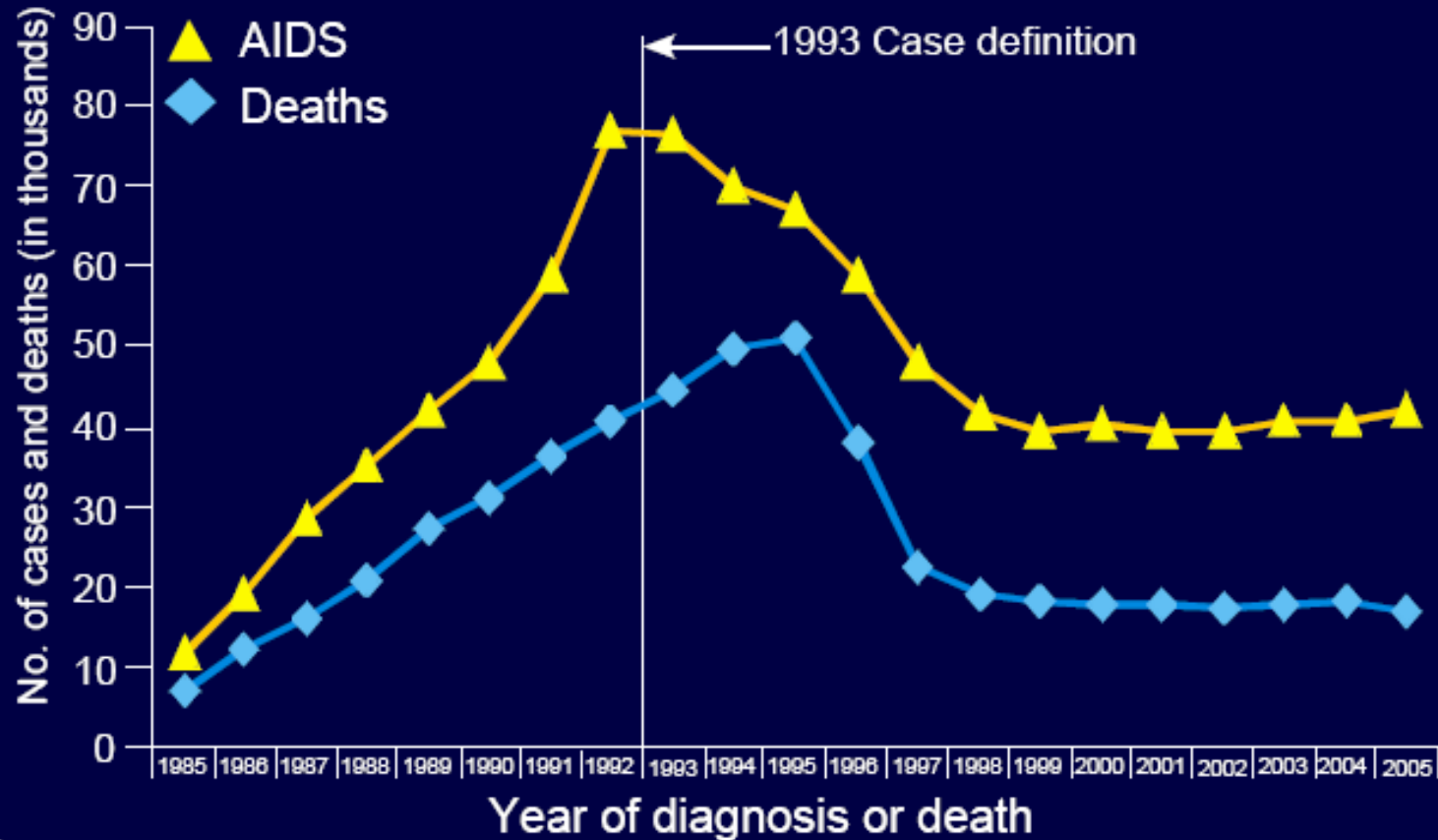

HIV Drug Resistance: How can new drugs or new drug classes help?

Daniel R. Kuritzkes, MD
Section of Retroviral Therapeutics
Brigham and Women's Hospital
Division of AIDS
Harvard Medical School



Estimated number of US AIDS cases and deaths in adults and adolescents 1985-2005

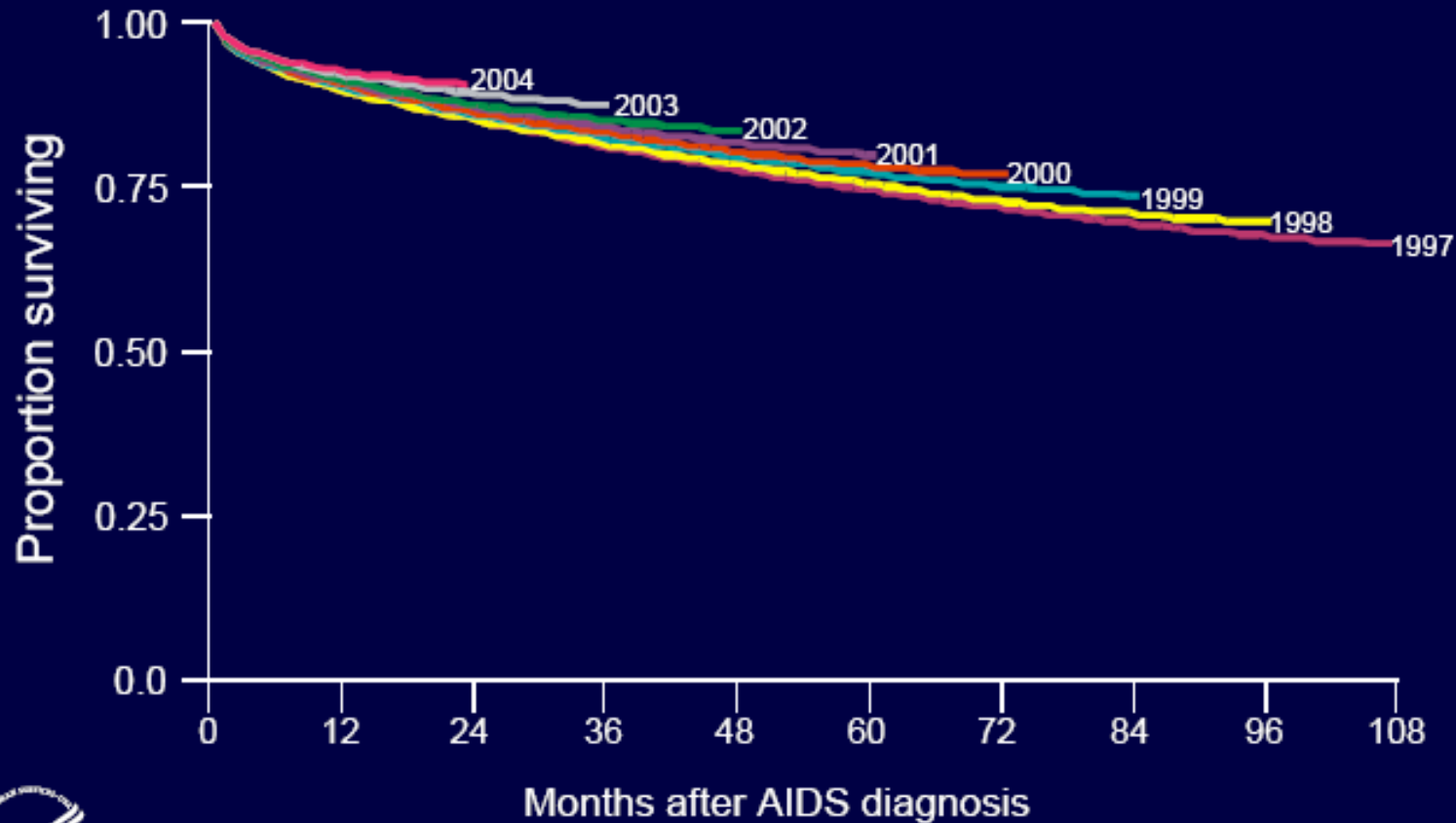


Note. Data have been adjusted for reporting delays.

