
HIV Resistance Testing Update

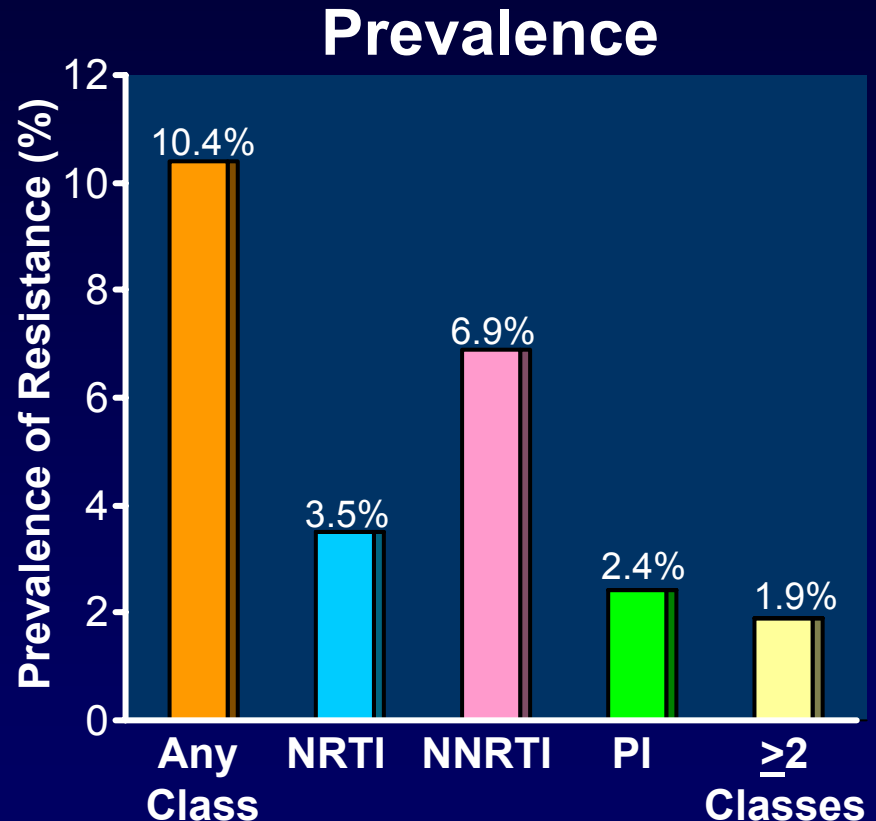
Mark Holodniy, MD, FACP

Stanford University

Resistance Epidemiology

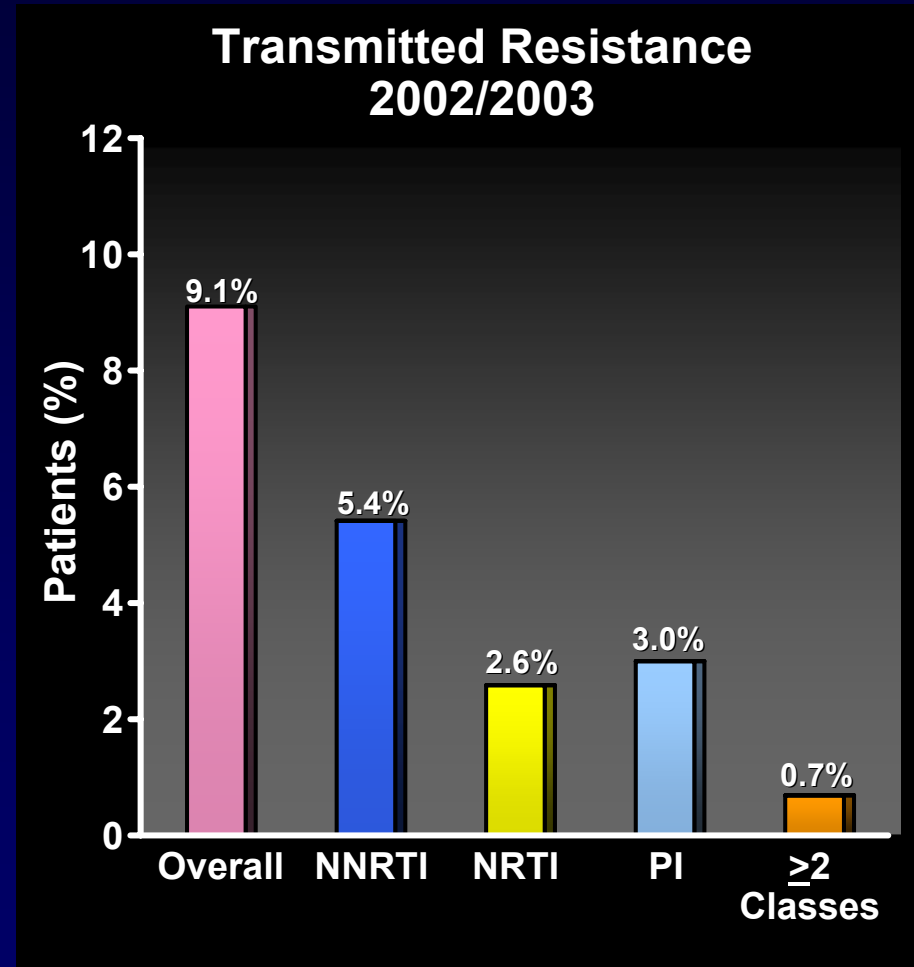
Primary Drug Resistance: March 2003-October 2006

- Data from 409 sites in 11 states
 - STD clinics (33.2%), counseling and testing (24.7%), private physicians (7.8%), hospitals (6.8%), other/unknown (33.5%)
 - Colorado, Illinois, Louisiana, Maryland, Massachusetts, Michigan, Mississippi, North Carolina, Seattle/King County, South Carolina, Virginia
- IAS-USA guidelines and Stanford online HIV Drug Resistance Database
- Prevalence data are consistent with earlier studies in the United States
 - Support the need for baseline resistance testing prior to the initiation of HAART

