The New Agents: Management of Experienced Patients and Resistance

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T.D.

- 45 year old man with HIV infection diagnosed in 2000
- On multiple non-suppressive ART regimens, including NRTIs, NNRTIs, PIs, with CD4 counts gradually dropping from high 400's to low 200's, VL 20K-100K
- His previous doctor said "Don't worry about numbers, as long as you feel good!"
- Now on ATV/r + EFV + TDF/FTC

HIV-1 Subtype:

	DRUG			PHENOSENSE™ SUSCEPTIBILITY		Evidence of Susceptibility		Net Assessment	
	Generic Name	Brand Name	Cutoffs (Lower - Upper)	Fold Change	Increasing ← Drug Susceptibility → Decreasing (.1 / 1 / 10 / 100)	Pheno Sense	Gene Seq		
NRTI	**Abacavir**	Ziagen	***(4.5 - 6.5)***	**6.66**		**N**	**N**	Resistant	
	Didanosine	Videx	***(1.3 - 2.2)***	**2.12**		**P**	**Y**	Partially Sensitive	19
	Emtricitabine	Emtriva	*(3.5)*	**>MAX**		**N**	**N**	Resistant	
	Lamivudine	Epivir	***(3.5)***	**>MAX**		**N**	**N**	Resistant	
	Stavudine	Zerit	***(1.7)***	**1.81**		**N**	**N**	Resistant	3
	Zidovudine	Retrovir	*(1.9)*	**20**		**N**	**N**	Resistant	3
	Tenofovir	Viread	***(1.4 - 4)***	**1.81**		**P**	**Y**	Partially Sensitive	3,19
	NRTI Mutations		D67N, K70R, M184V, T215F, K219E						
NNRTI	**Delavirdine**	Rescriptor	*(6.2)*	**36**		**N**	**N**	Resistant	
	Efavirenz	Sustiva	*(3)*	**>MAX**		**N**	**N**	Resistant	
	Nevirapine	Viramune	*(4.5)*	**>MAX**		**N**	**N**	Resistant	
	NNRTI Mutations		K101H/Q, Y188L						
PI	**Atazanavir**	Reyataz	***(2.2)***	**150**		**N**	**N**	Resistant	
		Reyataz / r‡	***(5.2)***	**150**		**N**	**N**	Resistant	
	Darunavir	Prezista / r §	***(10 - 90)***	**13**		**P**	**Y**	Partially Sensitive	19
	Fosamprenavir	Lexiva	*(2)*	**44**		**N**	**N**	Resistant	
		Lexiva / r‡	***(4 - 11)***	**44**		**N**	**N**	Resistant	
	Indinavir	Crixivan	*(2.1)*	**18**		**N**	**N**	Resistant	
		Crixivan / r‡	***(10)***	**18**		**N**	**N**	Resistant	
	Lopinavir	Kaletra	***(9 - 55)***	**46**		**P**	**N**	Partially Sensitive	
	Nelfinavir	Viracept	*(3.6)*	**104**		**N**	**N**	Resistant	
	Ritonavir	Norvir	*(2.5)*	**>MAX**		**N**	**N**	Resistant	
	Saquinavir	Invirase	*(1.7)*	**33**		**N**	**N**	Resistant	
		Invirase / r‡	***(2.3 - 12)***	**33**		**N**	**N**	Resistant	
	Tipranavir	Aptivus / r‡	***(2 - 8)***	**7.33**		**P**	**N**	Partially Sensitive	

trofile™
CO-RECEPTOR TROPISM ASSAY

biosciences

Moore Clinic/Johns Hopkins School of Med
600 Wolfe Street Carnegie 346
Baltimore, MD 21287
USA
Client: 02444 Project: 00073
Phone: (410)955-0708 Fax: (410)955-7733

Patient ID	Gender	Monogram Accession #
8-401-10-50	M	07-136827
Date Reported	Mode	Report Status
09/14/2007 14:07	F,M,W	FINAL
	Reference Lab ID	

D 21205 USA

Tropotype Result

R5 D/M X4

Virus uses CCR5 co-receptors to enter the CD4+ cell.

R5

Activity of CCR5 antagonist anticipated? ■ YES ☐ NO

ABOUT TROPISM

WHAT IS TROFILE™?
Trofile is a CLIA-validated*, cell-based approach to determine an individual's HIV co-receptor tropism (or "tropotype™"). Co-receptor tropism is defined as an interaction of a virus with a specific co-receptor on the target cell. To gain entry to the CD4+ cell (host), HIV must bind to the cell surface CD4 receptor and to one of two chemokine co-receptors (CCR5 or CXCR4) also present on the cell surface.

TROFILE VIRAL CLASSIFICATION
CCR5 (R5) Virus = Virus uses CCR5 chemokine co-receptor to enter the CD4+ cell.
DUAL/MIXED (D/M) Virus = Dual-tropic viruses can use either the CXCR4 or CCR5 co-receptors to enter the CD4+ cell. Mixed-tropic is a mixed population of both CCR5 and CXCR4 tropic viruses.
CXCR4 (X4) Virus = Virus uses CXCR4 chemokine co-receptor to enter the CD4+ cell.
Non-reportable = Your patient's tropotype could not be determined by the Trofile assay. Common causes of failure of the assay are viral load <1,000 copies/mL, reduced viral fitness, or compromised sample collection/handling.

CO-RECEPTOR ANTAGONISTS
A new class of drugs – co-receptor antagonists – provides a novel mechanism to inhibit the HIV viral replication cycle. These drugs work by binding to a specific chemokine receptor (CCR5 or CXCR4) and block the virus' ability to bind these co-receptors and initiate its entry into the host cell. Trofile can help determine whether a CCR5 antagonist or a CXCR4 antagonist may be an appropriate drug for your patient. Several clinical trials on CCR5 antagonists have demonstrated the positive and negative predictive value of Trofile in clinical settings.

* The Trofile assay meets the United States standards for performance characteristics and all other quality control and assurance requirements established by the Clinical Laboratory Improvement Amendments (CLIA). Trofile is a proprietary, recombinant virus, single replication cycle assay that uses the complete gp160 coding regions of HIV-1 to evaluate tropism.

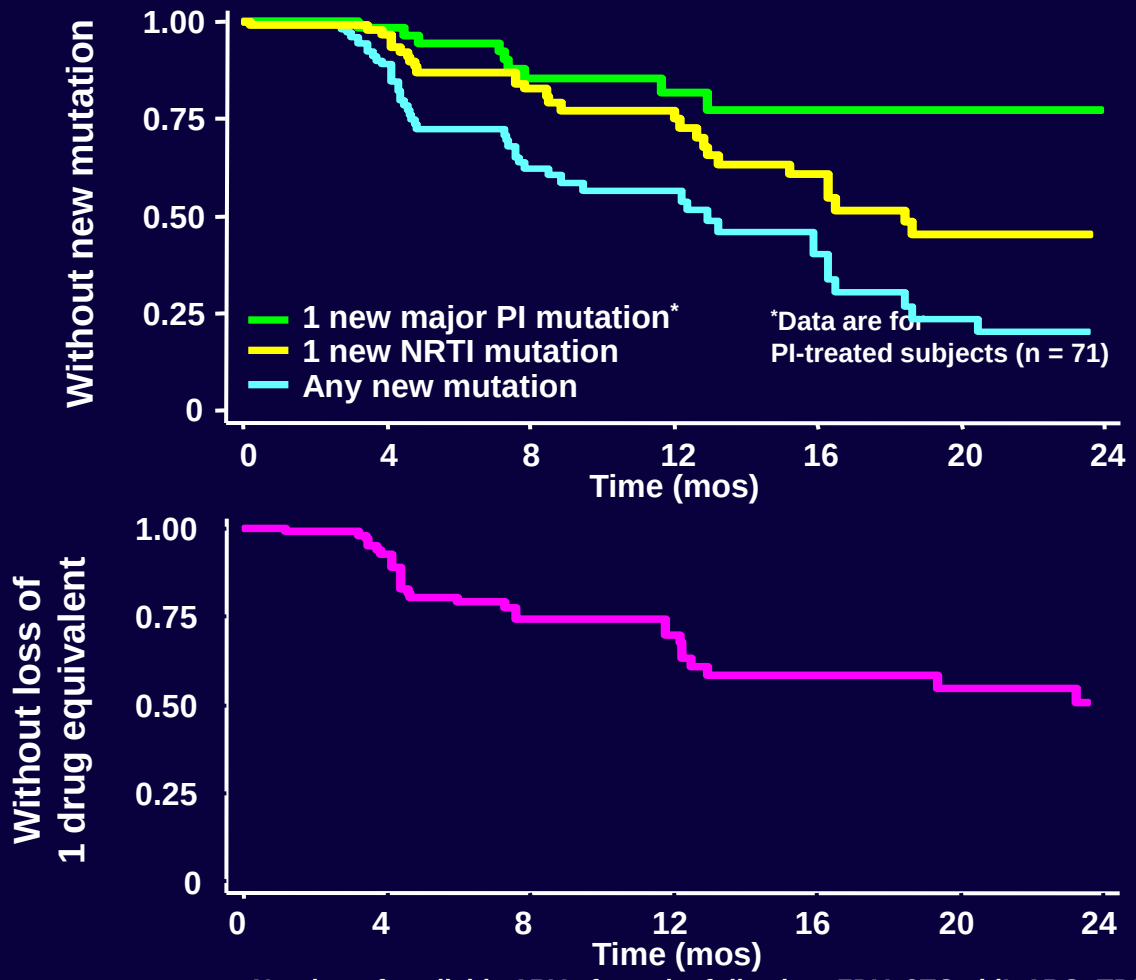
9/14/07

When to Modify Therapy

- Studies to date show better responses with earlier switches, as well as viral evolution at low-level viremia

The Rate of Losing Future Treatment Options

- SCOPE cohort: Treatment-experienced patients (n=106)
  - Stable ART for ≥120 days
  - VL > 1000 c/mL
  - ≥ 1 resistance mutation
  - Resistance testing every 4 mos until ART modification
- New mutations at 1 year
  - Any: 44% (95% CI 33–56)
  - NRTI: 23% (95% CI 15–34)
  - PI: 18% (95% CI 9–34)



Number of available ARVs from the following: ZDV, 3TC, ddI, ABC, TDF, EFV, IDV, NFV, SQV, RTV, APV, LPV

Hatano *et al*. *13th CROI* 2006; Poster 615

When to Modify Therapy

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- The risk of emergence of new mutations is highest in patients with little resistance

When to Modify Therapy

- Studies to date show better responses with earlier switches, as well as viral evolution at low-level viremia
- The risk of emergence of new mutations is highest in patients with little resistance
- The consequences of continued failure depend on the drugs being used:
  - Rapid, high-level resistance: 3TC, FTC, NNRTIs
  - Eventual, intermediate-level resistance: TDF, ABC
  - Cumulative resistance over time: AZT, d4T, unboosted PIs
  - Minimal resistance: boosted PIs (in PI-naïve pts)

Antiretroviral Agents Approved in the U.S. (April 2009)

NRTIs	NNRTIs	PIs
zidovudine (AZT) – *Retrovir* & generic	nevirapine (NVP) – *Viramune*	saquinavir (SQV) – *Invirase*
didanosine (ddI) – *Videx*, *Videx EC* & generic	delavirdine (DLV) – *Rescriptor*	indinavir (IDV) – *Crixivan*
stavudine (d4T) – *Zerit*	efavirenz (EFV) - *Sustiva*	ritonavir (RTV) – *Norvir*
lamivudine (3TC) – *Epivir*	etravirine (ETR) - *Intelence*	
abacavir (ABC) – *Ziagen*	**Nucleotide RTIs**	nelfinavir (NFV) – *Viracept*
emtricitabine (FTC) - *Emtriva*	tenofovir DF (TDF) -*Viread*	lopinavir/RTV (LPV/r) - *Kaletra*
CCR5 Inhibitors	**Fusion Inhibitors**	atazanavir (ATV) - *Reyataz*
maraviroc (MVC) - *Selzentry*	enfuvirtide (ENF, T20) - *Fuzeon*	fosamprenavir (FPV) - *Lexiva*
	Integrase Inhibitors	tipranavir (TPV) - *Aptivus*
	raltegravir (RAL) - *Isentress*	darunavir (DRV) - *Prezista*

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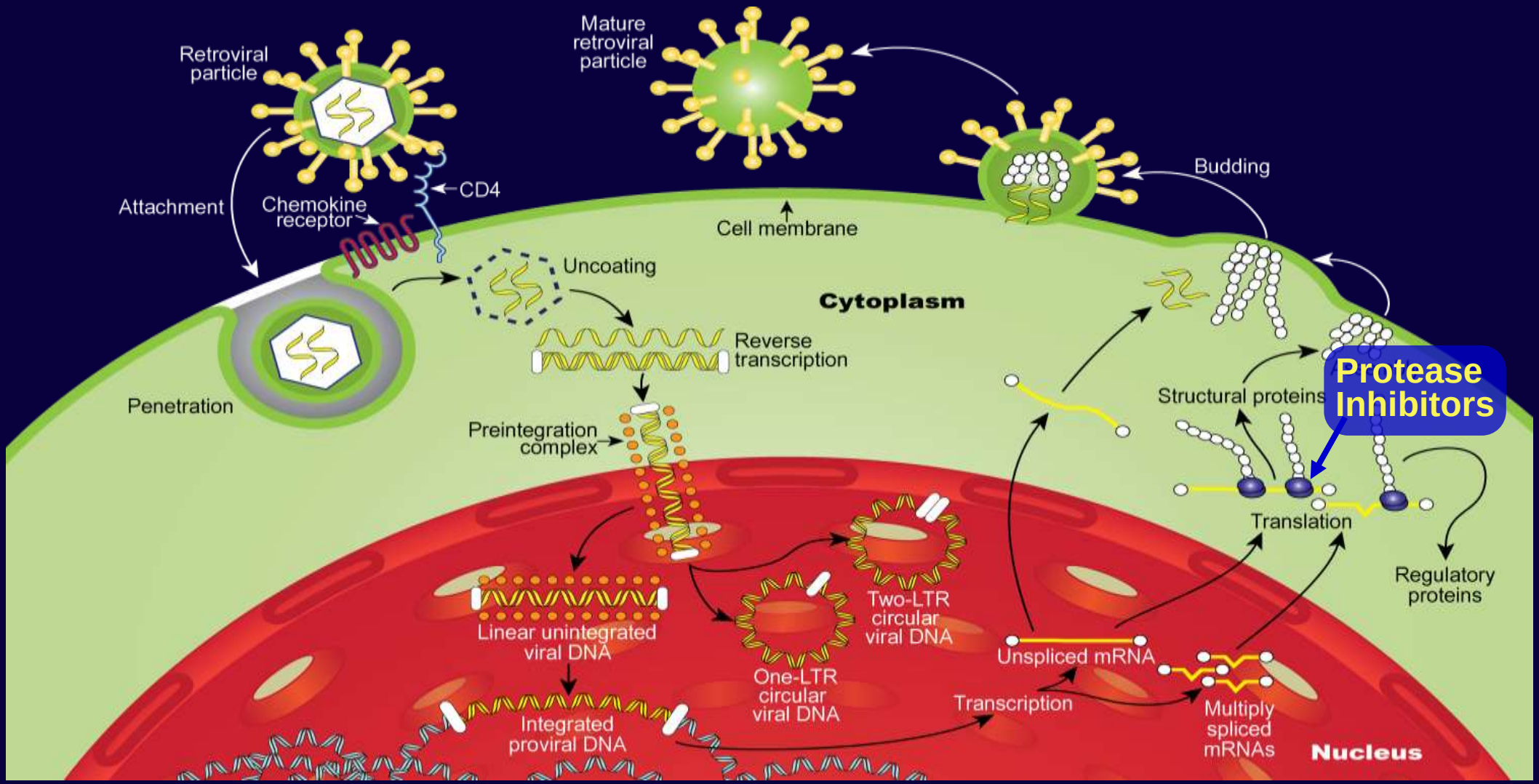
The HIV-1 Replication Cycle



RT = reverse transcriptase; LTR = long terminal repeat.

Resistance Patterns after PI Failure

Unboosted PIs

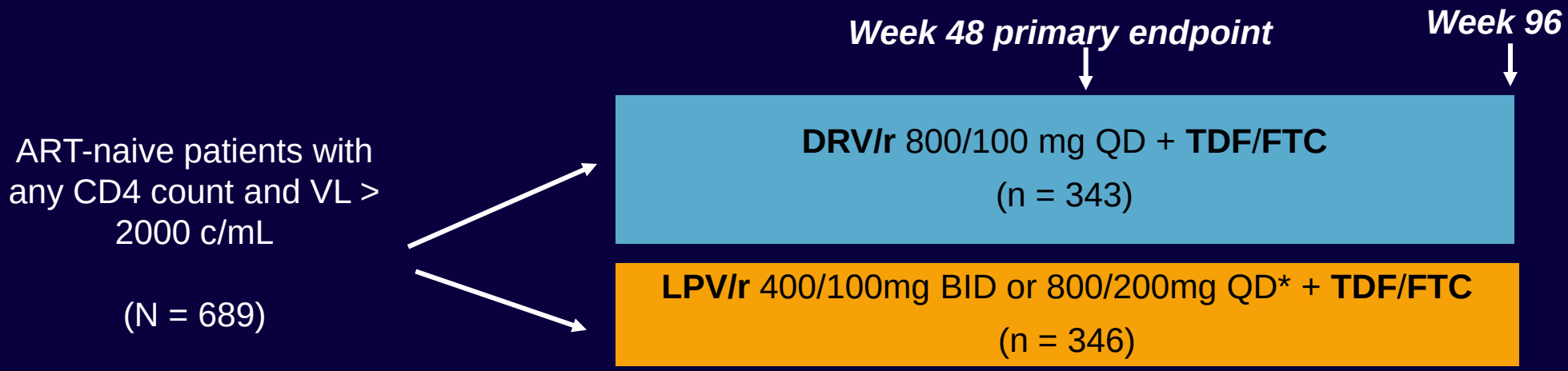
- NFV:
  - 30N: no cross-resistance
  - 90M: cross-resistance
- SQV:
  - 48V: no cross-resistance
  - 90M: cross resistance
- ATV:
  - 50L: no cross-resistance
- IDV:
  - Various mutations causing cross-resistance
- FPV
  - I54L/M, V32I + I47V: Variable cross-resistance

RTV-Boosted PIs

- No PI resistance after failure of:
  - LPV/r
  - FPV/r
  - SQV/r
  - ATV/r
  - DRV/r

