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Failure

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Trends in HAART Failure

- Retrospective cohort study (1995 to 2005)
- 33,381 patients on HAART
  - 46% had virologic failure
  - 28% changed HAART regimen after failure
  - 15% experienced a second virologic failure
  - 3% died

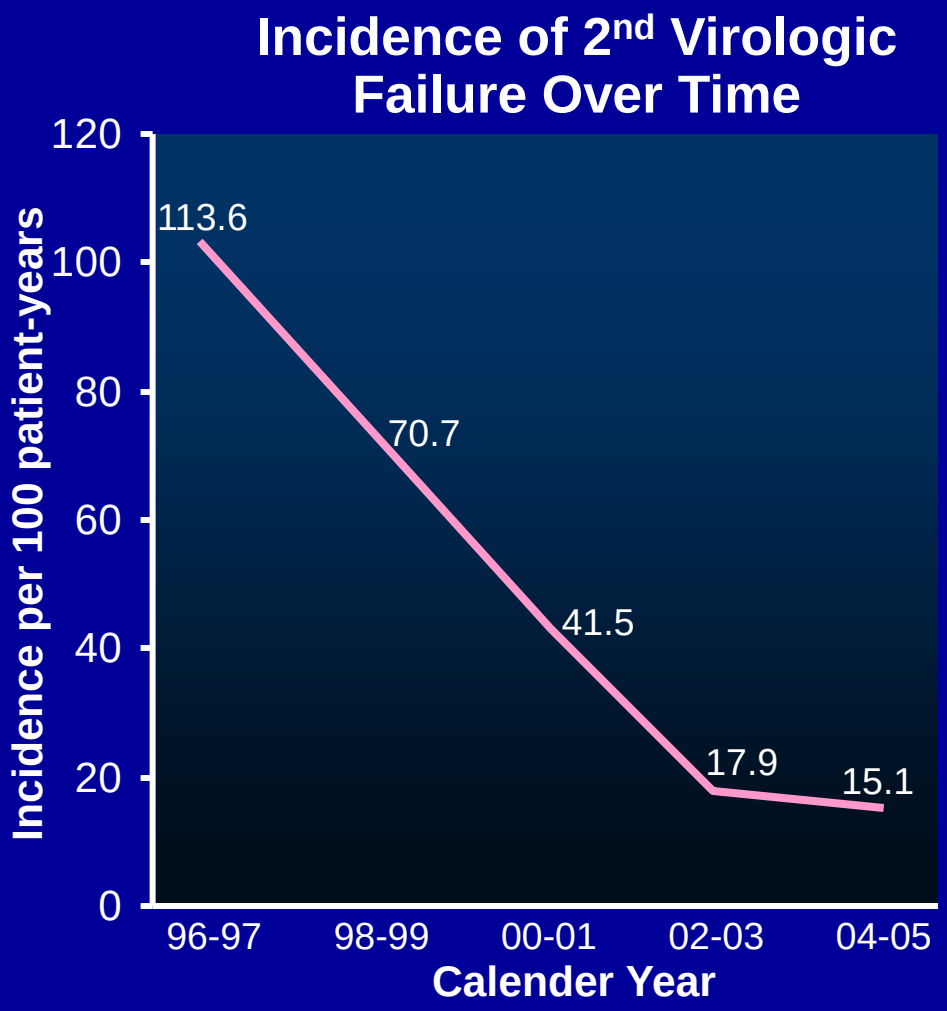
Baseline Characteristics

	Patients With 2nd Virologic Failure (n=5057)
Male (%)	85
HIV RNA (copies/mL)	15,723
Median CD4 (cells/mm^3)	222
Antiretroviral naïve at HAART initiation (%)	31
Median time from HAART initiation (years)	2.9
Prior AIDS-defining event (%)	37

Deeks S, et al. 15th CROI. Boston, 2008. Abstract 41.

Trends in HAART Failure

- Adjusted relative risk of second virologic failure has declined dramatically
  - Decreased from 1.46 (96-97) to 0.54 (04-05) per 100 patient-years
- No improvement in mortality
  - Median survival: 7.1 years
- Independent risk factors associated with increased risk of death
  - CD4 cell count and HIV RNA level at time of second virologic failure
  - No association
    - Prior treatment exposure
    - Pre-HAART



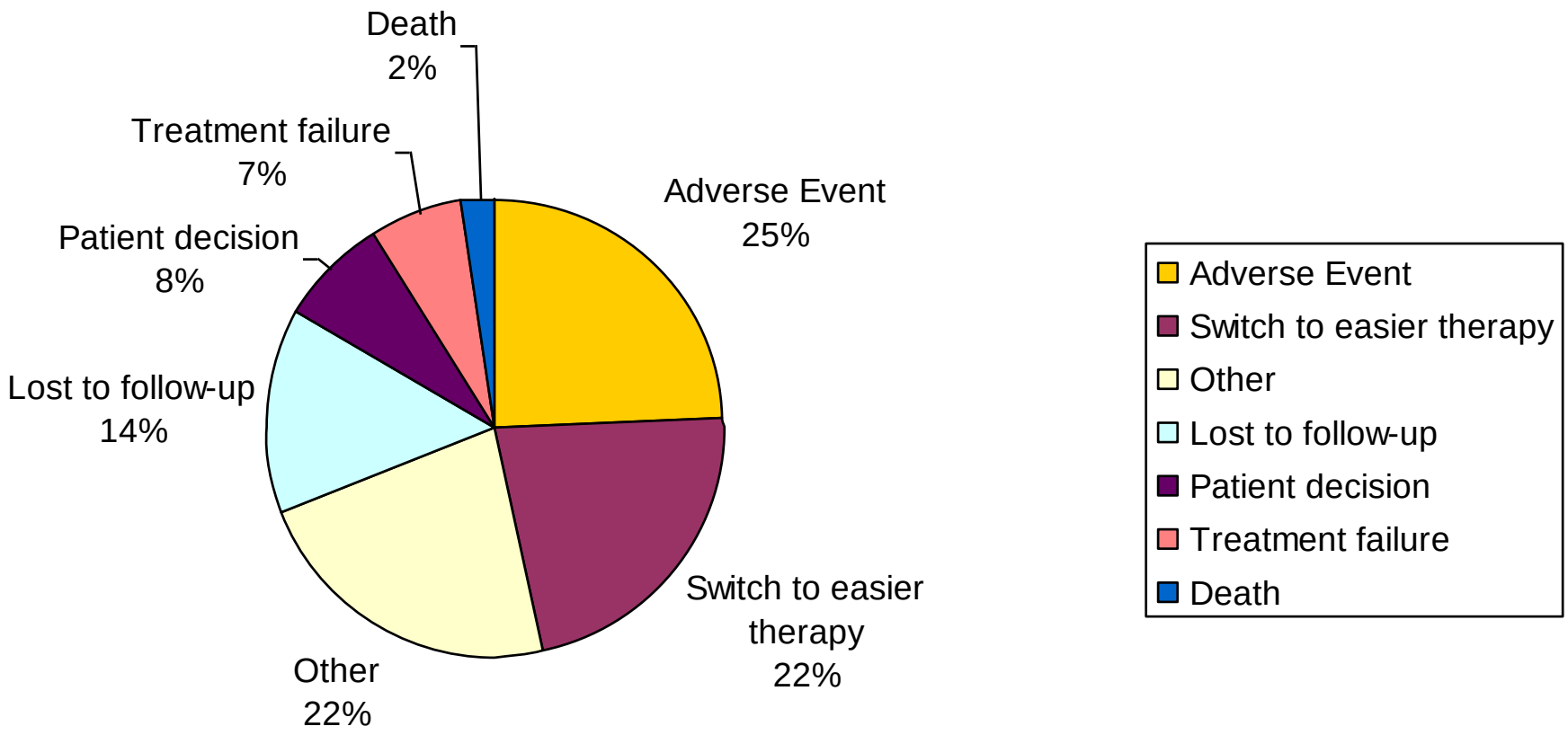
Deeks S, et al. 15th CROI. Boston, 2008. Abstract 41.

St-Pierre cohort : Viral load response to first line therapy

OT		2001	2002	2003	2004	2005	2006	2007
at month **12**	Number p with VL < 50	46	52	44	41	49	57	30
	Nb of patients tested	61	57	55	43	57	63	31
	% of patients with VL < 50	**75%**	**91%**	**80%**	**95%**	**86%**	**90%**	**97%**
ITT		**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**
at month **12**	Number p with VL < 50	82	98	87	76	72	84	37
	Nb of patients tested	109	124	113	94	95	108	47
	% of patients with VL < 50	**75%**	**79%**	**77%**	**81%**	**76%**	**78%**	**79%**
at month **24**	Number p with VL < 50	82	96	77	74	74	37	
	Nb of patients tested	107	118	98	97	96	46	
	% of patients with VL < 50	**77%**	**81%**	**79%**	**76%**	**77%**	**80%**	
at month **36**	Number p with VL < 50	80	70	69	72	34		
	Nb of patients tested	109	100	95	90	43		
	% of patients with VL < 50	**73%**	**70%**	**73%**	**80%**	**79%**		

St-Pierre cohort :

2.3.6.2. Reasons for stopping first line therapy in 2007



Failure of initial HAART regimens

Rate of failure of HAART regimens have decreased in developed countries because

- **Better tolerance of new regimens**
- **New regimens are easier to take**
  - **Less pill count**
  - **Once daily**
  - **No** food/ water restrictions

EACS definition of failure

Confirmed Plasma HIV RNA > 50 copies/ml

6 months after starting therapy

But real failure or blip?

Incidence of low-level viremia more frequent than high-level viremia

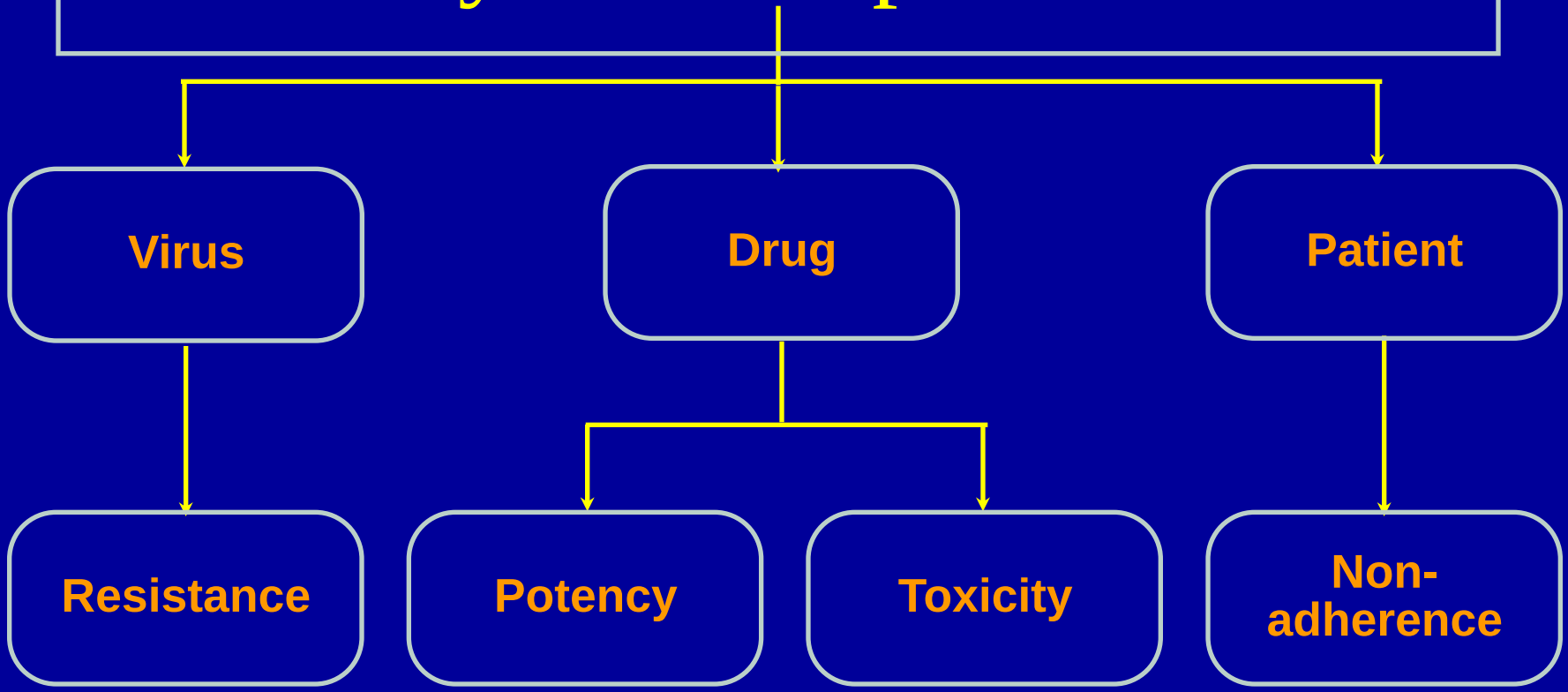
HIV-1 RNA Level During Follow-up, %	Study Cohort (N = 4447)
Persistently < 50 copies/mL	71.2
≥ 1 measurement > 50 copies/mL	28.8
≥ 1 measurement > 1000 copies/mL	6.7

van Sighem A, et al. J Acquir Immune Defic Syndr. 2008;48:104-108.

- After initial virologic suppression with cART, approximately 30% of patients experienced transient viremia
  - 7% classified as high level (> 1000 copies/mL)
- Low level viremia(50-1000 c/mL) is not associated with clinical events, development of high-level viremia, or changes in CD4+ cell counts
- High-level viremia is associated with occurrence of resistance and therapy changes

van Sighem A, et al. J Acquir Immune Defic Syndr. 2008;48:104-108.

Why do therapies fail?



Adherence

- **Adherence may be the single most important factor affecting treatment outcomes to HAART**

- **Many components contribute to non-adherence**

  - patient characteristics
  - clinical care settings
  - patient-provider relationships
  - drug regimens characteristics

Checking adherence

- Interview the patient to evaluate adherence and compliance
- Re-explain the objectives and modalities of the treatment ant the potential risks of poor adherence
- Exclude potential drug-drug or drug-food interactions
- Use TDM if needed (and if available ...)

Improving adherence

- Reduce tablet load (fixed-dose)
- Remove food restrictions
- Reduce dose frequency (qd)

➔ Adapt to P. way of life

- ➢ Provide nurse counselling
- ➢ Provide pill box
- ➢ Provide psychological support

Which Barriers to resistance ?

NRTIs

Few change per mutation

BUT

Toxicity

NNRTIs

High drug levels

BUT

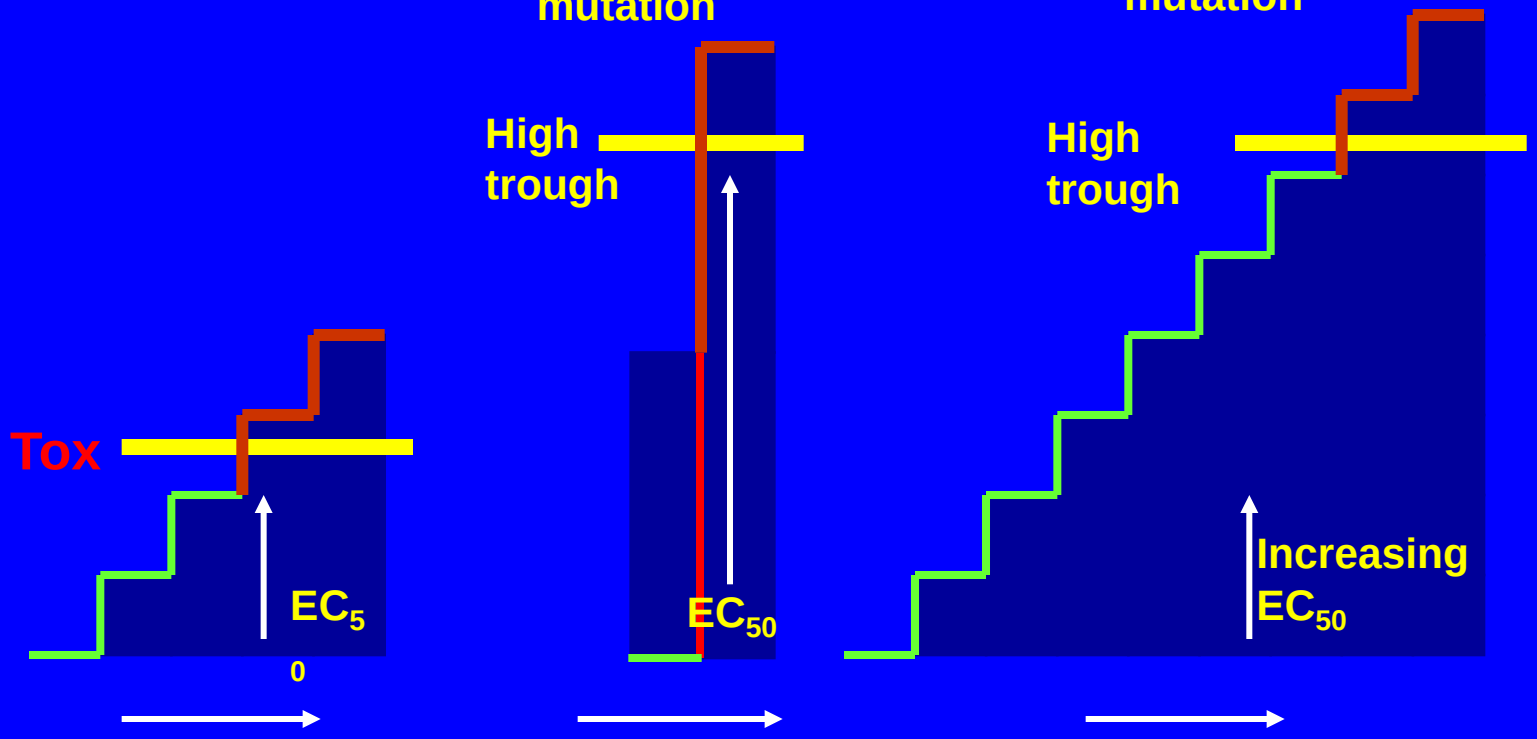
Large change per mutation

Boosted-PI

High drug levels

AND

Small change per mutation



Dale Kempf et al.

Which first-line ART ?

- « Boosted protease inhibitors have 60% lower risk of resistance compared with other classes « (Lima et al J Infect Dis July 2008)
- Factors associated with increased risk:=a higher baseline VL;an NNRTI-based combination;a high but still suboptimal adherence

Which options in case of failure ?

Management of failure

- **Decision to change treatment regimen must take into account :**
  - **the remaining treatment options**
  - **the level of failure based on kinetics of viral load and CD4 (decreased viral fitness)**
  - **the past treatment history, including resistance patterns, tolerability and adherence issues**

- **Choice of treatment will be based on the number of active drugs within each class (genotypic testing)**

ARV Failure; a historical perspective, before the 2006-08 new paradigm

FAILURE	First	Second-third	Multiple
Options	Many	Some	Few
Goals	VL	VL/CD4	CD4
Action	Adapt or switch	Wait or switch	**Do your best …**

Before 2006 :

1. Continue the same therapy
2. Stop therapy in order to revert to a wild type virus
3. Use a PI boosted regimen to try to overcome resistance
4. Re-cycle previous drugs
5. Use mega – or giga – HAART
6. Use new investigational agents, if available

Interruption of Therapy

?

