

CROI 2005 Update

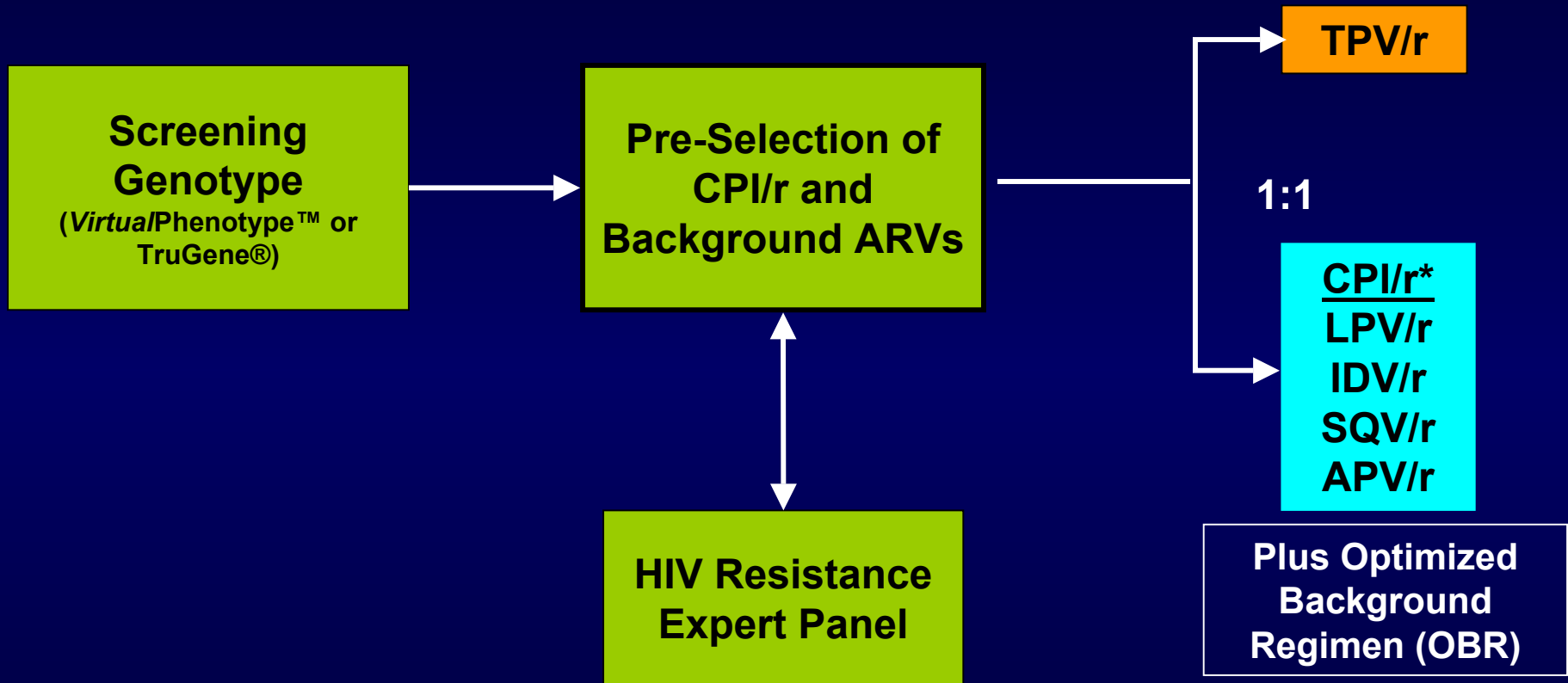
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UCSF

Tipranavir vs. TMC 114

RESIST Study Design



Failures in CPI arm after wk 8 could receive TPV in rollover study

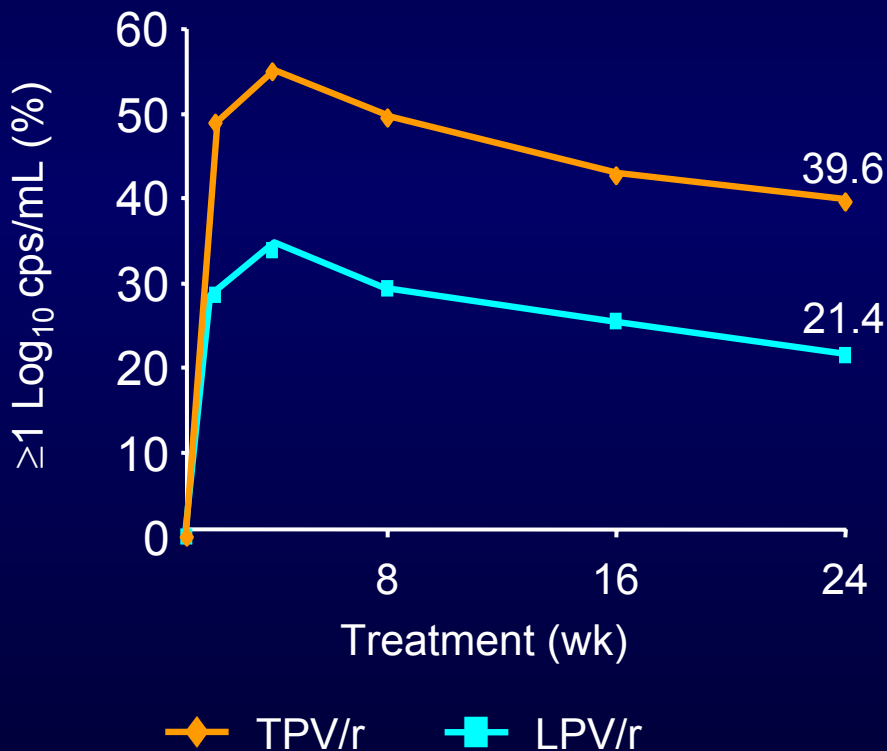
*CPI = comparator PI.