Revised June 2007



Proportion surviving in US after AIDS diagnosis 1997-2004



<http://www.cdc.gov/hiv/topics/surveillance/resources/slides/epidemiology/slides/EPI-AIDS.pdf>, Accessed May 11, 2008

FDA-Approved Antiretroviral Agents

- **NRTI**

- Zidovudine
- Didanosine
- Stavudine
- Lamivudine
- Abacavir
- Tenofovir*
- Emtricitabine
- ZDV/3TC
- ABC/3TC
- TDF/FTC

- **NNRTI**

- Nevirapine
- Delavirdine
- Efavirenz
- **Etravirine**

- **Protease Inhibitors**

- Saquinavir
- Ritonavir
- Indinavir
- Nelfinavir
- Fosamprenavir
- Lopinavir/ritonavir
- Atazanavir
- Tipranavir
- Darunavir

- **Fusion Inhibitors**

- Enfuvirtide (T-20)

- **CCR5 antagonists**

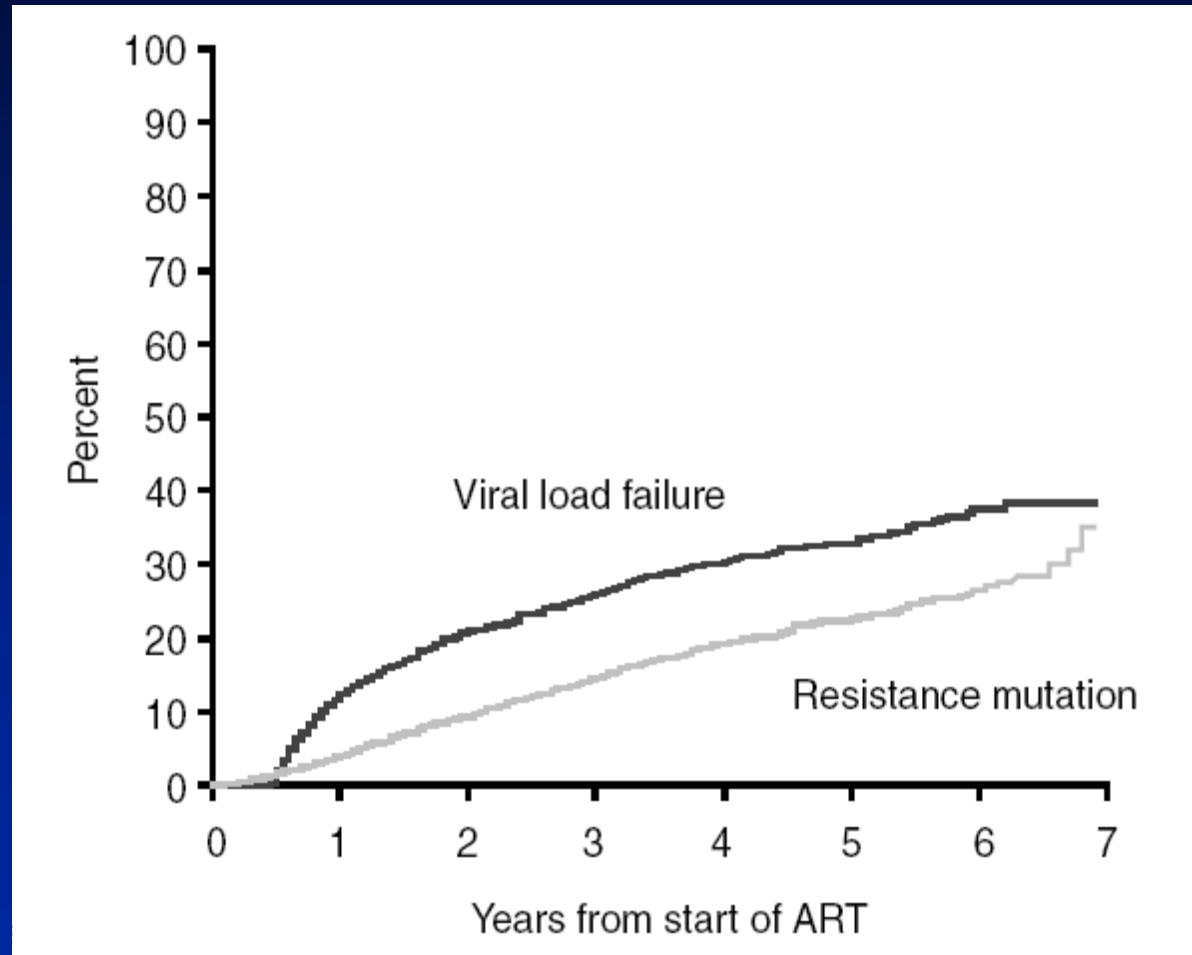
- **Maraviroc**

- **Integrase inhibitors**

- **Raltegravir**

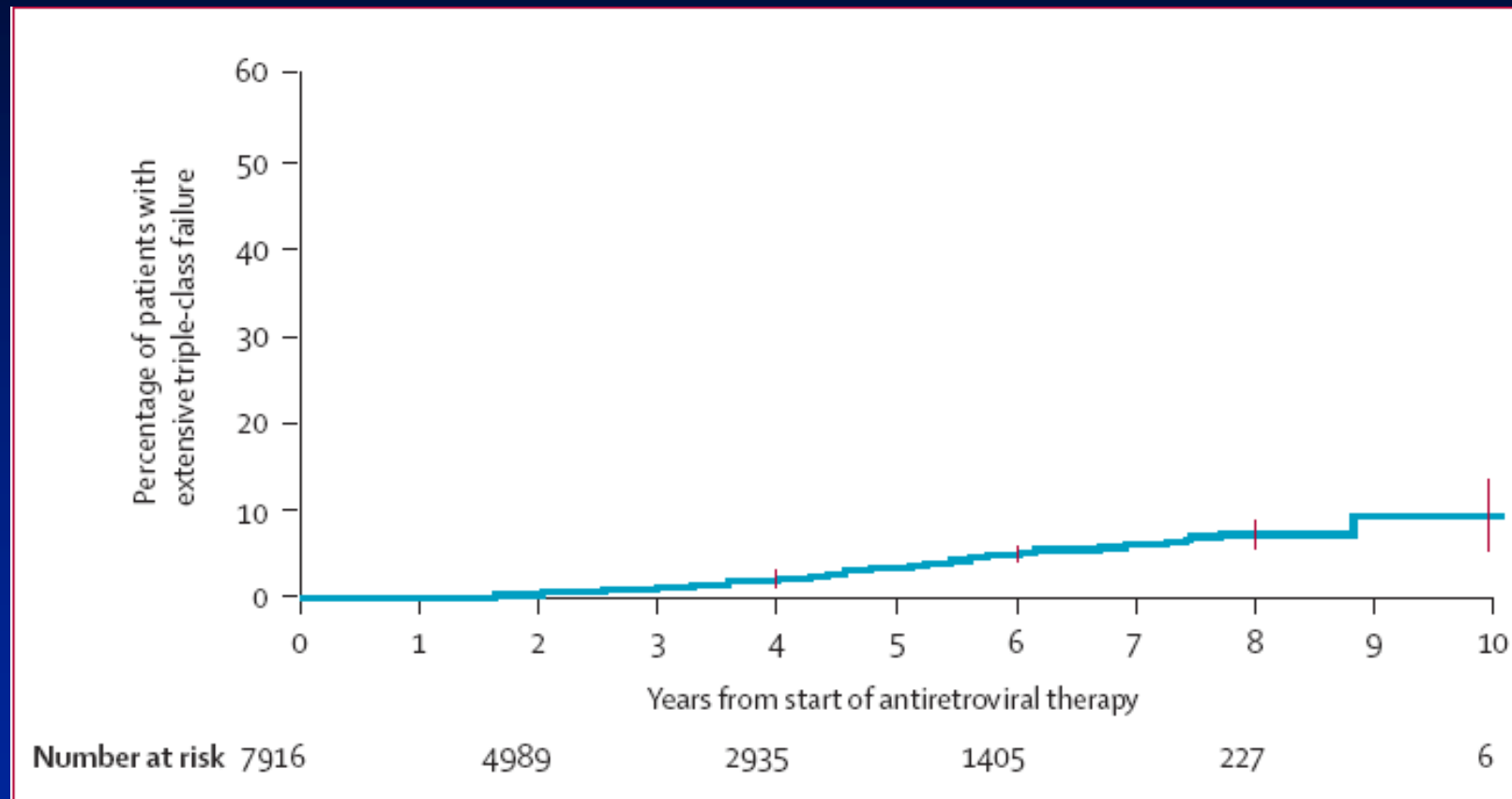
*Nucleotide RT inhibitor

Risk of Virologic Failure and HIV-1 Drug Resistance after starting ART



Phillips et al AIDS 2005

Risk of triple-class resistance: 2007



Phillips et al Lancet 2007; 370:1923-8.

