

# Treatment Experienced Patients: Update on Trials

Brad Hare, MD

Associate Professor of Medicine, UCSF

Medical Director, HIV/AIDS Clinic, San Francisco General Hospital

April 8, 2011



# Learning Objectives

Upon completion of this presentation, learners should be able to:

- Make ART changes in treatment experienced patients in response to
  - Resistance/Virologic failure
  - Tolerability/Toxicity
  - Simplification
- Cite clinical trials that support ART management in treatment experienced patients



# Off-Label Disclosure

Off-label/investigational uses may be discussed in this presentation, and I will identify those during the presentation



# Audience poll

In your practice, which of the following poses the greatest challenge in antiretroviral therapy management?

1. Choosing a first-line regimen for treatment naïve patients
2. Changing an existing regimen due to tolerability or toxicity
3. Changing an existing regimen for simplification
4. Changing an existing regimen due to virologic failure or resistance
5. Suppressing virus in a patient with high level resistance



# Case 1

- MJ is a 42yo gay man, diagnosed HIV+ in 2006. CD4 = 330 cells/mm<sup>3</sup>; HIV RNA = 90,000 c/mL. Started TDF/FTC/EFV in 2007. HIV RNA undetectable within 4 months. CD4 increased to 530. Recently lost his insurance and transferred to your practice. He has been skipping doses of his TDF/FTC/EFV to “stretch it out.”
- New labs at your first visit:
  - CD4 = 522 cells/mm<sup>3</sup>
  - HIV RNA = 1,743 c/mL



# Audience Question

Repeat HIV RNA is 1,133 c/mL.  
What do you do next?

1. Stress adherence and repeat HIV RNA in 1 month
2. Order genotype resistance testing
3. Switch to TDF/FTC + RAL
4. Switch to TDF/FTC + DRV/r

# Virologic Definitions

- ***Virologic suppression:*** A confirmed HIV RNA level below the limit of assay detection (e.g., <48 copies/mL).
- ***Virologic failure:*** The inability to achieve or maintain suppression of viral replication (to an HIV RNA level <200 copies/mL).
- ***Virologic rebound:*** Confirmed detectable HIV RNA (to >200 copies/mL) after virologic suppression.
- ***Persistent low-level viremia:*** Confirmed detectable HIV RNA levels that are <1,000 copies/mL.
- ***Virologic blip:*** After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.

# Virologic Definitions

- ***Virologic suppression:*** A confirmed HIV RNA level below the limit of assay detection (e.g., <48 copies/mL).
- ***Virologic failure:*** The inability to achieve or maintain suppression of viral replication (to an HIV RNA level <200 copies/mL).
- ***Virologic rebound:*** Confirmed detectable HIV RNA (to >200 copies/mL) after virologic suppression.
- ***Persistent low-level viremia:*** Confirmed detectable HIV RNA levels that are <1,000 copies/mL.
- ***Virologic blip:*** After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.

# Switch for Virologic Failure

- Change regimen as soon as possible to avoid progressive accumulation of resistance mutations
- Ideally, a new ARV regimen should contain at least two, and preferably three, fully active drugs on the basis of drug treatment history, resistance testing, or new mechanistic class
- Goal is to re-establish virologic suppression (e.g., HIV RNA <48 copies/mL)

# Genotype Results

- RT: M184V, K103N
- PRO: L63P

# Resistance Consequences of Initial NNRTI-Based Regimen Failure

■ Likely (> 30%)    
 ■ Less likely (10% to 30%)    
 ■ Rare (< 10%) or none

DHHS Preferred Regimens	HIV-1 RNA < 50 copies/mL at Wk 48, %	Detectable Resistance at VF*		
		NRTI		NNRTI
		M184V/I	Other	
EFV, TDF, FTC	80 (n = 244) <sup>[1]</sup>			
	82 (n = 230) <sup>[2]</sup>			
	90 <sup>†</sup> (n = 464) <sup>[3]</sup>			
EFV, TDF, 3TC	76 (n = 299) <sup>[4]</sup>			

\*For patients with available baseline and postfailure genotypes.

<sup>†</sup>96 wks.

1. Gallant JE, et al. N Engl J Med. 2006;354:251-260. 2. Lennox J, et al. Lancet. 2009; 5;374:796-806.

3. Daar E, et al. CROI 2010. Abstract 59LB. 4. Gallant JE, et al. JAMA. 2004;292:191-201.

Slide from Clinical Care Options.

# Audience Question

What regimen do you recommend next?

