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Orlando, FL

Challenges in the Management of Antiretroviral Experienced Patients

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Disclosure of Financial Relationships

This speaker has the following significant financial relationships with commercial entities to disclose:

Nature of Relationship	Commercial Interest
Grant/Research Support	Pfizer, Tibotec, Gilead
Consultant	none
Stockholder (directly purchased)	none
Honorarium	none
Speaker Bureau	Boehringer Ingelheim
Other Financial or Material Support	none

This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.

Learning Objectives

- Identify common reasons for treatment failure
- Describe therapeutic strategies for improving outcomes in treatment experienced patients
- Review resistance data from clinical trials of antiretroviral therapy

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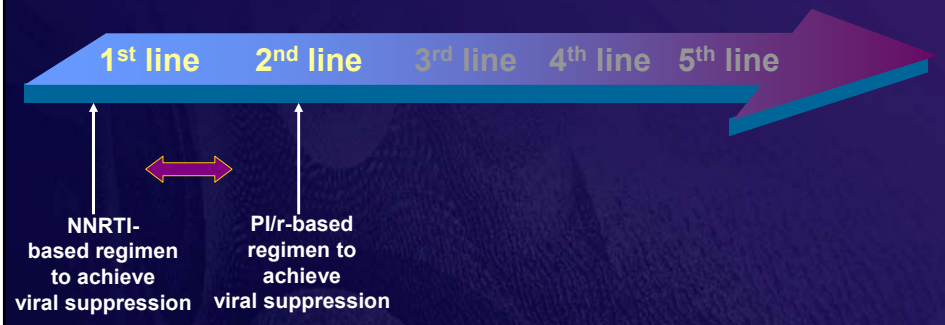
Treatment Algorithm: Evolution



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Treatment Algorithm: Pre 1995

How to maximize chance for virologic resuppression in treatment-experienced patients?

Switching ARV Therapy

- **Changes to initial therapy are common and most often due to**
  - Drug toxicity
  - Intolerance
  - Inconvenience *–or–*
  - Drug failure
- **When to change and what to change to depends on**
  - Reason for changing therapy
  - Whether in response to failure of initial or subsequent regimen
  - Availability of active drugs to construct a potent regimen

IAS-USA = International AIDS Society-USA panel
Adapted from Hammer S et al. *JAMA*. 2006;296:827-843.

Changes due to Toxicity, Intolerance, or Inconvenience

- Single drug substitutions may be indicated for persistent side effects or laboratory toxicity due to one agent
- Discontinue regimen when side effects or toxicity cannot be attributed to a single agent and is severe enough to require discontinuation

Adapted from: Hammer S et al. *JAMA.* 2006;296:827-843.

DHHS Guidelines: Definition of Virologic Failure

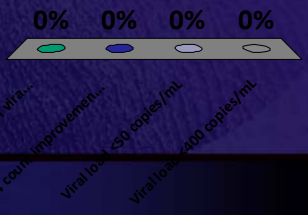
1. Confirmed HIV RNA >400 c/mL after 24 weeks *–or–*
2. HIV RNA >50 c/mL after 48 weeks *–or–*
3. Confirmed HIV RNA >400 c/mL after prior suppression to <400 c/mL

Adapted from DHHS Guidelines. Available at: http://aidsinfo.nih.gov/Default.aspx. Revision Nov 3, 2008

Question 1

What is the goal when changing antiretroviral regimens due to virologic failure?

1. 1 – 2 log decrease in viral load
2. CD4 count improvement regardless of viral load
3. Viral load <50 copies/mL
4. Viral load <400 copies/mL



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DHHS Guidelines: Changing ARV Therapy in Highly Experienced Patients

- **Use treatment history and past and current resistance tests to identify ≥2 fully active ARVs***
  - Including an ARV with a new mechanism of action (e.g., entry inhibitor, integrase inhibitor, CCR5 antagonist) to optimized background regimen can provide significant activity

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DHHS Guidelines: Changing ARV Therapy in Highly Experienced Patients

- **If <2 fully active ARVs, consider RTV-boosted PI and/or use of ARVs with partial activity**
  - Consider Decreased Replication Capacity/Fitness
- **Adding one active drug to a failing regimen is undesirable and leads to resistance**
  - May be necessary in patients with advanced disease (e.g., CD4 <100) and high risk of clinical progression
  - In stable patients, waiting may be appropriate if drugs likely to be effective are to arrive soon

Goals of Therapy for Treatment-Experienced Patients

- US DHHS Guidelines, January 29, 2008:
  "The goal of treatment for patients with prior drug exposure and drug resistance is to re-establish maximal virologic suppression, HIV-1 RNA < 50 copies/mL"
- IAS-USA Guidelines, August 2006:
  "Trials with newer antiretroviral agents have shown that it is possible to achieve plasma HIV-1 RNA levels below 50 copies/mL even in highly treatment–experienced patients"

1. DHHS Guidelines for Adults and Adolescents. Available at: http://www.aidsinfo.nih.gov/Guidelines. Revised Nov 3, 2008
2. 2. Hammer SM, et al. JAMA. 2006;296:827-843.

DHHS Guidelines: Assessment When Changing ARVs Due to Suspected Regimen Failure

- **Complete ARV history**
- **Clinical status**
- **Adherence, tolerability, drug interactions and PK issues**
- **Degree of ARV exposure**
  - First, second, or multiple failures
- **Resistance testing:**
  - Ideally while on failing regimen *–or–*
  - Within 4 weeks of discontinuation

Adapted from DHHS Guidelines. Available at: http://aidsinfo.nih.gov/Default.aspx. Nov 3, 2008.

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Current Guidelines for Resistance Testing

	IAS-USA[1]	DHHS[2]	European[3]
Primary/acute	Recommend	Recommend	Recommend
Postexposure prophylaxis			Recommend
Chronic, ARV-naive	Recommend *	Recommend	
ARV-failure	Recommend †	Recommend	Recommend
Pregnancy	Recommend	Recommend	Recommend

* If prevalence of drug resistance in untreated patients ≥ 5% (European: ≥ 10%); should be considered if the prevalence is unknown or if exposure to someone receiving antiretroviral drugs is likely.

† Resistance testing should also be considered if the HIV VL suppression achieved with a new antiretroviral regimen is not optimal.

1 Hammer SM, et al. JAMA. 2006;296:827-843; 2. Adapted from DHHS Guidelines. Available at: http://aidsinfo.nih.gov/Default.aspx. Revision Nov 3, 2008
. 3 Vandamme AM, et al. Antivir Ther. 2004;9:829-848.

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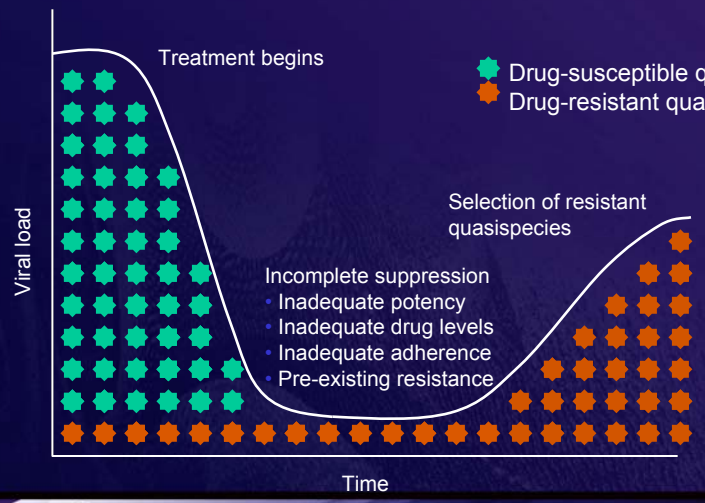
Selective Pressures of Therapy



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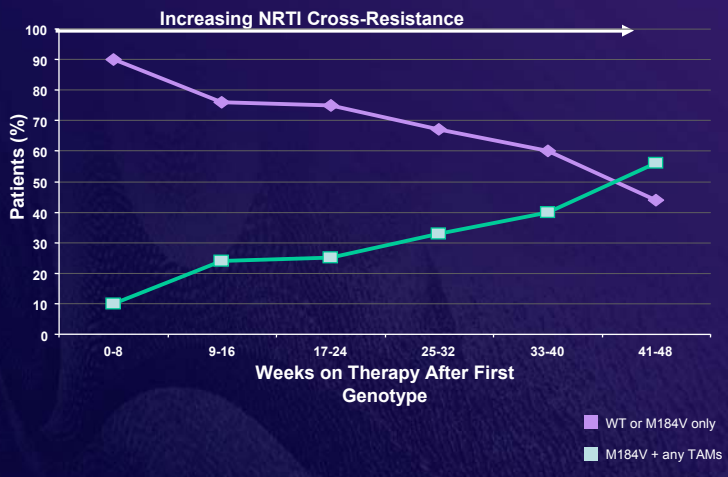
Winters et al. Antiretroviral Resistance and Options for Sequencing. www.clinicalcareoptions.com/HIV

Increasing TAMs After Initial Failure



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Regimen: zidovudine/lamivudine/abacavir.
Melby T, et al. 8th CROI (2001). Abst. 448.

