Management of Treatment-Experienced Patients: New Agents and Rescue Strategies

Joel E. Gallant, MD, MPH

Johns Hopkins University School of Medicine

When to Modify Therapy

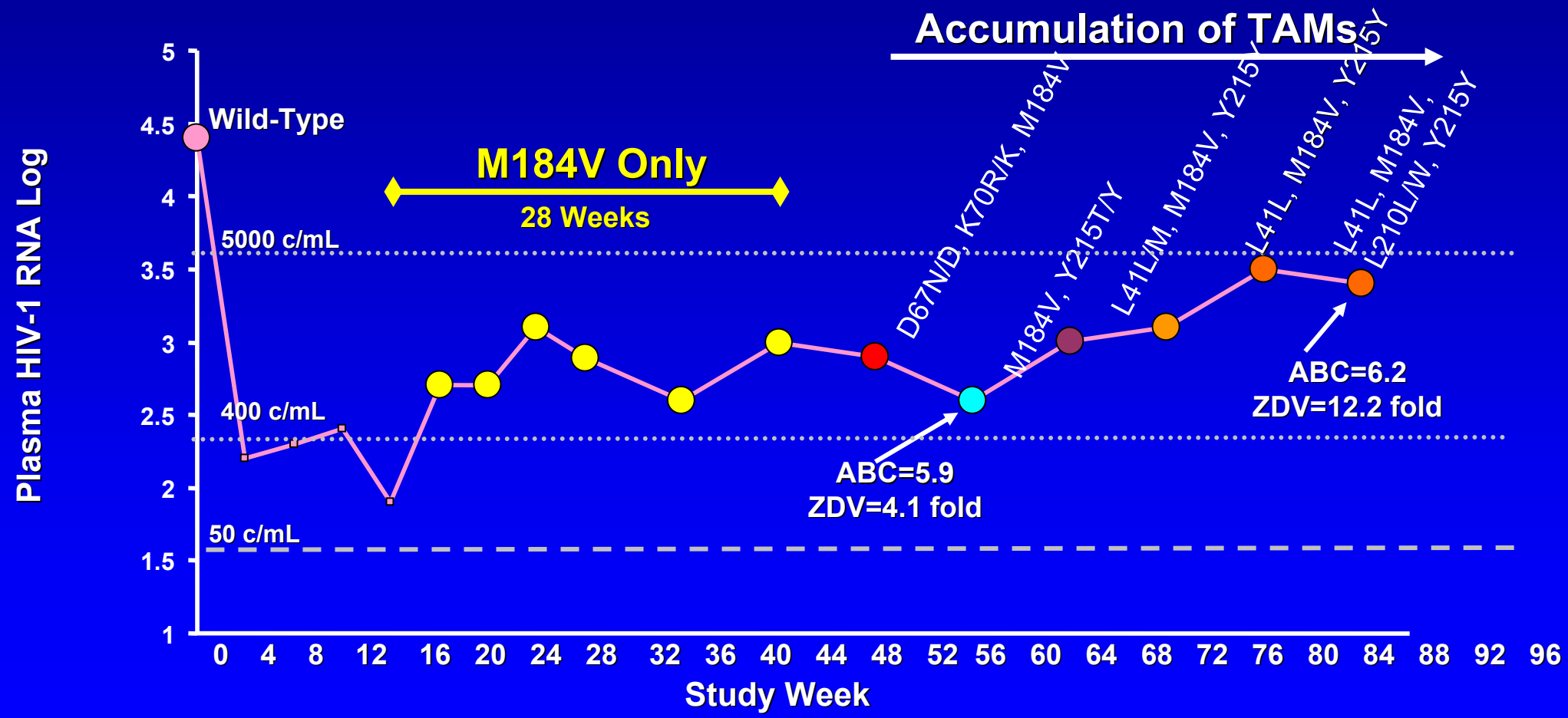
- Studies to date show better responses with earlier switches, as well as viral evolution at low-level viremia

Resistance Evolves Even With Stable Low-Level HIV Viremia

- 80% of patients with VL <10,000 developed new RT or PI mutations over 8 months [1]
  - » Most common NRTI mutations: K70R, D67N, V118I, L74V
- 90% of patients with VL <1,000 developed resistance over 14 months [2]
  - » Resistance to all on-treatment ARV was associated with VL increases >1000 (“progressive failure”)

1 Kantor, 9th CROI; 2002; Seattle. Abstract 566.
2 Coakley 9th CROI; 2002; Seattle. Abstract 556.; 2002;

Evolution of NRTI Resistance with Ongoing Virologic Failure
(CNA 3005: AZT + 3TC + ABC)



Melby T, et al. 8th CROI. Chicago, 2001. Abstract 448.

When to Modify Therapy

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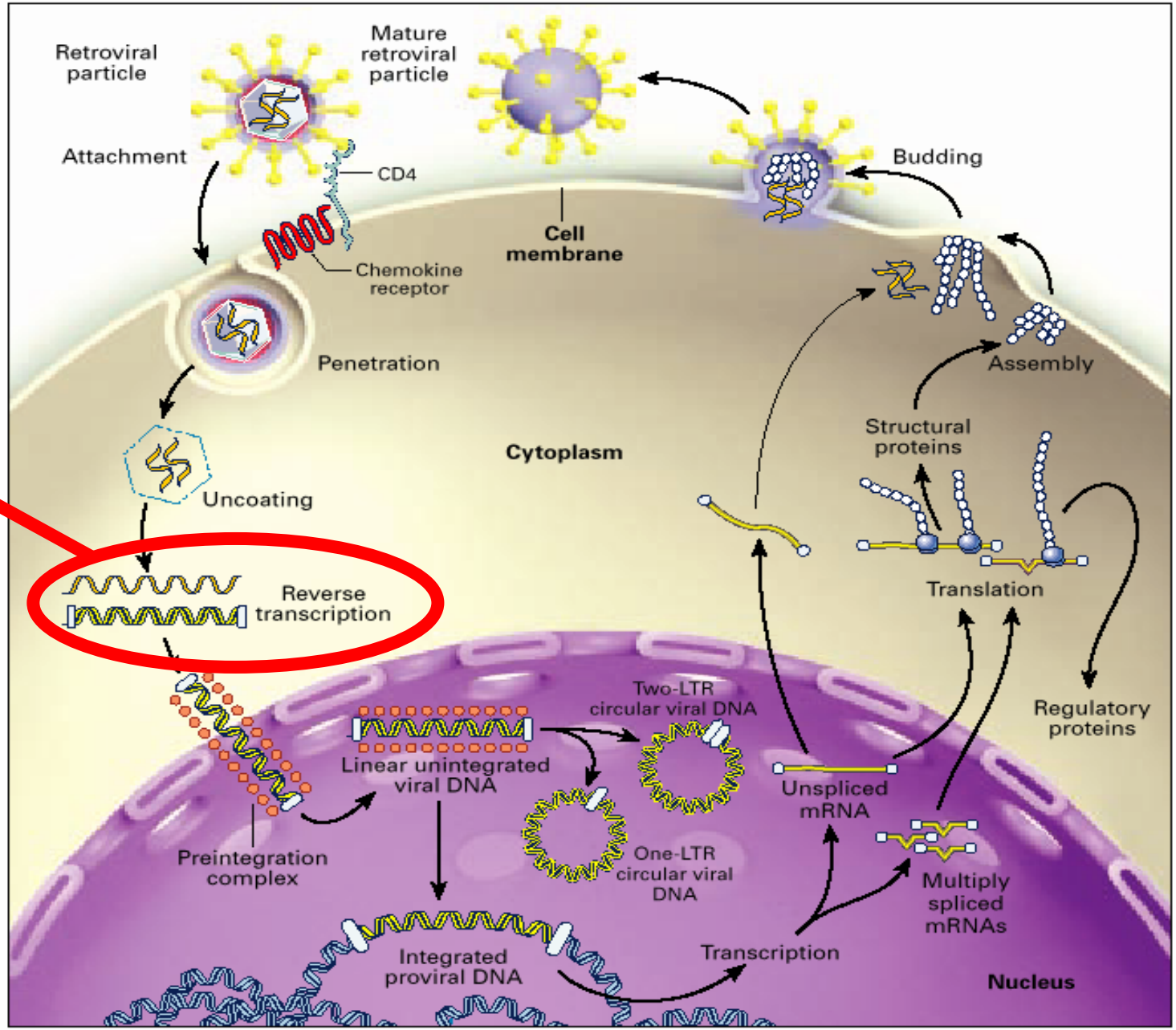
- The risk of emergence of new mutations is highest in patients with little resistance

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
- Early modification is especially important with regimens that contain “low genetic barrier drugs” (e.g. NNRTIs, 3TC, FTC)

HIV Lifecycle and Drug Targeting



NRTI Target

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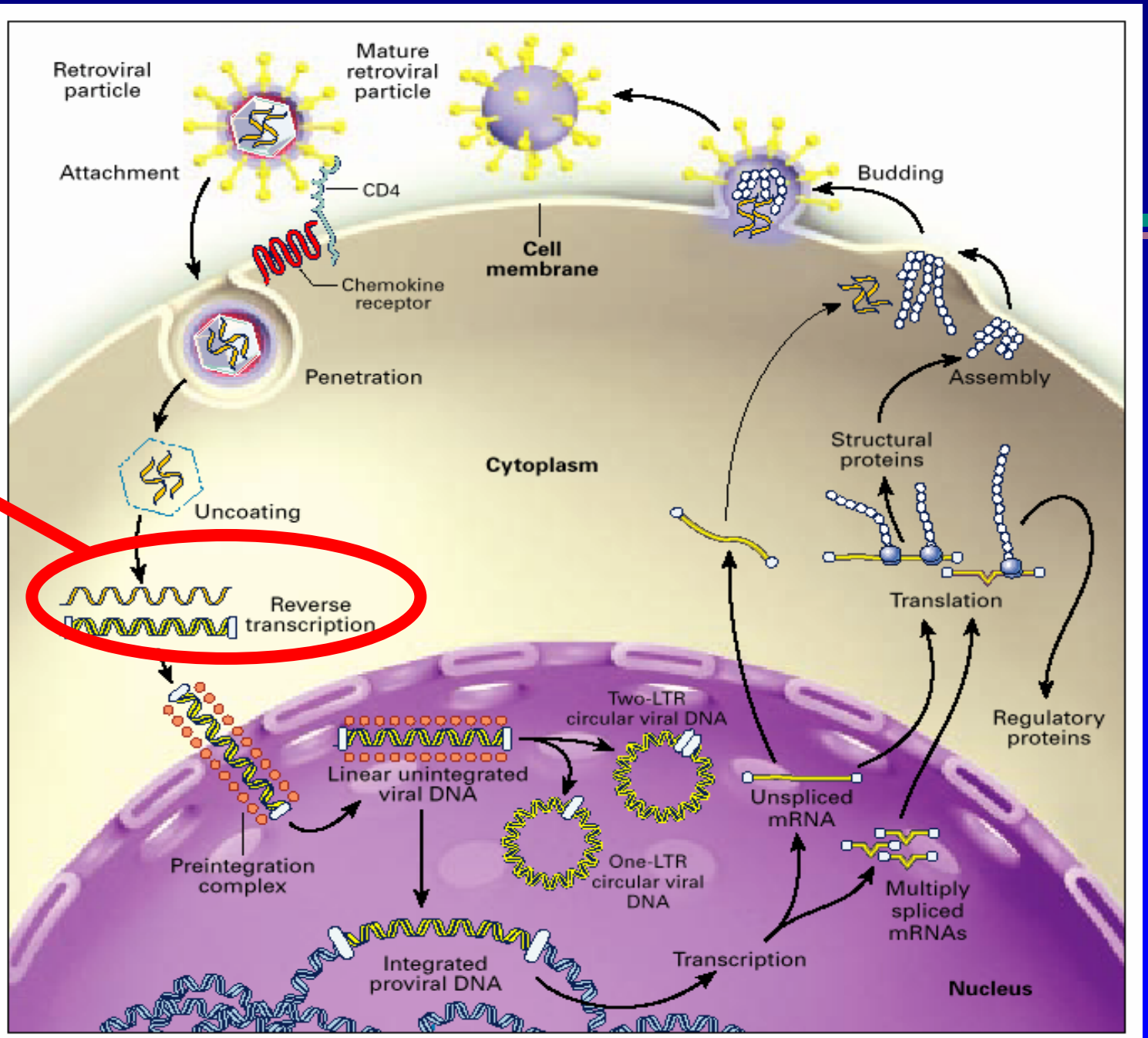
NRTI Sequencing Options After Failure of Specific NRTI Backbones

Initial Regimen	Likely Resistance Pattern	Most Active NRTIs
AZT/3TC d4T/3TC AZT/3TC/ABC	M184V +/- TAMs	Depends on number of TAMs and TAM pattern TDF or ddI may be most active NRTIs
TDF/3TC TDF/FTC	M184V +/- K65R	AZT + TDF + either 3TC or FTC (Resistance may be less common with FTC)
ABC/3TC	M184V +/- either L74V or K65R	AZT + TDF + either 3TC or FTC

Choose the next NRTIs based on resistance testing.