RT: M184V, K103N; PRO: L63P

1. TDF/FTC + lopinavir/ritonavir
2. TDF/FTC + darunavir/ritonavir
3. TDF/FTC + raltegravir
4. TDF/FTC + etravirine
5. TDF/FTC + darunavir/ritonavir + etravirine

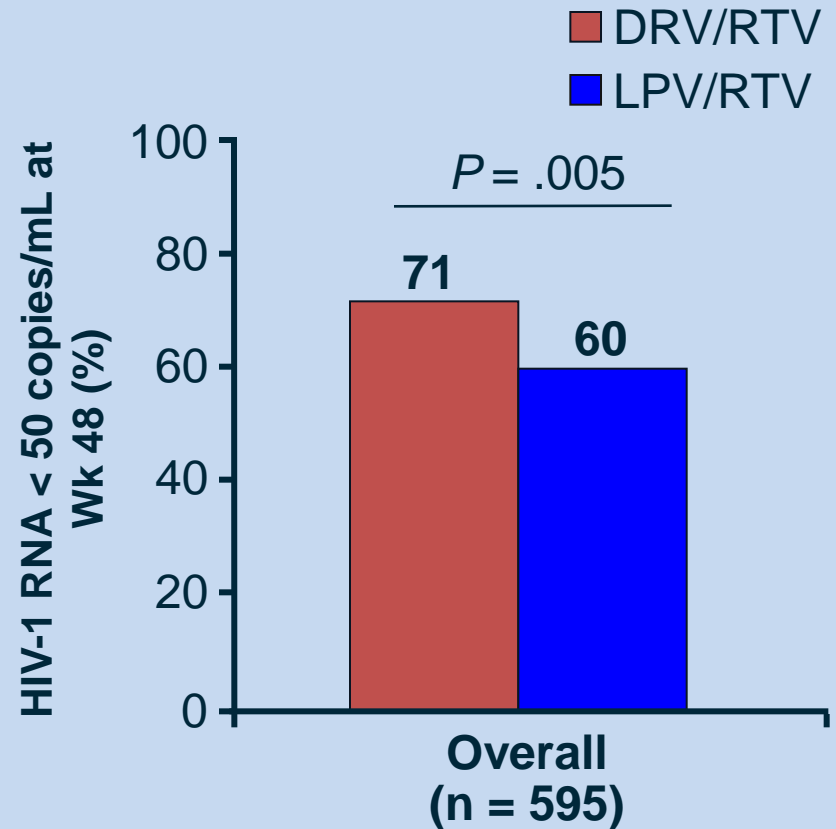
# NRTI + 3TC/FTC + Boosted PI Effective Second-line Regimen in Pts With M184V

- British Columbia HIV Drug Treatment Program, 2000-2006
- Pts with M184V ± NNRTI RAMs but no PI or other NRTI RAMs (N = 117)
- No significant difference in likelihood of HIV-1 RNA suppression between 3 types of second-line regimen
  - No advantage from including an additional active agent or removing lamivudine/emtricitabine

Second-Line Regimen	HR, Time to Virologic Suppression (95% CI)
3TC/FTC + NRTI + boosted PI	Ref
3TC/FTC + NRTI + boosted PI + additional active agent(s)	1.09 (0.60-1.96)
3TC/FTC-sparing NRTIs + boosted PI ± additional active agent(s)	0.61 (0.37-1.03)

# TITAN: Virologic Outcomes With DRV/RTV vs LPV/RTV in Tx-Experienced Patients

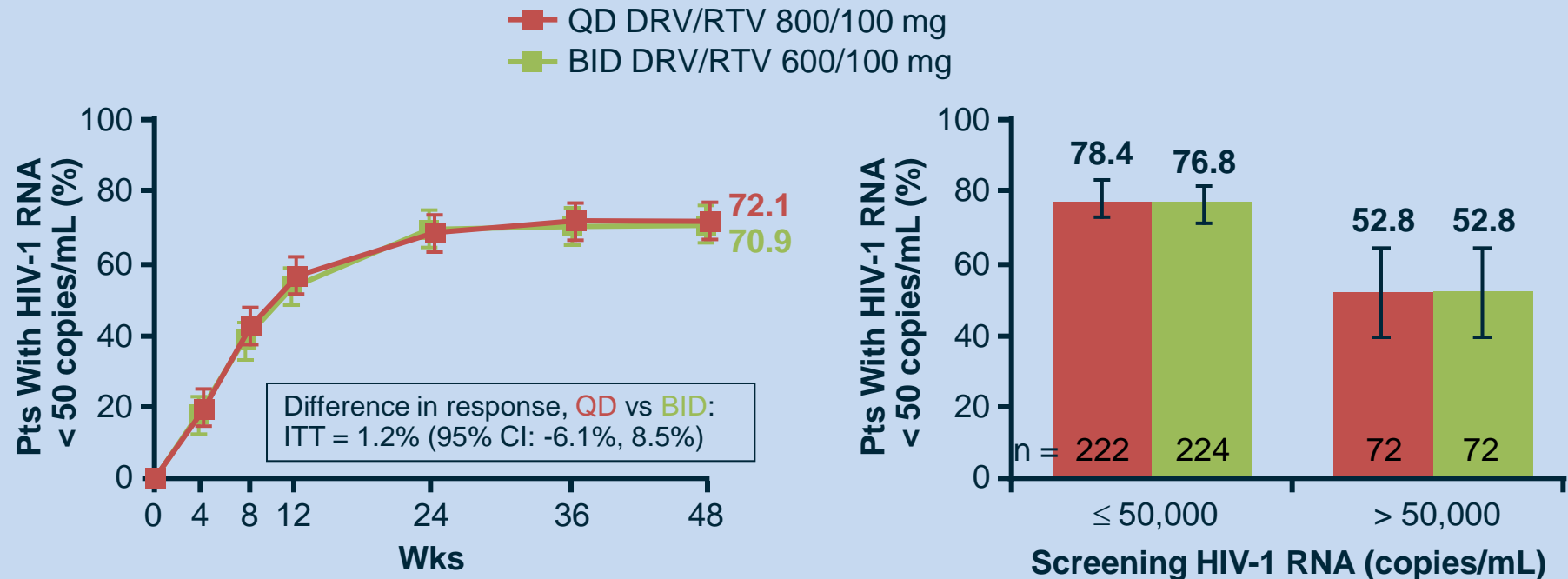
- DRV/RTV BID superior to LPV/RTV BID in rates of
  - HIV-1 RNA < 400 c/mL at Wk 48 (primary endpoint)<sup>[1]</sup>
  - HIV-1 RNA < 50 c/mL at Wk 48<sup>[1]</sup>
  - HIV-1 RNA < 400 c/mL at Wk 96<sup>[2]</sup>
- All analyses ITT-TLOVR