ARTEMIS: DRV/r vs LPV/r in Treatment-Naive Patients

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

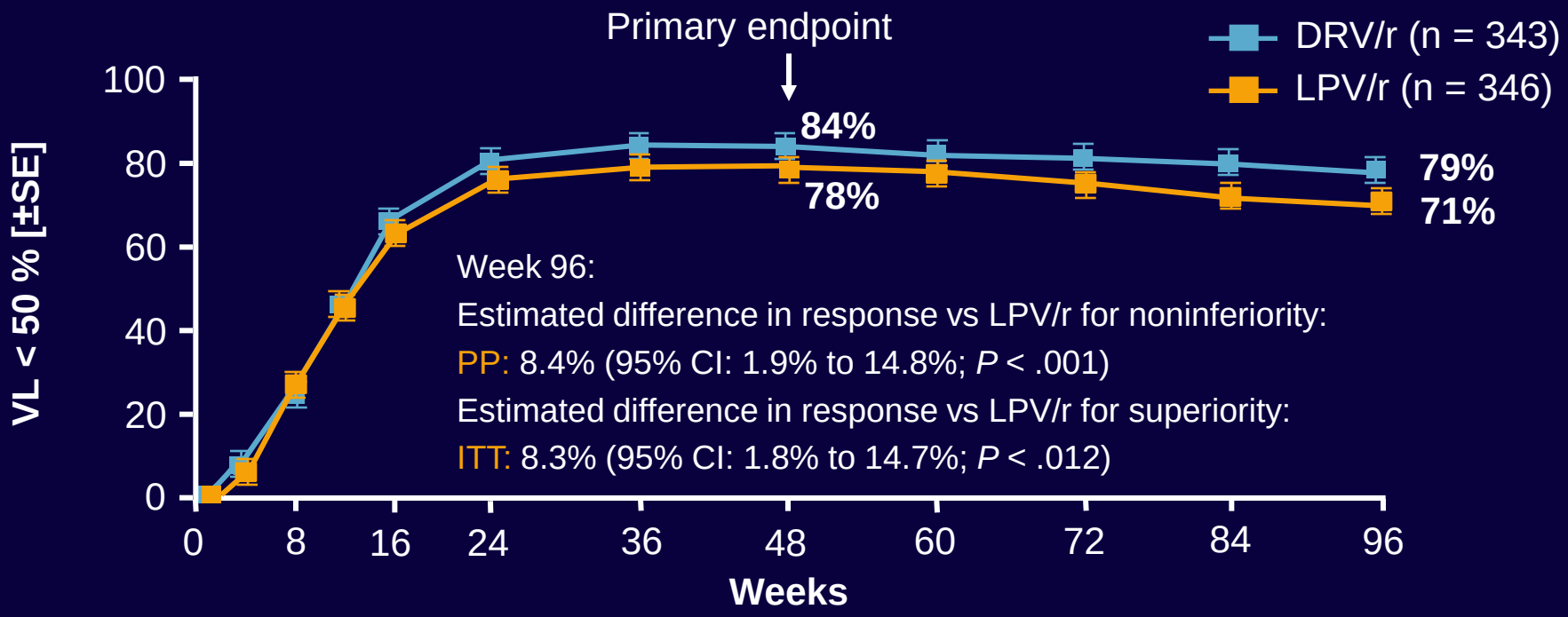


- Baseline disease characteristics in DRV/r vs LPV/r arms
  - Median VL: 70,800 c/mL vs 62,100 c/mL
  - Median CD4 count: 228 vs 218
- 83% of patients switched from capsule to tablet formulation of LPV/r during study; switch made according to local regulatory approval and drug availability

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

Mills A, et al. ICAAC/IDSA 2008. Abstract 1250c.

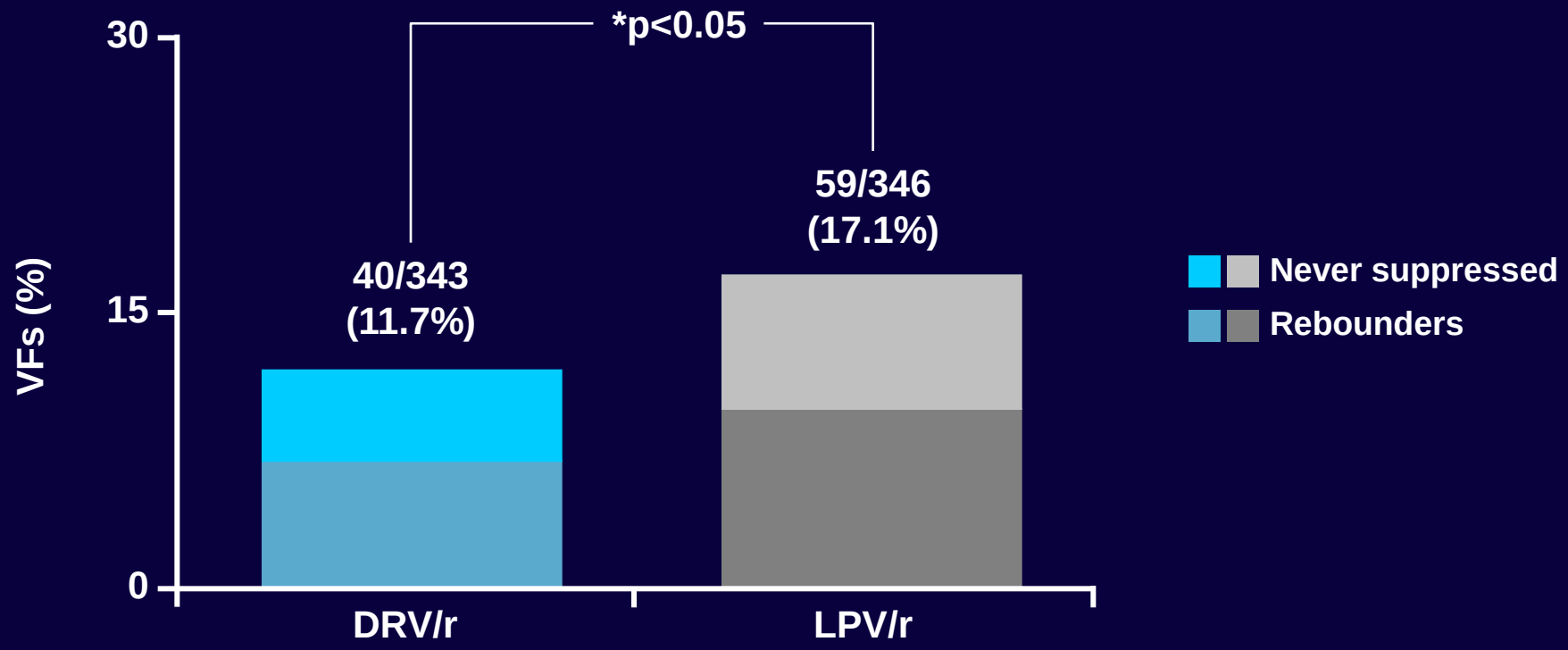
ARTEMIS: Week 96 Response to DRV/r vs LPV/r in Naive Patients



- Superiority at Week 96 also observed when DRV/r (n = 343) compared with subset of patients treated with twice-daily LPV/r only (n = 258)
  - 79% vs 72% (*P* = .038)

Mills A, et al. ICAAC/IDSA 2008. Abstract 1250c.

Virologic Failure Less Frequent with DRV/r than LPV/r



*Pearson chi-square test

ARTEMIS 96 week analyses

ARTEMIS: Resistance with Virologic Failure

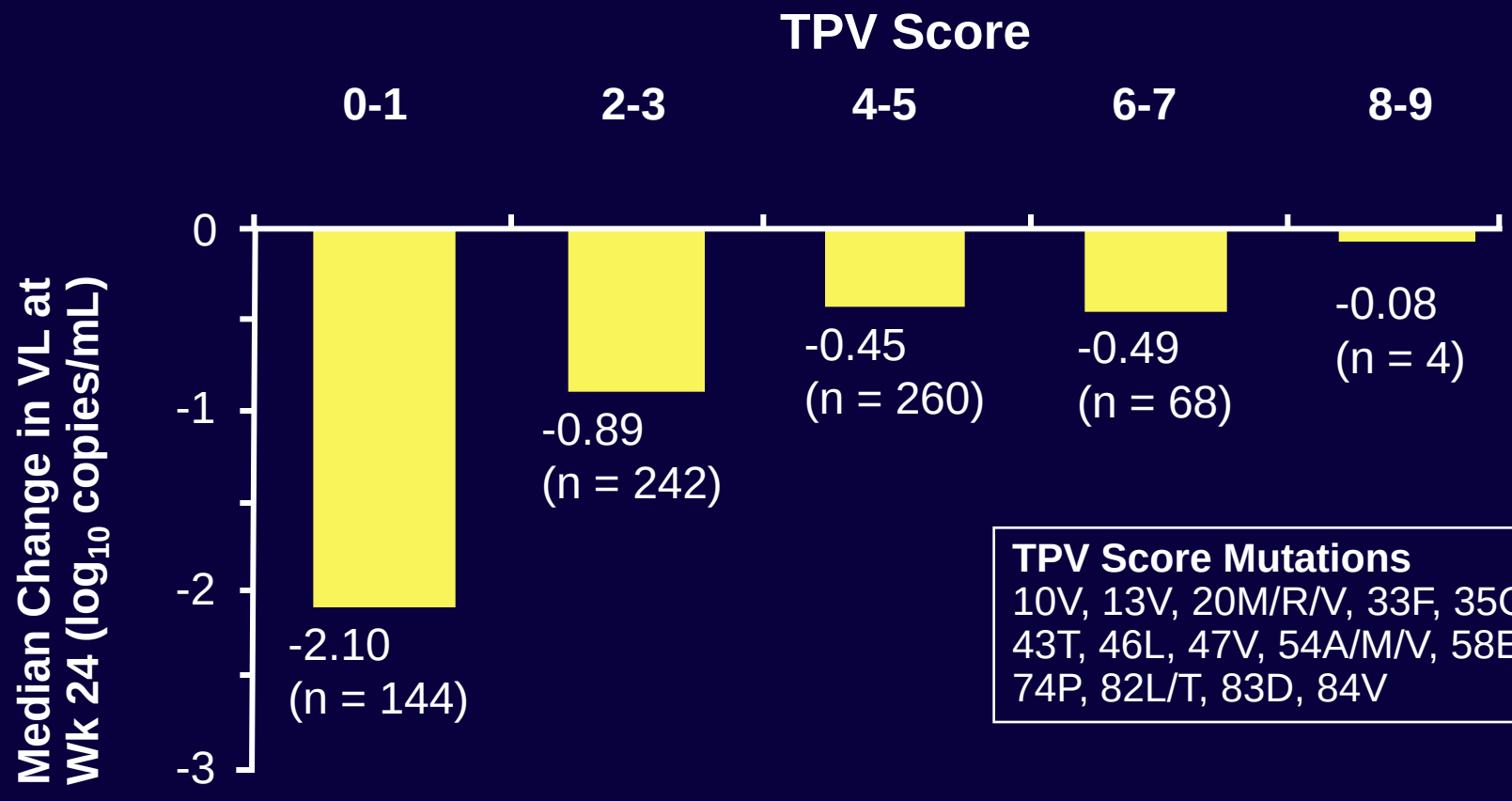
Number of patients, n	DRV/r (n=343)	LPV/r (n=346)
VFs	40	59
Paired genotypes	31	46
Developing major (IAS-USA) PI RAMs[1]	0	0
Developing minor (IAS-USA) PI RAMs[1]	4	7
Developing major non-polymorphic PI RAMs[2]	0	0
Developing minor non-polymorphic PI RAMs[2]	1	2
Developing (IAS-USA) NRTI RAMs[1]	2	5
Paired phenotypes	30	43
Loss of susceptibility to any PI*	0	0
Loss of susceptibility to FTC	1	4
Loss of susceptibility to TDF	0	0

*PREZISTA, LPV, APV, ATV, IDV, NFV, SQV and TPV

1. Johnson VA, et al. Top HIV Med 2007;15:119–25
2. Molina JM, et al. ICAAC/IDSA 2008. Abstract H-1250d

Lathouwers E, et al. 7th EHDRW 2009. Poster 58

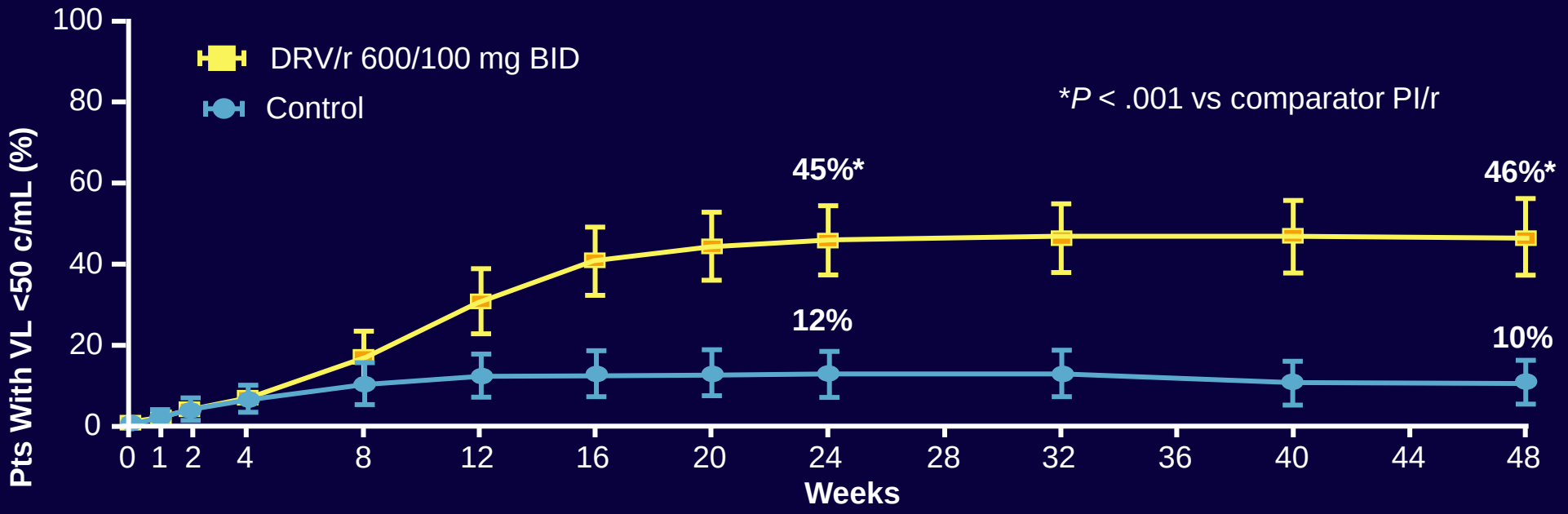
Relationship of TPV Score to TPV Phenotype Results and Response



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

Valdez H, et al. Antivir Ther. 2005;10:S29

POWER 1 and 2: VL <50 c/mL at Week 48 (ITT-TLOVR)

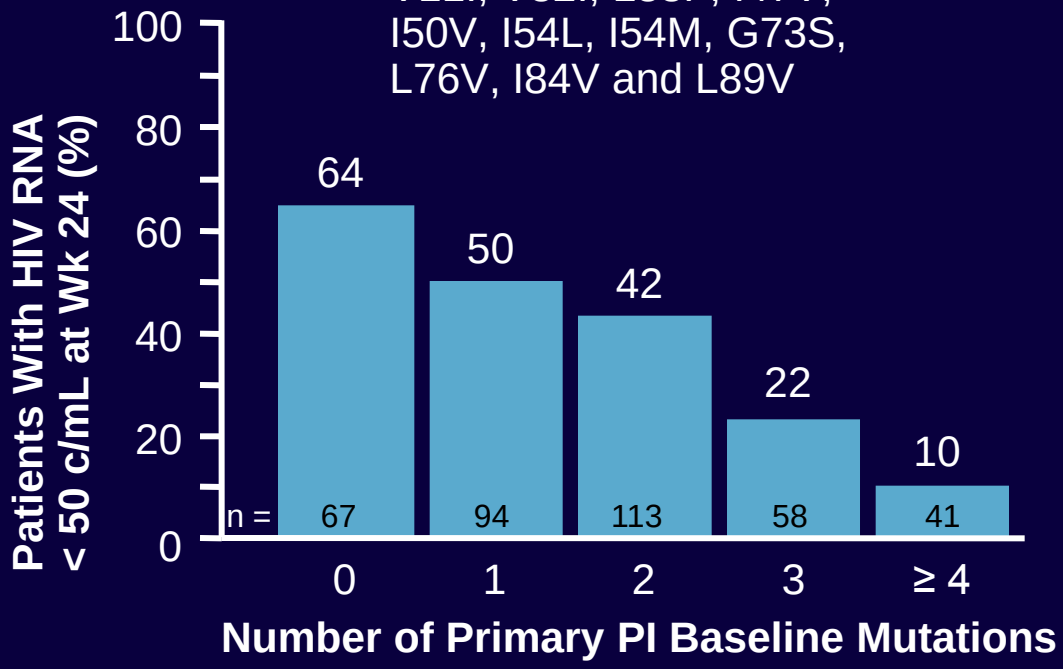


Not all patients had reached Week 48 at the time of analysis; patients who had not reached Week 48 were censored at their last available visit

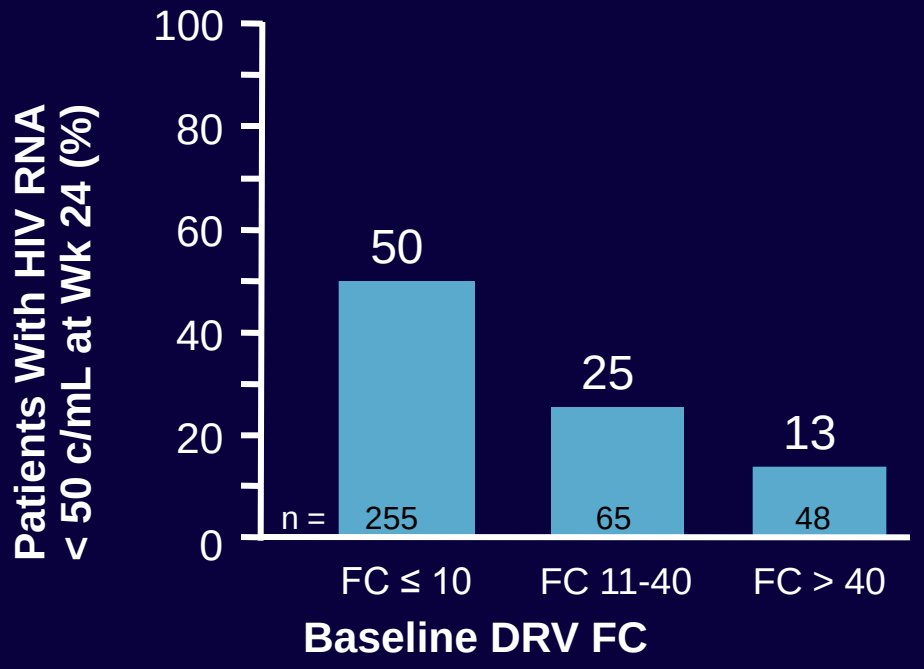
Lazzarin A, et al. IAC 2006. Abstract TUAB0104

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)



DeMeyer S, et al. Antivir Ther. 2006;11:S83.

TPV and DRV Mutations and Phenotypic Cut-offs

Similarities and Differences in Key Mutations

TPV	10V		13V	20M/R		**33F**	35G	36I	43T	46L	47V
DRV		11I			32I	33F					47V

TPV		54A/M/V	58E	69K	74P		**82L/T**	83D	**84V**		90M
DRV	**50V**	**54L/M**			74P	**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. Bacheler 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.