HIV Lifecycle and Drug Targeting

NNRTI Target



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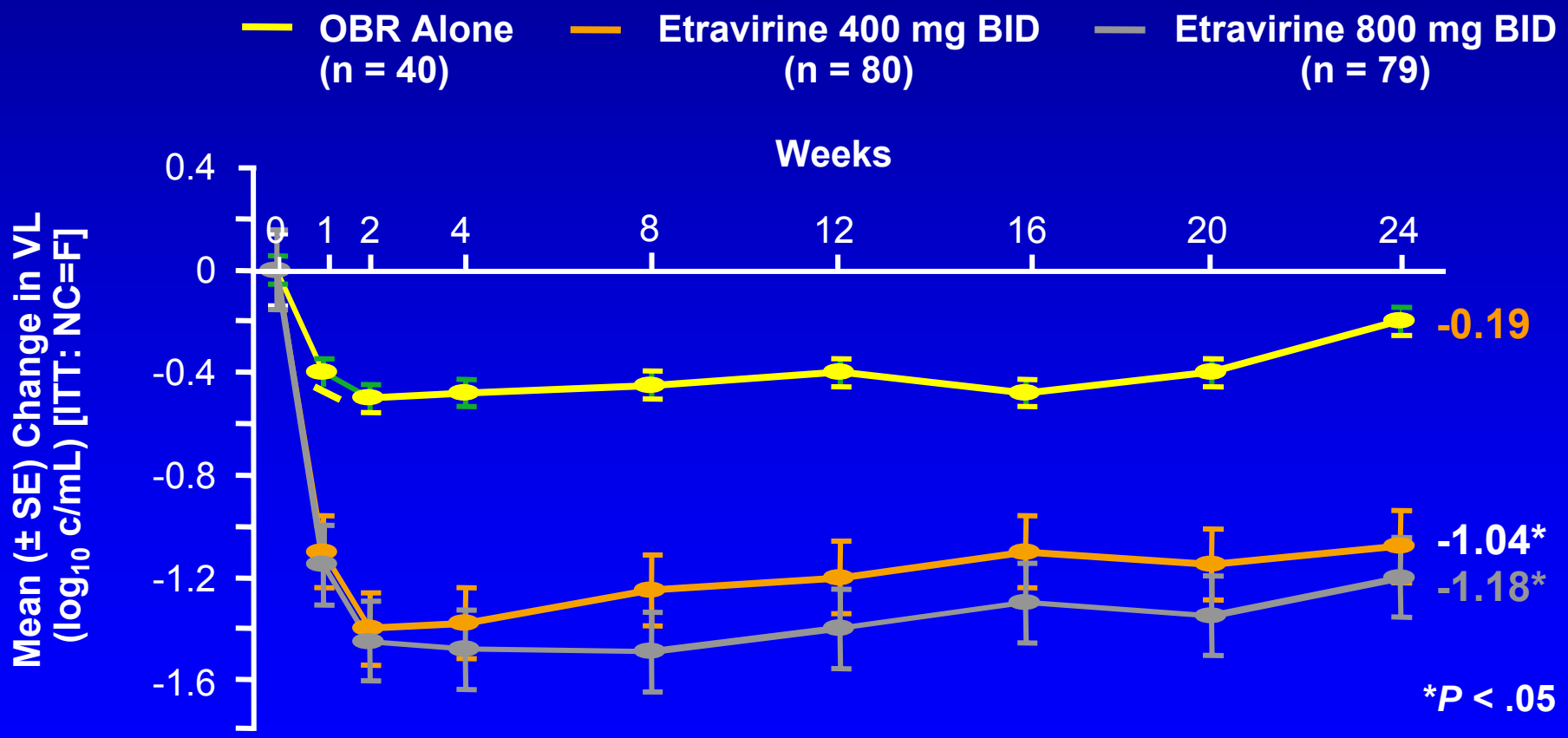
NNRTI Resistance

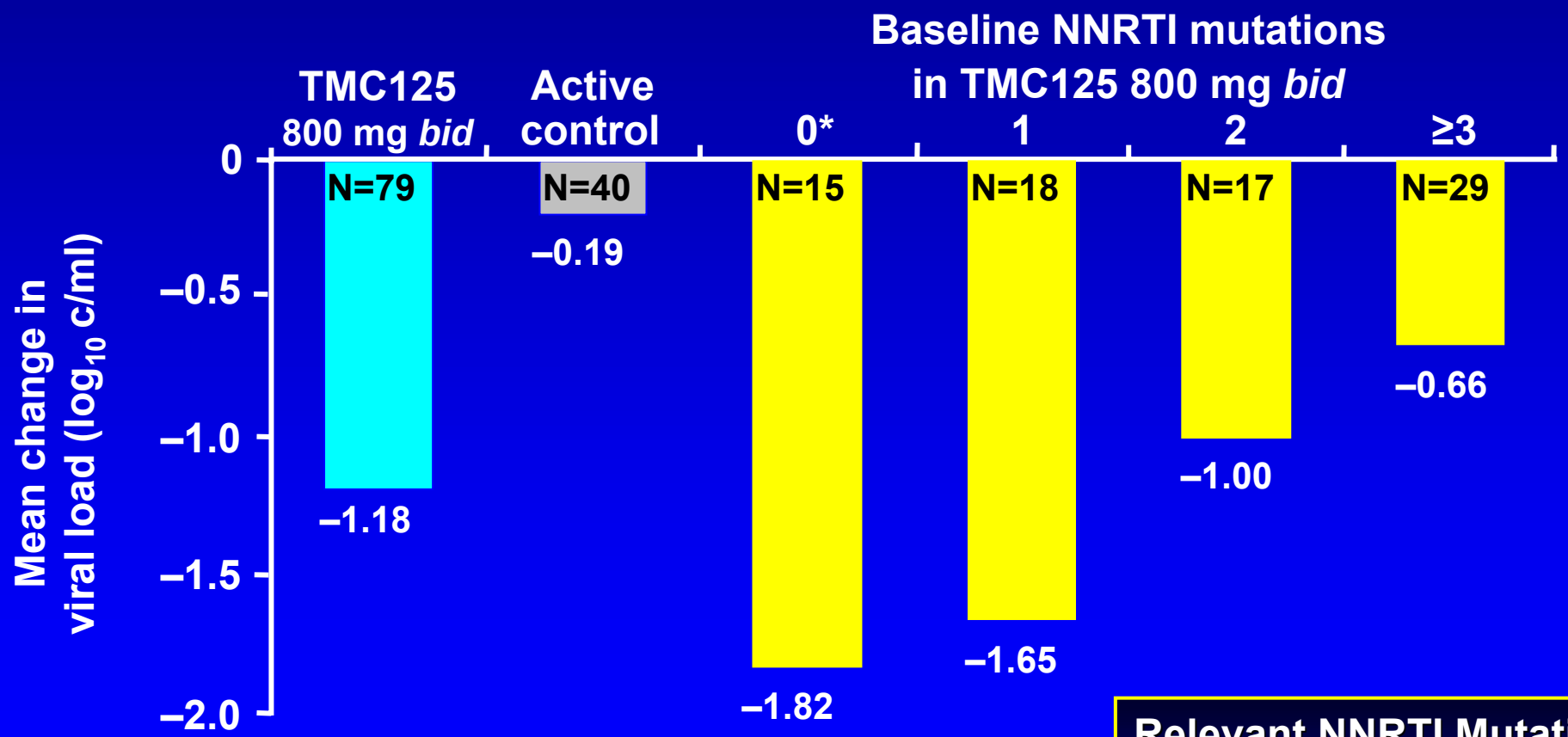
- Resistance mutations common at virologic failure
  - » May occur as 1st mutation, preceding M184V
- Limited prospects for sequential use of *current* NNRTIs:
  - » Poor results from NVP failure with 181C → EFV
  - » G190A/S, P225H cause DLV hypersusceptibility, but no clinical sequencing data
  - » 2nd generation NNRTIs promising: TMC125, TMC278

TMC125-C223: Virologic Response to Etravirine in Pts With NNRTI and PI Resistance



Grossman HA, et al. ICAAC 2005. Abstract H 416c.

TMC125-C223: NNRTI Mutations and Response to Etravirine at Week 24



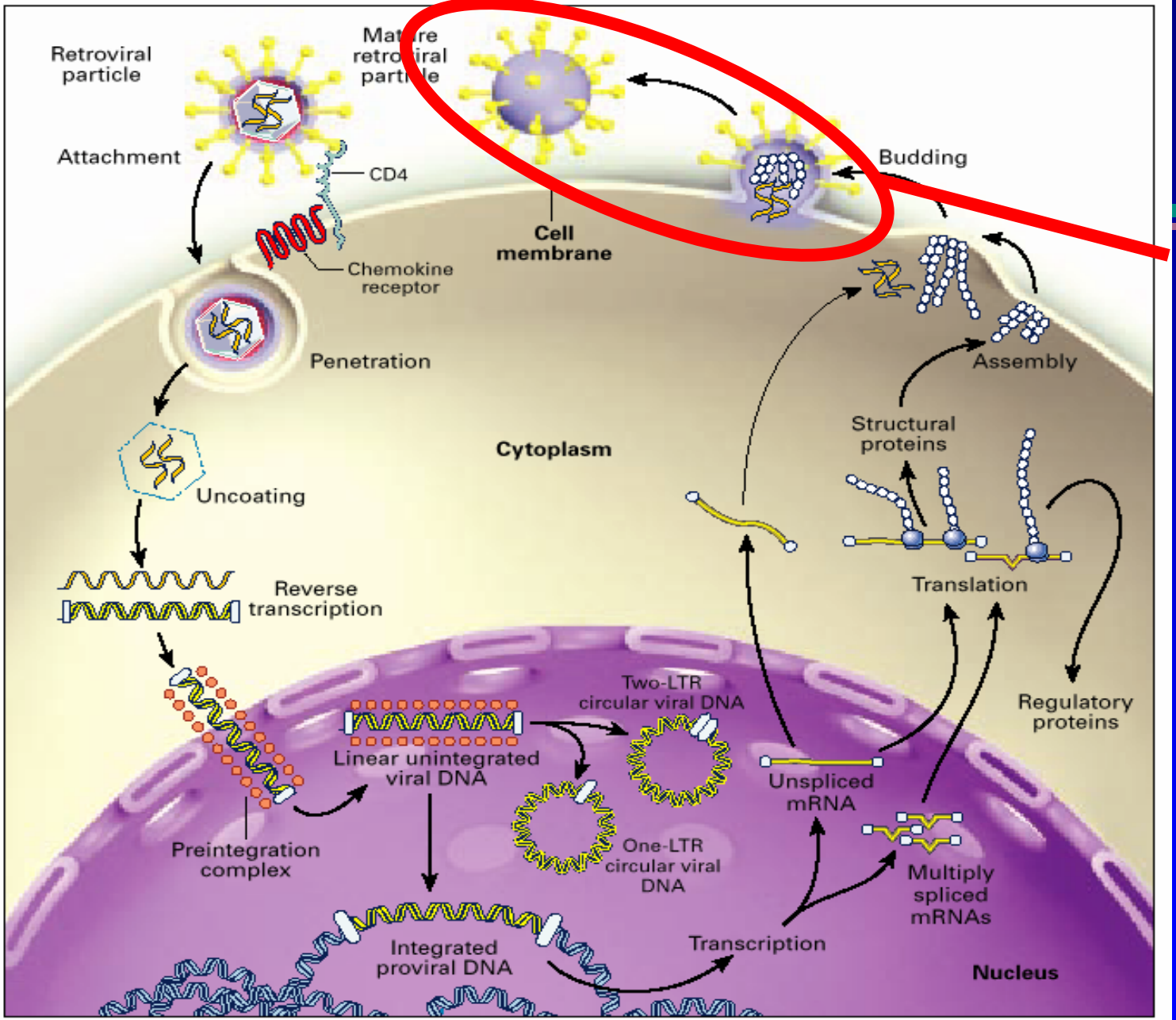
*All subjects had NNRTI mutations from prior genotyping

Relevant NNRTI Mutations:

K101P, V179E, V179F, Y181I, Y181V, G190S, M230L

Vingerhoets J, et al. 13th CROI, Denver, CO, February 5 §2006. Abst. 154

HIV Lifecycle and Drug Targets



PI Target

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Resistance Patterns after PI Failure