CDC Survey: Drug-Resistant HIV Among Newly Diagnosed Patients

Prevalence of Drug Resistance (%)

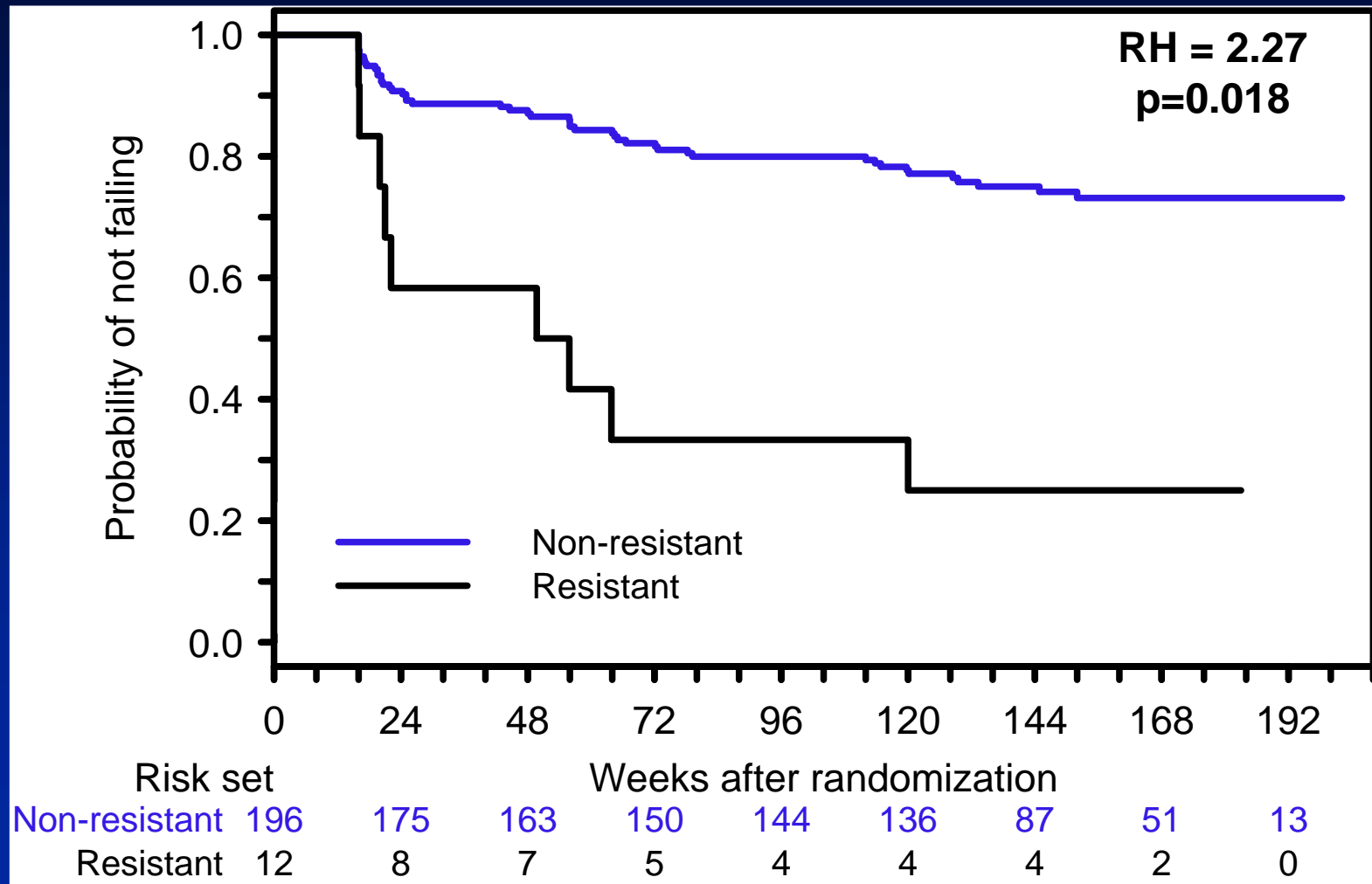
	1998 (n=257)	1999 (n=239)	2000 (n=299)	2003-2006 (n=3130)
Resistance to:				
Any drug	5.5	8.8	10.7	10.4
NRTI	5.1	7.1	7.7	3.6
NNRTI	0.4	2.1	1.7	6.9
PI	0	0.8	3.0	2.4
≥2 drug class	0	1.3	1.3	1.9

Bennett D et al. 9th CROI, Seattle, 2002. Abstract 372.

Bennett D et al. 12th CROI, Boston, 2005. Abstract 674.

Wheeler W et al. 14th CROI, Los Angeles, 2007, Abstract 648

NNRTI resistance and time to virologic failure in the randomly selected cohort



Kuritzkes et al J Infect Dis 2008;197:867-70.

Diversity of RNA Virus Populations

- Virus populations comprise a *quasispecies*
- Genetically distinct variants evolve from an initial oligoclonal inoculum
- Variants are generated by error-prone RNA-dependent polymerases

Drug-Resistant Mutants Preexist in Untreated Patients

- The HIV genome contains 10^4 nucleotides
- The mutation rate of HIV is $\sim 3 \times 10^{-5}$ nucleotides/ replication cycle
- $\sim 10^{10}$ virions are generated by $10^7 - 10^8$ rounds of replication each day

Rapid turnover of HIV quasispecies

- Approximately half of the virus population in plasma is cleared and replaced each day.
- High turnover allows rapid emergence of drug-resistant variants under selective pressure.
- Resistant variants replaced by residual wild-type virus if selective pressure is removed.
- Resting latently infected cells continue to harbor drug-resistant provirus.

Defining treatment failure

- **1st or 2nd regimen:**
 - Confirmed viremia (>50 copies/mL? >200 copies/mL?)
- **Subsequent regimens:**
 - Rising virus load
 - Declining CD4 count
 - Disease progression

Possible Causes of Treatment Failure

- Poor adherence
- Pharmacologic factors
- Host factors
- Limited potency of drug or regimen
- Drug resistance

Consequences of ongoing viral replication during HAART

- **Accumulation of drug resistance mutations**
- **Development of cross-resistance within multiple drug classes**
- **Greater difficulty in re-establishing virologic control with future regimens**
- **Eventual decline in CD4 counts leading to disease progression**

Managing drug-resistant HIV-1

- **Goal of therapy: complete virologic suppression**
- **Use resistance testing to guide regimen selection**
- **Combine new drugs with other active agents**
 - Newer protease inhibitors
 - 2nd-generation NNRTI
 - Integrase inhibitors
 - CCR5 antagonists
- **Use at least three active drugs to maximize magnitude and durability of response**
 - NRTIs may have less potency than suggested by resistance test results

Genotypic assays for drug resistance

- Determine presence or absence of specific changes in HIV-1 genes (PR, RT, IN, ENV).
- Pre-suppose knowledge of critical mutations.
 - Drug resistance is *inferred* by presence of known mutations.
- Various methods and platforms
 - FDA-approved kits versus “home brew”
- Require an interpretative algorithm