Tipranavir and Darunavir:
Side Effects and Toxicity

DRV/r

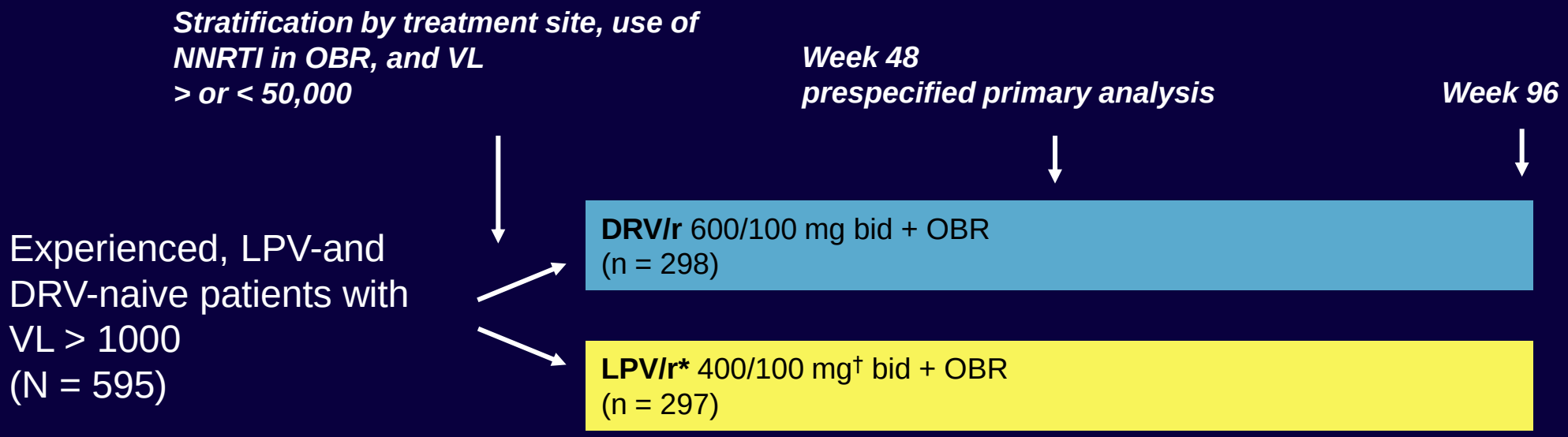
- Less diarrhea than LPV/r in TITAN
- More rash than LPV/r in TITAN

TPV/r

- More hyperlipidemia than other PIs
- More hepatotoxicity than other PIs
- Intracranial hemorrhage (head surgery, head trauma, or bleed diathesis)

If both drugs look equally active, DRV/r preferred

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.

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

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

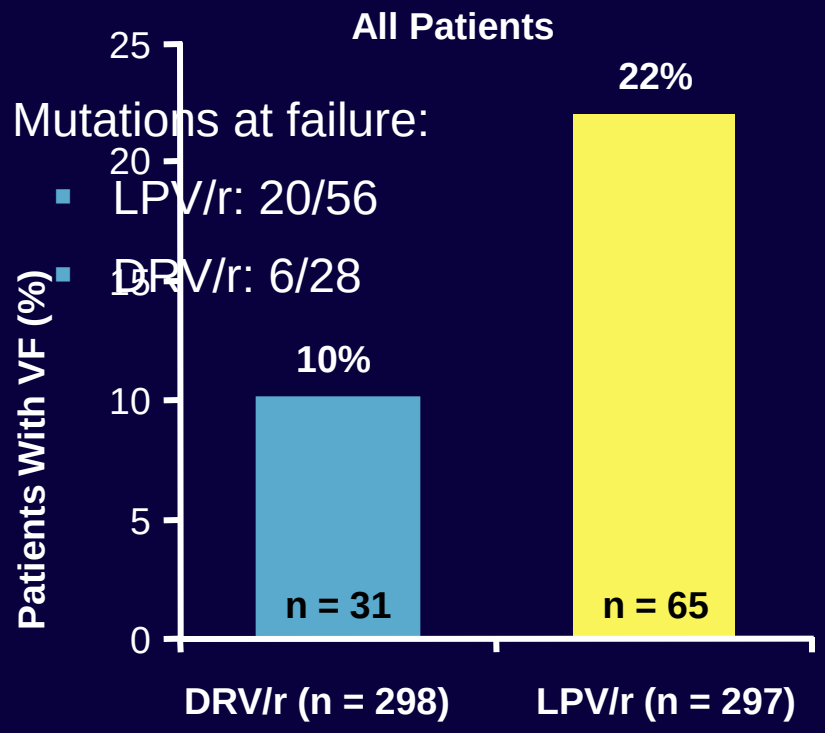
Patient Response, %	DRV/r	LPV/r	DRV/r-LPV/r, % (95% CI)*	Noninferiority *P* Value*	Superiority *P* Value*
Overall (n = 595)	71	60	11 (3 to 19)	< .0001	.005
LPV FC ≤ 40 (n = 569)	70	60	10 (2 to 18)	< .0001	.013
LPV FC ≤ 10 (n = 524)	70	63	7 (-1 to 16)	< .0001	.068

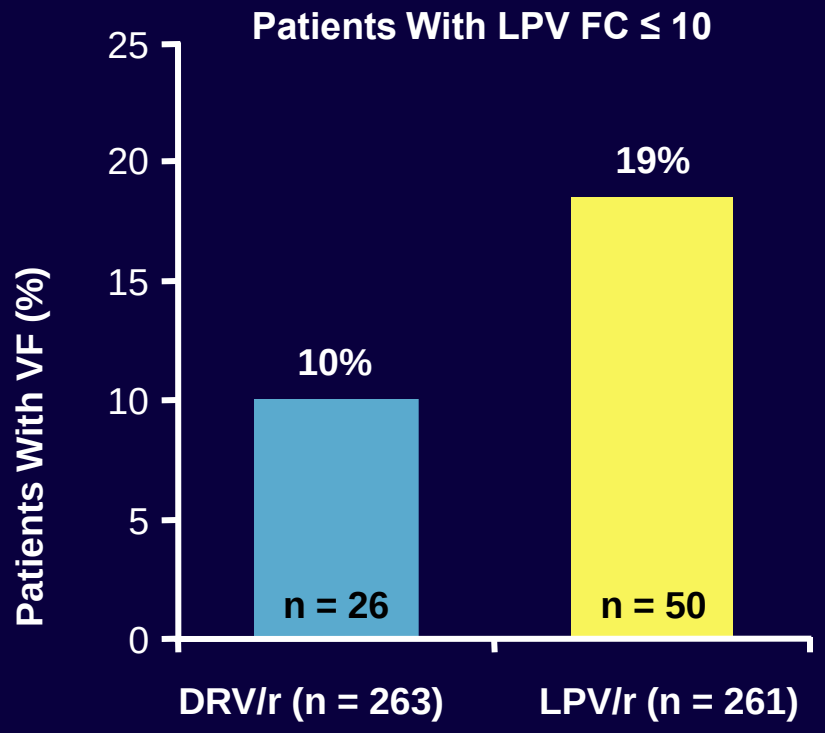
*Estimated from logistic regression model including treatment and stratification factors: baseline VL and use of NNRTIs in OBR.

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

TITAN: Virologic Failure Rates (ITT-TLOVR)

- Virologic failure = nonresponders and rebounders with VL > 400 c/Ml
- Mutations at failure:
  - LPV/r: 20/56
  - DRV/r: 6/28





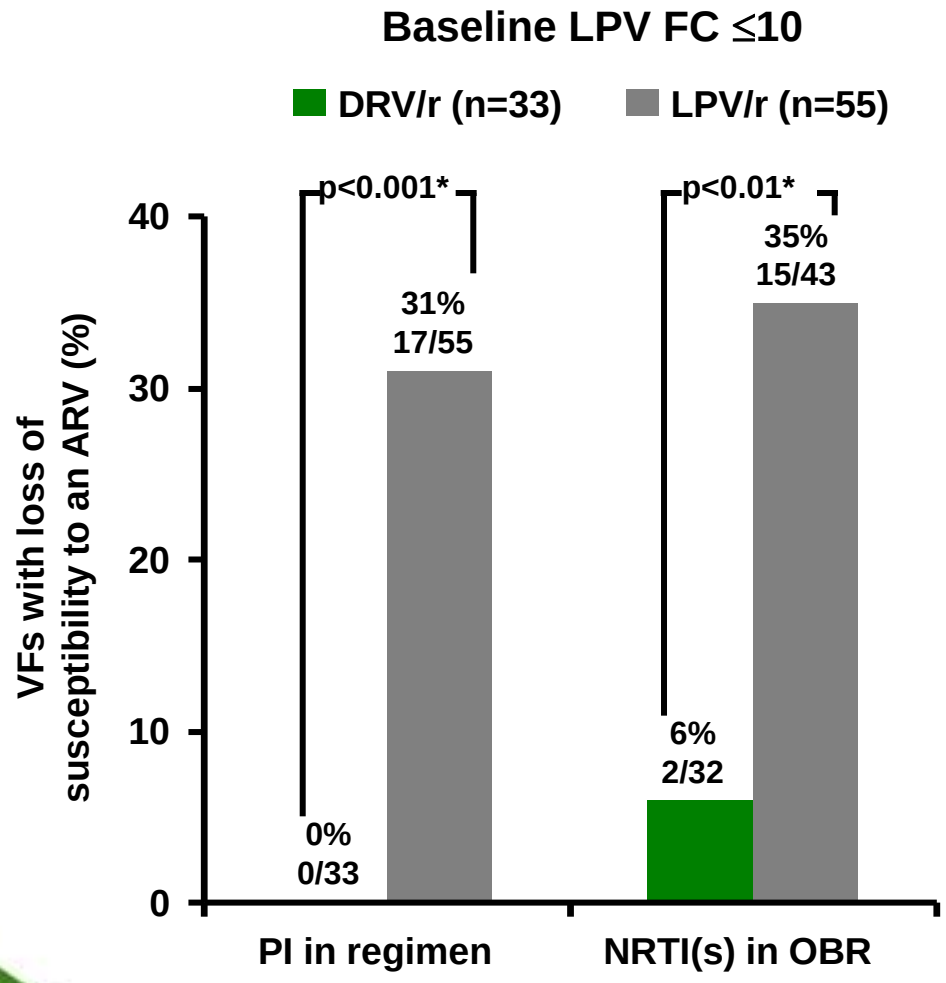
Valdez-Madruga J, et al. IAS 2007. Abstract TUAB101.
Madruga JV, et al. Lancet. 2007;370:49-58

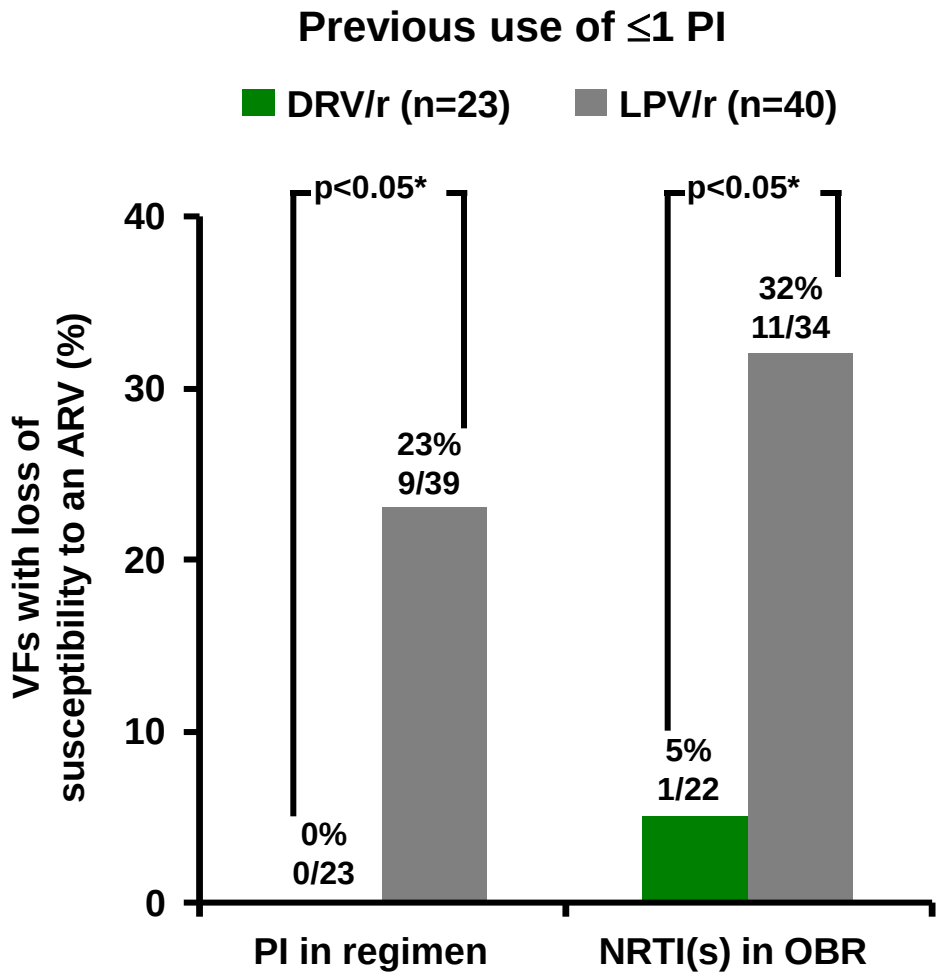
Primary PI mutations that developed in VFs

- **DRV/r group**
  - **6 VFs developed primary PI mutation(s)**
    - **V32I (n=3), I47V, and L76V (n=2), M46I, I54L and I54M (n=1)**
    - **all but M46I are DRV RAMs[1]**
    - **previously used 2–6 PIs**
- **LPV/r group**
  - **24 VFs developed primary PI mutation(s)**
    - **M46I (n=9), L33F, I47V, and L76V (n=4), M46L, and V82A (n=3), V32I, I47A, and I84V (n=2), I50V, I54M, V82S, and L90M (n=1)**
    - **all LPV RAMs[1]**
    - **previously used 1–4 PI(s)**

[1]Johnson VA, et al. Top HIV Med 2007;15:119–25
TITAN 96 week analysis

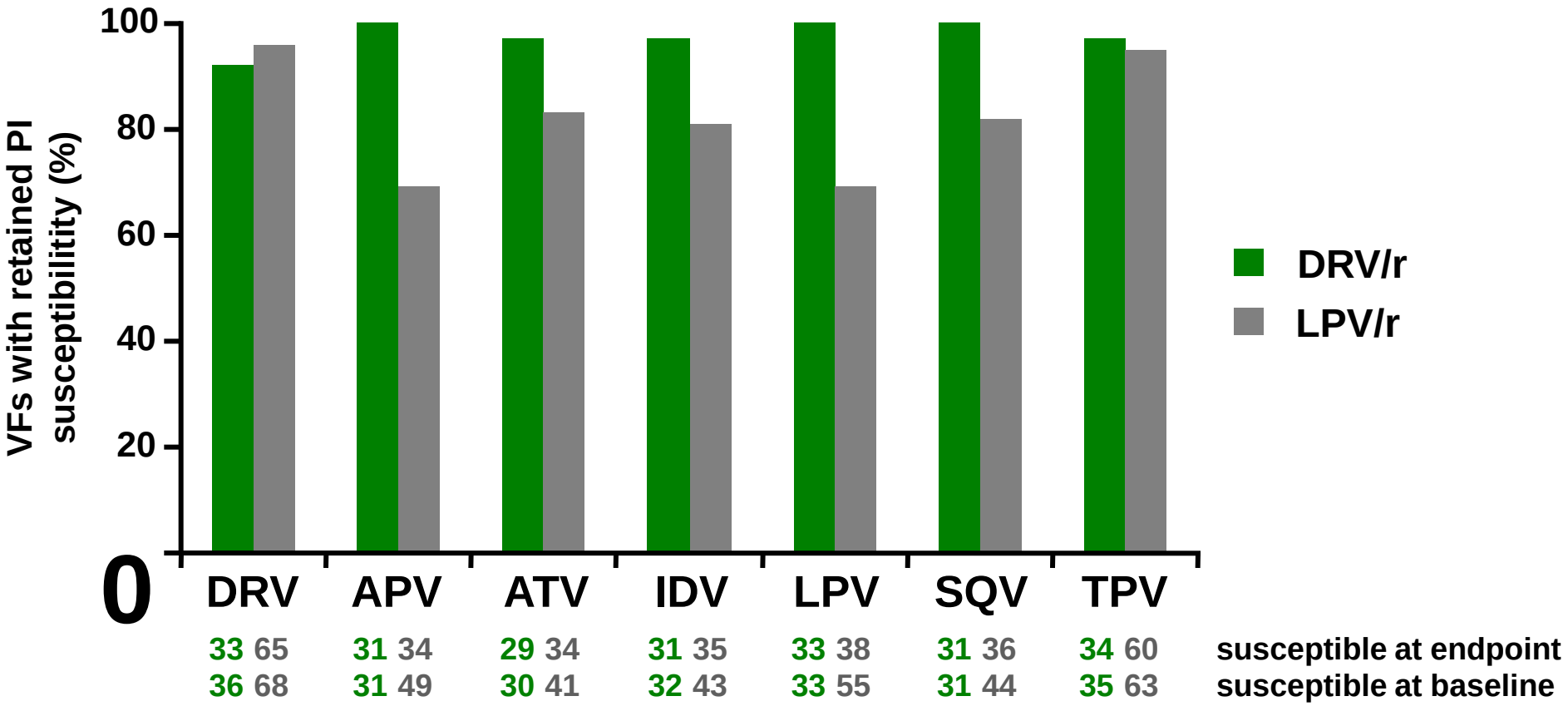
Fewer VFs on DRV/r than on LPV/r lost susceptibility to PI or NRTI(s) in the treatment regimen, after excluding patients with baseline LPV FC >10 or prior use of ≥2 PIs