Continuation of Therapy

Option 1 : Continuing therapy

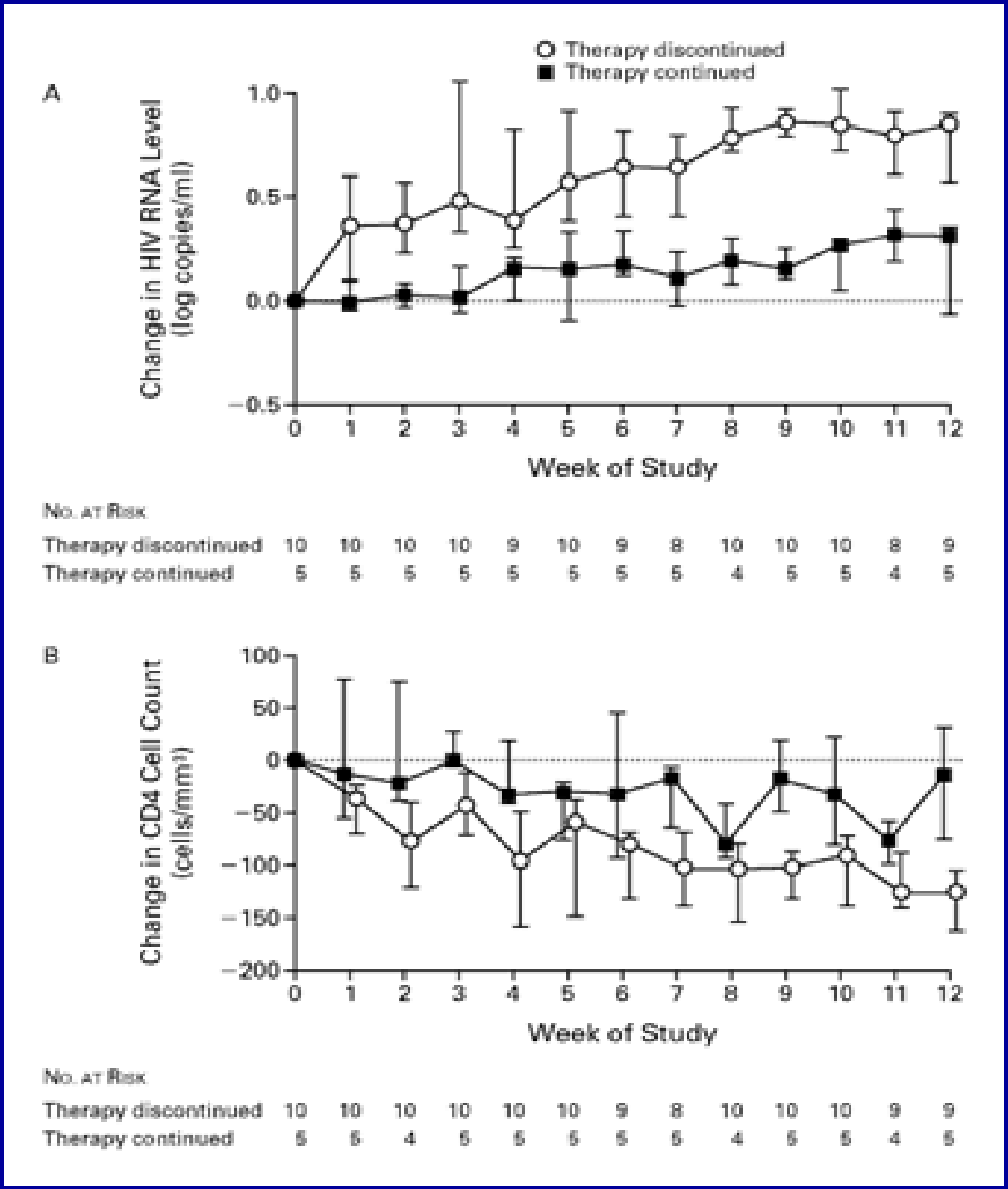
- **Patients with $CD_4 < 50$, failing all 3 classes, who continue therapy show better outcome, particularly those with more drugs (Miller et al., AIDS 2002)**
- **This is probably in relationship to viral fitness (Deeks et al., 2002)**
- **BUT this strategy may lead to development of further drug resistance, that could preclude the use of a new drug in an existing class**

Option 2 : Stopping therapy

- **The goal is to restore the more sensitive wild type virus**

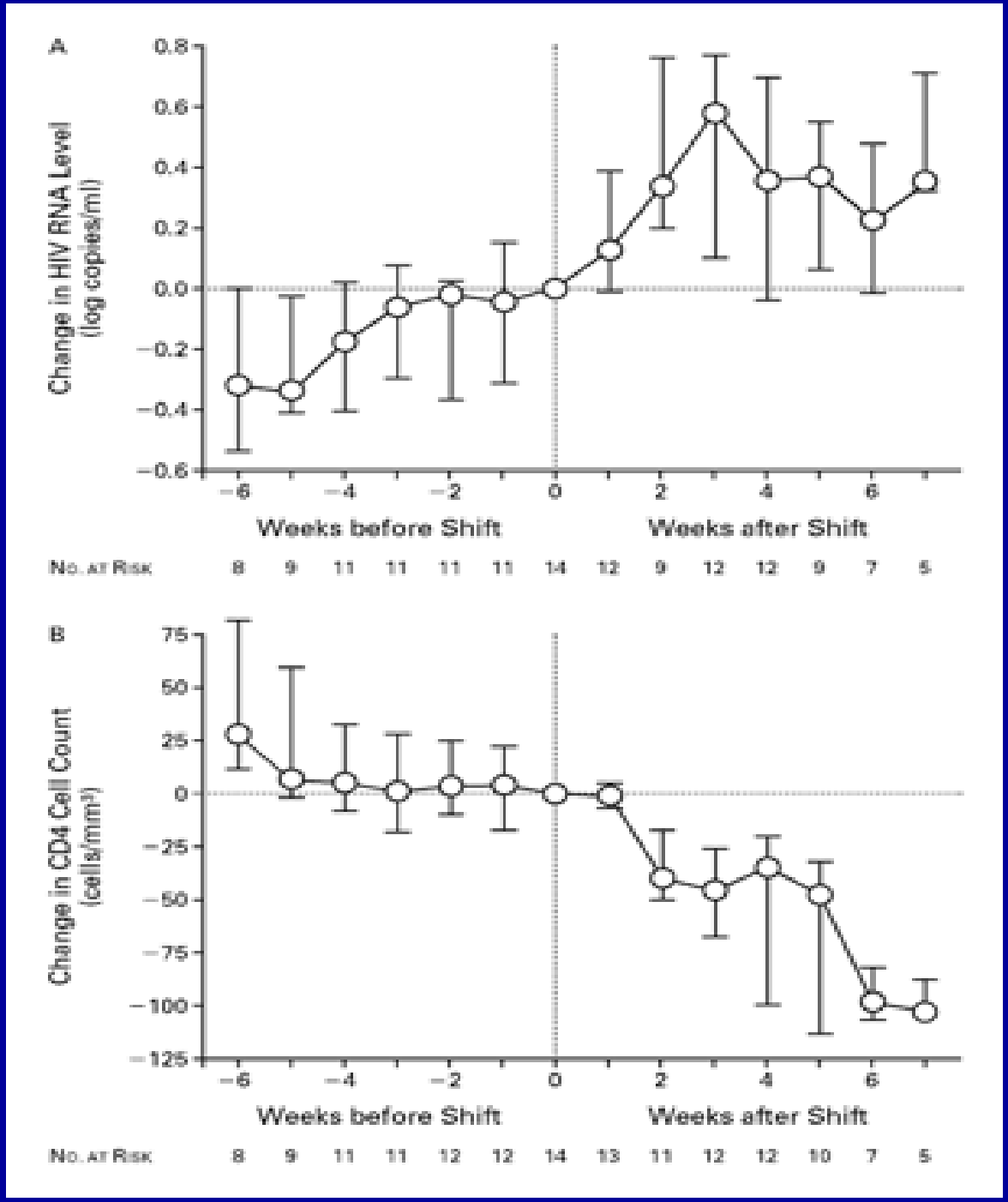
- **One study (Gighaart) suggests a benefit of this strategy in patients with very low CD_4 count, while studies in patients with higher CD_4 suggest that this strategy is counter productive**

Median changes in plasma viral load and CD_4 cells in failing patients continuing or discontinuing therapy



From Deeks et al., NEJM, 2001

Median changes in plasma viral load and CD_4 cells before and after switch of resistance in patients discontinuing therapy



From Deeks et al., NEJM, 2001

STI in patients with multiple failures

GIGHAART, Katlama et al., Boston 2003

- 70 patients randomized +/- STI 8 Weeks
- VL 5.3 log CD4 27/mm3 Median ARV 6.6 years

Results		No STI	STI	
At W 12/20	median VL	-0.37	-1.91	SS
	<400 cp	15%	38%	
At W 24/32	median CD4	+7	+51	
	>50 /mm3	25%	50%	NS
	HIV clinical events	3	5	
At W48/56	median VL	-0.37	-0.79	
	median CD4	+7	+69	

Option 3 : Use of boosted regimens

- **The aim is to overcome resistance due to suboptimal plasma drug level**

- **Ritonavir boosted regimens are widely used but the best results are usually obtained in the early stages of treatment (less mutations)**

Option 4 : Recycle drugs

- **The goal is to maintain the selective pressure for some specific mutations such as M184V**
- **The mutational effects on viral fitness may now be assessed by a replicative capacity assay**
- **Patients with discordance failure (virological but not CD_4) harbour viruses with lower replicative capacity (Deeks et al., 2001)**

Option 5 : Use Mega/Giga – HAART

- **The goal is to keep patients, who have no options, alive and well, until new drugs become available**

Option 6 : Use of new drugs

Enfuvirtide : Phase 3 Studies in Highly Experienced Patients

VL reduction

	Enfuvirtide +OB	**OB**	p
TORO 1	-1.70	-0.76	<0.0001
TORO 2	-1.43	-0.65	<0.0001

Injection site reactions were the most frequent AE's but with low discontinuation rate (3%)

Lalezari. NEJM 2003

Since 2006 :

1. **Use a genotype - driven salvage therapy plus**

2. **Use at least 2 new active agents**
   - **New PI: Tipranavir, Darunavir**
   - **New NNRTI: Etravirine**
   - **CCR5 inhibitors**
   - **Fusion inhibitors: enfuvirtide**
   - **Integrase inhibitors**

The new Paradigme for multi-experienced patients is to reach undetectable viral load

The « New Paradigme »

HIV-1 RNA suppression to < 50 copies/mL should be the therapeutic goal for treatment-experienced HIV-infected patients as defined by :

- 2006 US DHHS
- 2006 International AIDS Society-USA guidelines
- 2007 EACS guidelines

Week 48 Virologic Efficacy of New Drugs Defined as HIV-1 RNA < 50 c/mL

Study	Drug Regimen	HIV-1 RNA < 50 copies/mL, %
TORO [1]	Enfuvirtide + OBR OBR alone	18.3 7.8
RESIST [2]	Tipranavir + OBR Comparator PI + OBR	22.8 10.2
POWE [3]	Darunavir/ritonavir + OBR Comparator PI + OBR	45.0 10.0
DUET [4,5]	Etravirine + darunavir/ritonavir-containing OBR Placebo + darunavir/ritonavir-containing OBR	60.0 40.0
MOTIVATE [6]	Maraviroc QD + OBR Maraviroc BID + OBR Placebo + OBR	41.8 46.8 16.1
BENCHMRK [7,8]	Raltegravir + OBR Placebo + OBR	63.0 33.0

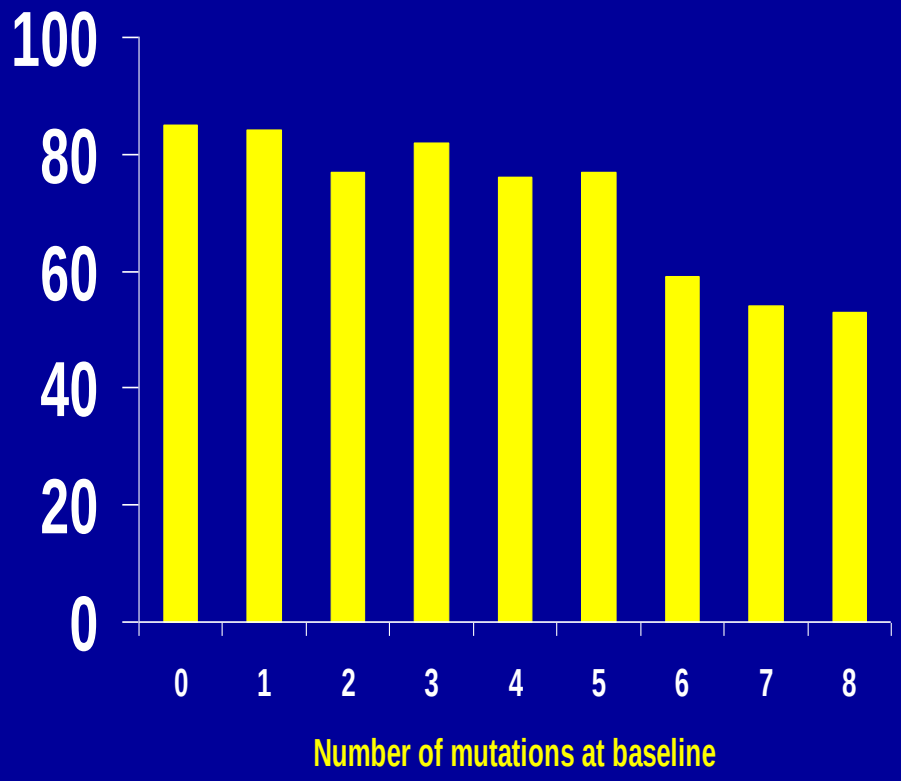
[1]. Nelson M, et al. J Acquir Immune Defic Syndr. 2005;40:404-412. [2]. Hicks CB, et al. Lancet. 2006;368:466-475. [3]. Clotet B, et al. Lancet. 2007;369:1169-1178. [4]. Haubrich R, et al. CROI 2008. Abstract 790. [5]. Johnson M, et al. CROI 2008. Abstract 791. [6]. Lalezari J, et al. ICAAC 2007. Abstract H-718a. [7]. Cooper DA, et al. N Engl J Med. 2008. In press. [8]. Steigbigel R, et al. N Engl J Med. 2008. In press.

New PI

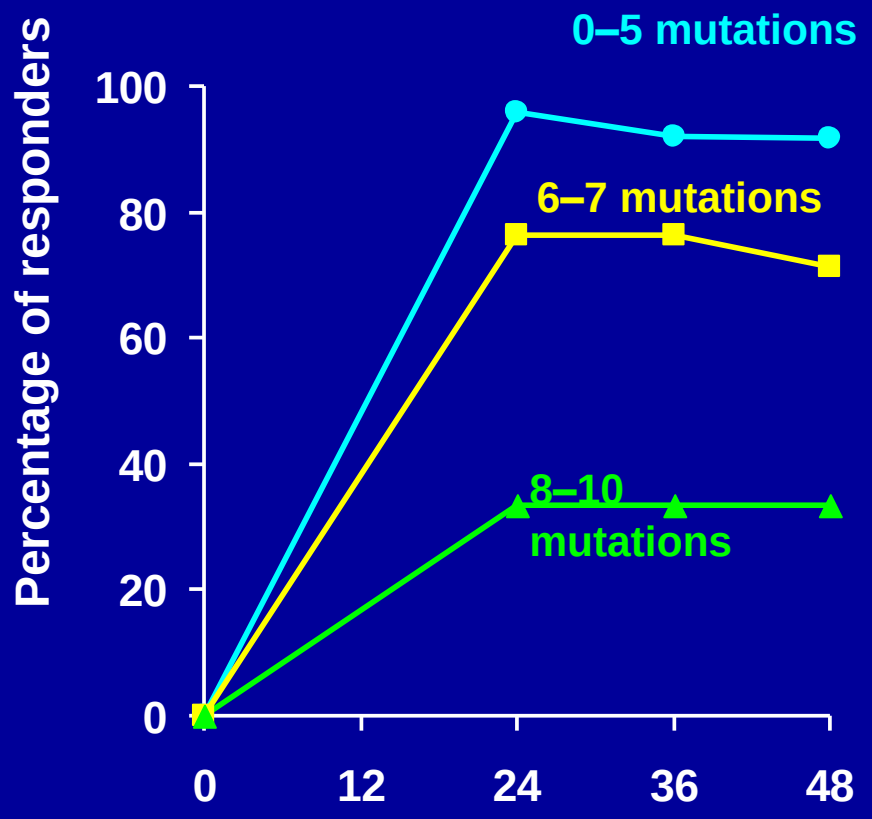
Tipranavir

Darunavir

Virologic response with respect to baseline number of LPV mutation



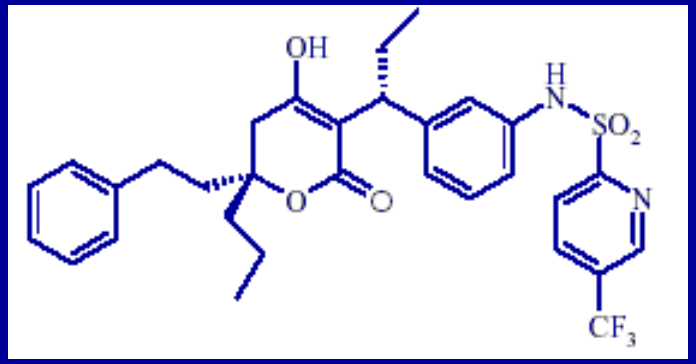
Calvez et al. Scotsdale resistance meeting, 2001



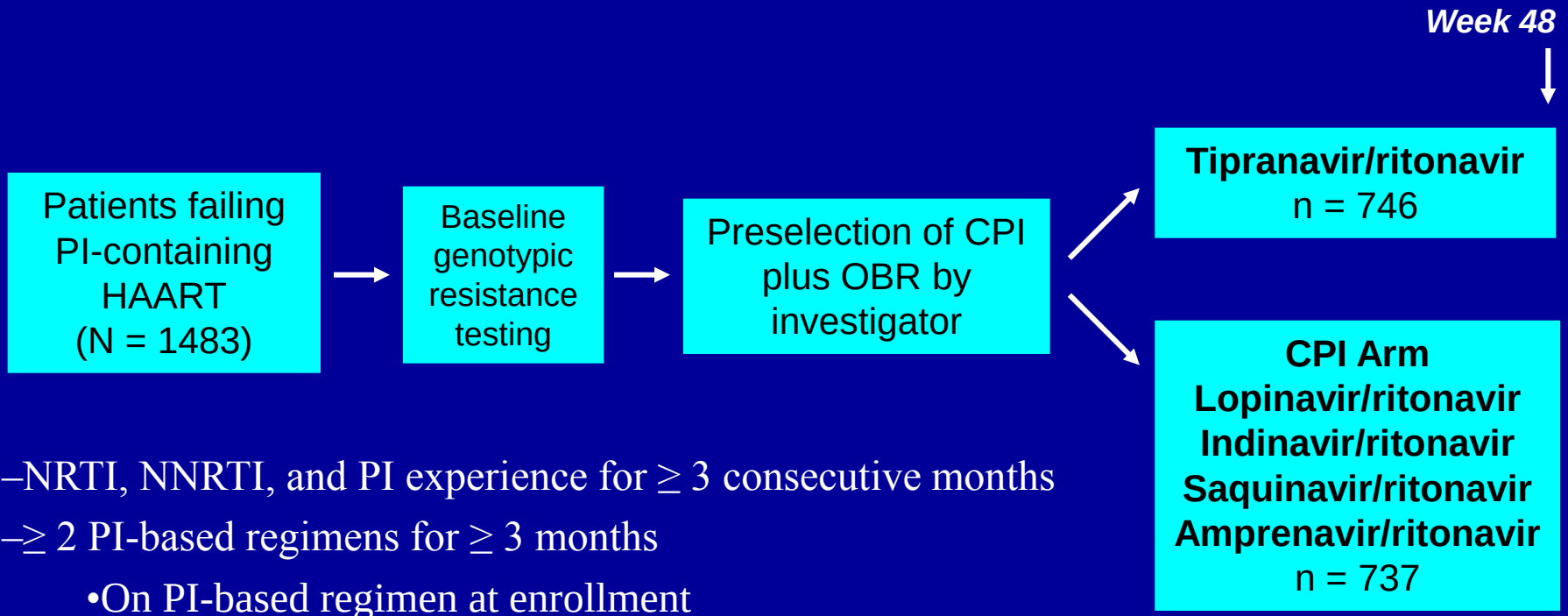
Kempf et al. Scotsdale resistance meeting, 2001

Tipranavir

- nonpeptidic PI with potent activity against PI-resistant HIV-1 both in vitro and in vivo
  - Approved in United States and Europe for use in PI-experienced patients in combination with ritonavir



Study Design RESIST 1 and 2 in which tipranavir plus OBR compared with r-boosted comparator PI (CPI) plus optimized background regimen (OBR)



–NRTI, NNRTI, and PI experience for ≥ 3 consecutive months

–≥ 2 PI-based regimens for ≥ 3 months

•On PI-based regimen at enrollment

–≥ 1 documented primary PI mutation (30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, 90M)

–≤ 2 mutations at codons 33, 82, 84, and 90

Outcome at Week 48	Tipranavir/Ritonavir (n = 746)	CPI/Ritonavir (n = 737)	*P* Value
Treatment response, %	33.6	15.3	< .0001
• In patients using ENF	48.5	20.0	< .0001*
• In patients using first-time ENF	58.5	21.6	< .0001
HIV-1 RNA < 400 copies/mL, %	30.4	13.8	< .0001
• In patients using ENF	43.2	18.5	< .0001*
HIV-1 RNA < 50 copies/mL, %	22.8	10.2	< .0001
• In patients using ENF	28.4	14.1	< .0001*
Mean HIV-1 RNA reduction, $\log_{10}$ copies/mL (SD)	1.14 (1.30)	0.54 (1.02)	< .0001
Mean CD4+ cell count increase, cells/mm^3 (SD)	45 (104)	21 (89)	< .0001

ENF, enfuvirtide; IQR, interquartile range.
*Comparison between use and nonuse of enfuvirtide within treatment arm.