Unboosted PIs

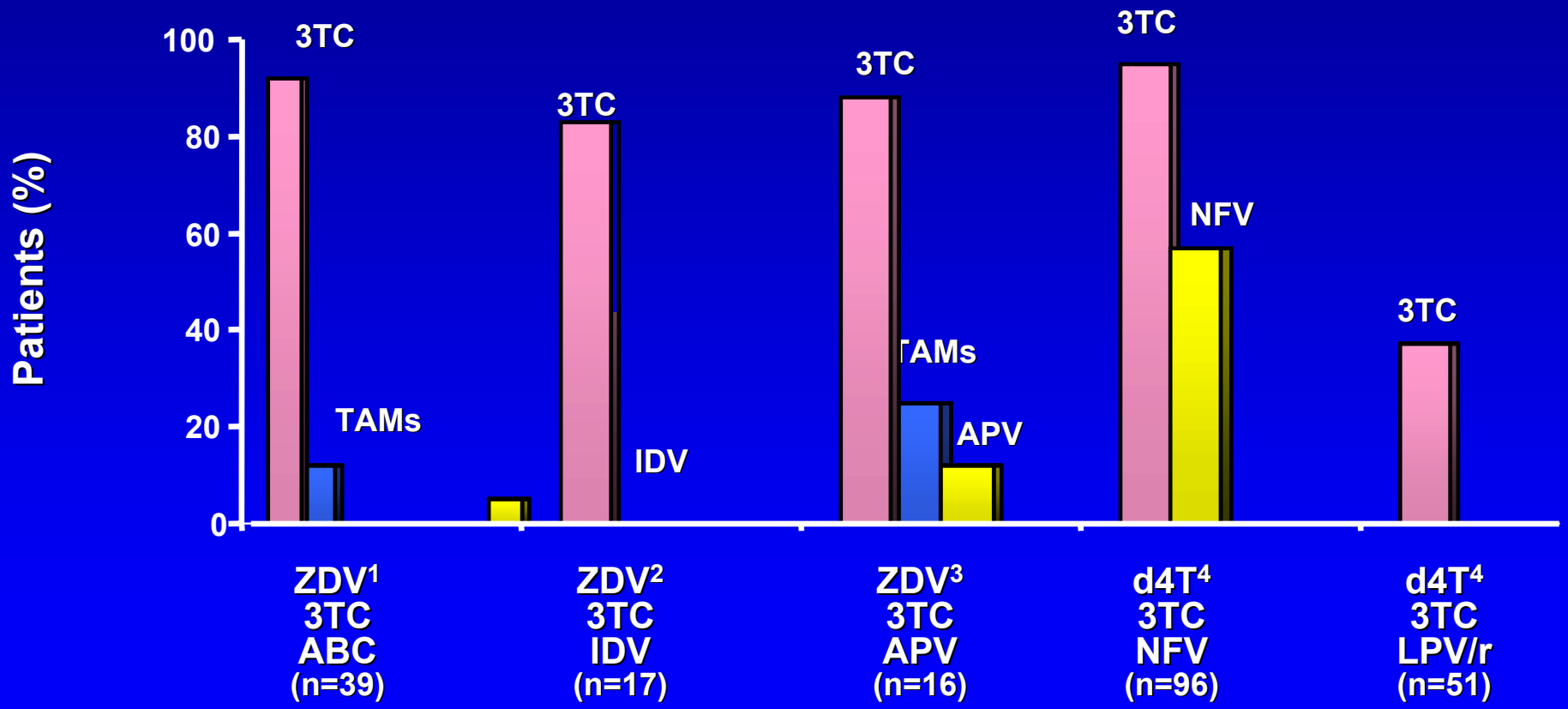
- NFV:
  - 30N: no cross-resistance
  - 90M: cross-resistance
- SQV:
  - 48V: no cross-resistance
  - 90M: cross resistance
- ATV:
  - 50L: no cross-resistance
- IDV:
  - Various mutations causing cross-resistance
- FPV
  - I54L/M, V32I + I47V: Variable cross-resistance

RTV-Boosted PIs

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

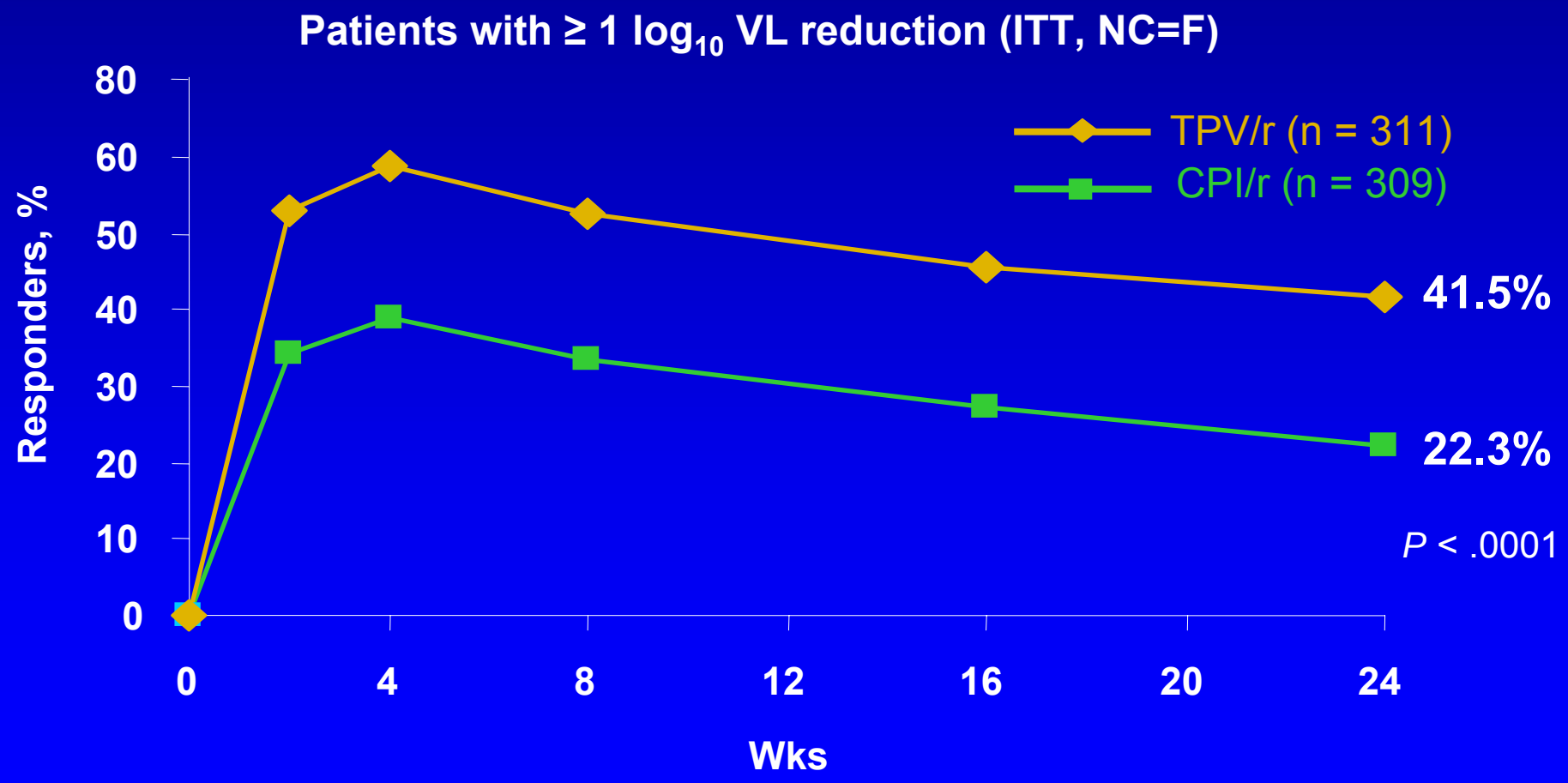
Choose the next PI based on resistance testing.

Resistance at Time of First Virologic Failure



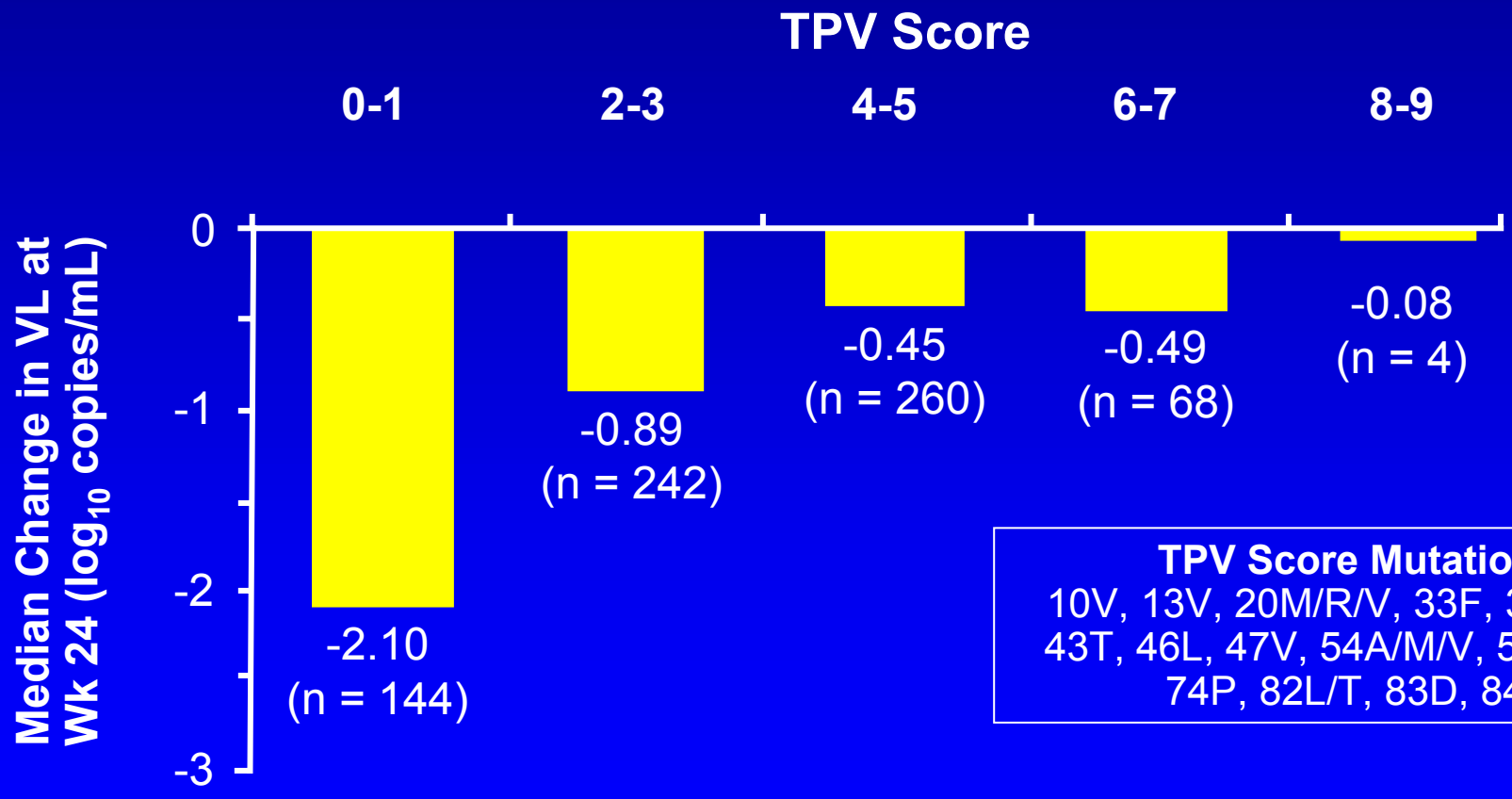
[1]Melby T. 8th CROI, 2001. Abstract 448; [2]Havlir D, et al. *JAMA*. 2000;283:229–234; [3]Rusconi S, et al. *Antiviral Ther*. 1998;3:203–207.
[4]Kempf D. 10th CROI. Boston, 2003. Abstract 600

RESIST-1: Superior Virologic Responses With Tipranavir/Ritonavir



Hicks C, et al. ICAAC 2004. Abstract 1137a.

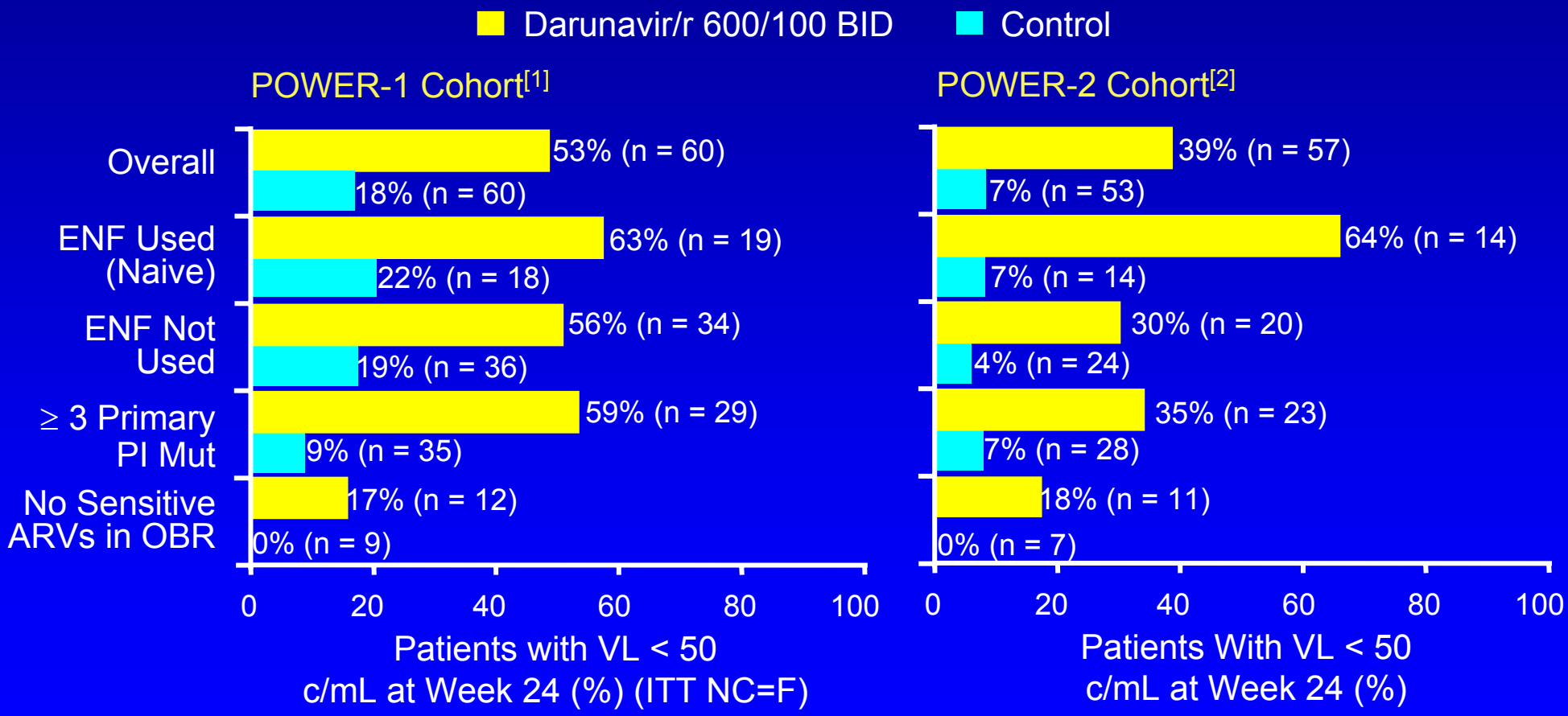
Relationship of TPV Score to TPV Phenotype Results and Response



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

Valdez H, et al. Resistance Workshop 2005. Abstract 27.

