

# HIV Drug Resistance Update 2007

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## Outline

- Indications for resistance testing
- Epidemiology of drug resistance
- Risk of triple class resistance and failure in HIV positive patients
- Impact of drug resistance on survival
- Choice of initial ART and impact on resistance in cohort studies and clinical trials
- Using resistance testing to choose among ritonavir-boosted PIs in salvage (darunavir and tipranavir)
- Tropism testing and development of resistance to CCR5 antagonists
- Virologic predictors of failure to etravirine
- Virologic predictors of failure to HIV integrase inhibitors

## When to Use Resistance Testing

	IAS-USA <sup>[1]</sup>	DHHS <sup>[2]</sup>	European <sup>[3]</sup>
Primary/acute	Recommend	Recommend	Recommend
Postexposure prophylaxis	—	—	Recommend
Chronic, Rx naive	Consider*	Recommend	Strongly consider*
Failure	Recommend	Recommend	Recommend
Pregnancy	Recommend	—	Recommend*
Pediatric	—	—	Recommend†

1. Hirsch MS, et al. Clin Infect Dis. 2003;37:113-128.
2. Available at: <http://www.aidsinfo.nih.gov>. Accessed May 4, 2006.
3. Vandamme AM, et al. Antivir Ther. 2004;9:829-848.

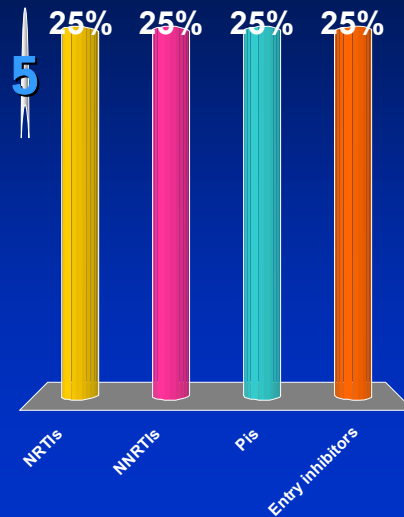
## Question 1

For which of the following classes of drugs has the prevalence of drug resistance in ARV-naive patients been highest in the US over the last 5 years?

- a. NRTIs
- b. NNRTIs
- c. PIs
- d. Entry inhibitors

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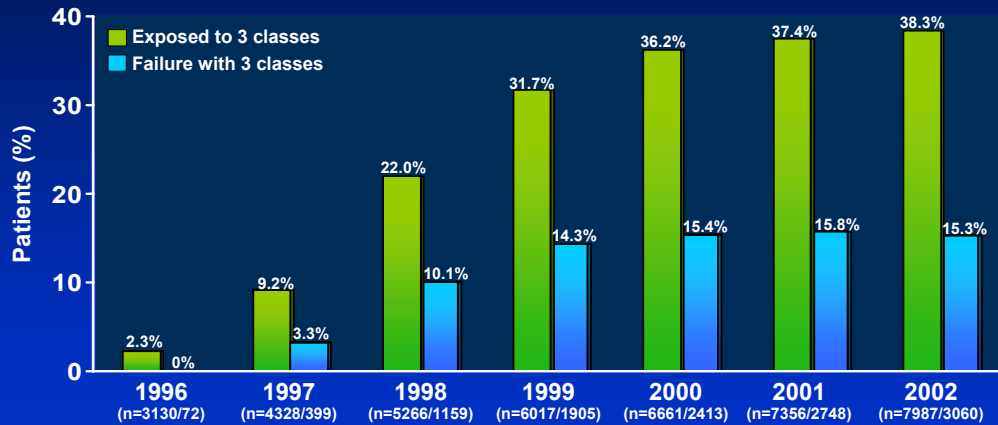


### Primary Drug Resistance: March 2003 – October 2006

- Data from 409 sites in 11 states
- STD clinics (33.2%), counseling and testing centers (24.7%), private practices (7.8%), hospitals (6.8%), other/unknown (33.5%)
- Data from Colorado, Illinois, Louisiana, Maryland, Michigan, Massachusetts, Mississippi, North Carolina, Washington, South Carolina, Virginia
- Prevalence of Drug Resistance:
  - Any class: 10.4%
  - NRTIs: 3.5 %
  - NNRTIs: 6.9%
  - PIs: 2.4%
  - ≥ 2 classes: 1.9%

Wheeler et al, 14<sup>th</sup> CROI, Los Angeles, 2007, Abstract 648

## UK CHIC Study: Triple-Class Exposure and Failure

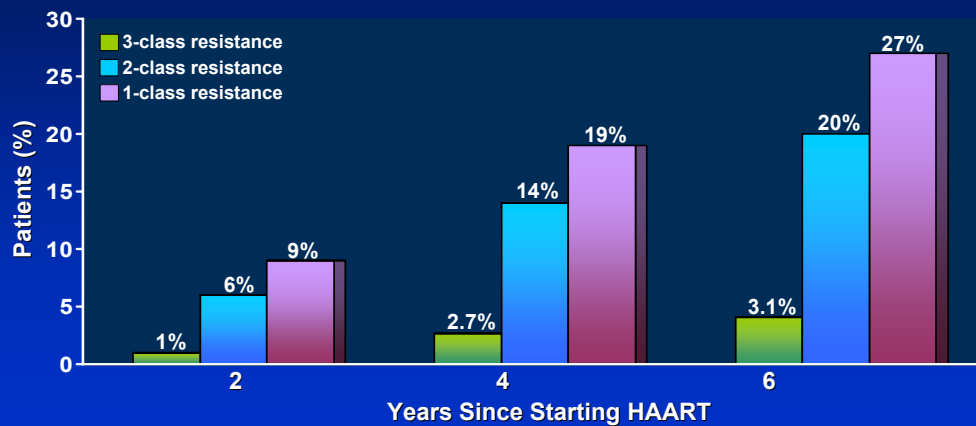


6 large HIV-treatment centers in southeast United Kingdom.