*Exact Chi-Squared Test; TITAN 96 week analysis

More VFs on DRV/r than on LPV/r retained susceptibility to PIs



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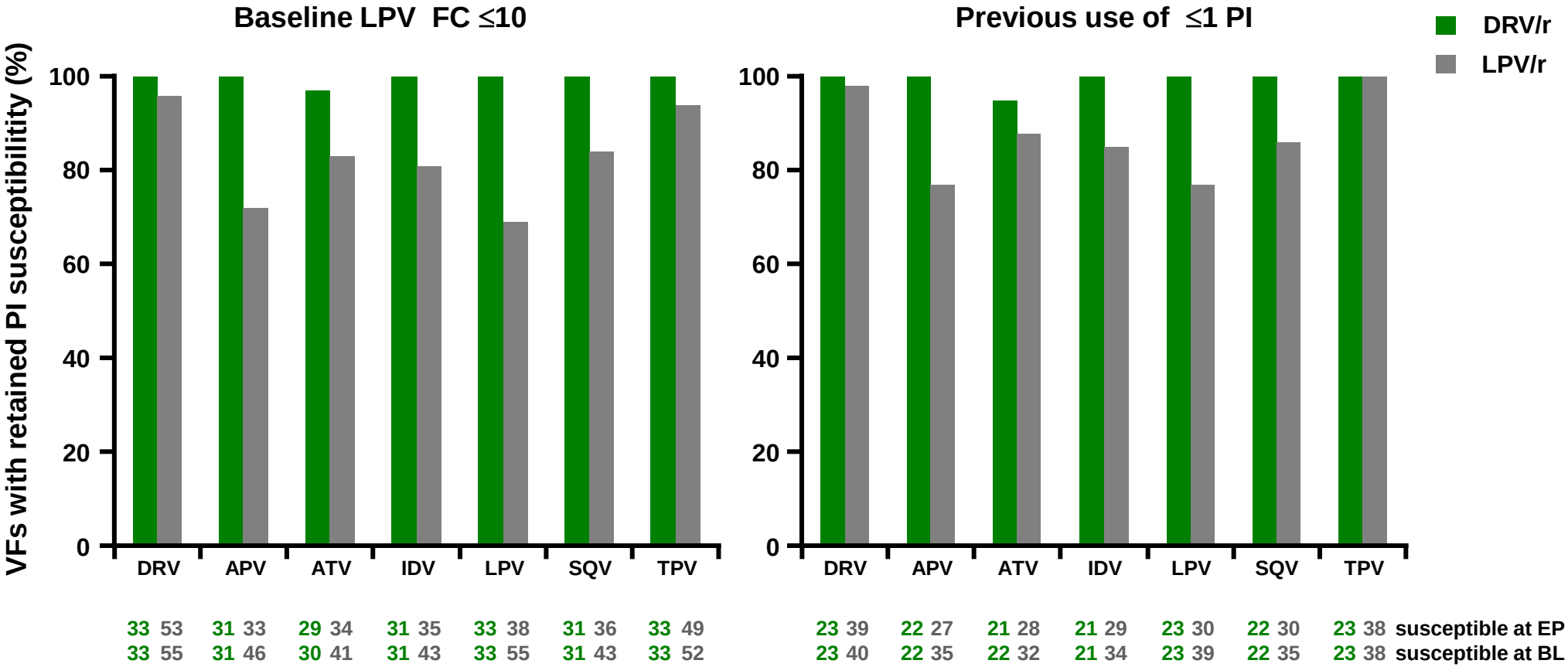
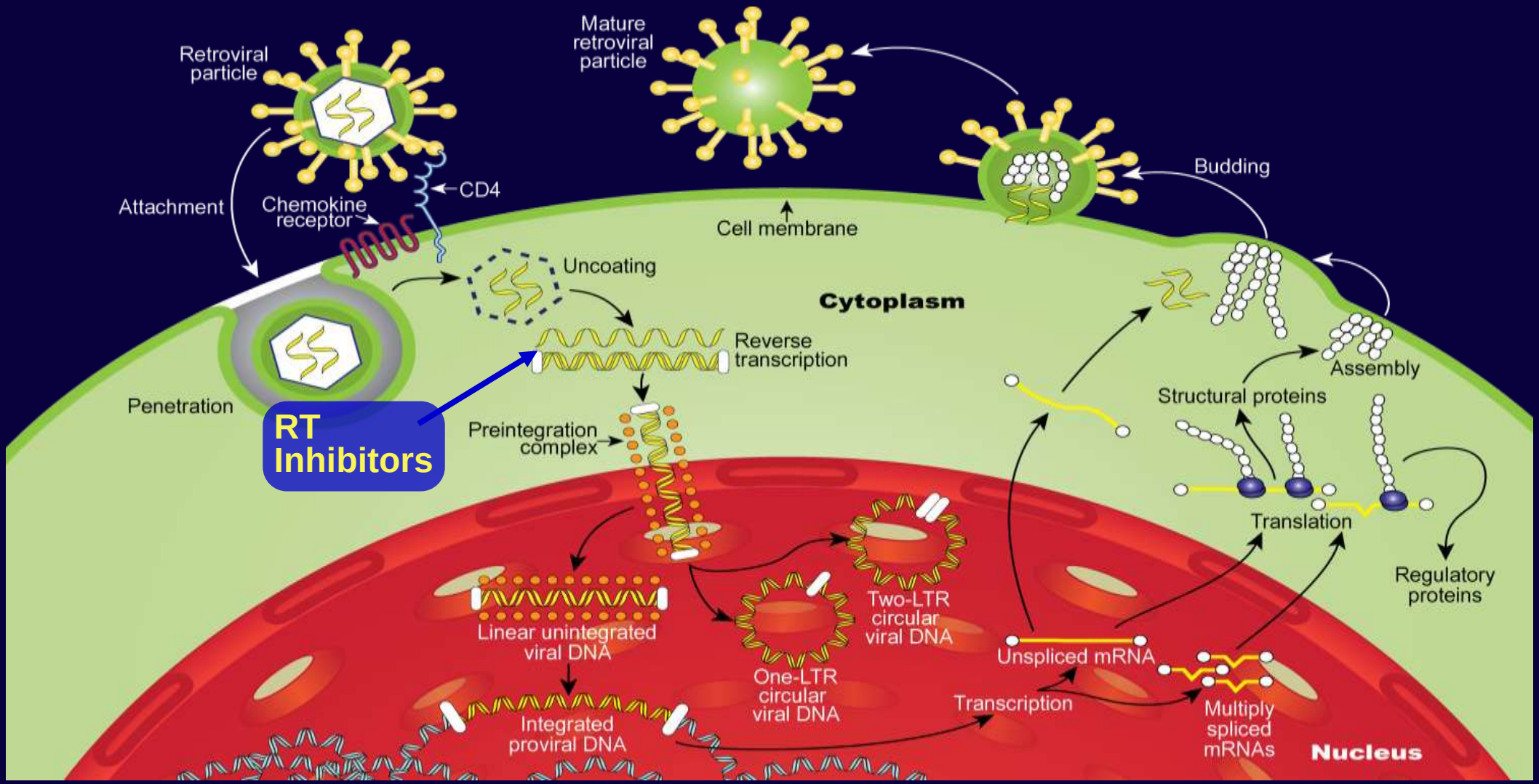


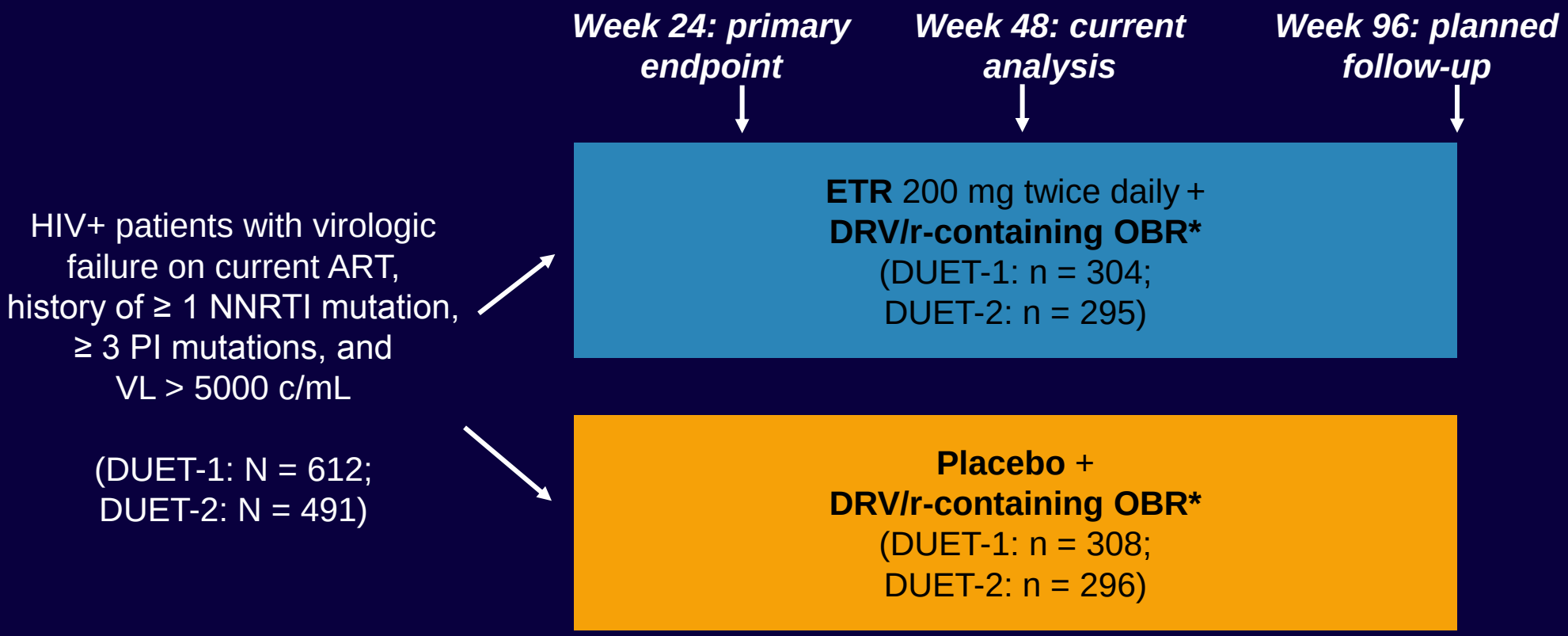
TITAN 96 week analysis

The HIV-1 Replication Cycle



RT = reverse transcriptase; LTR = long terminal repeat.

DUET-1 and -2: Etravirine + DRV/r-Containing OBR, Phase III Trials

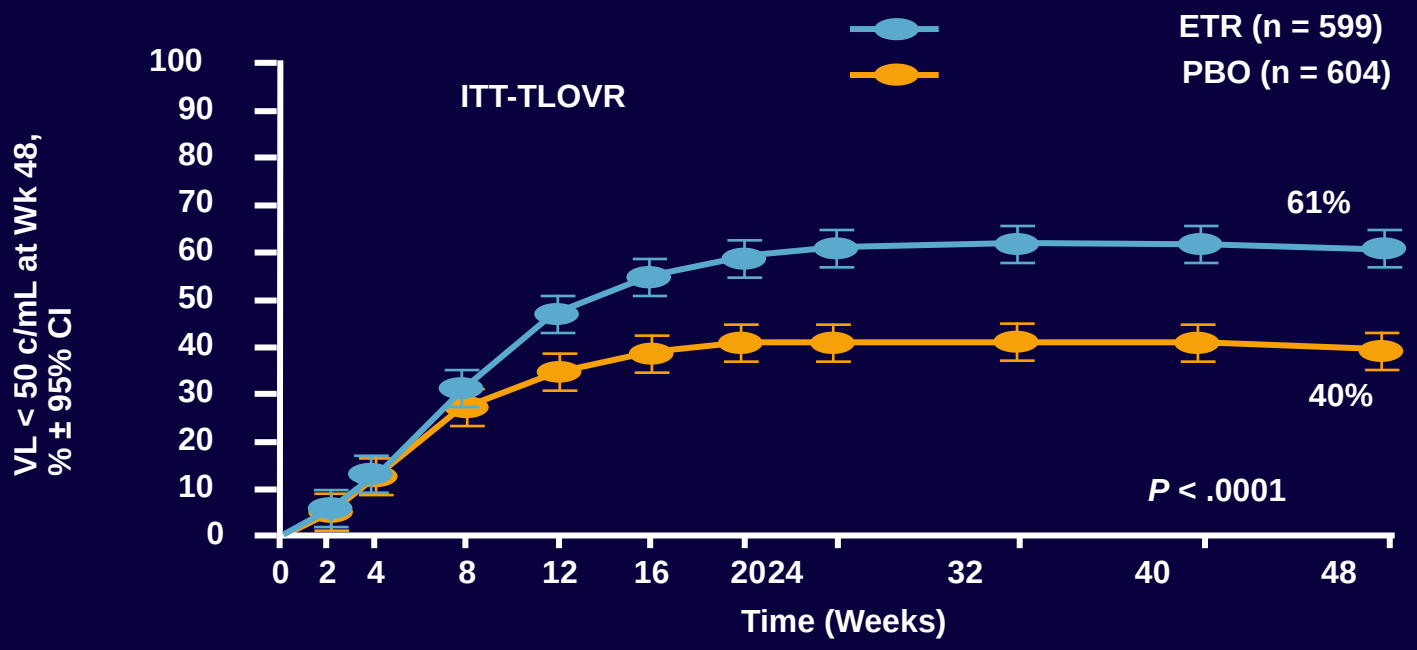


*Investigator-selected OBR comprising DRV/r 600/100 mg twice daily + ≥ 2 NRTIs ± ENF.

Cahn P, et al. IAC 2008. Abstract TUPE0047.

DUET-1 and -2: Etravirine vs. Placebo in Treatment-Experienced Patients

- Mean CD4 change at Week 48 significantly greater in ETR arm: +98 vs +73 i[1,2]



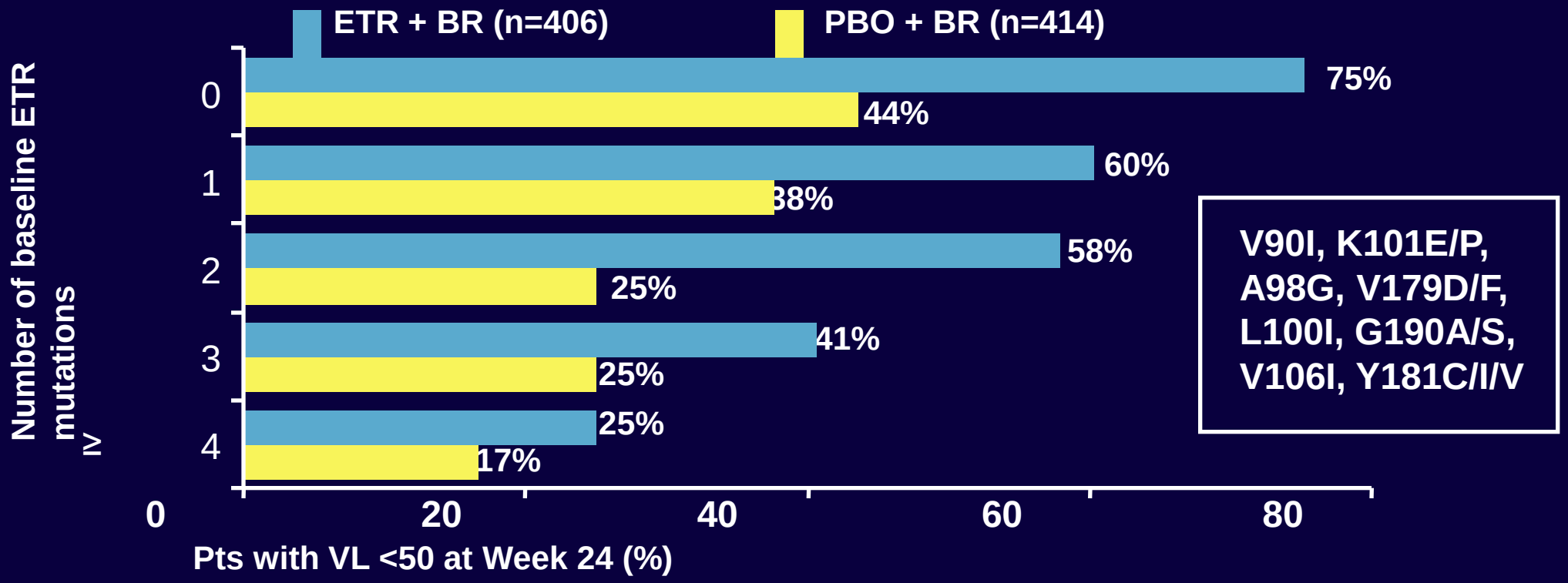
1. Haubrich R, et al. CROI 2008. Abstract 790; 2. Johnson M, et al. CROI 2008. Abstract 791;

Etravirine Resistance: Clinical Implications

- Effective against many NNRTI-resistant strains
  - K103N does not decrease susceptibility (and may *improve* activity[1])
  - Other NNRTI mutations vary in their effect on ETR activity
- Efficacy decreases with increasing NNRTI mutations
  - No benefit with continued EFV or NVP therapy after failure
  - Greater cross-resistance after failure of NVP than EFV[1]
  - Don't continue EFV or NVP in a non-suppressive regimen
- Use genotypes drawn at time of NNRTI failure to assess ETR susceptibility

1. Marcelin AG, et al. CROI 2009. Abstract 645

DUET: Response (<50 c/mL) by Number of ETR mutations



- Greatest added benefit with ETR vs. PBO seen in pts with <3 ETR mutations
- 86% of patients had <3 ETR mutations

Excludes pts who used de-novo ENF or discontinued except for virological failure

New Weighted Scores for ETR Susceptibility

Monogram

- 4: 100I, 101P, 181C/I
- 3: 138A/G, 179E, 190Q, 230L, 238N
- 2: 101E, 106A, 138K, 179L, 188L
- 1: 90I, 101H, 106M, 138Q, 179D/F/M, 181F, 190E/T, 221Y, 225H, 238T

- ≥ 4 = reduced susceptibility

Tibotec

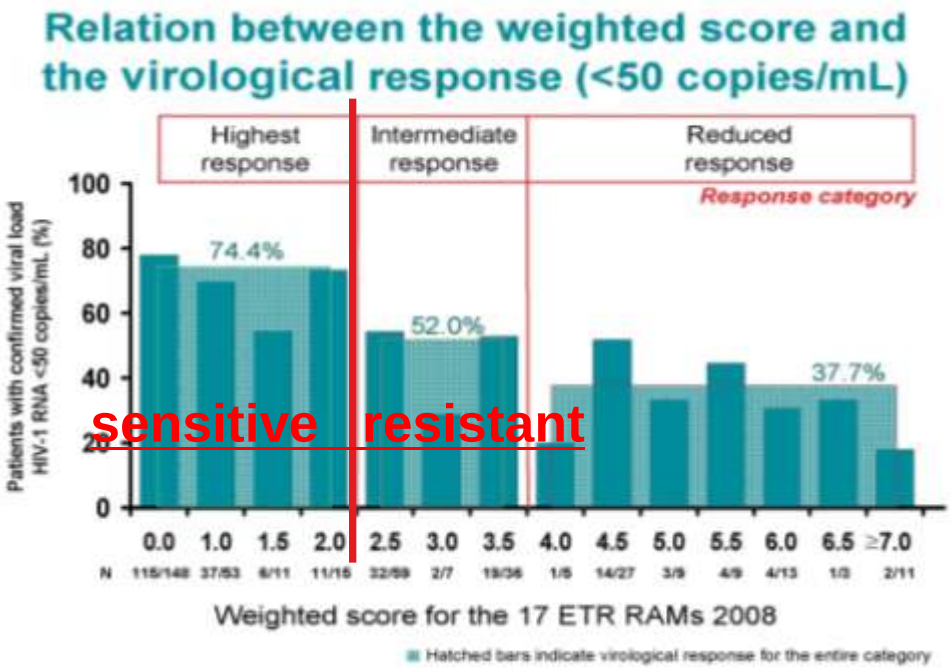
- 3: 181I/V
- 2.5: 101P, 100I, 181C, 230L
- 1.5: 138A, 106I, 190S, 179F
- 1: 90I, 179D, 101E, 101H, 98G, 179T, 190A