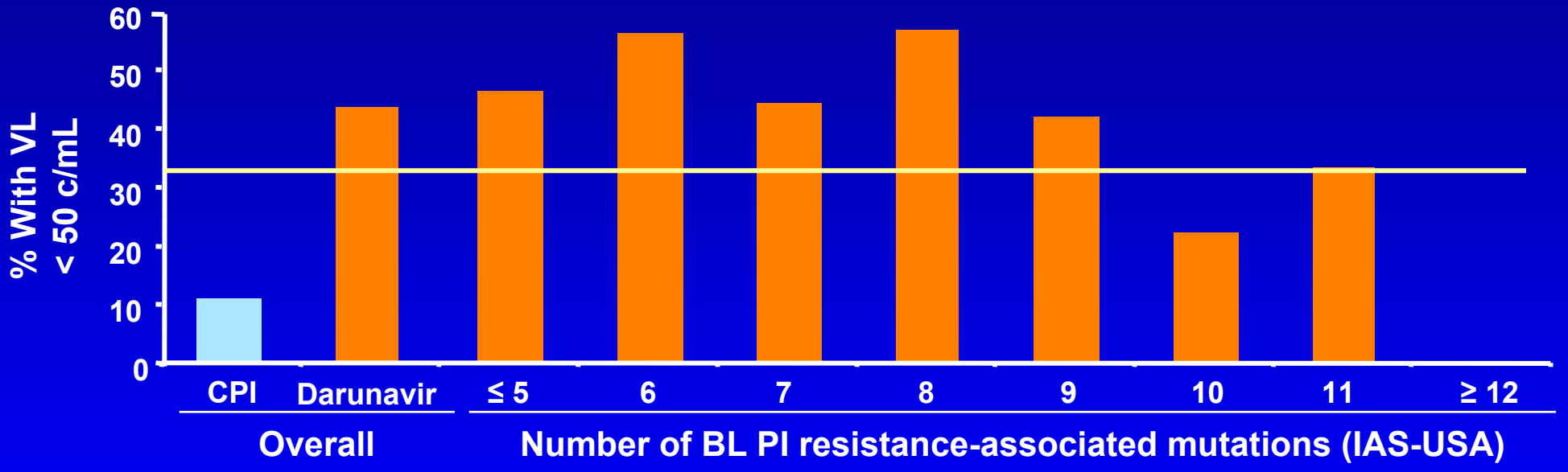
POWER: Subgroup Analyses of Response to Darunavir/r 600/100 BID



1. Katlama C, et al. IAS 2005. Abstract WeOaLB0102.

2. Wilkin T, et al. ICAAC 2005. Abstract H-413.

Effect of Baseline Resistance on Response to Darunavir

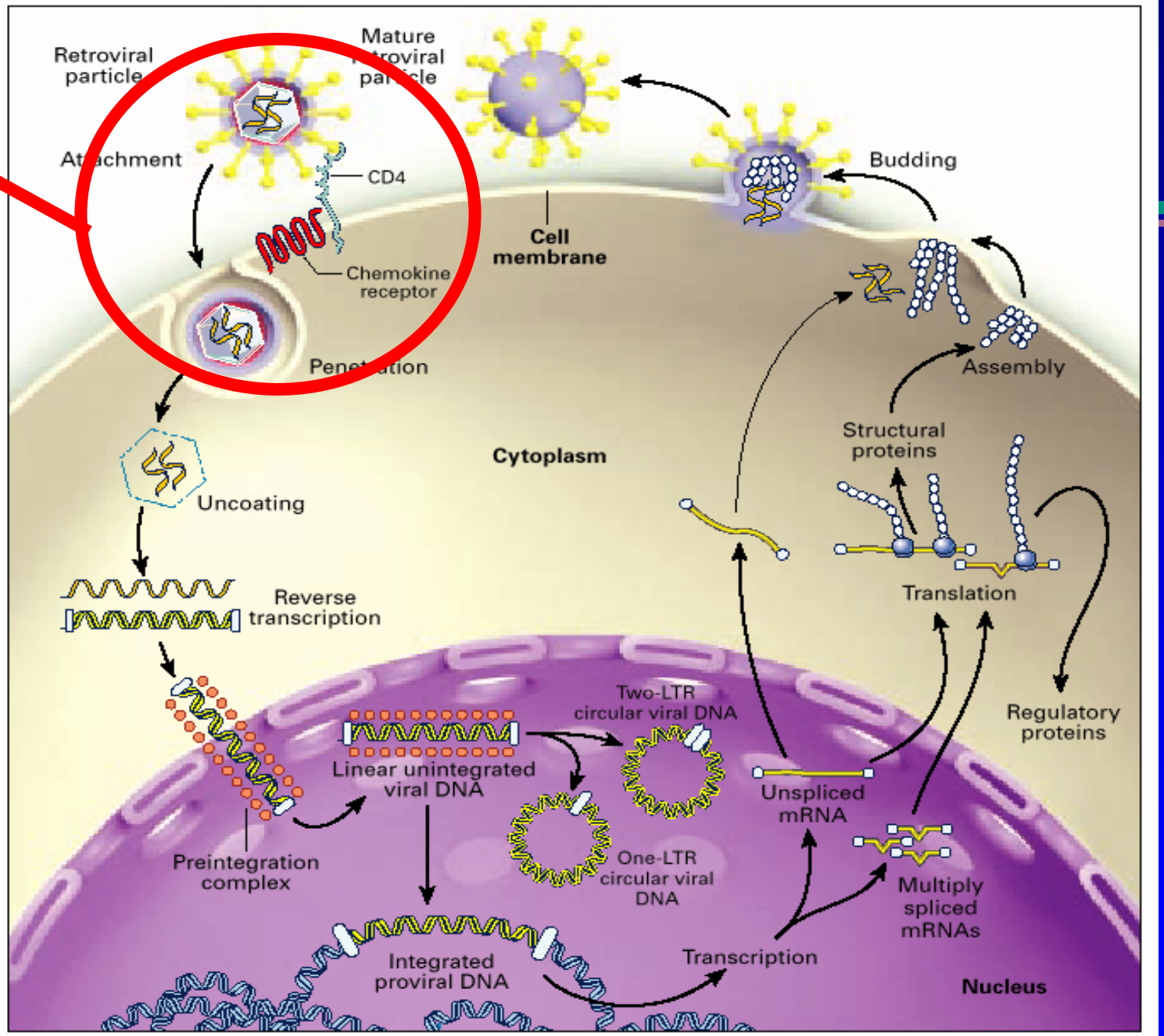


- BL mutations associated with diminished response (< 33% with VL < 50 c/mL)
  - » V11I, V32I, L33F, I47V, I50V, I54L, I54M, G73S, L76V, I84V and L89V (highlighted mutations emerged on therapy)
  - » Presence associated with a higher number of PI mutations
  - » Darunavir response remained higher than that of CPI

DeMeyer S, et al. CROI 2006. Abstract 157.

HIV Lifecycle and Drug Targeting

Entry Inhibitor target



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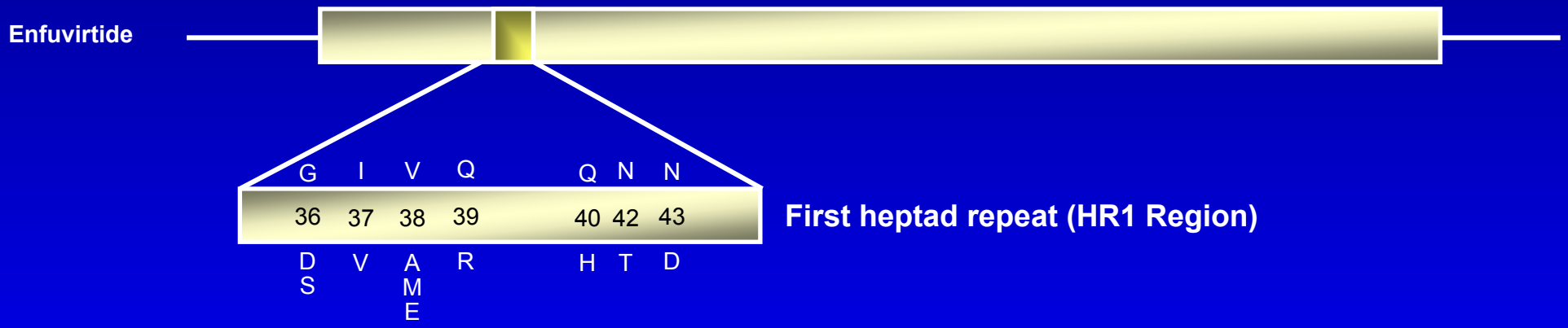
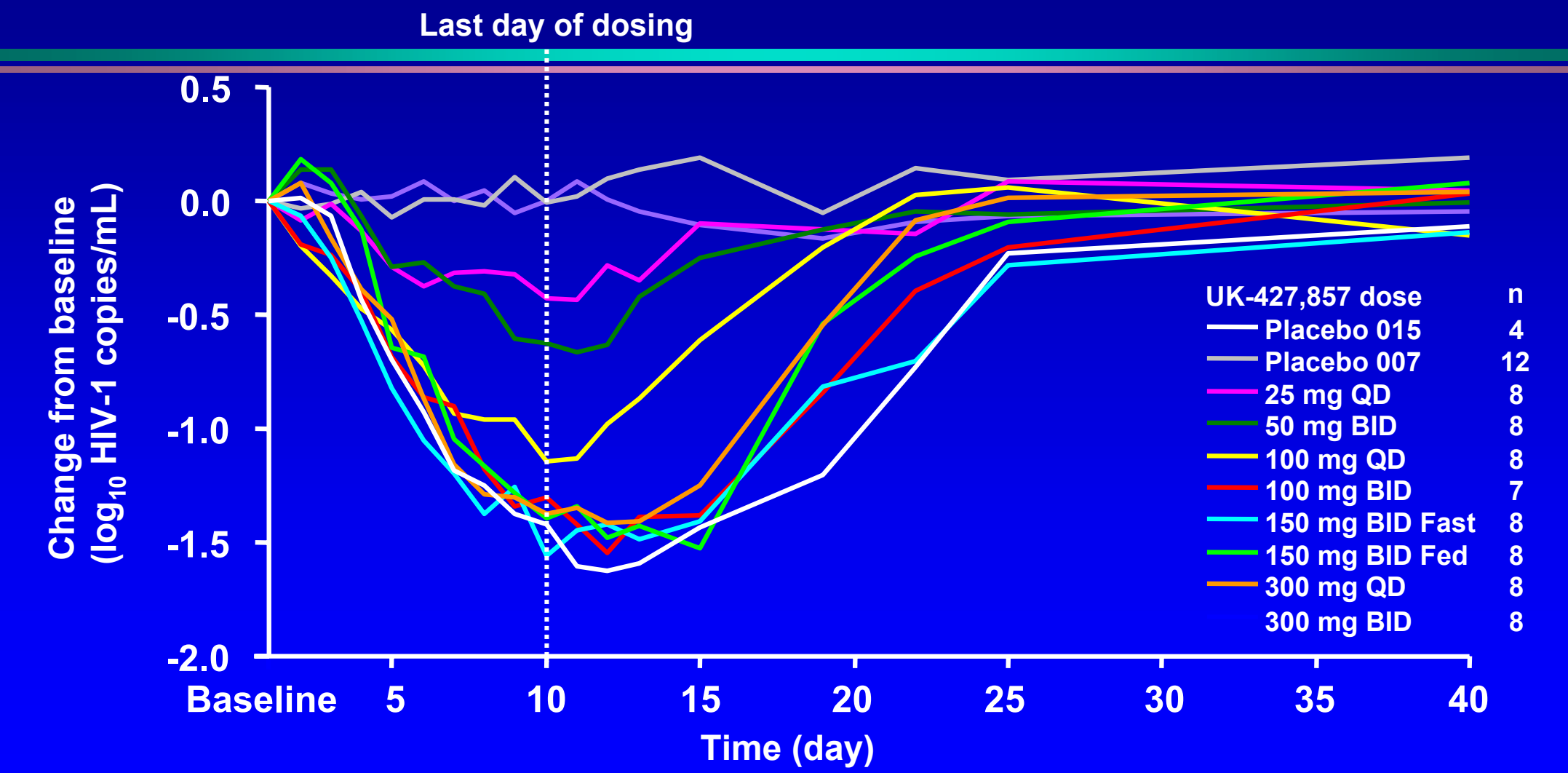
gp 41 *env* Mutations Associated With Enfuvirtide Resistance: IAS-USA 2005