Sabin CA, et al. *BMJ*. 2005;330:695-699.

## Long-Term Risk of Developing Drug Resistance on HAART: UK CHIC Study

### Time to Multi-Class Resistance

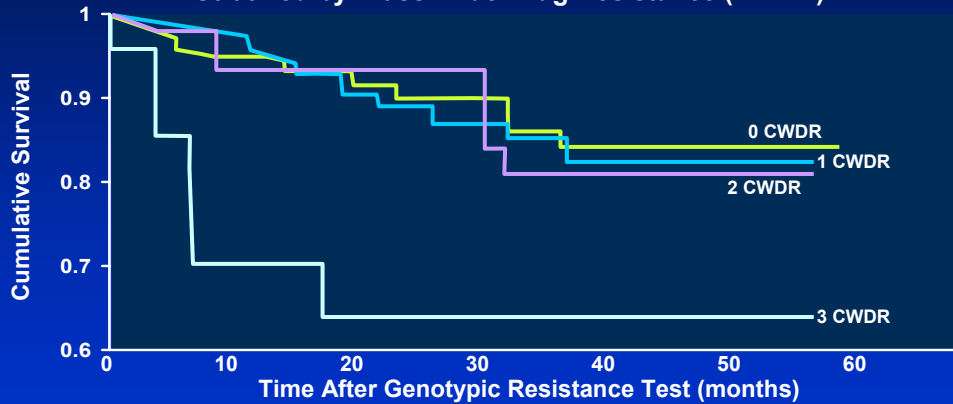


n=4306.  
Overall risk of treatment failure: 38% over 6 years.

Phillips AN, et al. *AIDS*. 2005;19:487-494.

## Increased Disease Progression With Class-Wide Drug Resistance

Cumulative Survival or Remaining Free of AIDS Events Stratified by Class-Wide Drug Resistance (CWDR)



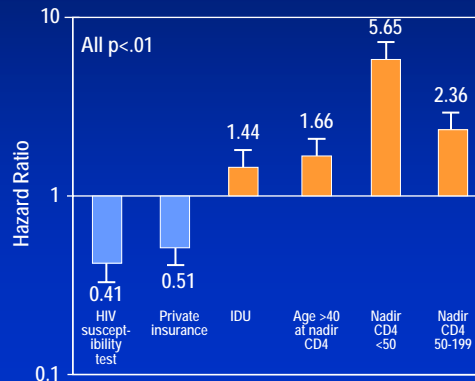
n=623 patients failed HAART and underwent genotypic testing, then were followed for a median of 19 months (IQR 12-29). Multivariate Cox's model: increased risk of death was significantly associated with higher HIV RNA, prior AIDS, and detection of 3 CWR (hazard ratio 5.34 [95% CI 1.76-16.24]).

Zaccarelli M, et al. *AIDS*. 2005;19:1081-1089.

## Resistance Testing and Clinical Outcomes

- HIV Outpatient Study (HOPS) cohort
  - Resistance testing in ART-experienced patients (n=1056)
  - No resistance testing in ART-experienced patients (n=3130)
- Resistance testing associated with
  - White
  - <40 years old
  - Privately insured
  - Lower CD4+
  - Higher HIV RNA
- In MV analysis, those with resistance testing had a 59% reduced risk of death

Cox proportional hazards analysis of independent variables and outcome of death among HAART-experienced patients (n=4186)



Palella F, et al. Presented at: 13th CROI Conference; Feb 5-8, 2006; Denver, Colo.

## Decline in Resistance Testing (2000-2006)

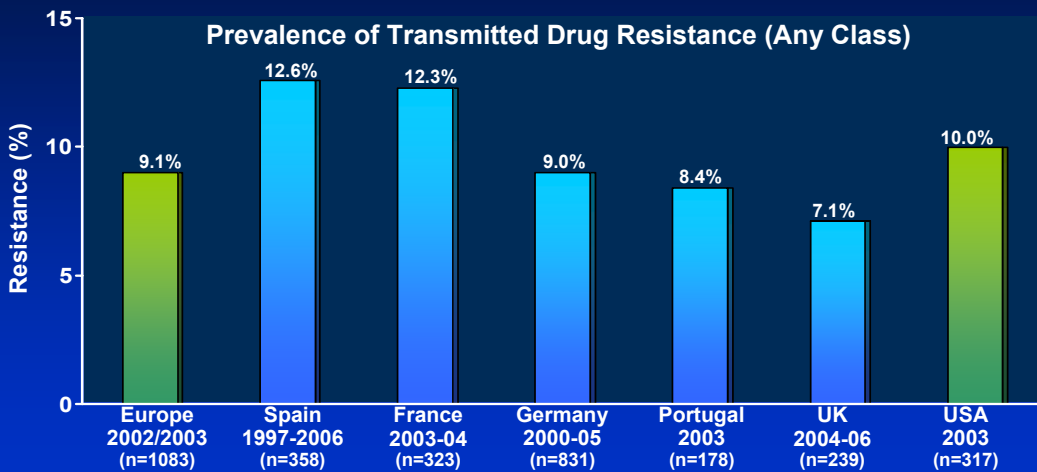
- **Madrid cohort**
  - Patients initiating antiretroviral therapy
- From 2000-2006, there was a significant decline in the proportion of patients:
  - Meeting criteria for resistance testing (HIV RNA >1000 copies/mL) ( $P < 0.0001$ )
  - With therapeutic failure (sustained HIV RNA >1000 copies/mL after 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.