Virologic Response Across TPV/r vs LPV/r Strata

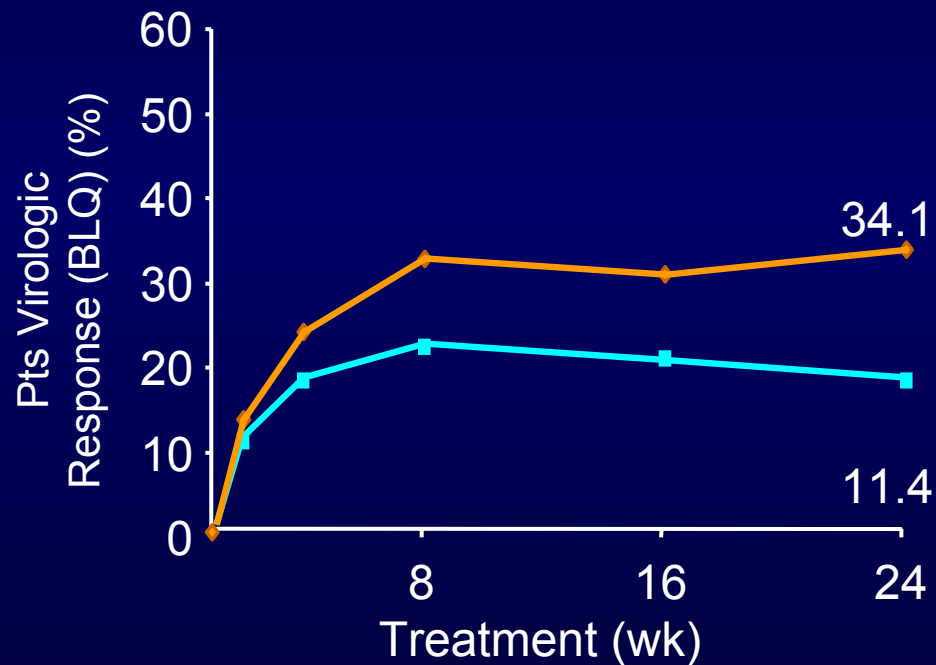
n = 293 on TPV/r

n = 290 on LPV/r

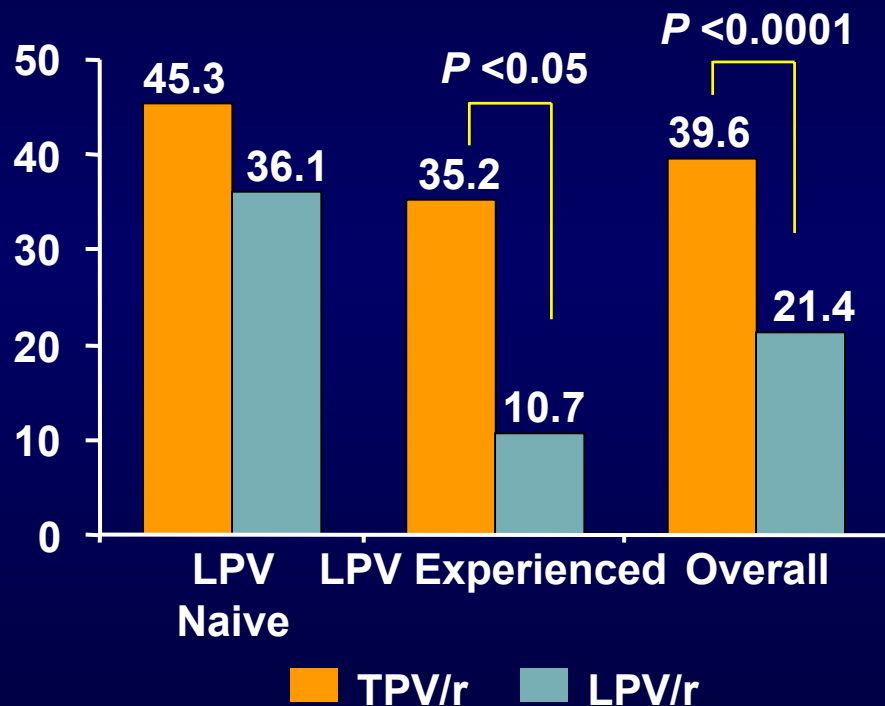
Treatment Response



Proportion <400 cps/mL

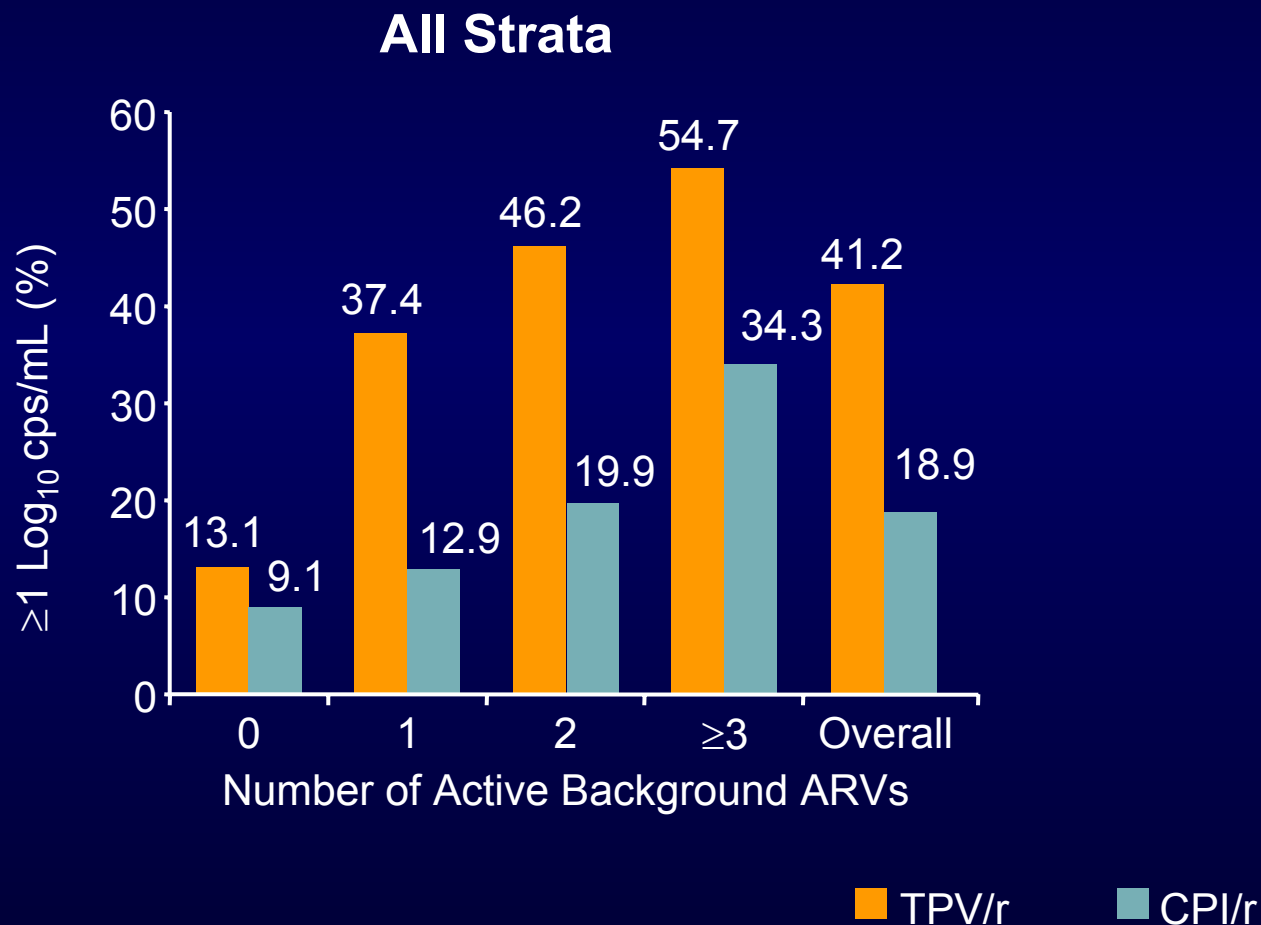


Comparison of Efficacy of TPV/r and LPV/r in LPV Stratum



LPV and TPV
comparable in