Patient Outcomes

- Several factors significantly and independently associated with treatment response to tipranavir/ritonavir:
  - ENF use: Odds Ratio 4.07 ; $P < .0001$
  - Higher tipranavir trough concentration ; Odds Ratio , 2.16 ; $P < .05$
  - Fewer baseline tipranavir mutations (0-2 vs 5-6): Odds Ratio , 0.14; $P < .0001$
- Other factors associated with treatment response to tipranavir/r
  - ≤ 2 primary PI mutations at baseline: 40.8% vs 31.5% ($P = .03$)
  - Prior treatment with ≤ 3 PIs: 40.9% vs 30.5% ($P = .007$)

Other Outcomes

- Incidence of exposure-adjusted adverse events similar between arms
- Significantly higher triglycerides, ALT/AST, and cholesterol in the tipranavir/ritonavir arm

Adverse Events and Grade 3/4 Laboratory Abnormalities, n (Rate per 100 Patient-Years)	Tipranavir/Ritonavir (n = 749)	CPI/Ritonavir (n = 737)	*P* Value
Any adverse event leading to study discontinuation	90 (12.4)	48 (10.6)	--
Triglycerides	184 (30.8)	94 (23.1)	< .0001
ALT	71 (10.1)	15 (3.3)	< .0001
AST	45 (6.3)	13 (2.9)	.002
Cholesterol	31 (4.3)	3 (0.7)	< .0001

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Tipranavir-r : Conclusions in highly experienced P.

- Associated with significantly superior treatment outcomes vs r-boosted CPI plus OBR through 48 weeks of treatment
  - Treatment response rate significantly higher with tipranavir/r
  - Significantly longer time to treatment failure with tipranavir/r
- Inclusion of enfuvirtide in OBR increased likelihood of effective treatment outcomes
- Safety profile similar to that of other r-boosted Pis

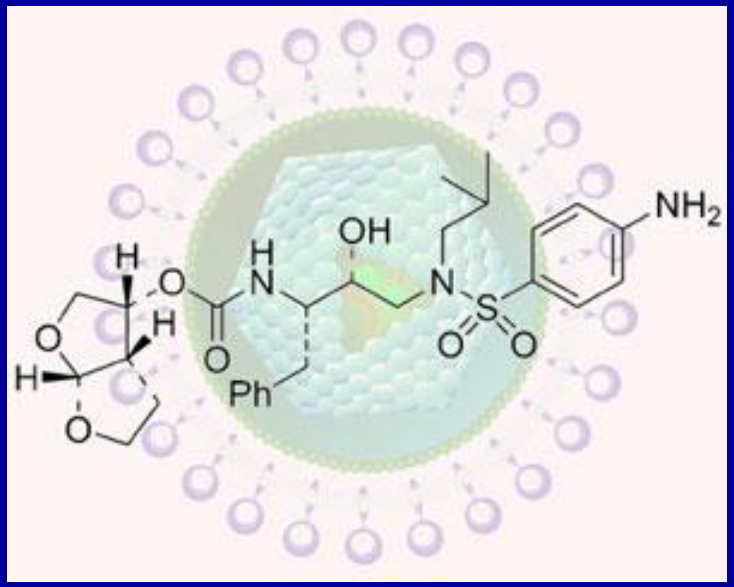
Disadvantages of Tipranavir-r

- 4 pills (2 Tipra+2 RTV 100mg) BID
- Liver toxicity
- Lipid profile is worsened

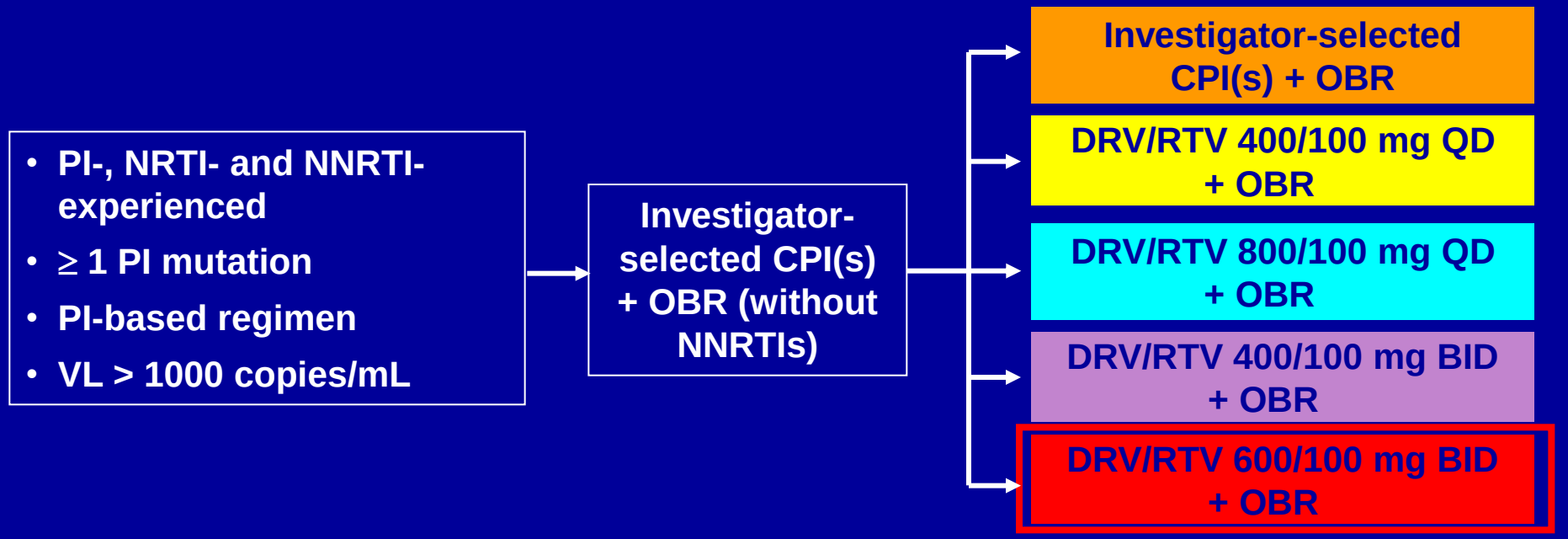
- Drug-drug interaction:
  - no other PI allowed
  - Etravirine not allowed

Darunavir

- Darunavir/ritonavir a potent boosted PI active against wild-type and many PI-resistant viruses[1]



POWER 1 and 2 : Study Design



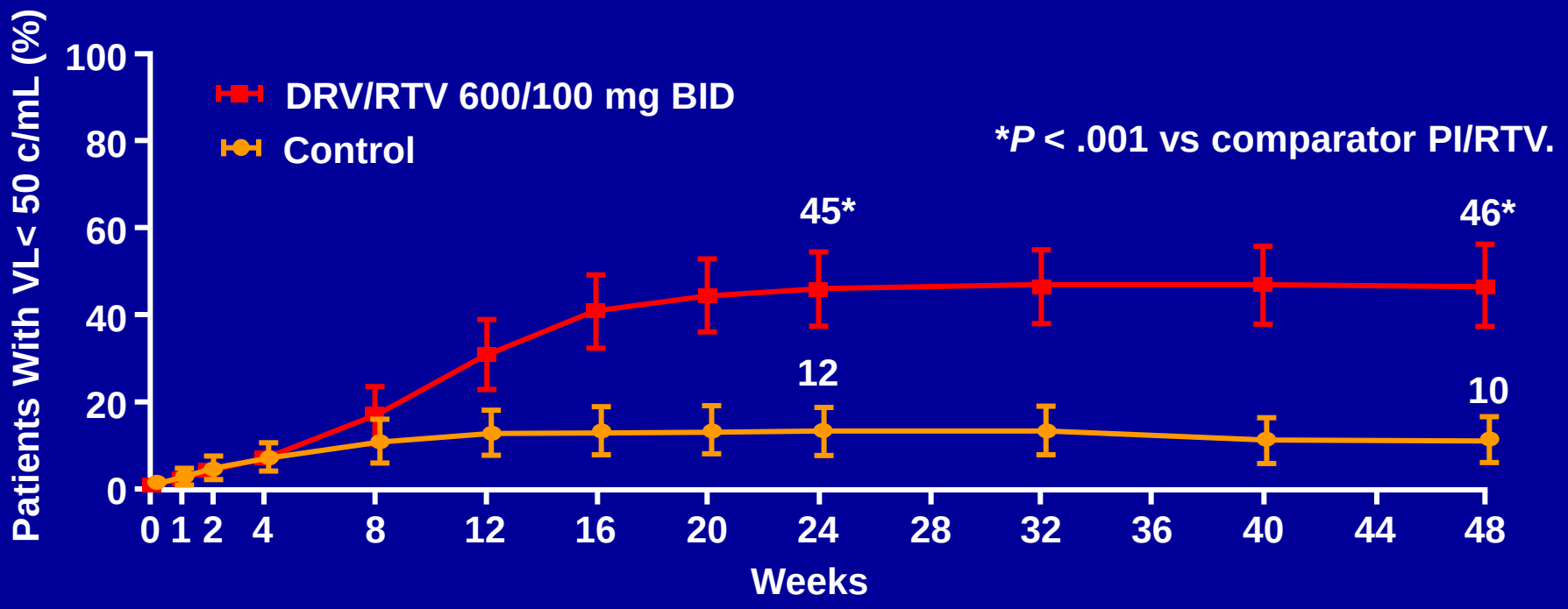
- DRV/RTV 600/100 mg BID provided greatest virologic response in Wk 24 analysis; Now ,FDA-approved dose for treatment-experienced pts

VL, viral load; OBR, optimized background regimen (NRTIs ± enfuvirtide)

Lazzarin A, et al. IAC 2006. Abstract TUAB0104.

POWER 1 and 2 : VL < 50 c/mL

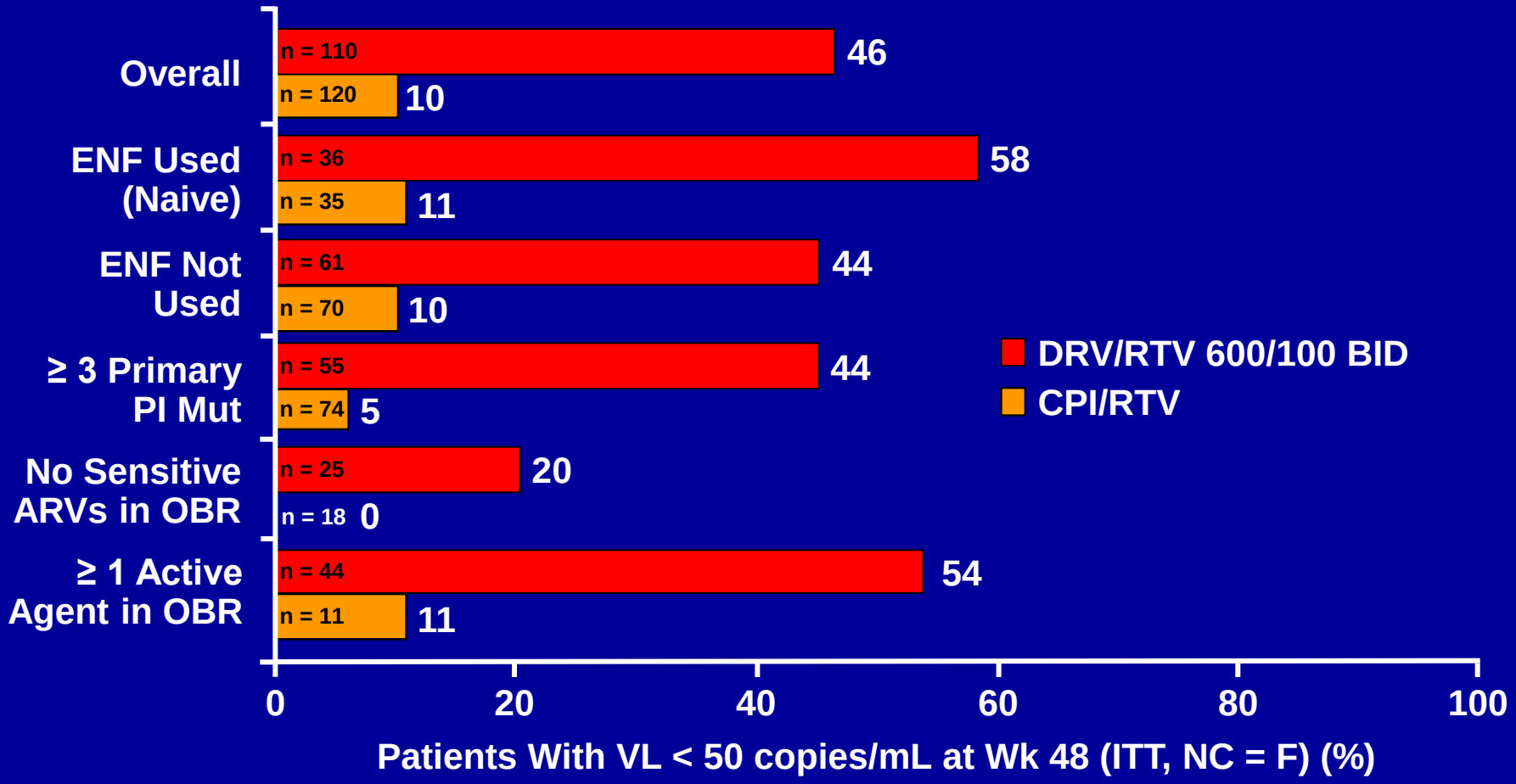
at week 48 (ITT-TLOVR)



Lazzarin A, et al. IAC 2006. Abstract TUAB0104.

POWER 1 and 2: VL < 50 c/mL

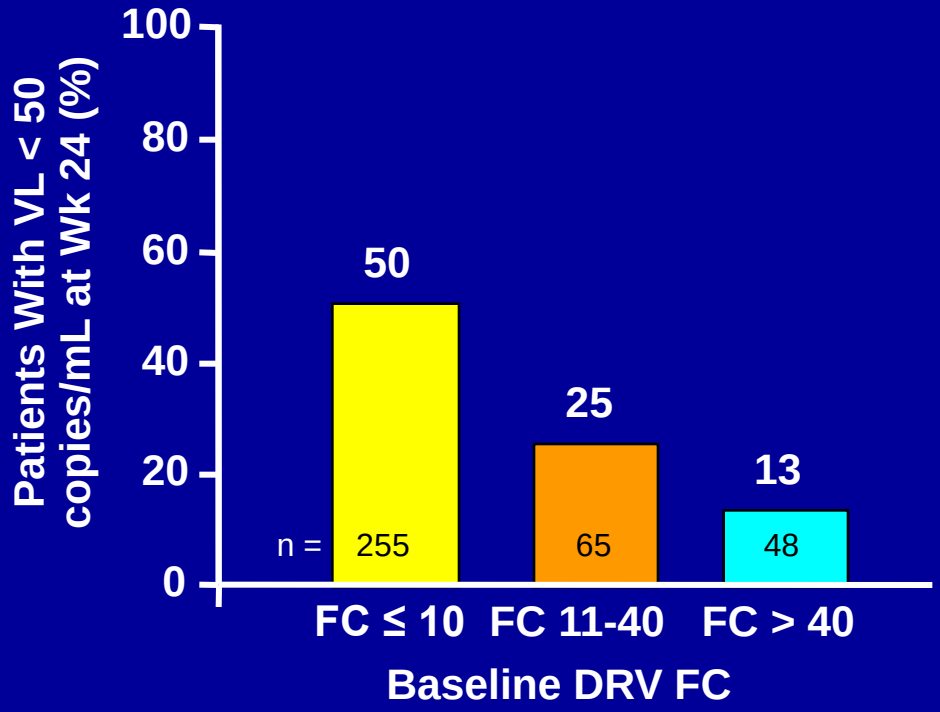
at Week 48 by Baseline Subgroups

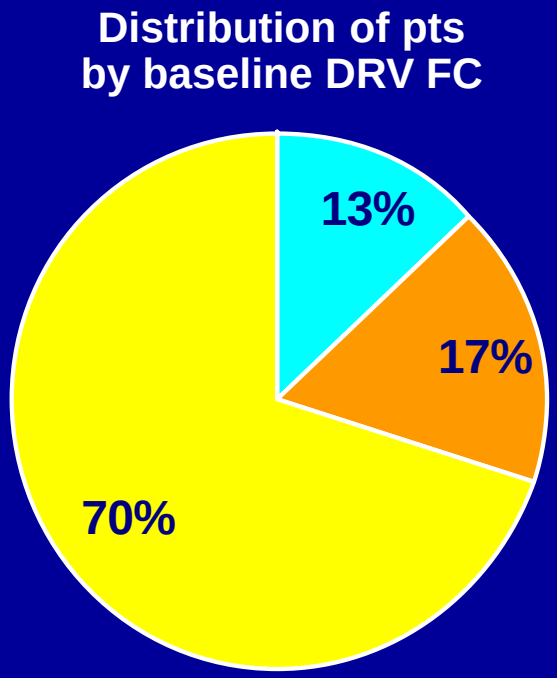


Lazzarin A, et al. IAC 2006. Abstract TUAB0104.