Hernandez B, et al. 8<sup>th</sup> ICDTHIV1, 2006; Glasgow, United Kingdom. Abstract P212.

## Transmitted Drug Resistance: A Global Concern



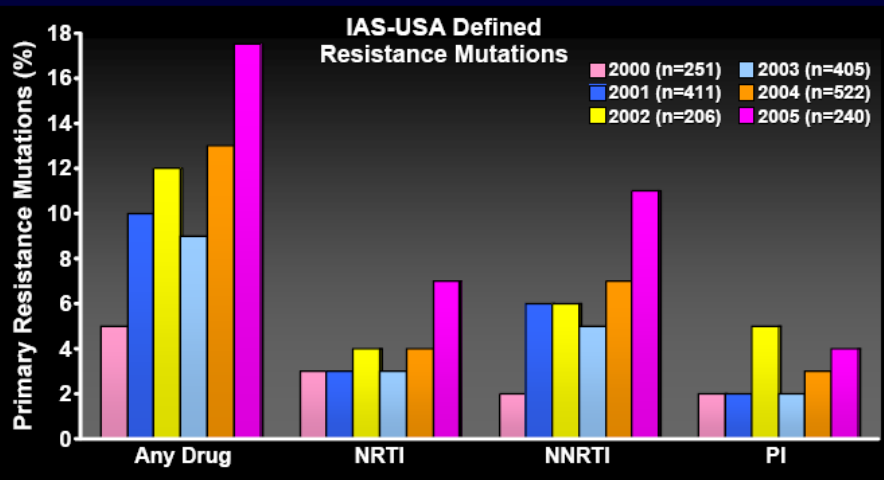
Booth CL, et al. *J Antimicrob Chemother.* 2007;59:1047-1056.  
 Wensing AM, et al. 16<sup>th</sup> IAC, 2006. Abstract TuAB0101.  
 De Mendoza C, et al. 14<sup>th</sup> CROI, 2007. Abstract 656.  
 Ross L, et al. *HIV Clin Trials.* 2007;8:1-8.

## Transmitted drug resistance

- Studies report prevalence of drug resistance in ARV-naïve patients:
  - Newly infected (11–15%)
  - Newly diagnosed (7–11%)
- Persistence of transmitted resistant virus in 14 patients
  - NNRTI resistance in 10/14 patients (median follow-up 2.1 years)
  - Resistant virus persistently detectable in 13/14 patients
  - Mean time to first detectable *wt/resistant* mixture was 103 weeks (95% CI: 49–216 weeks)
- Response to therapy in patients with transmitted resistance (AIEDRP Cohort)
  - NNRTI (n=67), PI (n=18), NRTI (n=25): some with MDR virus
  - 45% (38/84) failed to suppress, best response in those receiving >2 active drugs (p=0.01)

Little S, *et al.* 14<sup>th</sup> CROI, Los Angeles 2007, #60

## PREPARE Study: Drug Resistance in US Treatment-Naïve Patients



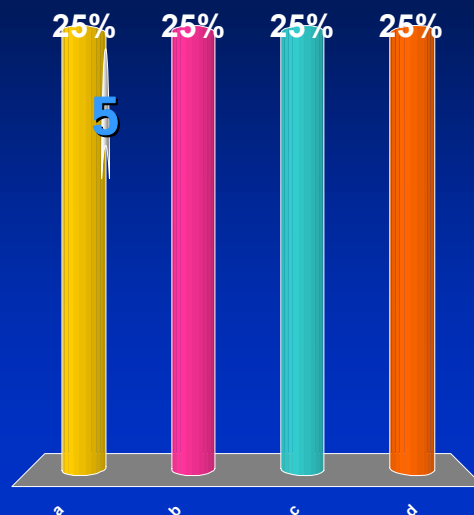
Ross L, *et al.* 46<sup>th</sup> ICAAC. San Francisco, 2006. Abstract H-993.

**Question 2: Virologic failure with which of the following regimens is likely to lead to multi-class resistance?**

- a. zidovudine, lamivudine, abacavir
- b. tenofovir, emtricitabine, lopinavir/ritonavir
- c. zidovudine, lamivudine, efavirenz
- d. tenofovir, emtricitabine, efavirenz

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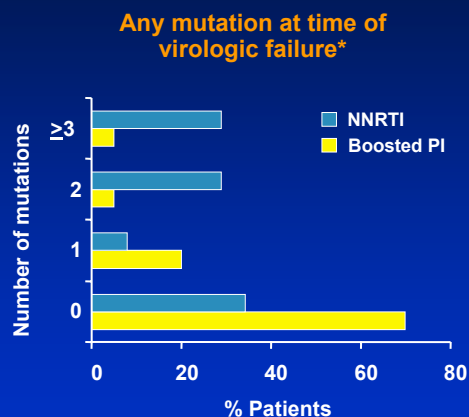


## Emergence of drug resistance after first line combination therapy in the Swiss cohort study

- Combination ARV therapy started Jan 1999 – Dec 2005 (n=1323)
  - Boosted PI (n=518)
  - NNRTI (n=805)
- Viral failure by third agent: in previously suppressed patients or HIV RNA >500 c/mL after more than 180 days of treatment
  - Boosted PI (n=4.6%)
  - NNRTI (n=5.6%)
  - No difference by regimen for virologic failure, but more discontinuations for adverse events with boosted PIs

### Conclusion

- ARV efficacy similar for all groups but more resistance emerged with NNRTI-based regimens