LPV-naïve patients

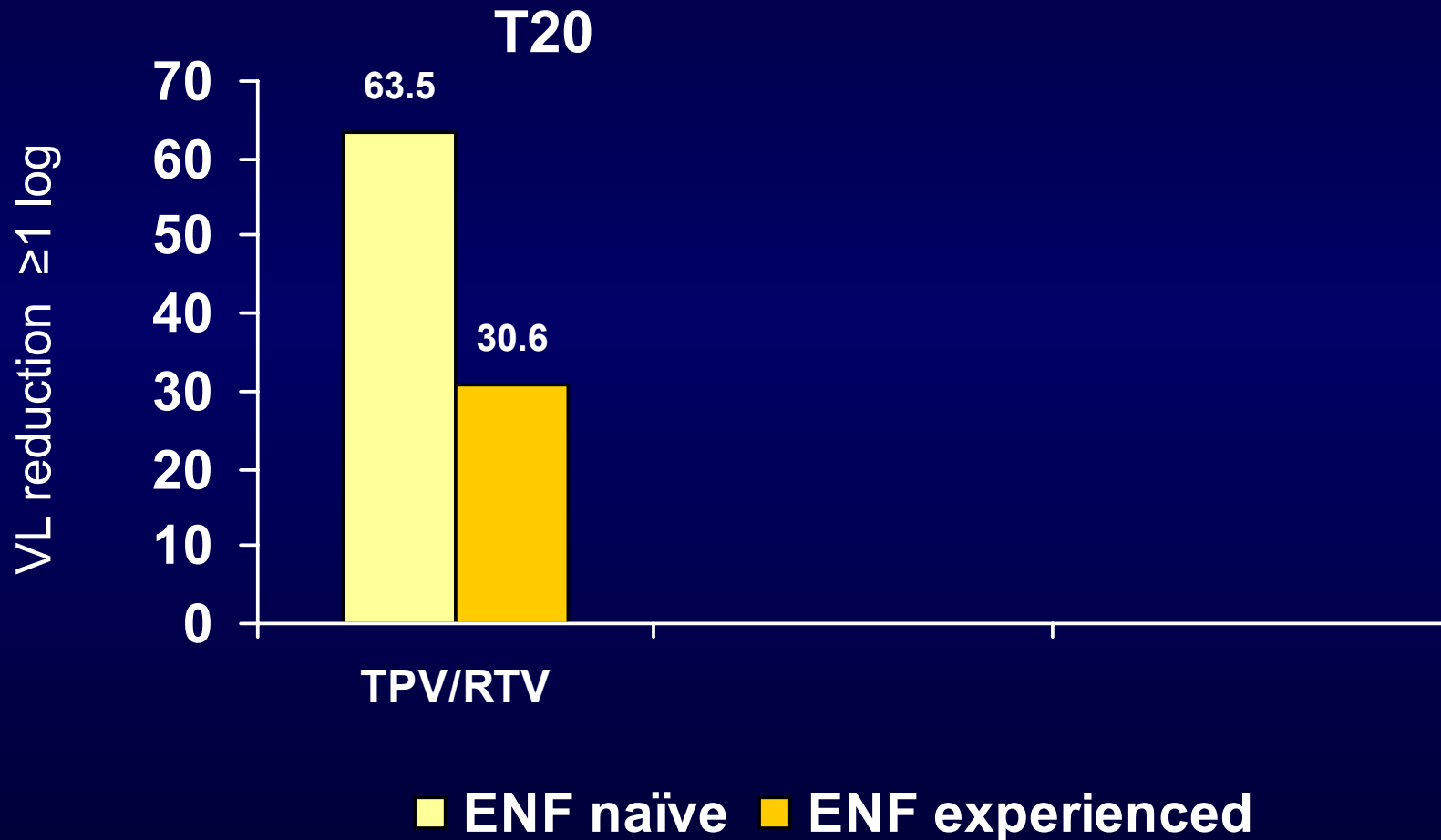
Relationship of Treatment Response to Number of Genotypically Active ARVs



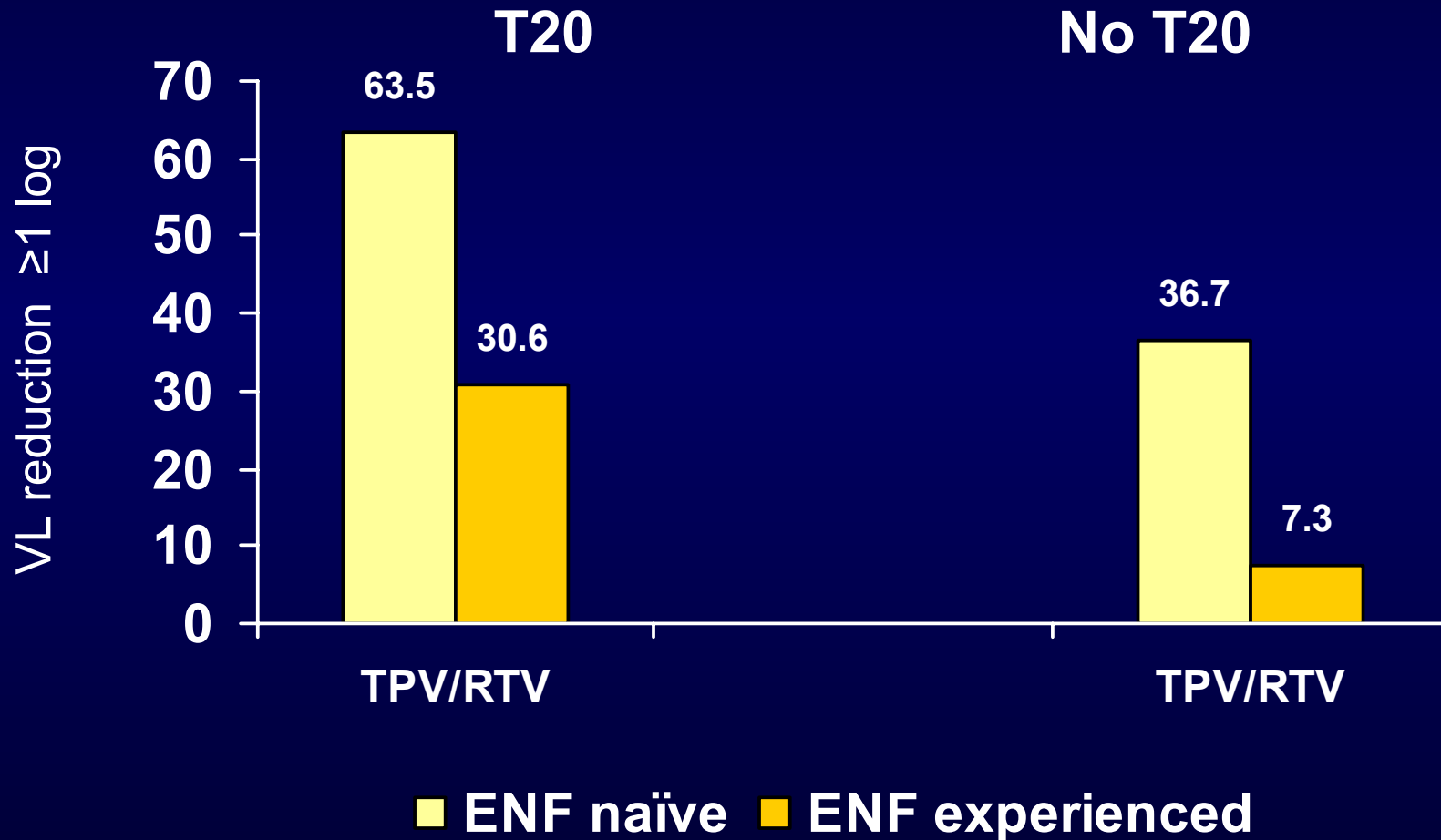
RESIST-1: Adverse Events

Grade 3/4 Lab AEs	TPV/r, %	CPI/r, %	<i>P</i> Value
ALT elevation	6.9	1.3	< .001
Cholesterol	4.2	0	< .001
Triglycerides	21.7	12.5	< .01

