Novel Strategies for the Management of the Heavily Pre-Treated Patient with Limited Options for Complete Suppression

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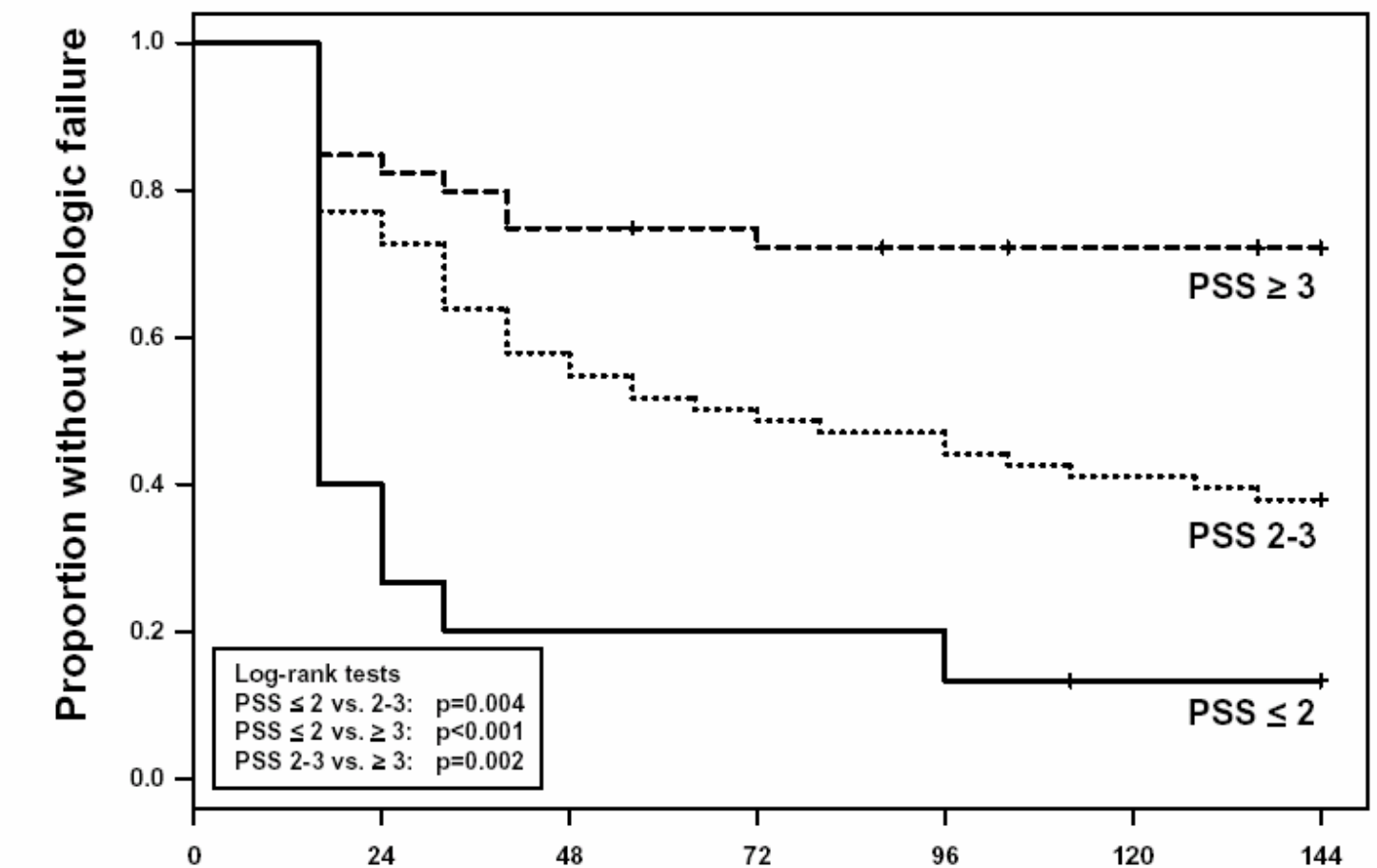
Outline

- How to switch versus when to switch?
  - How should we use new drugs as they become available?
  - Can we enhance the activity of existing drugs?
- Viral fitness
  - Is this simply phenomenology or can we manage patients based on alterations in viral fitness?
- Virulence/pathogenicity *(for those "CD4 lovers")*
  - Can we therapeutically alter the pathogenicity (not fitness) of HIV?
- Can we enhance immunologic control of HIV?
- Can we changes drugs before MDR emerges?

How to Switch?

Construct a regimen with two if not three fully effective agents that the patient is able to access and tolerate . . .

How to Switch: Use at least 3 fully effective drugs



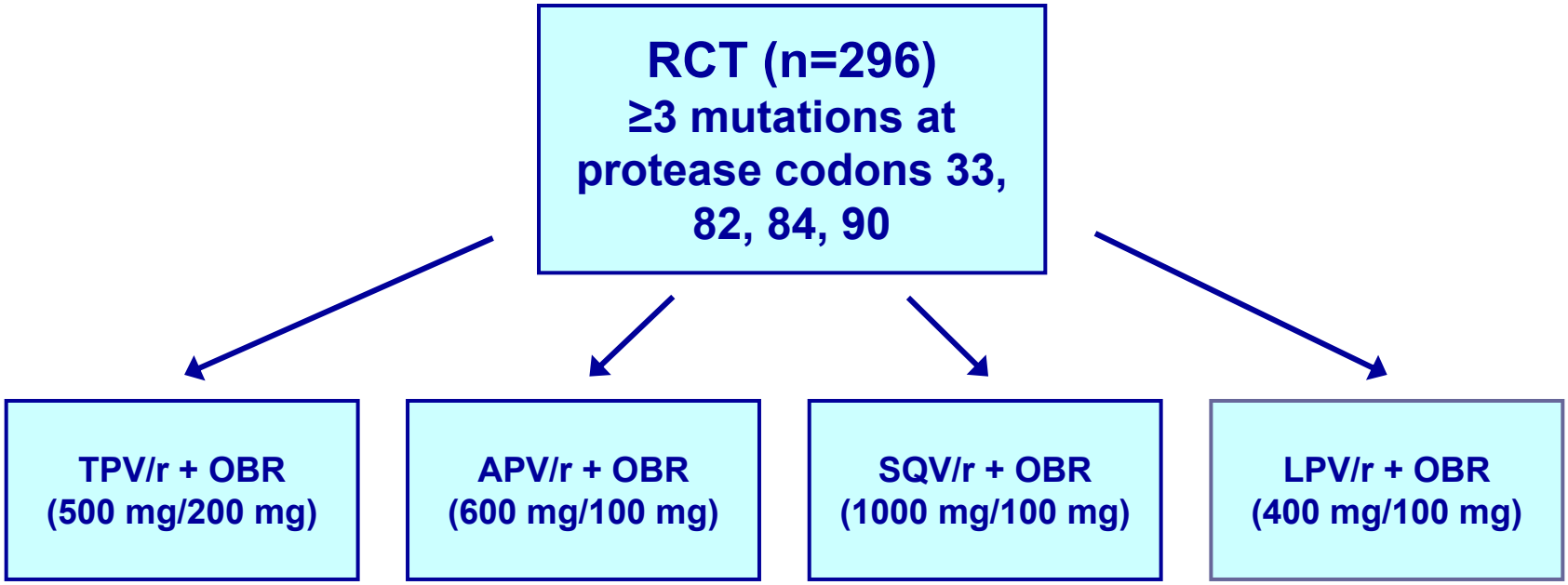
No. at Risk							
PSS ≥3	46	35	30	28	25	24	21
PSS 2-3	70	52	38	33	31	27	21
PSS ≤2	15	6	3	3	2	1	1

Katzenstein/Albrecht AIDS 2003

When will patients with MDR and limited options have at least 2 effective agents?

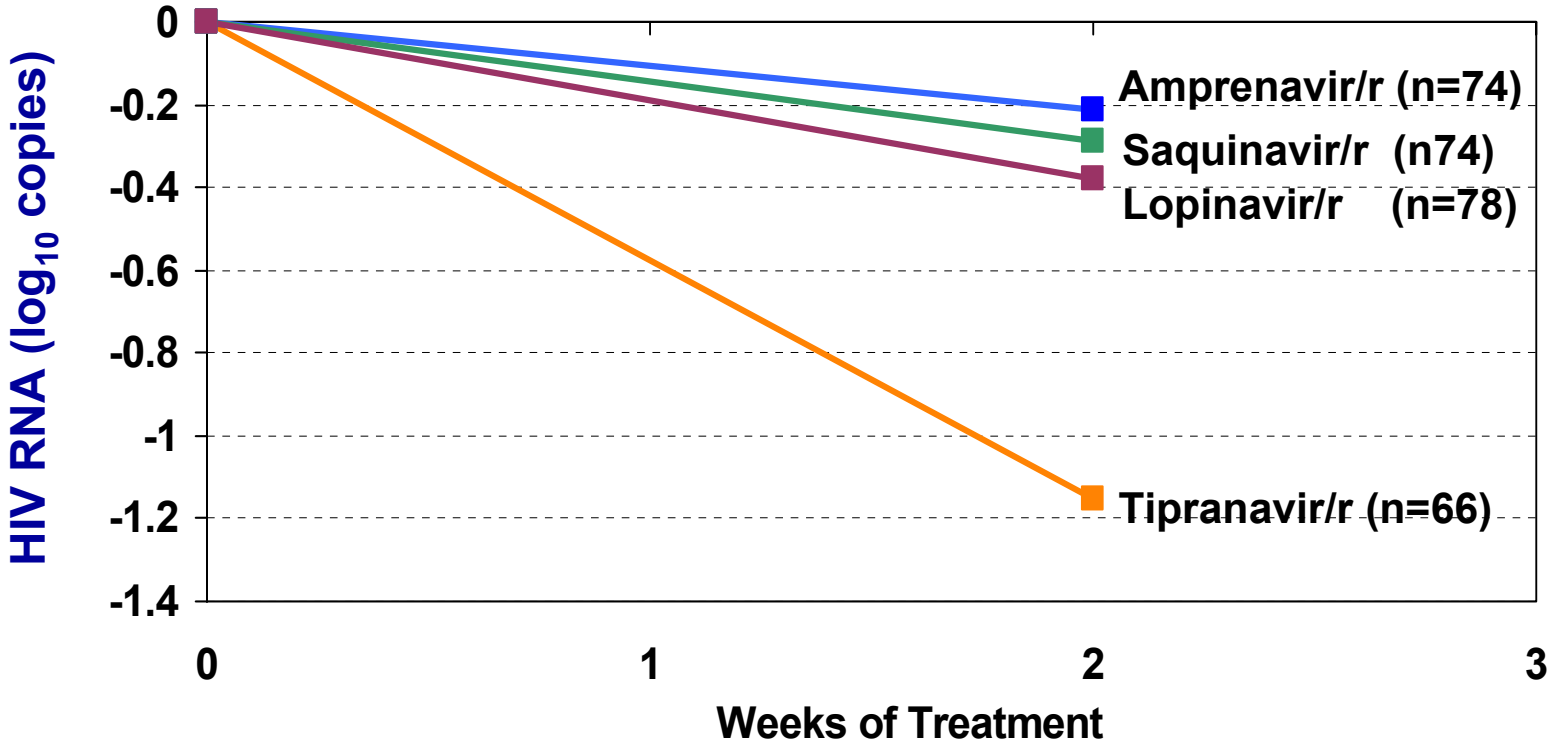
The question is when to switch, not how to switch

Tipranavir BI 1182.51: *Study design*



Curry K, et al. 5th International Workshop on Clinical Pharmacology of HIV Therapy; April 1-3, 2004; Rome, Italy

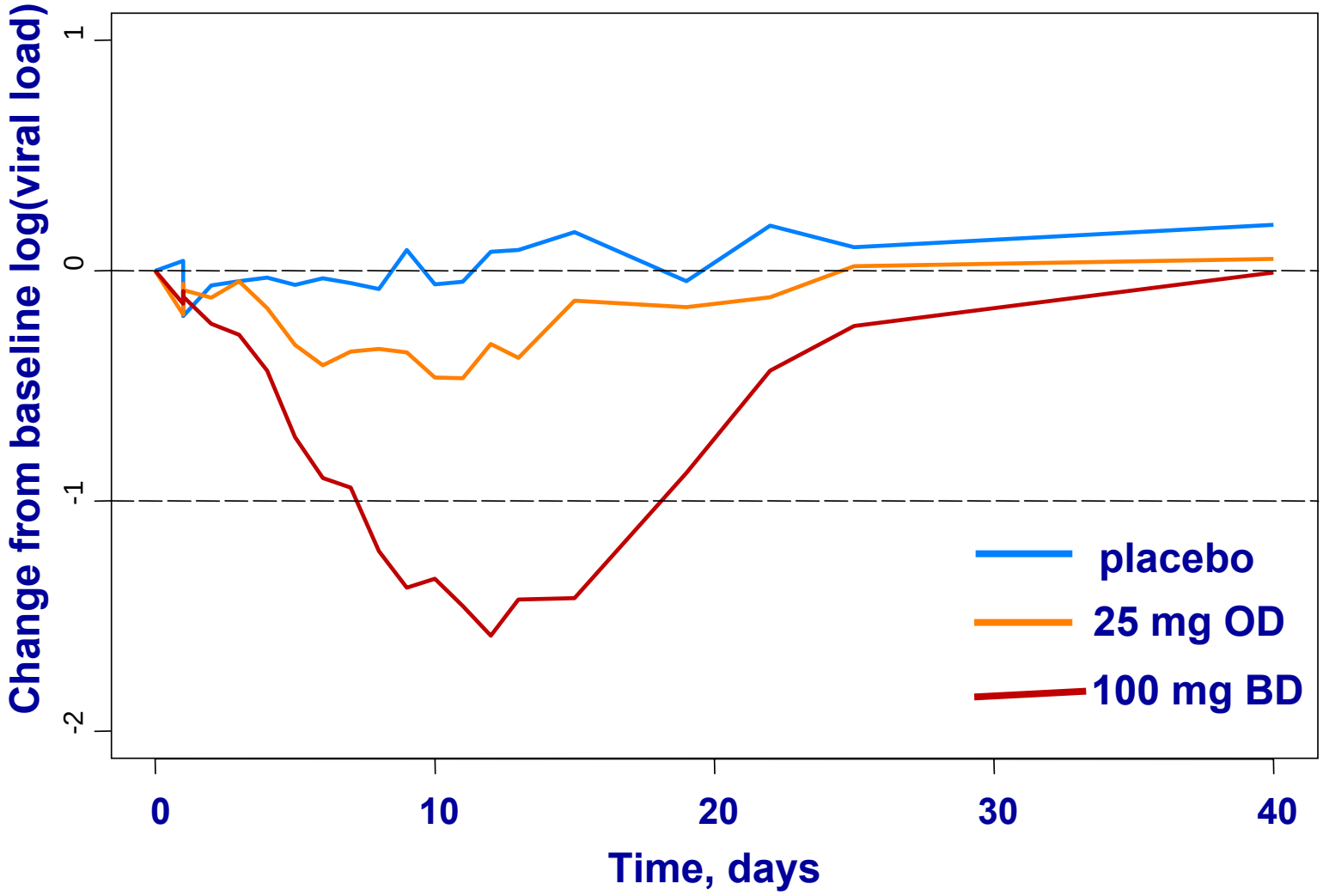
Tipranavir/ritonavir in “deep salvage”