- 0-2: 74% response
- 2.5-3.5: 52% response
- > 4: 38% response

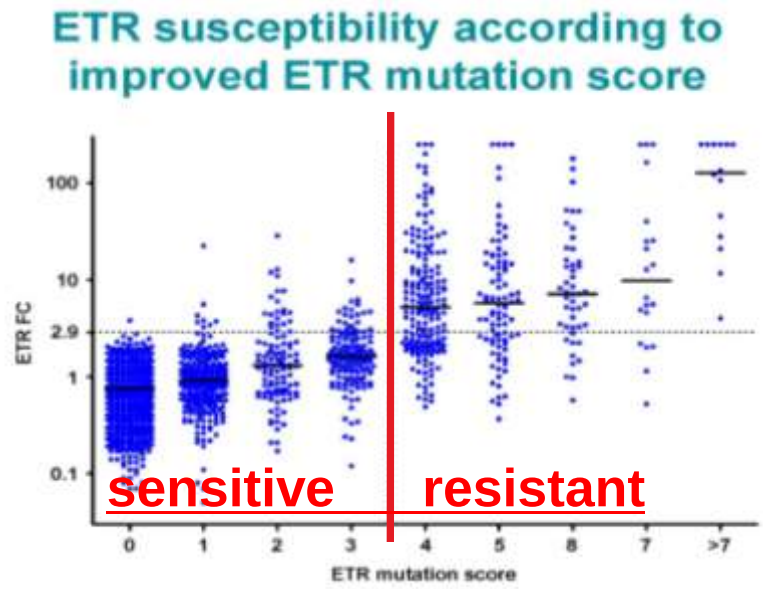
Methods

- A single cut-off was used to categorise samples as ‘sensitive’ or with reduced susceptibility (‘resistant’)

TBT score[1]



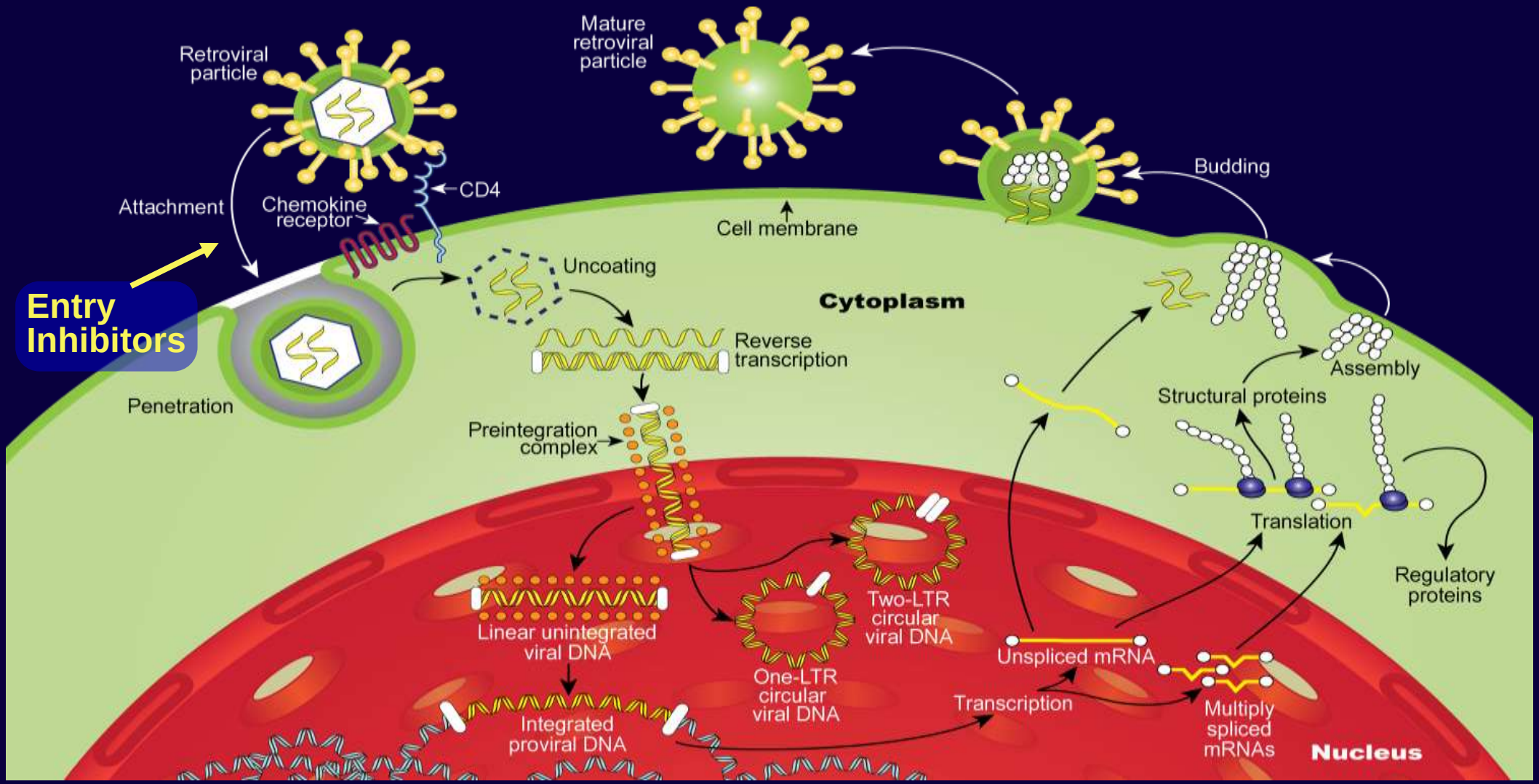
MGR score[2]



- These cut-offs were set at ‘2’ for the Tibotec algorithm and ‘3’ for the Monogram algorithm

1. Vingerhoets J, et al. Antivir Ther 2008;13(Suppl. 3): A26
2. Benhamida J, et al. Antivir Ther 2008;13(Suppl. 3): A142

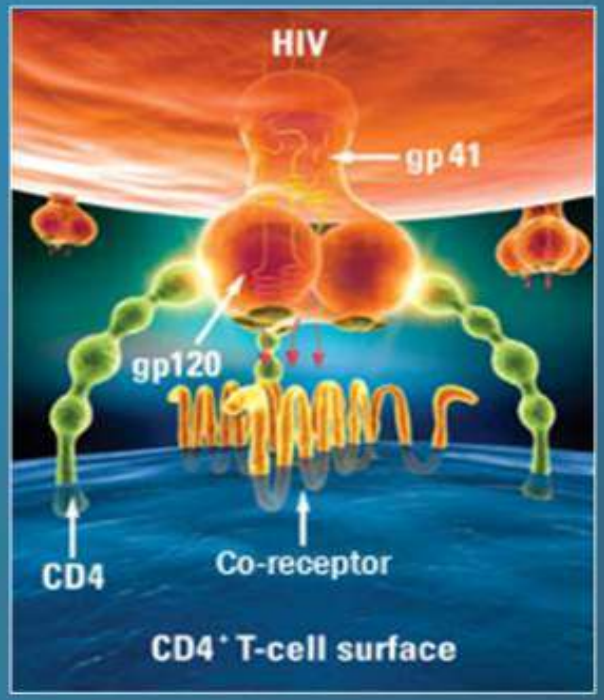
The HIV-1 Replication Cycle



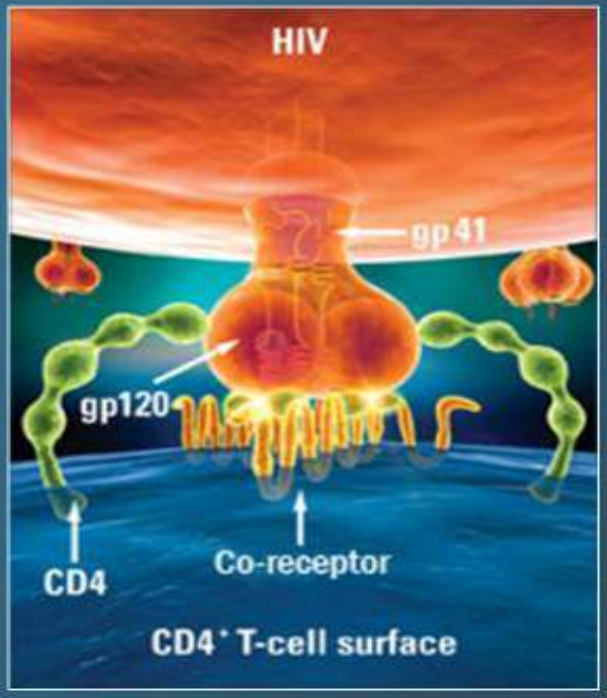
RT = reverse transcriptase; LTR = long terminal repeat.

To Enter a Healthy CD4+ T Cell, HIV Must Complete 3 Stages of Interaction

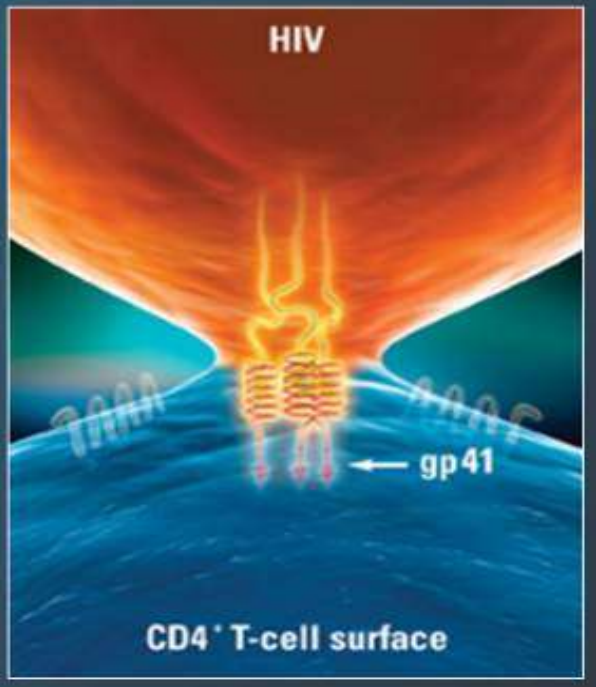
Attachment



Co-receptor Binding



Fusion



Westby M, van der Ryst E. *Antivir Chem Chemother*. 2005;16:339-354.

R5 Viruses

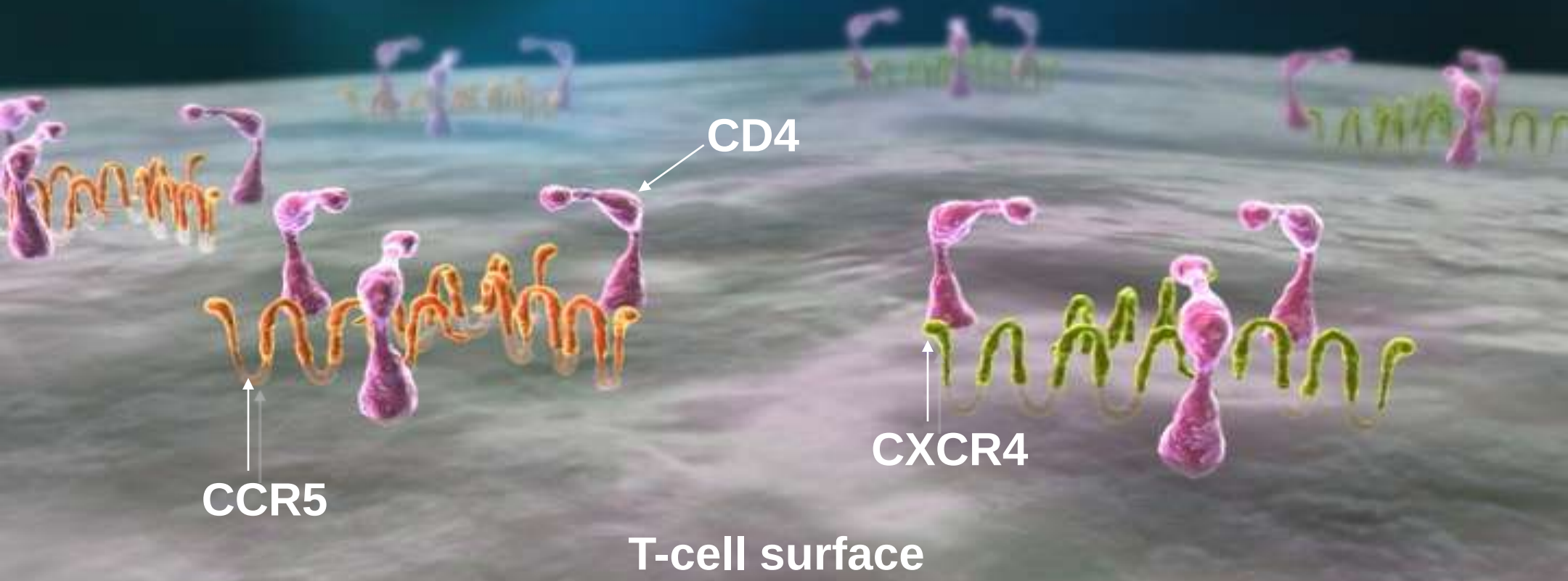
- Utilize the CCR5 co-receptor
- Also known as M-tropic or nonsyncytium inducing (NSI)
- Transmitted variants
- Prevalent in early disease

Dual Viruses

Can utilize either co-receptor

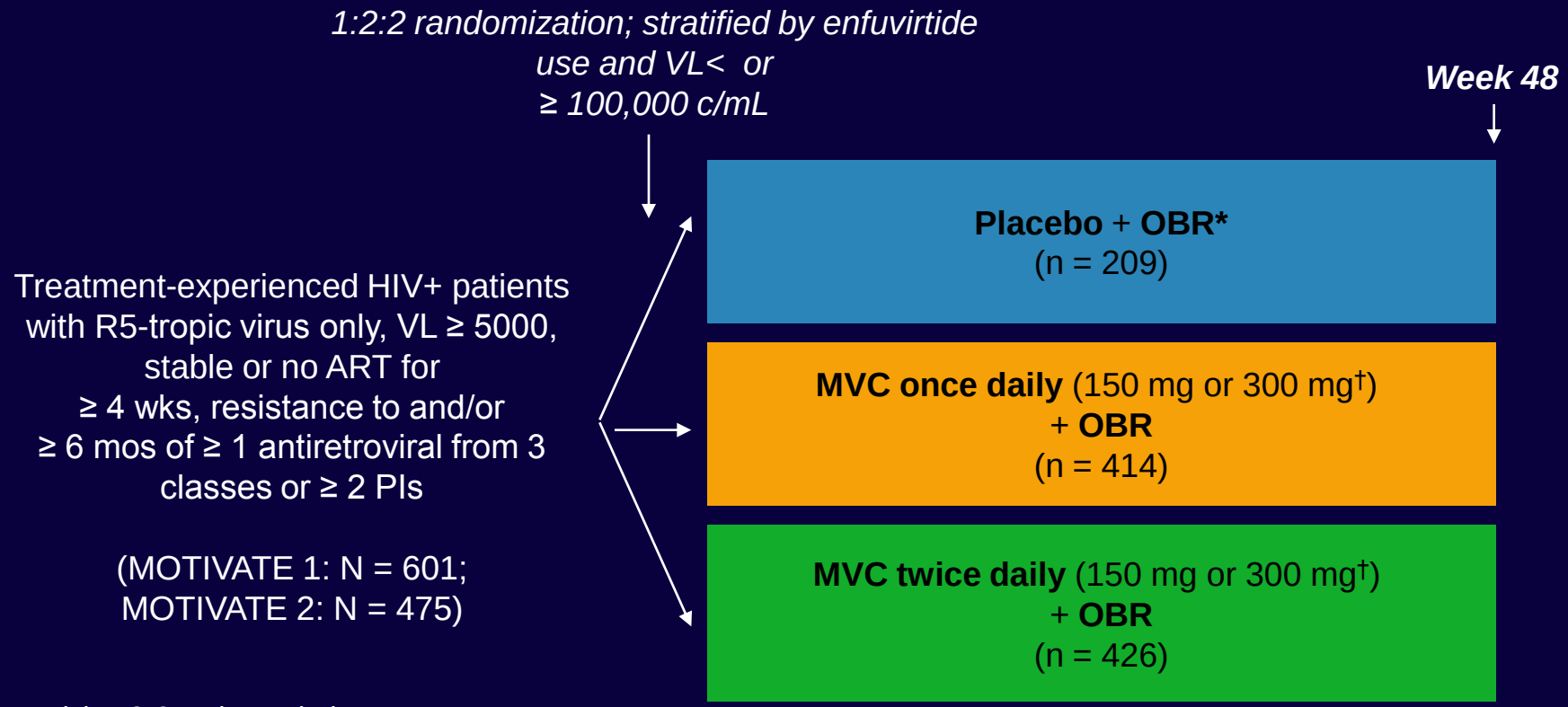
X4 Viruses

- 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



Berger EA, et al. *Nature.* 1998;391:240.