Effect of Baseline DRV Fold Change on Response to DRV

- **Baseline fold-change to DRV (by *Antivirogram*) was strong predictor of Week 24 response in POWER 1, 2, and 3**

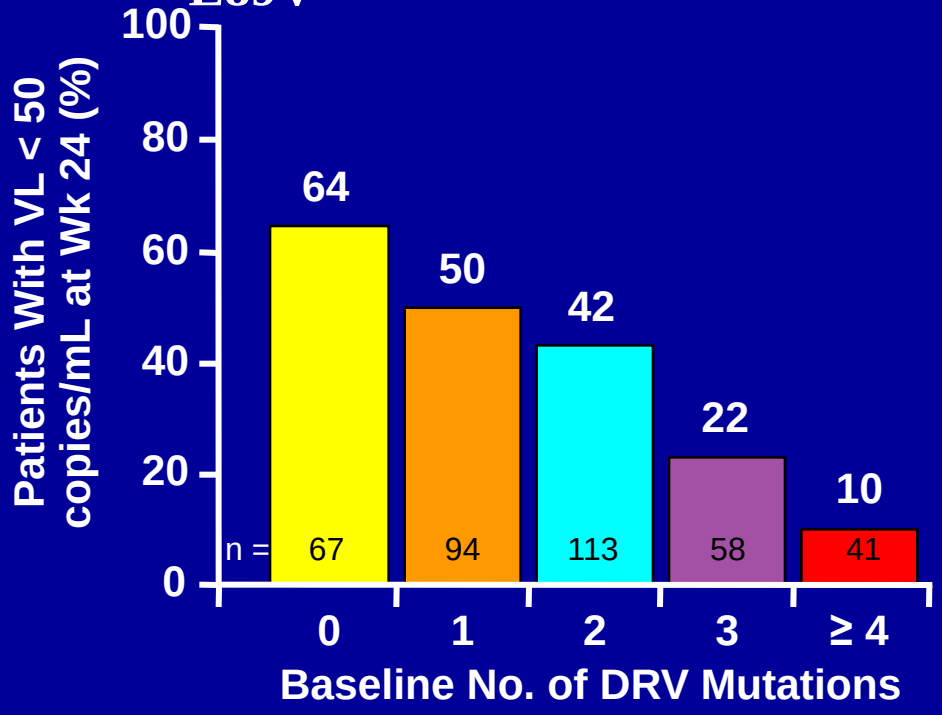


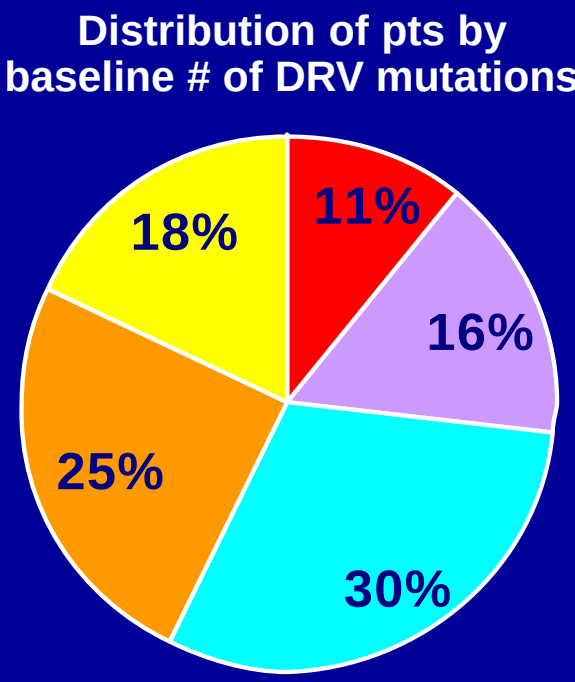


DeMeyer S, et al. Resistance Workshop 2006. Abstract 73.

Effect of Baseline DRV-associated Mutations on Response to DRV

- **11 PI resistance mutations associated with reduced response**
  - **V11I, V32I, L33F, I47V, I50V, I54L, I54M, G73S, L76V, I84V and L89V**





DeMeyer S, et al. Resistance Workshop 2006. Abstract 73.

Relationship Between Activity of OBR and Response to DRV/RTV 600/100

- **Highest rates of VL < 50 copies/mL in pts with ≥ 2 active agents in OBR[1]**
- No incremental benefit of active ENF if ≥ 1 active NRTI in OBR[1]
- Phenotypic susceptibility score (PSS) of OBR also predicted VL < 50 at Wk 24[2]
  - PSS ≤ 0.5: 34%
  - PSS 0.5-1.5: 49%
  - PSS > 1.5: 52%

Characteristic of OBR	VL < 50 at Wk 24, %
# of active agents	
• 0	26
• 1	46
• ≥ 2	49
Type of active agent	
• Active ENF only	43
• ≥ 1 active NRTI, no ENF	51
• ≥ 1 active NRTI + active ENF	53

1. Pozniak A, et al. BHIVA, 2006. Abstract P3.
2. Vangeneugden T, et al. Resistance Workshop, 2006. Abstract 1138.

Other Outcomes

- Most adverse events mild to moderate in severity
  - 25% of patients reported ≥ 1 grade 3 or 4 adverse event

Grade 3-4 Adverse Events With Incidence ≥ 2, %	Darunavir/Ritonavir (n = 298)
Diarrhea	14
Nausea	10
Elevated cholesterol	4
Elevated triglycerides	6
Elevated pancreatic amylase	7
Elevated ALT	2
Elevated AST	2

Molina JM, et al. J Acquir Immune Defic Syndr. 2007;46:24-31.

Summary of Key Conclusions

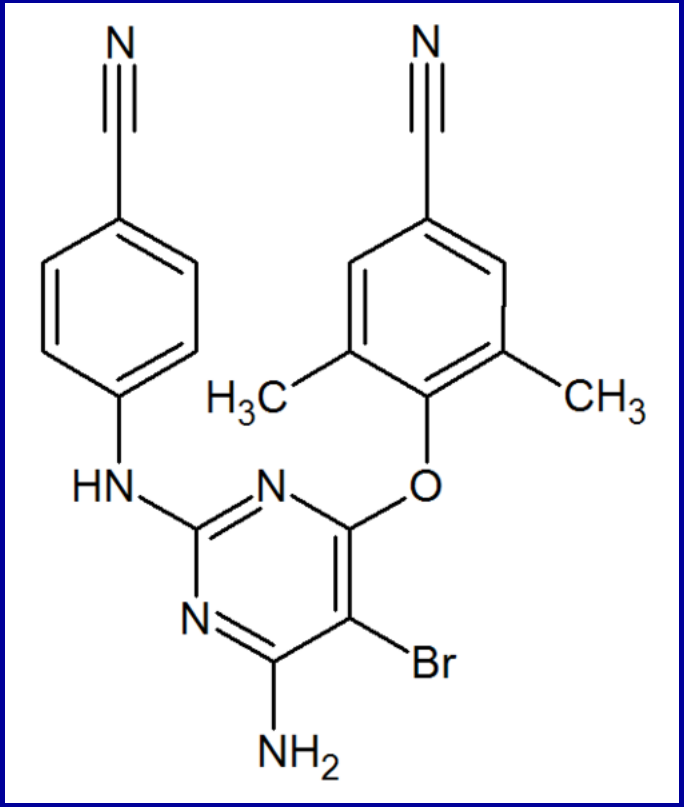
- Darunavir/ritonavir 600/100 mg twice daily safe and effective in treatment-experienced patients with drug-resistant HIV
  - Rates of virologic suppression is the highest in pts with > 1 active agent in OBR
  - Full susceptibility to darunavir strongest predictor of response
  - Safety profile of darunavir/r is good

Molina JM, et al. J Acquir Immune Defic Syndr. 2007;46:24-31.

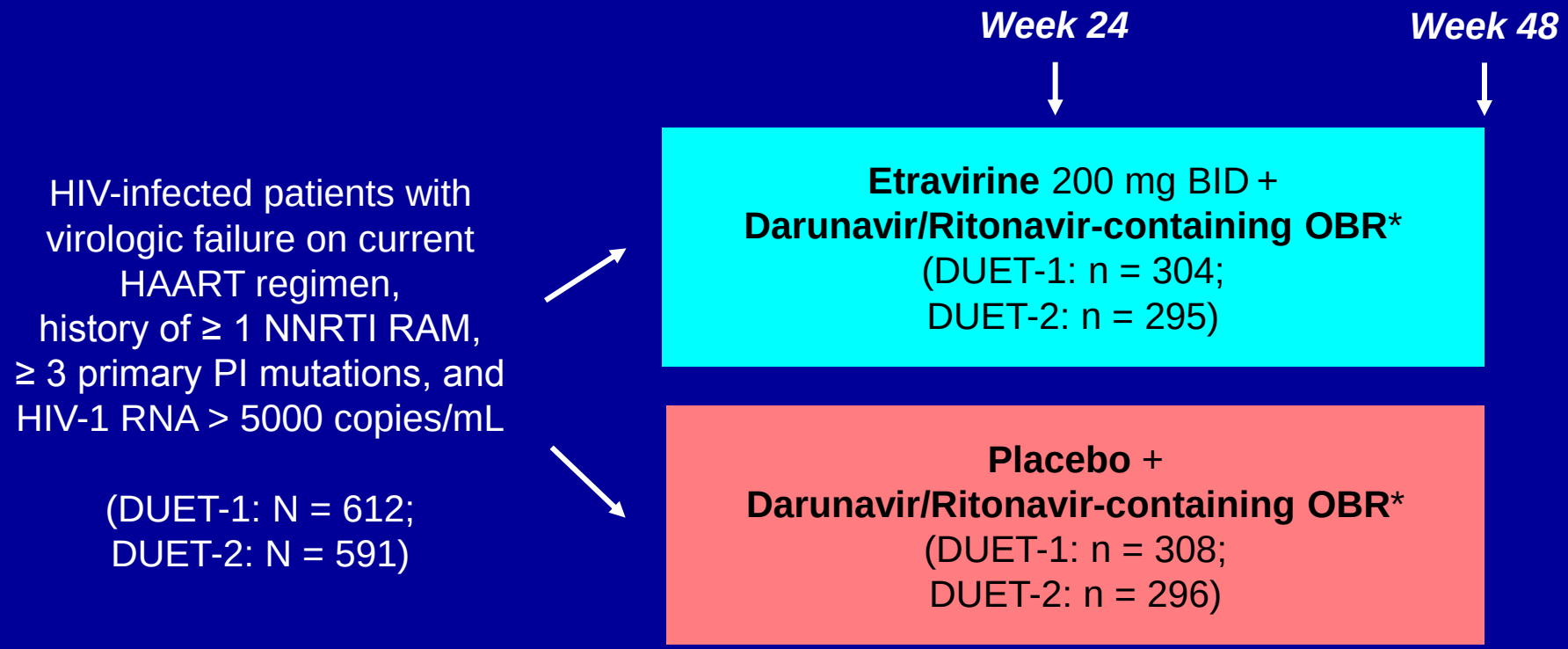
NNRTI

Etravirine

active against wild-type HIV and strains resistant to currently available NNRTIs in phase IIb trials



DUET-1[1] and 2[2] :assess long-term efficacy, safety, and tolerability of etravirine in treatment-experienced patients; 24-week results shown



*Investigator-selected OBR included darunavir/ritonavir 600/100 mg twice daily + ≥ 2 NRTIs ± enfuvirtide.

1. Madruga JV, et al. Lancet. 2007;370:29-38.
2. Lazzarin A, et al. Lancet. 2007;370:39-48.

Baseline Characteristics

Characteristic	DUET-1		DUET-2	
	Etravirine (n = 304)	Placebo (n = 308)	Etravirine (n = 295)	Placebo (n = 296)
Median HIV-1 RNA, log_{10}copies/mL (range)	4.8 (2.7-6.2)	4.9 (2.4-6.5)	4.8 (3.0-6.8)	4.8 (2.2-6.3)
HIV-1 RNA ≥ 100,000 copies/mL, %	39	41	37	31
Median CD4+ count, cells/mm^3 (range)	99 (1-789)	109 (1-694)	100 (1-708)	108 (0-912)
Median previous NRTIs, n	6	5	6	6
Median previous NNRTIs, n	1	1	1	1
Median previous PIs, n	4	5	5	5
≥ 4 NNRTI RAMs	21	20	20	17
≥ 4 NRTI RAMs	93	93	90	90
≥ 4 primary PI mutation	60	59	65	66
≤ 2 darunavir RAMs	59	58	56	56
Enfuvirtide use	40	41	52	53
• De novo	24	26	27	27
PSS 0 or 1*	50	46	51	58

*Lower clinical cutoff (10-fold) used to define susceptibility to darunavir.

Madruga JV, et al. Lancet. 2007;370:29-38. 2.
Lazzarin A, et al. Lancet. 2007;370:39-48.

Description of Analysis

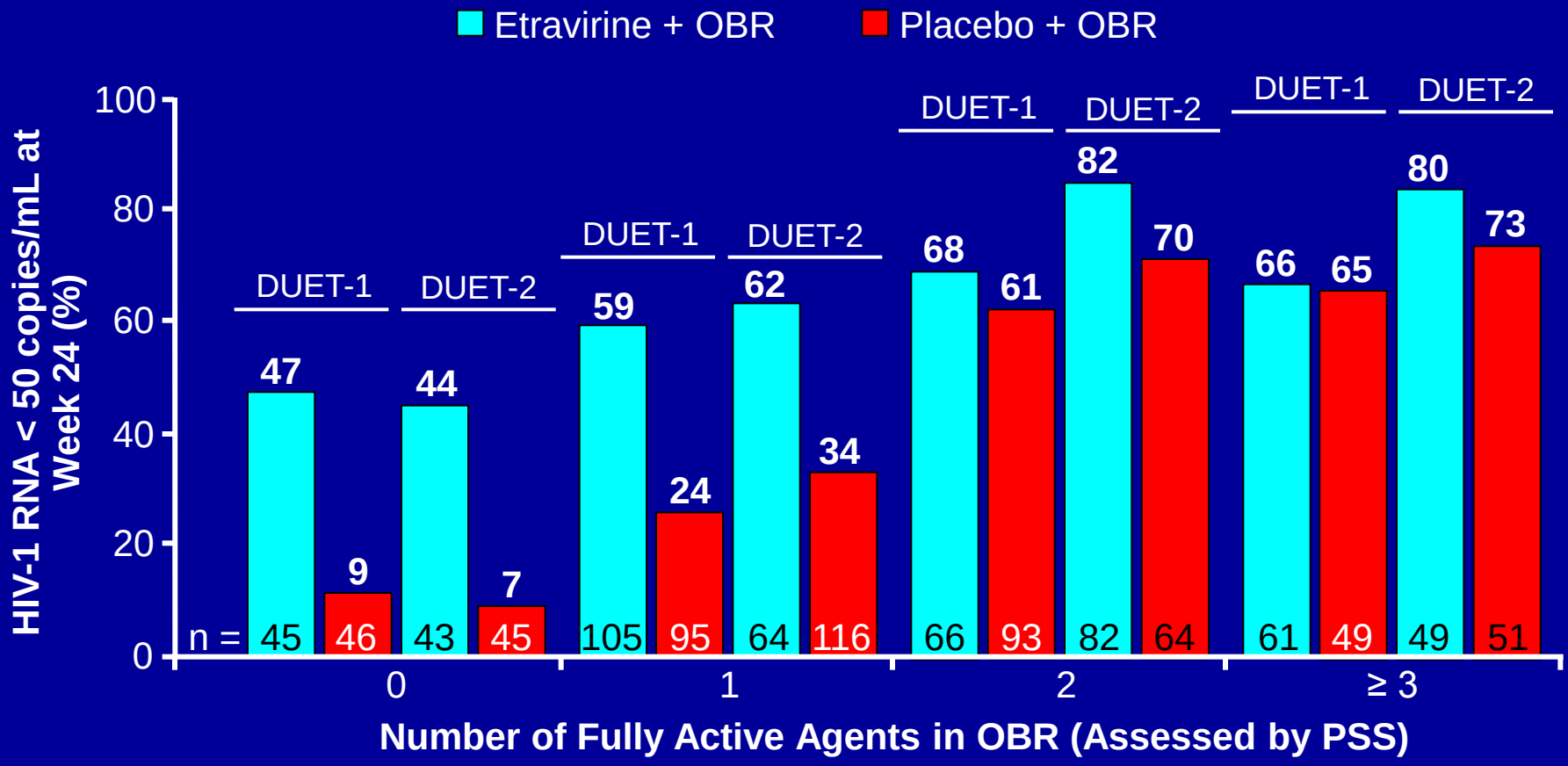
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Week 24
  - First trial to use HIV-1 RNA < 50 copies/mL as primary endpoint in treatment-experienced patients
- Secondary endpoints: HIV-1 RNA < 400 copies/mL at Week 24, change in HIV-1 RNA from baseline, change in CD4+ cell count from baseline, toxicity
- Analysis
  - Intent to treat, time to loss of virologic response
  - 95% power to detect significance

Madruga JV, et al. Lancet. 2007;370:29-38. Lazzarin A, et al. Lancet. 2007;370:39-48.

- Significantly more patients achieved HIV-1 RNA < 50 copies/mL with etravirine vs placebo
- Etravirine treatment resulted in greater CD4+ cell count increases from baseline compared with placebo (statistical significance reached in DUET-1 only)

Outcome at Week 24	DUET-1			DUET-2		
	Etravirine (n = 304)	**Placebo (n = 308)**	***P***	**Etravirine (n = 295)**	**Placebo (n = 296)**	***P***
HIV-1 RNA < 50 copies/ mL, %	56	39	.005	62	44	.0003
HIV-1 RNA < 400 copies/mL,%	74	51	.0001	75	54	.0001
HIV-1 RNA reduction, $\log_{10}$copies/mL	2.4	1.7	< .0001	2.3	1.7	< .0001
Mean increase in CD4+ cell count from baseline, cells/mm^3	89	64	.0002	78	66	.3692

Madruga JV, et al. Lancet. 2007;370:29-38.
Lazzarin A, et al. Lancet. 2007;370:39-48.



Madruga JV, et al. Lancet. 2007;370:29-38.
Lazzarin A, et al. Lancet. 2007;370:39-48.

- Patients reusing or not using enfuvirtide achieved greater response with etravirine vs placebo
  - Findings unchanged when further stratified by number of baseline NNRTI RAMs and fold change in darunavir susceptibility
- Among patients who used enfuvirtide de novo, no significant difference in response to etravirine compared with placebo

Outcome at Week 24, %	Enfuvirtide Reused or Not Used				Enfuvirtide Used de Novo			
	DUET-1		DUET-2		DUET-1		DUET-2	
	ETR (n = 230)	PBO (n = 229)	ETR (n = 216)	PBO (n = 215)	ETR (n = 74)	PBO (n = 79)	ETR (n = 79)	PBO (n = 81)
HIV-1 RNA < 50 copies/ mL	55*	33	58*	34	60	56	73	68
HIV-1 RNA < 400 copies/mL	70*	44	71*	45	84	73	86	78

Madruga JV, et al. Lancet. 2007;370:29-38. Lazzarin A, et al. Lancet. 2007;370:39-48.

Other Outcomes

- 13 baseline mutations associated with diminished response to etravirine:
  V90I, L100I, V106I, Y181C/I/V, A98G, K101E/P, V179D/F, G190A/S
  - Response diminished by ~ 20% in presence of 1 or 2 mutations
  - ≥ 3 mutations present at baseline in only 14% of study population
- Rash most common AE; most mild/moderate (grade 3: 1%; grade 4: 0%)

AEs Through Week 24, %	DUET-1		DUET-2	
	Etravirine (n = 304)	Placebo (n = 308)	Etravirine (n = 295)	Placebo (n = 296)
• Rash	20	10	14	9
• Central nervous system symptoms†	15	20	15	17
• Nausea	14	12	14	10
• Diarrhea	12	20	18	20
• Psychiatric event‡	10	14	16	17
• Headache	10	13	9	11
Combined grade 3 or 4 AEs	21	28	28	27

Madruga JV, et al. Lancet. 2007;370:29-38.
Lazzarin A, et al. Lancet. 2007;370:39-48.