Addition of T20 to TPV/r



Addition of T20 to TPV/r



TMC 114

- Metabolized by CYP 3A4 (RTV ↑ levels)
 - half life: ~10 hours

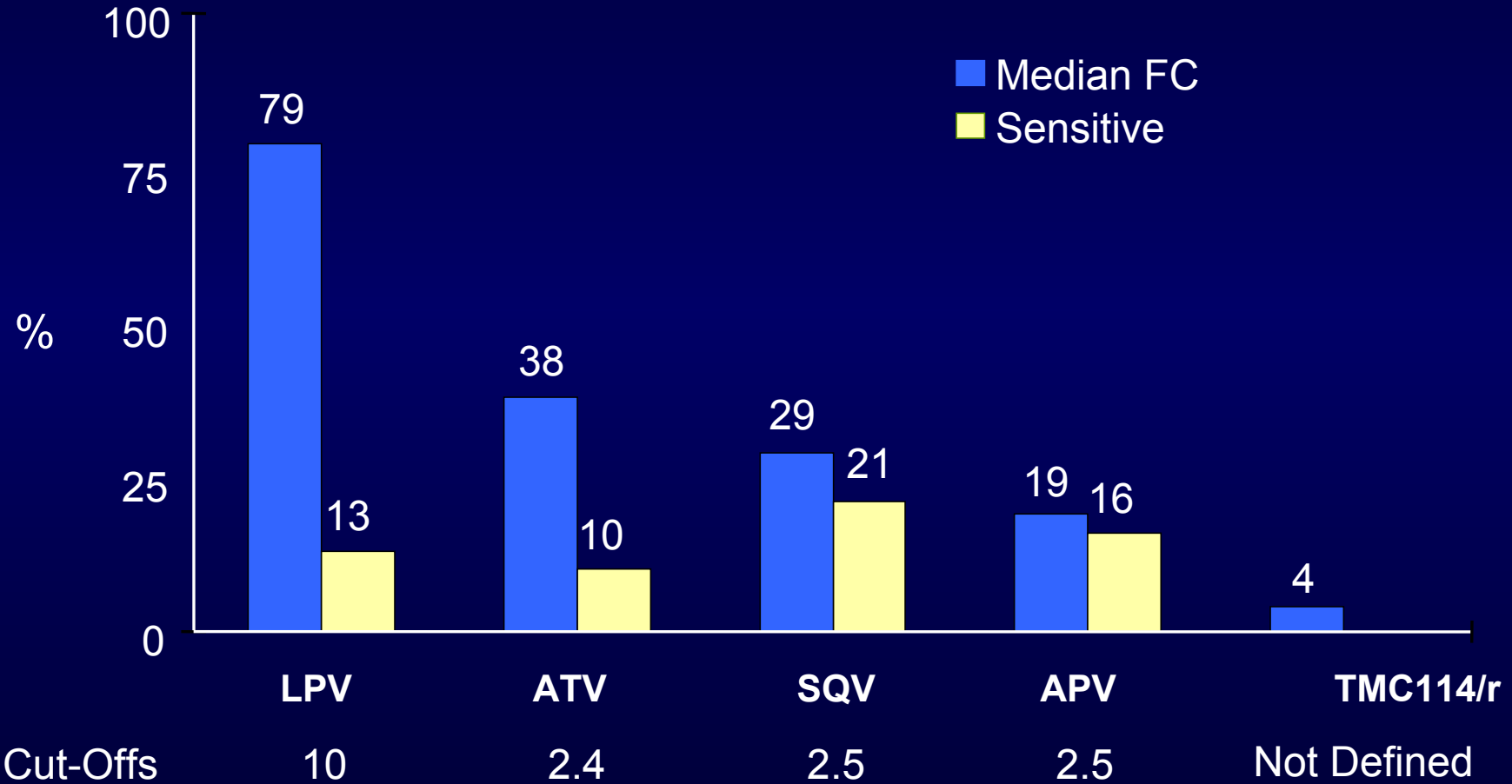
- Doses: TMC 114/RTV
 - 400/100 QD
 - 800/100 QD
 - 400/100 BID
 - 600/100 BID

Efficacy of TMC114/r in 3-Class–Experienced Pts

- At least 3-class experienced (PI, NRTI, NNRTI)
- On a PI-containing regimen
- ≥ 1 Primary PI mutation
- HIV RNA >1000 cps/mL, any CD4 cell count

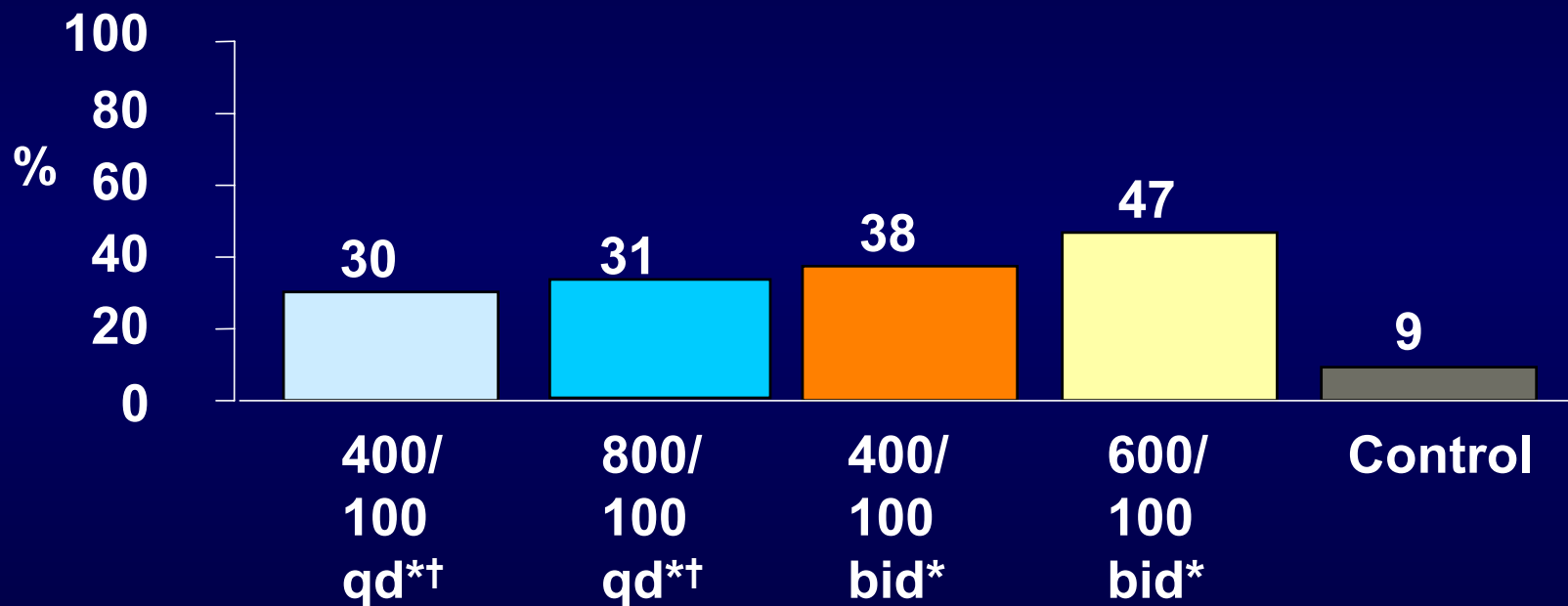
- Entry characteristics
 - N = 397 on TMC114/r, 100 on comparator PI
 - VL: TMC 4.61; control 4.47
 - CD4: TMC 136; control 163