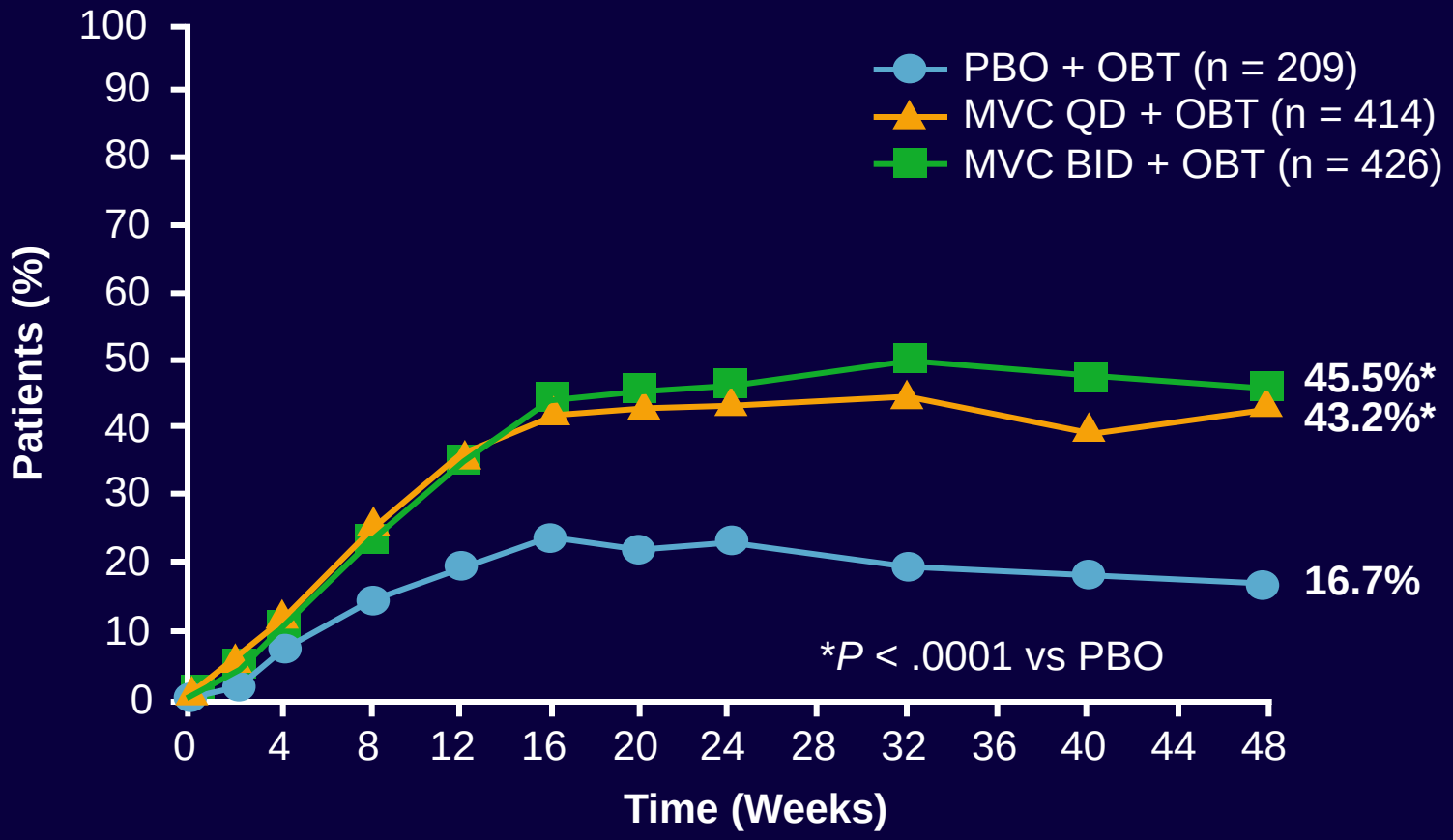
MOTIVATE-1 and -2: MVC + OBR vs Placebo + OBR, Phase III Trials



*OBR comprising 3-6 antiretroviral agents.
†Patients receiving PI (other than tipranavir) or delavirdine received 150 mg; all others received 300 mg.

1. Nelson M, et al. IAC 2008. Abstract TUPE0119.
2. Asmuth A, et al. IAC 2008. Abstract TUPE0050.

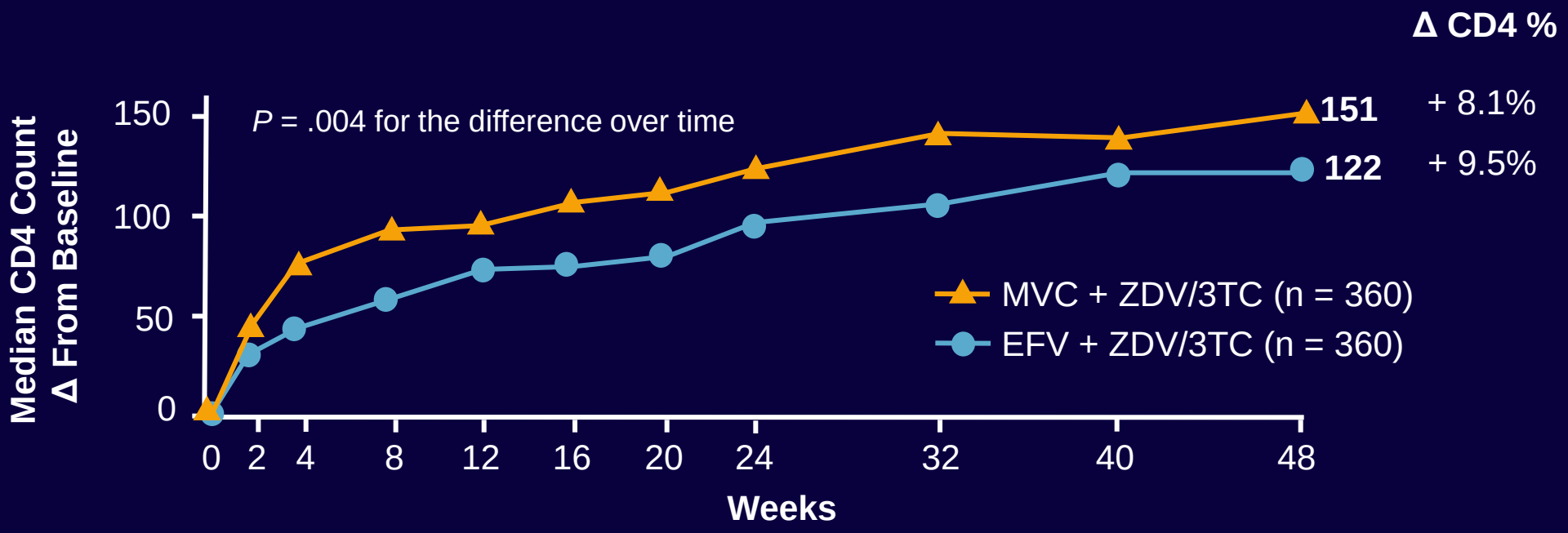
MOTIVATE 1 and 2: Maraviroc vs. Placebo in Experienced Patients with R5-tropic Virus



Hardy D, et al. CROI 2008. Abstract 792.

Effect of Maraviroc on CD4 Count

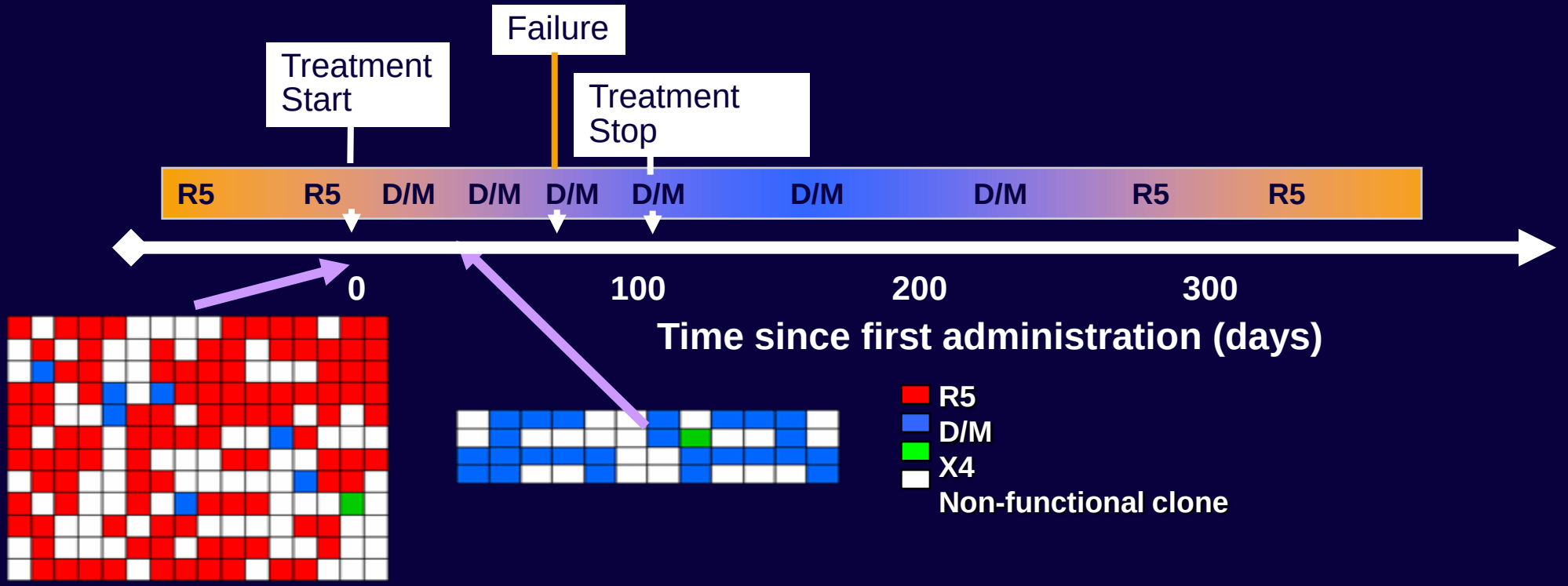
- Analysis of MERIT study[1]



- In separate study, addition of MVC in 9 patients with VL <50 but CD4 counts < 250 on current ART regimen did not significantly increase CD4count recovery with 5 mos of follow-up ($P > .39$)[2]

1. Lazzarin A, et al. ICAAC/IDSA 2008. Abstract 1248.
2. Paez S, et al. ICAAC/IDSA 2008. Abstract 1247.

Emergence of D/M tropic virus on CCR5 antagonist therapy



- Clonal and phylogenic 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

Lewis M, *et al. XVI IHIVDRW,* Barbados 2007, #56

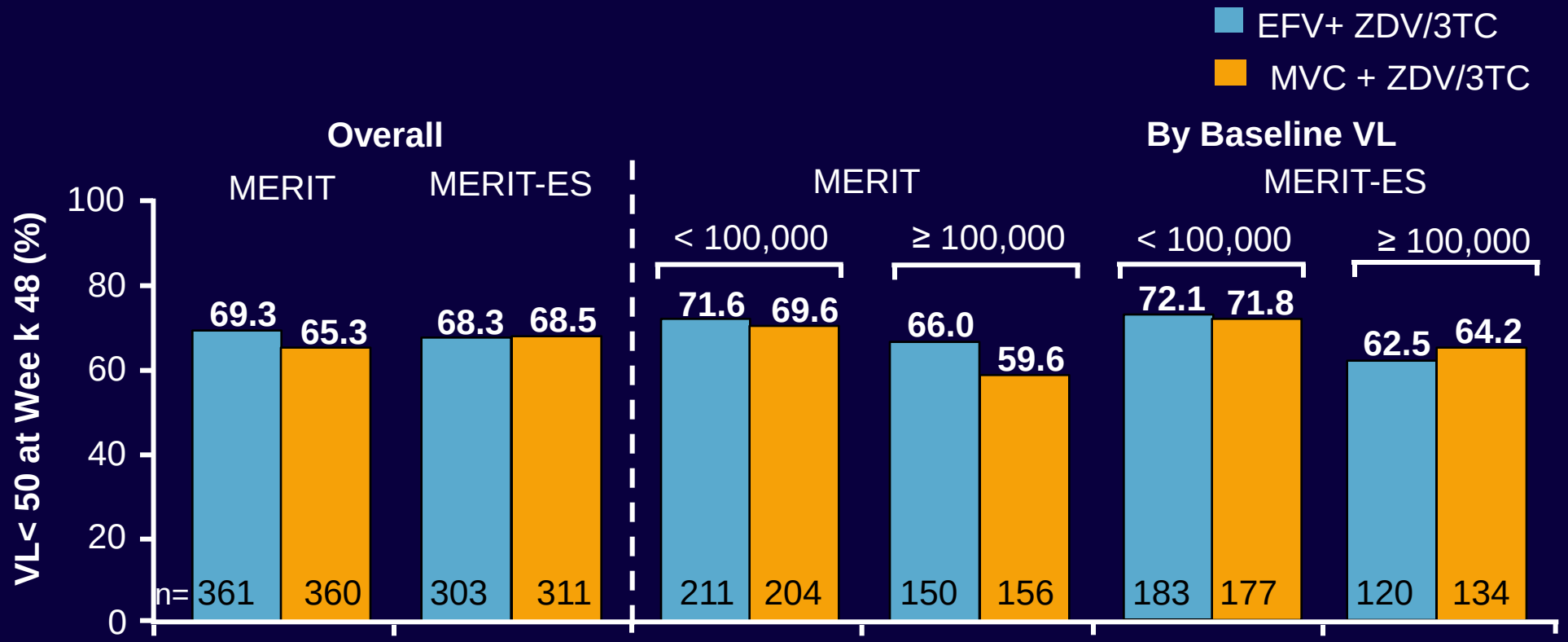
Tropism in Experienced Patients as Identified by Trofile (n= 6,857)

Study/Source	Population	N	R5	D/M	X4
MOTIVATE 1 & 2[4]	Experienced	2560	56%	41%	3%
TORO 1/2[5]	Experienced	612	50%	46%	4%
ACTG 5211[6]	Experienced	391	49%	47%	4%
SCOPE[7]	Experienced	186	60%	39.5%	0.5%
HOMER cohort[1]	Naive	979	82%	18%	<1%
C & W cohort[2]	Naive	402	81%	19%	<1%
Demarest[3]	Naive	299	88%	12%	0%
Pfizer 1026[4]	Naive	1428	85%	15%	<1

1 Brumme ZL, et al. *J Infect Dis.* 2005;192:466-474.
2 Moyle GJ, et al. *J Infect Dis*. 2005;191:866-872.
3 Demarest J, et al. *ICAAC* 2004. Abstract H-1136.
4 Coakley E, et al. 2nd Viral Entry Workshop, Abstract 8
5 Melby et al 13th *CROI 2006* Abstract 233.
6 Wilkin T, et al. *CROI* 2006. Abstract 655.
7 Hunt et al. *J Infect Dis*. 2006;194:926-30

Reanalysis of Virologic Efficacy in MERIT With Enhanced Tropism Assay

- Enhanced phenotypic tropism assay resulted in reclassification of 15% of patients from R5 to D/M at screening
  - Noninferiority criteria (rates of HIV-1 RNA < 50 copies/mL) met when D/M patients excluded

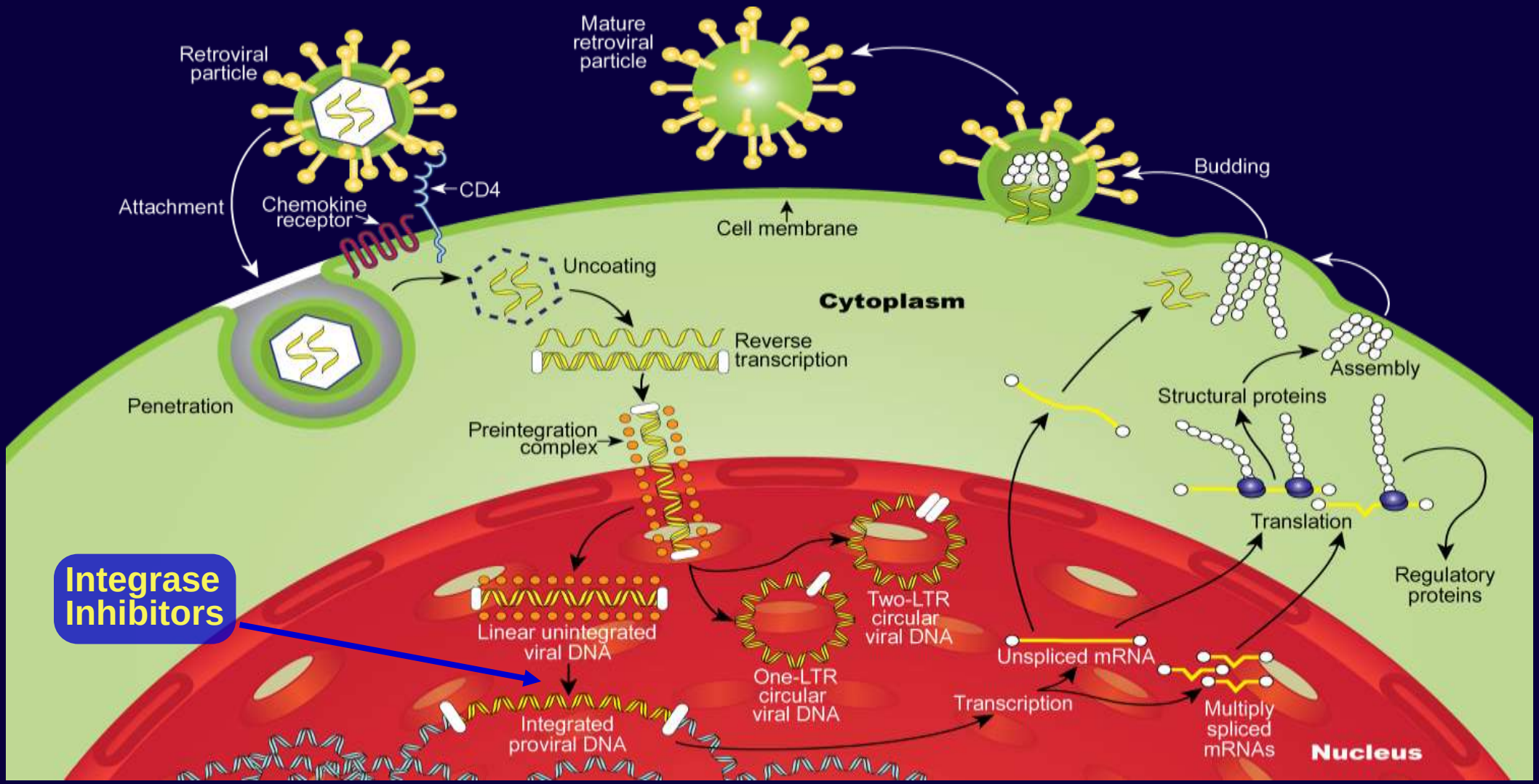


Saag M, et al. ICAAC/IDSA 2008. Abstract 1232a.