Types of Resistance Tests

- **Genotype**
  - HIV gene sequencing of the patient's virus to detect mutations known to confer drug resistance
- **Phenotype**
  - Measures ability of a recombinant virus derived from the patient sample to grow in different concentrations of antiretroviral drugs
- **"Virtual" phenotype**
  - Use of genotype results to predict phenotypic susceptibility based originally on database of paired genotype and phenotype data or, more recently, through scores derived from linear regression analysis

Hirsch MS, et al. Clin Infect Dis. 2003;37:113-128.

International AIDS Society–USA* Drug Resistance Mutations Group

Update of the Drug Resistance Mutations in HIV-1: December 2008

Victoria A. Johnson, MD, Françoise Brun-Vézinet, MD, PhD, Bonaventura Clotet, MD, PhD, Huldrych F. Günthard, MD, Daniel R. Kuritzkes, MD, Deenan Pillay, MD, PhD, Jonathan M. Schapiro, MD, and Douglas D. Richman, MD

Topics HIV Med. **16(5):138-145. Updates available at www.iasusa.org.**

*The International AIDS Society–USA (IAS–USA) is a not-for-profit, HIV clinical specialist-education organization.
It is entirely different from and not affiliated with the International AIDS Society (Stockholm, Sweden).

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Mutations Selected by nRTIs

Multi-nRTI Resistance: 69 Insertion Complex (affects all nRTIs currently approved by the US FDA)

M	A	▼	K	L	T	K
41	62	69	70	210	215	219
L	V	Insert	R	W	Y F	Q E

Multi-nRTI Resistance: 151 Complex (affects all nRTIs currently approved by the US FDA except tenofovir)

A	V	F	F	Q
62	75	77	116	151
V	I	L	Y	M

Multi-nRTI Resistance: Thymidine Analogue-associated Mutations (TAMs; affect all nRTIs currently approved by the US FDA)

M	D	K	L	T	K
41	67	70	210	215	219
L	N	R	W	Y F	Q E

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Johnson et al. *Topics HIV Med*. December 2008.
Update available at www.iasusa.org.

Mutations Selected by nRTIs

	41	65	67	70	74	115	184	210	215	219
Abacavir		K 65 R			L 74 V	Y 115 F	M 184 V			
Didanosine		K 65 R			L 74 V					
Emtricitabine		K 65 R					M 184 V/I			
Lamivudine		K 65 R					M 184 V/I			
Stavudine	M 41 L		D 67 N	K 70 R				L 210 W	T 215 Y/F	K 219 Q/E
Tenofovir		K 65 R		K 70 E						
Zidovudine	M 41 L		D 67 N	K 70 R				L 210 W	T 215 Y/F	K 219 Q/E

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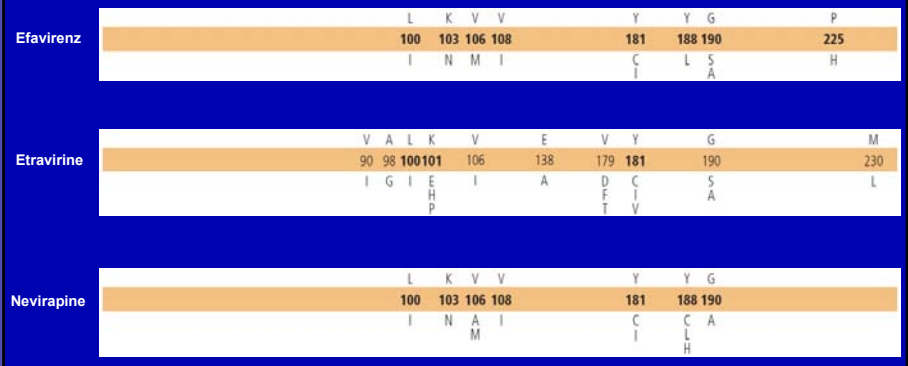
Johnson et al. *Topics HIV Med*. December 2008.
Update available at www.iasusa.org.

Mutations Selected by NNRTIs



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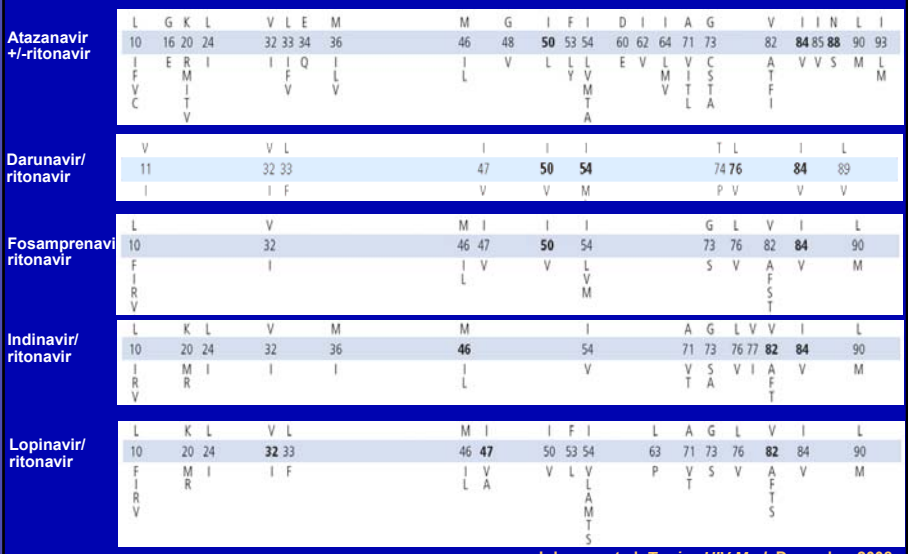
Johnson et al. *Topics HIV Med*. December 2008.
Update available at www.iasusa.org.

Mutations Selected by PIs



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Johnson et al. *Topics HIV Med*. December 2008.
Update available at www.iasusa.org.

Mutations Selected by PIs (cont)

Nelfinavir

L		D		M		M						A			V	V		I		N	L
10		**30**		36		46						71			77	82		84		88	**90**
F I		N		I		I L						V T			I	A F T S		V		D S	M

Saquinavir/ ritonavir

L		L					G		I		I		A	G		V	V		I			L
10		24					**48**		54		62		71	73		77	82		84			**90**
I R V		I					V		V L		V		V T	S		I	A F T S		V			M

Tipranavir /ritonavir

L	I	K		L	E	M		K		M	I		I	Q		H		T		V	N	I			L
10	13	20		**33**	35	36		43		46	**47**		54	**58**		69		**74**		**82**	83	**84**			90
V	V	M R		F	G	I		T		L	V		A M V	E		K		P		L T	D	V			M

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Johnson et al. *Topics HIV Med*. December 2008.
Update available at www.iasusa.org.

Mutations in the Envelope Gene Associated With Resistance to Entry Inhibitors

Enfuvirtide

G	I	V	Q	Q		N	N
36	37	38	39	40		42	43
D S	V	A M E	R	H		T	D

Maraviroc

See User Note

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Johnson et al. *Topics HIV Med*. December 2008.
Update available at www.iasusa.org.

Mutations in the Integrase Gene Associated With Resistance to Integrase Inhibitors

Raltegravir	Y 143 R H C	Q 148 H K R	N 155 H

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Johnson et al. *Topics HIV Med*. December 2008.
Update available at www.iasusa.org.