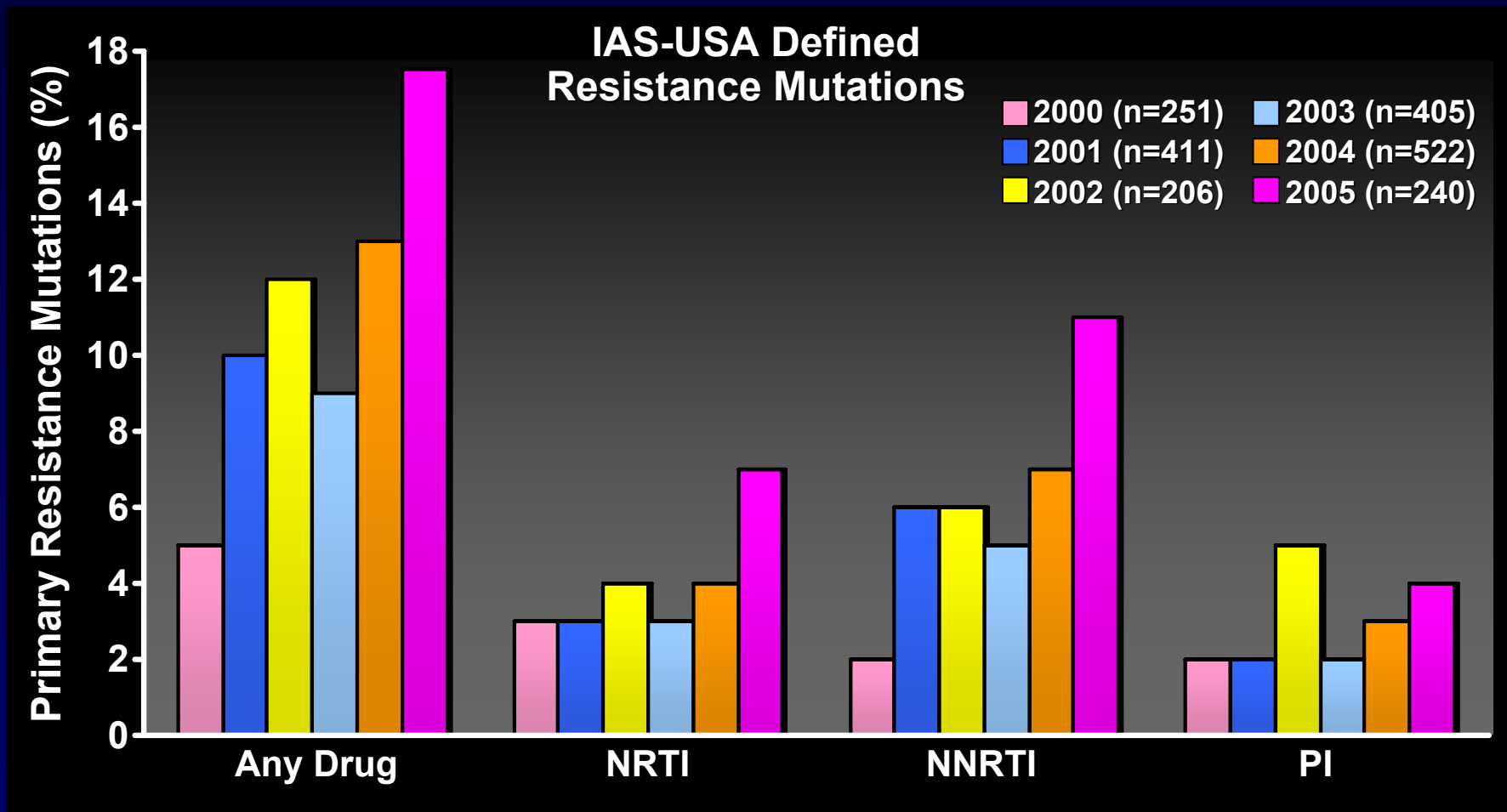


SPREAD Program Update: Transmitted Resistance 2002/2003

- Newly diagnosed patients from 17 European countries (n=1083)
- Baseline
 - HIV RNA: 4.83 log₁₀ copies/mL
 - Transmission category
 - MSM (44%), heterosexual (24%), high prevalence country (18%), IDU (8%), unknown (5%)
- Overall, 9.1% harbored drug resistance mutations
 - Less prevalent among non-clade B virus (6.3% vs 10.4%; *P*=0.03)
 - No difference between recently acquired infections versus infections of unknown duration (10.6% vs 8.7%)



PREPARE Study: Drug Resistance in US Treatment-Naïve Patients



UK CHIC Cohort: Risk of Developing ARV Resistance

- Analysis of those started on ≥ 3 ARVs
 - “Failure”: >400 c/mL after at least 4 mo Rx
- N = 10,603 patients
 - 58% 2 NRTI plus NNRTI
 - 10% 2 NRTI plus PI/r

“Extensive” drug resistance:
 ≥ 1 from drug from each category:
 (1) ZDV, D4T, 3TC, FTC
 (2) DDI, TDF, ABC
 (3) NVP, EFV
 (4) Any RTV-boosted PI

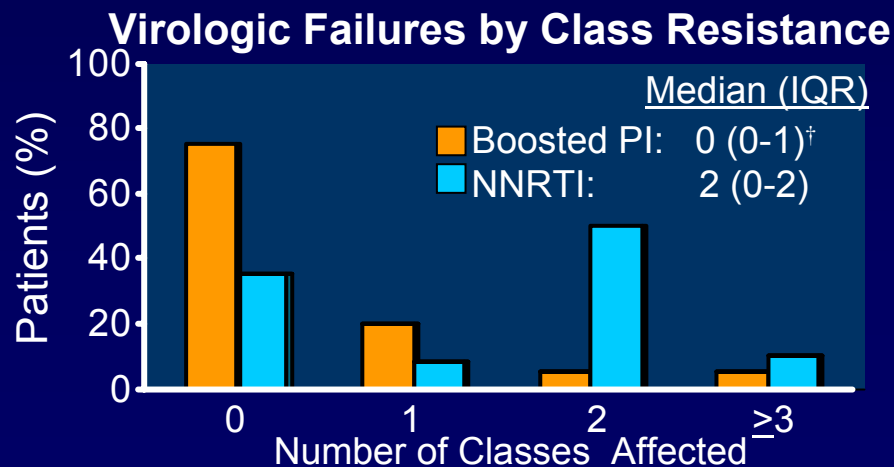
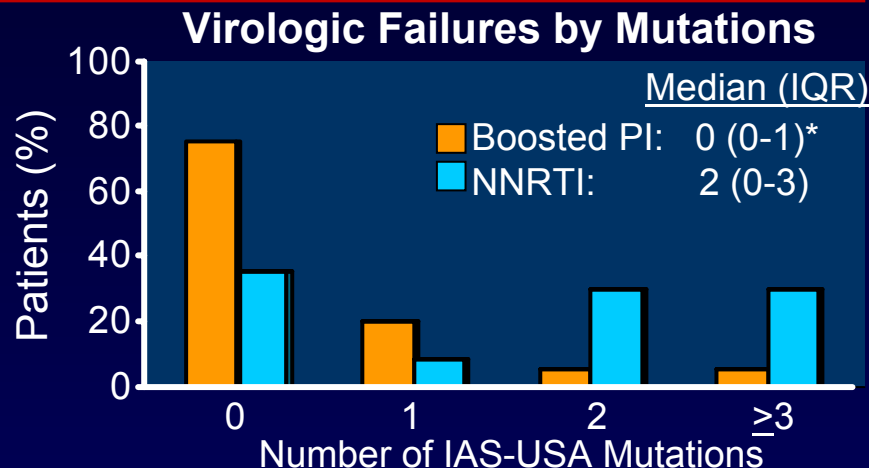
Years from start of ART	Resistance Present (%)				
	2	4	6	8	10
NRTIs	4%	9%	15%	21%	28%
PIs	2%	4%	8%	11%	16%
NNRTIs	13%	20%	26%	31%	35%
3-class resistance	2%	5%	9%	13%	20%
Extensive 3-class resistance	0%	1%	3%	5%	8%