The Role of Maraviroc

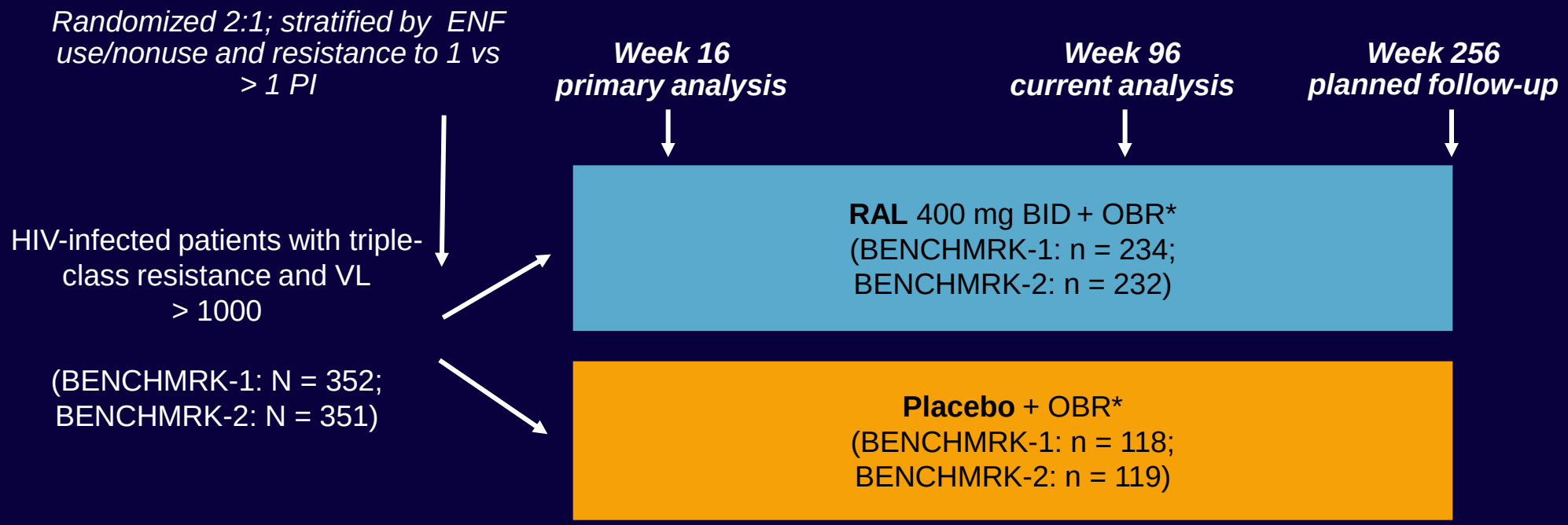
- Requires screening with expensive tropism (*Trofile*) assay (currently ~$2000 per test)
- ~50% of experienced patients not candidates for MVC due to presence of D/M or X4 virus
- D/M or X4 virus can be missed if present at <0.3% with enhanced susceptibility assay
- Most likely to work in naïve patients, but little rationale for use in first-line regimens

The HIV-1 Replication Cycle



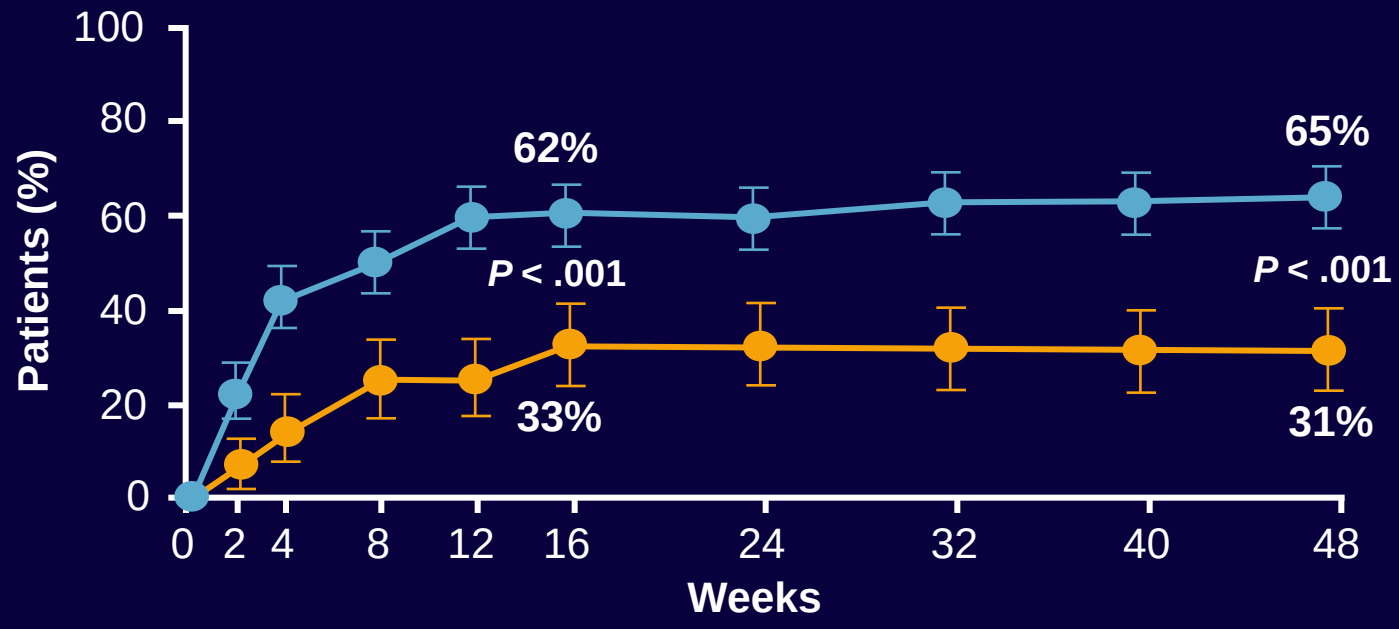
RT = reverse transcriptase; LTR = long terminal repeat.

BENCHMRK-1 & -2: RAL in Treatment-Experienced Patients



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

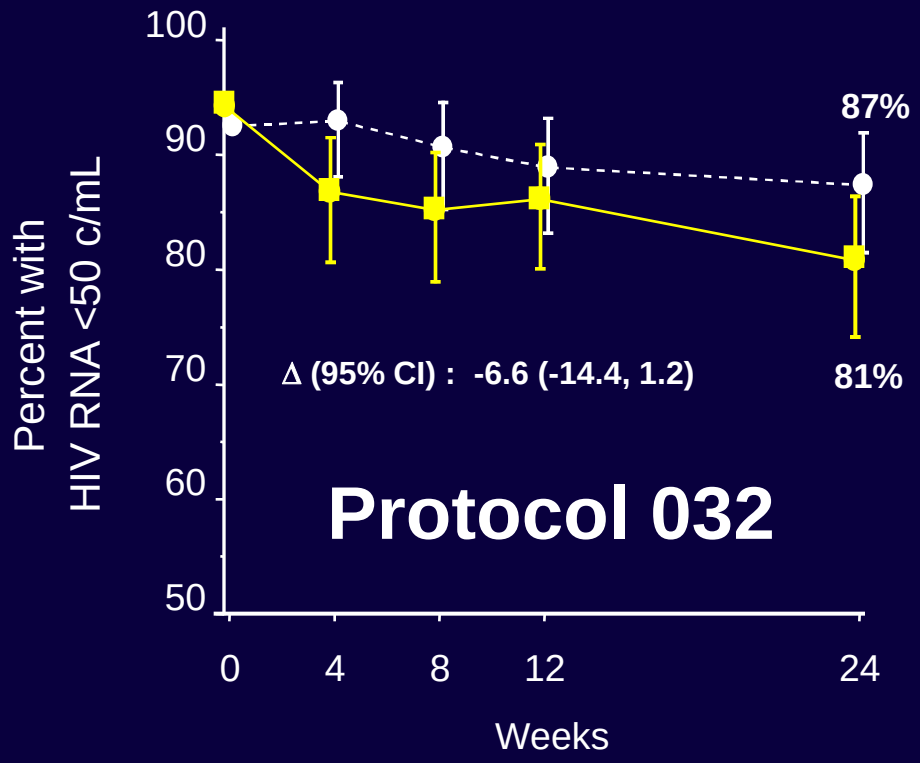
BENCHMRK-1: Raltegravir vs. Placebo in Experienced Patients

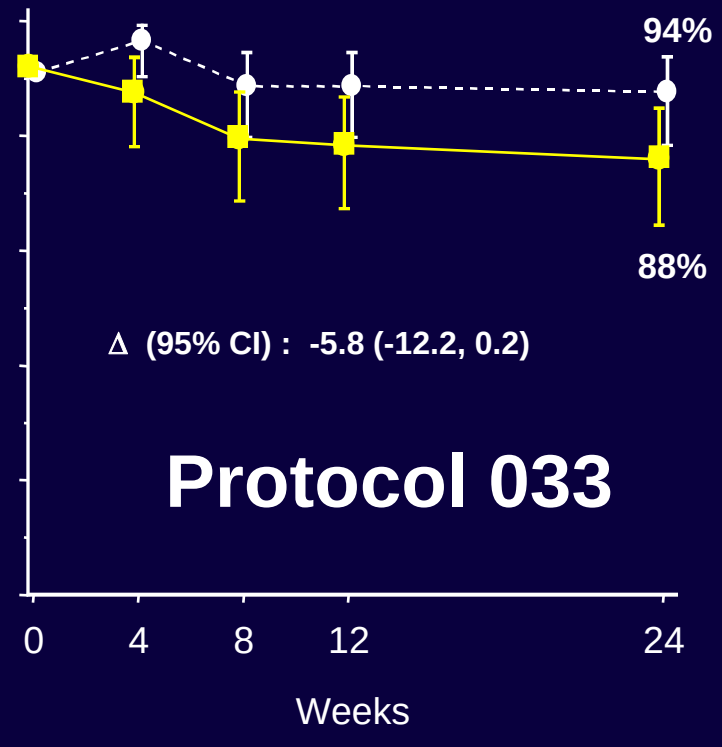


RAL n =	232	231	231	230	229	232	229	230	231
PBO n =	118	118	118	118	117	118	118	118	118

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

SWITCHMRK (Protocols 032 & 033): Percent with HIV RNA <50 C/mL (NC = F)





Number of Contributing Patients

RAL + ARTs	174	166	169	173	172	176	176	176	176	175
LPV/r + ARTs	174	171	171	171	174	178	178	177	177	178

Eron J, et al. CROI 2009. Abstract 70aLB

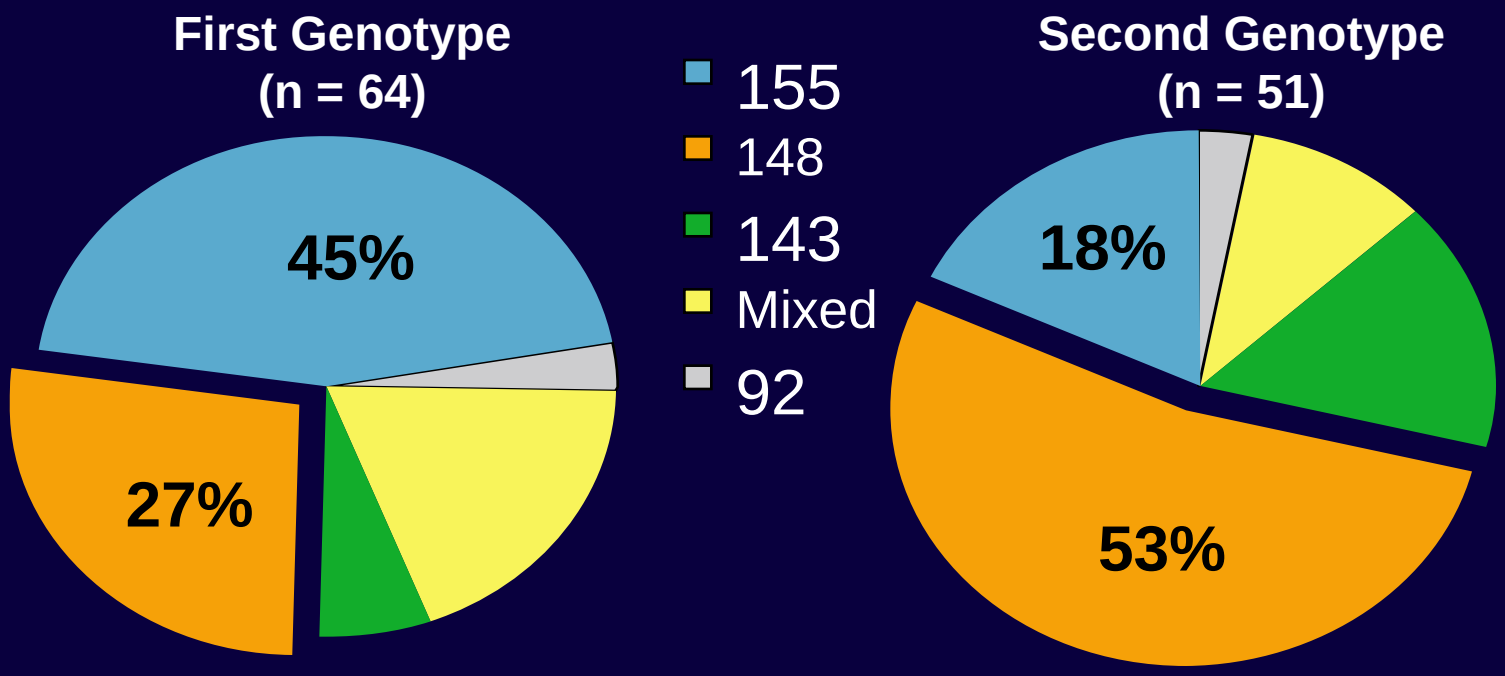
SWITCHMRK -1 and -2: Baseline Characteristics

Characteristic	Protocol 032		Protocol 033	
	RAL (n = 174)	LPV/r (n = 174)	RAL (n = 176)	LPV/r (n = 178)
Mean age	44.4	43.6	42.0	41.9
Sex (% female)	16.1	25.9	22.2	22.5
Race (% nonwhite)	16.1	19.0	51.7	54.5
VL ≤ 50 (%)	94.3	92.5	96.0	95.5
Mean CD4 count	478	508	471	482
LPV/r use ≤ 1 yr (%)	16.7	17.8	17.6	18.5
Med. Yrs of previous ART (range)	3.3 (0.3-22.3)	3.6 (0.5-20.2)	3.7 (0.5-19.2)	4.6 (0.6-16.3)
Med. # of previous ARV drugs (range)	5.0 (4.0-16.0)	5.0 (2.0-15.0)	5.5 (3.0-13.0)	6.0 (4.0-14.0)

Eron J, et al. CROI 2009. Abstract 70aLB.

BENCHMRK 1 & 2: Evolution from N155 to Q148 Mutations Over Time

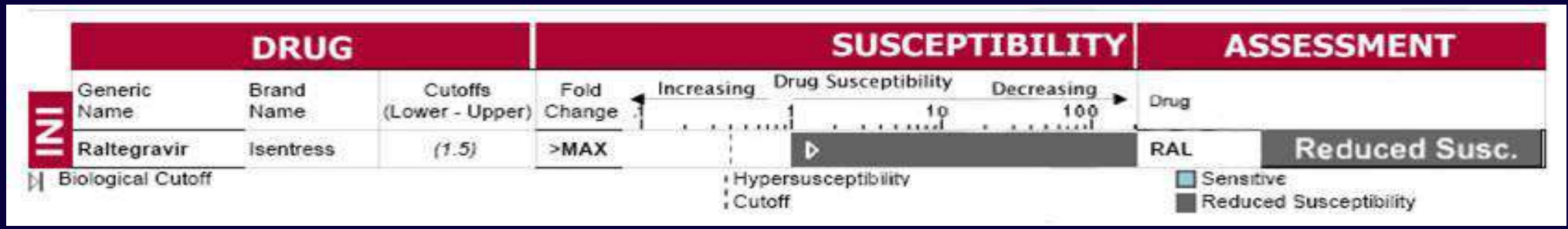
- Virologic failure in 105/462 patients receiving RAL
  - 94 had baseline & virologic failure samples
  - 30 had no genetic changes
  - 64 (68%) failures in current analysis



Hazuda D, et al. ICAAC/IDSA 2008. Abstract 898.

Integrase Assay Determines RAL Susceptibility

- Phenotypic integrase resistance assay now commercially available
  - Amplification threshold: VL > 500
  - Biological cutoff for RAL is FC > 1.5
  - Does not detail genotypic mutations

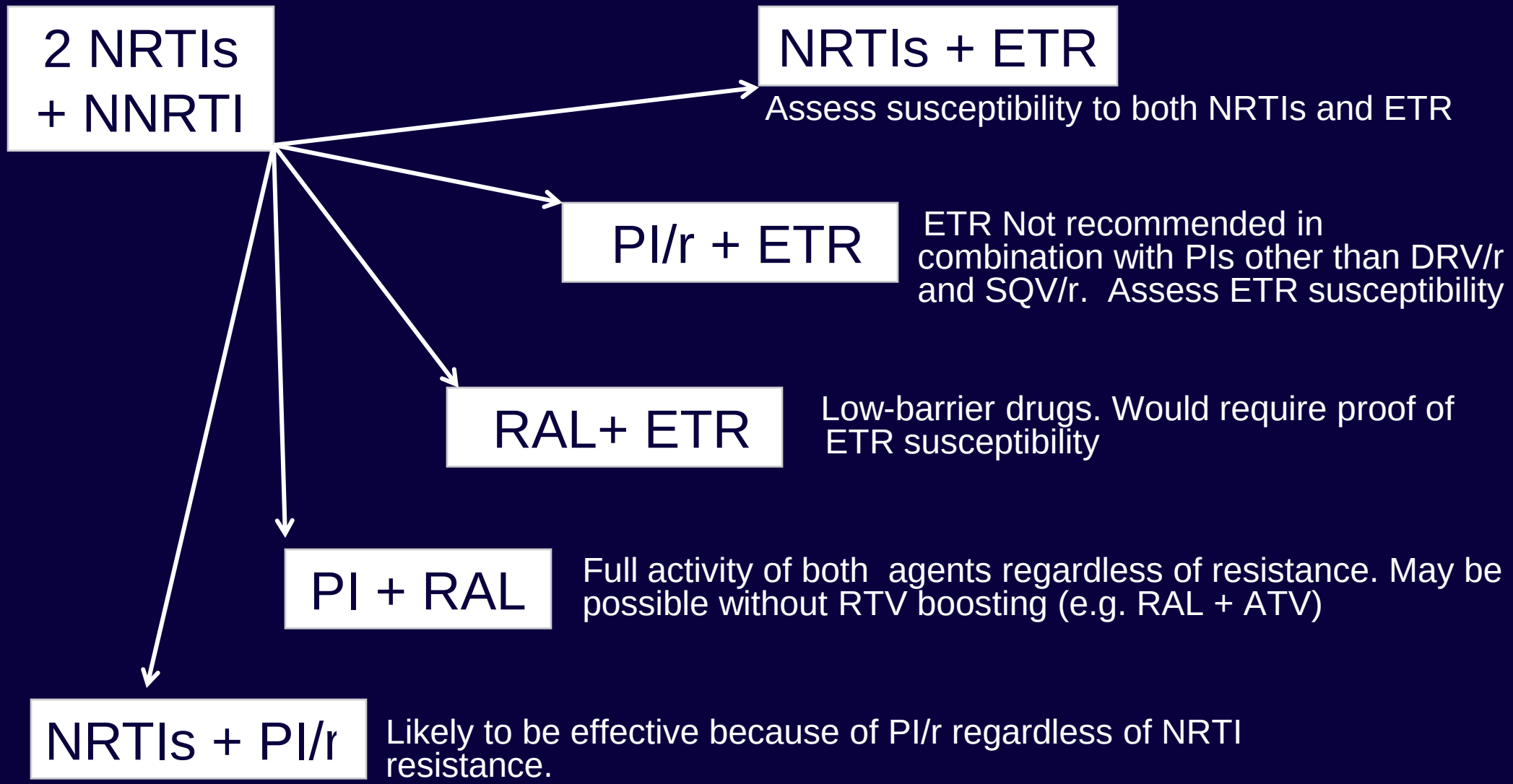


Fransen S, et al. ICAAC/IDSA 2008. Abstract 1214.