Drug Resistance Testing: Benefits and Limitations

Genotyping

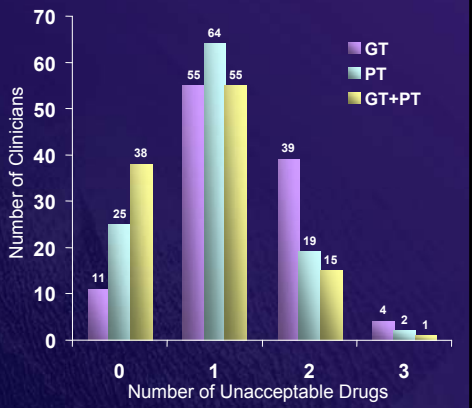
- Less cost
- Identification of mixtures
  - •E.g., 40% of M184V is needed before 3TC phenotype changes
- Identification of variants that reflect prior resistant variants
  - •E.g., T215C, D, N, S
- Major Limitation: Interpretation of complex mutational patterns or reliance on algorithm

Phenotyping

- Direct measure of susceptibility
- Detects Impact of some mutations missed by genotype
  - •E.g., <5% of G190S shifts NVP and EFV sensitivity
- Demonstrates effect of complex combinations of mutations
  - •Resistance and Cross-Resistance
  - •Resensitization
  - •Partial Activity
  - •Replication Capacity
- Ease of interpretation
- Major Limitation: Cost

Genotype + Phenotype Improve Selection of Active ARVs

- Clinicians (n=109) select ARVs for 10 cases based on only GT, PT, or both
  - All had ≥ 1 ARV with PT resistance
  - "Acceptable" defined by consensus of experts
- % median (range) of regimens with ≥3 acceptable ARVs:
  - GT: 65.1 (36.7 to 96.33)
  - PT: 85.8 (42.3 to 99)
  - PT+GT*: 86.2 (47.7 to 97.3)
- Sum: PT+GT had fewest "unacceptable" ARV choices



*(p < 0.001 for main effect of test in log linear models)
Zolopa A, et al. 12th CROI (2005), Abst. 727.

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How to Switch?

- **At least 2 "active" drugs as possible**
  - "Naïve" class: usually fully active
  - "Experienced" class: As active as possible based on resistance testing

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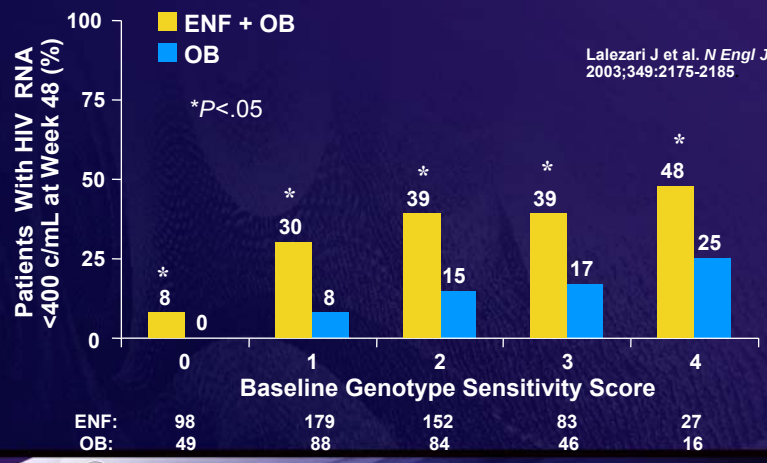
TORO Studies: More Active Drugs Matter



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Uncontrolled Viremia Is Unstable: Risk of New Mutations Leading to More Resistance and Cross-Resistance

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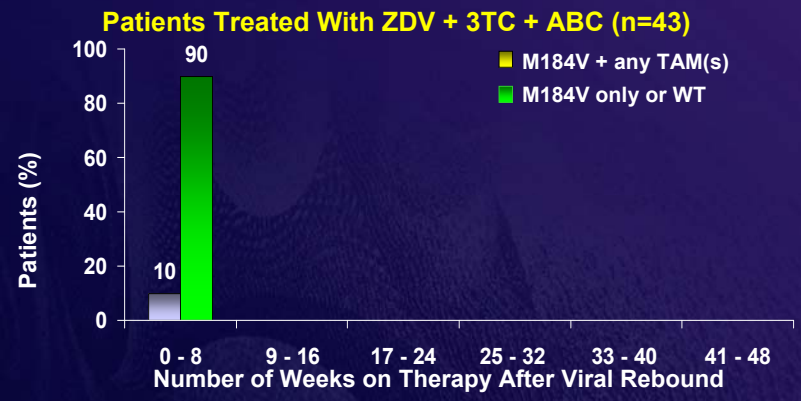
Risks of Nonsuppressive Treatment: Cumulative Resistance Mutations



Melby T et al. 8th Conference on Retroviruses and Opportunistic Infections; 2001. Abstract #448.

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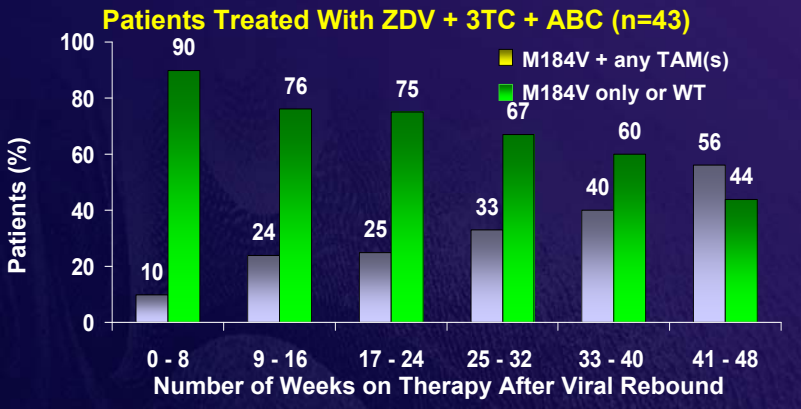
Risks of Nonsuppressive Treatment: Cumulative Resistance Mutations



Melby T et al. 8th Conference on Retroviruses and Opportunistic Infections; 2001. Abstract #448.

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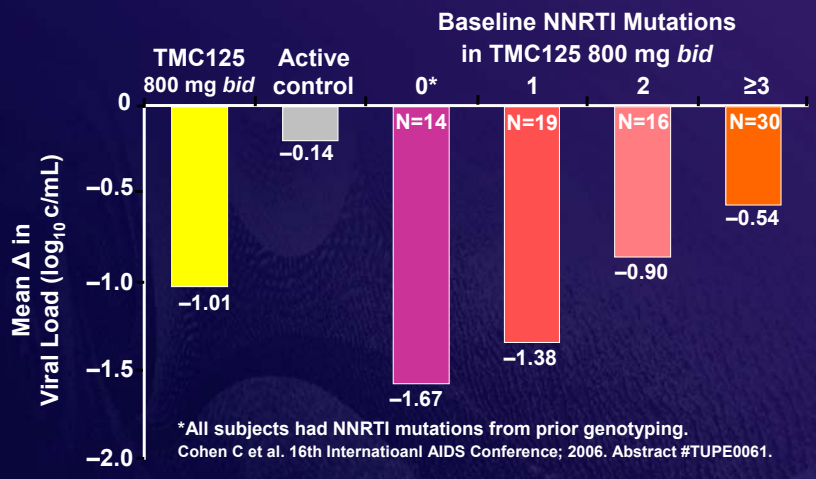
Etravirine (TMC 125): NNRTI Mutations and Response at 48 Weeks



*All subjects had NNRTI mutations from prior genotyping.
Cohen C et al. 16th Internatioanl AIDS Conference; 2006. Abstract #TUPE0061.