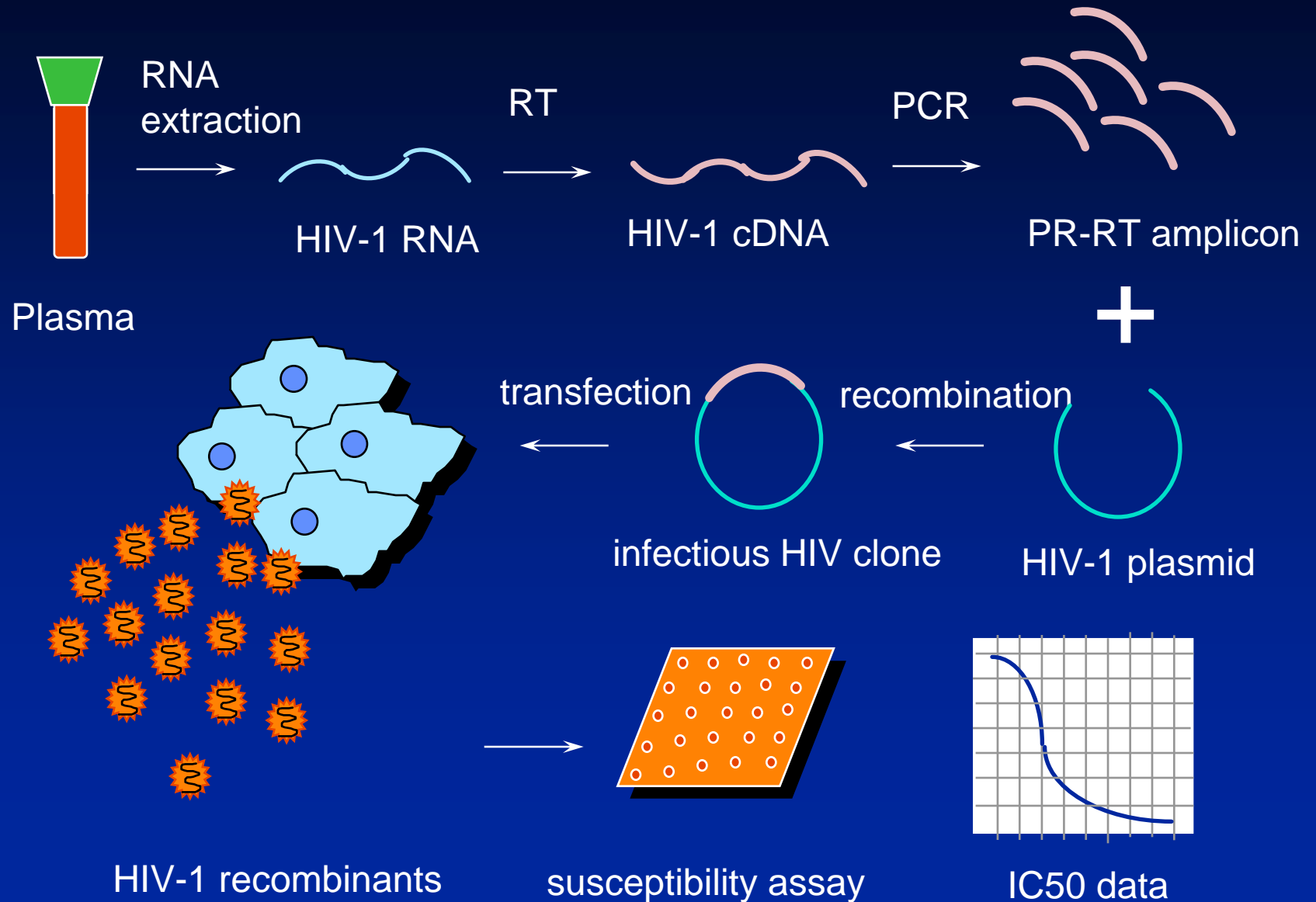
Phenotypic assays of drug resistance

- Measure the IC_{50} or IC_{90} for a drug by recombinant virus assay.
 - Antivirogram (Virco)
 - PhenoSense (ViroLogic)
 - Phenoscript (Viralliance)
- Changes >1.5- to 4-fold reliably detected.
- Clinically relevant “break points” have not been determined for all drugs.
 - Assays measure drug susceptibility
 - Definition of “resistance” requires clinical correlation

Virtual phenotype

- Interrogation and matching of the sample viral genotype to a large phenotype data base to identify identical or similar patterns of mutations
- Predicts likely phenotype based on average phenotype of matches
- Faster and less expensive than phenotyping
- “Cut-offs” for defining resistance determined as for phenotypes
- Requires current, relevant database that is constantly updated
- Rare or unusual genotypes difficult to interpret

HIV-1 drug resistance assays



Technical limitations of resistance assays

- Generally, plasma samples with >500-1000 copies/mL of HIV-1 RNA are needed to generate results.
- Species constituting $\geq 20\%$ of amplified product can usually be detected.
- False positive and negative results possible from carryover from other HIV-1 samples or from random polymerase errors during PCR.
- Need for industry-wide standardization and quality control.

Clinical situations in which resistance testing is recommended (IAS-USA)

- **Before initiation of antiretroviral therapy**
 - Primary (acute/early) infection
 - First evaluation of chronic HIV-1 infection
 - Treatment initiation for chronic HIV-1 infection
- **In antiretroviral-treated patients**
 - Treatment failure
- **Multiple regimen failure**
- **Pregnancy**

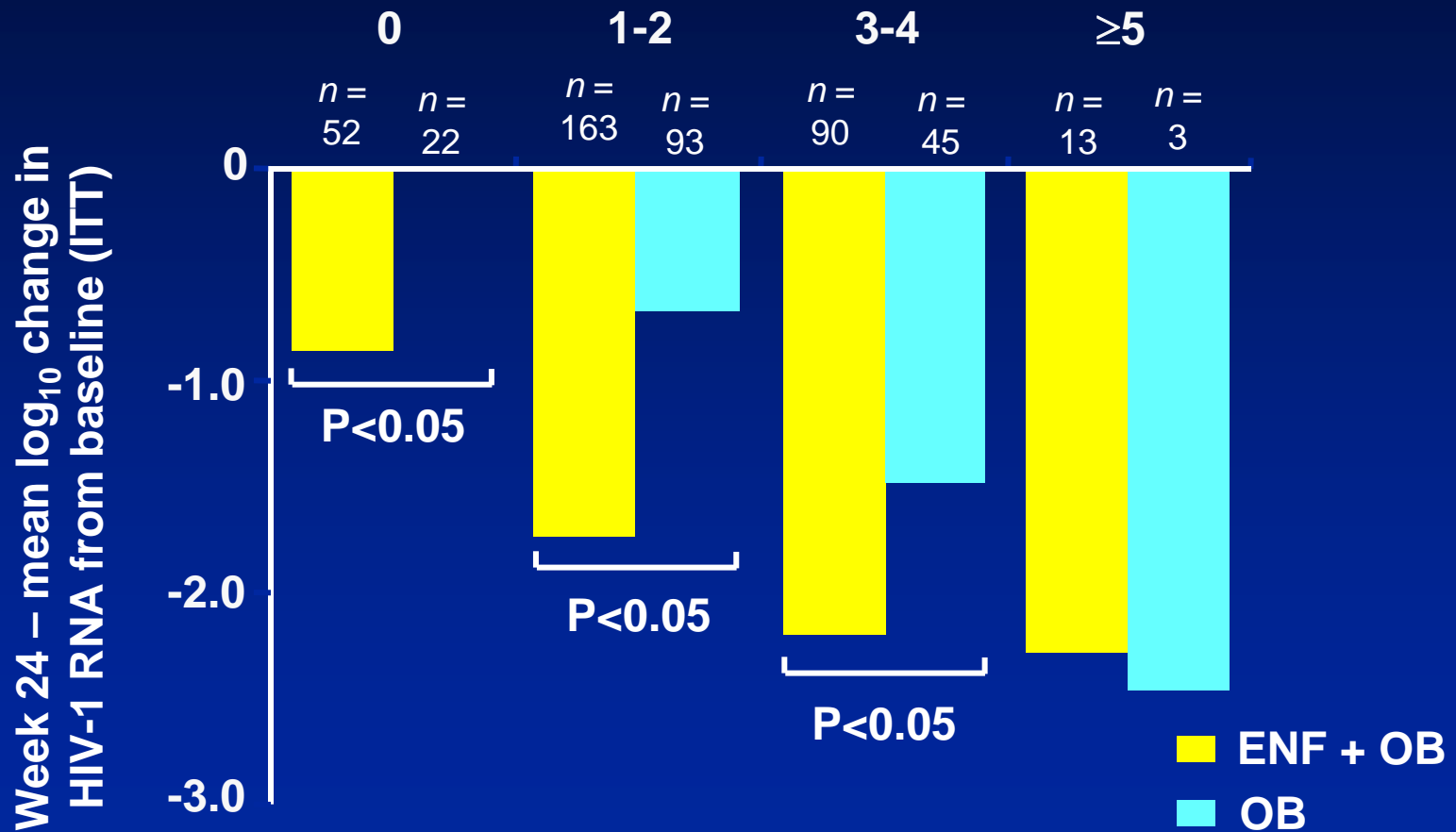
Hirsch et al *Clin Infect Dis* 2008;47:266-85.