The Role of Raltegravir

- Combined with other active drugs in experienced patients with resistant virus
- To replace other agents in patients experiencing toxicity
  - Consider activity of other agents in the regimen
  - Be especially careful when switching from a PI/r to RAL
- As alternative to PI therapy in patients failing initial NNRTI regimen
- As alternative to NNRTIs or PIs for initial therapy

Sequencing Options after First Failure



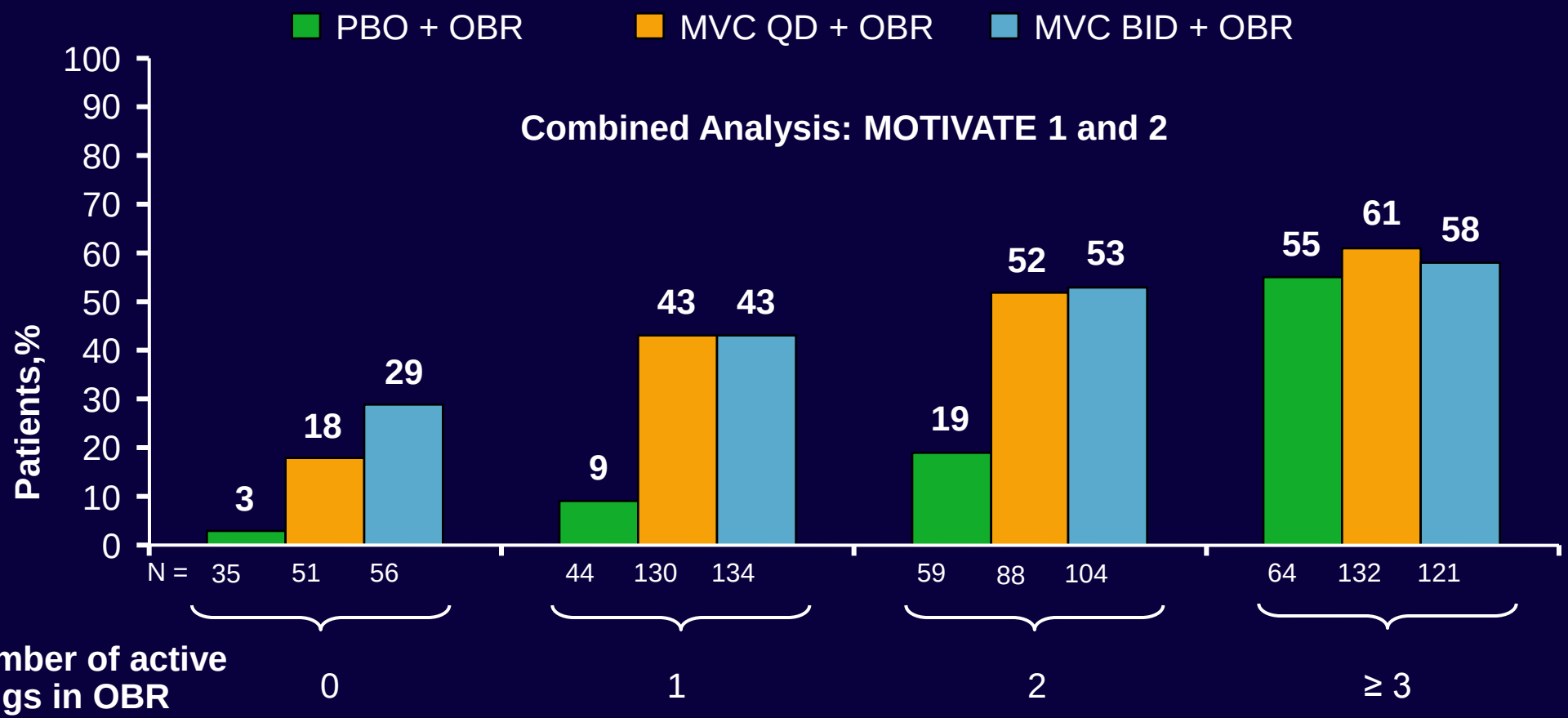
Treating the Highly Experienced Patient
Step 1: How Many Active Drugs are Available?

- Raltegravir: Assume activity if naïve to integrase inhibitors
- Darunavir or tipranavir: Assess susceptibility with phenotype, virtual phenotype, or *cumulative* genotype
- Etravirine: Assess ETR susceptibility, preferably using genotypes obtained at failure of prior NNRTIs
- Maraviroc: Assess tropism
- Enfuvirtide: Necessary in select cases(D/M-tropic with cross-resistance to DRV and ETR)
- NRTIs: Resistance likely. May have partial activity, but rarely count as fully active agents.

Treating the Highly Experienced Patient
Step 2: How Many Drugs do you Need?

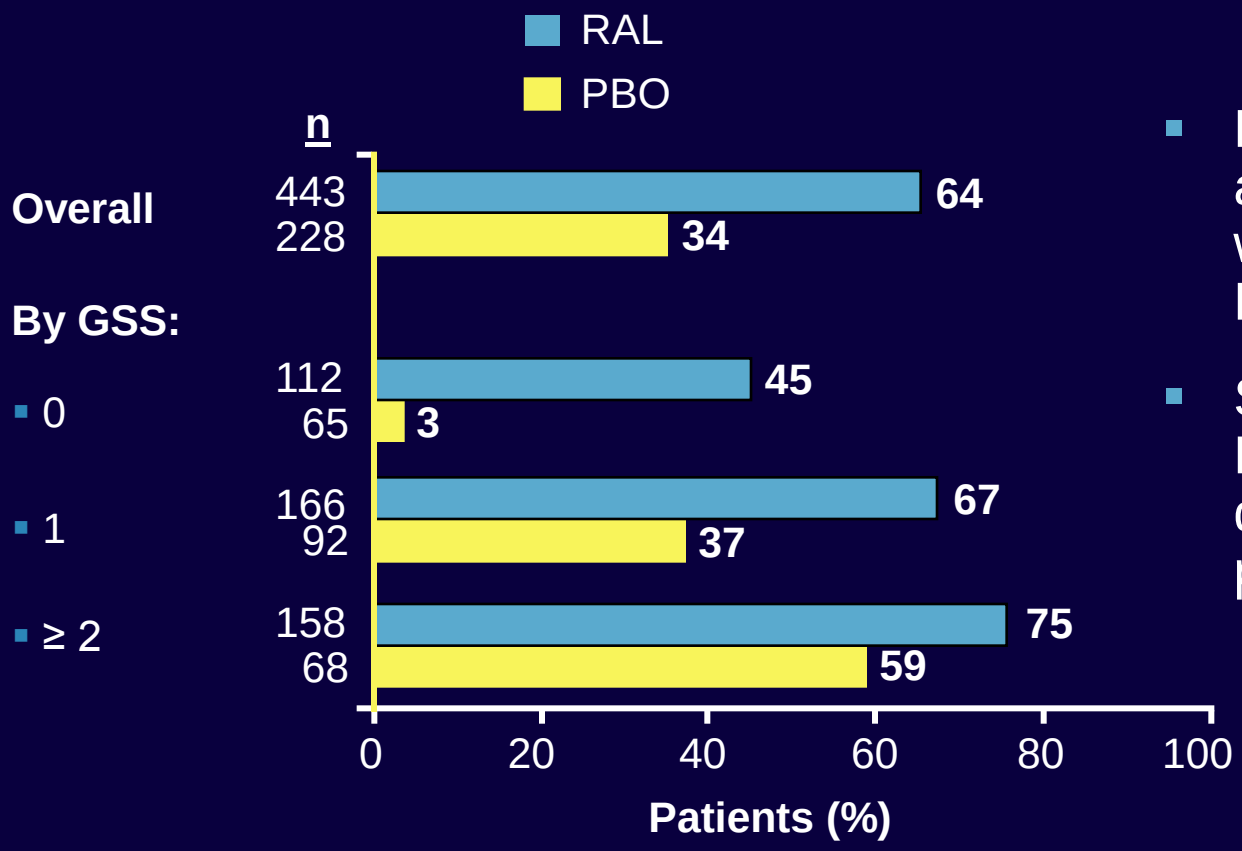
- Clinical trials suggest that patients should be treated with *at least* 2 fully active drugs

MOTIVATE 1 & 2: VL < 50 at Wk 24 by Number of Active Drugs in OBR



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

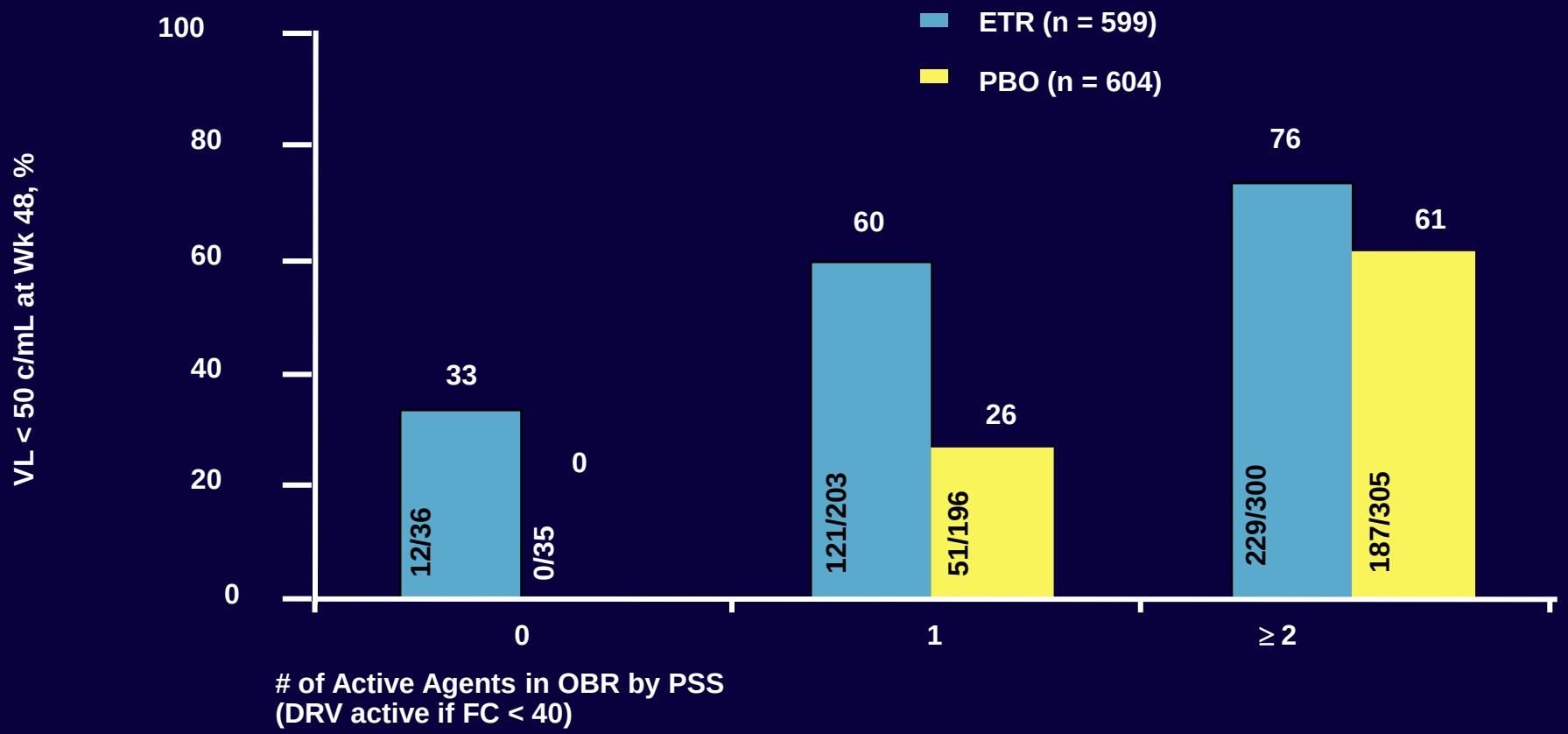
BENCHMRK-1 & -2: Undetectable VL at Week 48, Overall and by GSS



- Rates of virologic suppression also greater with RAL vs PBO when analyzed by baseline PSS
- Similar results when assessing PSS by number of fully active drugs and by number of fully or partially active drugs

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

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



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.

Treating the Highly Experienced Patient
Step 2: How Many Drugs do you Need?

- Clinical trials suggest that patients should be treated with *at least* 2 fully active drugs
- Considerations:
  - Partial susceptibility (PIs, ETR)
  - Low-level D/M or X4 virus (MVC)
- NRTI resistance common. Are NRTIs necessary?
  - To be determined by ACTG 5241

HIV-1 Subtype:

	DRUG			PHENOSENSE™ SUSCEPTIBILITY		Evidence of Susceptibility		Net Assessment	
	Generic Name	Brand Name	Cutoffs (Lower - Upper)	Fold Change	Increasing ← Drug Susceptibility → Decreasing (.1 / 1 / 10 / 100)	Pheno Sense	Gene Seq		
NRTI	**Abacavir**	Ziagen	***(4.5 - 6.5)***	**6.66**		**N**	**N**	Resistant	
	Didanosine	Videx	***(1.3 - 2.2)***	**2.12**		**P**	**Y**	Partially Sensitive	19
	Emtricitabine	Emtriva	*(3.5)*	**>MAX**		**N**	**N**	Resistant	
	Lamivudine	Epivir	***(3.5)***	**>MAX**		**N**	**N**	Resistant	
	Stavudine	Zerit	***(1.7)***	**1.81**		**N**	**N**	Resistant	3
	Zidovudine	Retrovir	*(1.9)*	**20**		**N**	**N**	Resistant	3
	Tenofovir	Viread	***(1.4 - 4)***	**1.81**		**P**	**Y**	Partially Sensitive	3,19
	NRTI Mutations		D67N, K70R, M184V, T215F, K219E						
NNRTI	**Delavirdine**	Rescriptor	*(6.2)*	**36**		**N**	**N**	Resistant	
	Efavirenz	Sustiva	*(3)*	**>MAX**		**N**	**N**	Resistant	
	Nevirapine	Viramune	*(4.5)*	**>MAX**		**N**	**N**	Resistant	
	NNRTI Mutations		K101H/Q, Y188L						
PI	**Atazanavir**	Reyataz	***(2.2)***	**150**		**N**	**N**	Resistant	
		Reyataz / r‡	***(5.2)***	**150**		**N**	**N**	Resistant	
	Darunavir	Prezista / r §	***(10 - 90)***	**13**		**P**	**Y**	Partially Sensitive	19
	Fosamprenavir	Lexiva	*(2)*	**44**		**N**	**N**	Resistant	
		Lexiva / r‡	***(4 - 11)***	**44**		**N**	**N**	Resistant	
	Indinavir	Crixivan	*(2.1)*	**18**		**N**	**N**	Resistant	
		Crixivan / r‡	***(10)***	**18**		**N**	**N**	Resistant	
	Lopinavir	Kaletra	***(9 - 55)***	**46**		**P**	**N**	Partially Sensitive	
	Nelfinavir	Viracept	*(3.6)*	**104**		**N**	**N**	Resistant	
	Ritonavir	Norvir	*(2.5)*	**>MAX**		**N**	**N**	Resistant	
	Saquinavir	Invirase	*(1.7)*	**33**		**N**	**N**	Resistant	
		Invirase / r‡	***(2.3 - 12)***	**33**		**N**	**N**	Resistant	
	Tipranavir	Aptivus / r‡	***(2 - 8)***	**7.33**		**P**	**N**	Partially Sensitive	

trofile™
CO-RECEPTOR TROPISM ASSAY

biosciences

Moore Clinic/Johns Hopkins School of Med
600 Wolfe Street Carnegie 346
Baltimore, MD 21287
USA
Client: 02444 Project: 00073
Phone: (410)955-0708 Fax: (410)955-7733

Patient ID	Gender	Monogram Accession #
8-401-10-50	M	07-136827
Date Reported	Mode	Report Status
09/14/2007 14:07	F,M,W	FINAL
	Reference Lab ID	

D 21205 USA

Tropotype Result

R5 D/M X4

Virus uses CCR5 co-receptors to enter the CD4+ cell.

R5

Activity of CCR5 antagonist anticipated? ■ YES ☐ NO

ABOUT TROPISM

WHAT IS TROFILE™?
Trofile is a CLIA-validated*, cell-based approach to determine an individual's HIV co-receptor tropism (or "tropotype™"). Co-receptor tropism is defined as an interaction of a virus with a specific co-receptor on the target cell. To gain entry to the CD4+ cell (host), HIV must bind to the cell surface CD4 receptor and to one of two chemokine co-receptors (CCR5 or CXCR4) also present on the cell surface.

TROFILE VIRAL CLASSIFICATION
CCR5 (R5) Virus = Virus uses CCR5 chemokine co-receptor to enter the CD4+ cell.
DUAL/MIXED (D/M) Virus = Dual-tropic viruses can use either the CXCR4 or CCR5 co-receptors to enter the CD4+ cell. Mixed-tropic is a mixed population of both CCR5 and CXCR4 tropic viruses.
CXCR4 (X4) Virus = Virus uses CXCR4 chemokine co-receptor to enter the CD4+ cell.
Non-reportable = Your patient's tropotype could not be determined by the Trofile assay. Common causes of failure of the assay are viral load <1,000 copies/mL, reduced viral fitness, or compromised sample collection/handling.

CO-RECEPTOR ANTAGONISTS
A new class of drugs – co-receptor antagonists – provides a novel mechanism to inhibit the HIV viral replication cycle. These drugs work by binding to a specific chemokine receptor (CCR5 or CXCR4) and block the virus' ability to bind these co-receptors and initiate its entry into the host cell. Trofile can help determine whether a CCR5 antagonist or a CXCR4 antagonist may be an appropriate drug for your patient. Several clinical trials on CCR5 antagonists have demonstrated the positive and negative predictive value of Trofile in clinical settings.

* The Trofile assay meets the United States standards for performance characteristics and all other quality control and assurance requirements established by the Clinical Laboratory Improvement Amendments (CLIA). Trofile is a proprietary, recombinant virus, single replication cycle assay that uses the complete gp160 coding regions of HIV-1 to evaluate tropism.

9/14/07

T.D.

- RAL: Naïve to integrase inhibitors: expect full susceptibility
- DRV/r: Phenotypic fold-change 13. Intermediate susceptibility range = 13-90. Expect good activity
- MVC: Has R5-tropic virus (by original assay). Expect good activity
- ETR: Was not available when he started his regimen.
  - Monogram score = 3 (101H=1 + 188L=2): expect activity
  - Tibotec score = 1 (101H=1): expect activity

T.D.

- T.D. was started on a regimen of DRV/r + RAL + MVC
- He tolerated it well and has now been on therapy for over 1 years
- His VL is <50, and his CD4 count is 535.

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.

The Next Drugs?

- Rilpivirine: NNRTI with promise for initial therapy. Probable cross-resistance with ETR
- Elvitegravir: Once-daily boosted integrase inhibitor. Cross-resistance with RAL
- Vicriviroc: Once-daily boosted CCR5 inhibitor. Will be ineffective in patients who fail MVC with D/M-tropic virus

Helpful Resources

- Johns Hopkins HIV Guide: (http: www.hopkins-hivguide.org)
- *Medical Management of HIV Infection* – J.G. Bartlett & J.E. Gallant
- Other useful websites:
  - Clinical Care Options: http://clinicaloptions.com/hiv/
  - Medscape: http://www.medscape.com/hiv-aidshome
  - Stanford HIV Resistance Database: http://hivdb.stanford.edu
  - DHHS Guidelines: http://www.aidsinfo.nih.gov