\*Mann-Whitney p=0.005

von Wyl V, et al. 14<sup>th</sup> CROI, Los Angeles 2007, #667

## Resistance emergence, on therapy, at time of failure (ACTG 5142)

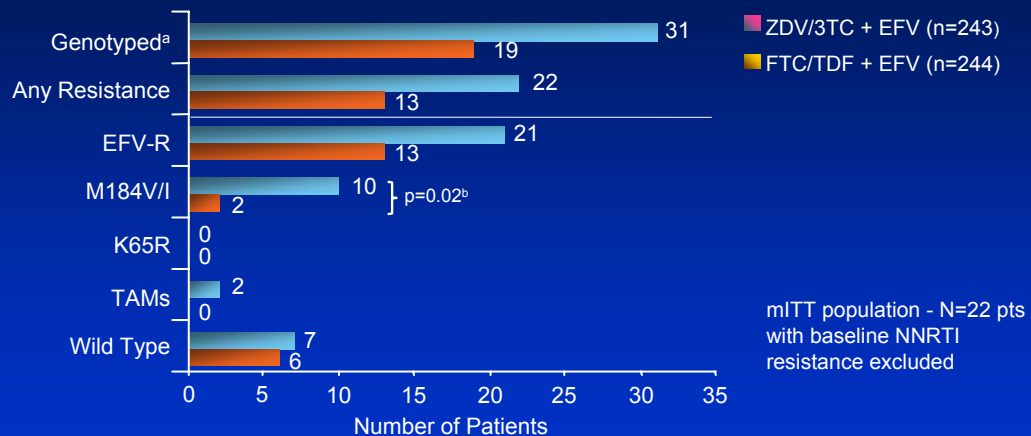
	LPV/RTV + 2 NRTIs (n = 253)	EFV + 2 NRTIs (n = 250)	LPV/RTV + EFV (n = 250)
Observed VF,* n	94	60	73
Genotypic assays, n	52	33	39
NRTI mutations, n (%)	8 (15)	11 (33)	4 (10)
• M184I/V, n	7	8	1
• K65R, n	0	3	0
NNRTI mutations, n (%)	2 (4)	16 (48)	27 (69)
• K103N, n	0	9	21
Major PI mutations,† n	0	0	2
Mutations in 2 classes, n	2	10	2

\*Defined as early: lack of suppression by 1 log<sub>10</sub> or rebound before Week 32; or late: failure to suppress to < 200 copies/mL or rebound after Week 32.

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

Riddler S, et al. IAC 2006. Abstract THLB0204.

## Update on Genotypic Resistance Development in GS 934 Study



a. Confirmed  $\geq 400$  copies/mL after week 8 or at discontinuation. Genotyping of 2 on ZDV/3TC failed for technical reasons. b. Fisher's exact test

McColl D, et al. 11th EACS; Madrid, Spain; October 24-27, 2007. PS3.1/08.

## Clinical cut-offs for genotypic scores

Genotype scores defined for RTV-boosted PIs in treatment-experienced subjects:

### Genotypic scores<sup>1,2,3</sup>

Drug	Resistance mutations	Genotypic cut-off
FPV/RTV	L10I/R/V/F, L33F, M36I, M46I/L, I54M/L/T/V, I62V, L63P, A71I/L/V/T, G73A/C/F/T, V82A/F/S/T, I84V, L90M	< 4
ATV/RTV	L10I/R/V/F, K20M/R, L24I, M46I/L, I54M/L/T/V, L63P, A71I/L/V/T, G73A/C/F/T, V77I, V82A/F/S/T, I84V, L90M	< 5
TPV/RTV	10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82 L/T, 83D, 84V	$\leq 5$
TMC 114/r	V11I, V32I, L33F, I47V, I50V, I54L, I54M, G73S, L76V, I84V, L89V	$\leq 3$

1. Pellegrin I, et al. 45th ICAAC, Washington DC 2005, #H-1058;

2. Pellegrin I, et al. *ibid*, H-1059;

3. Petropoulos C. 3rd IAS, Rio de Janeiro 2005, #MoFo0301

## New r/PI Monogram Phenotype Clinical Cutoffs

	Lower Value Fold Change	Upper Value Fold Change
ATV/RTV	< 5.2	< 5.2
FPV/RTV	< 4.0	> 11
LPV/RTV	< 9.0	> 55
SAQ/RTV	< 2.3	> 12
TPV/RTV	< 2.0	> 8.0
DRV/RTV	< 10.0	> 40

Coakley, 46<sup>th</sup> ICAAC, 2006, Abstract H-995

## TPV and DRV Mutations and Phenotypic Cut-offs

### Similarities and Differences in Key Mutations

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

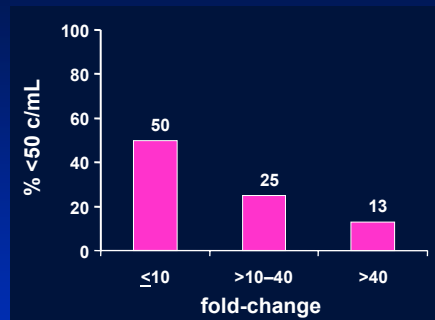
<b>TPV</b>	47V		54A/M/V	58E	69K		74P		82L/T	83D	84V
<b>DRV</b>	47V	50V	54L/M			73S		76V		84V	89V

Assay/ Cutoff	<i>PhenoSense</i> : FC for Reduced Activity	<i>PhenoSense</i> : FC for No Response	<i>VircoTYPE</i> : FC for Maximal Response	<i>VircoTYPE</i> : FC for Minimal Response
TPV <sup>(1,2)</sup>	≥ 2	≥ 8	< 1.2	≥ 5.4
DRV <sup>(3,4)</sup>	≥ 10	≥ 90	< 3.4	≥ 96.9

1. Oakley E, et al. Resistance Wkshp 2006. Abstract 71.
2. Bachelier 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.