Resources for interpreting HIV-1 drug resistance tests: Guides for the perplexed

- **IAS-USA**
 - www.iasusa.org/resistance_mutations/index.html
- **Stanford HIV-1 Drug Resistance Database**
 - <http://hivdb.stanford.edu>
- **Los Alamos National Laboratory HIV Sequence Database**
 - www.hiv.lanl.gov

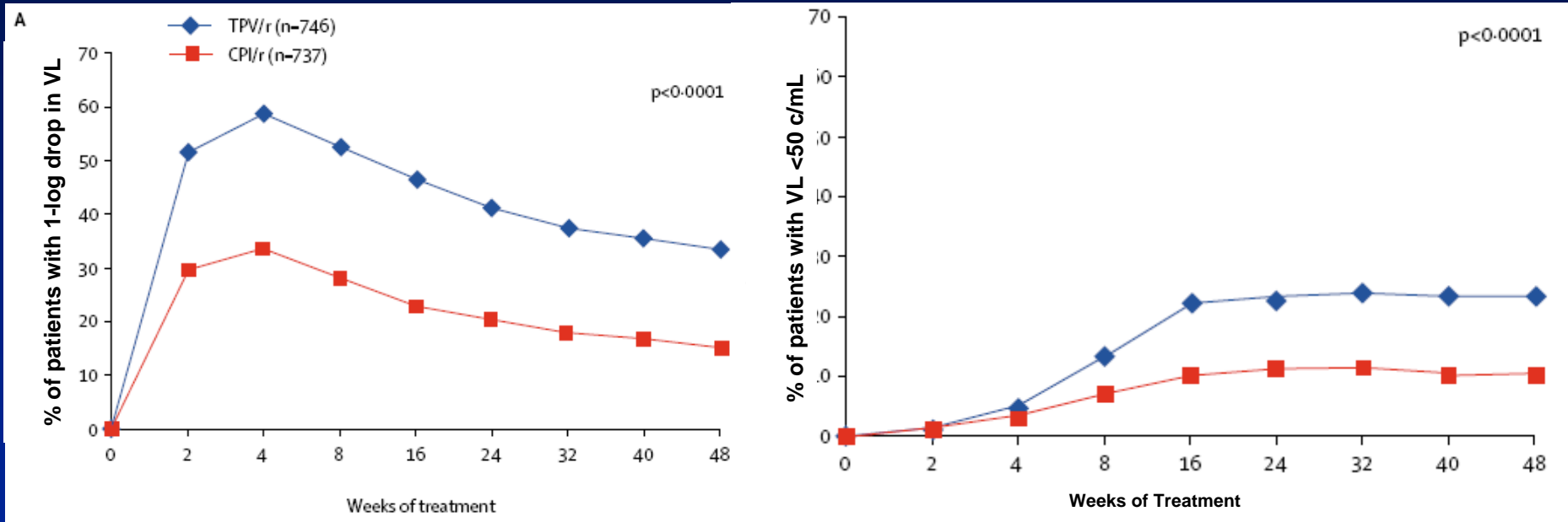
Activity of optimized background regimen and virologic response to enfuvirtide treatment

Response stratified by baseline genotypic sensitivity score (GSS)



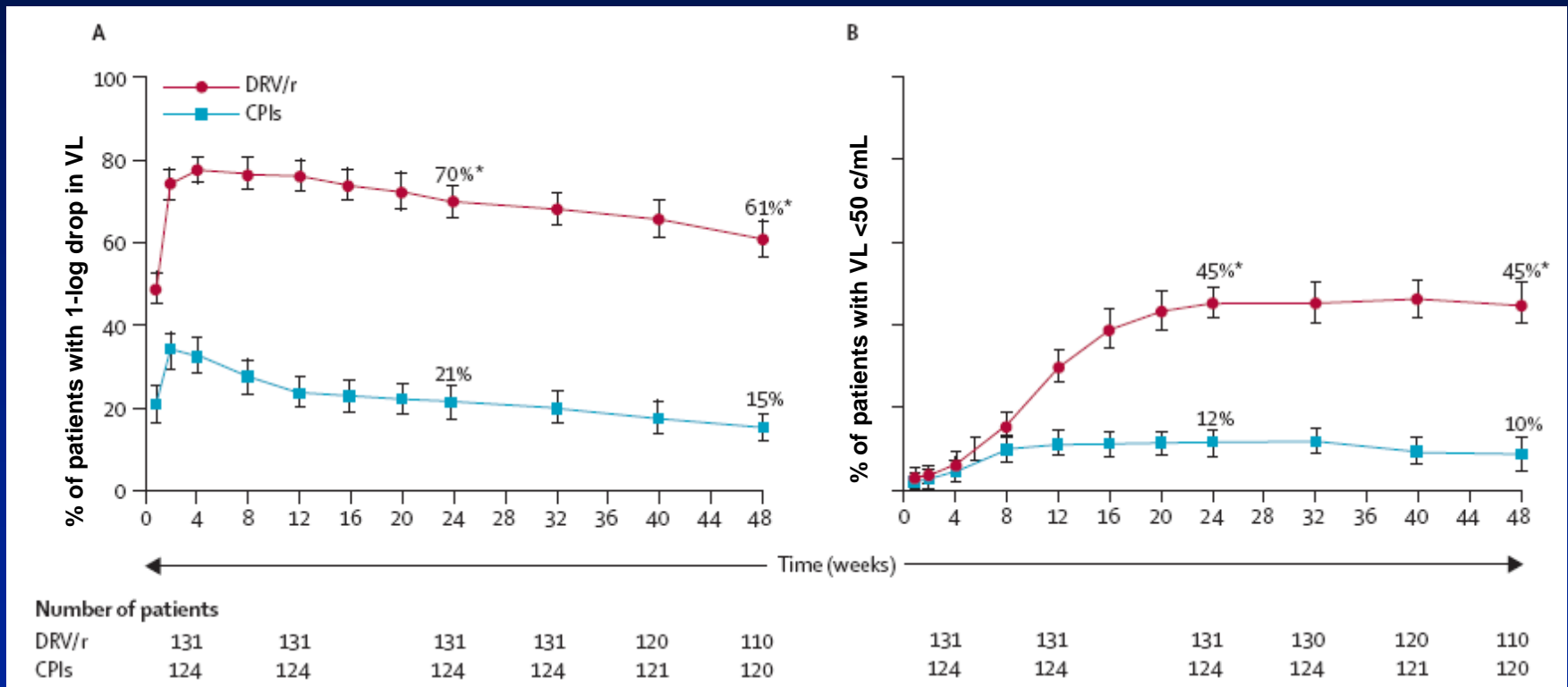
Based on Nelson et al JAIDS 2005; 40:404-12.

Tipranavir/ritonavir versus standard of care plus optimized background therapy



Hicks et al Lancet 2006; 368:466-375.

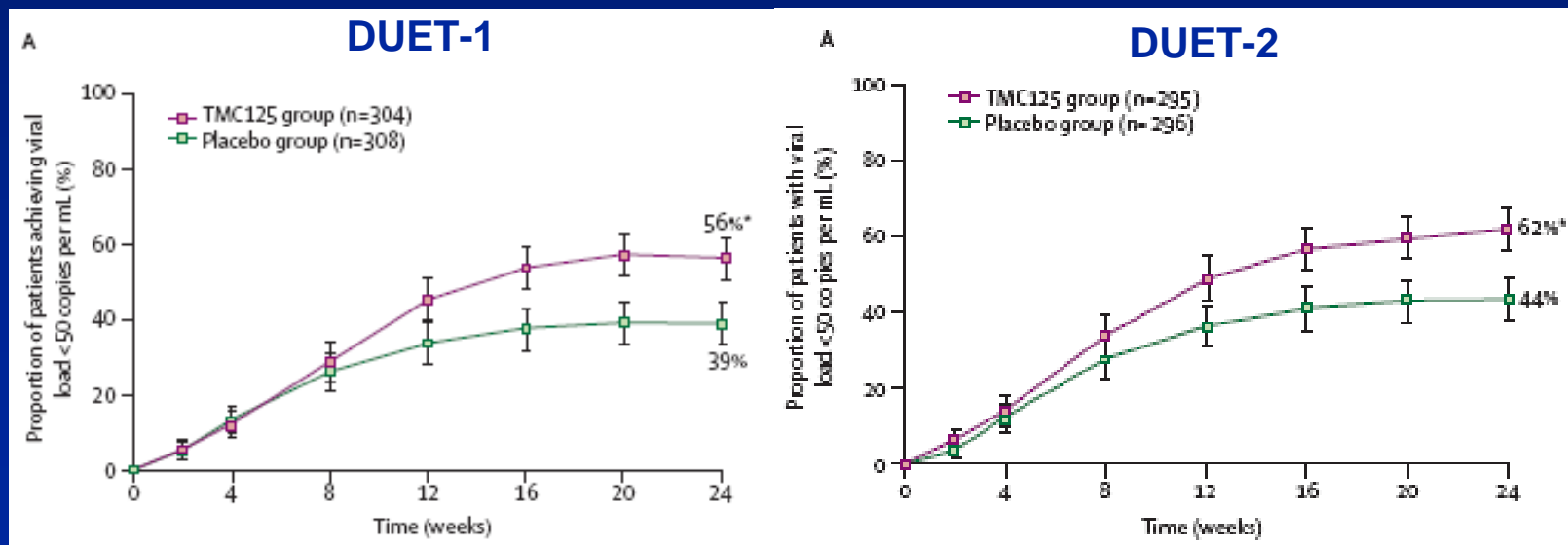
Darunavir/ritonavir versus standard of care plus optimized background therapy



Clotet et al Lancet 2007; 369:1169-78.