Median CD4+ T cell count 140, viral load 5.0 log

Curry K, et al. 5th International Workshop on Clinical Pharmacology of HIV Therapy; April 1-3, 2004; Rome, Italy

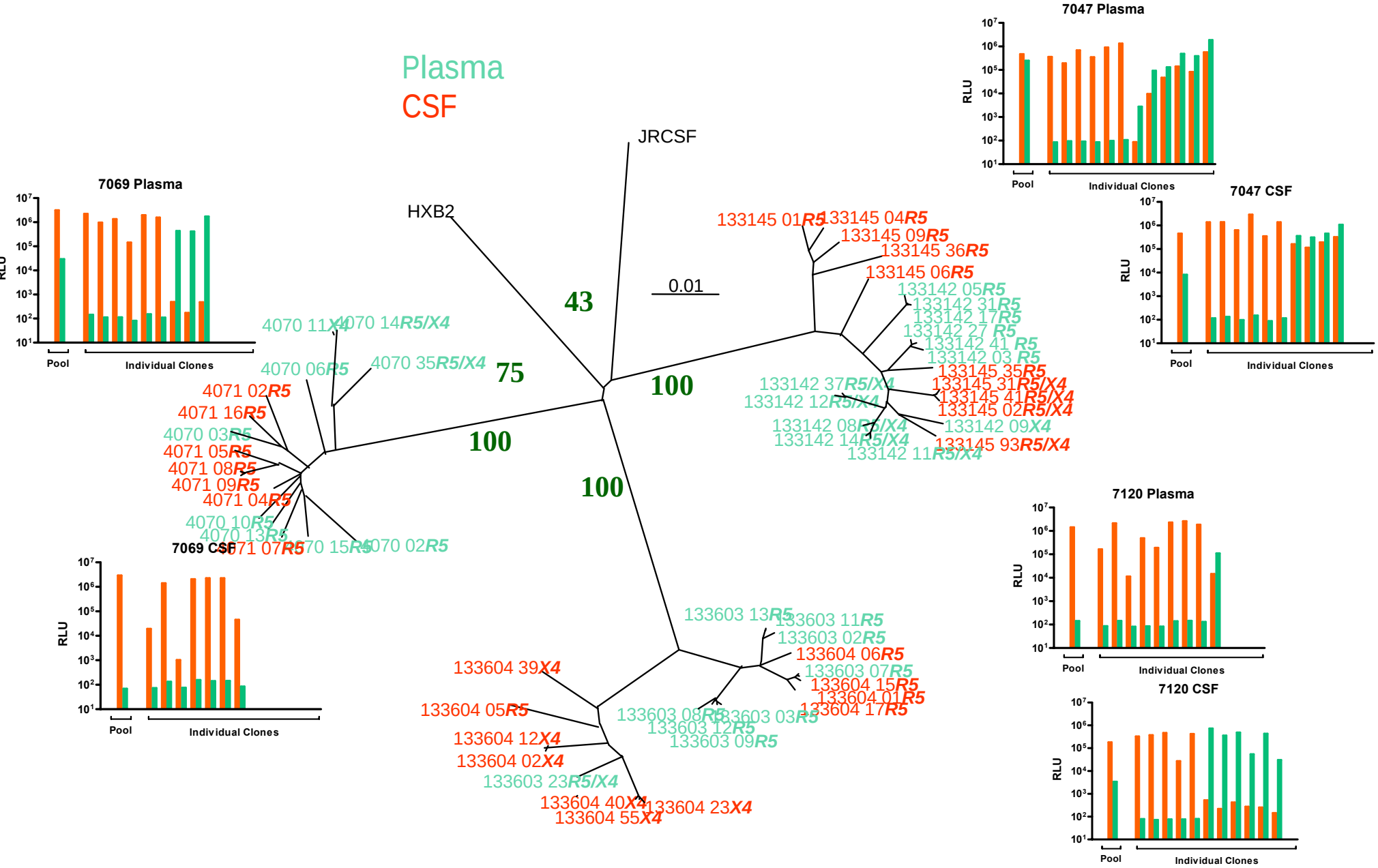
UK-427,857: CCR5 Antagonist (Entry Inhibitors)



10 day monotherapy study; 10 patients per arm; pure R5 (ViroLogic entry assay), VL > 5000, CD4 > 250

Phase III studies: The provider/patient perspective

- TORO
  - Good: liberal roll-over plan, access to state of art resistance testing, no limits on optimized background
  - Bad: only one “new” drug provided, thus forcing desperate patients with MDR to risk sequential monotherapy
- Alternative: no other drugs available
  - Use phase II to define anti-HIV potency and drug-specific adverse events for drugs A and B
  - Phase III: Randomize to OB vs. OB plus AB
  - Use naïve patients to more precisely define drug-specific safety
- Alternative: one other drug available (ie, T20)
  - Immediate switch to T20 plus drug A vs. delayed switch to T20 plus drug B, using comparison to TORO studies to define a priori what kind of response would be needed to prove that drug A was effective


Plasma
CSF
JRCSF
HXB2
0.01
43
75
100
100
100
133145 01R5
133145 04R5
133145 09R5
133145 36R5
133145 06R5
133142 05R5
133142 31R5
133142 17R5
133142 27 R5
133142 41 R5
133142 03 R5
133145 35R5
133145 31R5/X4
133145 41R5/X4
133145 02R5/X4
133142 09X4
133145 93R5/X4
133142 37R5/X4
133142 12R5/X4
133142 08R5/X4
133142 14R5/X4
133142 11R5/X4
4070 11X4
4070 14R5/X4
4070 06R5
4070 35R5/X4
4071 02R5
4071 16R5
4070 03R5
4071 05R5
4071 08R5
4071 09R5
4071 04R5
4070 10R5
4070 13R5
4071 07R5
4070 15R5
4070 02R5
133603 13R5
133603 11R5
133603 02R5
133604 06R5
133603 07R5
133604 15R5
133604 01R5
133604 17R5
133603 08R5
133603 03R5
133603 12R5
133603 09R5
133604 39X4
133604 05R5
133604 12X4
133604 02X4
133603 23R5/X4
133604 40X4
133604 55X4
133604 23X4
7047 Plasma
7047 CSF
7069 Plasma
7069 CSF
7120 Plasma
7120 CSF
RLU
Pool
Individual Clones

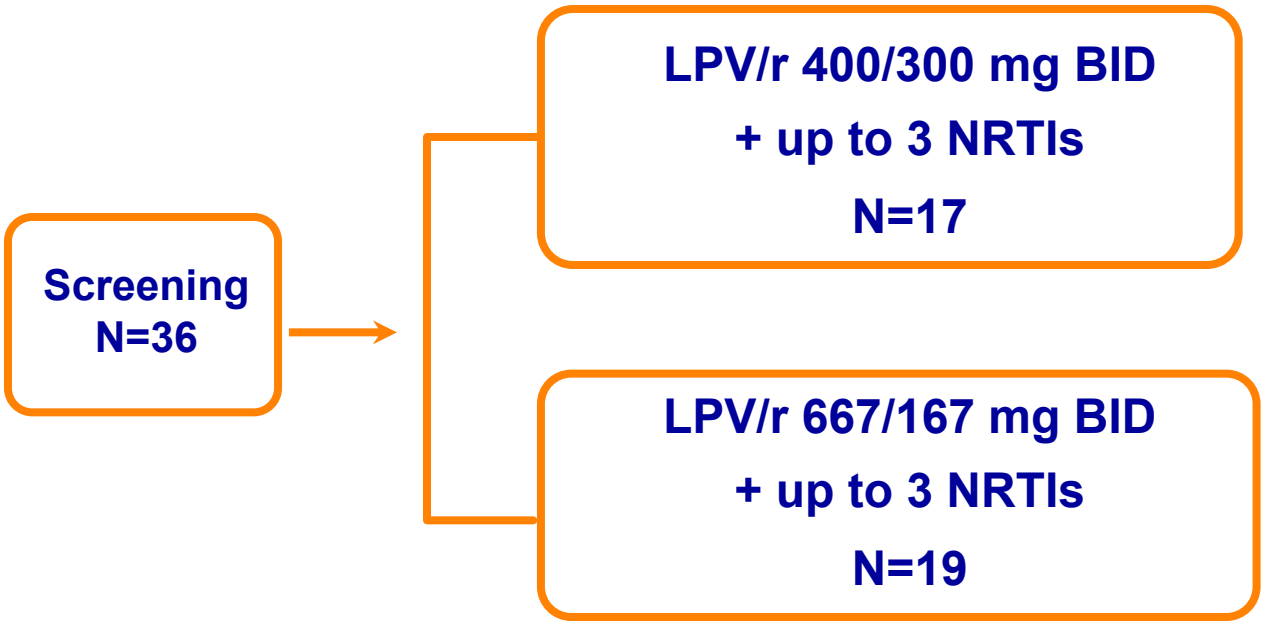
X4 Variants Emerge During Treatment with R5 Inhibitors

- One patient enrolled in a Phase II trial of UK-427,857 had dual tropic HIV at baseline
- Viral load did not change (or increased)
  - Dominant virus population shifted to mixture of dual tropic and X4 variants with complete loss of R5 variants
- Following cessation of treatment, R5 virus returned

M Westby et al, Abstract 538

Can partially effective drugs (or drug classes) become "fully" effective by increasing exposure?