Results at week 48 (CROI 2008)

	DUET-1		DUET-2	
	ETR	PBO	ETR	PBO
HIV-1 RNA < 50 copies/ mL	60	39	61	41
p		<.0001		<.0001
HIV-1 RNA < 400 copies/mL	71	47	72	48
p		<.0001		<.0001
Mean CD4 Change cells/mm3	103	74	94	72
p		.0025		.0160

Duet 1:Haubrich R Abstract 790

Duet 2: Johnson M Abstract 791

Summary of Key Conclusions

- Etravirine (TMC125) in combination with an OBR of darunavir/r and optimized NRTIs (with optional enfuvirtide) associated with significantly greater rates of HIV-1 RNA < 50 copies/mL at w48 in highly treatment–experienced (≥ 3 primary PI mutations) patients
- Etravirine also superior to placebo in increasing CD4+ cell counts from baseline
- Toxicity comparable in etravirine and placebo arms except rash

Madruga JV, et al. Lancet. 2007;370:29-38.
Lazzarin A, et al. Lancet. 2007;370:39-48.

Entry Inhibitors

HIV-1 Entry Inhibitors

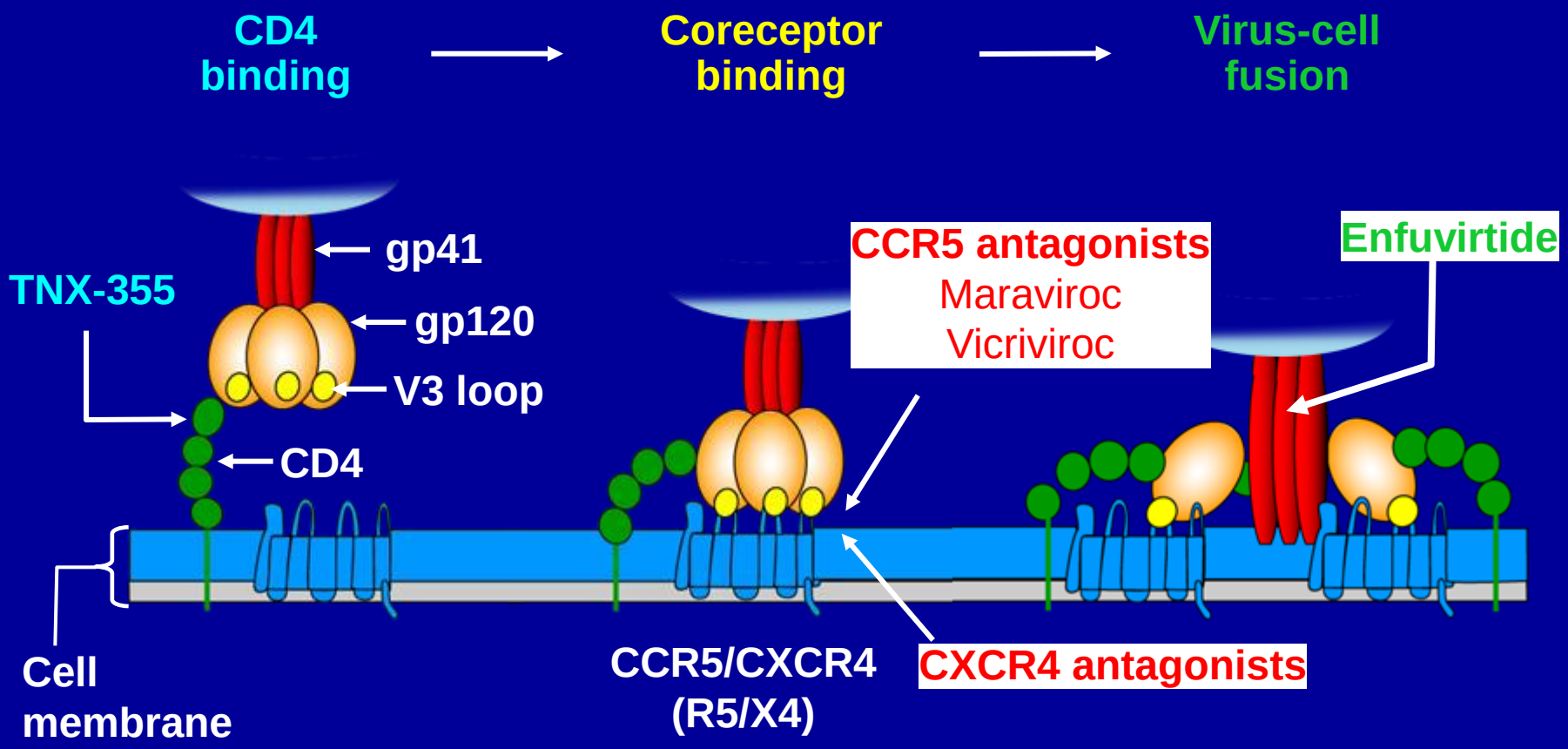
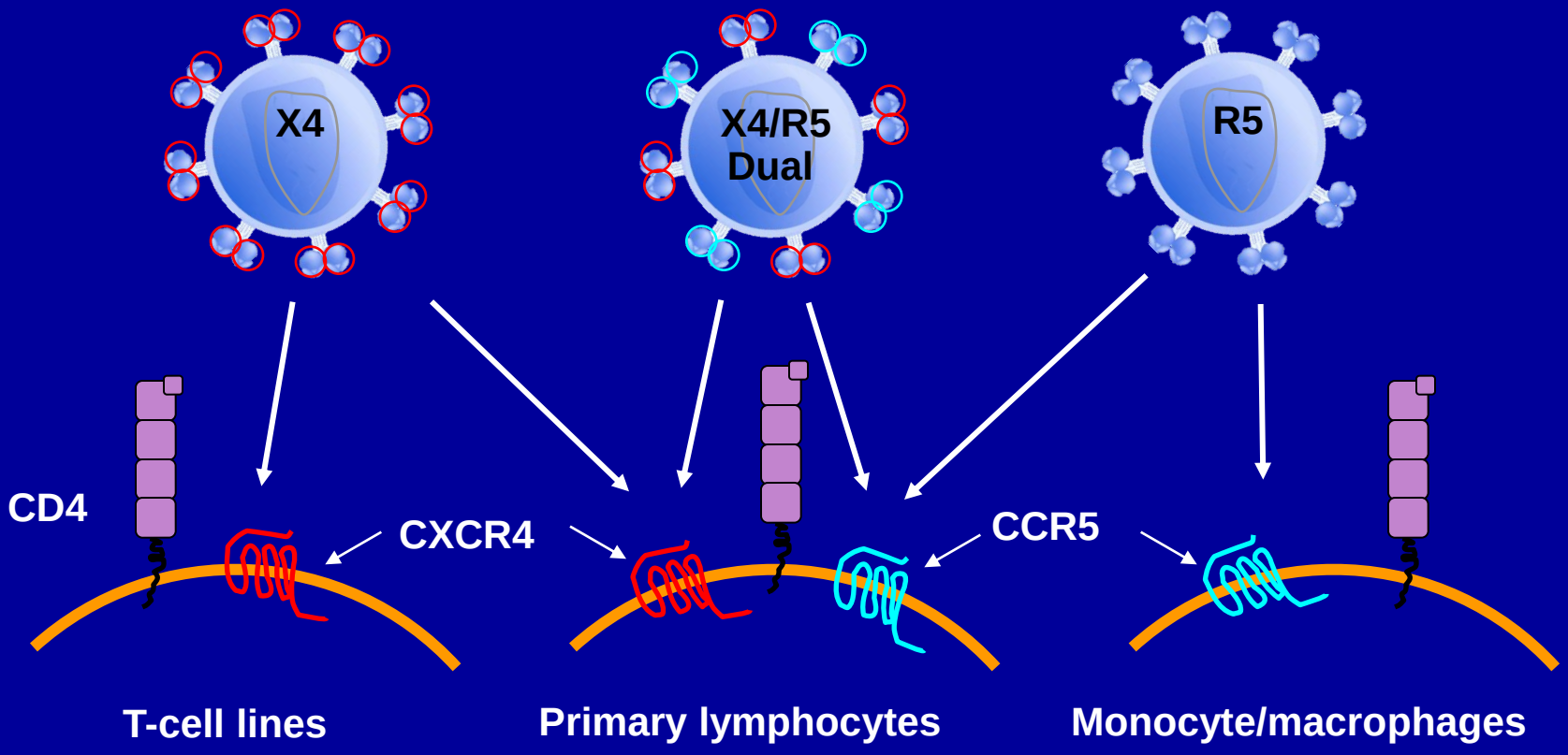


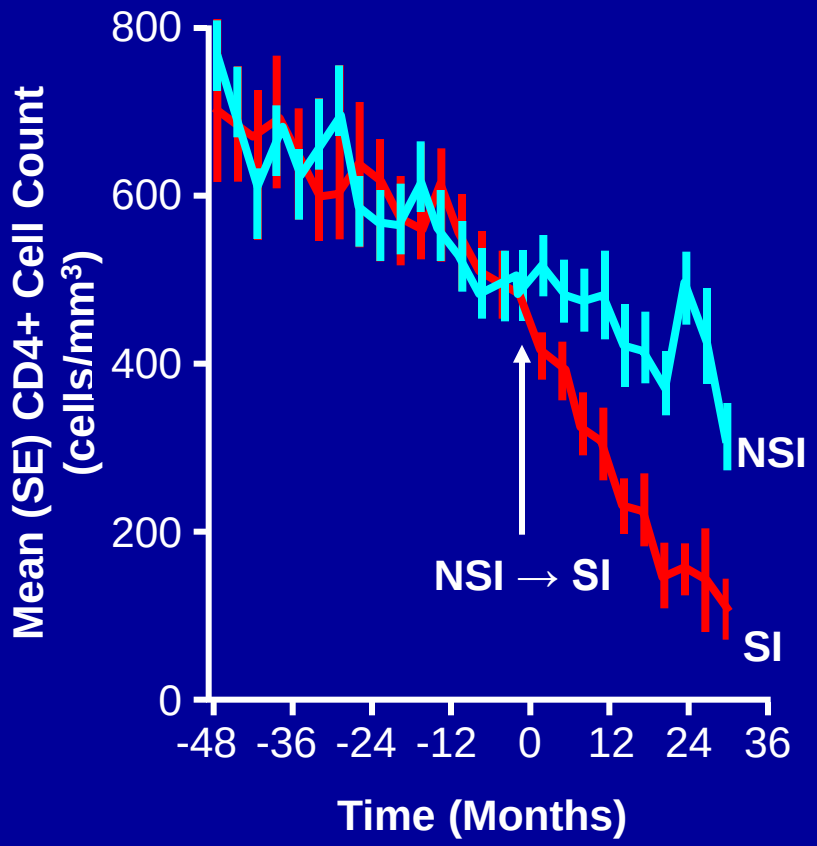
Figure adapted from Doms R, et al. Genes Dev. 2000;14:2677-2688.

Coreceptor Usage of HIV-1 Variants



Association Between Emergence of SI Virus and CD4+ Cell Count

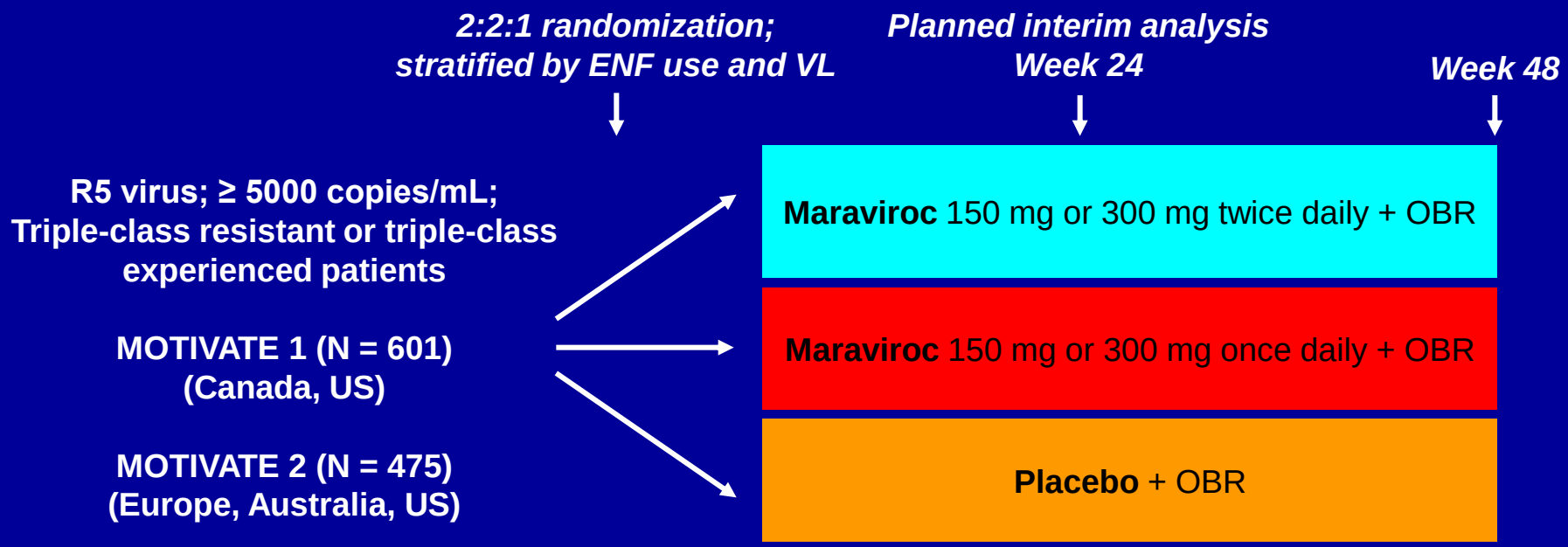
- NSI virus predominates early in disease
- Dual/mixed virus detected in approximately 50% of patients over time
- CD4+ cell count decline accelerated following detection of SI in patients in whom NSI-only virus was previously detected



Koot M, et al. Ann Intern Med. 1993;118:681-688.

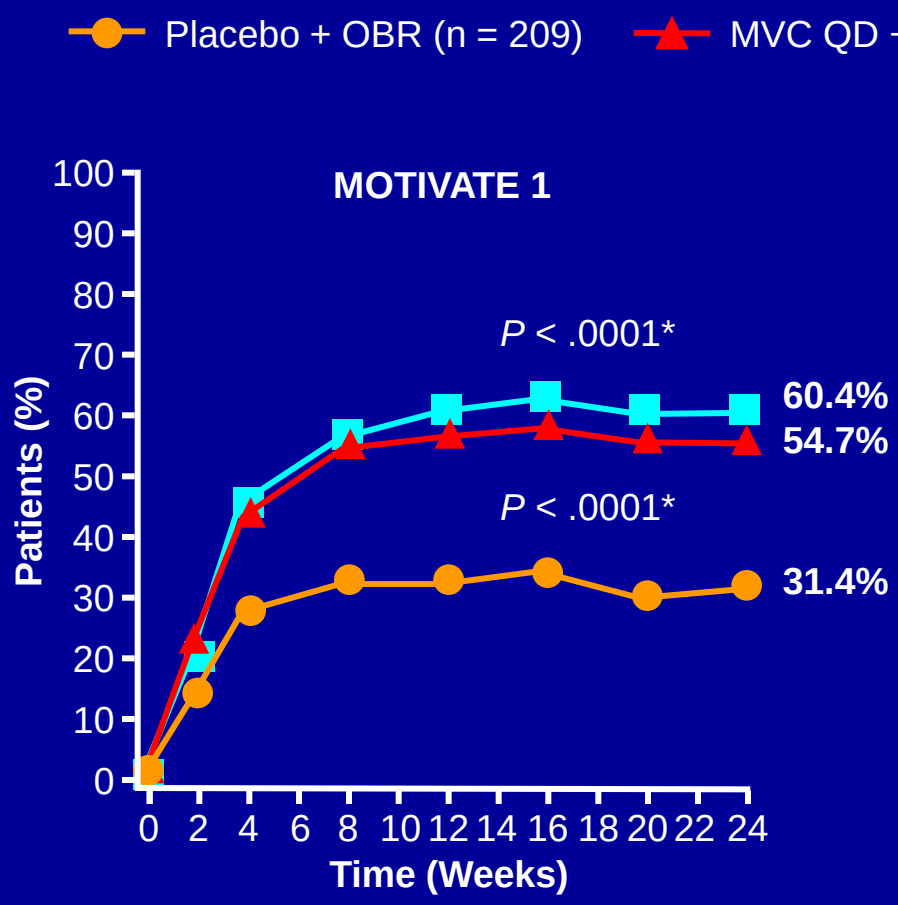
MOTIVATE : Maraviroc in Treatment-Experienced Patients With R5 Virus

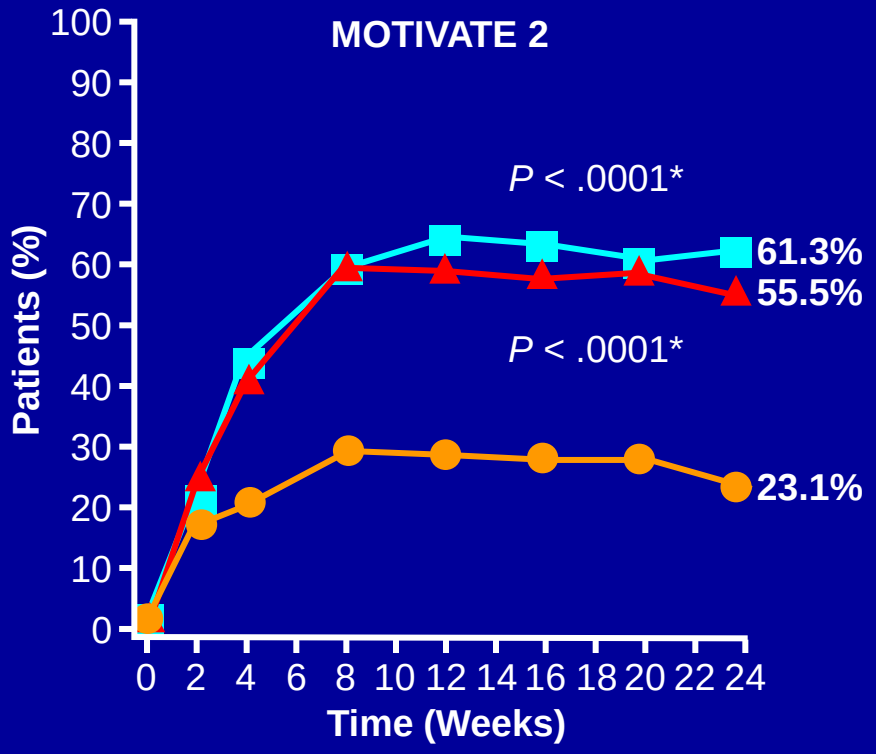
- Randomized, double-blind, placebo-controlled, parallel phase IIb/III studies
- Primary endpoint : mean change in VL at Week 24



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

MOTIVATE 1 and 2 : VL < 400 copies/mL (ITT, NC = F)