DUET-1 and -2: darunavir ± etravirine

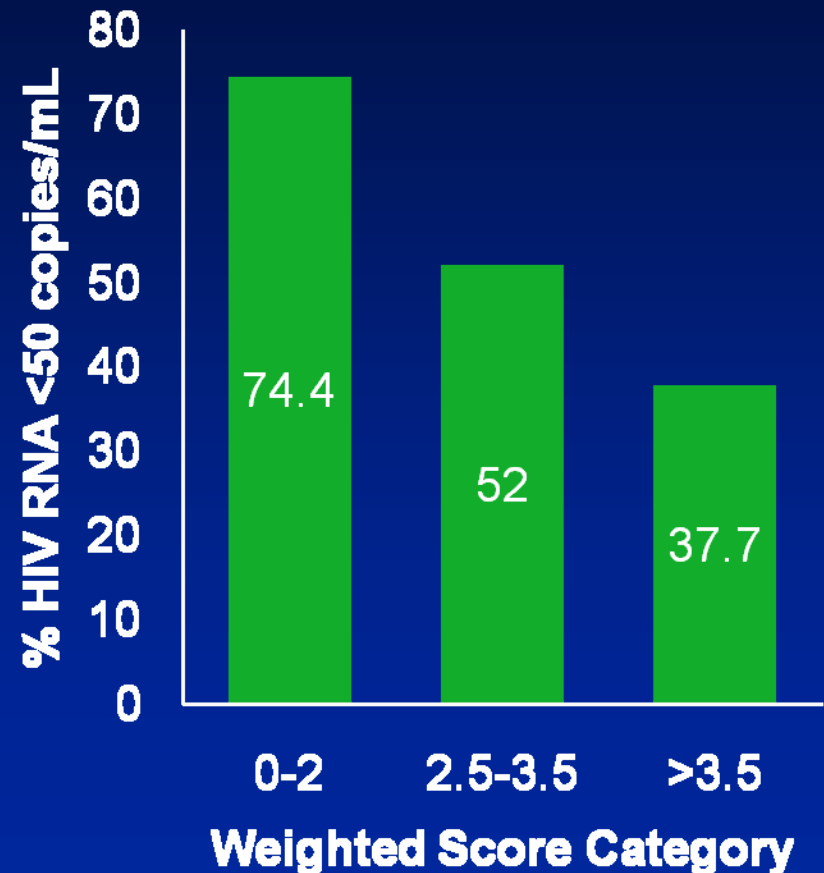
- Patients with triple class-resistant HIV-1 randomized to OBT+DRV/RTV ± etravirine (TMC125)
- Primary endpoint: % <50 c/mL at 24 weeks



Madruca et al Lancet 2007; 370:29-38
Lazzarin et al Lancet 2007; 370:39-48.

DUET-1 and -2: Predictors of ETR Response and Resistance at Failure

- ETR mutations (n=17) weighted based upon impact on response (weight factor)¹:
 - 3.0: Y181I/V
 - 2.5: L100I, K101P, Y181C, M230L
 - 1.5: V106I, V179F, E138A, G190S
 - 1.0: V90I, A98G, K101E/H, V179D/T, G190A
- Most common resistance mutations emerging at ETR failure in DUET trials: V179F/I and Y181C/I²



Adapted from Vingerhoets J, et al.

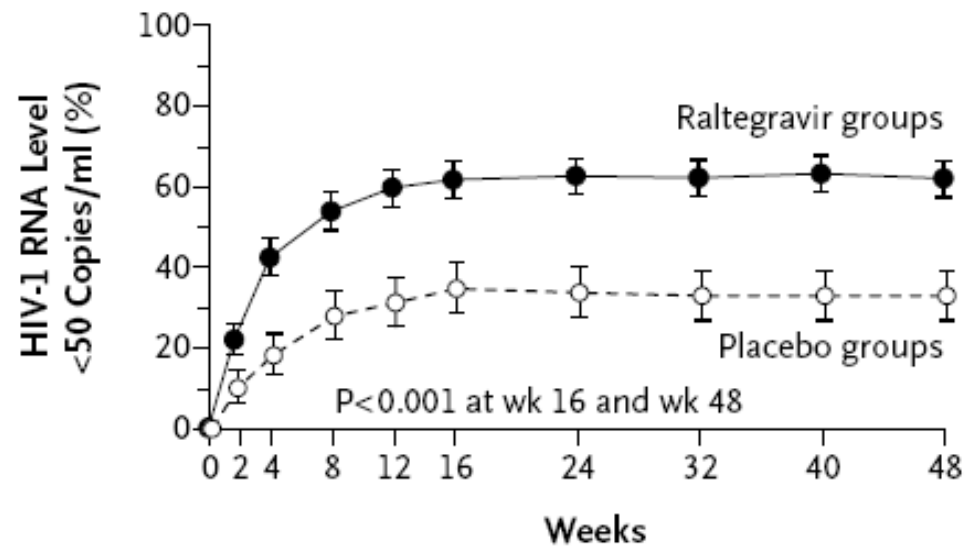
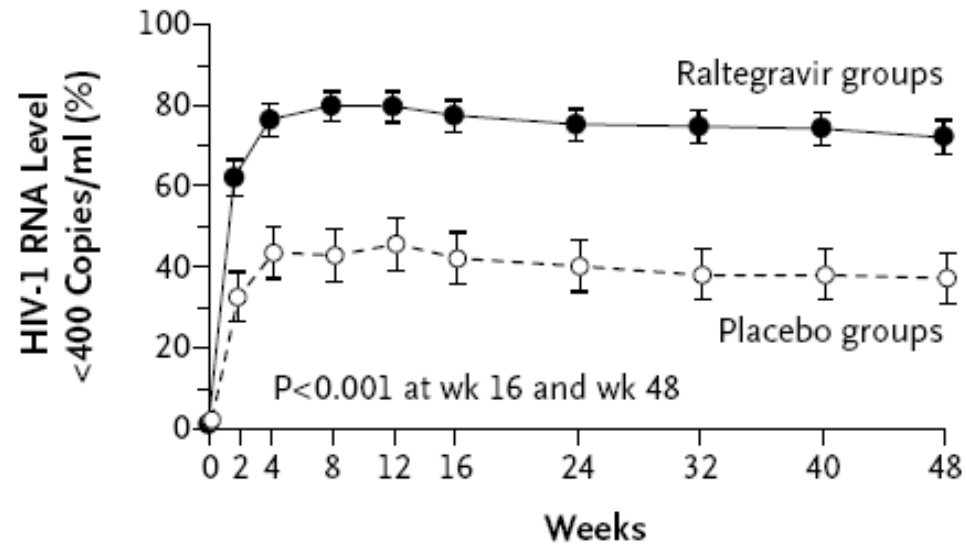
DUET-1 and -2: Any Grade AEs at Week 48

AEs Through Week 48, %	Etravirine (n = 599)	Placebo (n = 604)
AE of any grade	96	96
Rash* (all types)	19	11
Diarrhea	18	24
Nausea	15	13
Headache	11	13
Neurologic disorders	17	20
Psychiatric disorders	17	20
Hepatic AEs	7	6

*DUET-1 (ETR vs placebo): 22% vs 11%, $P = .0003$; DUET-2: 17% vs 11%, $P = .0577$