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Case Study 1

- 41 year old male, HIV diagnosed in 1999. No other past medical history
- Prior antiretrovirals – all changed due to virologic failure: AZT, D4T, DDI, NVP, NFV, IDV
- Current Regimen: co-formulated tenofovir/emtricitabine, abacavir, LPV/r

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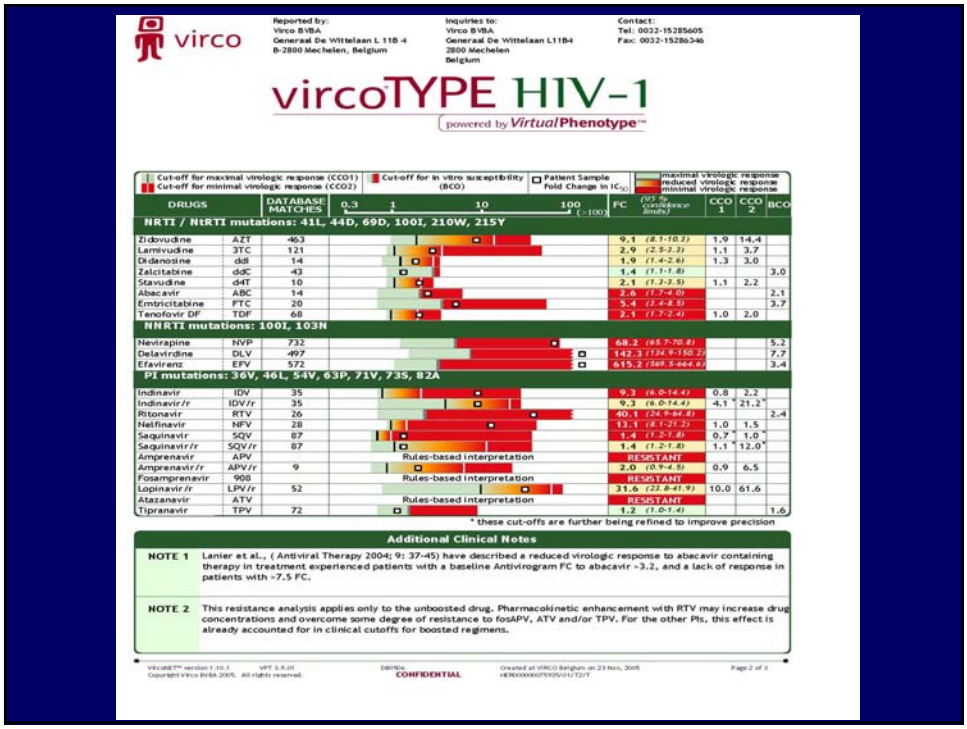

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Cut-off for maximal virologic response (CCO1)
Cut-off for minimal virologic response (CCO2)
Cut-off for in vitro susceptibility (BCO)
Patient Sample Fold Change in IC_{50}
maximal virologic response
reduced virologic response
minimal virologic response

DRUGS	DATABASE MATCHES	0.3 1 10 100 (>100)	FC (95 % confidence limits)	CCO 1	CCO 2	BCO
NRTI / NtRTI mutations: 41L, 44D, 69D, 100I, 210W, 215Y						
Zidovudine	AZT	463	9.1 (8.1-10.3)	1.9	14.4	
Lamivudine	3TC	121	2.9 (2.5-3.3)	1.1	3.7	
Didanosine	ddI	14	1.9 (1.4-2.6)	1.3	3.0	
Zalcitabine	ddC	43	1.4 (1.1-1.8)			3.0
Stavudine	d4T	10	2.1 (1.3-3.5)	1.1	2.2	
Abacavir	ABC	14	2.6 (1.7-4.0)			2.1
Emtricitabine	FTC	20	5.4 (3.4-8.5)			3.7
Tenofovir DF	TDF	68	2.1 (1.7-2.4)	1.0	2.0	
NNRTI mutations: 100I, 103N						
Nevirapine	NVP	732	68.2 (65.7-70.8)			5.2
Delavirdine	DLV	497	142.3 (134.9-150.2)			7.7
Efavirenz	EFV	572	615.2 (569.5-664.6)			3.4
PI mutations: 36V, 46L, 54V, 63P, 71V, 73S, 82A						
Indinavir	IDV	35	9.3 (6.0-14.4)	0.8	2.2	
Indinavir/r	IDV/r	35	9.3 (6.0-14.4)	4.1*	21.2*	
Ritonavir	RTV	26	40.1 (24.9-64.8)			2.4
Nelfinavir	NFV	28	13.1 (8.1-21.2)	1.0	1.5	
Saquinavir	SQV	87	1.4 (1.2-1.8)	0.7*	1.0*	
Saquinavir/r	SQV/r	87	1.4 (1.2-1.8)	1.1*	12.0*	
Amprenavir	APV	Rules-based interpretation		RESISTANT		
Amprenavir/r	APV/r	9	2.0 (0.9-4.5)	0.9	6.5	
Fosamprenavir	908	Rules-based interpretation		RESISTANT		
Lopinavir/r	LPV/r	52	31.6 (23.8-41.9)	10.0	61.6	
Atazanavir	ATV	Rules-based interpretation		RESISTANT		
Tipranavir	TPV	72	1.2 (1.0-1.4)			1.6

* these cut-offs are further being refined to improve precision

Additional Clinical Notes

NOTE 1 Lanier et al., (Antiviral Therapy 2004; 9: 37-45) have described a reduced virologic response to abacavir containing therapy in treatment experienced patients with a baseline Antivirogram FC to abacavir >3.2, and a lack of response in patients with >7.5 FC.

NOTE 2 This resistance analysis applies only to the unboosted drug. Pharmacokinetic enhancement with RTV may increase drug concentrations and overcome some degree of resistance to fosAPV, ATV and/or TPV. For the other PIs, this effect is already accounted for in clinical cutoffs for boosted regimens.

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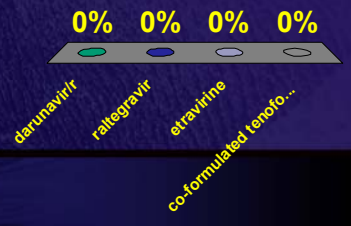
Question 2:
Which of the following are most likely to be effective drugs for this patient?

1. darunavir/r
2. raltegravir
3. etravirine
4. co-formulated tenofovir/emtricitabine



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Putting Together New Regimens: Antiretrovirals 2008 and Beyond

NRTIs
- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

NNRTIs
- Delavirdine
- Efavirenz
- Nevirapine
- Etravirine
- Rilpivirine*

Protease Inhibitors (PIs)
- Atazanavir
- Darunavir†
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir†

Entry Inhibitors
- Enfuvirtide
- Maraviroc
- Vicriviroc*

Integrase Inhibitors
- Raltegravir
- Elvitegravir*

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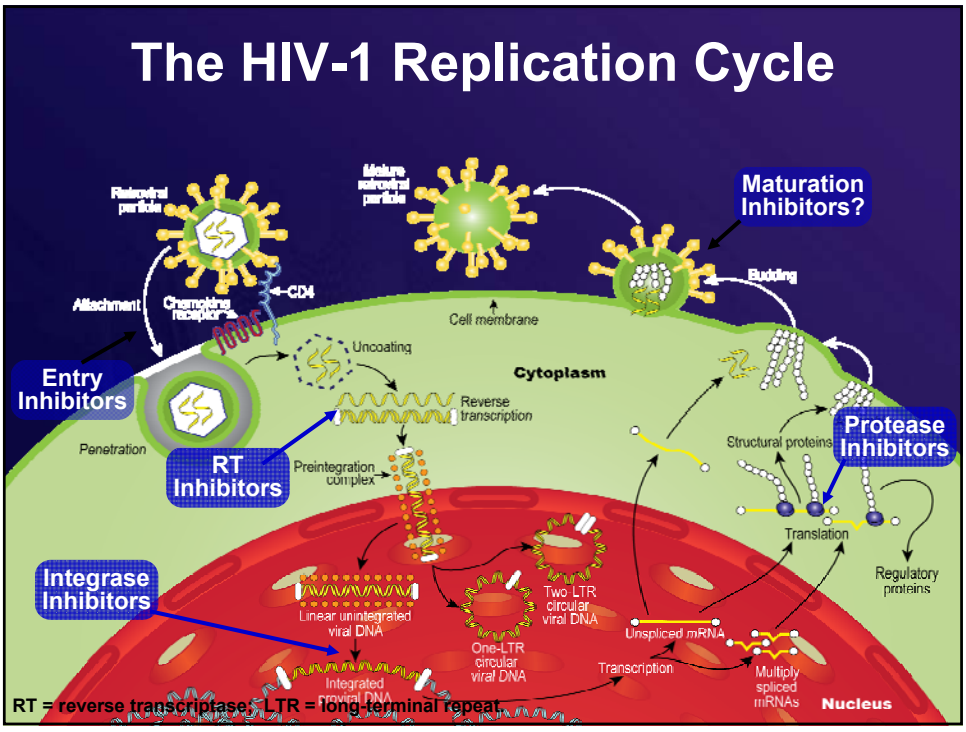
The HIV-1 Replication Cycle

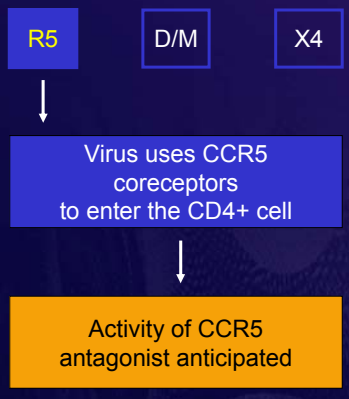


RT = reverse transcriptase; LTR = long-terminal repeat.