Baseline PI Susceptibility



Virologic Response

HIV RNA <50 cps/mL at Wk 24: ITT NC = F



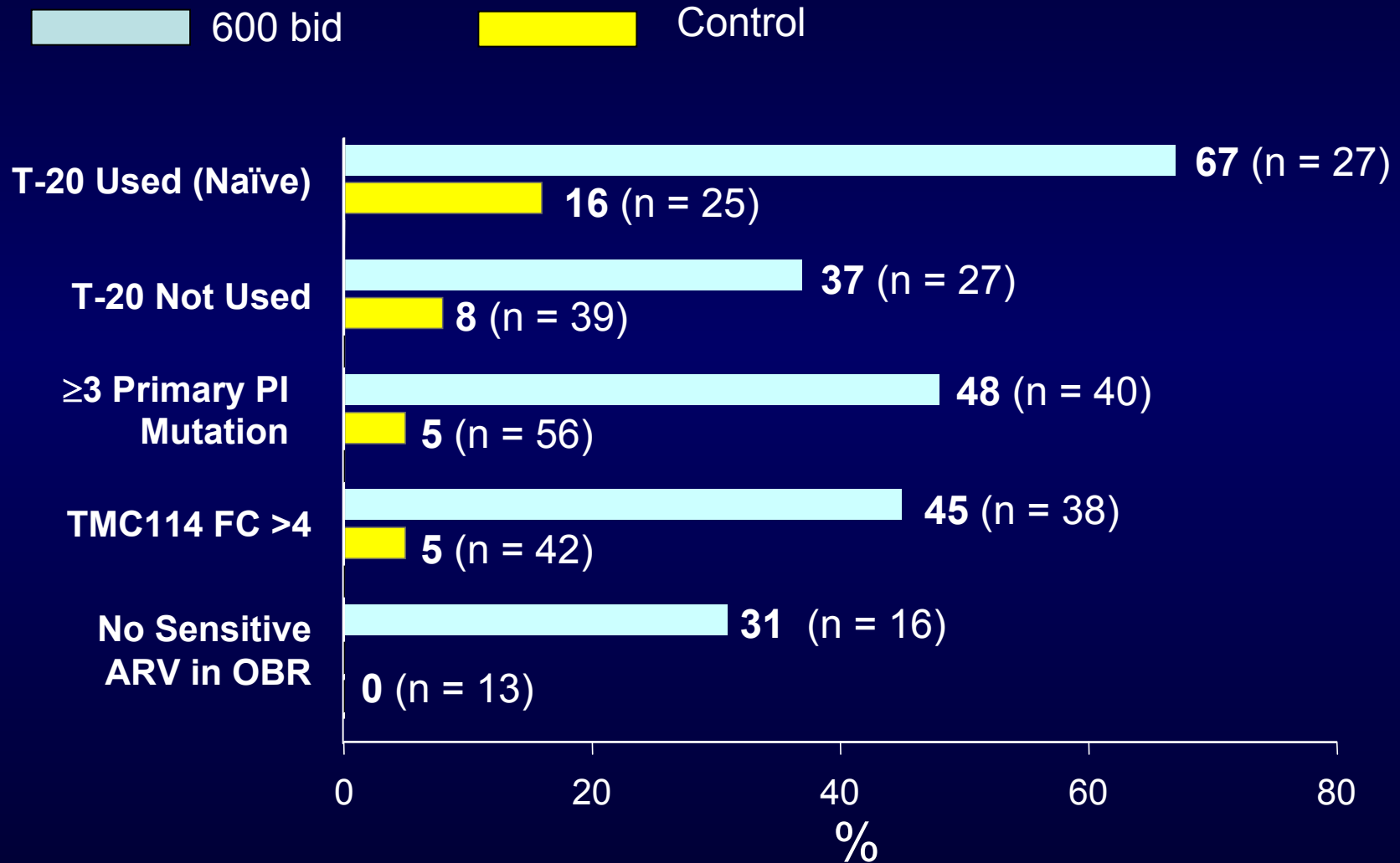
C = F (non-completers = failures).

vs control P <0.001; †vs 600 BID, P <.05.

Katlama C, et al. 12th CROI, 2005; Abst. 16

600 bid Dose: Subset Analysis

HIV RNA <50 at Wk 24: ITT NC = F

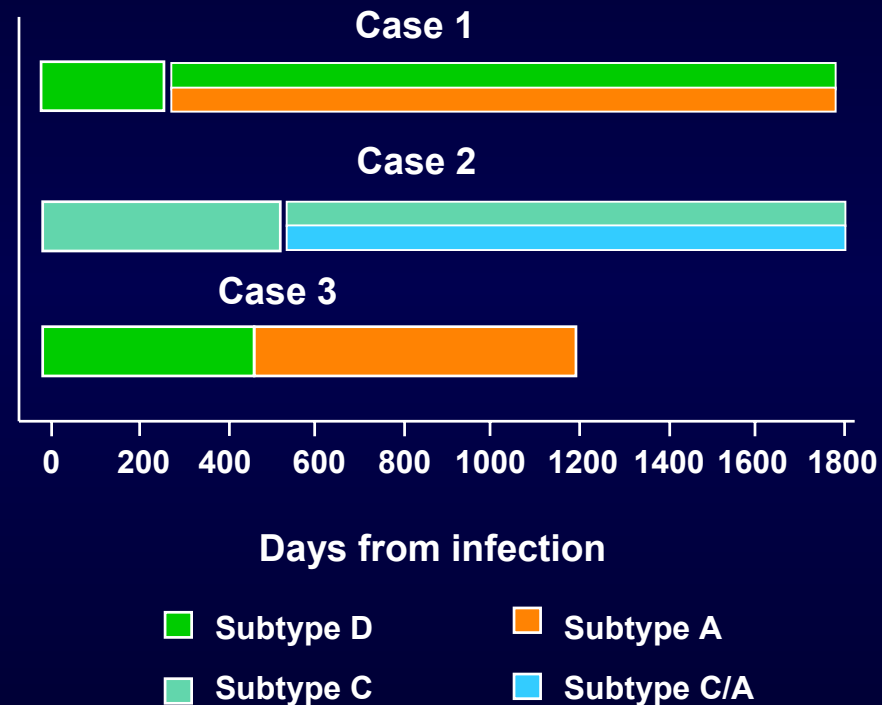


Pathogenesis

HIV-1 Superinfection

Mombasa cohort (n=20)

- Subtype C or D infection
- More prevalent subtype A superinfection in 3/20 subjects
- ~6 would have been predicted

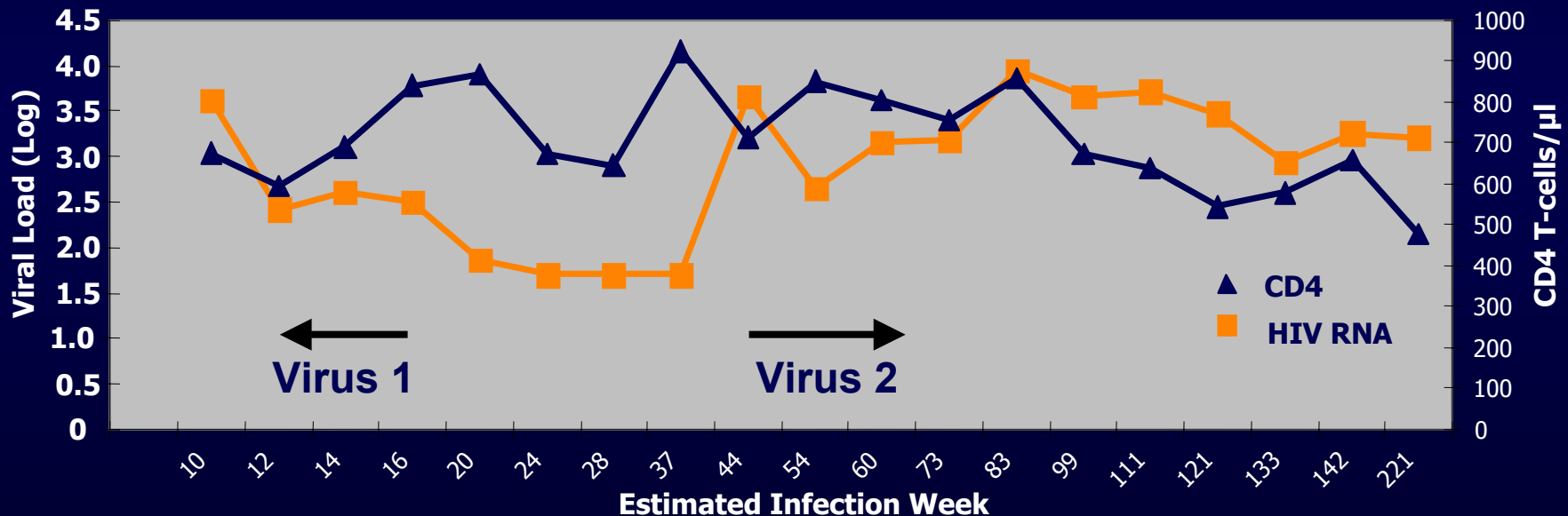


HIV-1 Superinfection: UCSF Options (n=104)