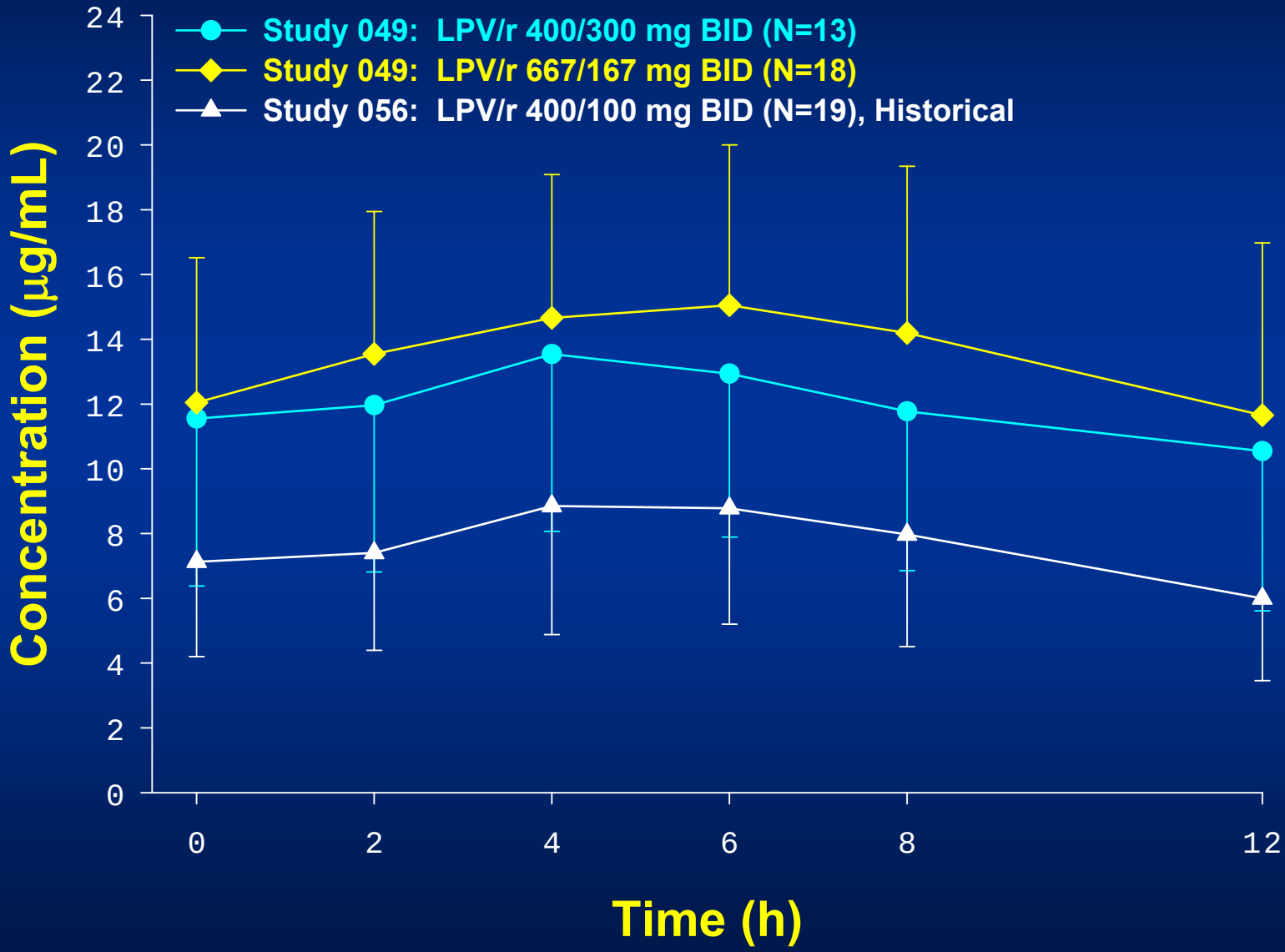
Abbott Study 049 Design



Open-label, multi-center study in HIV-infected subjects

- **Multiple PI-experienced, NNRTI-experienced**
- **HIV RNA > 1000 copies/mL**

Abbott 049: Steady-State Lopinavir Mean (SD) Concentrations

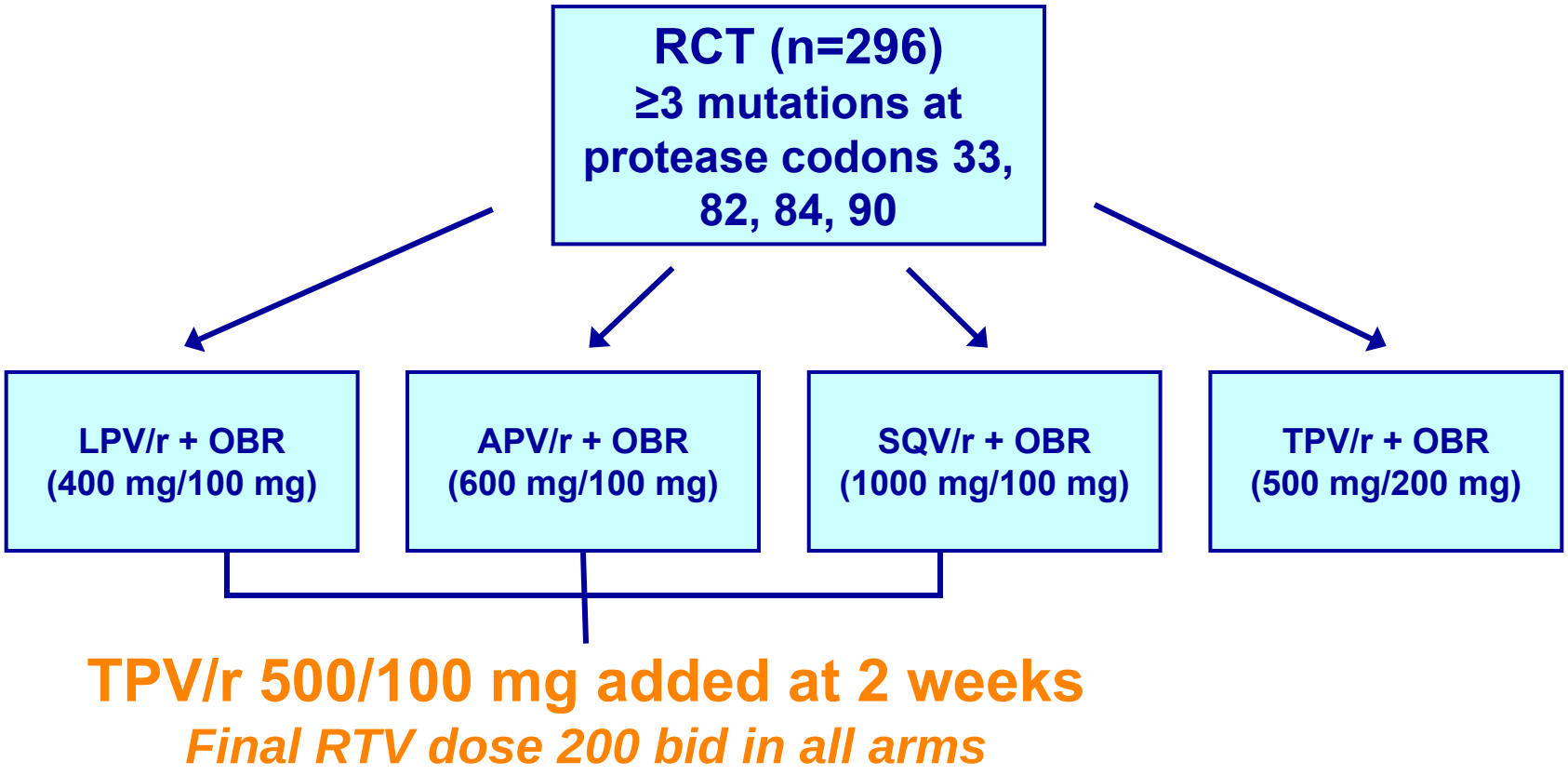


Flexner C, et al., Poster# 843, 2nd IAS Conf, Paris, July 2003

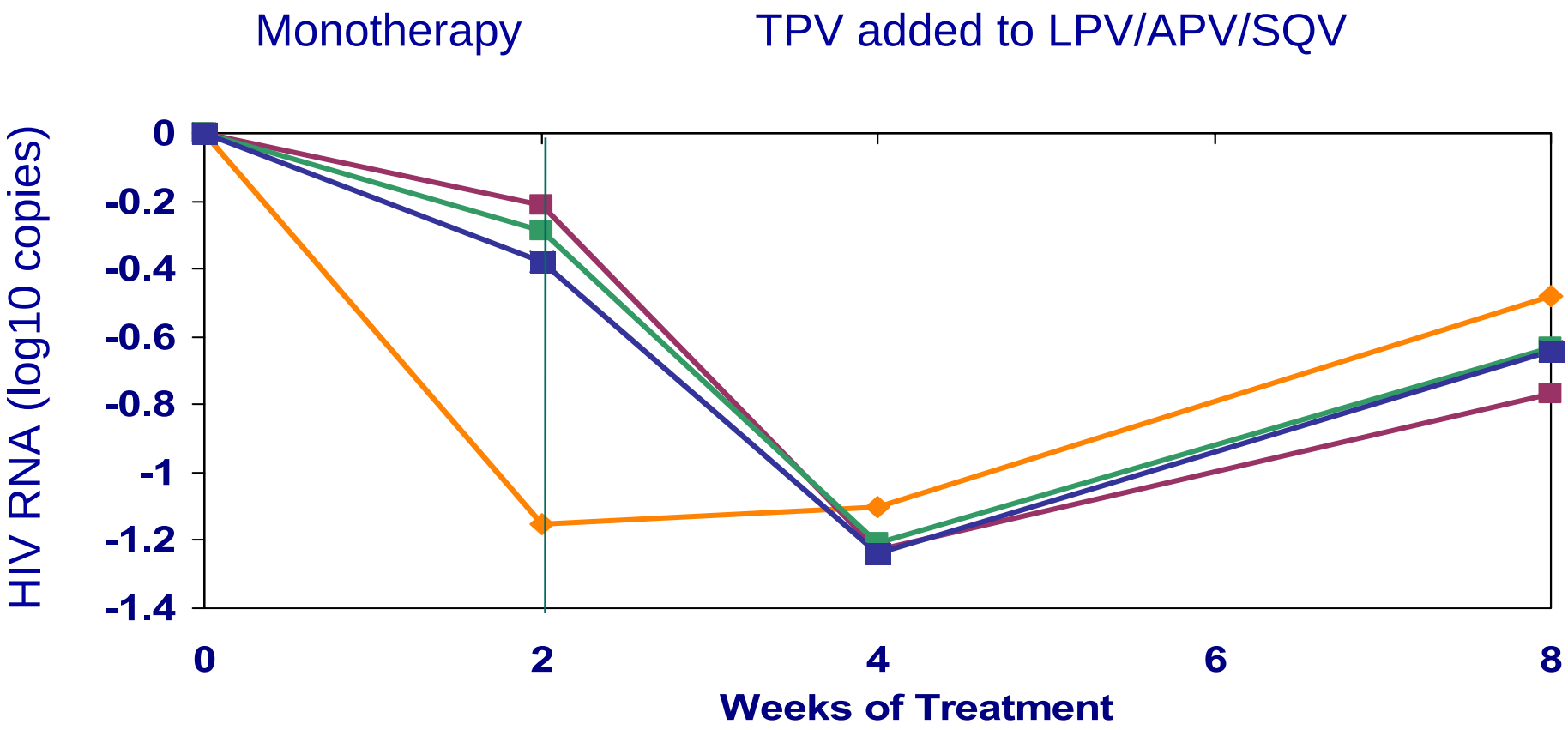
Abbott 049: Predictors of a viral load < 400 (week 48)

Predictor	Unadjusted	Adjusted
Baseline VL	0.01	NS
Fold change IC50	0.02	NS
Number of LPV mutations	0.04	NS
Active NRTIs	0.02	0.04
LPV IQ	***0.002***	***0.007***

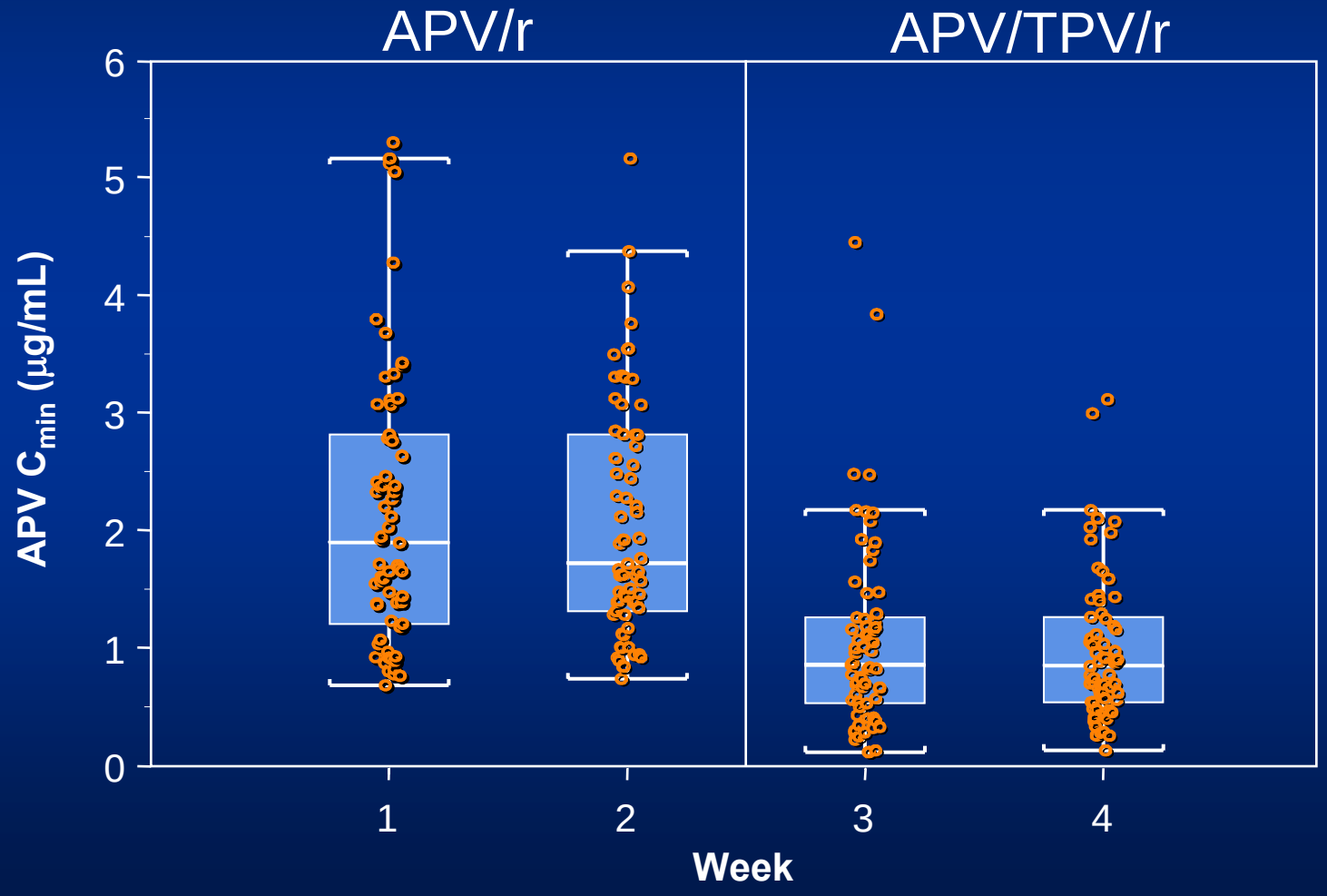
Tipranavir BI 1182.51: Controlled study of Dual Boosted PIs



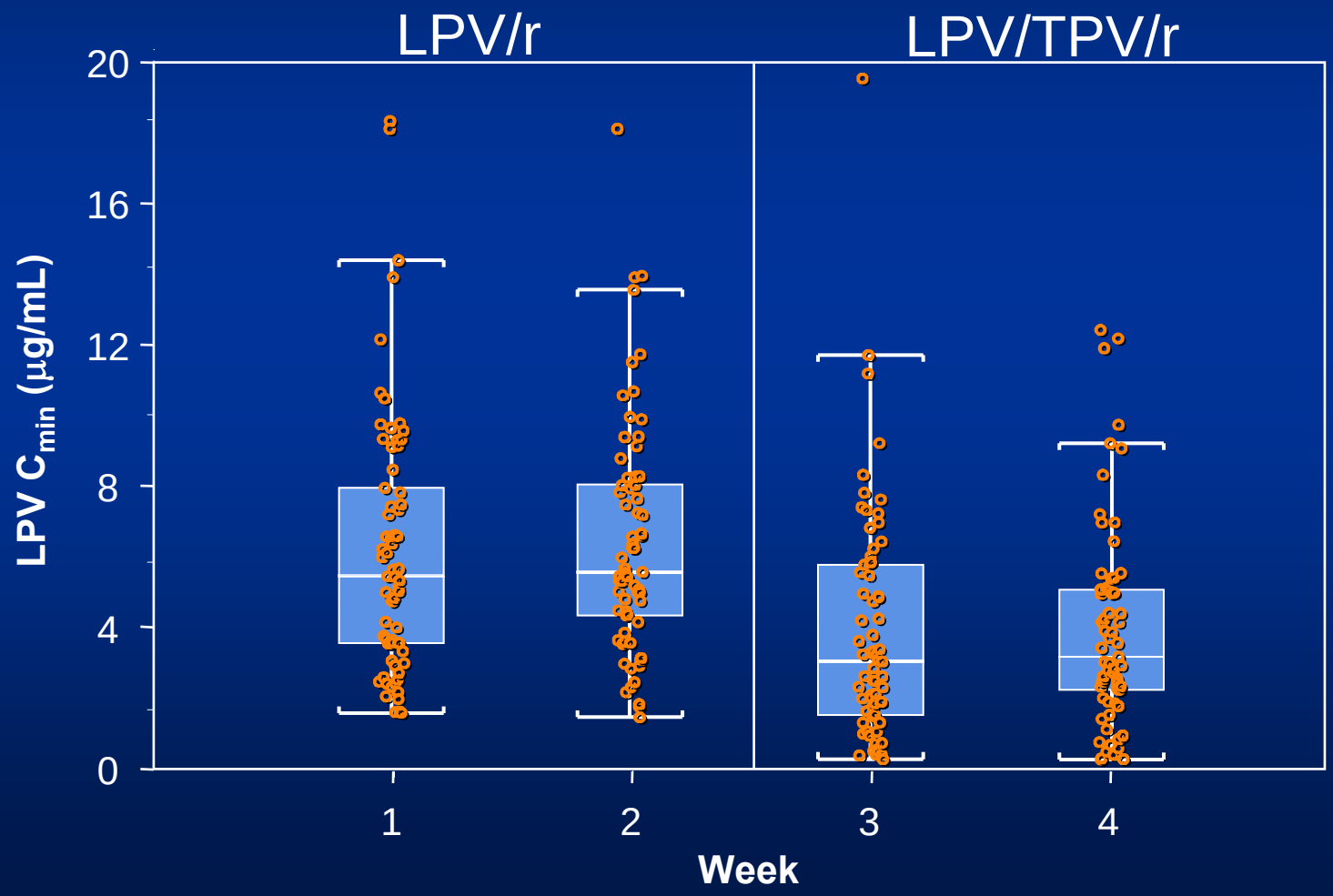
Dual boosted PI therapy vs. RTV/TPV in “deep salvage”