New Agents

- **Recently Approved Classes:**
  - CCR5 receptor antagonists
    - maraviroc
  - Integrase Inhibitors
    - raltegravir
- **Recently Expanded Classes:**
  - Protease Inhibitors
    - Darunavir
  - NNRTIs
    - etravirine

Tropism Testing



Standard *Trofile* assay[1]

- Proven negative predictive value
- Detects X4 virus with 100% accuracy when X4 comprises ≥ 10% of viral population

Enhanced *Trofile* assay[2]

- Increased sensitivity by 10- to 100-fold over standard *Trofile* assay
- Retrospective analysis of ACTG 5211 study of VCV: identified more patients with D/M virus at screening vs standard tropism assay
  - 25 of 116 subjects reclassified with D/M virus at screening
  - 15 of 25 patients received VCV; 12 (80%) experienced VF with D/M virus by standard tropism assay

1. Gulick R, et al. IAC 2006. Abstract THLB0217.
2. Reeves J, et al. CROI 2008. Abstract 869.

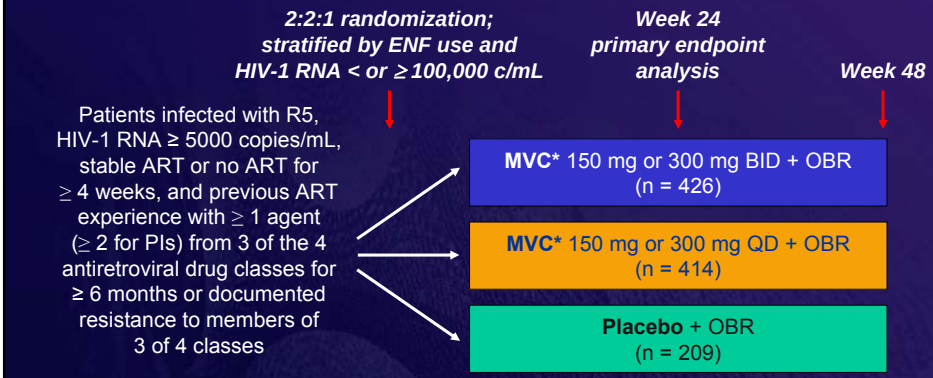
Prevalence of Coreceptor Tropism

Study	Population	Sample, n	R5 Only, %	D/M, %	X4 Only, %
Demarest et al[1]	**Naive**	**325**	**88**	**12**	**0**
HOMER[2]	**Naive**	**979**	**82**	**18**	**0.1**
Moyle et al[3]	**Naive**	**402**	**81**	**19**	**NA**
Study 1026[4]	**Naive**	**1428**	**85**	**15**	**< 1**
Demarest et al[1]	**Experienced**	**117**	**67**	**28**	**5**
Moyle et al[3]	**Experienced**	**161**	**78**	**22**	**NA**
SCOPE[5]	**Experienced**	**186**	**60**	**39.5**	**0.5**
Melby et al[6]	**Experienced**	**724**	**50**	**48**	**2**
Wilkin et al[7]	**Experienced**	**391**	**49**	**47**	**4**
MOTIVATE 1 & 2[4]	**Experienced**	**2560**	**56**	**41**	**3**

1. Demarest J, et al. ICAAC 2004. Abstract H-1136. 2. Brumme ZL, et al. J Infect Dis. 2005;192:466-474. 3. Moyle GJ, et al. J Infect Dis. 2005;191:866-872. 4. Coakley E, et al. 2nd Viral Entry Workshop 2006. Abstract 8. 5. Wilkin T, et al. CROI 2006. Abstract 655. 6. Melby T, et al. J Infect Dis. 2006;194:238-246. 7. Wilkin T, et al. Clin Infect Dis. 2007;44:591-595.

MOTIVATE 1 & 2: MVC in Treatment-Experienced Patients With R5 Virus

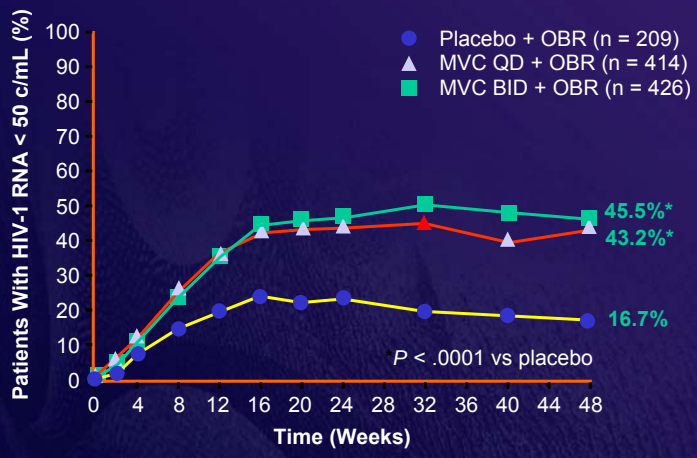
- **Randomized, double-blind, placebo-controlled, phase IIb/III study**



*Patients receiving PI (except TPV) or delavirdine received 150 mg; all others received 300 mg.

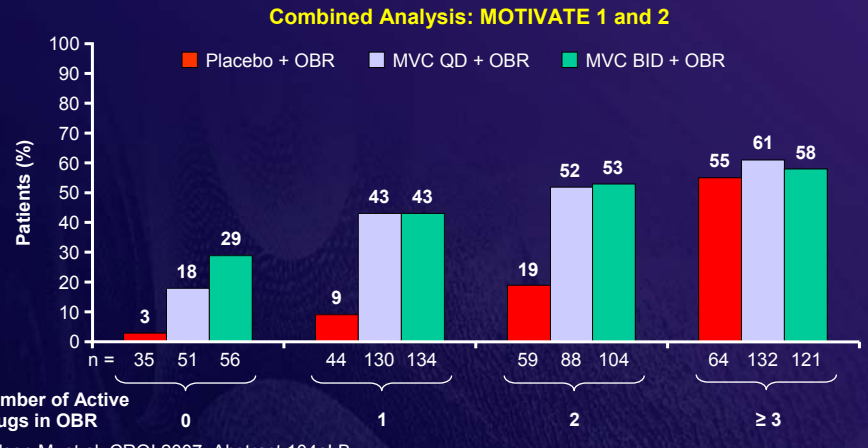
Hardy D, et al. CROI 2008. Abstract 792.

MOTIVATE 1 & 2: Combined Virologic Efficacy at Week 48



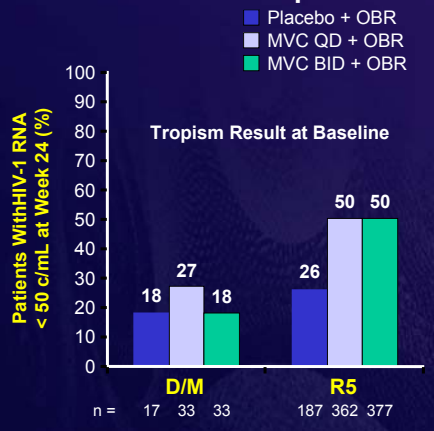
Hardy D, et al. CROI 2008. Abstract 792.

MOTIVATE 1 & 2: HIV-1 RNA < 50 c/mL at Wk 24 by No. of Active Drugs in OBR



Nelson M, et al. CROI 2007. Abstract 104aLB.
Lalezari J, et al. CROI 2007. Abstract 104bLB.