Maraviroc: Change in HIV RNA



Study A4001007/1015

Fätkenheuer G *et al*.15th IAC 2004. Abstract TuPeB4489

Update on CCR5 inhibitors

Aplaviroc (GSK)

- Phase IIb/III trials recently stopped due to hepatotoxicity
- 4 (1%) treatment-emergent grade 3/4 ALT and total bilirubin >1.5x ULN

Vicriviroc (Schering-Plough)

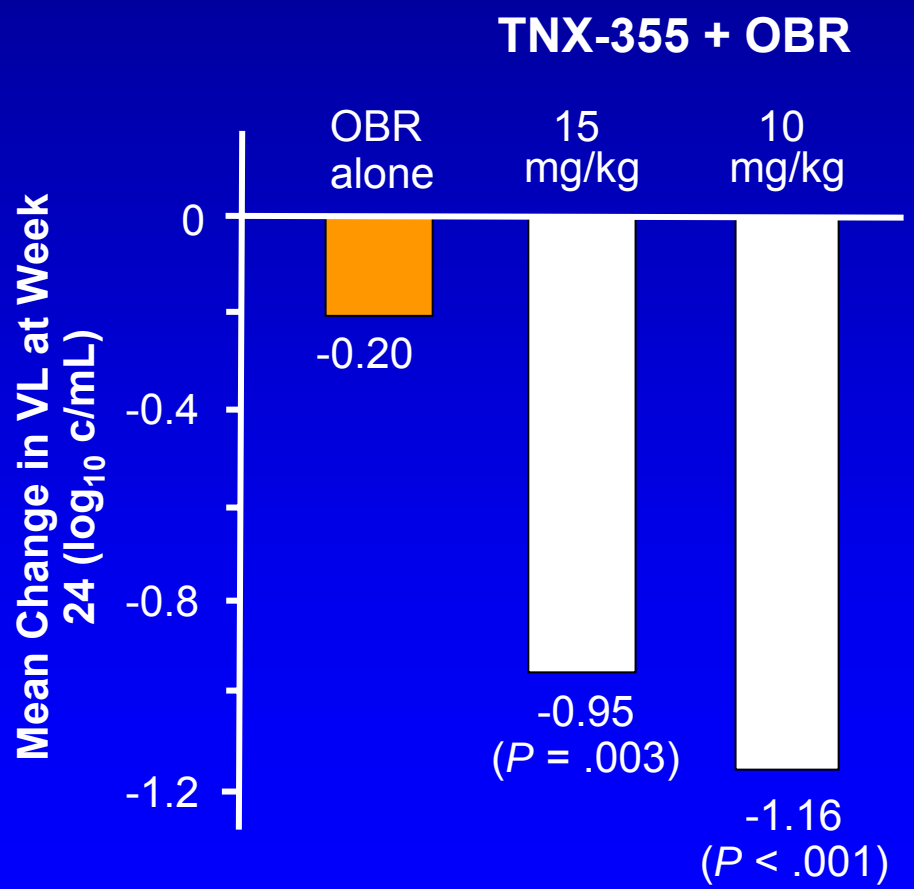
- Study in ART-naïve stopped because of high rate of failure vs. EFV
- May have been due to study design
- Studies in experienced patients ongoing

Maraviroc (Pfizer)

- Studies ongoing in naive and experienced patients
- 1 case with increased LFTs under review

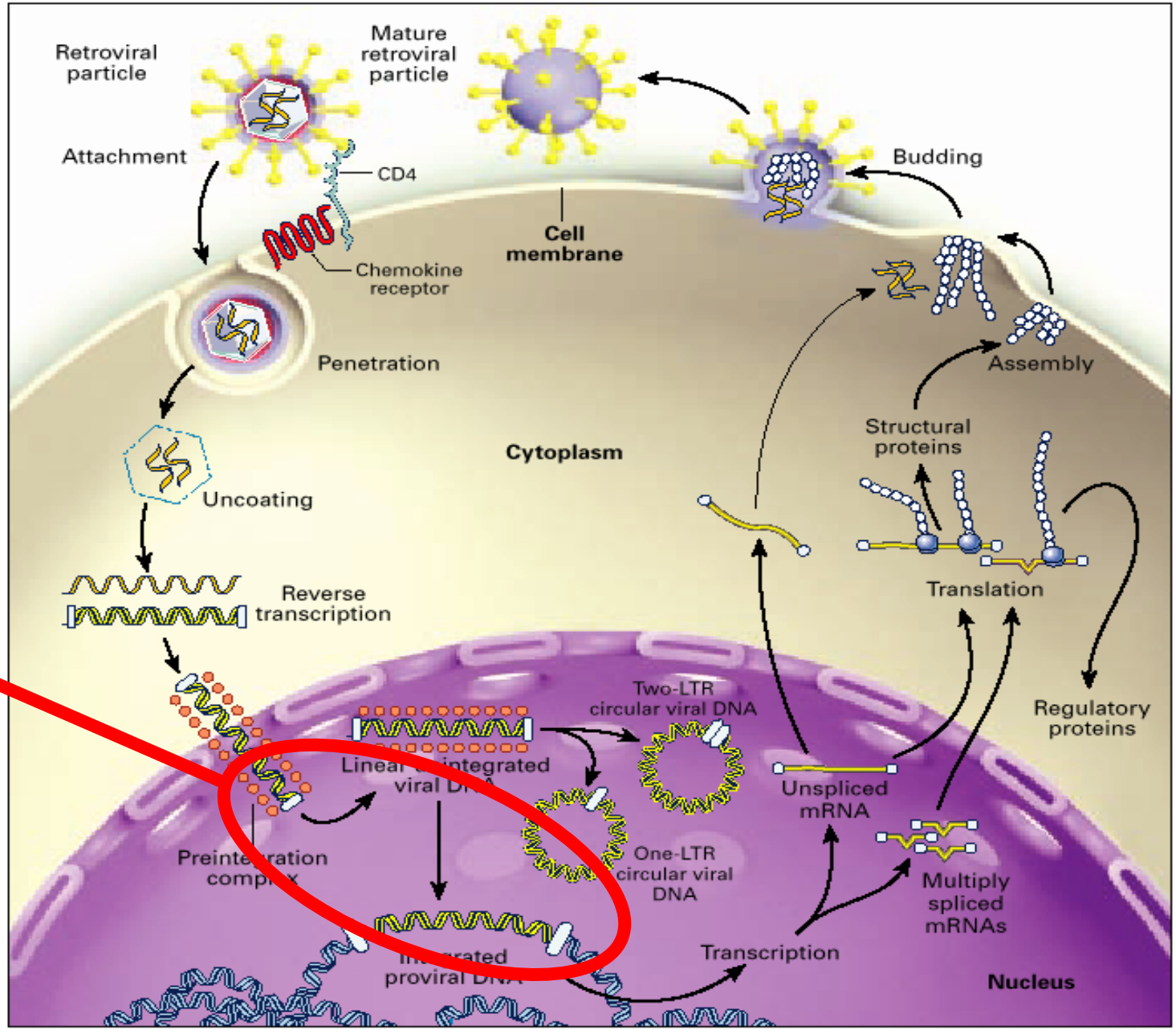
TNX-355: Novel Entry Inhibitor

- Anti-CD4 monoclonal antibody blocks gp120 attachment to CD4 receptor
  - » Delivered by IV infusion
- Phase II randomized trial in 82 3-class experienced patients [1]
  - » TNX-355 + OBR or OBR alone
  - » TNX-355 doses:
    - – 15 mg/kg IV every 2 wks
    - – 10 mg/kg IV every wk x 8 wks, then 10 mg/kg every 2 wks



Norris D, et al. ICAAC 2005. Abstract LB2-26.

HIV Lifecycle and Drug Targets



Integrase Inhibitors

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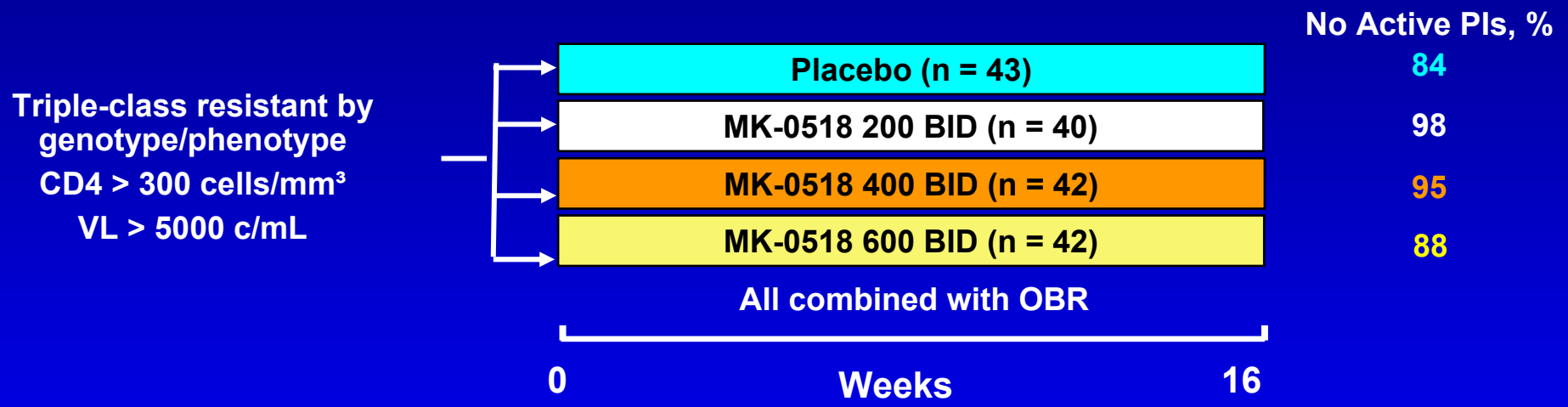
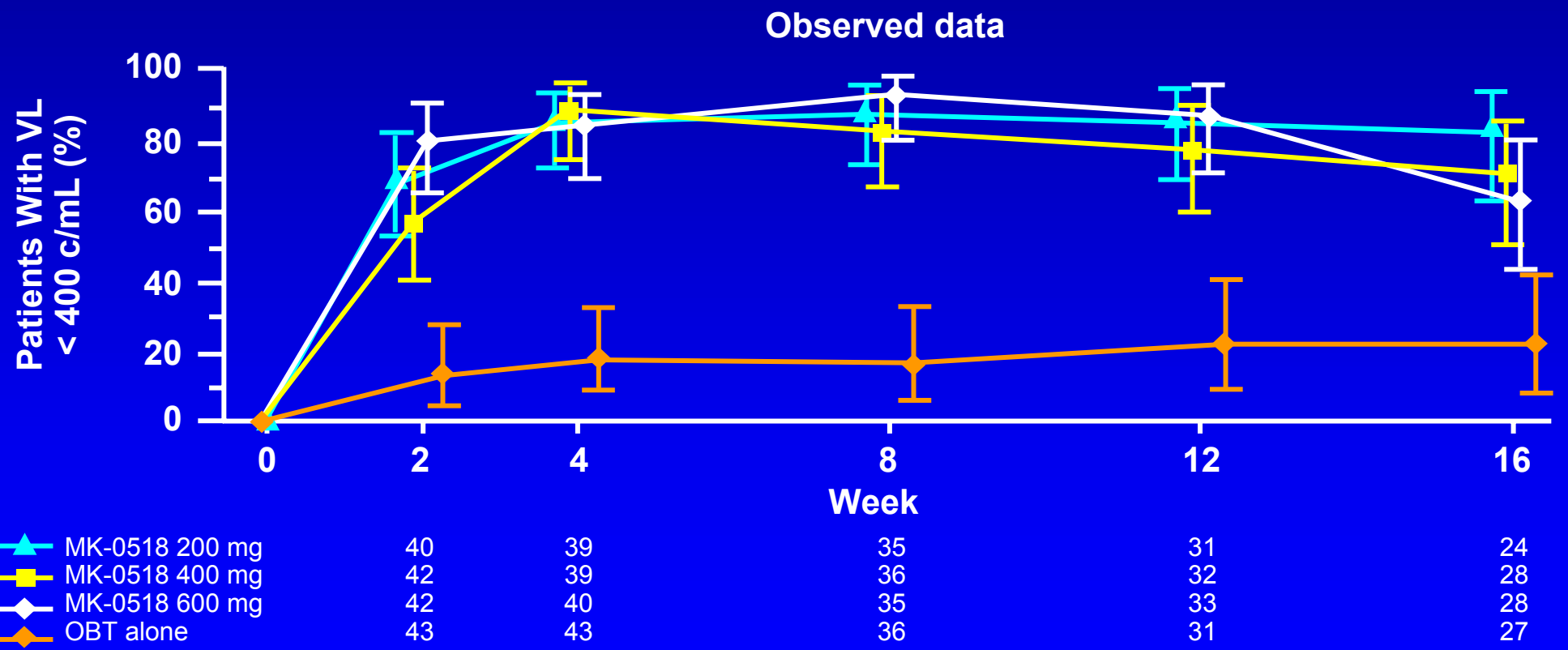
Integrase Inhibitor: MK-0518