1. Madruga JV, et al. Lancet. 2007;370:49-58. 2. De Meyer S, et al. Glasgow 2008. Abstract O424.

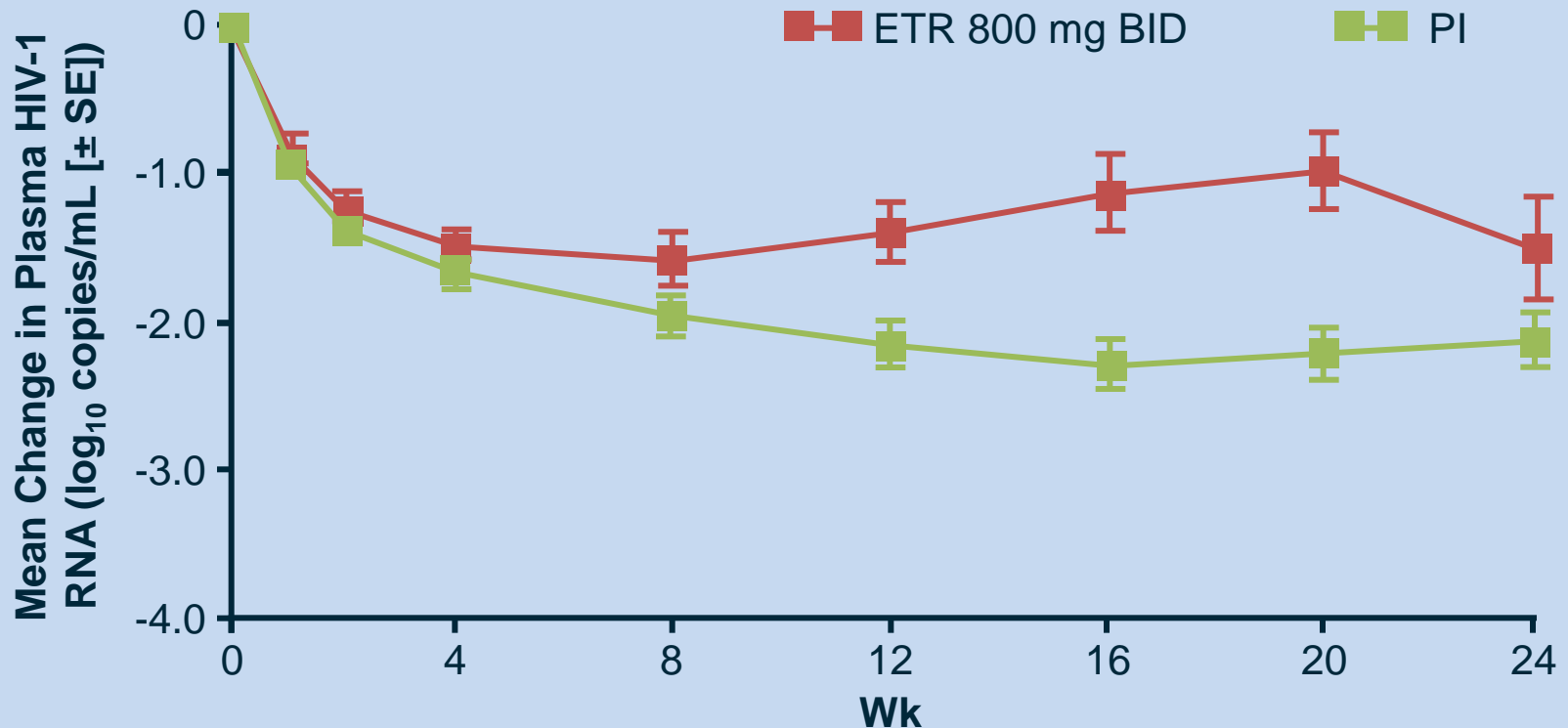
# ODIN: HIV-1 RNA < 50 copies/mL at Wk 48

## Overall and by Screening HIV-1 RNA



- Similar CD4+ cell count increase between arms
  - QD DRV/RTV : +100 cells/mm<sup>3</sup>
  - BID DRV/RTV : +94 cells/mm<sup>3</sup>

