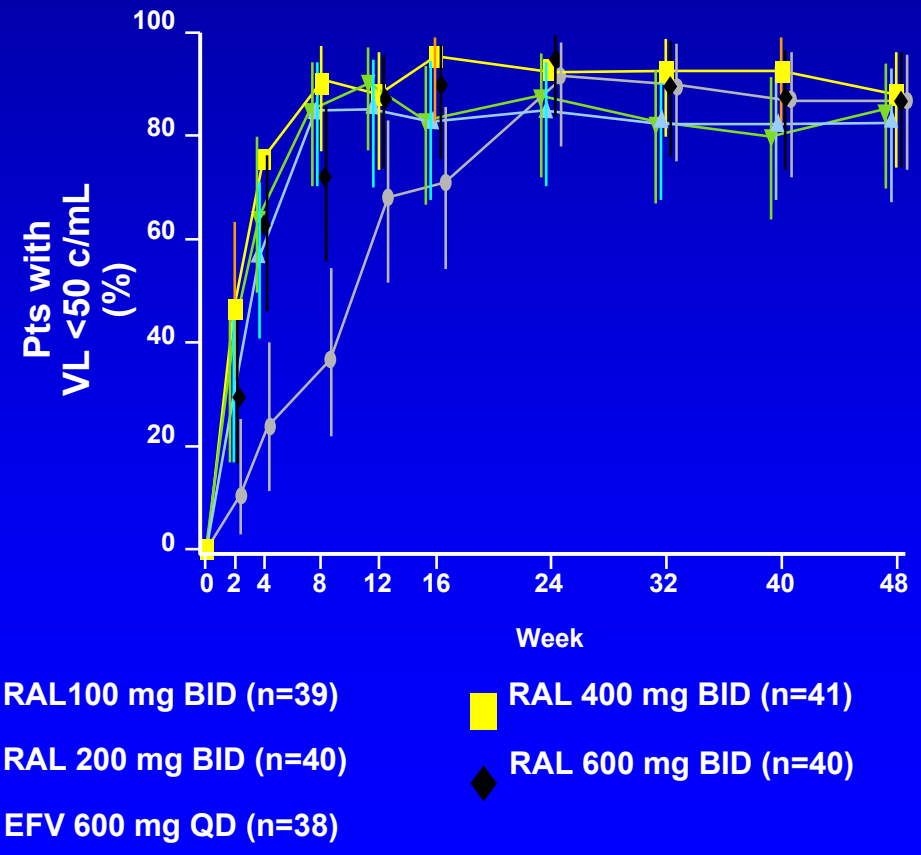
Raltegravir (RAL) vs. EFV in ART-naive patients

- Pts randomized to TDF/3TC + EFV or RAL at 100, 200, 400 or 600 mg BID
 - » Mean VL 4.6–4.8 log
 - » Mean CD4 271–338
- AEs similar
 - » More CNS AEs with EFV
 - » Lower TC, LCL, TG with RAL

Virologic failures

- RAL, n=5 (3%)
 - » 2 with integrase mutations; both N155H, 1 with multiple mutations
 - » 3TC resistance (n=4)
 - » K65R (n=1)
- EFV, n=1 (3%)
 - » K65R and G190E

VL <50 c/mL (95% CI) [NC=F]



Cross-Resistance Between Integrase Inhibitors

- *In vitro* patterns of resistance suggest cross-resistance between elvitegravir (EVG) and raltegravir (RAL)

Drug	H51Y	E138K	S142G	Q148R	E138K S147G Q148R	N155H
EVG	4.0	0.7	8.0	118	175	38
RAL	0.9	0.9	1.0	20	34	23

■ FC ≤2.5; ■ FC >2.5; ■ FC >10

- Patients viremic on EVG trial crossed over to RAL
 - » One week mono-substitution, then optimized regimen
- Results: 2 pts enrolled; study stopped due to <0.3 log decline at Day 7 after switch in both
 - » Major BL GT mutations: (1) N155H; (2) H51Y / E138K / S147G / Q148R

The Role of Integrase Inhibitors

- Can be used at any stage of disease/therapy
- Potential uses:
 - » As alternative to PI therapy in patients failing initial NNRTI regimen
 - » To replace other agents in patients experiencing toxicity (e.g., ENF, thymidine analog NRTIs, PIs)
 - » As alternative for initial therapy agents

Whither Enfuvirtide?