Predictors of *greater* risk

- Lower CD4 at baseline, younger age, non-gay risk group

Swiss HIV Cohort Study: Resistance With First-Line Boosted PI- and NNRTI-Based Regimens

- **Patients initiating HAART (1999-2005)**
 - **Boosted PI (n=508)**
 - Lopinavir/ritonavir (75.5%)
 - Indinavir + RTV (10.8%)
 - Atazanavir + RTV (8.9%)
 - **NNRTI (n=805)**
 - Efavirenz (91.4%)
 - >94% received lamivudine or emtricitabine-based NRTI combination
- **69 virologic failures**
 - Boosted PI: 4.6%
 - HAART
 - NNRTI: 5.6%
- **Resistance test at failure: 84%**
- **Conclusion**
 - Both regimens have similar potency
 - In virologic failure, boosted PI regimens lead to less resistance



* $P=0.0048$ and † $P=0.0016$ (Mann-Whitney)

von Wyl V, et al. 14th CROI. Los Angeles, 2007. Abstract 667.

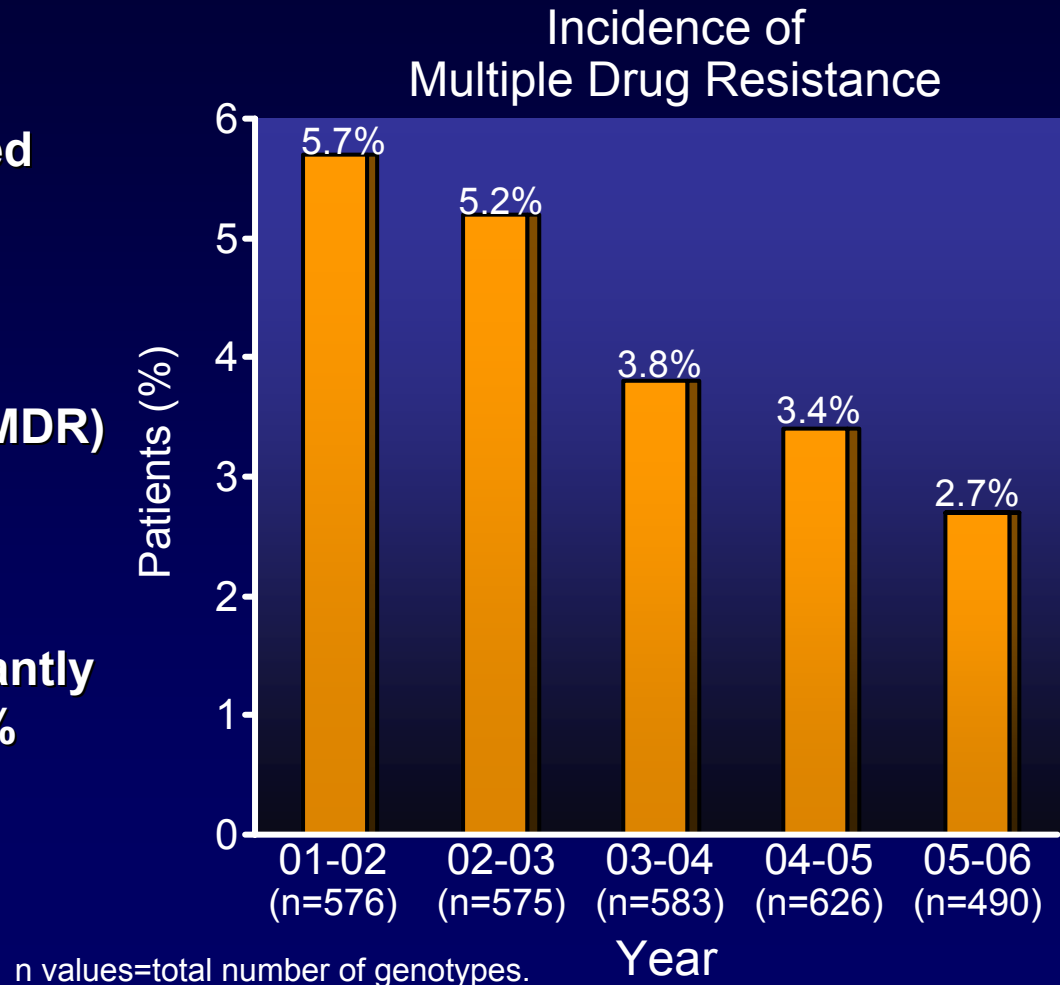
Declining Incidence of Multidrug Resistance in Portugal (2001-2006)

- Portuguese Resistance Database

- 2373 treatment-experienced patients
- >1 genotype between July 2001 and March 2006
- Multiple drug resistance (MDR)
 - >2 drug classes

- From 2001 to 2006

- Incidence of MDR significantly declined from 5.7% to 2.7% ($P=0.016$)
 - May reflect the increased efficacy of HAART



Decline in Resistance Testing (2000-2006)

- **Madrid cohort**
 - Patients initiating antiretroviral therapy
- **From 2000-2006, there was a significant decline in the proportion of patients:**
 - Meeting criteria for resistance testing (HIV RNA >1000 copies/mL) ($P<0.0001$)
 - With therapeutic failure (sustained HIV RNA >1000 copies/mL after 6 months of HAART) ($P<0.0001$)
- **Declines may be due to greater efficacy of new regimens**

	Incidence (%)	
	HIV RNA >1000 Copies/mL	First Therapeutic Failures
2000 (n=1211)	14.4	100
2001 (n=1201)	10.7	61.2
2002 (n=1183)	11.1	57.3
2003 (n=1113)	10.2	56.6
2004 (n=1375)	7.8	52.3
2005 (n=1376)	4.6	38.1
2006 (n=1204)	3.4	43.9

n values=total number of patients treated.

Resistance Assays and New Technology

Standard Versus Sensitive Genotyping Methods: Definitions

- **Standard genotyping**
 - Sequencing the total virus population in plasma
- **Allele-specific PCR**
 - Use of specific primers to detect the presence of specific mutant sequences in the viral population
 - More sensitive than standard genotyping
- **Single-genome sequencing**
 - Sequencing individual viral genomes
 - Can detect the presence of minor variants but sensitivity depends on number of genomes sequenced

Real-Time Allele-Specific PCR: Incidence of Transmitted Resistance May Be Higher

Mutation	New Mutations Detected in Wild Type (n=205)	Resistant HIV (n=302)	
		New Mutations Detected (%)	Increase in Mutations (%)
NRTI			
M41L	4.5	10	70
K70R	5.0	6	60
Y181C	1.5	6	260
M184V	1.5	2	23
T215Y	1.0	3	20
T215F	2.0	5	340
NNRTI			
K103N	4	1	5
PI			
L90M	1.5	3	25

Wild-type samples (US) taken from 205 newly diagnosed, treatment-naïve patients: 2003-2005.