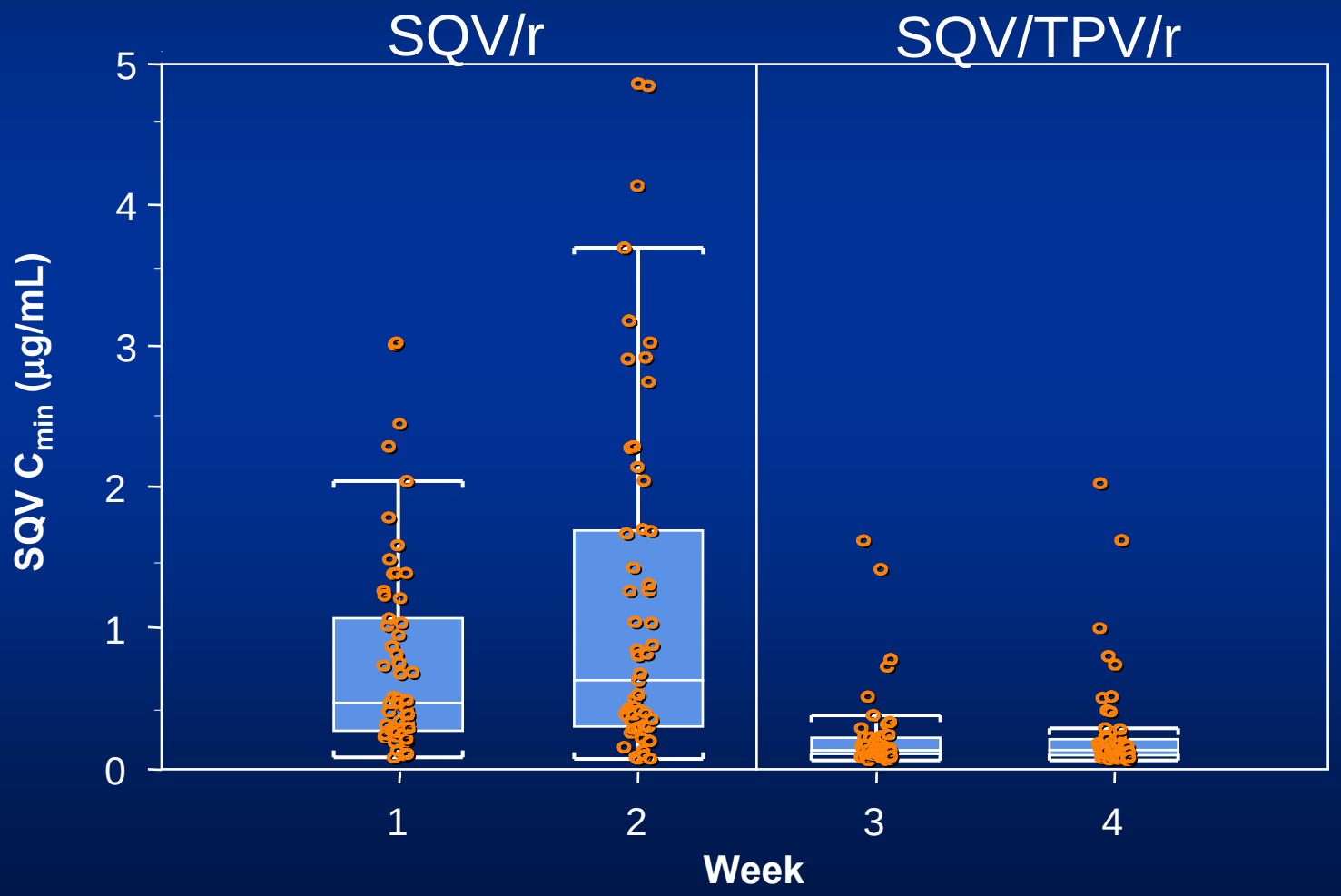
APV trough plasma concentrations before and after TPV/r



LPV trough plasma concentrations before and after TPV/r



SQV trough plasma concentrations before and after TPV/r



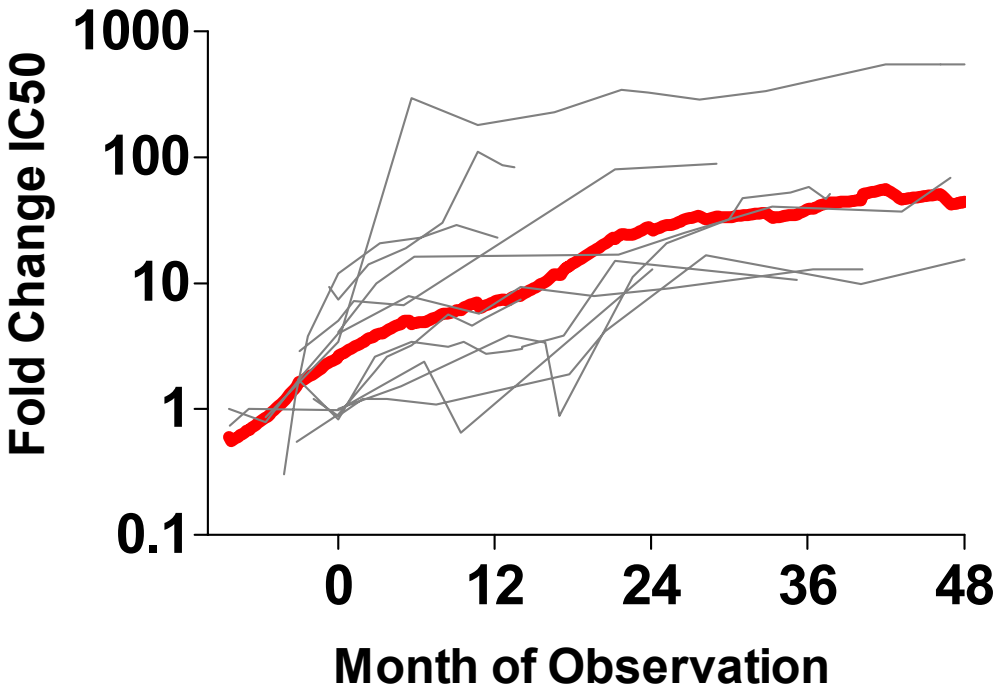
Summary: How to switch

- Although new drugs are being developed, practical and perhaps regulatory barriers prevent these new drugs from being used in an optimal manner
- Limited data exists to support strategies aimed at enhancing the exposure of existing drugs, but this remains an open question
- It also remains unclear whether having two inhibitors with unique resistance patterns works better than one inhibitor

What should be done until an effective switch strategy can be performed?

Viral Fitness (Replicative Capacity)

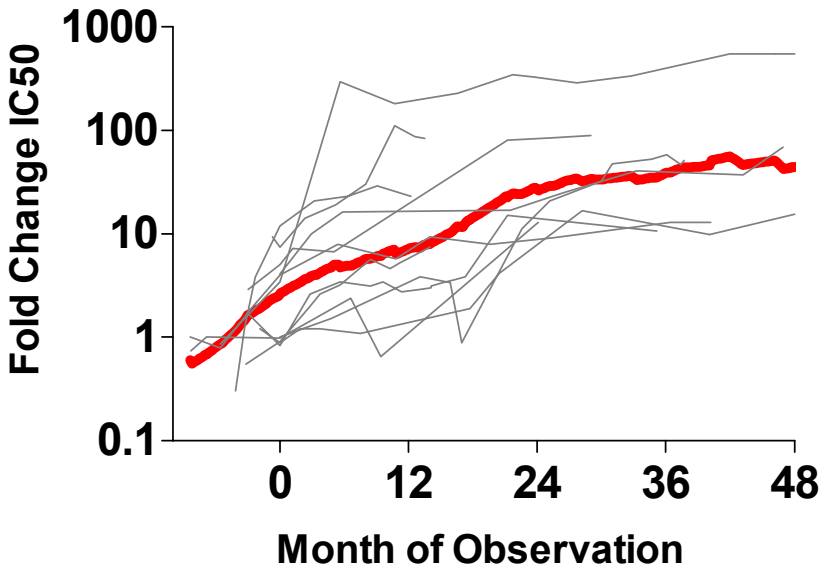
Failure to Switch Risks Future Options

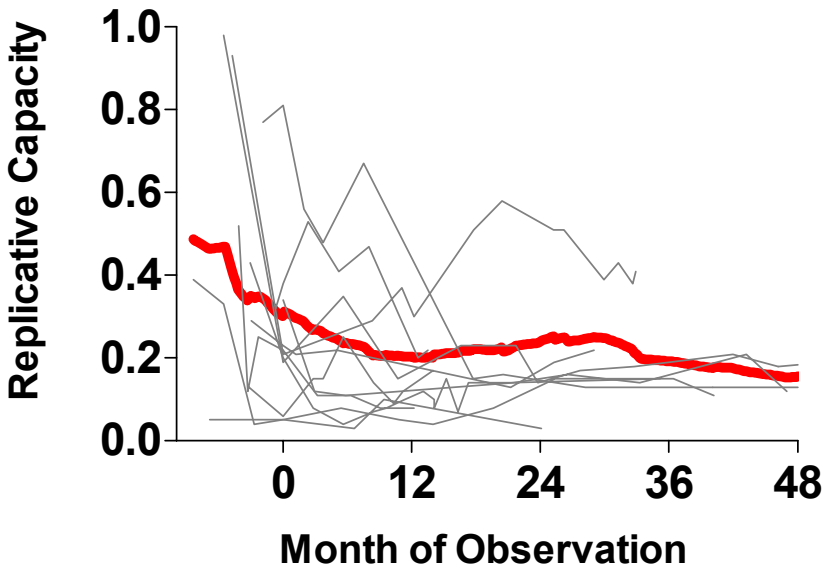


Change in protease inhibitor phenotype in 11 patients who had a transient virologic response to HAART and did not switch

J Virology 2002; 76:11104-12

Viral Evolution during Long-term Failure of HAART

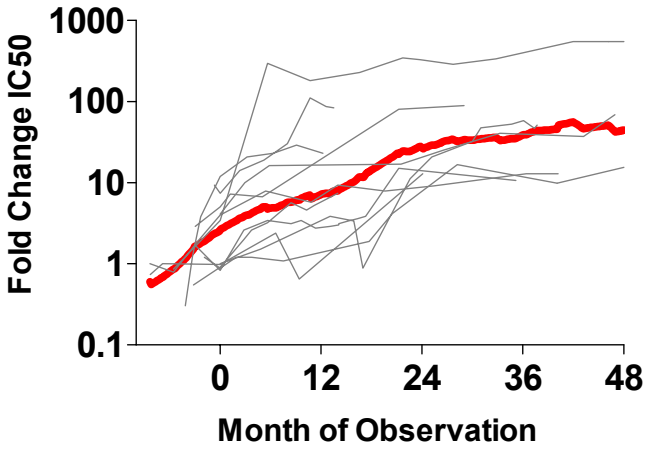


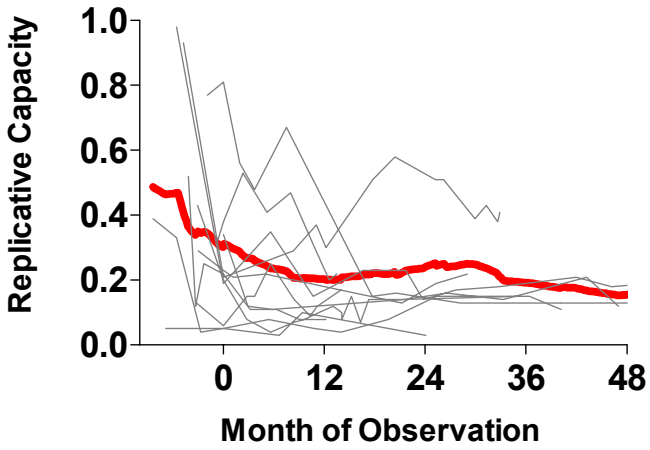


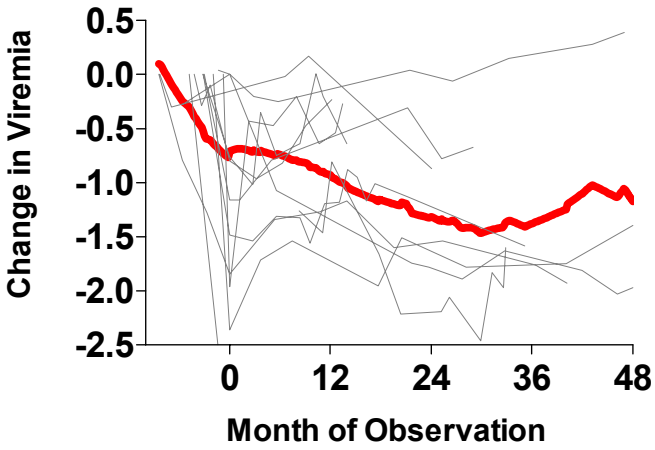
Replicative capacity decreases and remains low as PI resistance increases