- Most patients with VL < 50 on ENF will substitute a new agent:
 - » RAL > ETR > MVC
- Patients with R5-tropic virus and/or virus susceptible to DRV, TPV, or ETR *may* not need ENF
- ENF has improved outcome in TORO,^[1] RESIST,^[2] POWER,^[3] MOTIVATE,^[4,5] BENCHMRK^[6,7]
- ENF will still be necessary in highly-experienced pts (D/M-tropic virus, cross-resistance to DRV, TPV, ETR)

1. Trottier B, et al. J Acquir Immune Defic Syndr. 2005;40:413-421. 2. Farthing C, et al. ICAAC 2006. Abstract H-1385. 3. Clotet B, et al. Lancet. 2007;369:1169-1178. 4. Nelson M, et al. CROI 2007. Abstract 104aLB. 5. Lalezari J, et al. CROI 2007. Abstract 104bLB. 6. Cooper D, et al. CROI 2007. Abstract 105aLB. 7. Steigbigel R, et al. CROI 2007. Abstract 105bLB.

Other Drugs in the Pipeline - 1

- NRTIs

- » Apricitabine: Active against virus with M184V, TAMs
- » Fosavudine: Active against virus with multiple TAMs

- NNRTIs

- » Rilpivirine: Once-daily dosing, may be better tolerated than EFV, requires gastric acid for absorption
- » UK-453,061: Active against NNRTI-resistant virus

- Integrase Inhibitors

- » Elvitegravir: Once-daily dosing with RTV boosting ,cross-resistance with RAL

Other Drugs in the Pipeline - 2

- CCR5 Inhibitors
 - » Vicriviroc: Once-daily dosing with RTV boosting
 - » INCB 9471: Once-daily dosing
 - » PRO 140: Monoclonal antibody given by periodic IV infusion
- Maturation Inhibitor
 - » Bevirimat: In clinical trials

Treating the Highly Experienced Patient

Step 1: How Many Active Drugs are Available?