Resistant HIV samples (US and Canada) taken from 302 patients with ≥ 1 drug resistance mutation: 1998-2004.

Non-Detected Mutations Can Impact First-Line Response

- Retrospective analysis of treatment-naïve patients receiving efavirenz + abacavir/lamivudine (n=138)
 - Controls (HIV RNA <50 copies/mL)
 - Virologic failure (HIV RNA >50 copies/mL) by 48 weeks
- Highly sensitive real-time PCR
 - Revealed >2 times as many mutations in previously treatment-naïve patients
- All patients with K103N or Y181C (NNRTI), or M184V (NRTI) mutations experienced virologic failure regardless of whether detected by standard genotype or real-time PCR

	Standard Genotype	Real-Time PCR	Total (n=138)
K103N	2/138	4/136	6
Y181C	1/138	1/138	2
M184V	1/138	3/137	4
Total	4	8	12

Value of Proviral Resistance Testing

- 95 HAART experienced patients on treatment, had both plasma RNA and PBMC DNA fractions analyzed
- 27% showed same number and type of mutations in both compartments, 73% were discordant samples (DS)
- 51% > # mutations in plasma, 37% > # mutations in PBMC
- Treatment interruption in 5 patients resulted in decline of mutations in plasma, but not PBMC
- Analysis of mutations in PBMC DNA due to persistence may be a useful adjunct in genotypic resistance testing

In Vitro Drug Susceptibility Cut-Off Values for PIs

	Clinical Cut-Off		Biological Cut-Off
	1 (lower limit)	2 (upper limit)	
Amprenavir + ritonavir	1.2	9.6	--
Atazanavir	--	--	2.4
Darunavir + ritonavir	3.4	96.9	--
Indinavir + ritonavir	10.6	40.1	--
Lopinavir/ritonavir	9.7	56.1	--
Nelfinavir	1.3	7.3	--
Saquinavir + ritonavir	7.1	26.5	--
Tipranavir + ritonavir	1.2	5.4	--

vircoTYPE clinical cut-offs: predicted fold-change by multiple linear regression to 56,017 sequences submitted for routine resistance analysis from 2004-2005.

Clinical cut-off

Maximal response to PI: fold-change \leq clinical cut-off 1.

Reduced response to PI: fold-change between clinical cut-off values

Minimal response to PI: fold-change $>$ clinical cut-off 2.

Biological cut-off

PI susceptible: fold-change \leq biological clinical cut-off

PI resistant: fold-change $>$ biological cut-off.

RESIST Trials: Defining Lower and Upper Phenotypic Clinical Cut-Off Values

	563 RESIST Samples (%)				
	LCCO	UCCO	Susceptible	Intermediate	Resistant
Tipranavir + ritonavir	2.0	8.0	53	36	12
Saquinavir + ritonavir	2.3	12.0	17	27	56
Amprenavir + ritonavir	4.0	11.0	26	25	49
Lopinavir/ritonavir	9.0	55.0	18	27	55

LCCO: lower clinical cut-off (baseline fold-change where HIV RNA response first begins to decline relative to wild type.

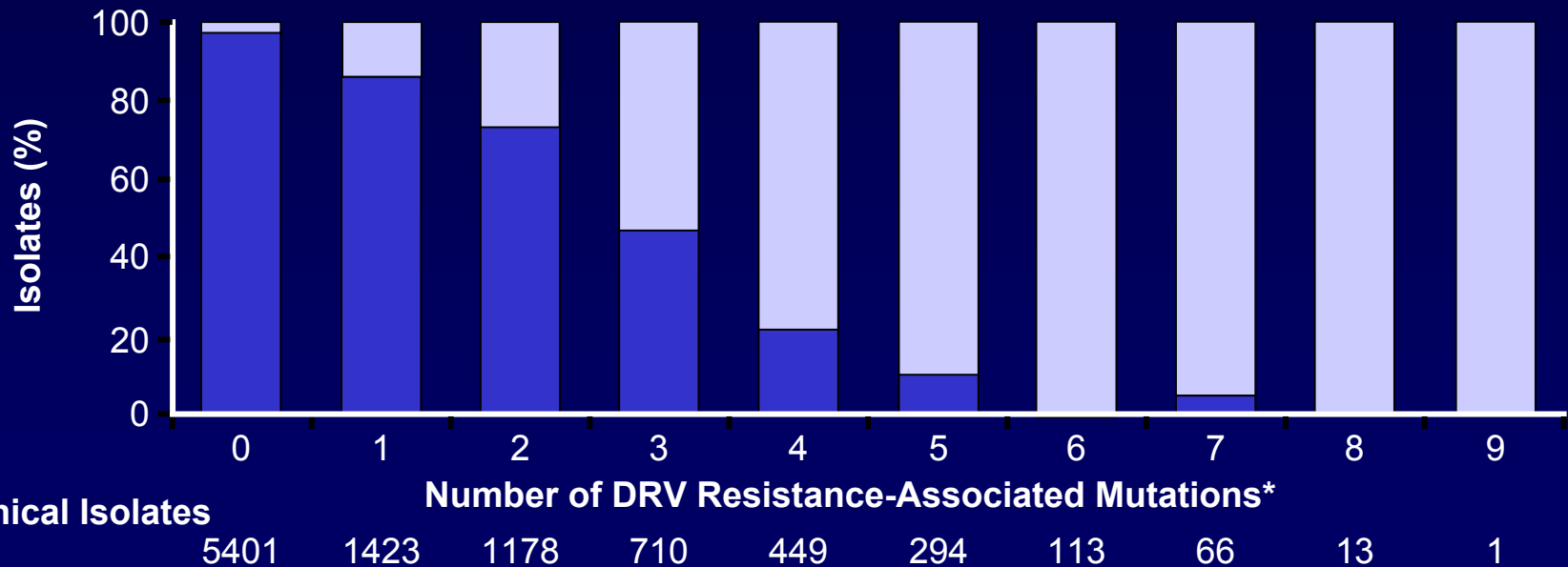
UCCO: upper clinical cut-off (fold-change above which the attributable HIV RNA response $<0.3 \log_{10}$ copies/mL.