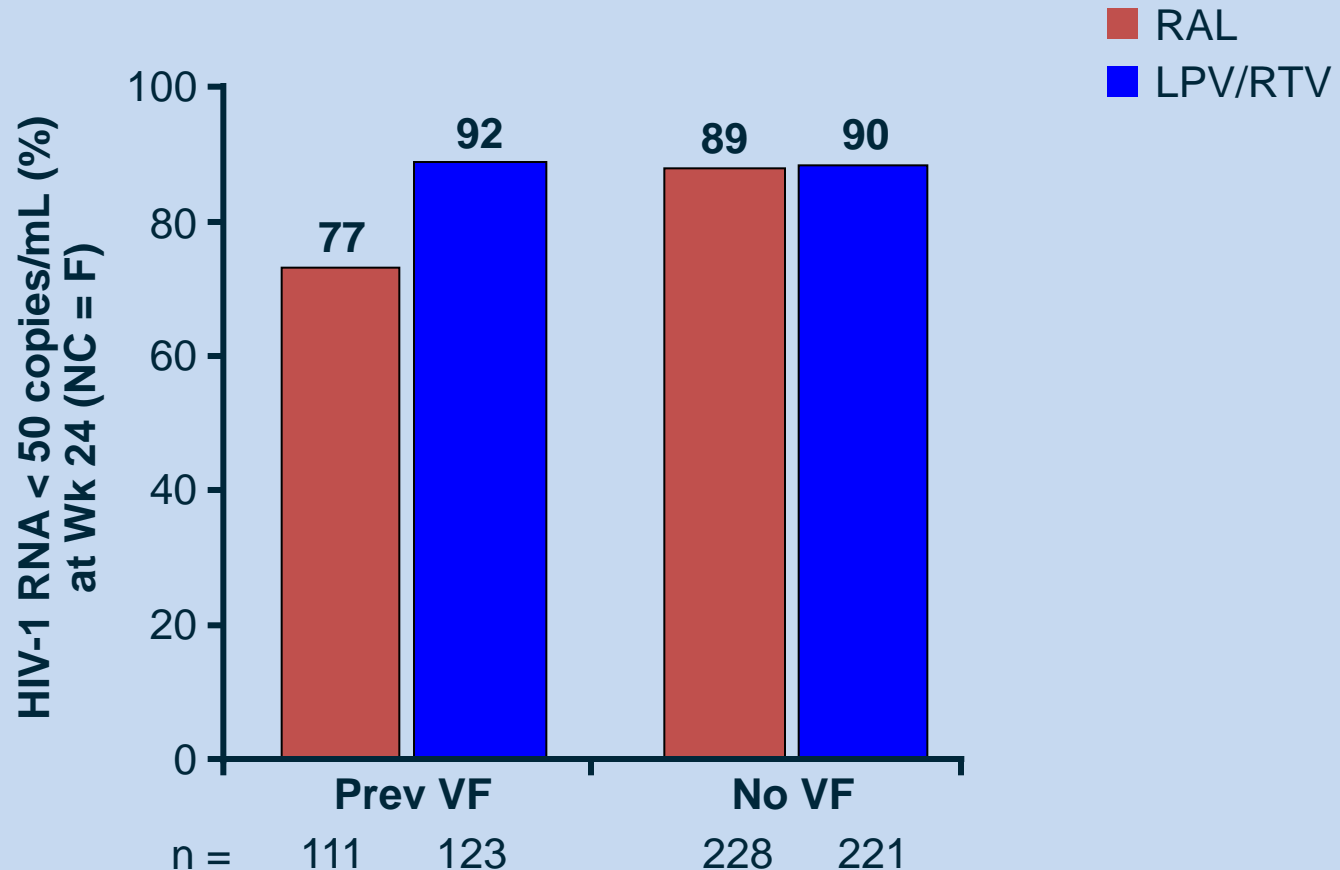
# TMC125-C227: Virologic Response to ETR vs PI in NNRTI-Experienced Patients



ETR, n	59	55	47	40	28	17	8
Control, n	57	55	56	53	52	41	52

Impact of reverse transcriptase resistance on the efficacy of TMC125 (etravirine) with two nucleoside reverse transcriptase inhibitors in protease inhibitor-naïve, nonnucleoside reverse transcriptase inhibitor-experienced patients: study TMC125-C227. Ruxruntham K, et al. HIV Med. Vol ;9:883-896 .Copyright © 2009. Reproduced with permission of John Wiley & Sons, Inc.. Slide from Clinical Care Options.

# Virologic Suppression in SWITCHMRK in Patients With and Without Previous Virologic Failure



# Case 2

- LV is a 41yo AAM, diagnosed HIV+ in 2003 with PcP. CD4 = 78 cells/mm<sup>3</sup>; HIV RNA = 134,000 c/mL. Started on ZDV/3TC + lopinavir/ritonavir in 2003. HIV RNA undetectable since month 3 of treatment. Excellent adherence and tolerance.
- Medical history: HTN
- Meds: HCTZ
- Current labs:
  - CD4 = 372 cells/mm<sup>3</sup>
  - HIV RNA < 40 c/mL

# Case 2

- He has been resistant to treatment modification
  - “Don’t rock the boat”
- Started a new job with longer evening hours and has been missing evening doses of meds 2-3 times per week due to falling asleep early
- Still hesitant, but now open to a regimen change, preferably once daily
  - “... And *no* side effects”
- Lipids and renal function are normal
- Nonsmoker

# Audience Question

What would you recommend next?