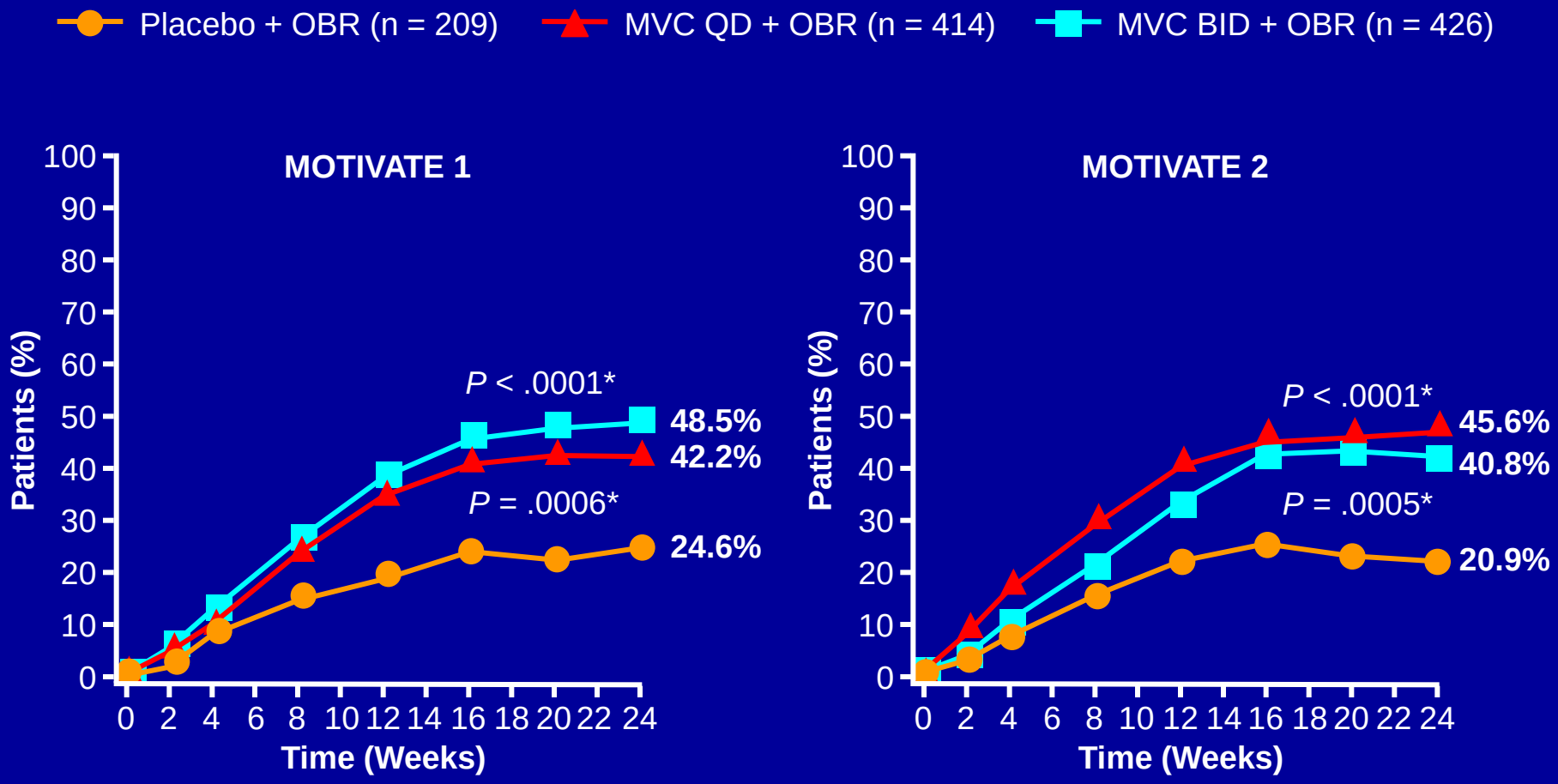




**P* values vs placebo at Week 24.

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

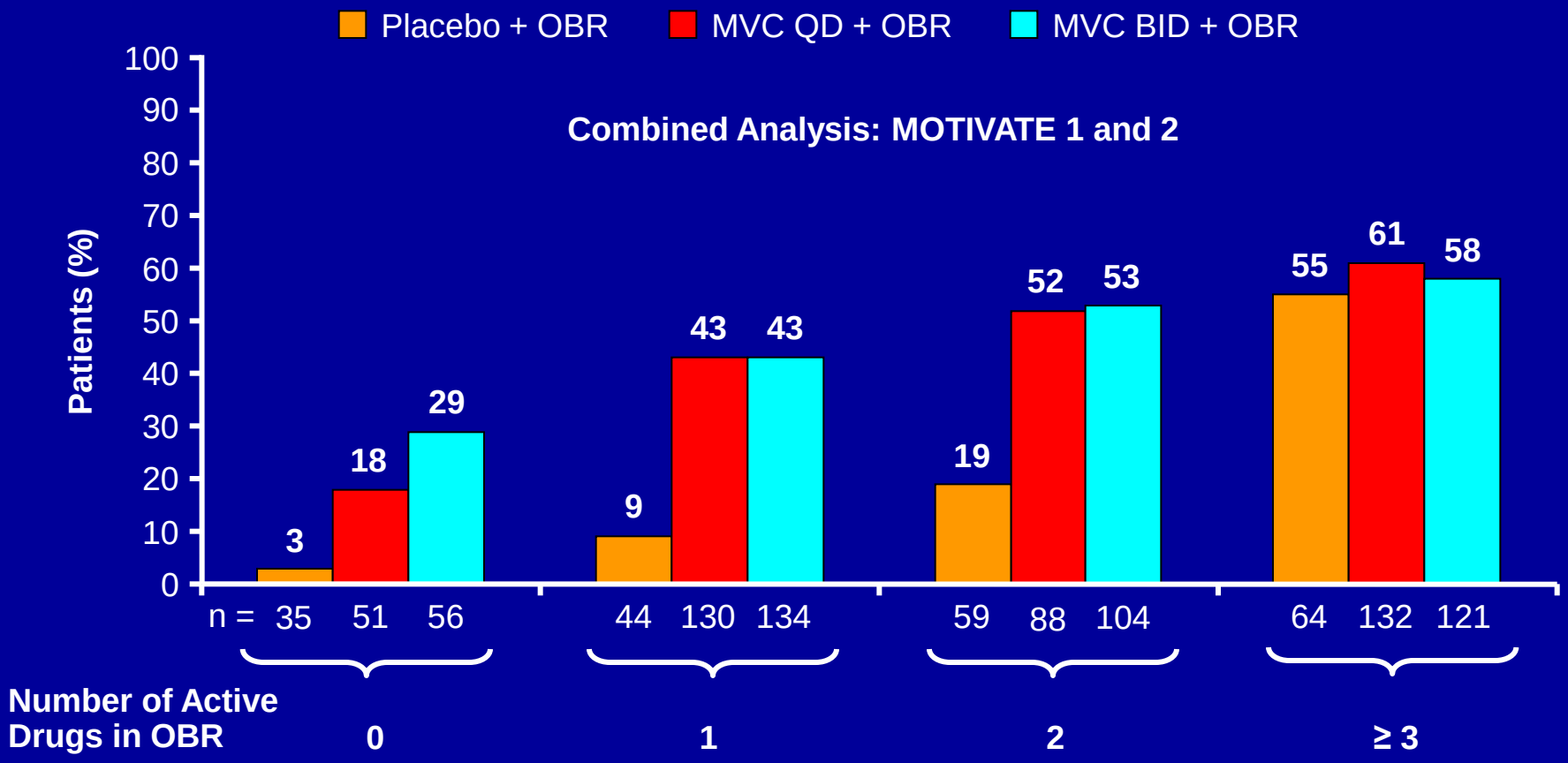
MOTIVATE 1 and 2: VL < 50 copies/mL (ITT, NC = F)



*P values vs placebo at Week 24.

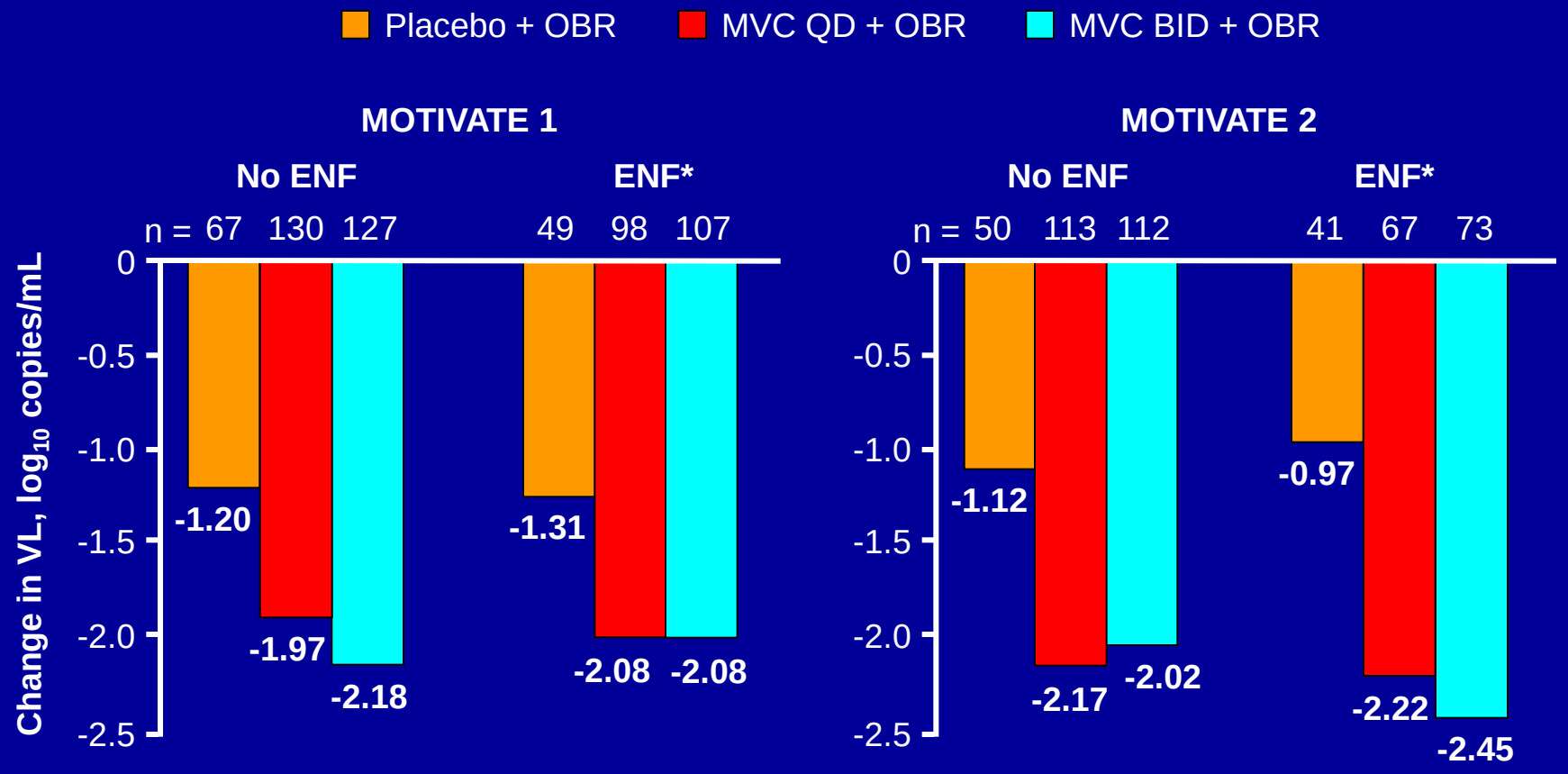
Nelson M, et al. CROI 2007. Abstract 104aLB.
Lalezari J, et al. CROI 2007. Abstract 104bLB.

MOTIVATE 1 and 2 : VL < 50 c/mL 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.

MOTIVATE 1 and 2 : Mean Change in VL at Wk 24 by ENF Use in OBR



*Includes all those who received ENF as part of OBR, whether ENF naive or experienced.

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

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

Mean Change in CD4+ Cell Count 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)
In 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)

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

- ~ 8% of patients experienced shift in detected tropism between screening and baseline
- Among patients with treatment failure, shift in detected tropism more common among maraviroc vs placebo recipients
- Among maraviroc recipients with tropism results at time of failure, approximately 2/3 had dual/mixed or X4 virus detected

MOTIVATE 1 and 2 : Adverse Events and Resistance

- Similar incidence of adverse events in maraviroc and placebo arms
  - Similar low incidence of hepatotoxicity in maraviroc and placebo arms
  - Lymphoma diagnosed in 3 patients in maraviroc arms and 2 patients in placebo arms
- Resistance
  - Mutations seen in V3 loop among patients who failed on the maraviroc arms with R5 virus
  - No signature R5 mutations have been defined yet

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

Advantages and Disadvantages of CCR5 Antagonists

Advantages

- Novel antiretroviral class
- Effective against NRTI-, NNRTI-, PI-, and ENF-resistant virus
- Synergistic with ENF in vitro
- Short-term tolerability data promising
- Orally administered

Disadvantages

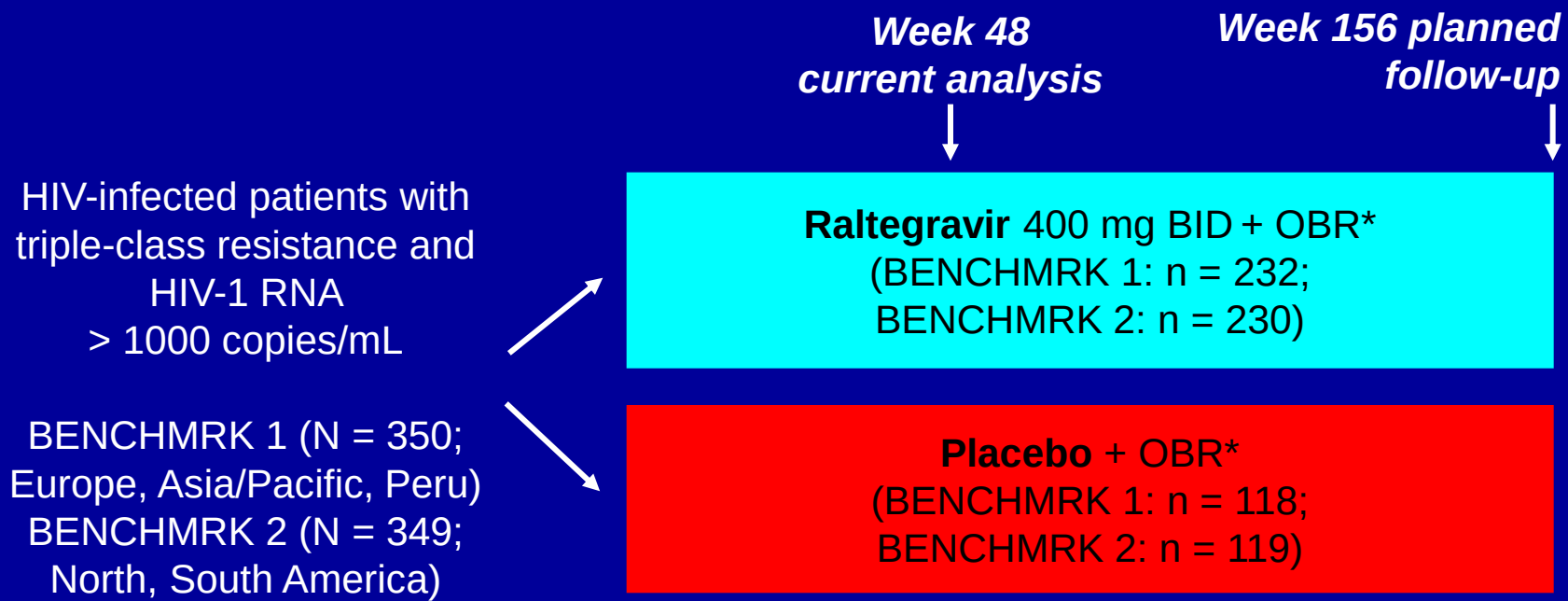
- May not be effective for significant portion of patient population—those with X4 or D/M virus
- Uncertain risk/implications of emerging D/M or X4 virus
- Long-term safety and resistance not well defined
- Cost and availability of tropism assay
- Drug interactions: complexity of dosing with PI

Clinical Trials of Integrase Inhibitors

Integrase Enzyme

- Viral enzyme essential to replication of both HIV-1 and HIV-2
- Integration
  - Follows reverse transcription, where DNA copy of HIV-1 RNA synthesized after infection
  - Essential step before viral DNA can be transcribed back into viral RNA
  - Incorporates or “integrates” viral DNA into host cell’s DNA

BENCHMRK 1 & 2 Phase III : RAL in Treatment-Experienced Pts



*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. NEJM359:339, July 24, 2008

BENCHMRK 1: BL Characteristics

Characteristic	Raltegravir + OBR (n = 234)	Placebo + OBR (n = 118)
Mean HIV-1 RNA, $\log_{10}$ copies/mL	4.6	4.5
Median CD4+ cell count, cells/mm^3	140	105
AIDS diagnosis, %	94	89
Median duration of ARV exposure, yrs	11	10
GSS = 0, %	30	29
GSS = 1, %	33	41
PSS = 0, %	19	18
PSS = 1, %	29	33
First-time use of DRV in OBR, %	27	25
First-time use of ENF in OBR, %	21	20

Steigbigel RT, et al. N Engl J Med. 2008.

BENCHMRK 2 : BL Characteristics

Characteristic	Raltegravir + OBR (n = 230)	Placebo+ OBR (n = 119)
Mean HIV-1 RNA, $\log_{10}$ copies/mL	4.7	4.7
Median CD4+ cell count, cells/mm^3	102	132
AIDS diagnosis, %	91	92
Median duration of ARV exposure, yrs	10	10
GSS = 0, %	20	27
GSS = 1, %	44	40
PSS = 0, %	10	19
PSS = 1, %	34	28
First-time use of DRV in OBR, %	45	50
First-time use of ENF in OBR, %	19	20

Steigbigel RT, et al. N Engl J Med. 2008.