Predictive Value of DRV Mutations Confirmed in Clinical Isolates

- Panel of 9668 HIV-1 clinical isolates submitted for routine resistance testing used to validate predictive value of DRV resistance-associated mutations*

DRV Susceptibility

FC \leq 10 FC $>$ 10



*V11I, V32I, L33F, I47V, I50V, I54L, I54M, G73S, L76V, I84V, and L89V

DRV/r Susceptibility Category by Susceptibility to APV/r, TPV/r, LPV/r

		N	DRV/r S	DRV/r PS	DRV/r R
APV/r	S	997	100%	0%	0%
	PS	525	99.8%	0.2%	0%
	R	1340	39%	50%	12%
TPV/r	S	1451	89%	8.9%	1.8%
	PS	793	66%	30%	3.7%
	R	618	35%	49%	16%
LPV/r	S	945	99.7%	0.3%	0%
	PS	720	85%	15%	0.3%
	R	1197	41%	47%	13%

- N=2682 samples with \geq major PI mutation since May 2006
- High level Cross Resistance to DRV infrequent (<17%) - due to lower IC50 / greater potency of DRV and ~2 fold higher free drug levels
- Note: 35% of DRV/r still at least partially S to TPV/r

Cutoffs: Suscept/Res	Lower CCO	Upper CCO
DRV/r	10	90
APV/r	4	11
TPV/r	2	8
LPV/r	9	65

TPV and DRV Mutations and Phenotypic Cut-offs

Similarities and Differences in Key Mutations

TPV	10V		13V	20M/R/V		33F	35 G	36I	43T	46L
DRV		11I			32I	33F				

TPV	47V		54A/M/ V	58E	69K		74P		82L/ T	83D	84V	
DRV	47V	50V	54L/M			73S		76 V			84V	89V

Assay/ Cutoff	Monogram: FC for Reduced Activity		Monogram: FC for No Response		Virco: FC for Maximal Response		Virco: FC for Minimal Response	
TPV ^[1,2]	≥ 2		≥ 8		< 1.2		≥ 5.4	
DRV ^[3,4]	≥ 10		≥ 40		< 3.4		≥ 96.9	

1. Oakley E, et al. Resistance Wkshp, 2006. Abstract 71. 2. Bacheler L, et al. Euro Resistance Wkshp, 2006. Abstract 40. 3. De Meyer S, et al. Resistance Wkshp, 2006. Abstract 73. 4. Winters B, et al. Resistance Wkshp, 2006. Abstract 160.

NRTI Mutations: Correlation With Replicative Capacity and Reduced Drug Susceptibility

Number of primary NRTI mutations	Replicative Capacity	Samples With Reduced Susceptibility to ≥ 1 Drug (%)		
		NRTI	NNRTI	PI
0 (n=14,363)	97.8	3.4	33.6	12.6
1 (n=4092)	68.9	93.9	53.8	33.0
2 (n=1559)	61.5	94.2	66.6	48.9
3 to 4 (n=4189)	54.3	99.4	66.6	73.3
5 to 6 (n=2516)	46.6	100	75.1	84.4
7 to 8 (n=133)	43.9	100	75.2	82.0

Samples collected analyzed between January 2003 and December 2005 (n=35,222).

Data from emtricitabine, tipranavir, and zalcitabine not available.

Reduced susceptibility: fold-change in IC_{50} above the PhenoSense GT specific drug cut-off value.

Selected Clinical Trial Resistance Results

Study 934: 96-Week Resistance Results

- Resistance analysis excludes patients with baseline NNRTI resistance mutations
 - 11 in each group
- At week 96, patients in the emtricitabine + tenofovir DF group had:
 - Significantly less M184V/I than those in the zidovudine/lamivudine group
 - No emergence of K65R

	Number of Patients	
	FTC + TDF (n=244)	ZDV/3TC (n=243)
Genotypes performed	14*	29
Wild types	4	7
Any resistance	10	20
Any efavirenz	10	18
Any M184V/I	2 [†]	9
Any TAMs	0	0
K65R	0	0

*P=0.017; †P=0.036 versus zidovudine/lamivudine.

KLEAN Study: 48-Week Resistance Results

	Number of Patients	
	Lopinavir/r	Fosamprenavir + RTV
Virologic failure (HIV RNA >400 copies/mL)	24 (5%)	16 (4%)
Genotype assays	21	14
No treatment-emergent mutations	14	10
TAMs (M41M/L)	1	0
Lamivudine (M184I, M184V, M184M/V)	4	3
NNRTI (V106V/A)	2	0
PI (I54I/L, K20K/R, I62I/V)	2	2

ACTG 5142: Resistance Mutations at Failure

Patient Samples, n	LPV + NRTIs	EFV + NRTIs	LPV + EFV
Observed virologic failure	94	60	73
Genotypic assays*	52	33	39
Any PI mutations	20	13	18
Major PI mutations†	0	0	2
NRTI mutations	8	11‡	4
NNRTI mutations	2§	16	27¶
Mutations in 2 classes	2§	10‡	2

*Some genotype assays pending.

†30N, 32I, 33F, 46I, 47A/V, 48V, 50L/V, 82A/F/L/S/T, 84V, 90M.

‡ $P < .05$ vs LPV/EFV.

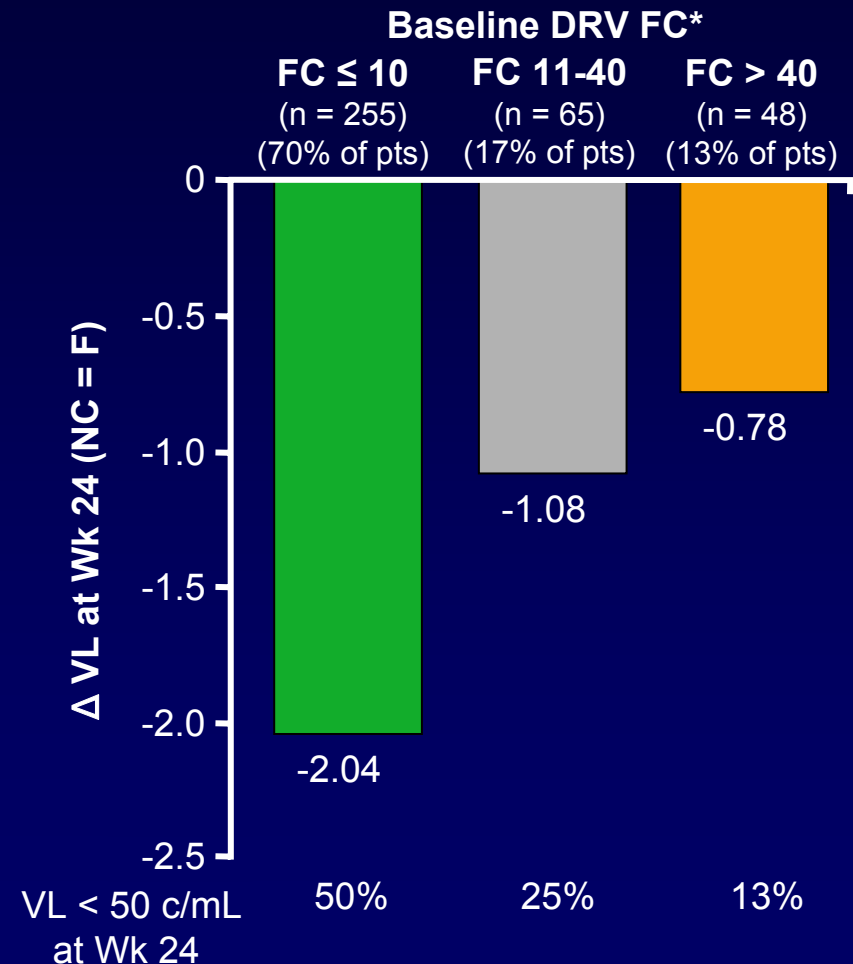
§ $P < .05$ vs EFV.