Barbour et al; J Virology 2002; 76:11104-12

Viral Evolution during Long-term Failure of HAART



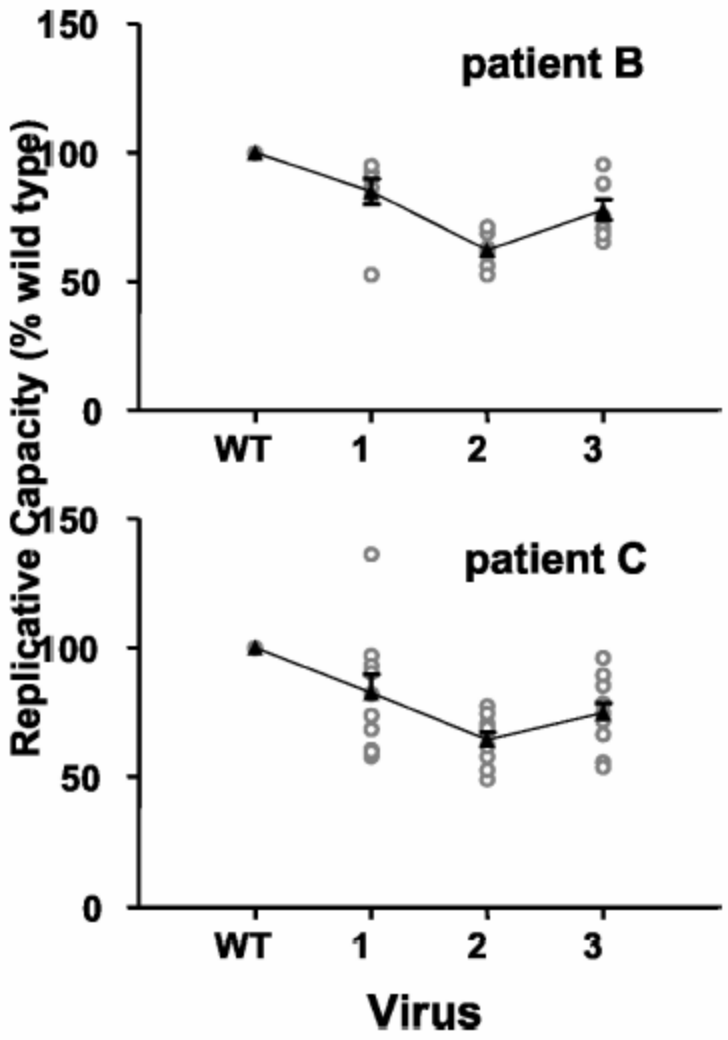




HIV may be constrained in its ability to become both highly resistant and highly fit, thus resulting in durable partial suppression

J Virology 2002; 76:11104-12

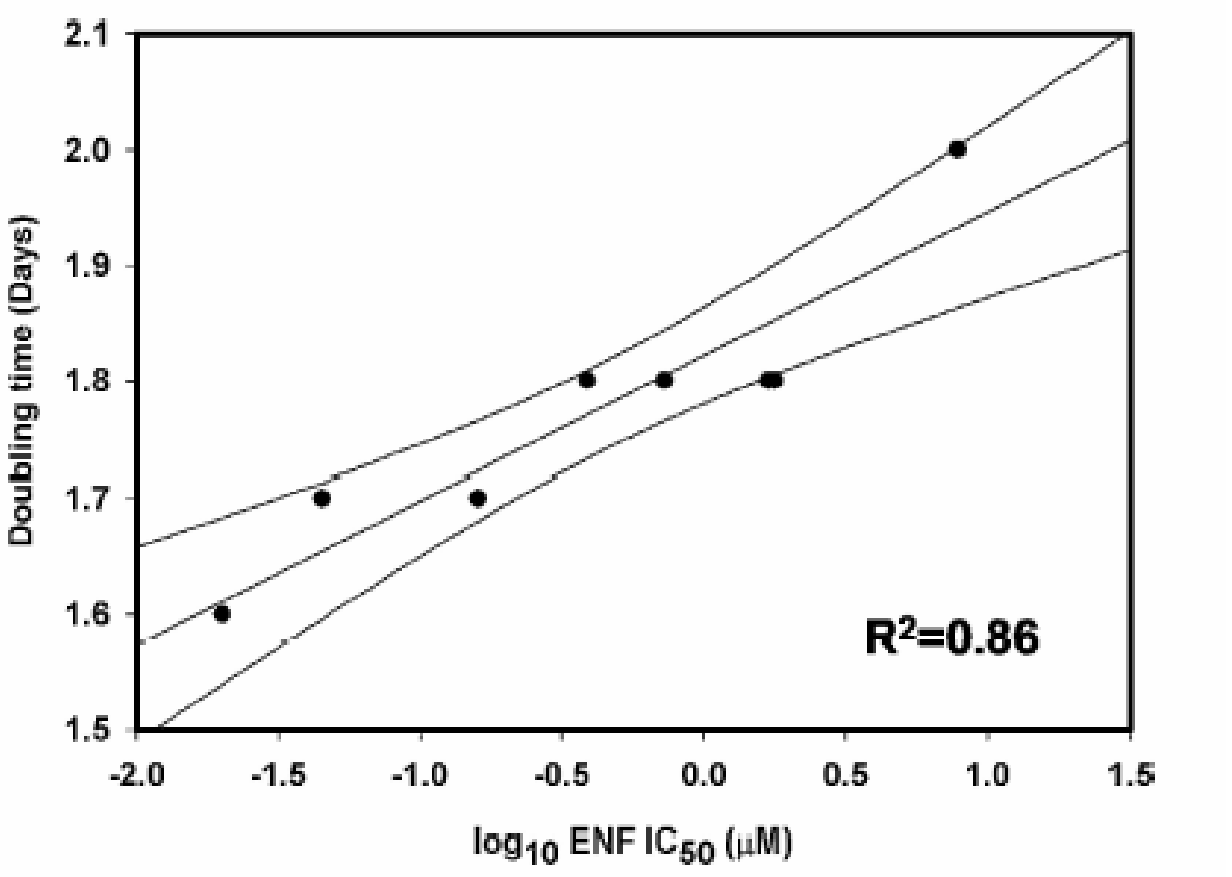
Viral Evolution during Long-term Failure of HAART



Replicative capacity (% of WT) declines as PI resistance increases, at least for the first two to three years

Charpentier, Hance. J Virology 2004; 78:4234-47

Viral Evolution during Long-term Failure of Enfuvirtide



Doubling time (measured in absence of drug) increases as enfuvirtide IC50 increases

Lu, Kuritzkes. J Virology 2004; 78:4628-37

Fitness: Summary

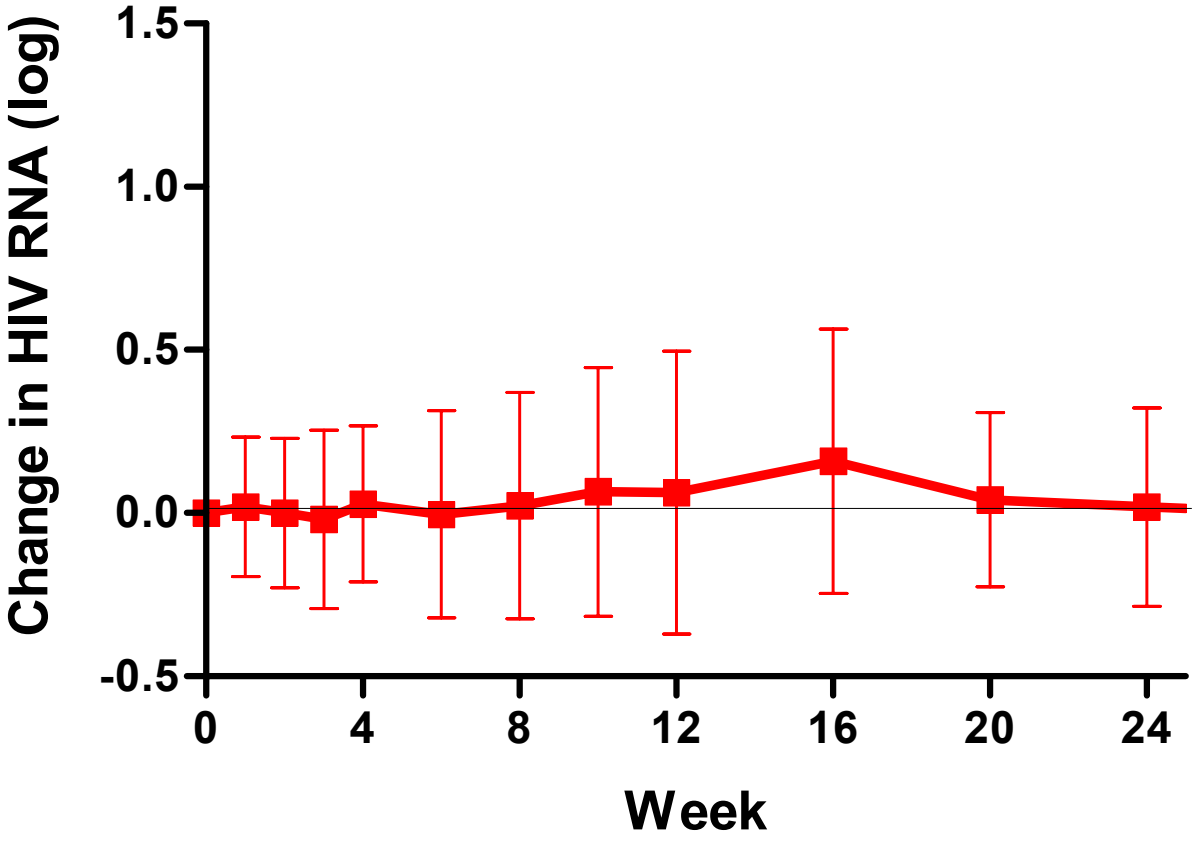
- Some drugs select for mutations which reduce replicative capacity
  - Protease inhibitors
  - Enfuvirtide
  - NRTIs: 3TC, tenofovir (K65R), others
- Replicative capacity may decrease with time (as resistance increases) for protease inhibitors and perhaps enfuvirtide

Fitness: Future Directions

- Are there resistance pathways which are less favorable to the virus?
  - Is it possible to design strategies that constrain the capacity of the virus to become resistant only at the cost of lower RC (and, therefore, lower on treatment viral loads)

- Once a virus with reduced RC has been established, what strategies should be considered to maintain those mutations (while limiting drug exposure and or further viral evolution)?

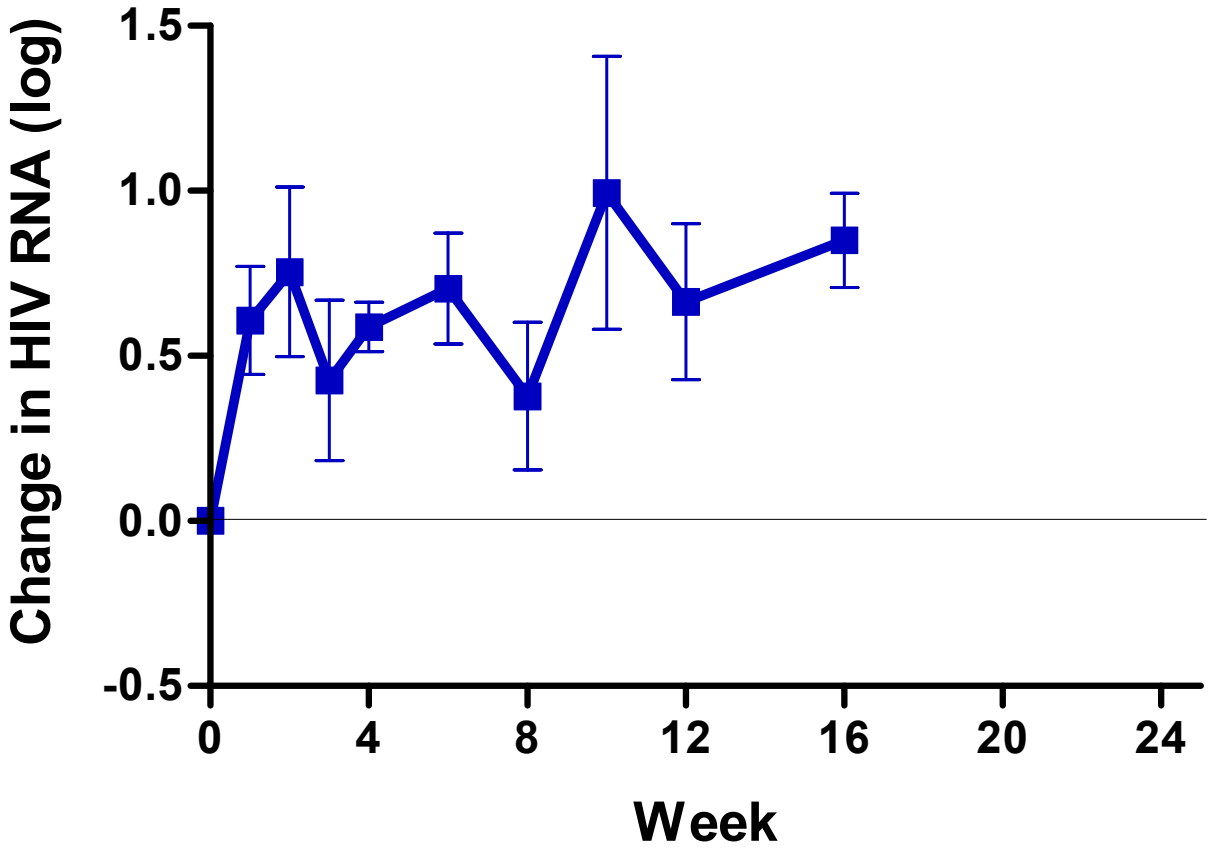
Protease Inhibitor Interruption (n=18)
(continued reverse transcriptase inhibitor therapy)



3 of 18 patients had a consistent increase in viremia (> 0.5 log) prior to week 24

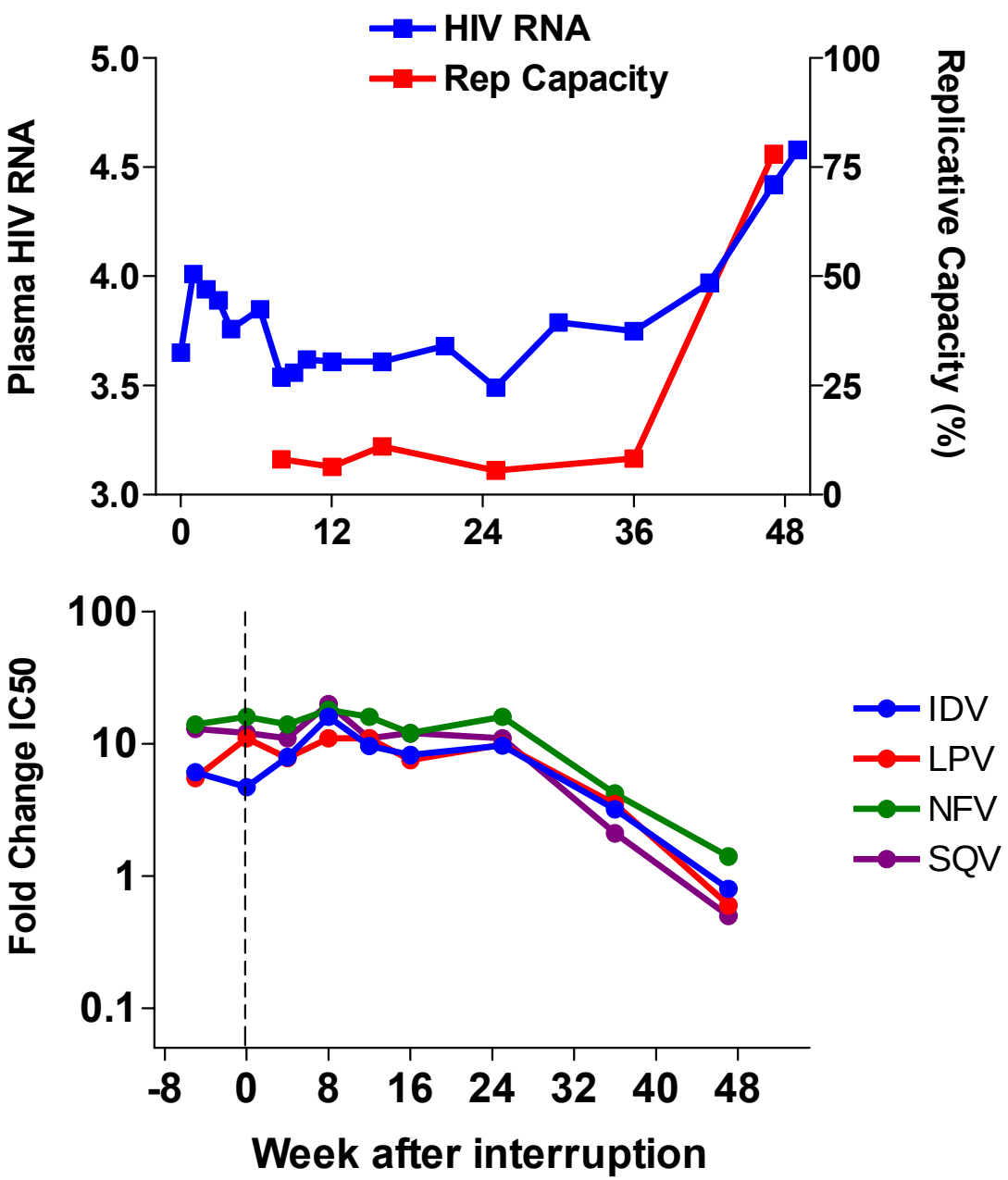
Mean change in viral load: 0.005 log copies/week
(95% CI: -0.01 to +0.02)