1. Continue the same regimen
2. Switch to TDF/FTC/EFV
3. Switch to TDF/FTC\* + once daily LPV/r
4. Switch to TDF/FTC\* + once daily other PI
5. Switch to TDF/FTC\* + once daily RAL

\*or ABC/3TC

# Switching for Simplification

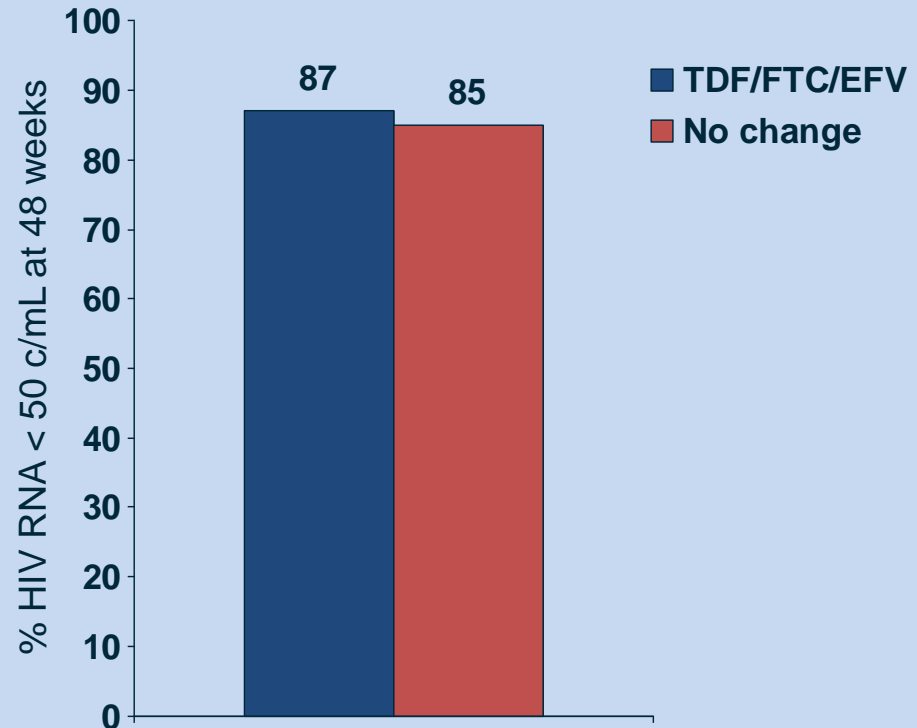
- Rationale:
  - To improve the patient's quality of life
  - To maintain long-term adherence
  - To avoid toxicities that may develop with prolonged ARV use
  - To reduce the risk of virologic failure

# Switching for Simplification

- Good candidates include:
  - Those who are receiving treatments that are no longer recommended as preferred or alternative choices for initial therapy
  - Those who were prescribed a regimen in the setting of treatment failure at a time when there was an incomplete understanding of resistance or drug-drug interaction data
  - Those who were prescribed a regimen prior to the availability of newer options or formulations that might be easier to administer and/or more tolerable
- Those without suspected drug-resistant virus may be easier to simplify than those with documented or suspected drug-resistant virus

# Switch to TDF/FTC/EFV

- Pts on stable ART with HIV RNA < 200 c/mL for 3 months, randomized to:
  - No change in ART (N=97)
  - Change to TDF/FTC/EFV (N=203)
- Discontinuations
  - AEs: 5% (TDF/FTC/EFV) vs 1% (No change arm)
    - Mainly CNS symptoms
  - Voluntary withdrawals: 2% (TDF/FTC/EFV) vs 7% (No change arm)
- Concern for switch if prior NRTI resistance is present