¶ $P < .05$ vs LPV.

POWER 1, 2, 3: Effect of Baseline Resistance on Response to DRV/r

- Baseline fold change was strongest predictor of Week 24 response by unadjusted analysis
- 11 mutations associated with reduced response
 - V11I, V32I, L33F, I47V, I50V, I54L, I54M, G73S, L76V, I84V, and L89V
 - 73% of pts had ≤ 2 of these mutations

No. of BL mutations (n)	0	1	2	3	≥ 4
% with VL < 50, Wk 24	64	50	42	22	10



IMPACT: Resistance After Treatment With ATV-Based Regimen

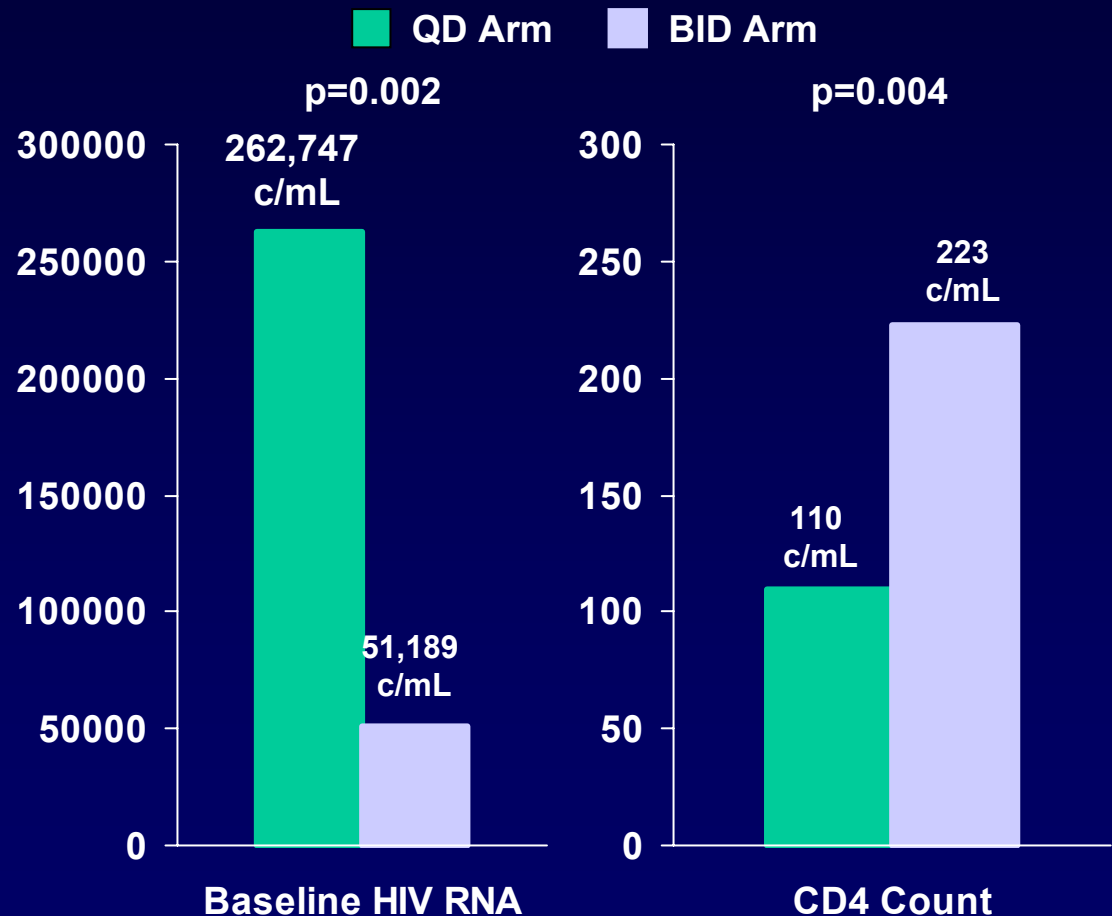
- First interim analysis of I50L prevalence in patients failing ATV-containing regimens
 - Overall prevalence: 9.4%
 - No primary PI mutations (including I50L) on failure of initial ATV/RTV

Patients Failing ATV and ATV/RTV-Based Regimens	With I50L, n (%) (n = 12)	Without I50L, n (%) (n = 116)
Failed on ATV or ATV/RTV as Initial PI		
ATV	0 (0)	3 (3)
ATV/RTV	0 (0)	9 (8)
Failed on ATV/RTV in Later Regimen		
Prior regimens		
Boosted PI	7 (58)	88 (76)
Unboosted PI	5 (42)	16 (14)

The DAUFIN Study

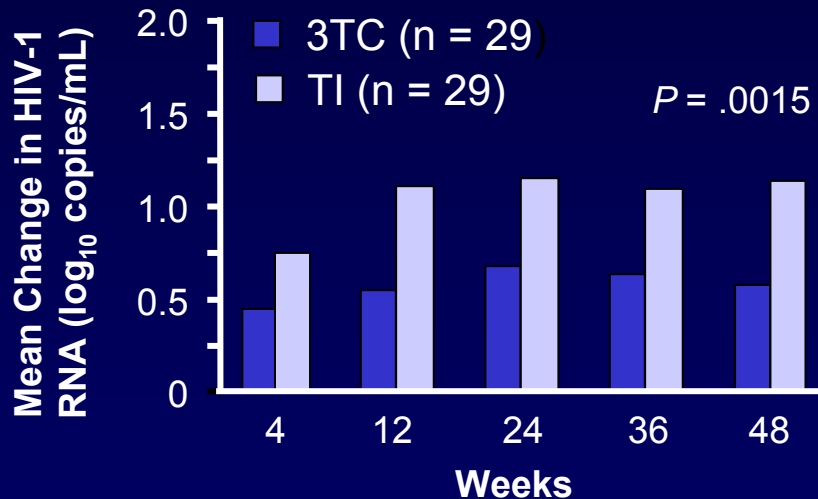
- NVP 200 BID/ZDV/3TC BID vs. NVP 400/TDF/3TC QD
- Trial terminated early due early virologic failures (N=71)
- 9/36 subjects on QD NVP arm had virologic failure
- Mutational patterns: K65R in 6/9 virologic failures with 2 class mutations
- The higher virologic failure rate was not associated with lower NVP troughs