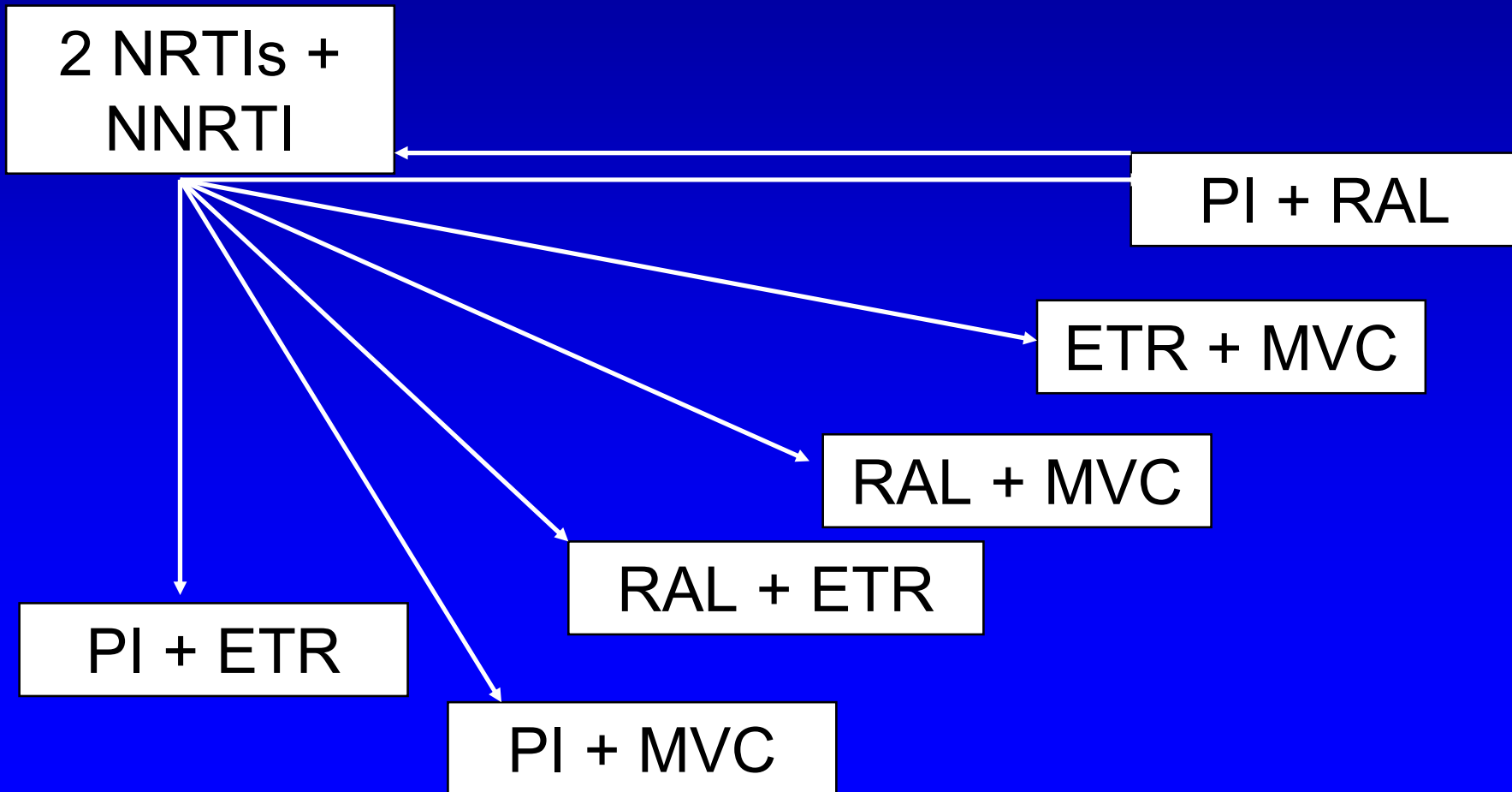
- Raltegravir: *“The free space on the BINGO card”*
- Assess tropism: Consider MVC if R5 tropic
- Assess PI susceptibility
 - » Use phenotype if possible
- Assess ETR susceptibility
 - » May require review of old genotypes
- ENF
 - » ENF-naïve or -experienced
 - » Patient’s willingness to inject

Treating the Highly Experienced Patient

Step 2: How Many Drugs do you Need?

- Current salvage studies suggest that 2 potent, *active* drugs may be enough
- A 3rd active drug may provide some additional benefit
- Considerations:
 - » Partial susceptibility (PIs, ETR)
 - » Low-level D/M or X4 virus (MVC)
- Do you still need NRTIs?
 - » ACTG 5241

New Sequencing Options for First Failure



The Future of Drug Resistance

- TAMs: Iatrogenic, preventable mutations caused by continued therapy on failing TA-based regimens
- PI mutations: Preventable result of use of unboosted PIs and/or continued therapy on failing PI-based regimens
- M184V, NNRTI mutations: Here to stay
- K65R, L74V: Can occur early, but remain uncommon
- ENF mutations: Common with early ENF failure
- CCR5 inhibitor mutations: Selection of pre-existing D/M or X4 virus may be more common cause of failure
- Integrase mutations: Expect them, with potential for within class cross-resistance

The Goal of Therapy

The goal of therapy is virologic suppression to <50 c/mL in *all* patients.

-DHHS & IAS-USA Guidelines

1. US Department of Health and Human Services. Available at: <http://aidsinfo.nih.gov/guidelines>. Accessed May 7, 2007.
2. Hammer S, et al. JAMA. 2006;296:827-843_.