## Phenotypic and genotypic determinants of darunavir resistance

- combined analysis of POWER 1, 2, 3
  - DRV/RTV 600 mg/100 mg BID + OBR arms at Week 24;  $n=377$
  - Phenotype by Antivirogram®
- fold-change in  $EC_{50}$  strongest predictor of Week 24 outcome
  - Clinical cut-offs established at <10-fold, >40-fold
- mutations associated with decreased response include
  - V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, L89V
- viruses with >3 DRV resistance mutations had median  $IC_{50}$  >10-fold



# BL DRV mut., Wk 24	Mean $\Delta$ HIV RNA ( $\log_{10}$ )	Patients <50 c/mL
0-2	-2.1	50%
3	-1.12	22%
≥4	-0.46	10%

De Meyer S, et al. *HIV8*, Glasgow 2006, #P196

## Weighing the mutations associated with a diminished response to darunavir

Estimated increase in FC

< 2

2 to 3

3 to 4

> 4

Mutations

V11I  
I54L  
G73S  
L89V

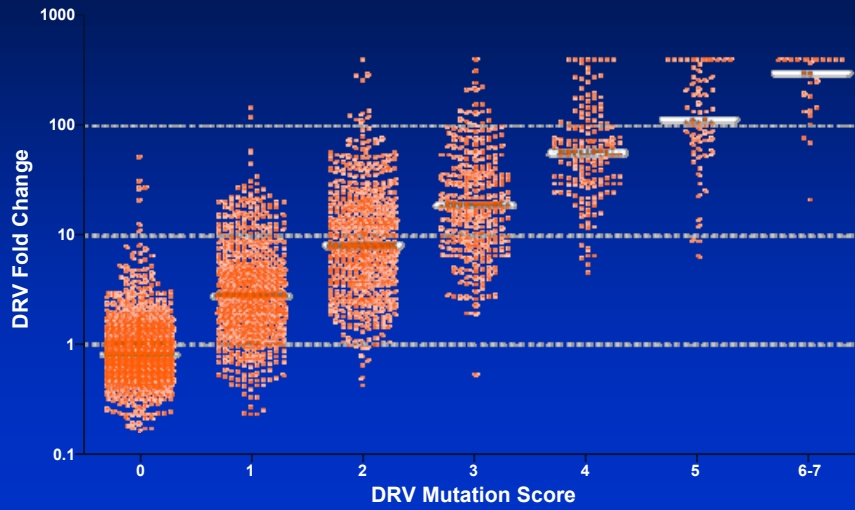
V32I  
L33F  
I47V

I54M  
L76V  
I84V

I50V

Determined by multiple regression analyses of the 1,405 screening samples from the POWER 1, 2 and 3 studies

## DRV Mutation Score Performance



## TITAN: Subgroup and resistance analyses

- New PI mutations: 21% of DRV and 36% of LPV failures
- New NRTI mutations: 14% of DRV and 27% of LPV failures

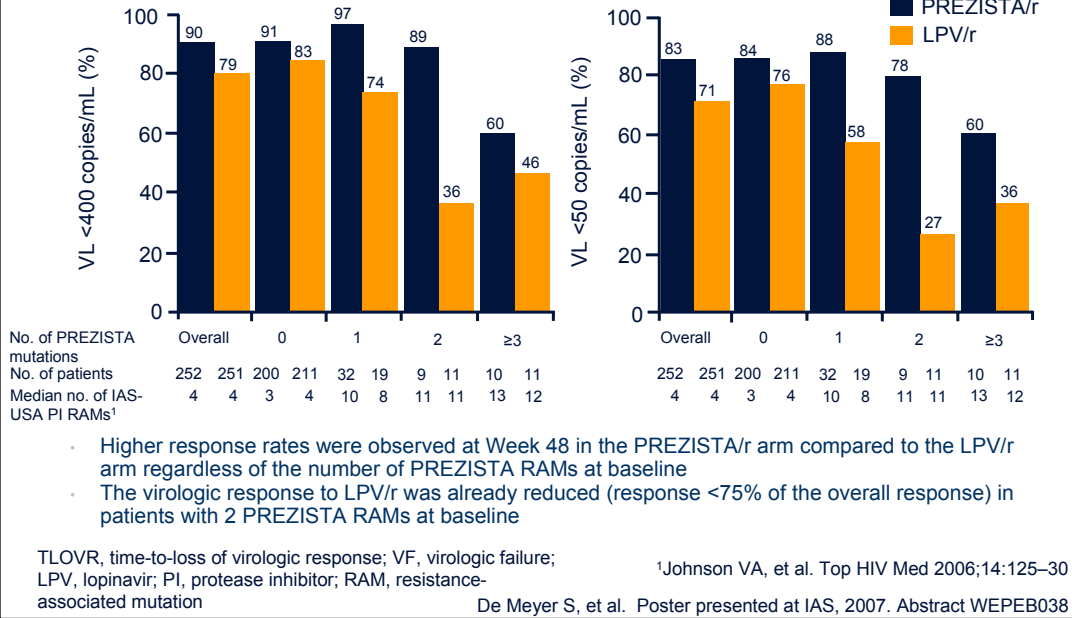
### Subgroup analyses at Week 48

HIV RNA	DRV	LPV	Difference	p (superiority)
<50 c/mL LPV FC $\leq$ 40	70%	60%	10%	0.013*
<50 c/mL LPV FC $\leq$ 10	70%	63%	7%	0.07*
<400 c/mL <6 LPV mutations	91%	85%	6%	Not done
<400 c/mL $\geq$ 6 LPV mutations	86%	41%	45%	Not done