(3.8%) cases; 2.1/100 person-years (95% CI: 0.6, 5.2)

One subject had WT to NNRTI resistant (V108I)

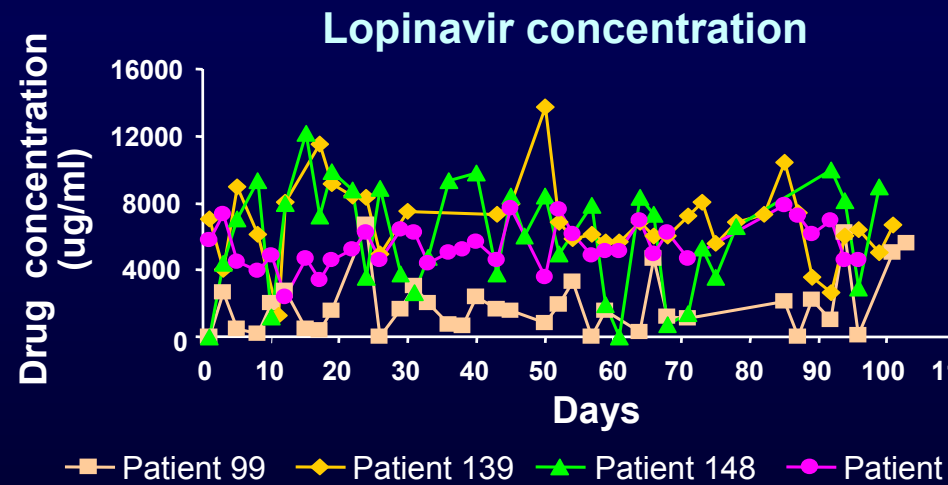
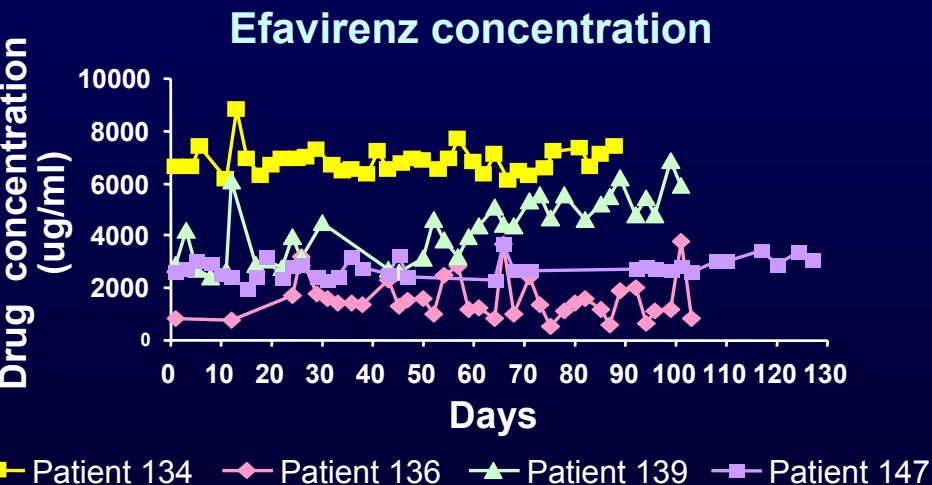
Superinfection associated with increased viremia



Superinfection has not yet been reported in chronically infected patients or in antiretroviral treated patients

Pathogenesis of low-level viremia

- 10 aviremic subjects had sampling qod x 10 weeks
- “Blips”: 26/713 samples (3.6%)
 - Not present on repeat (lab variation?)
 - Not related to drug concentration
 - Not associated with viral evolution (JAMA 2005)



PK variance (coefficient of variability) – median 26% for NNRTI, 43% for PI

Anti-viral host responses

• APOBEC3G:

- Cytidine deaminase
- APOBEC3G is packaged into virions
- Cytidine deaminases: deaminates nucleotides within single stranded viral cDNA (G-to-A mutations), rendering subsequent viruses defective
- Vif: binds to and inhibits APOBEC3G activity by targeting it for ubiquitination (signal for degradation)

Anti-viral host responses

- TRIM5 α
 - 40 genes of the TRIM family in humans human.
 - Inhibit post-entry infection, likely by altering HIV uncoating
 - Species-specific: small changes prevent HIV from replicating in old world monkeys

How does HIV cause AIDS?

- Acute HIV associated with rapid depletion of CCR5+ memory CD4 T cells in intestines (where high proportion of cells are activated)
 - Seen in macaques but not natural hosts
 - Most (~40%) of CD4+ T cells contain HIV
 - 50% of total body CD4+ T cells are depleted within first few months
- Depletion persists into chronic infection, not reversed by HAART
- HIV-associated immune activation results in accumulation of HIV-specific and other memory T cells within lymph nodes
 - Associated with collagen deposition (not reversed by HAART)
- Acute HIV results in immediate decrease in thymocyte proliferation

Anti-viral host responses

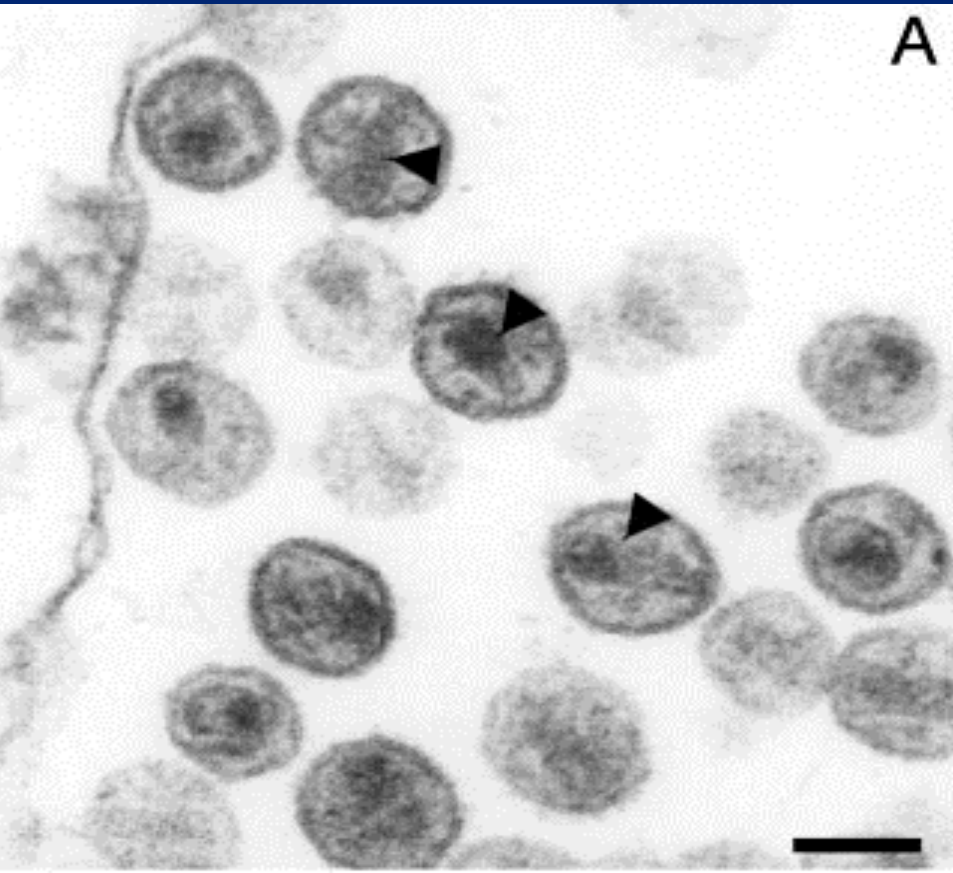
- Pathogenic SIV/HIV infection results in T cell activation; in contrast, limited activation observed in natural hosts
- Comparative study of infected SM vs. macaques
 - Macaques: ~25% to 50% of PDCs express CCR7
 - Sooty mangabeys: Most PDCs do not express CCR7
- PDCs from macaques but not SM are susceptible to activation via TLR-9 ligands (GpG) and SIV