BENCHMRK 1 & 2: Efficacy by BL HIV-1 RNA and CD4+ Cell Count

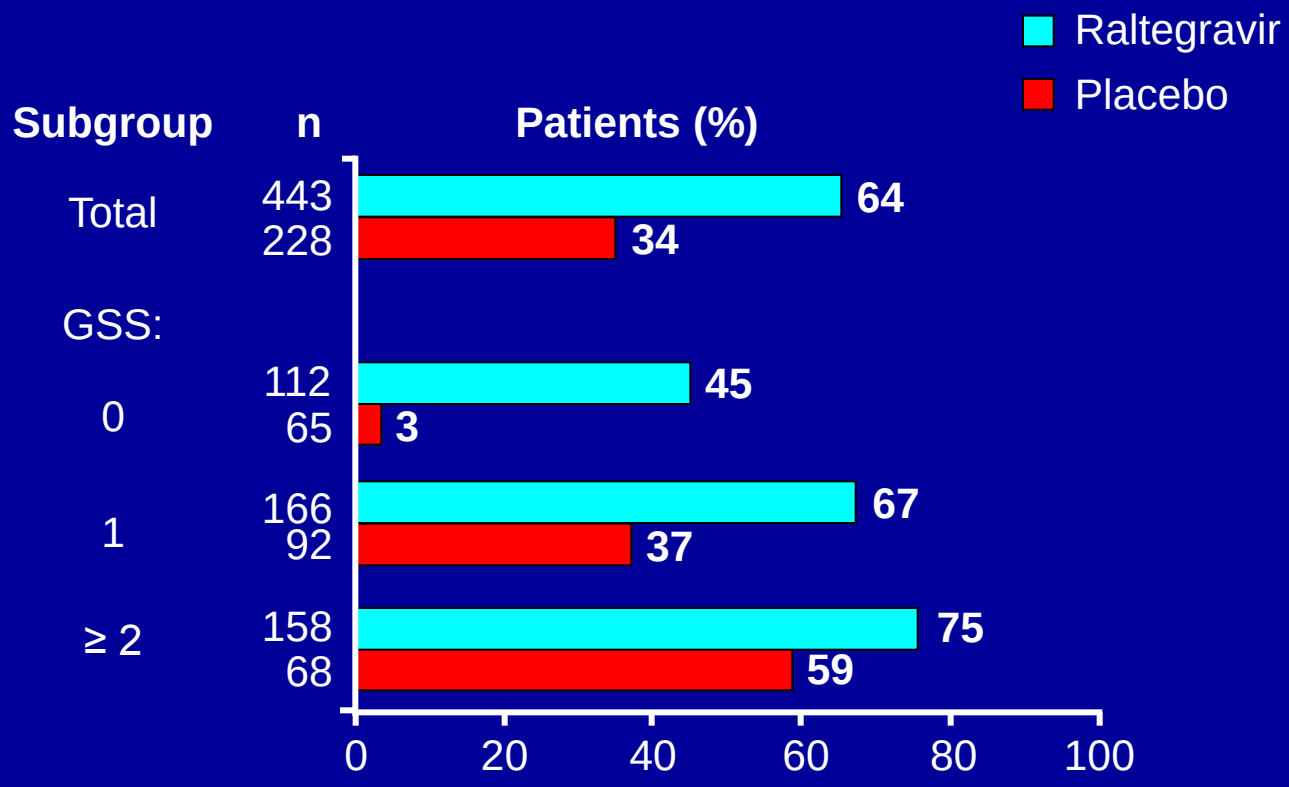
Patient Group, %	HIV-1 RNA < 50 copies/mL at Week 48*	
	Raltegravir + OBR (n = 443)	Placebo + OBR (n = 228)
All patients	64	34
HIV-1 RNA at BL, copies/mL		
• > 100,000	48 (n = 156)	16 (n = 76)
• ≤ 100,000	73 (n = 287)	43 (n = 152)
CD4+ cell count at BL, cells/mm^3		
• ≤ 50	50 (n = 139)	20 (n = 75)
• > 50 to ≤ 200	67 (n = 167)	39 (n = 82)
• > 200	76 (n = 136)	44 (n = 71)

*Virologic failures carried forward.

Steigbigel RT, et al. N Engl J Med. 2008.

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

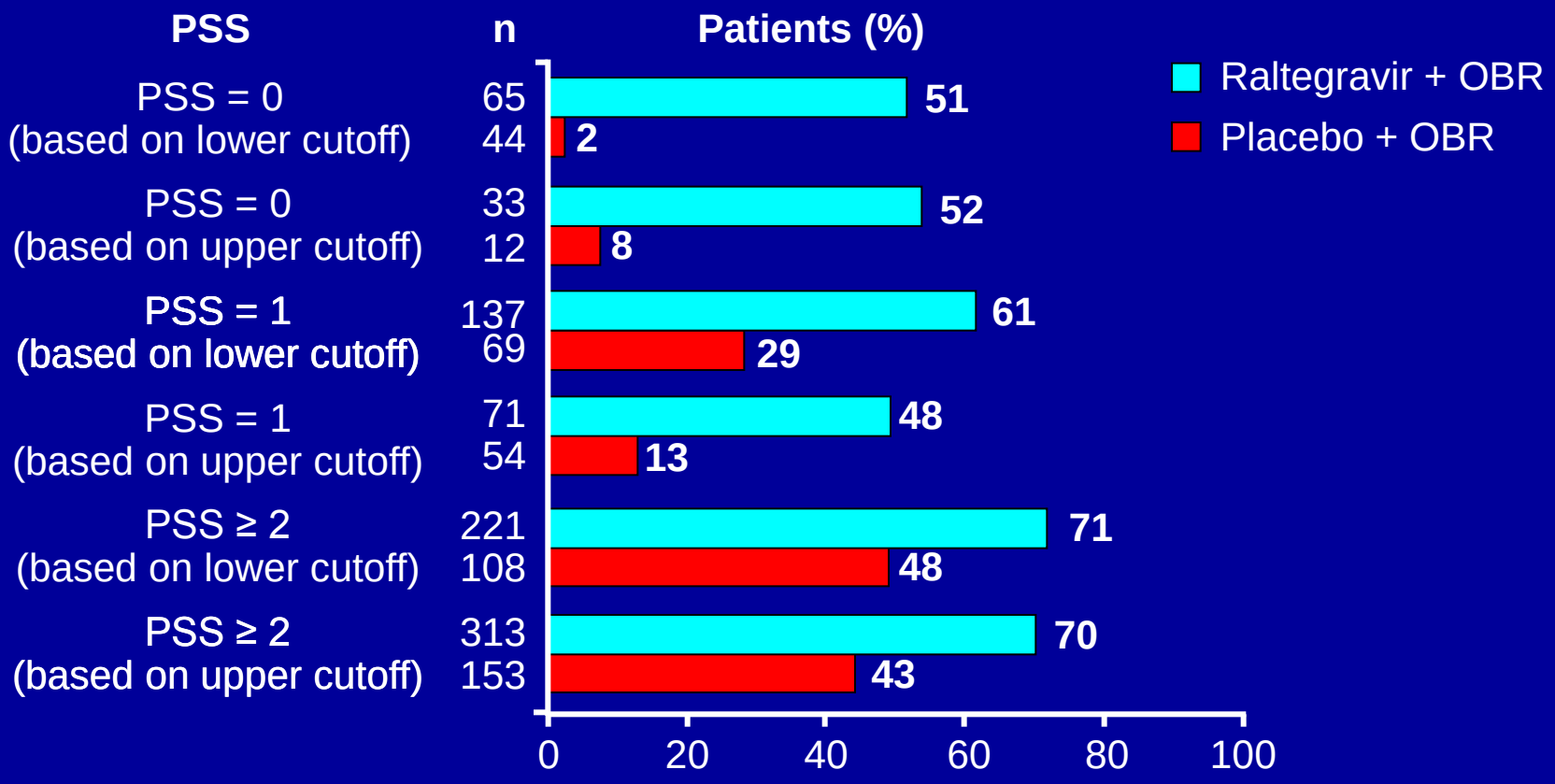
*The genotypic sensitivity score is the total number of antiretroviral drugs used as part of the optimized background therapy to which a patient's HIV was fully susceptible, as determined with the use of genotypic resistance testing.



David A. Cooper et al. N Engl J Med. 2008.

BENCHMRK 1 & 2: HIV-1 RNA < 50 c/mL at Week 48 by BL PSS*

* The phenotypic sensitivity score



David A. Cooper et al. N Engl J Med. 2008.

BENCHMRK 1 & 2: Virologic Failure, Resistance Through Week 48

- Virologic failure generally associated with mutations at Q148 or N155, in combination with at least 1 other mutation
- Virologic failure*: BENCHMRK 1 (n = 50); BENCHMRK 2 (n = 48)
  - Virologic failure defined as
    - < 1 $\log_{10}$ ↓ HIV-1 RNA from BL and > 400 c/mL at Week 16 *or*
    - > 1 $\log_{10}$ ↑ HIV-1 RNA above nadir or > 400 c/mL from nadir after response of < 400 c/mL (on 2 consecutive measurements ≥ 1 week apart)

*In patients for whom integrase genotypic data were available.

David A. Cooper et al. N Engl J Med. 2008.

BENCHMRK 1 & 2: Adverse Events Through Week 48

- Clinical adverse events
  - Raltegravir groups: 89%
  - Placebo groups: 87%
  - Considered treatment related in each group: 54%
- Laboratory adverse events
  - Raltegravir groups: 23%
  - Placebo groups: 22%
  - Considered treatment related: 14% and 13%, respectively
- Most common drug-related clinical adverse events in both treatment groups
  - Diarrhea, nausea, headache
- Most common drug-related laboratory adverse events
  - Increased serum lipid, aminotransferase, creatinine levels

Steigbigel RT, et al. N Engl J Med. 2008.

EACS Management of virologic failure

If Plasma HIV RNA confirmed > 500/1000 copies/ml, change regimen as soon as possible: what to change will depend on the resistance testing results:

- No Resistance mutations found: re-check for adherence, perform TDM
- Resistance mutations found: switch to a suppressive regimen based on drug history; multidisciplinary experts discussion advised

Goal of new regimen:

Plasma HIV RNA < 400 c/ml after 3 months

Plasma HIV RNA < 50 c/ml after 6 months

EACS In case of resistance mutations demonstrated

General recommendations :

- Use 2 or preferably 3 active drugs in the new regimen (including active drugs from previously used classes)
- Any regimen should use at least 1 drug from a class not used previously e.g. fusion, integrase or CCR inhibitor
- Defer change if < 2 active drugs available, based on resistance data, except in patients with low CD4 count (<100/mm3) or with high risk of clinical deterioration for whom the goal is the preservation of immune function through partial reduction of Plasma HIV RNA (> 1 log reduction) by recycling.
- If limited options, consider experimental and new mechanistic drugs, favouring clinical trials (but avoid functional monotherapy)
- Treatment interruption is not recommended

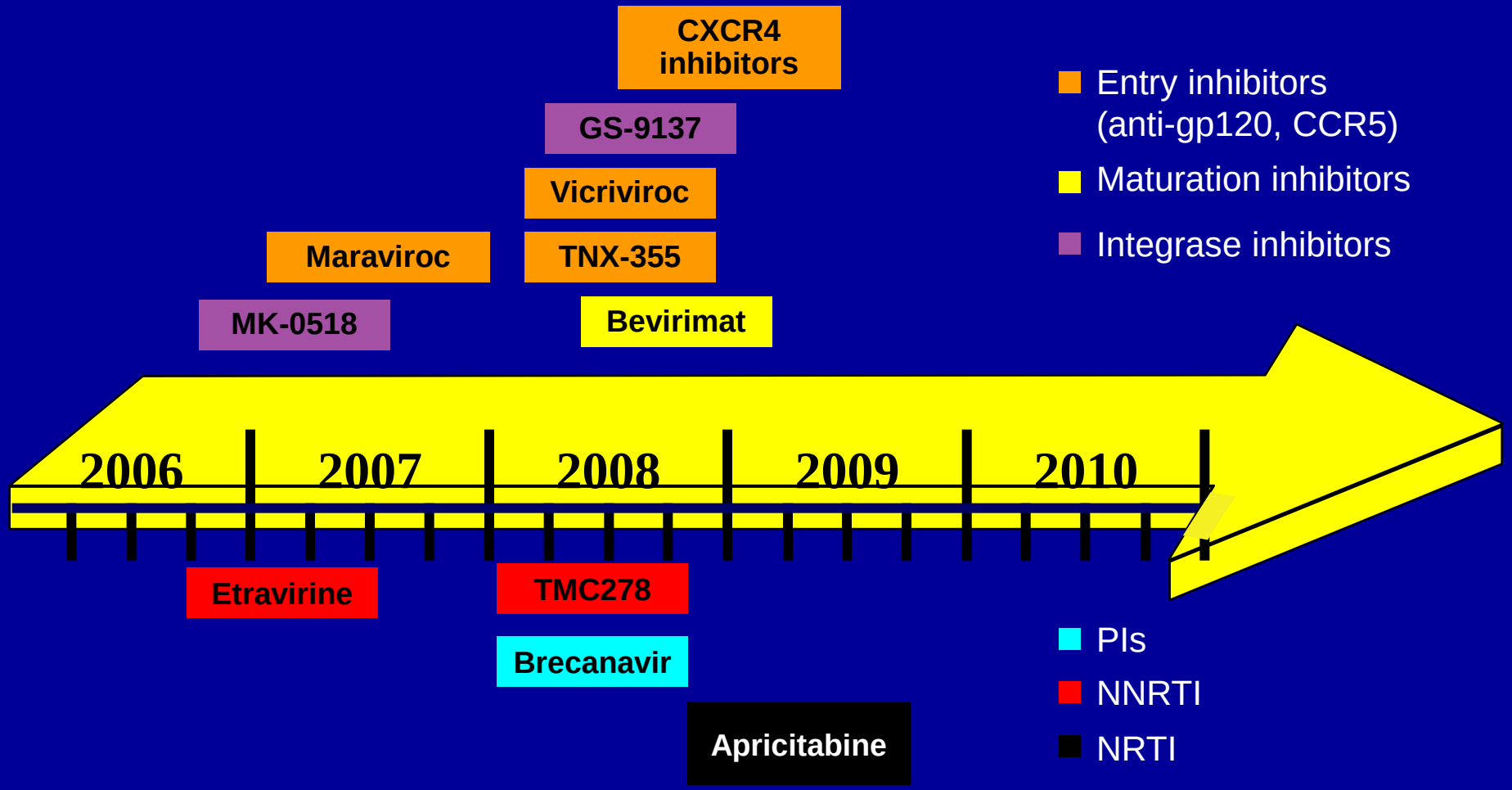
EACS In case of resistance mutations demonstrated

Optimisation of new regimen :

- Avoid NNRTI in NNRTI-experienced patients; Etravirine potentially active in selected NNRTI-resistance profiles
- Consider continuation of 3TC or FTC even if documented resistance mutation (M184V/I)
- Select other potentially active NRTI(s), on treatment history and full resistance (past and present) evaluation
- Select 1 active ritonavir-boosted PI. If at all possible avoid double boosted PIs
- Always check for drug-drug-interactions, and when necessary perform TDM of drugs of new regimen if available

If many options are available, criteria of preferred choice include : simplicity of the regimen, toxicity risks evaluation, drug-drug-interactions, future salvage therapy

Estimated Timeline for Availability of New Antiretrovirals



Conclusions (1)

- Failure of therapy is multifactorial.The virologic failure is a progressive increase of HIV RNA that further leads to a decrease in CD4 cells.
- Prevention of therapeutic failure starts as soon as first-line therapy detect defect in adherence due to any reasons.
- Identification of therapeutic failure should mobilize treating HIV physicians.

Conclusions (2)

- An optimal analysis of the failing situation must be performed with ARV history and resistance assays results .
  → an « expert group » decision is the ideal situation.
- Do not jeopardize any chance for success therapy by using a single new potent drug
- Combining new drugs is the only solution to multi salvage situations

The near future of Antiretroviral therapy ?

…at least and unfortunately in developped countries only …

TRIO Study : Combining Raltegravir, Darunavir and Etravirine

24 Week Phase II, non-comparative, Multicenter Trial

- All pts viremic on current regimen (n=103)
  - HIV RNA > 1000 /mL, any CD4 count
- Documented multidrug-resistant virus
  - ≥ 3 NRTI mutations
  - ≥ 3 major PI mutations
    - Susceptible to DRV : ≤ 3 DRV mutations*
  - Previous virologic failure on NNRTIs
    - Susceptible to ETR : < 3 ETR NNRTI mutations
- All initiate Raltegravir, Darunavir and Etravirine (naïve to all)
  - Additional ARVs allowed : NRTIs and ENF (based on clinical judgment)

Yazdanpannah, et al. 17th IAC; Mexico City, Aug 3-8, 2008; Abst. THAB0406.

TRIO Study : Baseline Characteristics

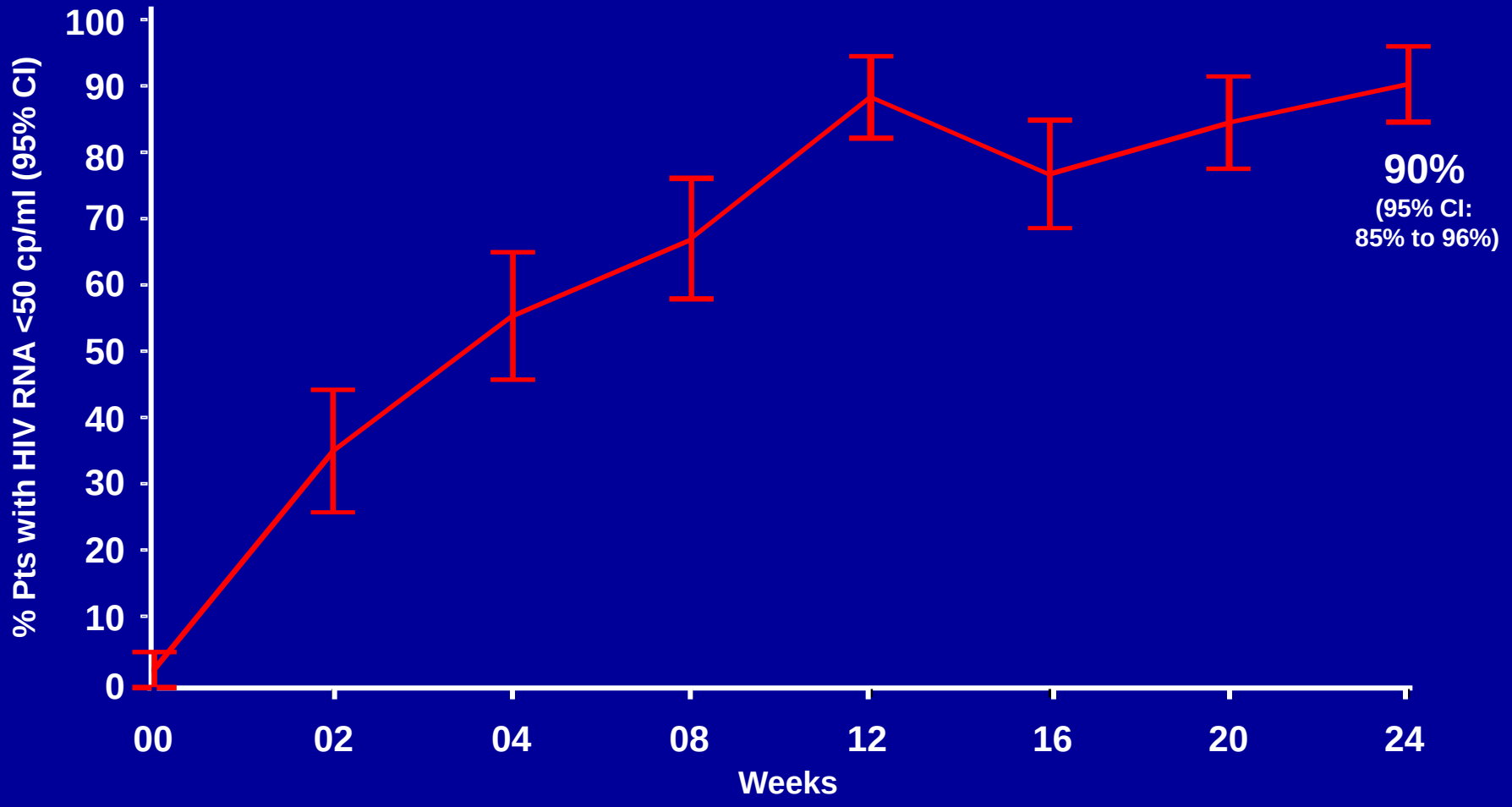
HIV RNA log_{10}, copies/mL, median (IQR)	4.0	(3.6 – 4.6)
CD4 cells/mm^3, median (IQR)	255	(132 – 350)
# mutations at screening, median (IQR)		
Major PI	4	(3 – 5)
NRTIs	5	(4 – 6)
NNRTIs	1	(0 – 2)
% with 0 / 1 / 2 / 3 mutations		
DRV	4% / 31% / 30% / 35%	
ETR	34% / 31% / 31% / 3%	

Additional ARVs in Optimized Background Regimen:

- None 14%
- NRTIs 83%
- Enfuvirtide (most – 10/12 - ENF naive) 12%

Yazdanpannah, et al. 17th IAC; Mexico City, Aug 3-8, 2008; Abst. THAB0406.