De Meyer S, et al. 4<sup>th</sup> IAS, Sydney 2007, #WEPEB038

\*p (non-inferiority) <0.001

## TITAN: Virologic Response According to PREZISTA RAMs (TLOVR non-VF)

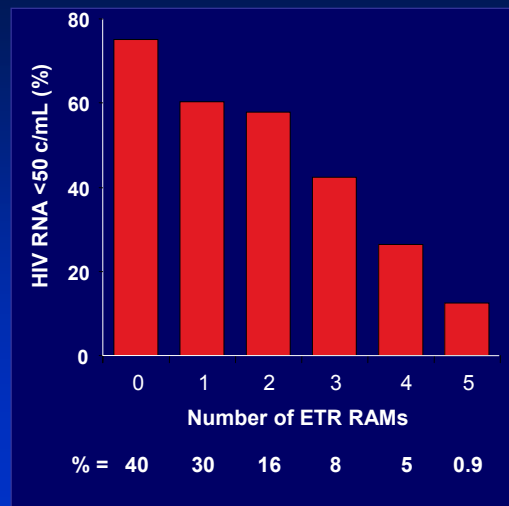


## DUET 1 and 2: Virologic response (<50 c/mL) in etravirine arms by BL mutations at Week 24

- 13 BL resistance-associated mutations (RAMs) associated with a decreased response to ETR:

V90I	K101E/P
A98G	V179D/F
L100I	G190A/S
V106I	Y181C/I/V

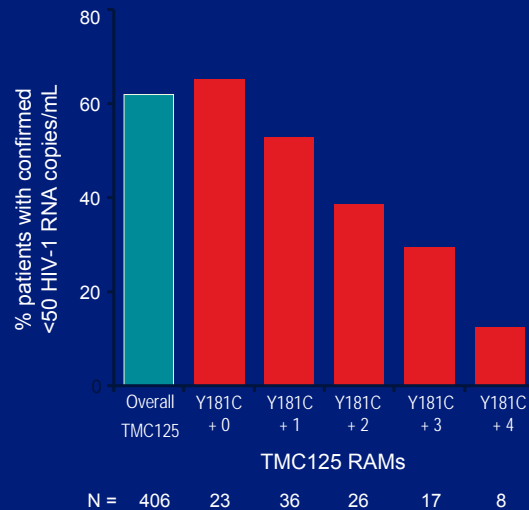
- If ≥3 mutations present, response similar to PBO
- Note: 14% had ≥3 ETR RAMs



Katlama C, et al. 4<sup>th</sup> IAS, Sydney 2007, #WESS204:2

## Effect of Y 181C on Etravirine Response Rates in DUET 1 and 2

- Y181C is a common mutation conferring resistance to currently available NNRTIs
- The TMC125 response rate is not compromised when Y181C is present, with either 0 or 1 other TMC125 RAM
- When Y181C is present with two or more TMC125 RAMs (13% of all patients), response rates were substantially reduced



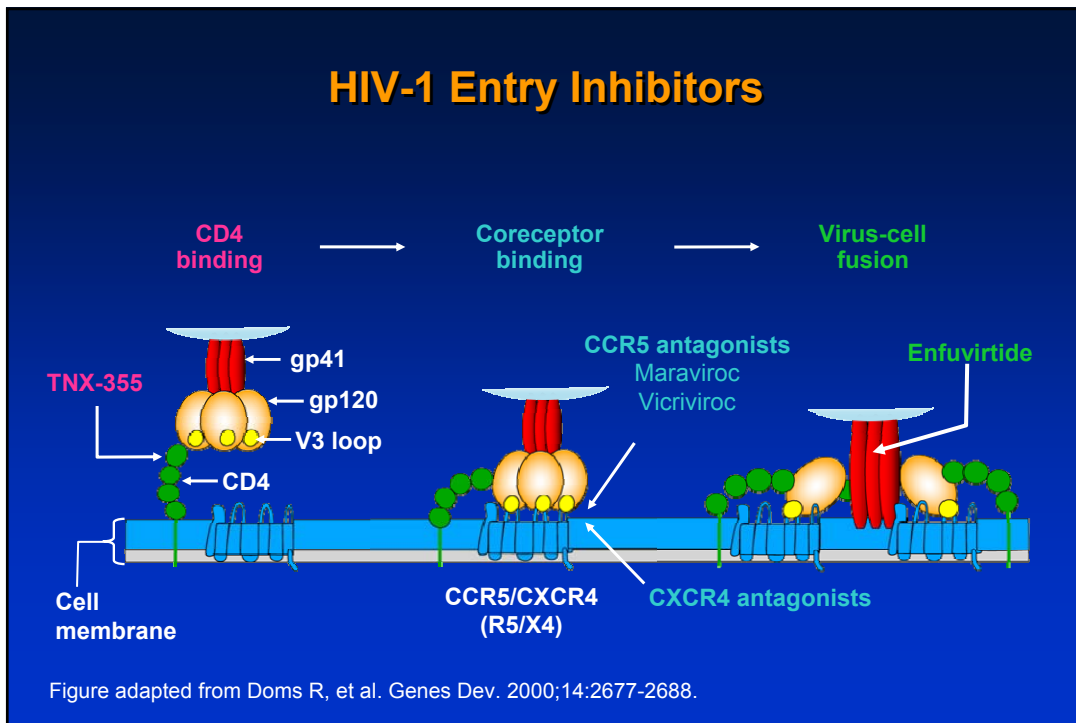
Katlama C, et al. 4th IAS, Sydney 2007, #WESS204:2