Subset of Virologic Failures

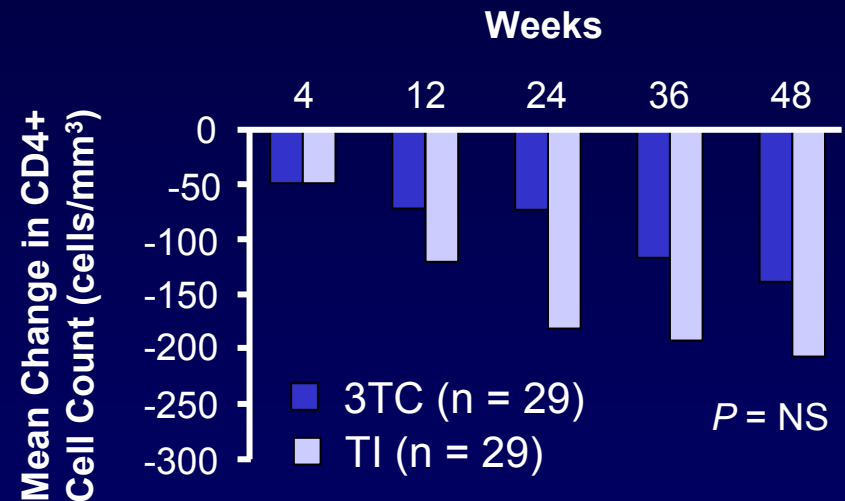


3TC Alone vs Treatment Interruption in Patients Failing 3TC-Based Treatment

Mean VL Increase (ITT)



Mean CD4+ Decrease (ITT)



- In contrast to treatment interruption arm, 3TC alone resulted in
 - Smaller recovery in replication capacity
 - No further selection of resistance mutations
- Reduced failure predicted only by BL CD4 >500, nadir > 300*

Discontinuing 3TC in Virologically Suppressed Patients With M184V

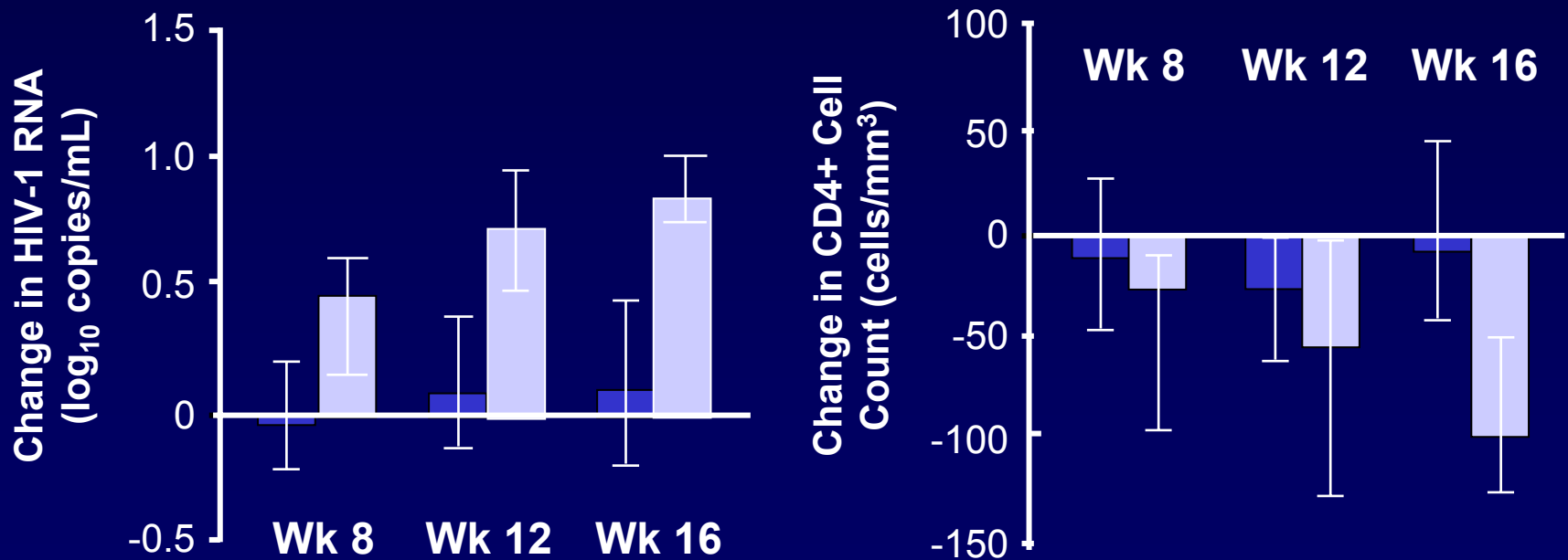
- **Randomized pilot study of continued vs discontinued 3TC in patients with viral suppression and M184V/I**
 - HIV-positive, HBV-negative adults (N = 21)
 - VL < 50 copies/mL on therapy including 3TC with ≥ 3 other drugs, ≥ 2 of which were active
 - Previous detection of M184V/I
- **VL, CD4+ count, safety, and quality of life assessed through 48 weeks**

Number of Patients With VL < 50 copies/mL		
	Continue 3TC (n = 8)	Discontinue 3TC (n = 13)
Week 12	7/7	11/12
Week 24	8/8	13/13
Week 48	6/7	11/11

- **No virologic failures occurred by Week 48**
- **Discontinuing 3TC may be safe in presence of ≥ 2 active drugs when VL < 50 copies/mL**

NRTIs Retain Activity Even With Drug Resistance

- Discontinue PIs, continue NRTIs (n = 15)
- Discontinue NRTIs, continue PIs (n = 5)



Studies of Enfuvirtide Resistance and Effects of Discontinuation

- Low genetic barrier to ENF resistance^[1]
 - Resistance to ENF present at earliest time of virologic failure
 - Failure often associated with rapid viral rebound to baseline
- Conflicting data on benefit of continued ENF therapy
 - ENF stopped in 22 patients with detectable viremia on ENF^[2]
 - Minimal viral rebound despite ↑ fitness, return of ENF susceptibility
 - ENF added to failing regimen (n = 54)^[3]
 - V38A/E mutation detected most frequently, in approximately 28%
 - Associated with CD4+ count increase despite virologic failure

1. Beatty G, et al. CROI 2005. Abstract 581. 2. Deeks S, et al. CROI 2005. Abstract 680.

3. Aquaro S, et al. CROI 2006. Abstract 596.

New Drugs and Resistance

Effect of Baseline Resistance on Response to Etravirine

Number of Baseline NNRTI Mutations (Number of Patients)	Viral Load Reduction at Week 24 (log ₁₀ copies/mL)
0 (n = 15)	-1.82
1 (n = 18)	-1.65
2 (n = 17)	-1.00
≥ 3 (n = 29)	-0.66