- Multicenter, double-blind randomized study
- Preliminary data reported
- Endpoints
  - » HIV-1 RNA, CD4 counts at 16 weeks
  - » Safety
- No boosting effect of ritonavir with this compound

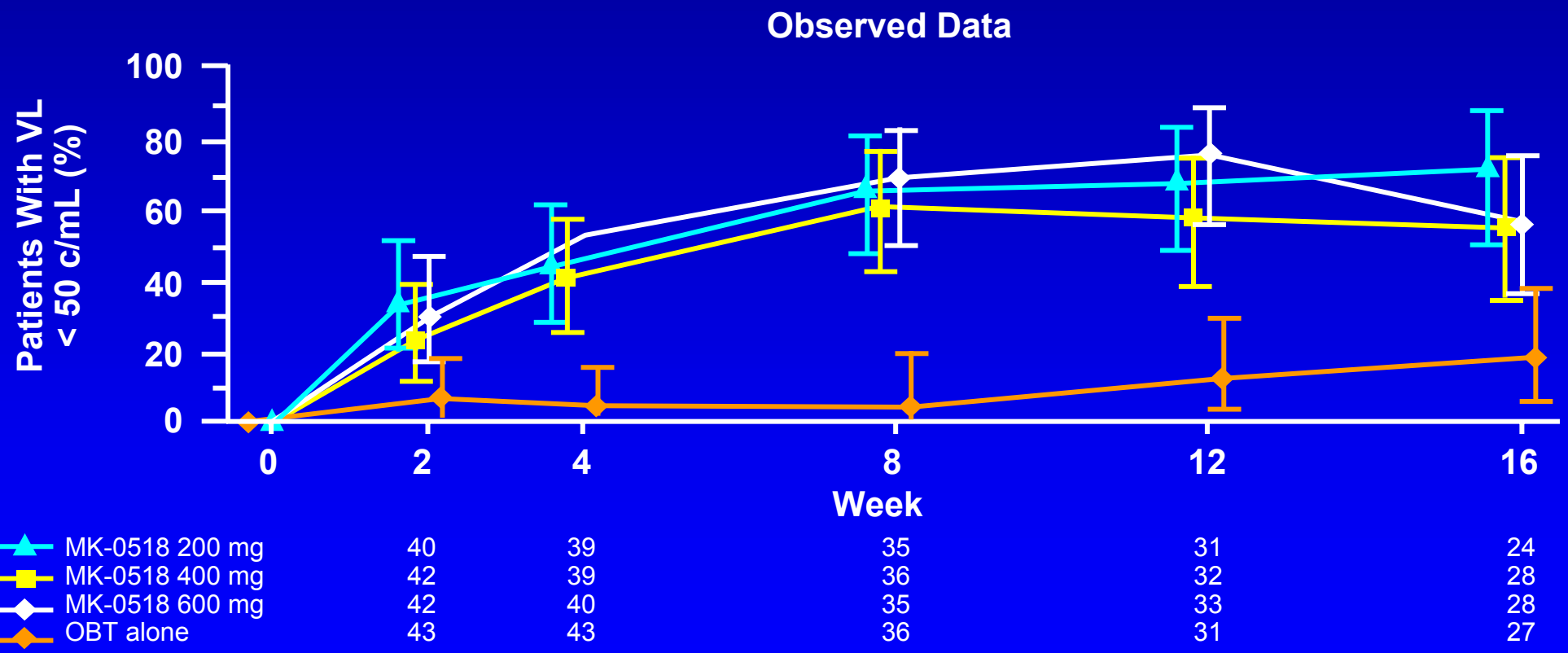
Grinsztejn B, et al. CROI 2006. Abstract 159LB.

MK-0518: Viral Suppression < 400 c/mL Through Week 16



Grinsztejn B, et al. CROI 2006. Abstract 159LB.

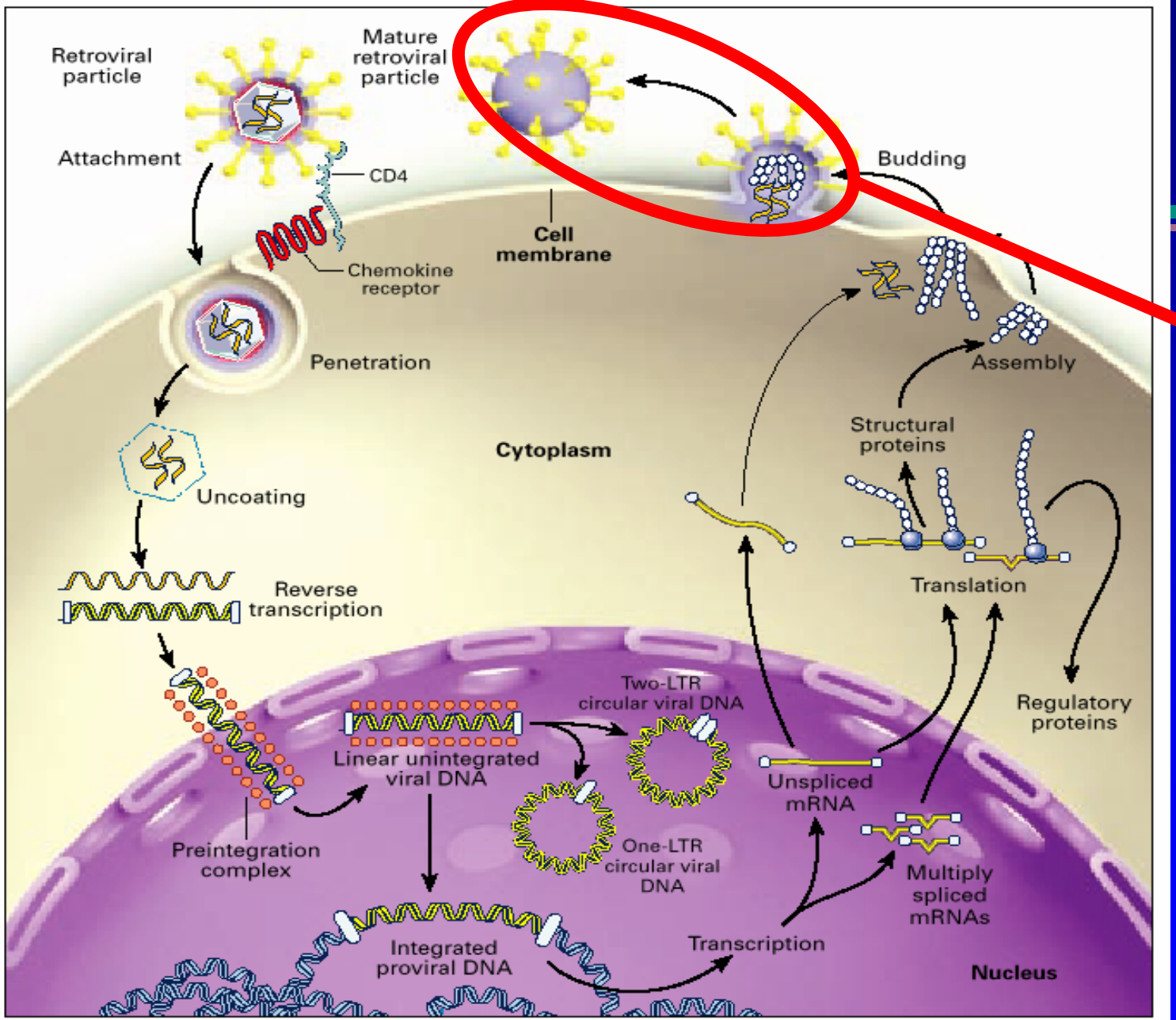
MK-0518: Viral Suppression < 50 c/mL Through Week 16



- Adverse events similar to placebo

Grinsztejn B, et al. CROI 2006. Abstract 159LB.

HIV Lifecycle and Drug Targets



Maturation Inhibitors

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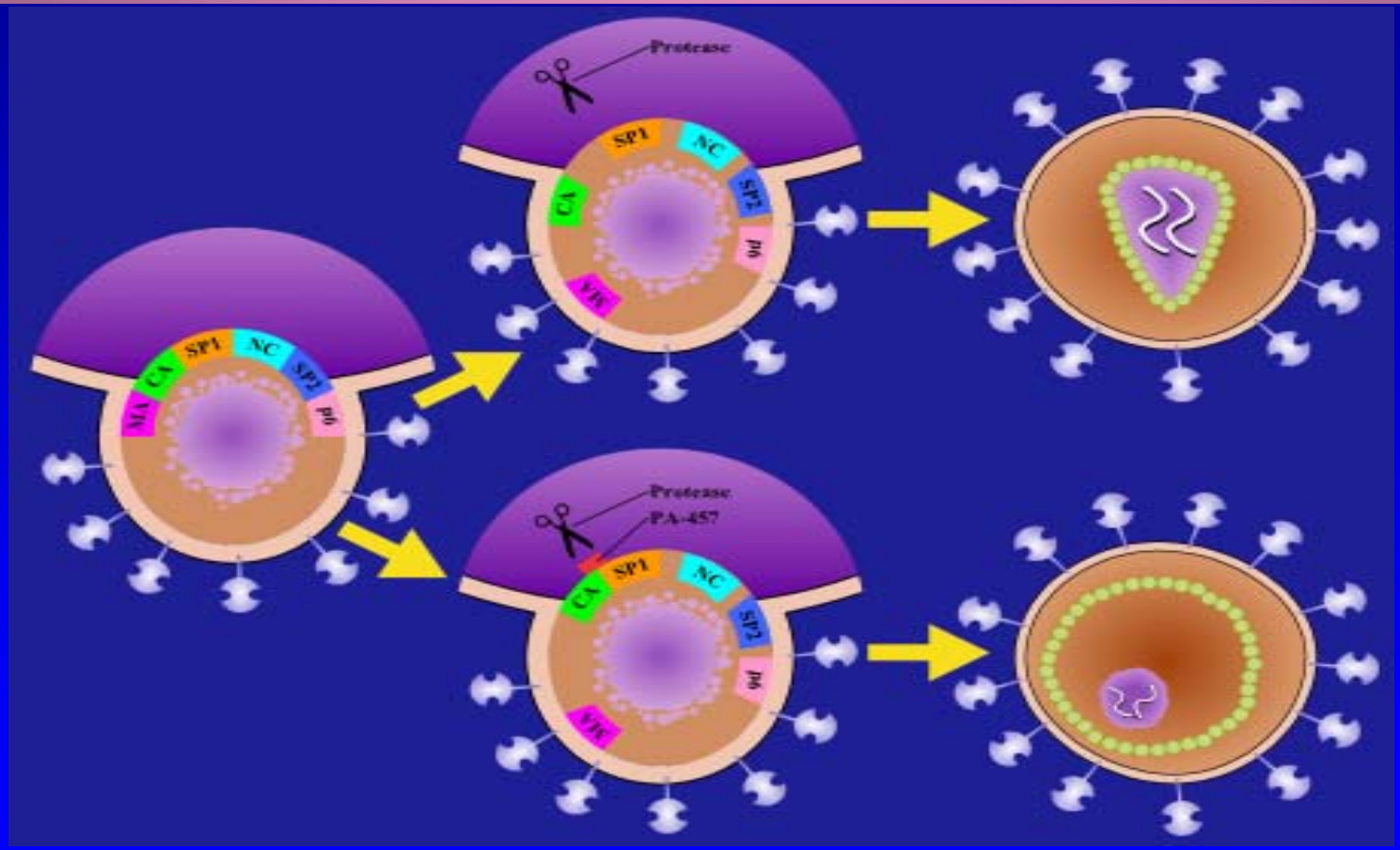
Maturation Inhibitors (PA-457):