## Baseline NNRTI resistance: Predictive of virologic failure

- Retrospective analysis of 138 ART-naïve pts from study CNA30024 (ABC/3TC + EFV vs ZDV/3TC + EFV)
- ~50% of study population experienced virologic failure (HIV RNA >50 c/mL) during the study
- Standard genotypic sequencing identified 4 patients with baseline resistance (K103N, Y181C, M184V)
- Using ultrasensitive assays, baseline samples re-evaluated for K103N, Y181C, M184V present at frequencies below detection level of standard sequencing
- Ultrasensitive testing found 8 additional samples with K103N, Y181C, M184V; all 12 patients experienced virologic failure during the study

Johnson J, et al 15<sup>th</sup> IHDRW, Sitges 2006, #69

## HIV-1 Entry Inhibitors

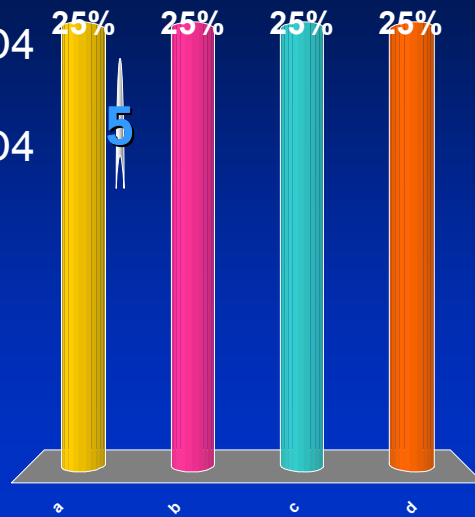


**Question 3: Which of the following patients is least likely to have R5-tropic HIV?**

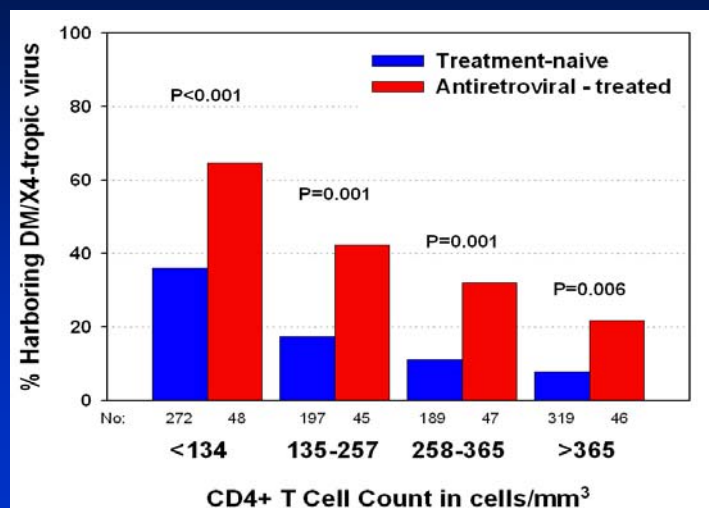
- a. ARV naive patient with CD4 count of 50
- b. ARV naive patient with CD4 count of 200
- c. ARV experienced patient with CD4 count of 50
- d. ARV experienced patient with CD4 count of 200

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- b. ARV naive patient with CD4 count of 200
- c. ARV experienced patient with CD4 count of 50
- d. ARV experienced patient with CD4 count of 200



**Tropism Profile in SCOPE and HOMER Cohorts are Influenced by CD4 Counts and by Treatment Status**



- Tropism profiles in treatment naïve and experienced groups are distinct

Hunt et al., JID, 2006, 194:926-30

## Summary: Monogram Tropism Assay

Assay Attribute	Current Performance
Turnaround time	16 days
Minor variant detection	100% at 10% mixture 85% at 5% mixture
Viral load sensitivity	≥ 1,000 copies/mL (> 95%)
Assay failure rate	5% (n = 23,000)

## Co-receptor tropism switches in drug-resistant virus

- Viremic patients (SCOPE Cohort) on stable ARV with tropism assessed q4 months (n=76)
  - Median HIV RNA 3.8 log<sub>10</sub> c/mL, CD4= 241 cells/uL
- Baseline Tropism
  - R5 only- 52 (68%)
  - DM 22 (29%)
  - X4 only 2 (3%)
- Longitudinal tropism
  - R5 to DM (12%) over 1 yr (3 with low X4 RLU, 1 R5 to DM to R5)
  - DM to R5 (11%) over 1 yr
  - DM to X4 only (8%)
- Increased risk of R5 to DM in those CCR5Δ32 (n=3)

Hunt P et al *CROI 2007*, Los Angeles Abstract #619

## Switches in Tropism from Screening to Baseline Visits in MOTIVATE, ACTG 5211 and MERIT Studies

- Of 1049 subjects in MOTIVATE 1 and 2 studies, 8% changed tropism from screening visit to baseline (approximately 4 – 6 weeks)
- In this group, response to maraviroc treatment was consistent with the results of study A4001029 in subjects with D/M tropic virus
- In ACTG 5211, of 118 subjects screened R5, subsequently 10% to D/M; again virologic response was inferior in those who switched tropism as compared with majority of patients who did not switch tropism
- In naïve patients (MERIT Study), incidence of tropism switch from screening to baseline only 4 – 5 %

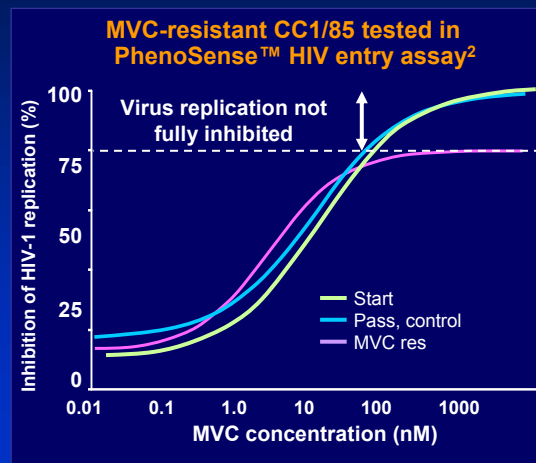
## CCR5 antagonist resistance

### Phenotypic resistance<sup>1</sup>

- Decreased maximum percentage inhibition in U87 cells(eg, Monogram assay)
- *In vitro* selected resistant virus often cross-resistant to other CCR5 inhibitors
- Shift in IC<sub>50</sub> in PBMC