MOTIVATE 1 & 2: Virologic Outcomes Based on Tropism and Resistance



- **At Week 48, ~ 50% of patients in QD arm and ~ 63% of BID arm of MOTIVATE 1 who had tropism results available had D/M or X4 virus at time of failure[1]**
- **Analysis of MVC resistance in 36 patients with R5 virus at failure[2]**
  - Among those failing with R5 virus, 43% had evidence of MVC resistance
  - gp120 V3 loop mutations important in conferring genotypic resistance to MVC

1. Van der Ryst, et al. ICAAC 2007 Abstract H-715.
2. Lewis M, et al. CROI 2008. Abstract 871.

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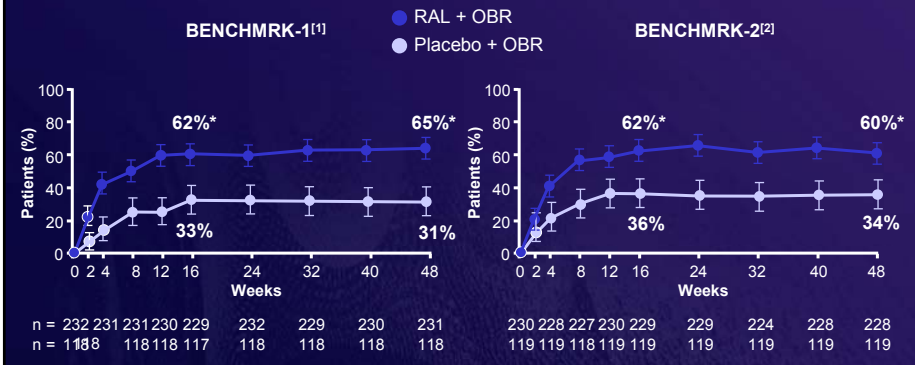
BENCHMRK-1 & -2: Patients With HIV-1 RNA < 50 c/mL at Week 48



*P < .001 for RAL vs placebo, derived from a logistic regression model adjusted for baseline HIV-1 RNA level (log_{10}), first ENF use in OBR, first DRV use in OBR, active PI in OBR.

1. Cooper DA, et al. CROI 2008. Abstract 788. 2. Steigbigel R, et al. CROI 2008. Abstract 789.
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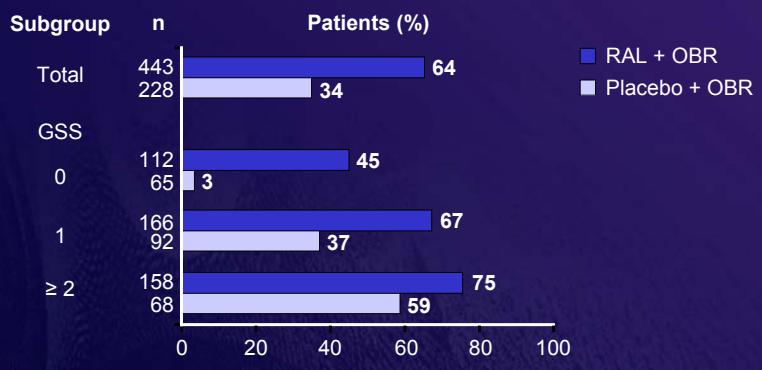
BENCHMRK-1 & -2: HIV-1 RNA < 50 c/mL at Week 48, Overall, and by Genotypic Susceptibility Score



Cooper DA, et al. CROI 2008. Abstract 788. Steigbigel R, et al. CROI 2008. Abstract 789. Adapted with permission of Merck & Co., Inc., Whitehouse Station, New Jersey, USA, Copyright © 2008 Merck & Co., Inc. All Rights Reserved.

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BENCHMRK-1 & -2: Resistance Analysis and Cross Resistance to elvitegravir

- **67% (63/94) of patients* in BENCHMRK-1 and -2 with virologic failure had ≥ 1 mutation in integrase**
- **Virologic failure generally associated with mutations at Q148 or N155, in combination with at least 1 other mutation**
- **Separate report of 2 patients with virologic failure on EVG/RTV, with no HIV-1 RNA response during first week after switch to RAL**
  - Suggests high level of cross-resistance between EVG and RAL

*In patients for whom integrase genotypic data were available at baseline and follow-up.

1.Cooper DA, et al. CROI 2008. Abstract 788. 2. Steigbigel R, et al. CROI 2008. Abstract 789. 3. DeJesus E , et al. IAS 2007. Abstract TUPEB032

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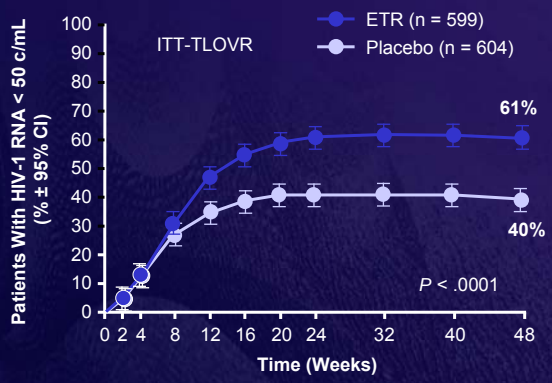
DUET-1 and -2: VL < 50 c/mL at Wk 48,Overall, and by Active Agents in OBR

- Mean change in CD4+ cell count at Week 48 significantly greater in ETR arm: +98 cells/mm^3 vs +73 cells/mm^3 in placebo[1,2]



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

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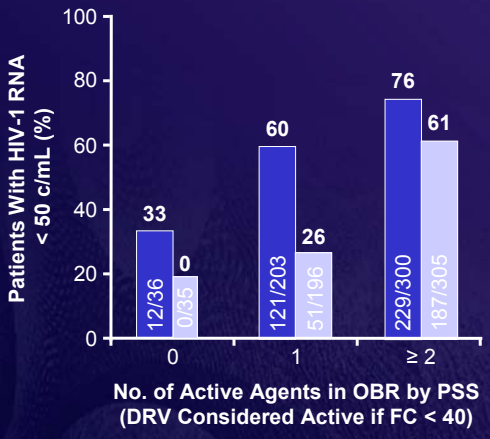
DUET-1 and -2: HIV-1 RNA < 50 c/mL at Week 48 by Phenotypic Susceptibility Score



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

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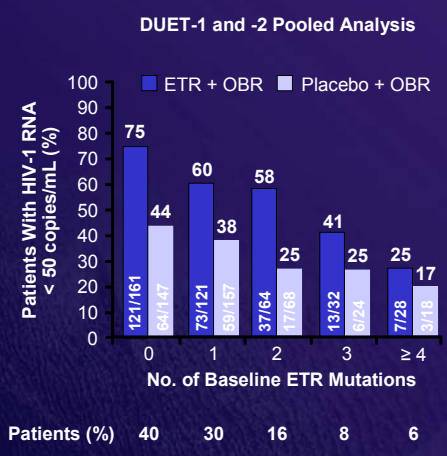
DUET-1 and -2: Predictors of ETR Response and Resistance at Failure

- **13 mutations associated with ETR resistance**
  - V90I
  - L100I
  - V106I
  - Y181C/I/V
  - A98G
  - K101E/P
  - V179D/F
  - G190A/S
- **Presence of ≥ 3 ETR mutations associated with response similar to overall placebo + OBR response**
  - 14% of patients had ≥ 3 ETR resistance mutations at baseline
- **Most common resistance mutations emerging at ETR failure in DUET trials: V179F/I and Y181C/I**



Cahn P, et al. ICAAC 2007. Abstract H-717.
Intelence [package insert]. Raritan, NJ: Tibotec Therapeutics; 2008.

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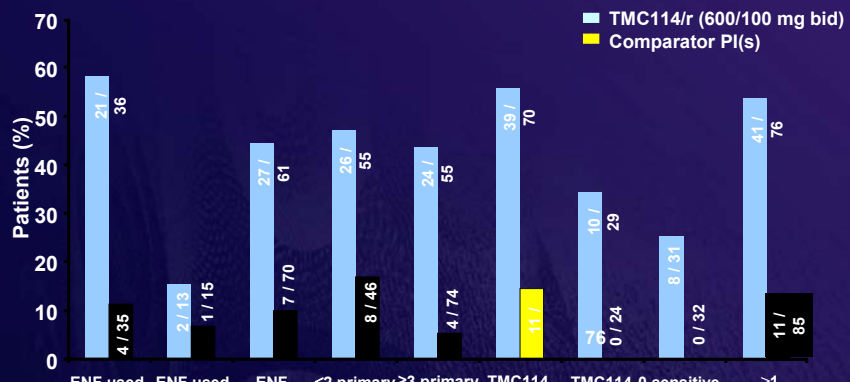
POWER 1 and 2: HIV RNA <50 Copies/mL Week 48 (ITT-TLOVR)



FC = fold change in EC_{50}.

