

# Antiretroviral Therapy: New Drugs, New Formulations, New Ideas, New Strategies

Prof. Ian Sanne  
Director Clinical HIV Research Unit  
University of the Witwatersrand  
and  
Managing Director Right to Care

# Why We Need New Antiretroviral Agents

- Treatment-Naive Individuals
  - Well tolerated, highly active, convenient antiretroviral therapy for ALL individuals who need treatment
    - Women of child-bearing potential
    - Individuals with TB and other complex medical illnesses
    - Patients with transmitted drug-resistant virus
      - Risk of minority variants
  - Very long term toxicity of therapy is not known

# Why We Need New Antiretroviral Agents

- Treatment-Experienced Individuals
  - Expand treatment choices
    - Avoid complex regimens and toxic agents
  - Full suppression of HIV replication in patients with resistant HIV-1
    - Developed World – multi-drug resistant variants
      - 5-10% of patients in care have  $\geq 3$  class resistance
      - Greater success in patients with less extensive resistance?
    - Developing World – highly NRTI-resistant variants
      - Currently limited treatment choices

# How Might Therapy of Treatment Naïve Patients Change?

- Alternatives to FDC of EFV or NVP plus 2 NRTI
- Alternatives to RTV-boosted PI
- Alternatives to NRTI

# Question

- With 1<sup>st</sup> or 2<sup>nd</sup> line therapy which agent gives your patients the most trouble with tolerability?
  1. Efavirenz
  2. Nevirapine
  3. Ritonavir
  4. Tenofovir
  5. Stavudine
  6. Zidovudine
  7. Atazanavir
  8. Other

# Alternatives To Efavirenz or Nevirapine

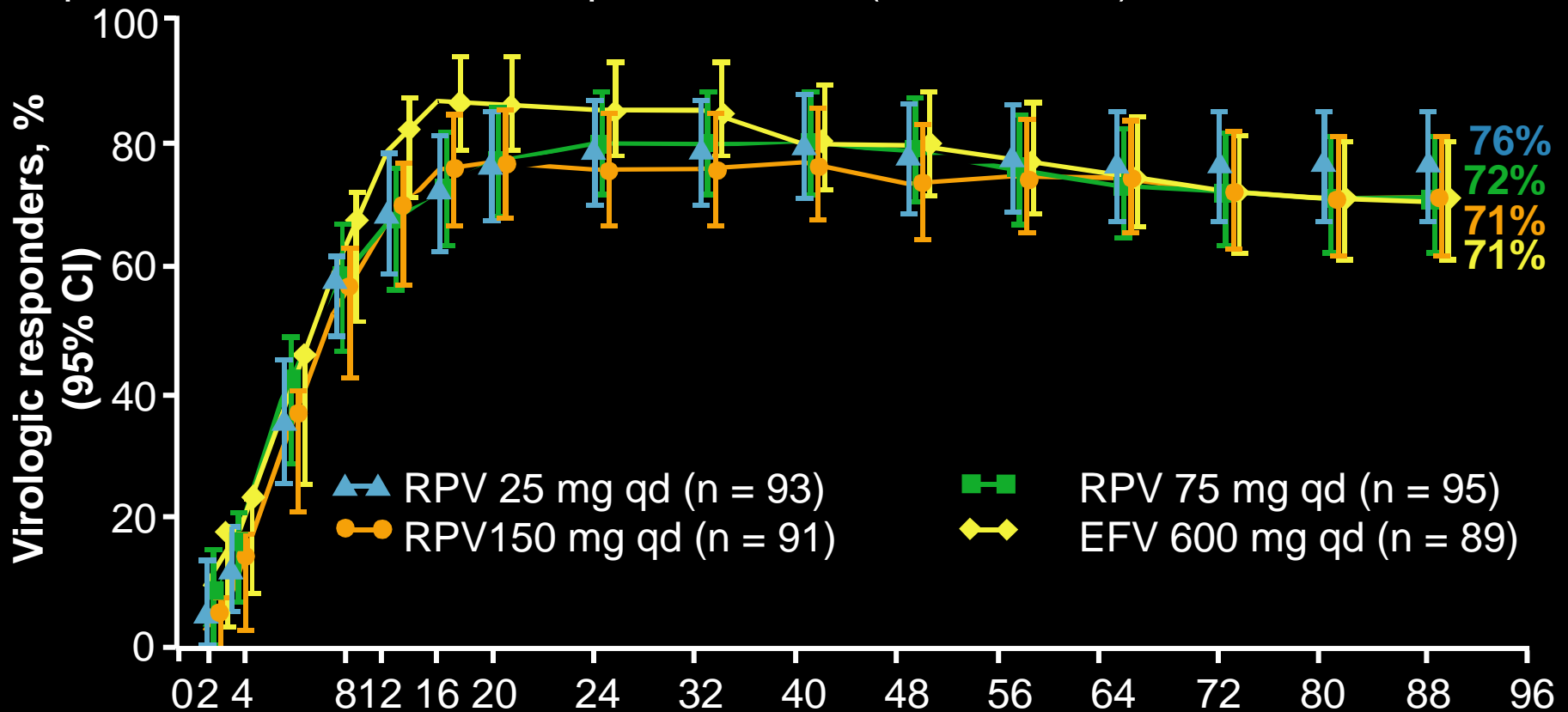
# Integrase Inhibitors

- Raltegravir
  - Potent, rapid suppression; very well tolerated over 48 wks
    - 97% of subjects in BENCHMRK had initial response
  - High risk of resistance in treatment failure
  - Twice daily dosing with modest drug interactions
    - Metabolized by glucuronidation
- Elvitegravir
  - Potent in phase IIa and IIb studies
  - Phase III study started
  - Cross resistance likely with raltegravir
  - Once daily but requires RTV co-administration.