- Each of the following mutations, always in combination with up to 4 other mutations, was associated with a mean FC > 10
 - K101P, V179E, V179F, Y181I, Y181V, G190S, M230L
 - For V179E, V179F, G190S, or M230L, the additional mutations always included Y181C when the FC > 10
- No single NNRTI drug resistance mutation was associated with FC > 10
 - Required multiple mutations (≥ 4)

Etravirine Response at 24 Weeks: Impact of Baseline K103N and Y181C

	All Patients	All without K103N	All with K103N	All without Y181C	All with Y181C
n	66	43	23	43	23
Mean change in log copies/mL	-1.41	-1.40	-1.43	-1.,70	-0.86
Mean change in log copies/mL*	-1.25	-1.16	-1.32	-1.41	-1.08

*Adjusted for baseline viral load, CD4, use of enfuvirtide, and total NNRT mutations

Study C227 Stopped by DSMB Due To Poor Virologic Response to TMC125

- Phase II study in 116 PI-naïve, NNRTI-experienced patients
 - ≥ 1 NNRTI resistance associated mutation
 - Baseline
 - HIV RNA: 4.32 log₁₀ copies/mL
- Week 12: decline of HIV RNA >1 log₁₀ copies/mL
 - TMC125 arm: 57%
 - Control (investigator selected PI arm): 91%
- TMC125 failures were strongly associated with the number of baseline NRTI and NNRTI mutations
 - 37% recycled 1 NRTI
 - 33.7% had ≥ 3 NRTI associated mutations
 - 40.7% had 2 NNRTI mutations
- Results from present study contrast with those from other TMC125 trials conducted in US and Europe, which had promising outcomes in patients with first NNRTI failures with early virologic failure

Integrase Resistance Mutations

- Data from Merck Phase III studies¹:
 - Virologic rebound in 16% RAL versus 51% on control arm
 - Two pathways to resistance:

Primary	Secondary
N155H	E92Q, V151I, T97A, G163K, L74M
Q148K/R/H	G140S/A, E138K

- Elvitegravir resistance mutations *in vitro*²
 - Two pathways to resistance:

Primary	Secondary
T66I	F121Y, S153Y, R263K
E92Q	S147G, H51Y, E157Q

- Concern for cross resistance between these by *in vitro* fold change

1. Cooper D and Steigbigel R, et al. 14th CROI, Los Angeles, CA, February 25-28, 2007. Absts. 105aLB and 105bLB.
2. Jones G, et al. Ibid. Abst.627.

BENCHMARK 1 and 2: Combined Virologic Subgroup Analyses at Week 16

- Similar trends were seen among patients with a GSS or PSS 0/1 score
- Fewer virologic failures in the raltegravir + OBT arm compared with the OBT arm alone
 - 16% versus 51%
- Raltegravir failure
 - Generally associated with N155H or Q148K/R/H

	HIV RNA <400 Copies/mL (%)	
	Placebo	Raltegravir
Overall	43	79
By ARTs in OBT		
<u>Enfuvirtide</u> <u>Darunavir</u>		
Yes Yes	87	98
Yes No	63	90
No Yes	55	90
No No	29	74
Baseline HIV RNA		
<100K	55	88
>100K	19	64

* $P < 0.001$ versus placebo + OBT.

Cooper D, et al. 14th CROI. Los Angeles, 2007. Abstract 105aLB.
Steigbigel R, et al. 14th CROI. Los Angeles, 2007. Abstract 105bLB.

Entecavir

- Entecavir (ETV) previously thought to have no HIV activity
- Study evaluating ETV in HIV infected patients
 - ETV potently inhibits HIV in vitro at an IC₅₀ between 0.1 and 1 nM
 - 3 HIV/HBV pts treated with ETV had significant decline in HIV RNA of ~1-3 log₁₀ copies/mL
 - 1 pt had emergence of M184V mutation while samples for other 2 patients not available
 - At start of ETV, and at 4 and 6 months following start, 0%, 61% and 100% of HIV clones harbored M184V
- ETV may have some anti-HIV activity and use of it in HIV/HBV co-infected patients not on HAART may lead to HIV resistance
- ETV package insert has been modified to reflect this concern

Maraviroc Resistance

- **Maraviroc resistant viruses are characterized by plateau in maximum percentage inhibition (MPI) (usually < 95%) rather than a shift in IC50**
- **Those who fail a maraviroc-containing regimen (R5 at baseline), do so with an X4 using virus**
- **No evidence that change in tropism on maraviroc are caused by mutation of R5 virus**
- **Associated with HIV-1 envelop V3 loop mutations (I26V and others). No consistent mutation or set of mutations were found to confer resistance (n =5)**
- **No evidence that failure of maraviroc containing-regimen will lead to cross resistance to enfuvirtide**

Guidelines for the Use of Resistance Testing

	DHHS ¹	IAS-USA ²
Primary/acute infection	Recommended	Recommended* Consider [†]
Chronic infection	Recommended	Recommended* Consider [†]
Virologic failure during therapy	Recommended	Recommended
Suboptimal suppression of HIV RNA	Recommended	Consider
Discontinuation of drugs	Not recommended	--
HIV RNA <1000 copies/mL	Not recommended	Not recommended

*If the prevalence of transmitted HIV drug resistance is >5%.

[†]If the prevalence of transmitted HIV drug resistance is unknown, but considered likely due to high ART use in the population.

¹Available at: <http://aidsinfo.nih.gov/Default.aspx>. Revision October 10, 2006.

²Hammer S, et al. *JAMA* 2006;296:827-843.

Novel Strategies: Patients With Few Available Options

- **Recommended**
 - **Pharmacokinetic enhancement**
 - **Therapeutic drug monitoring**
 - **Re-treating with prior medications**
 - **Use of empiric multidrug regimens**
 - **New antiretroviral drugs**
- **Not recommended**
 - **Structured treatment interruptions**

Guidelines for Choosing a Nonsuppressive “Holding Regimen”

- **Never use an NNRTI**
 - NNRTI mutations have no beneficial impact on fitness
 - Accumulation of additional mutations may result in cross-resistance to second-generation NNRTIs
- **Always use 3TC or FTC**
 - Simple and well-tolerated drugs
 - M184V decreases fitness
 - Increased activity of ZDV, d4T, TDF
- **Choose PIs and/or NRTIs based on resistance and tolerability/ toxicity considerations**
- **Continue therapy until availability of at least 2 new active drugs**

When to Consider Investigational Agents

- Management of highly experienced patients with highly resistant HIV has been and continues to be the use of as many active drugs as possible
- Use of resistance testing while on the selective pressure of failing ART is mandatory in this population
- For patients with limited treatment options, 3 major new drugs/drug classes should become available in the next 12-18 months
 - New NNRTI: TMC125 (etravirine)
 - CCR5-antagonists: maraviroc
 - Integrase inhibitors: MK-0519, GS-9137