Reverse Transcriptase Inhibitor Interruption (continued Protease Inhibitor Therapy)



7 of 7 patients had an immediate and durable increase in viremia (> 0.5 log) *with no early change in genotype*

Delayed loss of M184V associated with continued rise in viremia

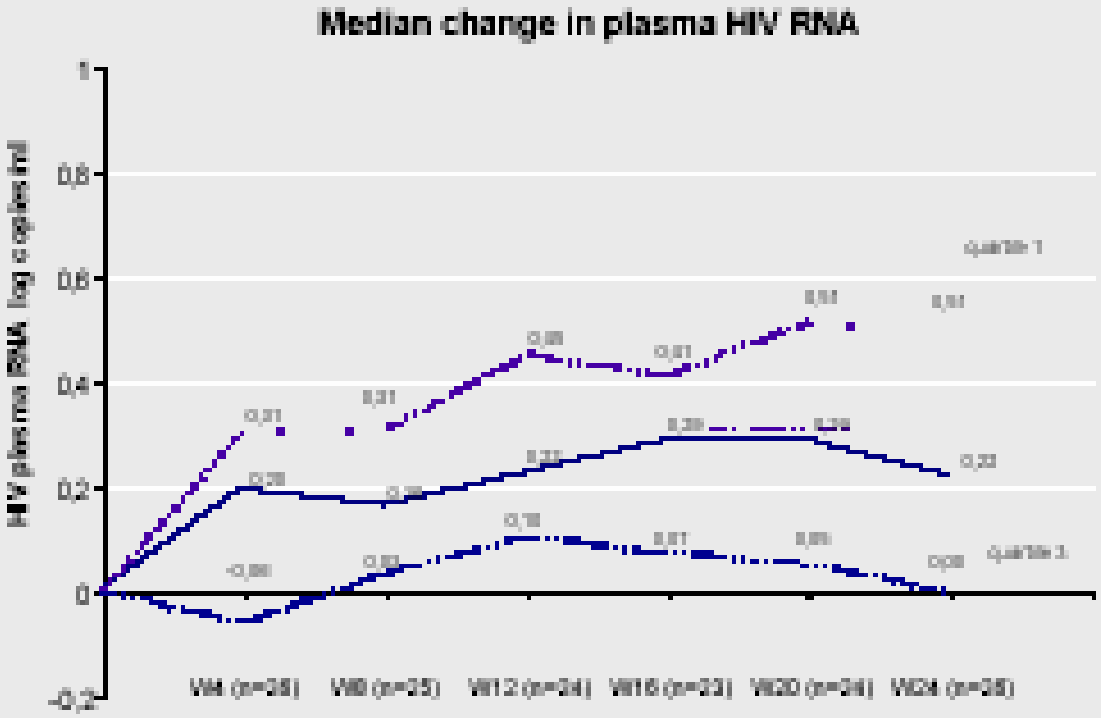


Interruption of PI

Delayed increase in viremia

Temporally associated with loss of PI associated mutations and increased replicative capacity

Vista ANRS 109: Reduced drug pressure to maintain MDR

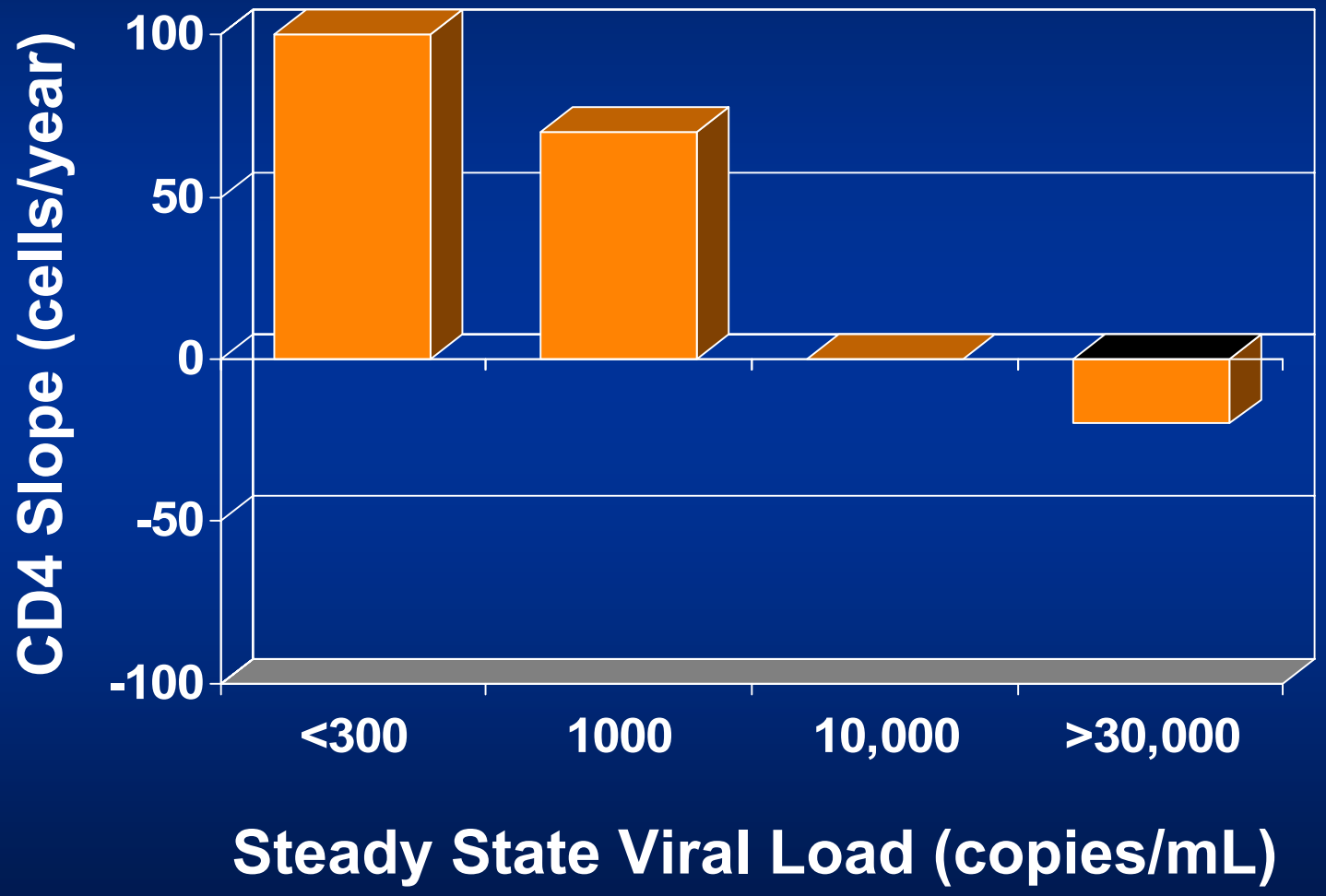


- **Low dose RTV/IDV and 3TC "calibrated" to prevent WT rebound while limiting further evolution (n=28)**
- **Median increase in VL at week 24 was 0.2 log (p=0.003)**
- **Slope in CD4 cell count decrease during the study did not significantly change**
- **No significant changes in the numbers of resistance mutations were seen in PR or in RT**

Launay O, et al. 11th CROI, San Francisco, #649

Why not alter the “pathogenicity” of the virus therapeutically?

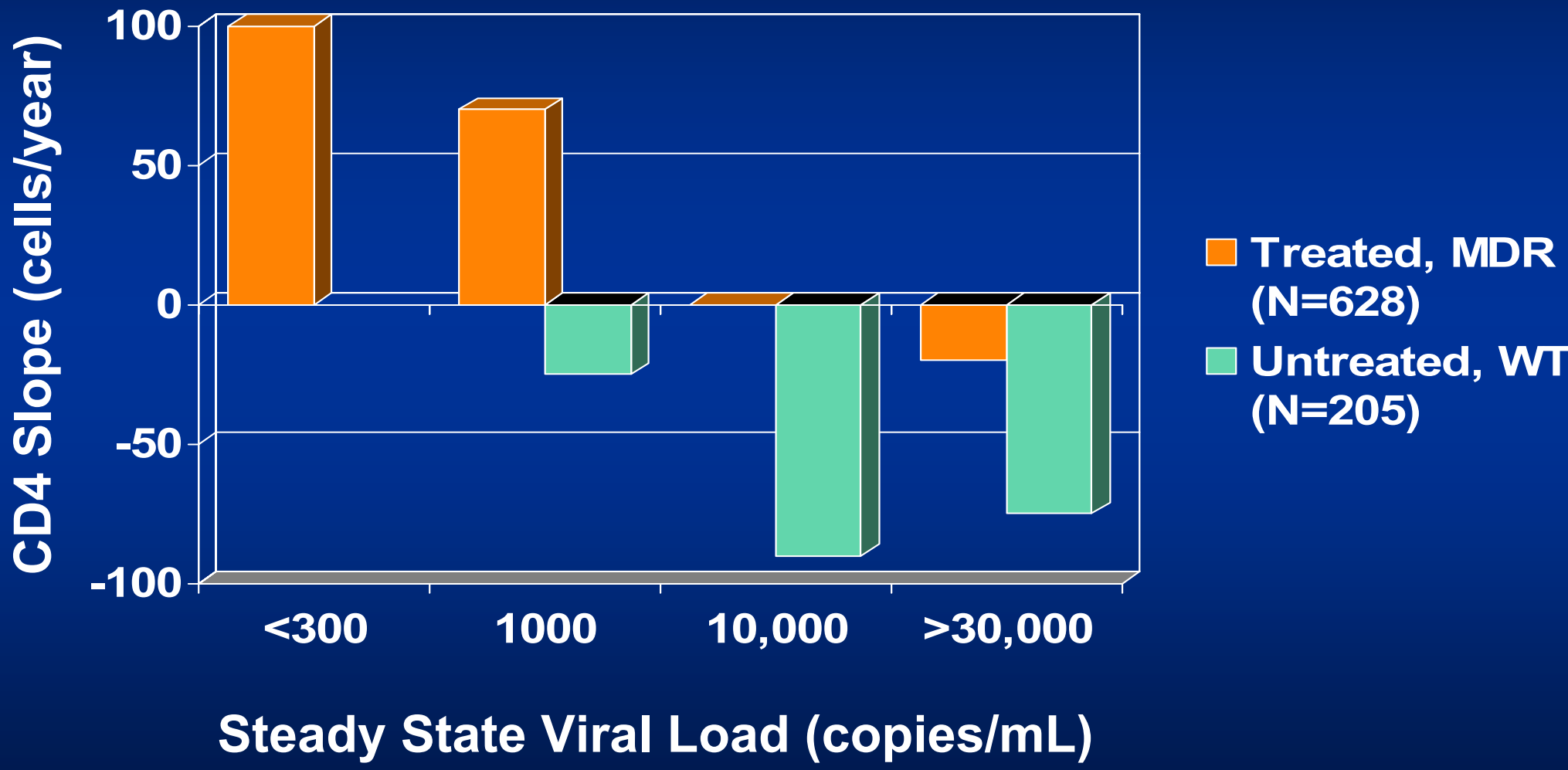
PLATO: Reduced virulence of immunopathogenicity of MDR HIV



Change in CD4 stratified by steady-state VL during long-term virologic failure (N=628)