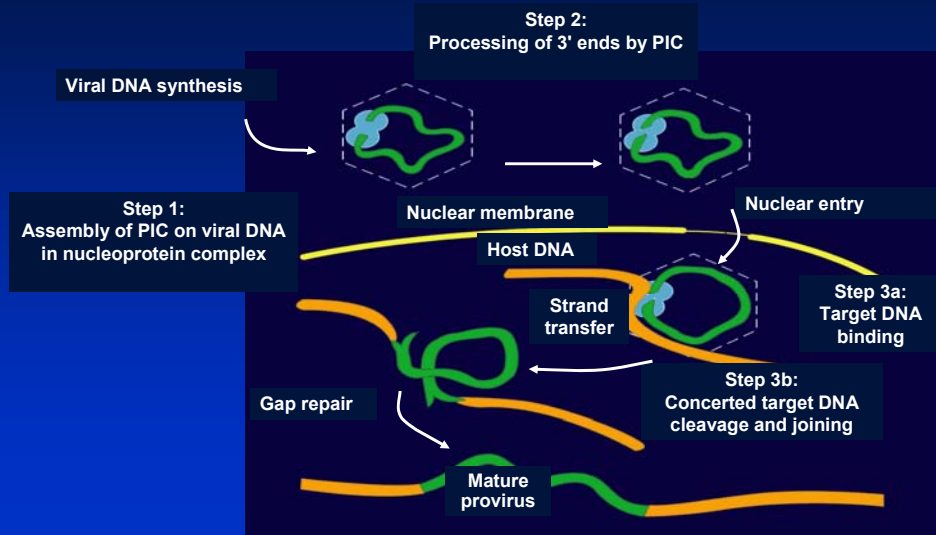
### MOTIVATE 1 and 2 MVC failures<sup>2</sup>

- ~65% with dual/mixed tropic virus with phenotypic resistance
- 4/12 who had R5 only at failure had phenotypic resistance
  - No specific amino acid pattern changes



1. Moore J, et al. 4<sup>th</sup> IAS, Sydney 2007, #TUBA102; 2. Mori J, et al. XVI IHIVDRW, Barbados 2007, #10

## Role of HIV Integrase



Hazuda D, et al. Science. 2000;287:646-650.

## Integrase inhibitor resistance mutations

### RAL resistance

- Initial *in vivo* data from Phase III studies<sup>1,2</sup>
- Virologic rebound in 16% RAL (32/41 showed integrase changes) vs 51% in control arm
- Two mutually exclusive pathways to resistance:

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

- “Next-generation”<sup>3</sup> inhibitor?: MK2048 active *in vitro* despite primary resistance mutations
- Note: Concern for cross-resistance to RAL identified by *in vitro* fold change<sup>3</sup>

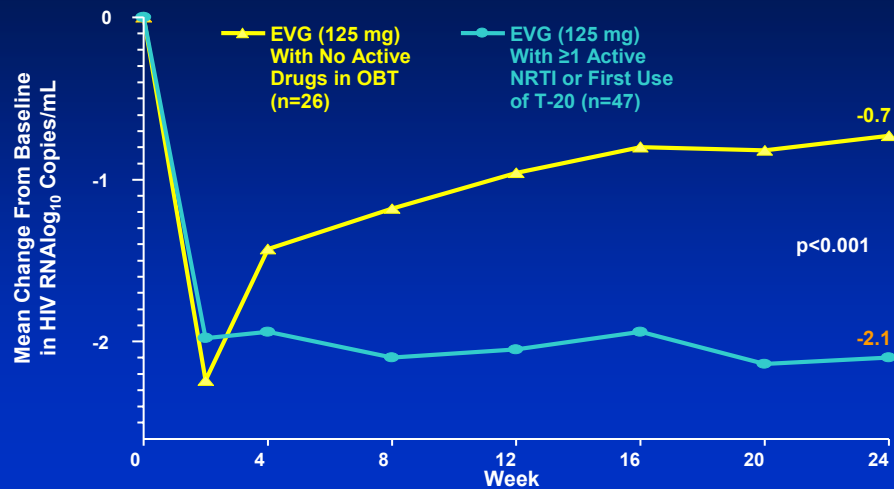
### Elvitegravir resistance

- Elvitegravir (GS-9137) resistance mutations *in vitro*<sup>4</sup>
- Two pathways identified:

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

1. Cooper D, et al. 14<sup>th</sup> CROI, Los Angeles 2007, #105aLB;  
 2. Steigbigel R, et al. *ibid.*, #105bLB; 3. Wai, IBID # 87; 4. Jones, #627

## Change in HIV RNA With elvitegravir (125 mg) Influence of Activity of OBT\*



\*Data from EVG (125 mg) patients after addition of a PI were excluded

Zolopa A, et al. 14th CROI, Los Angeles, CA, February 25-28, 2007. Abst. 143LB.

## Conclusions

- Drug resistance may become less common in patients with good adherence as more potent, well tolerated drugs are available
- Clinical trials continue to provide new data about drug combinations that are less likely to select for resistance
- Commercially available assays have poor sensitivity for resistance to minority quasispecies (<10% of population)
- Viral tropism is a new predictor of response to R5 antagonists
- New assays for integrase and R5 inhibitors will be needed to assess for the development of resistance to these new classes