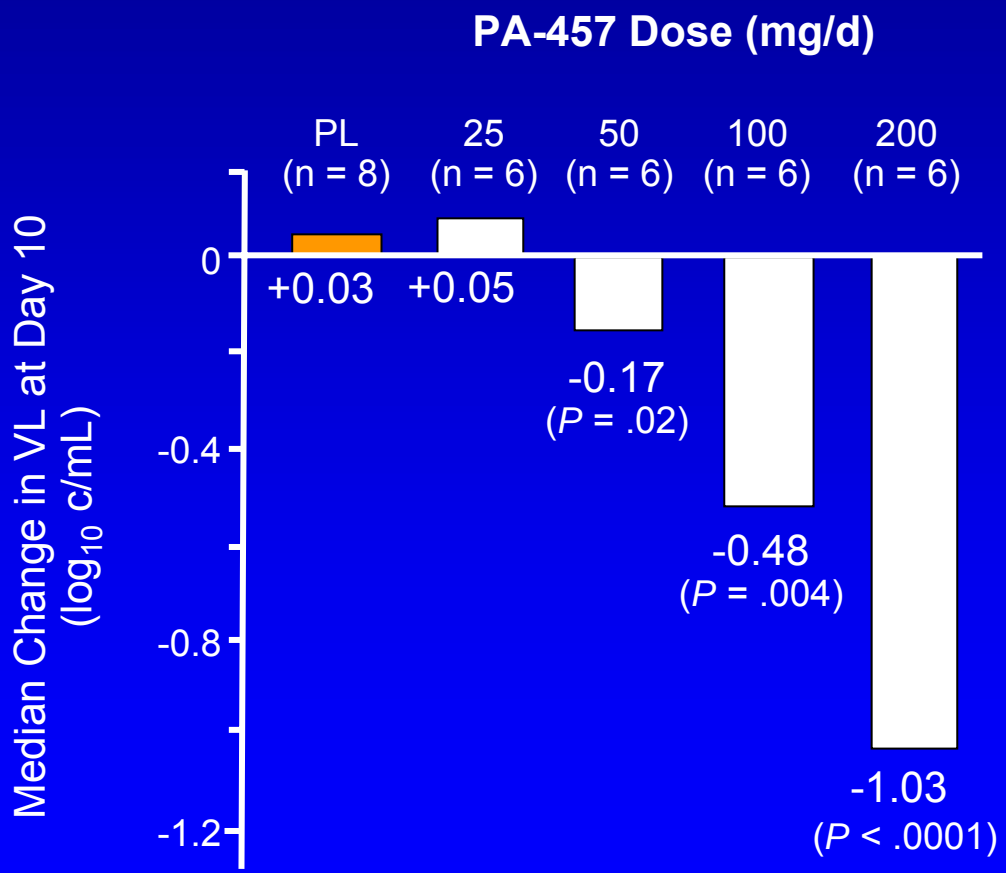
Blocks cleavage of capsid precursor to mature p24



Viral Budding and Maturation

PA-457: Virologic Response to Novel Maturation Inhibitor Monotherapy

- Randomized, phase IIa study of 10-day monotherapy in 32 HIV-infected pts
  - » Med. 1 $\log_{10}$ VL reduction with PA-457 200 mg/d
- Generally well tolerated



Beatty G, et al. ICAAC 2005. Abstract H 46d.

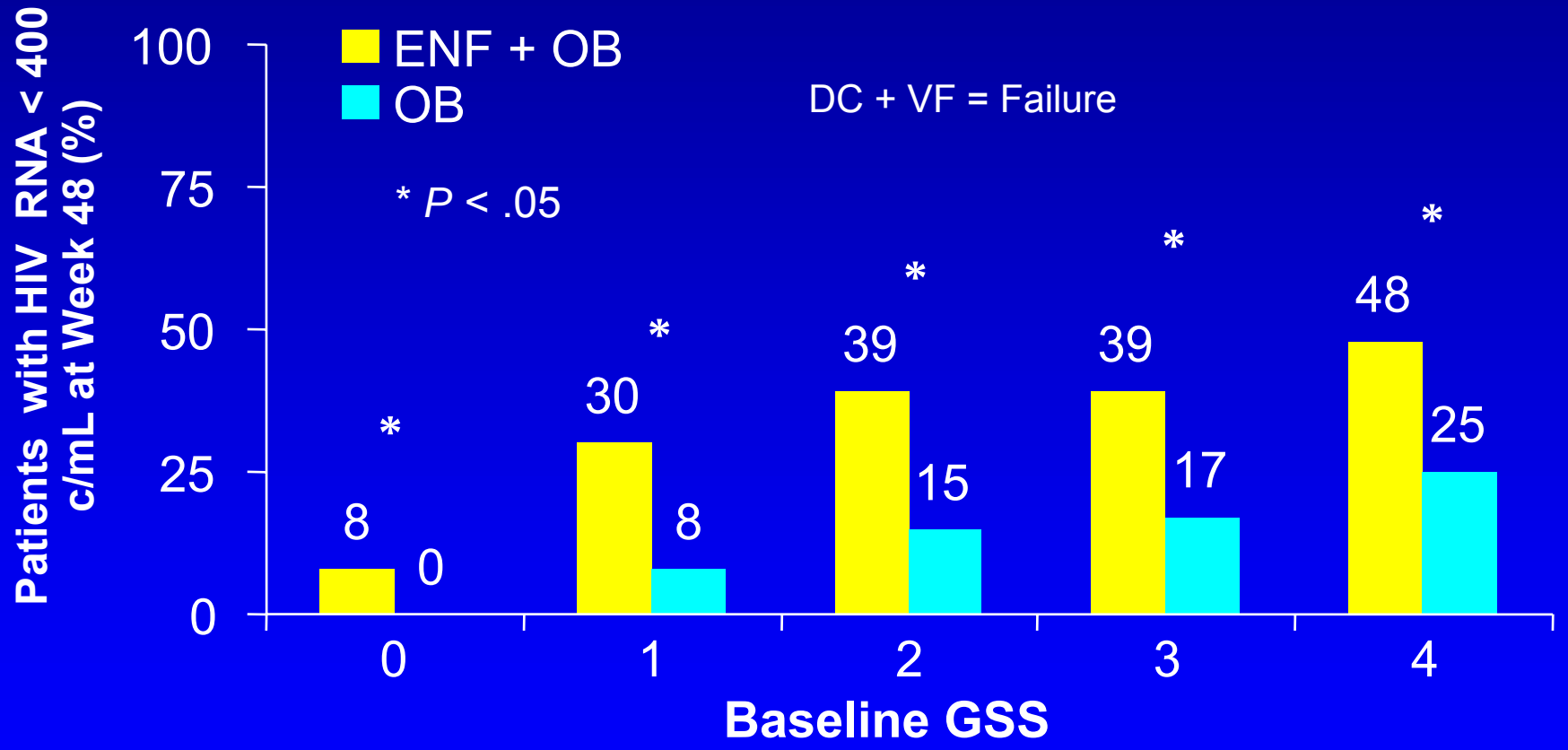
Goals of Therapy With Multi-Drug Resistant HIV

- Access to ≥ 2 active agents:
  - » Completely suppress viral load
  - » Now applies to an increasing number of “salvage” patients
- Access to < 2 active agents:
  - » Reduce viral load by ≥1 $\log_{10}$
  - » Stabilize CD4 count
  - » Minimize drug toxicity
  - » Prevent clinical progression and death
  - » Avoid new resistance mutations that could eliminate future options
  - » Avoid “monotherapy” with new drugs

Considerations for Salvage Therapy

- In combination therapy, only the active drugs count

In Combination Therapy, Only the Active Drugs Count



ENF:	98	179	152	83	27
OB:	49	88	84	46	16

Miralles D, et al. ICDT HIV 2004.

Considerations for Salvage Therapy

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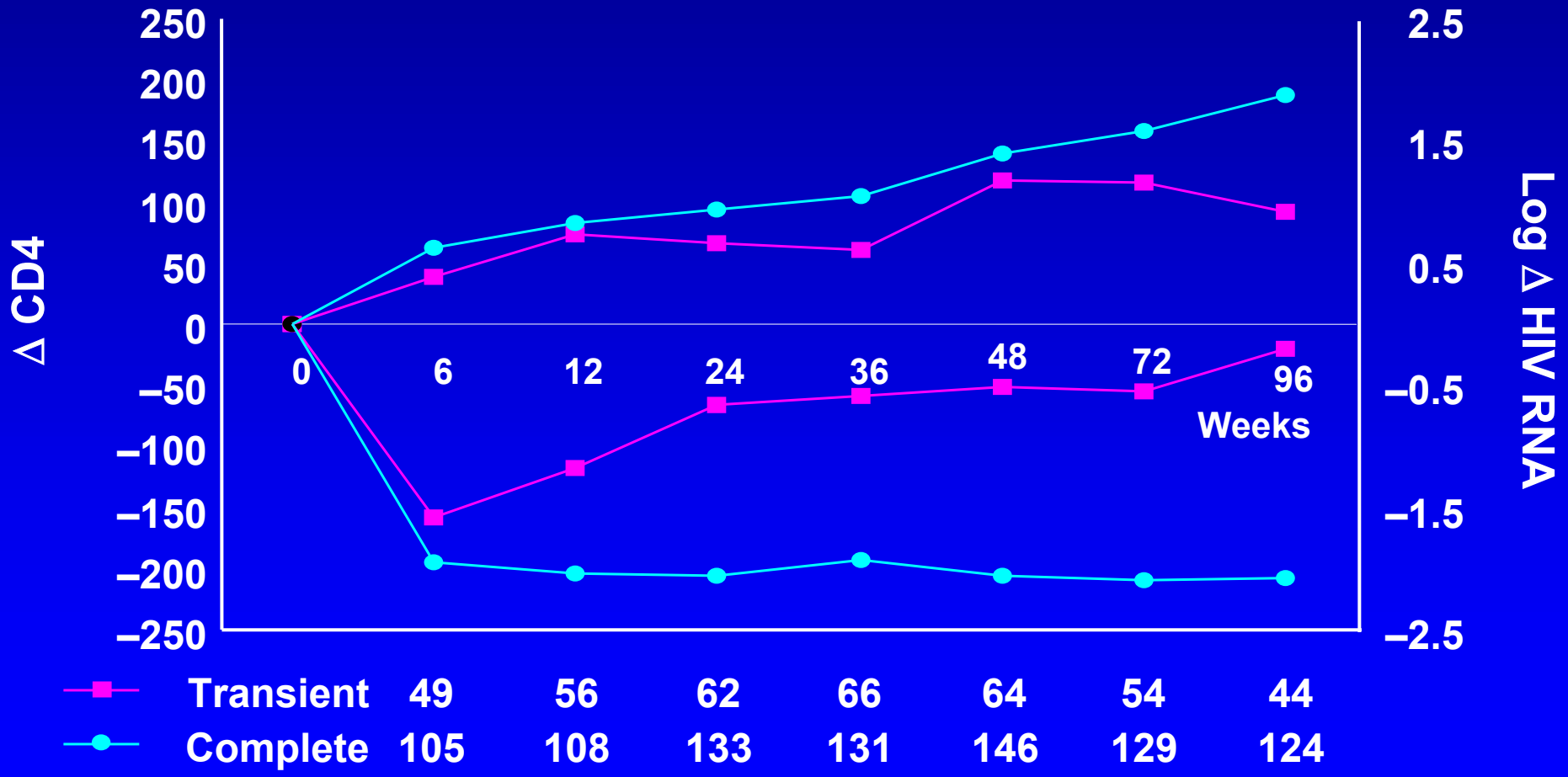
Considerations for Salvage Therapy

- In combination therapy, only the active drugs count
- A new drug may not be an active drug
- When to use a new drug, and when to wait