Misc

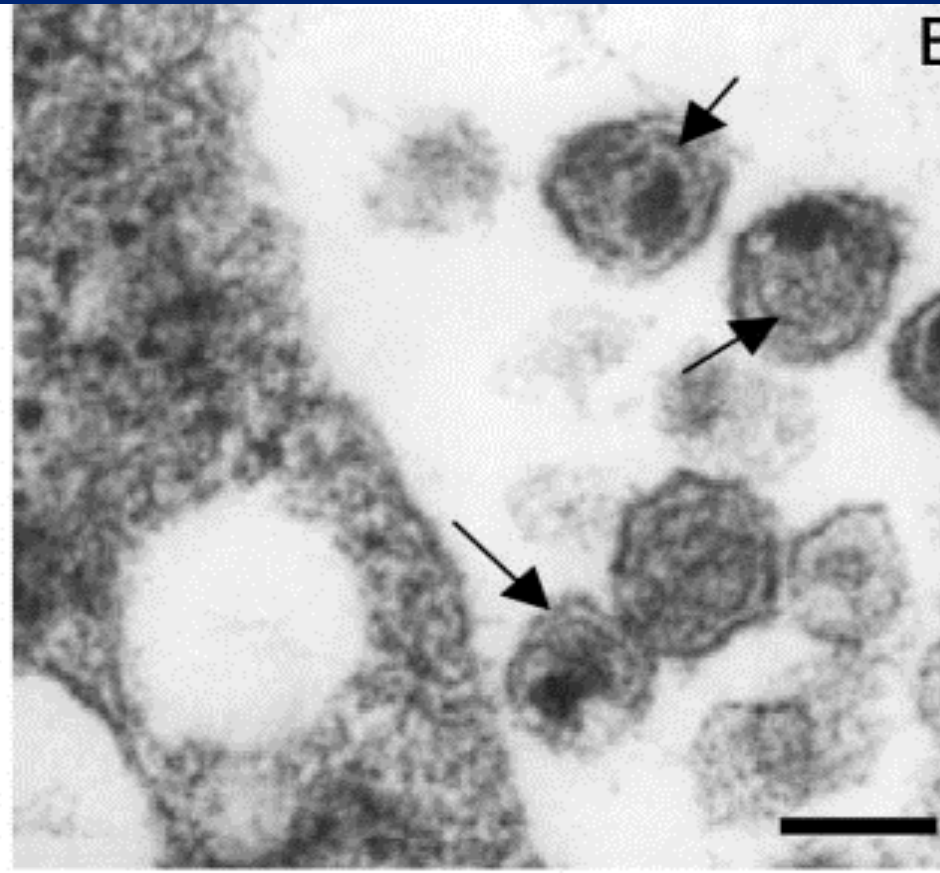
New Drugs

Maturation inhibitors

not treated



treated with PA-457

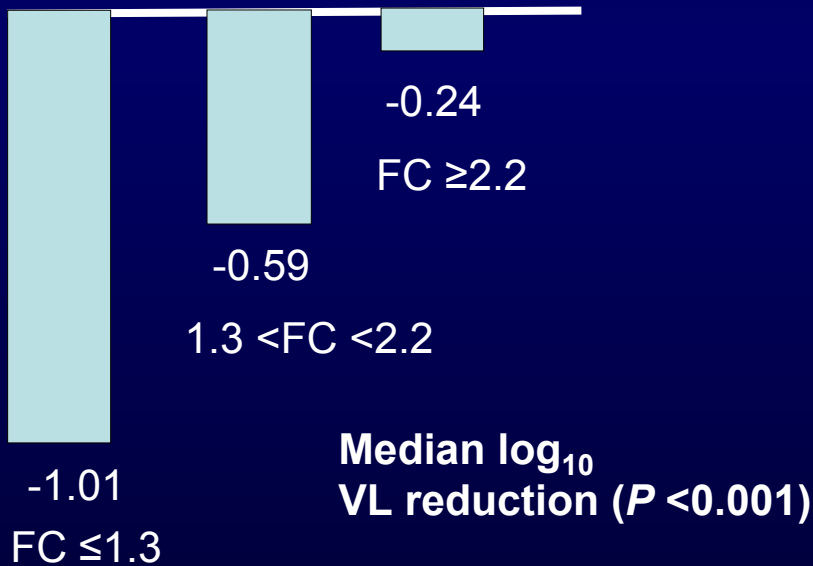


Prediction of ddl Early Viral Load Reduction

Jaguar: tients with virological failure on HAART

ddl (n = 110, 98 evaluable)

ddl placebo (n = 58)



**Response >0.5 log drop
Probability of response**

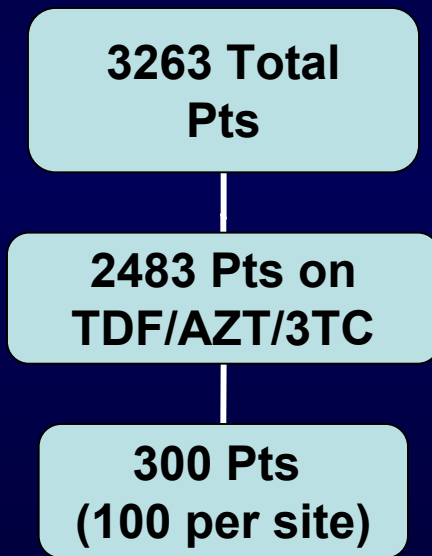
≤1.3	83%
>1.3 – <2.2	50%
≥2.2	29%

Selection of resistance mutations during STI

- TIBET: STI until CD4 < 350 vs. continued therapy in patients with undetectable viral load
 - Resistance tested in PMBCs and plasma
- 31 patients on NRTI-containing regimens at time of STI
 - 23 patients with archived TAMs: no new TAMs selected during 1st, 2nd, or 3rd STI
 - 8 patients without archived TAMs: no TAMs selected during 1st, 2nd, or 3rd STI
- 19 patients on NNRTI-containing regimens at time of STI
 - No patient had archived NNRTI mutations but 8/19 selected mutations during the 1st or 2nd STI

ZDV/3TC/TNF: Viable Option?