Walmsley S et al. 16th International AIDS Conference; 2006. Abstract #TUAB0104.

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Tipranavir and Darunavir Mutations

TPV*	10V		13V	20M/R/V		33F	35G	36I	43T	46L	47V
DRV†		11I			32I	33F					47V

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

*TPV mutations: 0–1: best response; 2–7 intermediate response; ≥8: no response
†DRV mutations: ≥3: decreased response

Kohlbrenner VM et al. 13th International HIV Drug Resistance Workshop; 2004. Abstract #129; DeMeyer SD et al. *Antivir Ther.* 2006;11:S83.

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Using The Newest PIs: The Role of Adding a New Class

Haubrich R *et al*. 43rd Annual Meeting of the Infectious Diseases Society of America; 2005. Abstract #785; Lazzarin A et al. *N Engl J Med.* 2003;348:2186-95; Moyle GM et al. 12th Annual Meeting of the British HIV Association; 2006. Poster #P1.

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Case Study 3

- **53 y.o. woman, HIV+ Dx 1985**
- **CD4 cell count: 10 cells/mm^3**
- **Viral load: >750,000 c/mL**
- **Prior Rx: almost everything**
- **No current Rx: off meds x 20 months;**
  - Was intolerant of last regimen:
  - LPV/r, APV, ABC/3TC
  - 2007 resistance assays available while on that regimen

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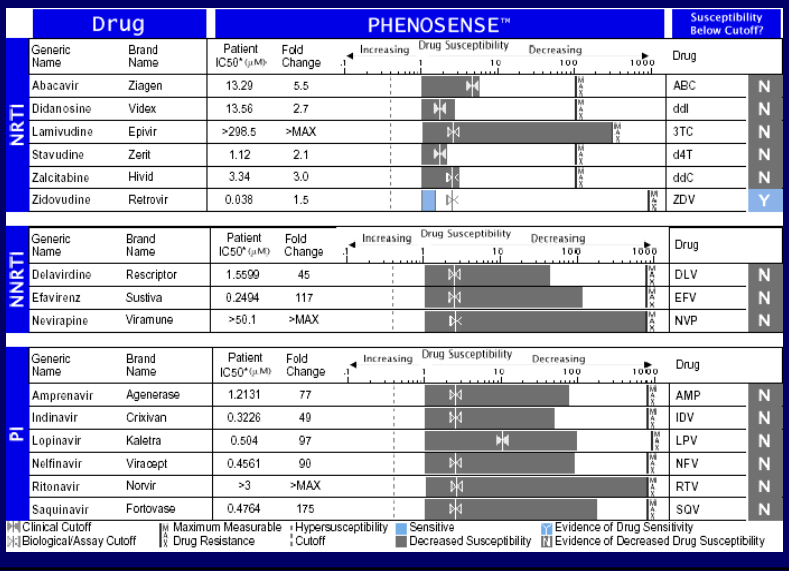
Genotype/Virtual Phenotype

NRTI / NtRTI mutations: 41L, 44D, 67N, 74V, 118I, 181C, 184V, 210W, 215Y, 219N						
Retrovir®	Zidovudine	AZT	384	7.7	4.0	
Epivir®	Lamivudine	3TC	945	47.3	4.5	
Videx®	Didanosine	ddI	171	2.9	2.0	
Hivid®	Zalcitabine	ddC	197	2.4	2.0	
Zerit®	Stavudine	d4T	682	1.9	1.7	
Ziagen®	Abacavir	ABC	221	5.4	3.0	3.2
Emtriva®	Emtricitabine	FTC		Rules-based interpretation	Resistance likely	
Viread®	Tenofovir DF	TDF	2,055	1.5	3.0	
NNRTI mutations: 101Q, 108I, 181C, 184V, 190A						
Viramune®	Nevirapine	NVP	417	65.2	8.0	
Rescriptor®	Delavirdine	DLV	518	40.1	10.0	
Sustiva®, Stocrin®	Efavirenz	EFV	408	151.0	6.0	
PI mutations: 10I, 20I, 36I, 46I, 71V, 71T, 71I, 74S, 77I, 90M						
Crixivan®	Indinavir	IDV	193	36.1	3.0	
Norvir®	Ritonavir	RTV	183	194.9	3.5	
Viracept®	Nelfinavir	NFV	196	43.5	4.0	
Invirase®, Fortovase®	Saquinavir	SQV	476	36.7	2.5	
Agenerase®	Amprenavir	APV	54	36.9	2.0	
A component of Kaletra®	Lopinavir	LPV	24	92.9	2.5	10.0
Reyataz™	Atazanavir	ATV	75	84.8	2.4	

Phenotype



Drug			PHENOSENSE™			Susceptibility Below Cutoff?
	Generic Name	Brand Name	Patient IC50* (μM)	Fold Change	Drug	
NRTI	Abacavir	Ziagen	13.29	5.5	ABC	N
	Didanosine	Videx	13.56	2.7	ddI	N
	Lamivudine	Epivir	>298.5	>MAX	3TC	N
	Stavudine	Zerit	1.12	2.1	d4T	N
	Zalcitabine	Hivid	3.34	3.0	ddC	N
	Zidovudine	Retrovir	0.038	1.5	ZDV	Y
NNRTI	Delavirdine	Rescriptor	1.5599	45	DLV	N
	Efavirenz	Sustiva	0.2494	117	EFV	N
	Nevirapine	Viramune	>50.1	>MAX	NVP	N
PI	Amprenavir	Agenerase	1.2131	77	AMP	N
	Indinavir	Crixivan	0.3226	49	IDV	N
	Lopinavir	Kaletra	0.504	97	LPV	N
	Nelfinavir	Viracept	0.4561	90	NFV	N
	Ritonavir	Norvir	>3	>MAX	RTV	N
	Saquinavir	Fortovase	0.4764	175	SQV	N

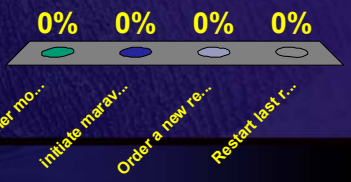
Increasing Drug Susceptibility Decreasing (.1, 1, 10, 100, 1000)

Clinical Cutoff | Biological/Assay Cutoff | Maximum Measurable | Drug Resistance | Hypersusceptibility | Cutoff | Sensitive | Decreased Susceptibility | Evidence of Drug Sensitivity | Evidence of Decreased Drug Susceptibility

Question 3

What is the most appropriate next step?

1. restart her most recent regimen
2. initiate maraviroc, darunavir/r, co-formulare tenofovir/emtricitabine
3. Order a new resistant assay and tropism assay
4. Restart last regimen except for lamivudine due to its significantly elevated fold change



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When Should Switching Be Delayed?

- **When the chance of resuppression is "low"**
  - Insufficient "active" drugs available
  - New, active agents anticipated soon
- **When the risk from immunocompromise is low**

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Partial Suppression Can Minimize the Immunologic Consequences of Viremia

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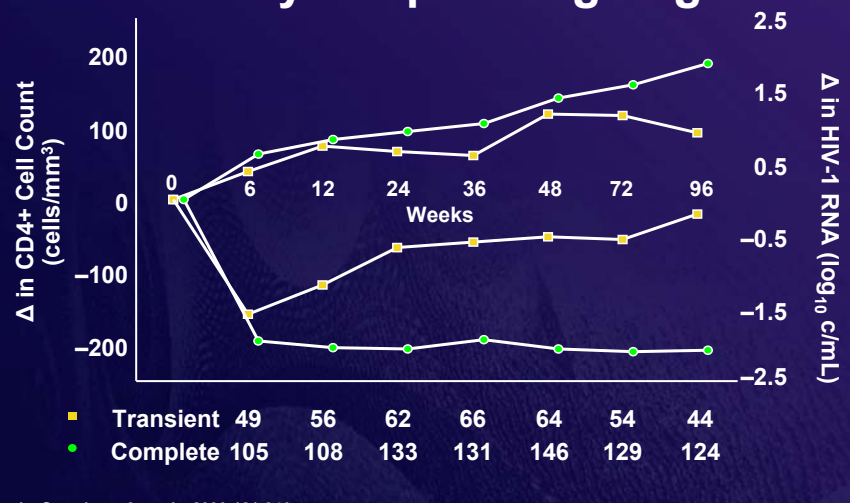
CD4 Stability Despite Ongoing Viremia



Deeks S et al. *J Infect Dis.* 2000;181:946.