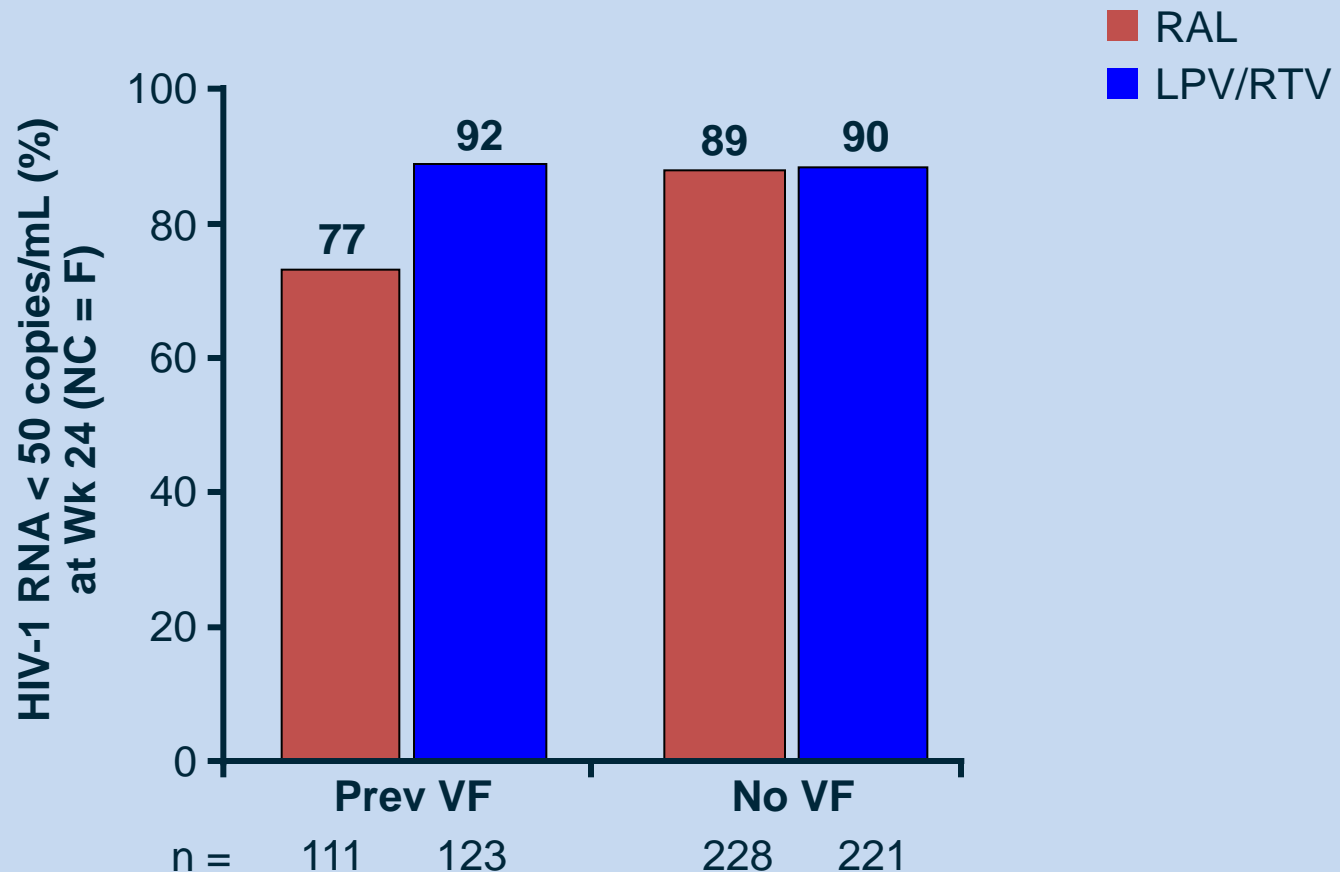
# Switch to Atazanavir/ritonavir

- Pts with HIV RNA < 200 c/mL on LPV/r for  $\geq 6$  months randomized to:
  - Continue LPV/r BID (N=127)
  - Change to ATV/r qD (N=121)
  - No change in NRTIs
- Discontinuations due to AEs were 5% in each arm
- Triglycerides and total cholesterol decreased in ATV/r arm

Results at 48 weeks

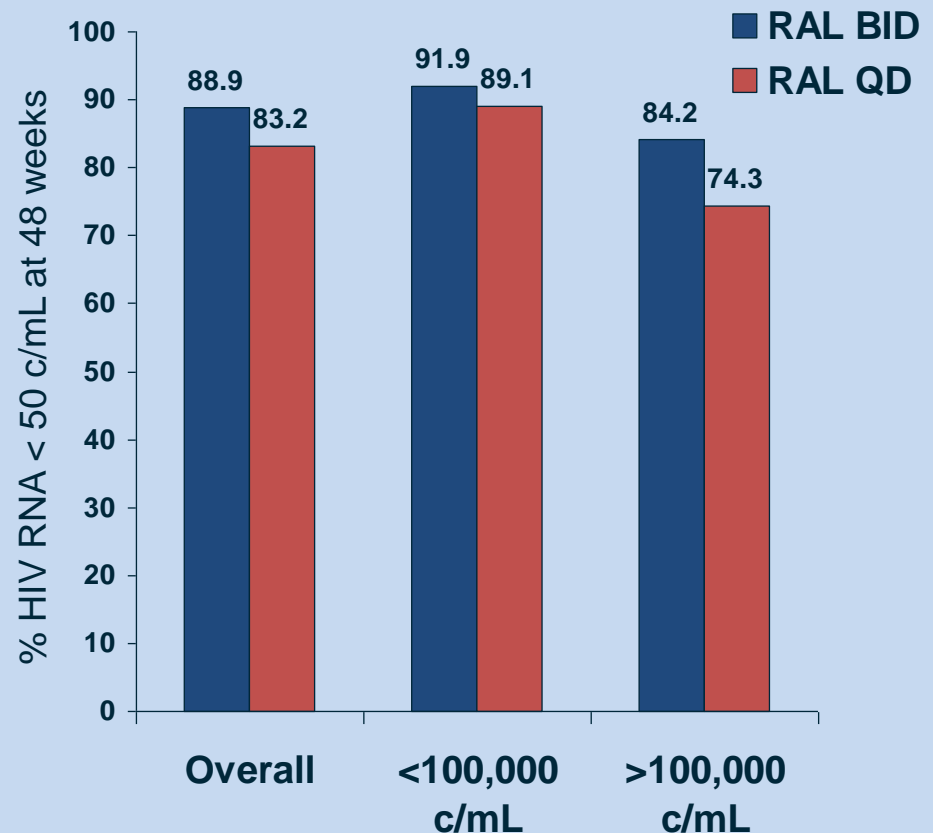
	LPV/r	ATV/r
Treatment failure	20%	17%
Virologic failure	7%	5%