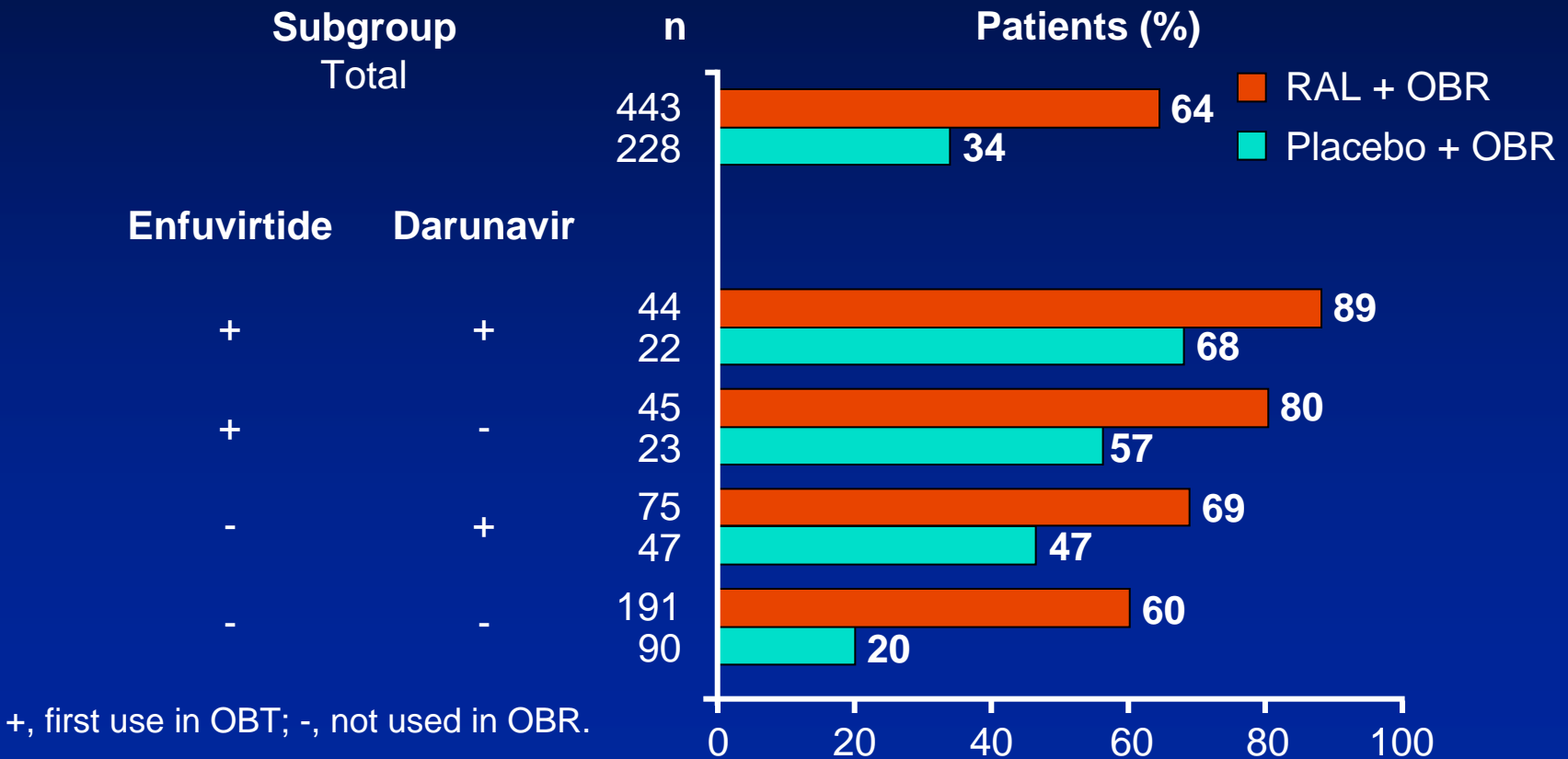
Haubrich R, et al. CROI 2008. Abstract 790.
Johnson M, et al. CROI 2008. Abstract 791.

Combined BENCHMRK data



Steigbigel et al
NEJM 2008

BENCHMARK-1 & -2: HIV-1 RNA < 50 c/mL at Week 48 by Select ARVs



Clinical and Laboratory AEs in BENCHMRK

Adverse Event	BENCHMRK-1		BENCHMRK-2		Combined BENCHMRK Studies	
	Raltegravir Group (N=232)	Placebo Group (N=118)	Raltegravir Group (N=230)	Placebo Group (N=119)	Raltegravir Groups (N=462)	Placebo Groups (N=237)
	<i>number of patients (percent)</i>					
Clinical adverse event						
≥1 Event	211 (90.9)	100 (84.7)	206 (89.6)	109 (91.6)	417 (90.3)	209 (88.2)
Drug-related event	113 (48.7)	64 (54.2)	140 (60.9)	67 (56.3)	253 (54.8)	131 (55.3)
Serious event	46 (19.8)	21 (17.8)	36 (15.7)	24 (20.2)	82 (17.7)	45 (19.0)
Serious drug-related event	7 (3.0)	1 (0.8)	4 (1.7)	6 (5.0)	11 (2.4)	7 (3.0)
Death†	3 (1.3)	3 (2.5)	7 (3.0)	3 (2.5)	10 (2.2)	6 (2.5)
Laboratory adverse event						
≥1 Event	62 (26.7)	25 (21.2)	56 (24.3)	30 (25.2)	118 (25.5)	55 (23.2)
Drug-related event	38 (16.4)	17 (14.4)	30 (13.0)	15 (12.6)	68 (14.7)	32 (13.5)
Serious event	2 (0.9)	0	1 (0.4)	1 (0.8)	3 (0.6)	1 (0.4)
Serious drug-related event	0	0	0	0	0	0
Death	0	0	0	0	0	0

Steigbigel et al NEJM 2008

Common drug-related AEs

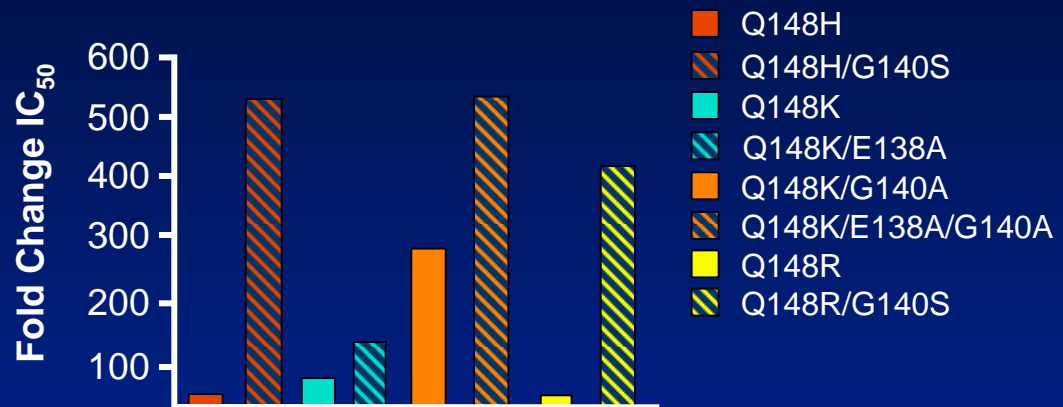
Event or Abnormality	BENCHMRK-1		BENCHMRK-2		Combined BENCHMRK Studies	
	Raltegravir Group (N=232)	Placebo Group (N=118)	Raltegravir Group (N=230)	Placebo Group (N=119)	Raltegravir Groups (N=462)	Placebo Groups (N=237)
Common drug-related clinical adverse event of moderate-to-severe intensity — no. (%)†						
Diarrhea	6 (2.6)	5 (4.2)	14 (6.1)	5 (4.2)	20 (4.3)	10 (4.2)
Nausea	2 (0.9)	3 (2.5)	9 (3.9)	4 (3.4)	11 (2.4)	7 (3.0)
Headache	5 (2.2)	3 (2.5)	7 (3.0)	0	12 (2.6)	3 (1.3)
Fatigue	1 (0.4)	0	6 (2.6)	2 (1.7)	7 (1.5)	2 (0.8)
Reaction at injection site	6 (2.6)	4 (3.4)	7 (3.0)	5 (4.2)	13 (2.8)	9 (3.8)
Pain at injection site	5 (2.2)	1 (0.8)	2 (0.9)	1 (0.8)	7 (1.5)	2 (0.8)