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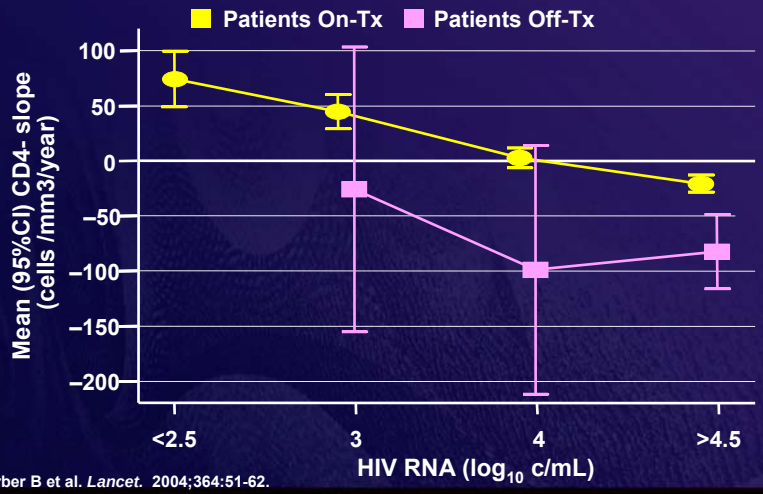
CD4 Slopes: On-Treatment vs Off-Treatment



Ledergerber B et al. *Lancet.* 2004;364:51-62.

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What contributes to partial suppression despite resistance?

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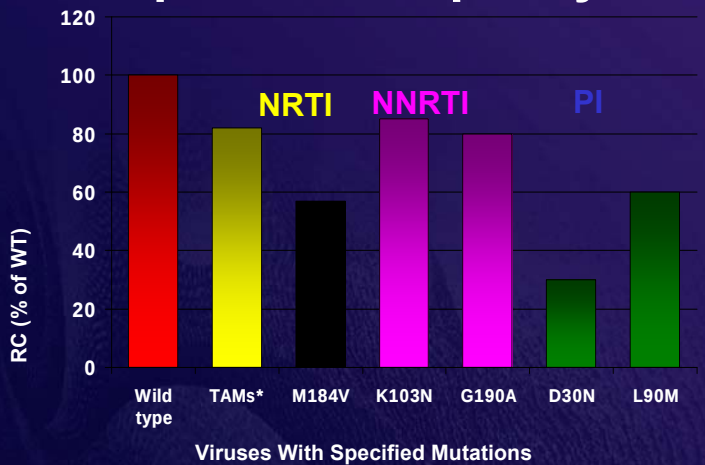
Mutations and Impact on Replicative Capacity



McColl DJ et al. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2004. Abstract #H-178.

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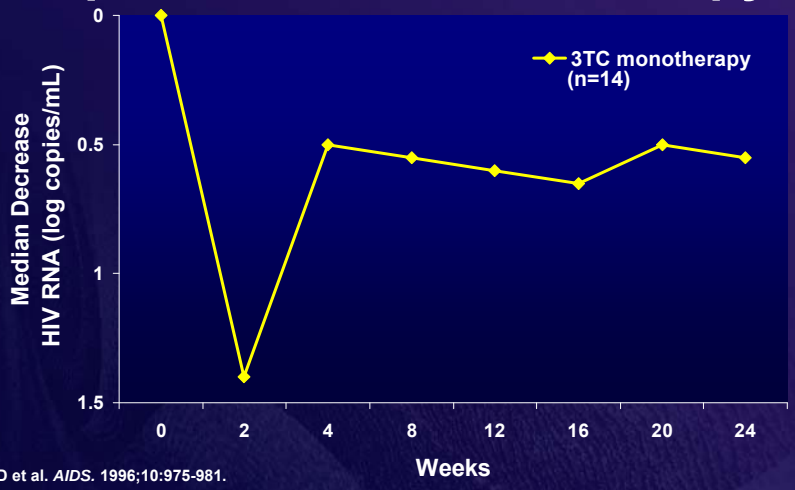
Response to 3TC Monotherapy



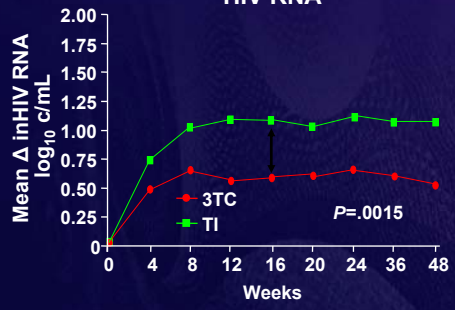
Kuritzkes D et al. *AIDS*. 1996;10:975-981.

E-184V Study: 3TC Monotherapy vs Treatment Interruption (TI)

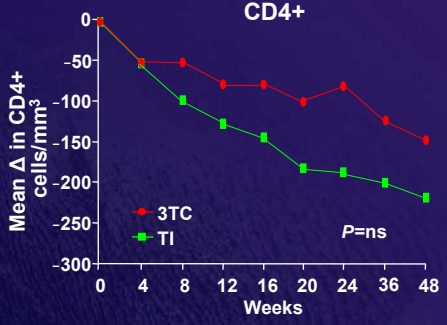
- Prospective, open-label randomized study (*n*=29 in both groups); on 3TC-containing regimen

- HIV RNA >1000 c/mL
- CD4+ >500 c/mm^3
- Have M184V mutation

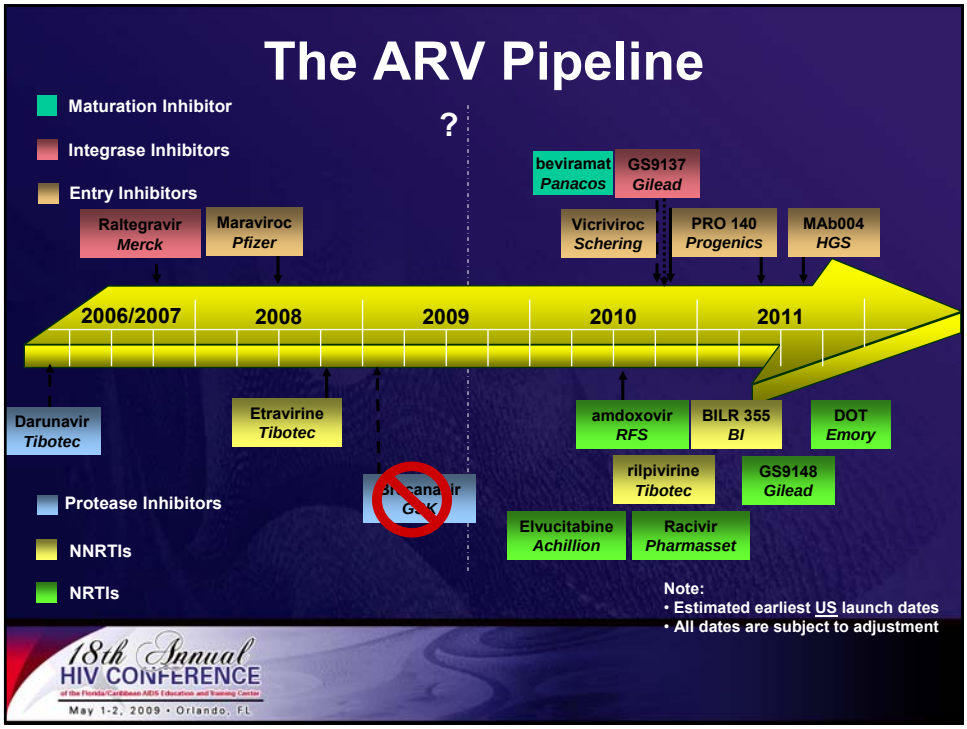
HIV RNA



CD4+



Castagna A et al. 3rd Annual meeting of the International AIDS Society; 2005. Abstract #WeFo0204.



Summary

- **Preventing resistance essential**
- **Increasing options for active regimens despite resistance**
- **Timing of when to switch complex**
  - When suppression likely, *or*
  - When clinical progression likely
- **Defining an active regimen easier**
  - At least 2 active drugs, often including
    - An agent from a new class
    - "Second generation" agents within existing classes

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