# Virologic Suppression in SWITCHMRK in Patients With and Without Previous VF



# QDMRK: Raltegravir Once vs. Twice Daily in Treatment-Naïve Patients

- Treatment Naïve patients randomized to:
  - TDF/FTC + RAL 800 mg qD (N=382)
  - TDF/FTC + RAL 400 mg BID (N=386)
- Study stopped early
  - Failed to meet pre-specified parameters for non-inferiority
  - Differences accentuated in high baseline HIV RNA
  - More RAL resistance in qD arm (N=9 vs N=2)



Note: Once daily dosing of RAL is off-label

# Case 3

- CH is a 34yo Latina, diagnosed HIV+ in 2008. CD4 = 278 cells/mm<sup>3</sup>; HIV RNA = 28,000 c/mL. Genotype showed no resistance mutations. Started on TDF/FTC + atazanavir/ritonavir in 2008. HIV RNA undetectable since month 3 of treatment. Excellent adherence and tolerance.
- Medical history: HTN, insulin resistance
- Meds: Metoprolol
- Current labs:
  - CD4 = 402 cells/mm<sup>3</sup>
  - HIV RNA < 40 c/mL

# Case 3

- She has experienced a gradual decrease in GFR, now at 54 mL/min (normal at baseline)
- Urinalysis shows trace protein only

# Audience Question

What would you recommend next?

1. Continue same regimen and repeat labs in one month
2. Continue same regimen and adjust dose of NRTIs
3. Change NRTIs
4. Change atazanavir/ritonavir
5. Change all drugs in her regimen

# Switching for Toxicity

- In treatment-experienced patients with suppressed viremia, change individual antiretroviral drugs to reduce or manage toxicity, as needed

# Case 4

- 62yo white man, diagnosed HIV+ in 1990 with h/o KS, PcP x2, cryptosporidiosis.
- Prior treatment not entirely clear, but includes:
  - ZDV monotherapy
  - Dual NRTIs – 3TC, d4T, ddl
  - Full dose RTV, IDV, LPV/r
  - EFV, NVP
- Current regimen: ZDV/3TC + TDF + LPV/r
- Current labs:
  - CD4 = 188 cells/mm<sup>3</sup>
  - HIV RNA = 12,203 c/mL

# Case 4

	DRUG		PHENOSENSE™ SUSCEPTIBILITY				Evidence of Susceptibility		Net Assessment	
	Generic Name	Brand Name	Cutoffs (Lower - Upper)	Fold Change	Increasing Drug Susceptibility	Decreasing	Pheno Sense	Gene Seq		
NRTI	Abacavir	Ziagen	(4.5 - 6.5)	4.21			Y	N	Sensitive	16
	Didanosine	Videx	(1.3 - 2.2)	1.54			P	N	Partially Sensitive	
	Emtricitabine	Emtriva	(3.5)	>MAX			N	N	Resistant	
	Lamivudine	Epivir	(3.5)	>MAX			N	N	Resistant	
	Stavudine	Zerit	(1.7)	1.50			Y	Y	Sensitive	3
	Zidovudine	Retrovir	(1.9)	5.58			N	N	Resistant	3
	Tenofovir	Viread	(1.4 - 4)	1.21			Y	Y	Sensitive	3
NRTI Mutations			D67N, T69D, K70R, V118I, M184V, T215V, K219Q							
NNRTI	Delavirdine	Rescriptor	(6.2)	63			N	N	Resistant	
	Efavirenz	Sustiva	(3)	8.33			N	N	Resistant	
	Nevirapine	Viramune	(4.5)	25			N	N	Resistant	
NNRTI Mutations			K103N							
PI	Atazanavir	Reyataz	(2.2)	36			N	N	Resistant	
		Reyataz / r*	(5.2)	36			N	N	Resistant	
	Darunavir	Prezista / r <sup>9</sup>	(10 - 90)	2.49			Y	N	Sensitive	16
	Fosamprenavir	Lexiva	(2)	7.15			N	N	Resistant	
		Lexiva / r*	(4 - 11)	7.15			P	N	Partially Sensitive	
	Indinavir	Crixivan	(2.1)	8.00			N	N	Resistant	
		Crixivan / r*	(10)	8.00			Y	N	Sensitive	16
	Lopinavir	Kaletra	(9 - 55)	31			P	N	Partially Sensitive	
	Nelfinavir	Viracept	(3.6)	6.73			N	N	Resistant	
	Ritonavir	Norvir	(2.5)	>MAX			N	N	Resistant	
	Saquinavir	Invirase	(1.7)	54			N	N	Resistant	
	Invirase / r*	(2.3 - 12)	54			N	N	Resistant		
Tipranavir	Aptivus / r*	(2 - 8)	6.57			P	Y	Partially Sensitive	19	
PI Mutations			I13V, L33F, F53L, I54V, L63P, A71V, G73S, I84V, L90M							

# Case 4

## Tropotype Result



Dual/Mixed virus population can use CXCR4 and/or CCR5 co-receptors to enter the CD4+ cell.