Steigbigel et al NEJM 2008

Signature and Secondary Mutations Affecting Susceptibility to RAL

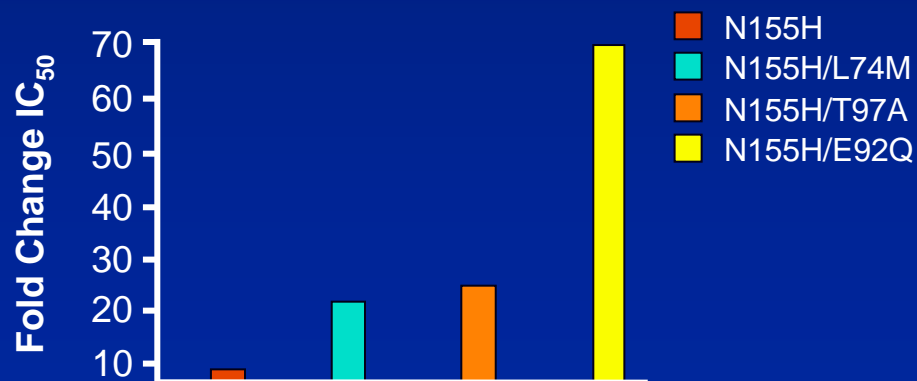
Q148 Pathway

Q148 key mutation emerges, associated with secondary mutations



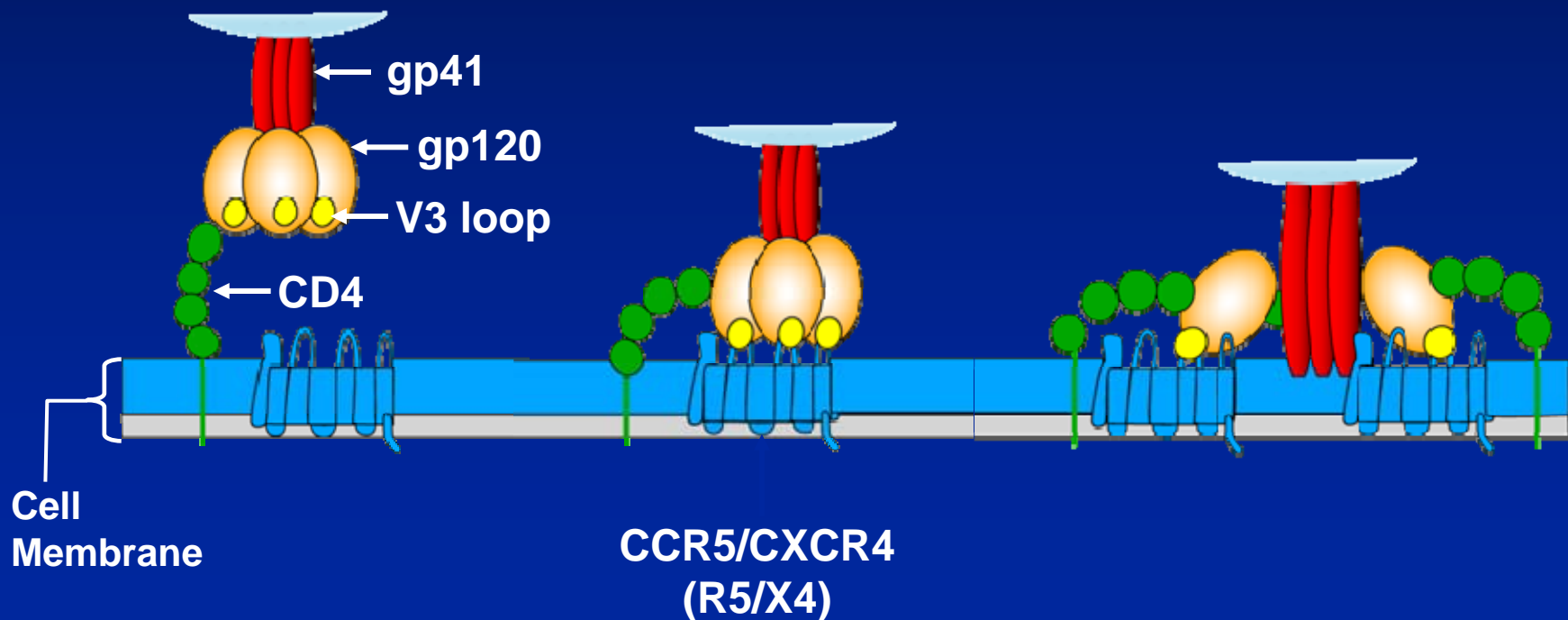
N155 Pathway

N155H key mutation emerges, associated with secondary mutations



Mechanism of HIV-1 entry

CD4 Binding → **Co-receptor Binding** → **Virus-Cell Fusion**

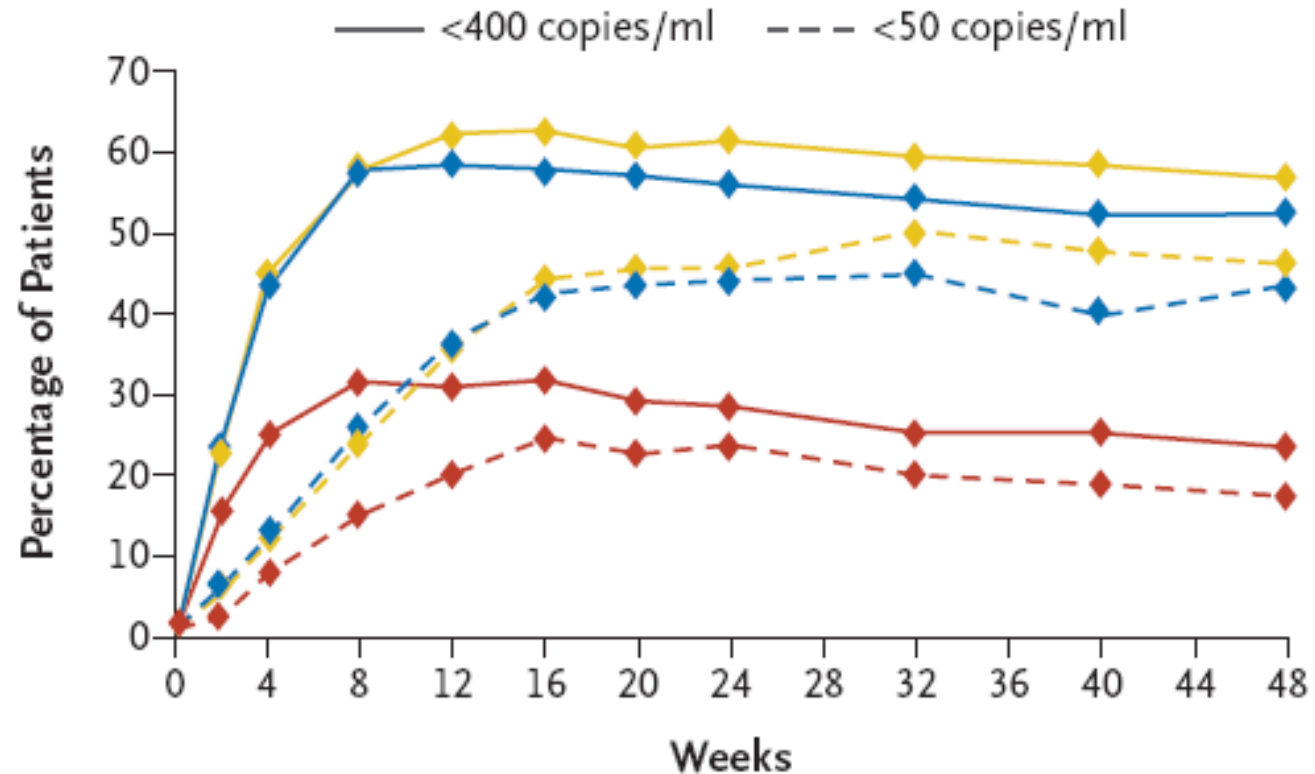


Adapted from Doms et al. Genes Dev. 2000;14:2677-2688.

MOTIVATE 1 & 2 Results

— Placebo plus OBT — Maraviroc once daily plus OBT — Maraviroc twice daily plus OBT

A HIV-1 RNA Suppression



MOTIVATE 1 & 2 Adverse Events

	Placebo (N= 209)	Maraviroc Once Daily (N= 414)	Maraviroc Twice Daily (N= 426)
Duration of treatment — patient-yr	111	300	309
Patients with ≥ 1 adverse event (of any grade) — no. of patients (%)			
All causes [†]	177 (85)	375 (91)	393 (92)
Related to treatment	94 (45)	205 (50)	219 (51)
Grade 2–4 adverse events (all causes) occurring in at least 5% of patients — no. of patients (%)			
Diarrhea	20 (10)	43 (10)	32 (8)
Fatigue	13 (6)	13 (3)	21 (4)
Fever [‡]	9 (4)	9 (2)	24 (6)
Headache [§]	12 (6)	22 (5)	9 (2)
Nausea	15 (7)	25 (6)	25 (6)
Upper respiratory tract infection	3 (1)	16 (4)	20 (5)
Death [¶]	2 (1)	6 (1)	9 (2)
Category C (AIDS-defining) adverse events — no.			
Total no. of category C events	19	32	23
No. of patients (%)	16 (8)	29 (7)	23 (5)
Aspartate aminotransferase elevation (maximum, all causes, without regard to baseline) — no. of patients/total no. of patients (%) ^{††}			
Grade 3 (>5 to $10 \times$ upper limit of normal)	6/207 (3)	12/408 (3)	14/421 (3)
Grade 4 ($>10 \times$ upper limit of normal)	0/207	4/408 (1)	6/421 (1)
Alanine aminotransferase elevation (maximum, all causes, without regard to baseline) — no. of patients/total no. of patients (%) ^{††}			
Grade 3 (>5 to $10 \times$ upper limit of normal)	6/207 (3)	16/408 (4)	7/421 (2)
Grade 4 ($>10 \times$ upper limit of normal)	1/207 (<1)	2/408 (<1)	4/421 (1)

Summary

- **New antiretroviral agents have greatly improved options for highly treatment-experienced patients**
- **It should be possible to achieve durable virologic suppression in most such patients**
- **Regimens should include 3 fully active drugs whenever possible, in order to avoid developing resistance to these newer drugs**