DART: Large RCT comparing intensive vs. clinical monitoring and continuous vs. intermittent therapy in treatment naïve symptomatic patients with CD4 < 200



Baseline (n=300)

CD4	100
HIV RNA	289,00 (23% > 750)

Results: Intent-to-Treat (week 24)

HIV RNA <50 cps/mL	51%
HIV RNA <400 cps/mL	68%

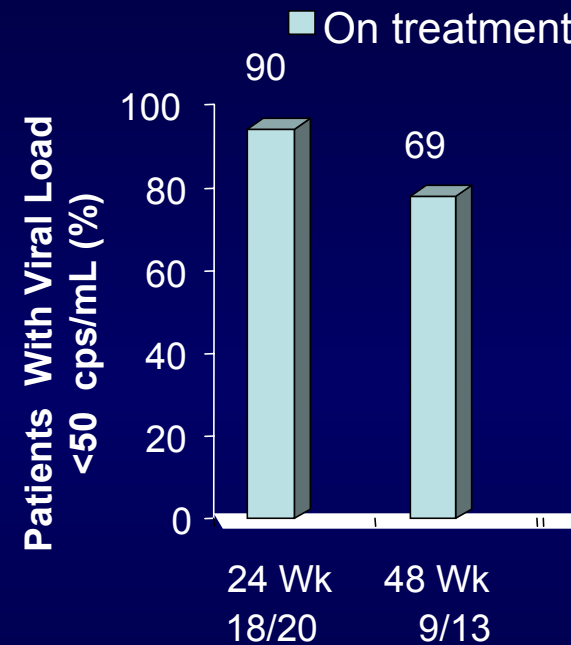
Potential benefits

- Limited PK interactions with TB therapy, no known teratogenicity, limited hepatic toxicity, preservation of options?

Triple Nucleoside Regimens: ZDV/3TC/TDF

Baseline Characteristics (n=42):

Median CD4 cell count	233 c/mm ³ (23–425)
Median HIV-1 RNA	4.88 log (3.14 log – >5.87 log)
HIV-1 RNA >5 log	19/42 pts (45%)



Genotypic analysis on 4 pts with virologic failure (on treatment):

- M4IL + T215N (present at baseline)
- K70R (mixture) + T215F (mixture) + M184V
- D67N (mixture) + K70R + K219E (mixture) + M184V
- K65R

Immune Based Therapy

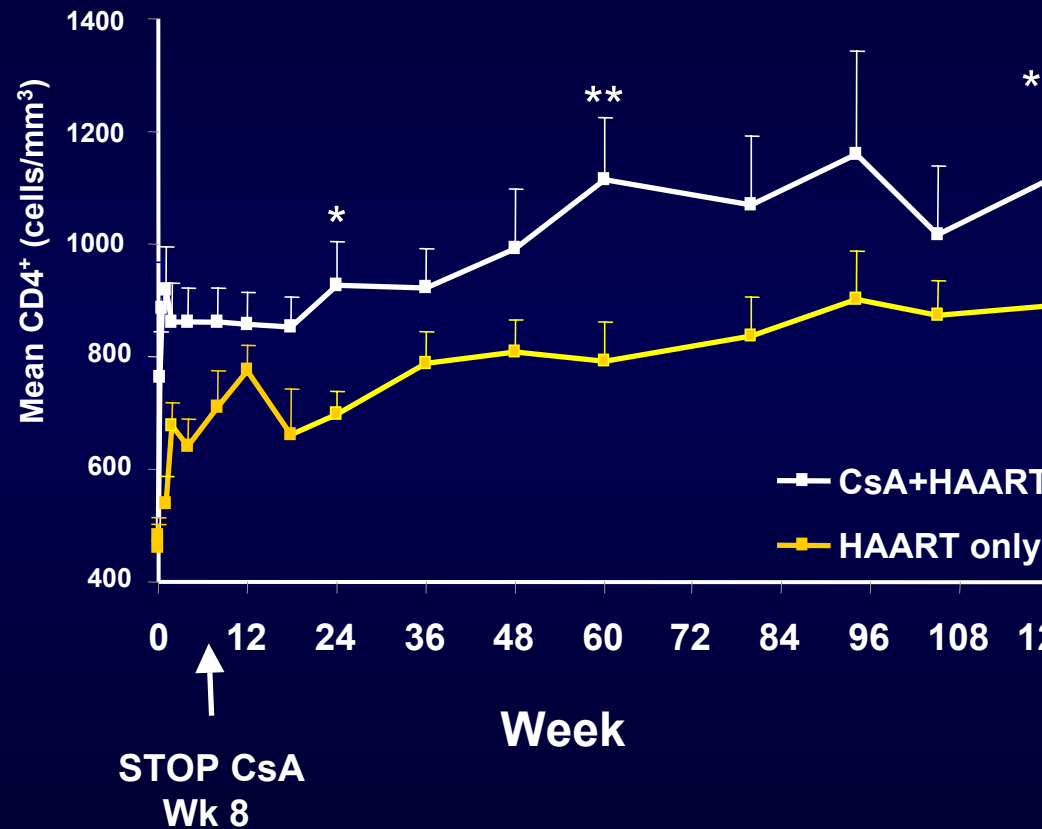
Cyclosporin for acute HIV infection

Cyclosporin (CsA) down-regulates genes essential for activation of CD4+ lymphocytes

Acute HIV receiving:

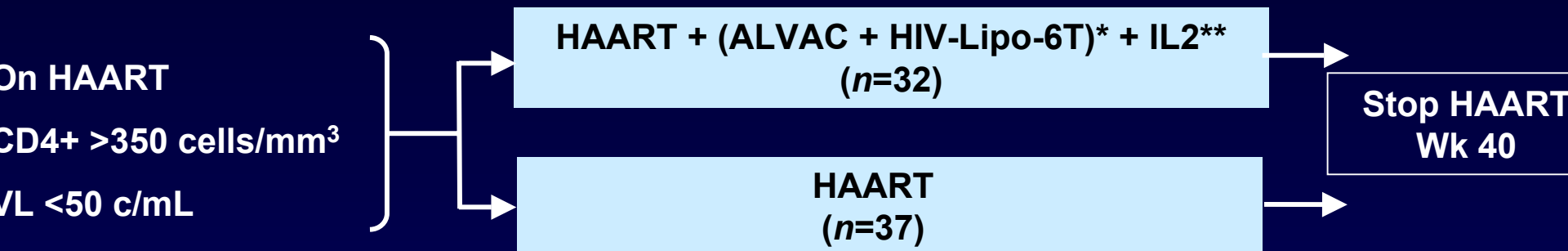
- HAART ($n=43$)
- HAART + CsA x 8 weeks (dosed to achieve levels >1000 ng/mL)

VL reduction over time similar in both groups, though more reached <50 c/mL in the CsA group at Weeks 18, 24, and 36 ($p<0.011$)



* $p=0.006$, ** $p=0.015$, *** $p=0.07$

Therapeutic vaccines (ANRS-093 Study)



*At Wks 0, 4, 8, 12; **At Wks 16, 24, 32

	HAART	HAART + Vaccine	p-value
Median time off HAART (days)	89	177	0.01
Pts off HAART at Wk 100	19%	38%	0.085

- HIV-specific LPR (pre- and post-IL2) significantly correlated with total time off HAART

Short-term monotherapy with integrase inhibitor L-870,810

Study design

Randomized, double-blind, placebo-controlled, 10-day dose-finding study

ARV-naïve or -experienced patients off therapy ≥ 3 months

200 mg BID ($n=7$) vs 400 mg BID ($n=17$) vs placebo ($n=6$)