X4 infectivity near limit of detection. Tropism results determined near the limit of detection may be variable on subsequent retest of sample.

D/M

**Activity of CCR5 antagonist anticipated?**

- YES  
 NO

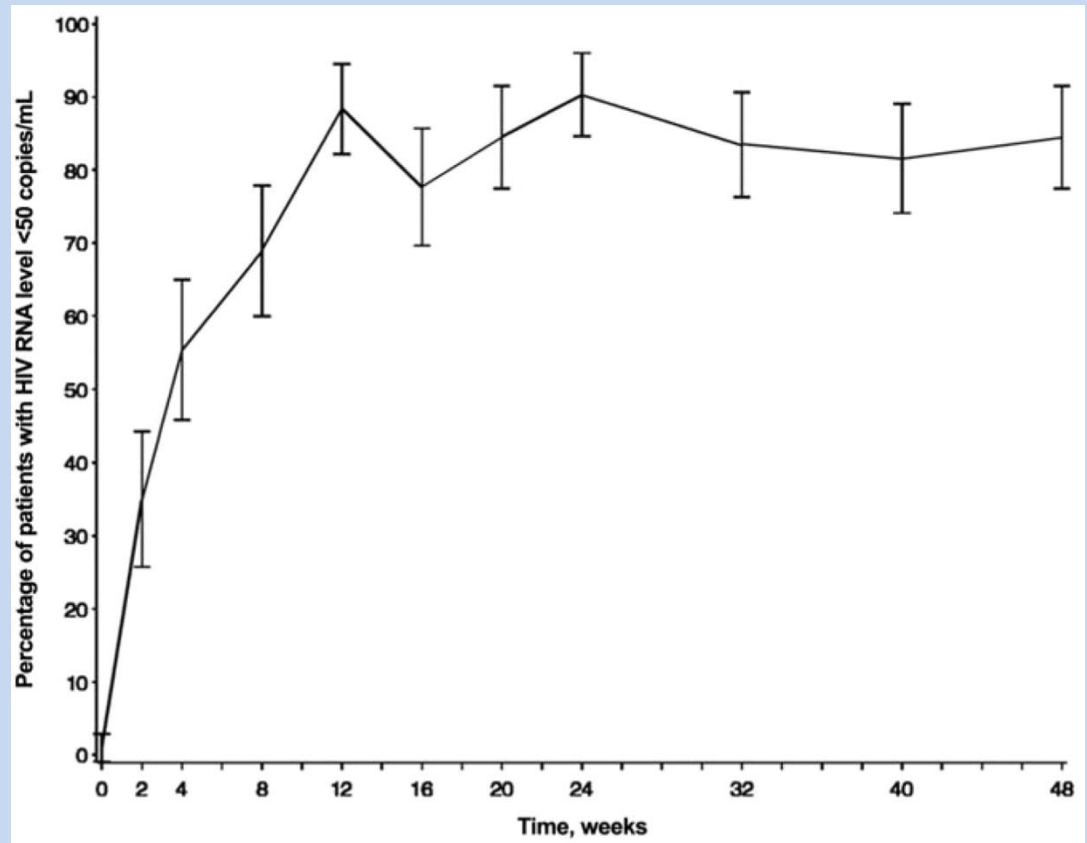
# Audience Question

Which medication(s) would you include in the next regimen?

1. Darunavir
2. Etravirine
3. Raltegravir
4. Maraviroc
5. 1 & 2, but not 3 or 4
6. 1 & 2 & 3, but not 4

# ANRS TRIO Study

- Pts with 3-class resistance and/or experience and HIV RNA > 1,000 c/mL (N=103)
- Naïve to RAL, DRV and ETR
- Received regimen of RAL + DRV/r + ETR
  - 87% also received NRTIs or T-20 (n=12)



# Audience Question

Would you include NRTIs in the next regimen?

1. Yes, at least two
2. Yes, lamivudine only
3. No

**More Data To Come ...**

# Summary

- Goals in management of the treatment-experienced patient include:
  - Maintaining virologic suppression
  - Improving the patient's quality of life
  - Encouraging long-term adherence
  - Avoiding toxicities that may develop with prolonged ART use
  - Reducing the risk of virologic failure
- Changes in ART may be made for virologic failure, toxicity or regimen simplification
- Use of clinical trial data can help guide regimen changes in these situations, but more studies are needed

**Thank You**