Ledergerger et al., in press

PLATO: Steady State Viremia and Rate of CD4+ Cell Decline



Ledergerger et al., in press

Virus/Host Interactions Determine Disease Outcome

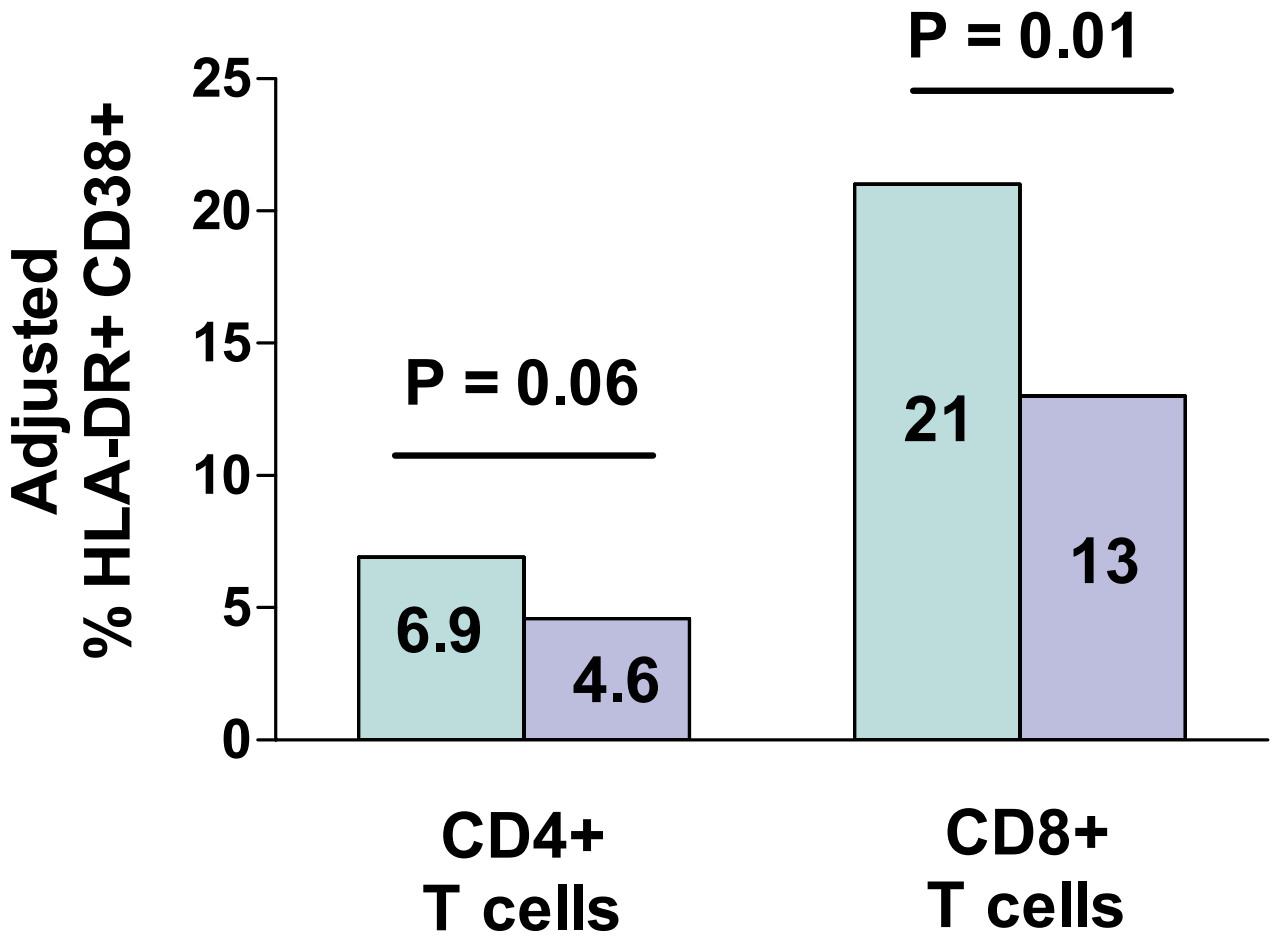
Sooty Mangabey

- Natural host of SIV
- SIV infects and kills CD4 T cells at high rates
- High levels of viremia
- Minimal CD4 T-cell losses
- *No increase in* T-cell Activation

Rhesus Macaque

- Not natural host of SIV
- SIV infects and kills CD4 T cells at high rates
- High levels of viremia
- Rapid CD4 T-cell losses
- *Large increase in* T-cell Activation

T cell activation in UCSF SCOPE Cohort

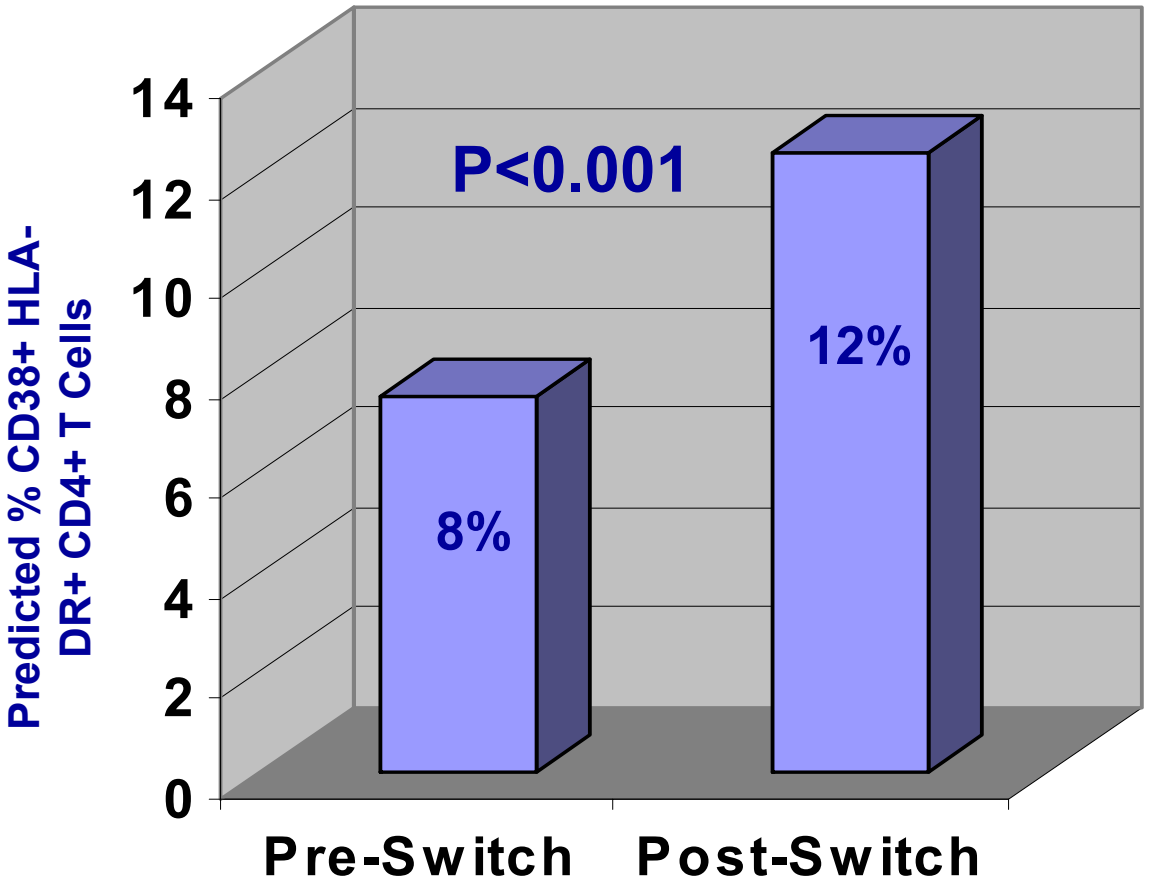


T cell activation is higher in untreated patients than treated patients, after adjusting for level of viremia

**The adjusted mean activated T cells was estimated using multivariable linear regression. Adjusted for viremia, hepatitis C, nadir CD4+ T-cell count*

Hunt et al; CROI 2003

Changes in T Cell Activation After Phenotypic Switch to Wild- Type Susceptibility In 20 Patients Discontinuing All Antiretrovirals



Adjusted mean changes in T cell activation were predicted using a mixed effects repeated measures model and adjusting for changes in plasma HIV RNA levels and other factors

(Hunt et al, XII Int HIV Drug Res Workshop, 2003)

Virulence: Future Directions

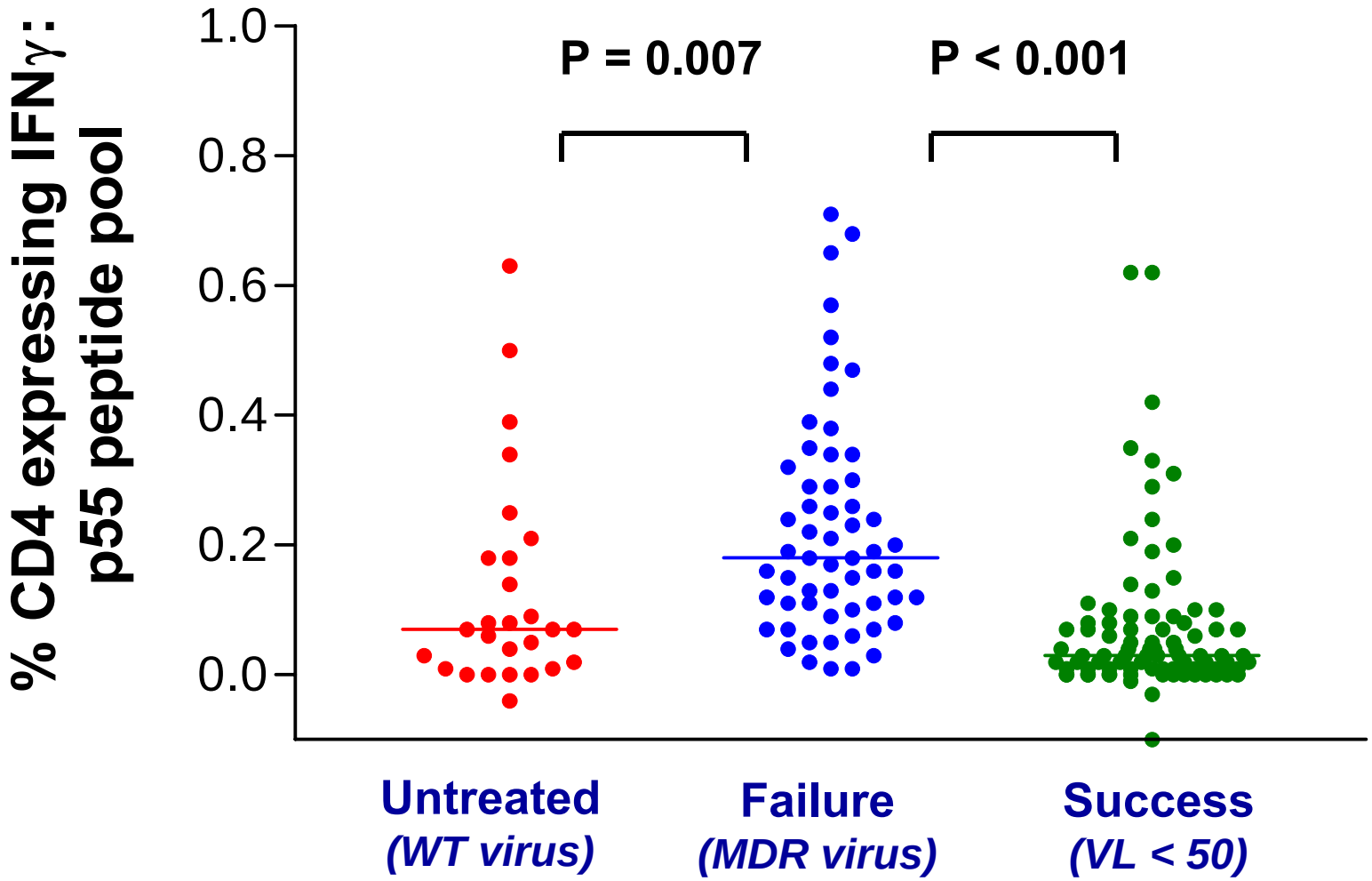
- What defines the host-specific pathogenicity/virulence of HIV?
- If immune activation, is there any role for:
  - Immunosuppressents
    - Prednisone, mycophenolic acid, cyclosporin . . .
  - IL-2 (up regulate Tregs)
  - IL-10

Can we alter the help the immune system control MDR HIV?

Hypothesis

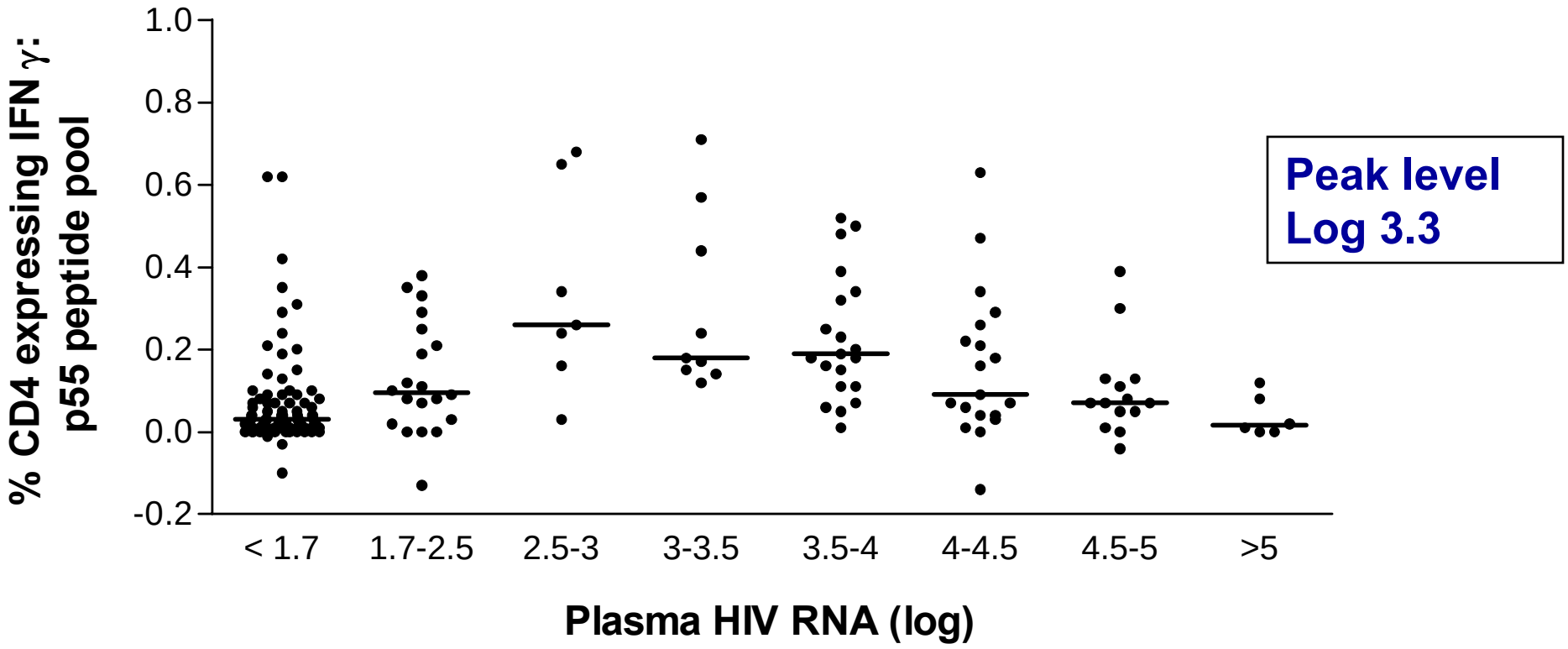
Drug-resistant HIV-1 variants—which are less fit and perhaps less "virulent" — might replicate to levels that are sufficient to stimulate but not deplete HIV-1-specific CD4+ and CD8+ T-cells

Gag-Specific CD4+ T Cell Response (n=175) (γ IFN-bright)