When to Use a New Drug, and When to Wait

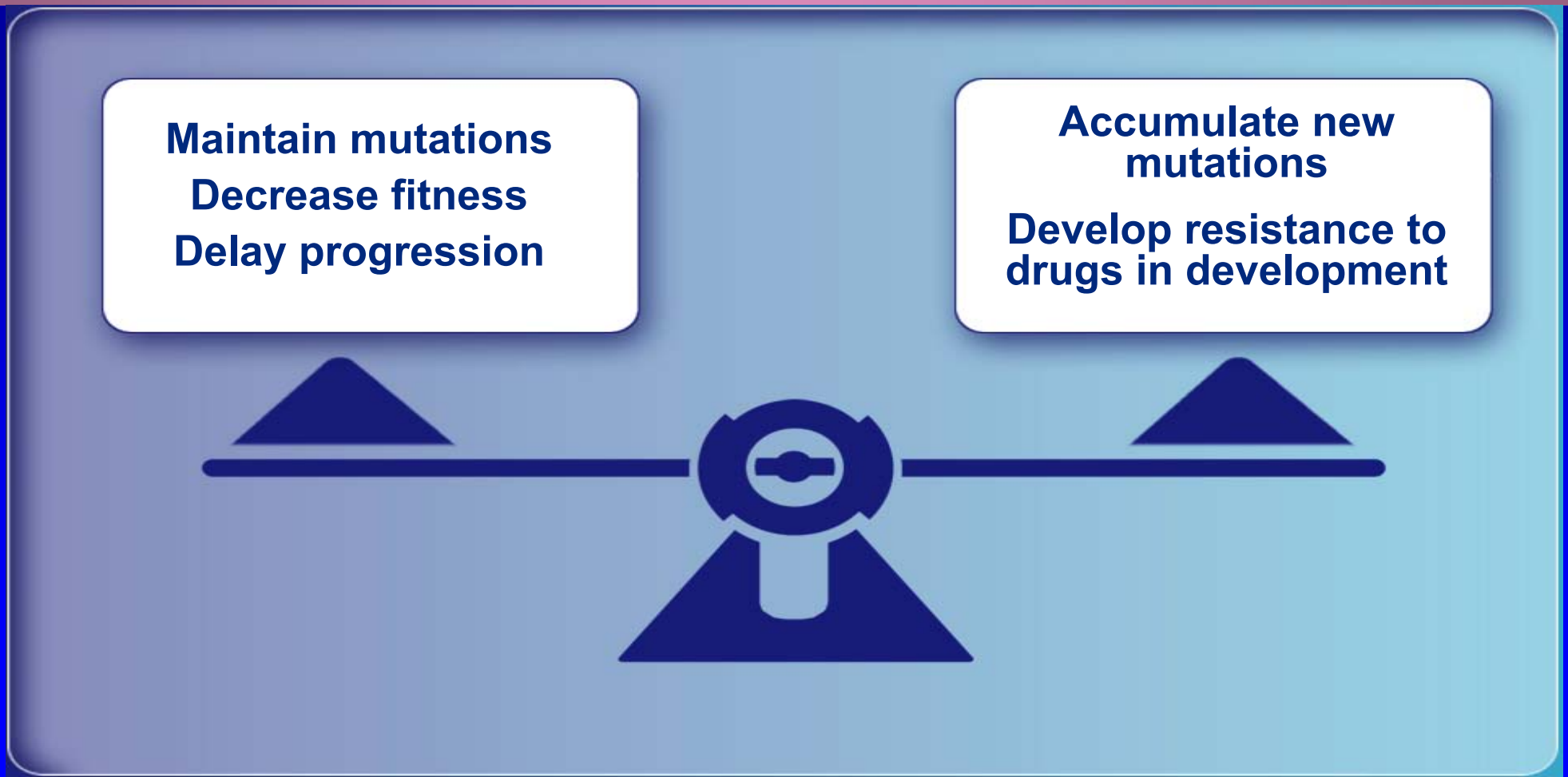
- What is prognosis with continued non-suppressive therapy?
- What are the resistance consequences of continued non-suppressive therapy?
- How can I maintain the “right” mutations without allowing the “wrong” ones to emerge?
- When will new drugs be available, and will they be active against the patients virus?

CD4-VL Disconnect:
Can Impaired Fitness Be Used Strategically?



Deeks. *J Infect Dis* 2000;181:946.

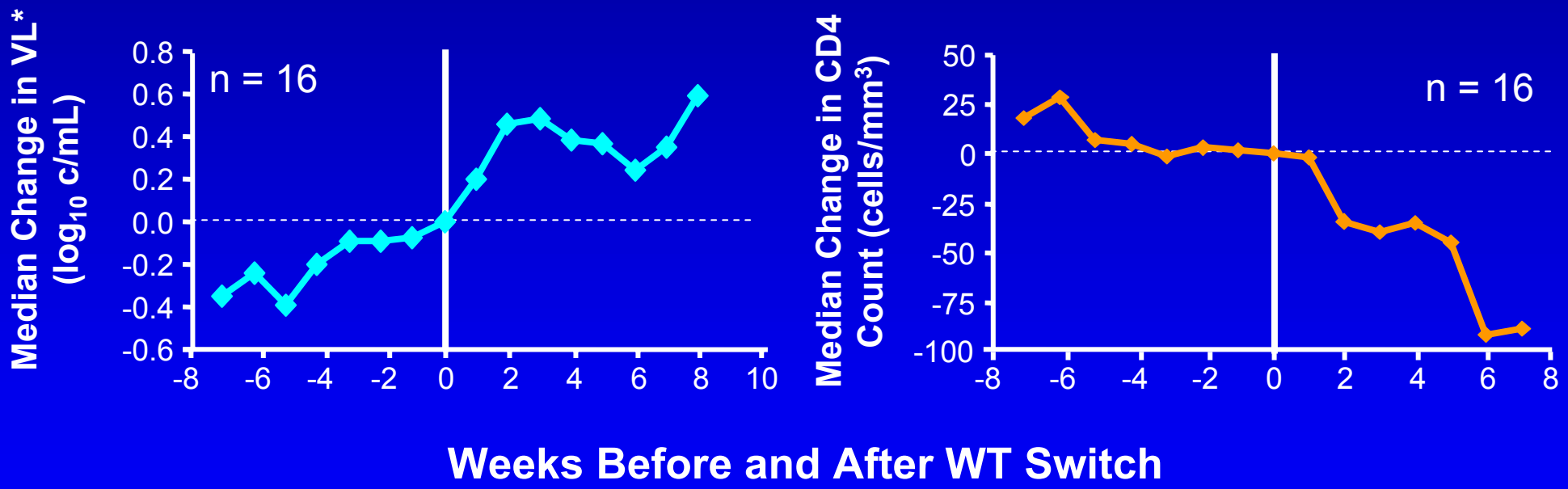
Continued Therapy in Patients With Virologic Failure: A Delicate Balance



Considerations for Salvage Therapy

- In combination therapy, only the active drugs count
- A new drug may not be an active drug
- When to use a new drug, and when to wait
- Waiting: Choosing a “holding regimen”

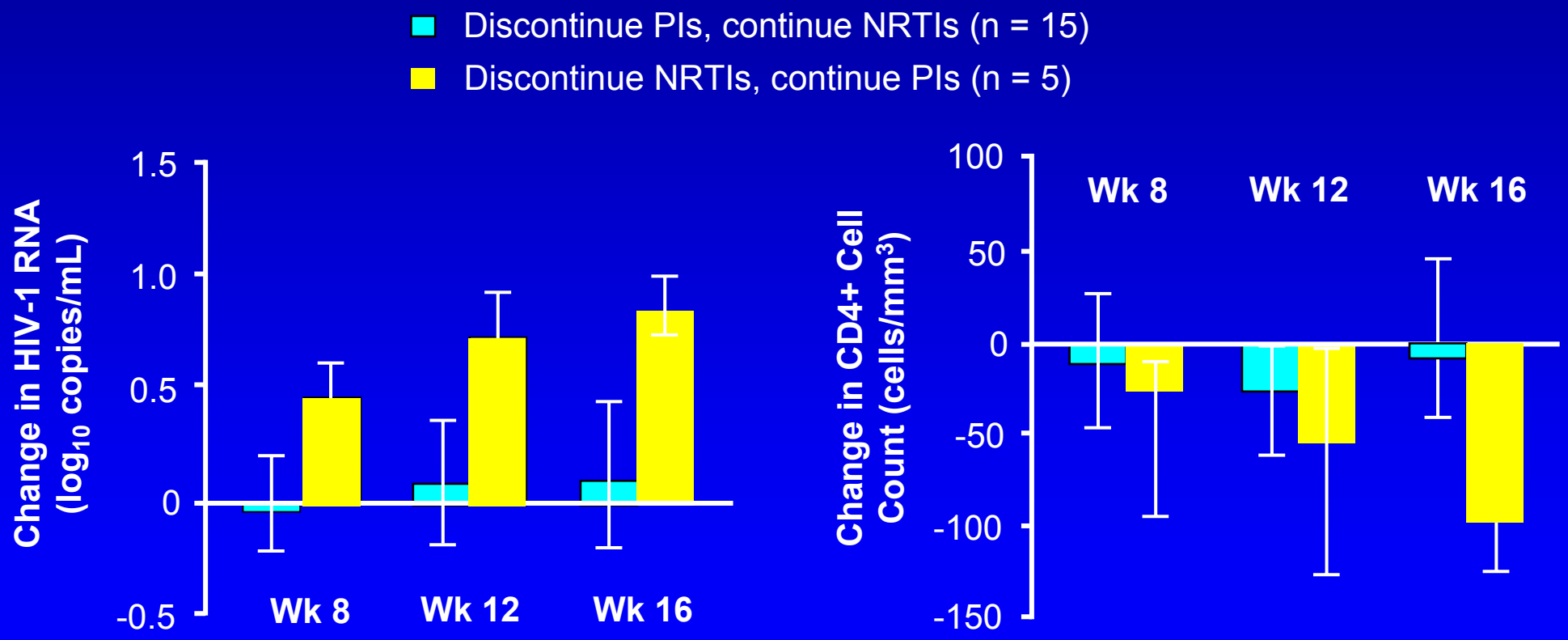
The Cost of Treatment Interruption in Treatment-Experienced Patients



*3 subjects excluded because baseline VL near upper LOQ

Deeks SG, et al. N Engl J Med. 2001;344:472-480.

Partial Treatment Interruption

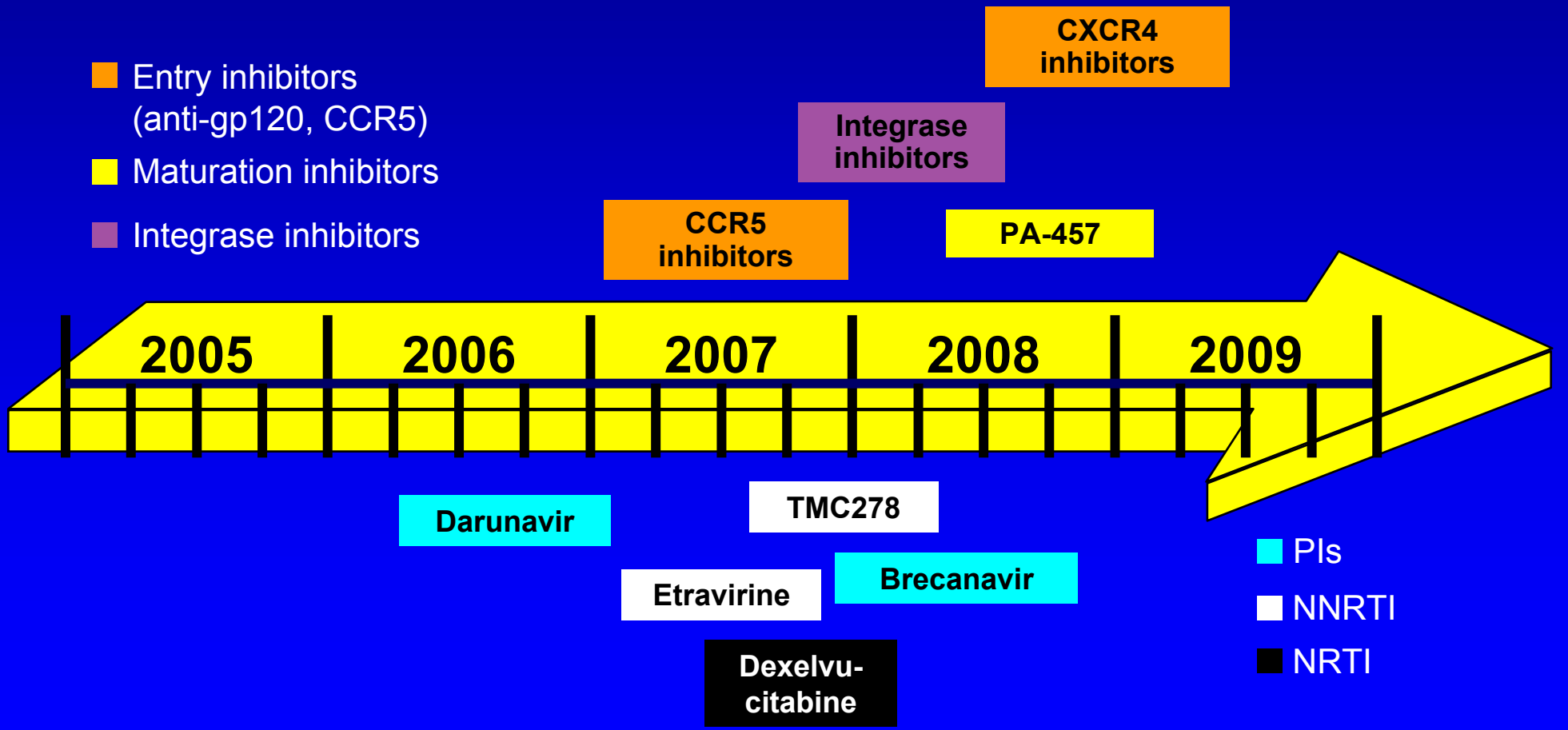


Deeks SG, et al. J Infect Dis. 2005;192:1537-1544.

Guidelines for Choosing a Non-Suppressive "Holding Regimen"

- *Never* use an NNRTI
  - » NNRTI mutations have no beneficial impact on fitness
  - » Accumulation of additional mutations may result in cross-resistance to 2nd generation NNRTIs
- *Always u*se 3TC or FTC
  - » Simple and well tolerated drugs
  - » M184V decreases fitness
  - » Increased activity of AZT, d4T, TDF
- Choose PIs and/or NNRTIs based on resistance and tolerability/toxicity considerations

Timeline for New Antiretrovirals



Using of New Agents: Too Soon, Too Late, or Just Right?

- Too soon:
  - » New drug used in combination with inactive or partially active drugs despite relatively preserved CD4 count
- Too late:
  - » New drug deferred until the patient's virus is resistant to all other available drugs
- Just right:
  - » New drug combined with other active new agents, or use deferred until other new agents available

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