TRIO Study : Primary Outcome at 24 Weeks (ITT, M=F)



Yazdanpannah, et al. 17th IAC; Mexico City, Aug 3-8, 2008; Abst. ThAB0406.

How to choose a salvage therapy ?

Week 48: results in press: NEJM

- Episodes of low-level viremia less likely associated with clinical event or change in therapy than episodes of high-level viremia
  - Low-level viremia
    - Without clinical event or therapy change : 79.6%
    - Change in therapy occurred : 13.9%
  - High-level viremia
    - Without clinical event : 41.7%
    - Change in therapy occurred : 52.3%
- CD4+ cell counts increased during periods of virologic suppression but decreased during episodes of **high** level viremia

van Sighem A, et al. J Acquir Immune Defic Syndr. 2008;48:104-108.

Viremia :
Low level 50-1000 cp/ml
High level >1000 cp/ml

- After achieving virologic suppression, many patients experience **transient**, measurable viremia while on antiretroviral therapy [1,2]

- Transient viremia is associated with
  - Low-level viral replication
  - Activation of latently infected cells and subsequent viral production
  - Rise in target cell availability

1. Easterbrook PJ, et al. AIDS. 2002;16:1521-1527.
2. Havlir DV, et al. JAMA. 2001;286:171-179.

Nucleosides Analogues (NRTI) Resistance

- very common
- mutations archived ≈ indefinitely
- cross-resistance between NRTIs ++

AZT-D4T

- high cross-resistance
- > 3 TAMs including T215 F ↘ D4T efficacy

DDI

- antiviral efficacy ↘ if ≥ 3TAMS including T215 F

Abacavir

- antiviral efficacy ↘ if ≥ 4 mut. among 41,67,74,184,210,215

Nucleosides Analogues (NRTI) resistance

- 3TC induces M184V. high level of resistance for intrinsic antiviral activity
- M184V reduces viral fitness
- M184V prevents accumulation of other mutations(K65R)
- Data suggest a benefit to maintain M184V in a regimen

Management of failure on first line therapy

Failure is defined as the detection of a viral load greater than 50 copies ≥ 6 months after the initiation of a first treatment regimen

↓

- **Interview the patient to evaluate adherence and compliance**
- **Re-explanation of the objectives and modalities of the treatment and the potential risks of poor adherence**
- **Exclusion of potential drug-drug or drug-food interactions**

↓

Re-Test viral load : If detectable :

- Resistance testing

- Therapeutic drug monitoring

Adding new drugs / drugs with a remaining sensitivity is a key issue in the succes of a salvage regimen

Management of virologic failure
General measures (1)

If **50<** Plasma HIV RNA **<500-1000 copies/ml**

- Check for **adherence**
- Check Plasma HIV RNA 1 to 2 months later
- Improve boosted PI's PK (if applicable)

Management of virologic failure
General measures (2)

- **Perform resistance testing** (if plasma HIV RNA levels >500-1000 copies/ml) and obtain historical resistance testing for archived mutations
- Review antiretroviral history
- Identify treatment options, active, potentially active drugs/combinations

Failure in (multi)experienced patients

1) Patients who have been treated suboptimally in the past, have a long treatment history and have developed sequential resistance complex pattern of resistance which makes viral suppression difficult

2) Patients who have been unable to comply to and/or to tolerate their previous regimens less complex pattern of resistance but compliance and tolerability issues for the long term

Resistance testing : impact on treatment

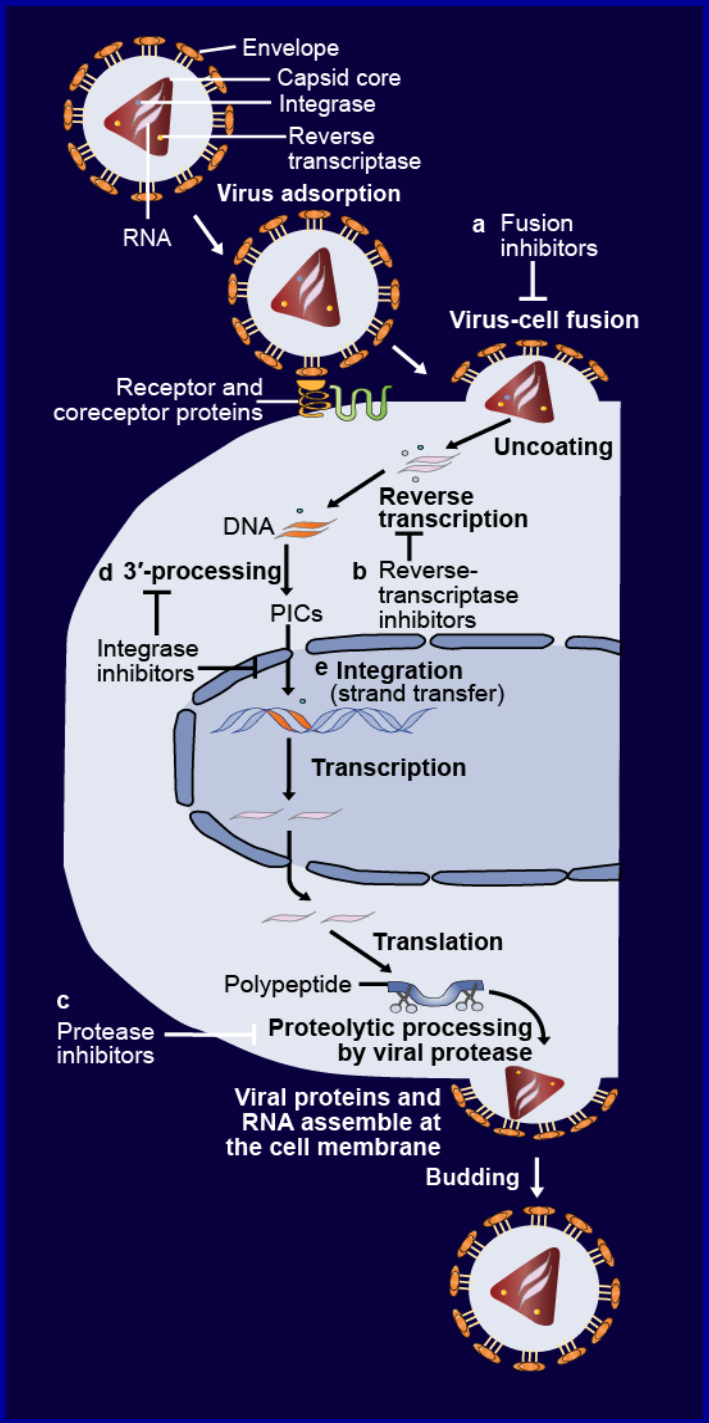
- **Decision to change treatment regimens must take into account :**
  - the remaining treatment options
  - the level of failure based on kinetics of viral load and CD4 (decreased viral fitness)
  - the past treatment history, including resistance patterns, tolerability and adherence issues
  - Co-infections and comorbidities

Treatment interruption in salvage therapy : a case for caution

- **May be associated with rapid decline of CD_4**
- **Need to optimalize OI prophylaxis**
- **Optimal time for re-initiation of therapy is not established**

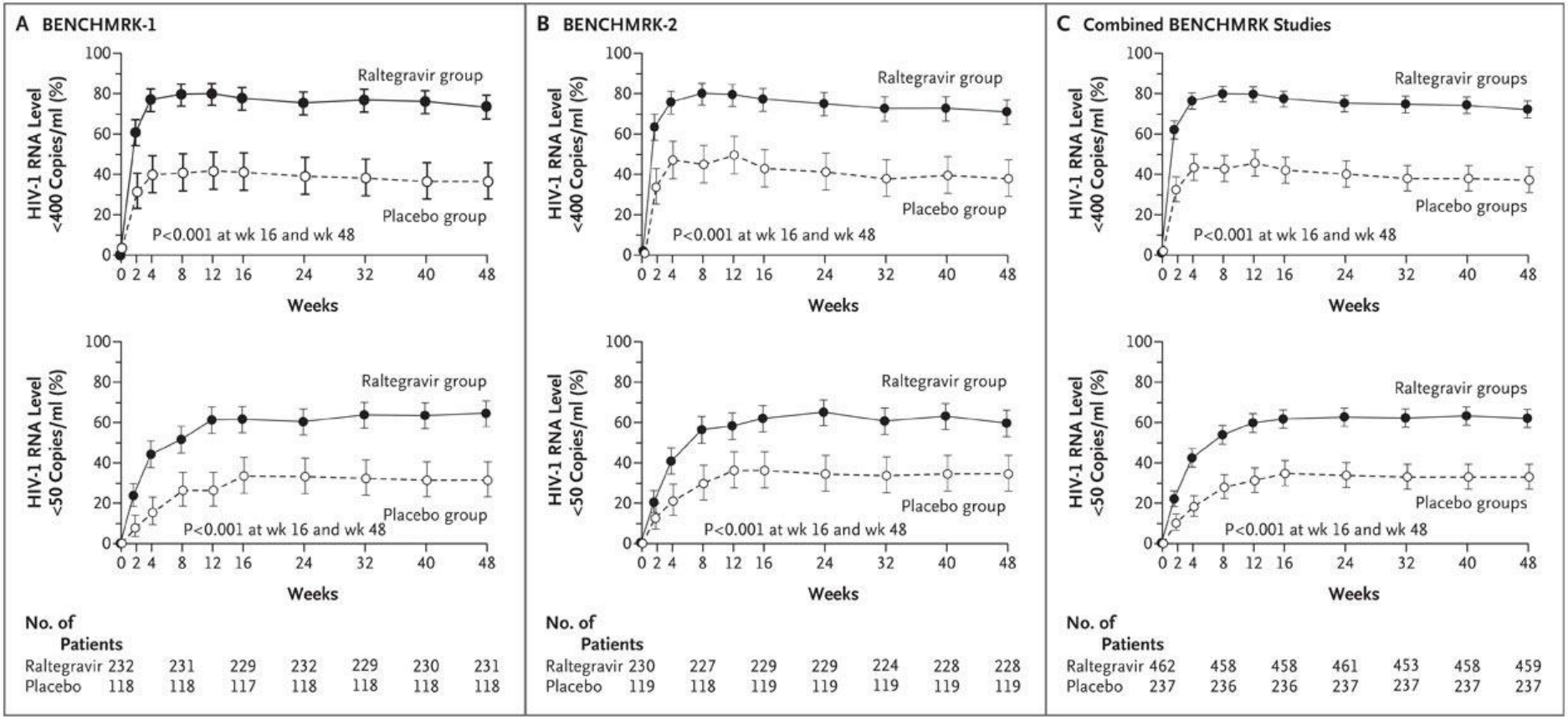
HIV Replication Cycle and Drug Targets

a. Entry inhibitors
b. Reverse transcriptase inhibitors
c. Protease inhibitors
d. 3′-processing inhibitors
e. Strand transfer inhibitors



Pommier Y, et al. Nat Rev Drug Discov. 2005;4:236-248.

Percentage of Patients with Plasma HIV-1 RNA Levels of Less Than 400 or Less Than 50 Copies per Milliliter during the BENCHMRK Studies, According to Study Group



Steigbigel RT et al. N Engl J Med 2008;359:339-354

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

	Raltegravir + OBR (n = 232)	Placebo + OBR (n = 118)	*P* Value
HIV-1 RNA < 50 c/mL (NC = F), %	65	31	< .001
HIV-1 RNA < 400 c/mL (NC = F), %	74	36	< .001
Mean change in HIV-1 RNA vs BL, $\log_{10}$ c/mL	-1.7	-0.7	< .001
Mean change in CD4+ cell count vs BL, cells/mm^3	120	49	< .001

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

Steigbigel RT, et al. N Engl J Med. 2008.

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

	Raltegravir + OBR (n = 232)	Placebo + OBR (n = 119)	*P* Value
HIV-1 RNA < 50 c/mL (NC = F), %	60	34	< .001
HIV-1 RNA < 400 c/mL NC = F), %	71	38	< .001
Mean change in HIV-1 RNA vs BL, $\log_{10}$ c/mL	-1.8	-0.9	< .001
Mean change in CD4+ cell count vs BL, cells/mm^3	98	40	< .001

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

Steigbigel RT, et al. N Engl J Med. 2008.

TRIO Study : Combining Raltegravir, Darunavir and Etravirine

24 Week Phase II, non-comparative, Multicenter Trial

- All pts viremic on current regimen (n=103)
  - HIV RNA > 1000 /mL, any CD4 count
- Documented multidrug-resistant virus
  - ≥ 3 NRTI mutations (2006 IAS list)
  - ≥ 3 major PI mutations (2006 IAS list)
    - Susceptible to DRV (using 1st Power algorithm): ≤ 3 DRV mutations*
  - Previous virologic failure on NNRTIs
    - Susceptible to ETR (using 1st Tibotec analysis of ETR RAMs): < 3 ETR NNRTI mutations
- All initiate Raltegravir, Darunavir and Etravirine (naïve to all)
  - Additional ARVs allowed : NRTIs and ENF (based on clinical judgment)

* V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V and L89V

Yazdanpannah, et al. 17th IAC; Mexico City, Aug 3-8, 2008; Abst. THAB0401a

Option 6 : «Continuous» genotypic - driven salvage therapy

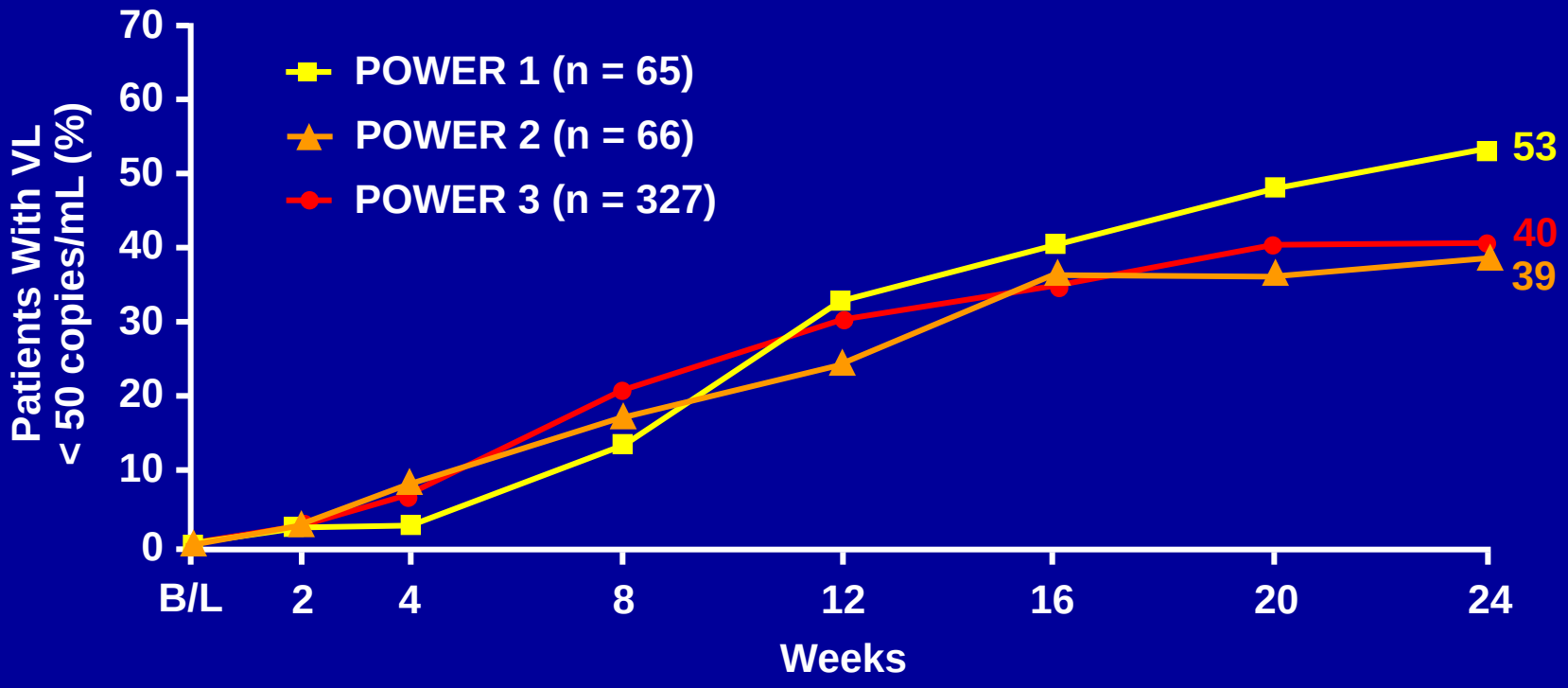
- **The goal is to achieve a selective pressure by using a genotypic-driven salvage therapy that is changed as soon as emergence of new resistant variants is documented**

  Maggiolo et al. (Barcelona 2000)

  - 34 multi class experienced patients
  - VL every 2 months
  - Therapy changed if VL > 10.000, based on genotype
  - Over 24 months, VL contained below 11.000 copies and CD4 increase of 84 cells (with max. 4 drugs)

POWER 3 : VL < 50 copies/mL at Week 24 by ITT-TLOVR

- POWER 3: ongoing phase III open-label study, DRV/RTV 600/100 mg[1]
- Safety analysis similar to POWER 1 and 2[2]



1. Molina JM, et al. IAC 2006. Abstract TUPE0060.
2. Madruga V, et al. IAC 2006. Abstract TUPE0062.

POWER 3 Study Confirms Safety and Efficacy of Darunavir/Ritonavir in Treatment-Experienced Patients

J Acquir Immune Defic Syndr. 2007;46:24-31.

- POWER 1 and 2 studies demonstrated efficacy and safety of darunavir/ritonavir in treatment-experienced individuals
  - Parallel dose-ranging trials in treatment-experienced patients
- Current POWER 3 study designed to provide additional data on efficacy and safety of darunavir/ritonavir 600/100 mg in treatment-experienced, HIV-infected patients

Description of Current Analysis

- Data for RESIST 1 and 2 pooled in current analysis, given similar study design and patient demographics
- Patients assessed at Weeks 2, 4, 8, 16, 24, 32, 40, and 48 for clinical and laboratory evaluations
- Primary endpoints
  - Treatment response, defined as confirmed reduction in HIV-1 RNA ≥ 1 log10 copies/mL at Week 48
  - Time to treatment failure
- Safety assessed via adverse-event monitoring
  - Adverse events and laboratory abnormalities graded according to Division of AIDS grading scale
  - Total cholesterol abnormalities graded according to Common Toxicity Criteria Scale
- Intent-to-treat analyses using noncompletion-equals-failure and last-observation-carried-forward methods

Main Findings

- Darunavir/ritonavir plus OBR associated with substantial virologic responses and immunologic improvement at Week 24

Outcome at Week 24	Patients
> 1 $\log_{10}$ copies/mL reduction in HIV-1 RNA, %	65
HIV-1 RNA < 400 copies/mL, %	57
HIV-1 RNA < 50 copies/mL, %	40
Mean change in HIV-1 RNA, $\log_{10}$ copies/mL	-1.65
Mean change in CD4+ cell count, cells/mm^3	+80

Molina JM, et al. J Acquir Immune Defic Syndr. 2007;46:24-31.

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, %
• FC < 10 (n = 87)	64.4
• FC 10-40 (n = 19)	57.9
• FC > 40 (n = 8)	62.5

De Jesus E, et al. ICAAC 2007. Abstract 367.

Various Causes of failure

- Non-adherence : Side effects
  Complex regimens
  Lifestyle conflicts

- Toxicity

- Pharmacologic variations : drug-drug interaction
  pregnancy

- Infection with resistant HIV-1 strains

- Selection of resistant HIV-1 strains