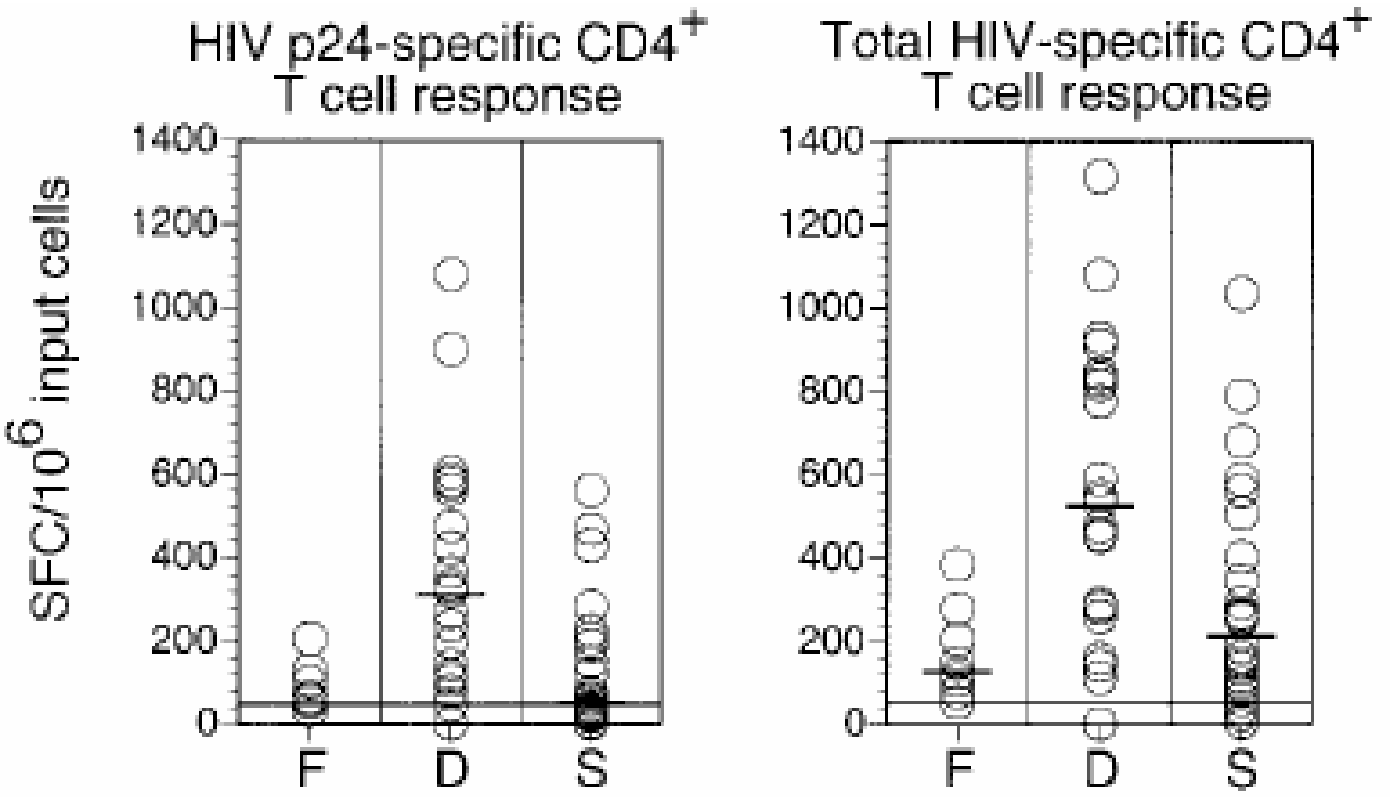
J Infect Disease 2004; 189:312-21.

Gag-Specific CD4+ T Cells (γ IFN-bright)



J Infect Disease 2004; 189:312-21.

HIV-specific T cells and "discordant" responses



HIV-specific CD4+ T cell responses as defined by inteferon-ELISPOT (P < 0.01 for discordant vs. either of the other two groups)

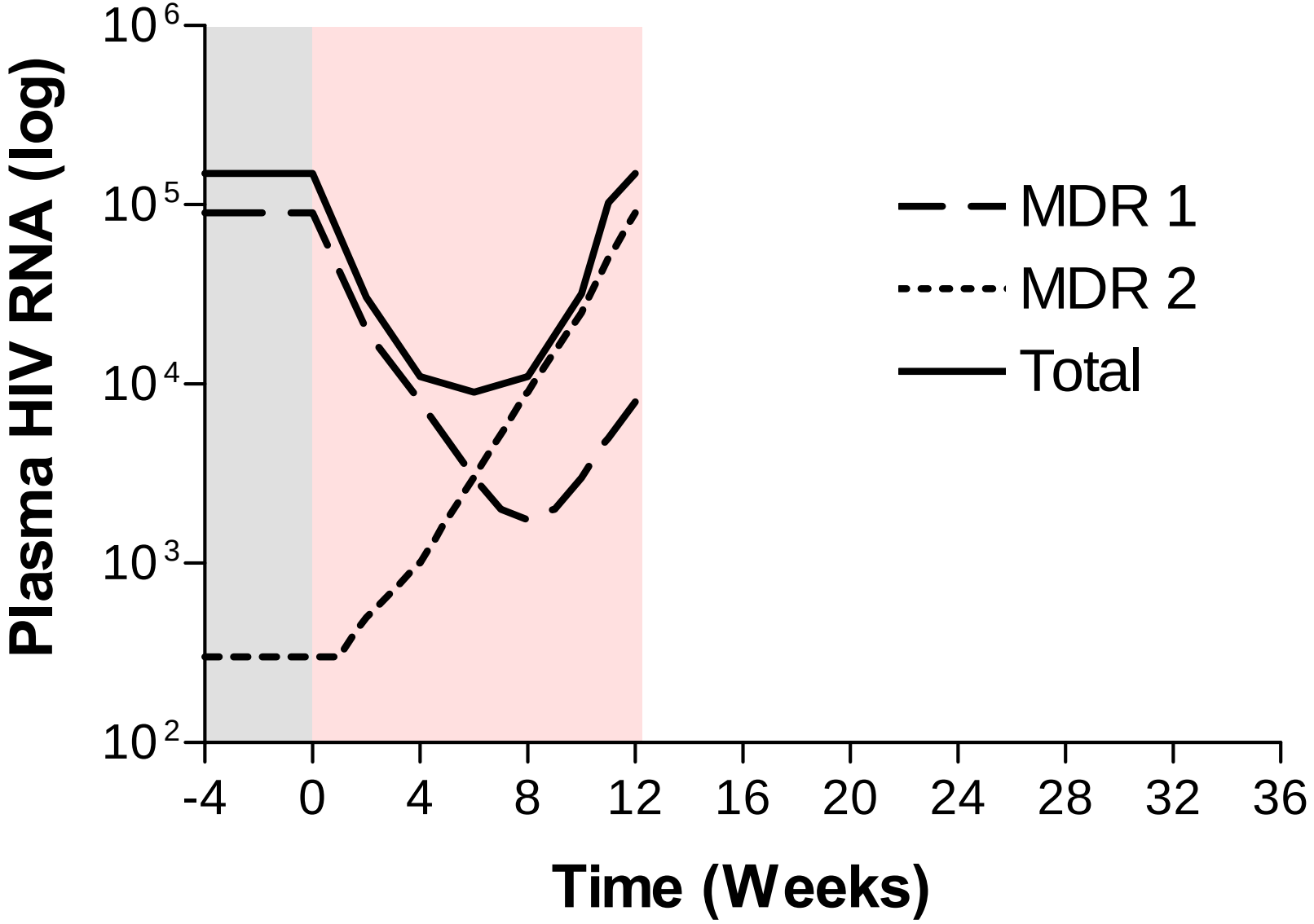
Price et al; J. Virology 2003

Immunologic control of HIV

- High HIV-specific CD4+ T cell responses associated with durable control of drug-resistant HIV
  - Cause and effect
- Can we vaccinate patients epitopes containing drug-resistant HIV?
  - Supported by unpublished work linking HLA type to viral evolution
- Can HIV-specific immunity be enhanced with novel therapeutic strategies, including treatment intensification and/or use of immunomodulatory agents?

Other approaches?

Sequential or Cyclic Salvage Therapy



Maggiolo AIDS 2002;16:298-99

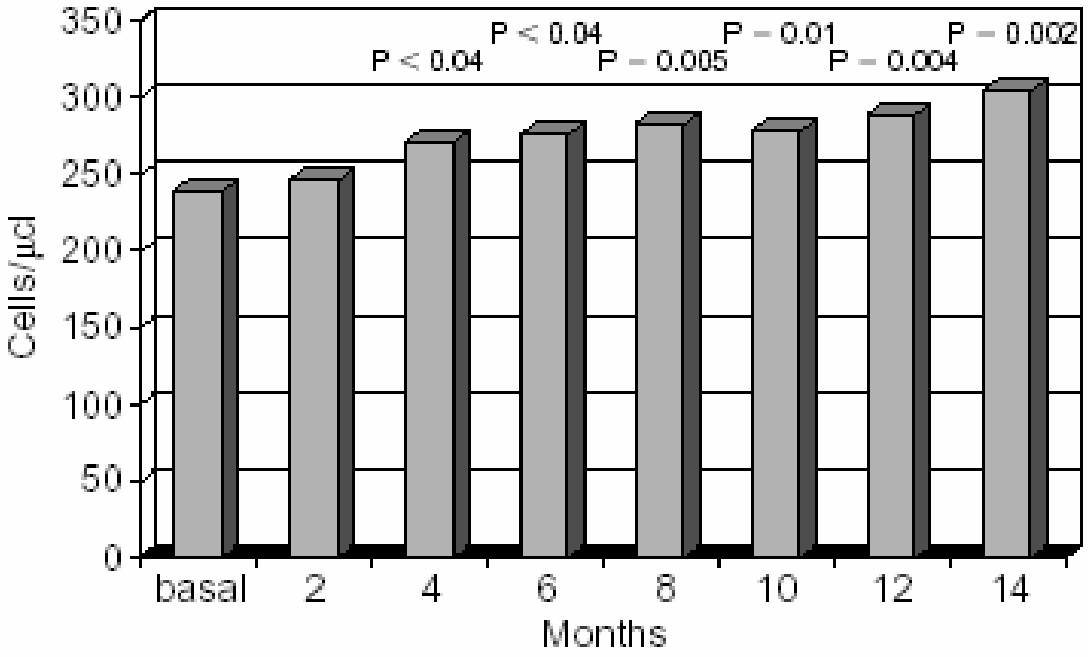
Strategic Selective Treatment

Three-class failure, VL > 10,000 (n=34)

Genotypic-driven switch strategies whenever VL increases to > 10K

Four or fewer drugs given

Limited disease progression observed



Maggiolo AIDS 2002;16:298-99

Summary

- We need more effective drugs which patients can access and tolerate
- Until then, the issue really is how to keep patients out of trouble while preserving future options
  - When to switch (when is OK to not switch)
  - Partial or selective treatment interruptions vs. dose reduction
  - Diagnostics: RC, immune activation, tropisms . . .
- Future directions which are not really on anyone's radar screen include: immune suppressants, immune enhancers (including HIV vaccines), strategies to decrease "fitness" and/or pathogenicity, cyclic therapy . . .

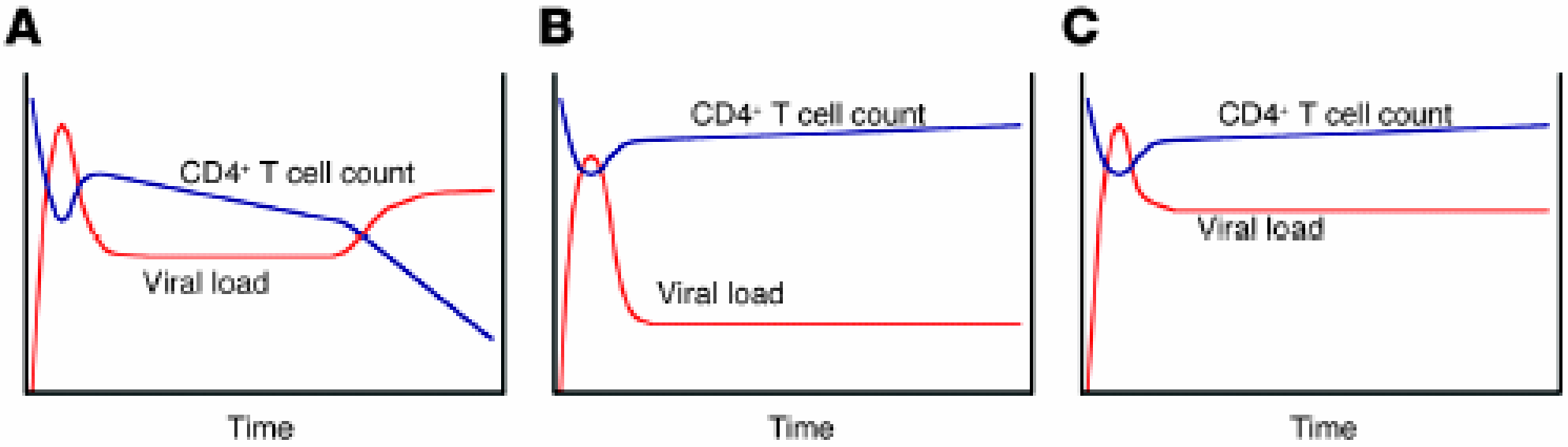
Clinical Trial Designs

Can we avoid TORO-like studies in the future?

Phase III studies: The provider/patient perspective

- TORO
  - Good: liberal roll-over plan, access to state of art resistance testing, no limits on optimized background
  - Bad: only one “new” drug provided, thus forcing desperate patients with MDR to risk sequential monotherapy
- Alternative: no other drugs available
  - Use phase II to define anti-HIV potency and drug-specific adverse events for drugs A and B
  - Phase III: Randomize to OB vs. OB plus AB
- Alternative: one other drug available (ie, T20)
  - Immediate switch to T20 plus drug A vs. delayed switch to T20 plus drug B, using comparison to TORO studies to define a priori what kind of response would be needed to prove that drug A was effective

The immune response to AIDS virus infection: good, bad, or both?



Wild-Type HIV-1

Reduced Fitness (HIV under treatment)

Reduced Virulence

Journal of Clinical Investigation, 2004

Drug-resistant HIV as an "attenuated vaccine"

Drug-resistant variants spare intrathymic T-cell production (SCID-hu) and are associated with lower levels of T-cell turnover and activation in vivo, thereby permitting the continued production and survival of HIV-1-specific CD4+ and CD8+ T-cells

(Stoddart and McCune, Nature Med 2001; Deeks JID 2002)