**A high likelihood of success is dependent on additional active agents**

# Rilpivirine (TMC278) vs EFV: HIV-1 RNA < 50 copies/mL at Week 96

- Treatment-naive patients with HIV-1 RNA  $\geq 5000$  copies/mL randomized to rilpivirine or efavirenz, both plus 2 NRTIs (ITT-TLOVR)





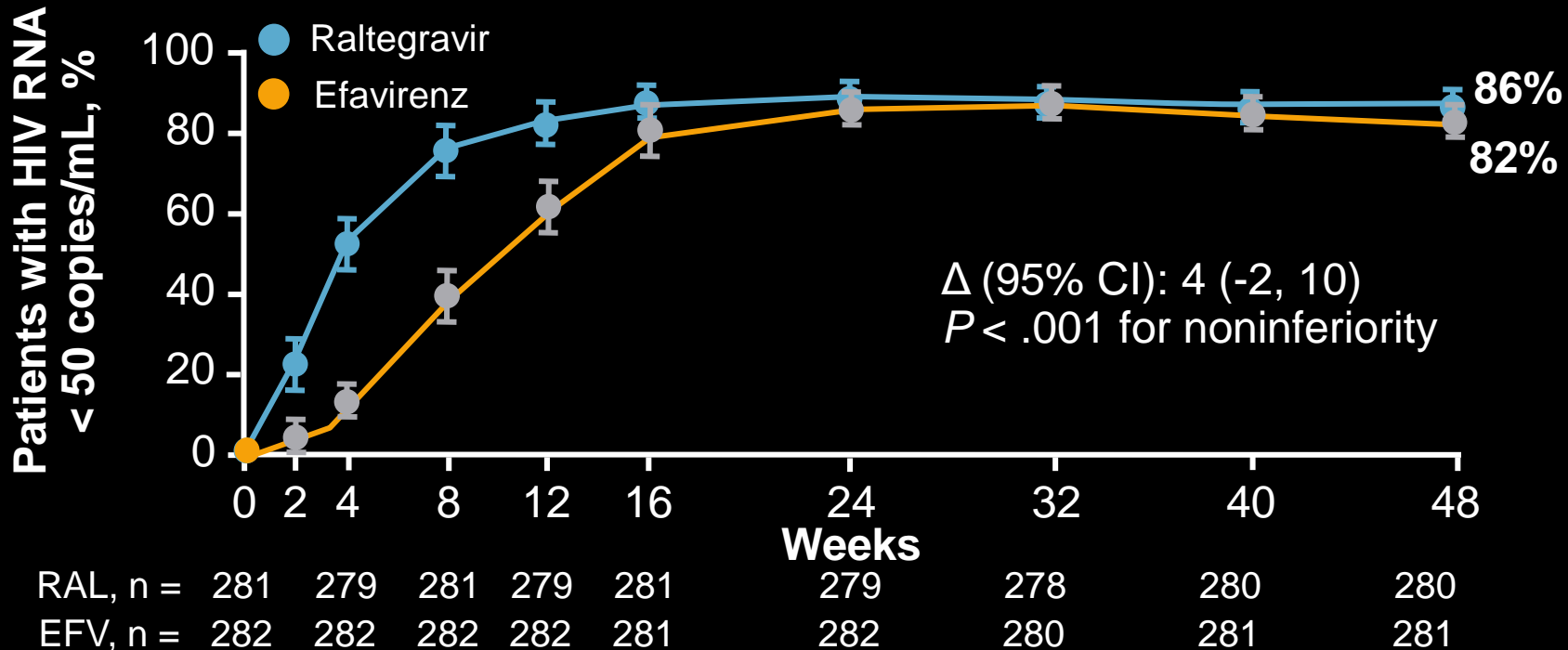
# Adverse Events and Resistance Similar with Rilpivirine vs Efavirenz

- Incidence of any adverse events similar in rilpivirine and efavirenz arms
  - More rash with efavirenz vs rilpivirine: 21% vs 9% ( $P < .01$ )
  - More nervous system disorders with efavirenz vs rilpivirine: 48% vs 31% ( $P < .01$ )
  - More neuropsychiatric adverse events with efavirenz vs rilpivirine: 21% vs 16%
- NNRTI resistance associated mutations emerged at a similar rate with rilpivirine vs efavirenz
- QTc interval increased in all study arms through Week 48, then plateaued
  - QTc prolongation lowest with 25 mg/day dose which has been selected for ongoing phase III trial

# ECHO and THRIVE

- Two parallel, placebo-controlled Phase III studies of rilpivirine (TMC 278) 25 mg once daily dose
- ECHO = RPV vs. EFV each with TDF/FTC
  - N = 680 patients; fully enrolled with primary endpoint 48 wks
- THRIVE = RPV vs. EFV with TDF/FTC or ABC/3TC or ZDV/3TC
  - N = 680; still enrolling as of 3/29/09

# STARTMRK: Virologic and Immunologic Efficacy at Week 48

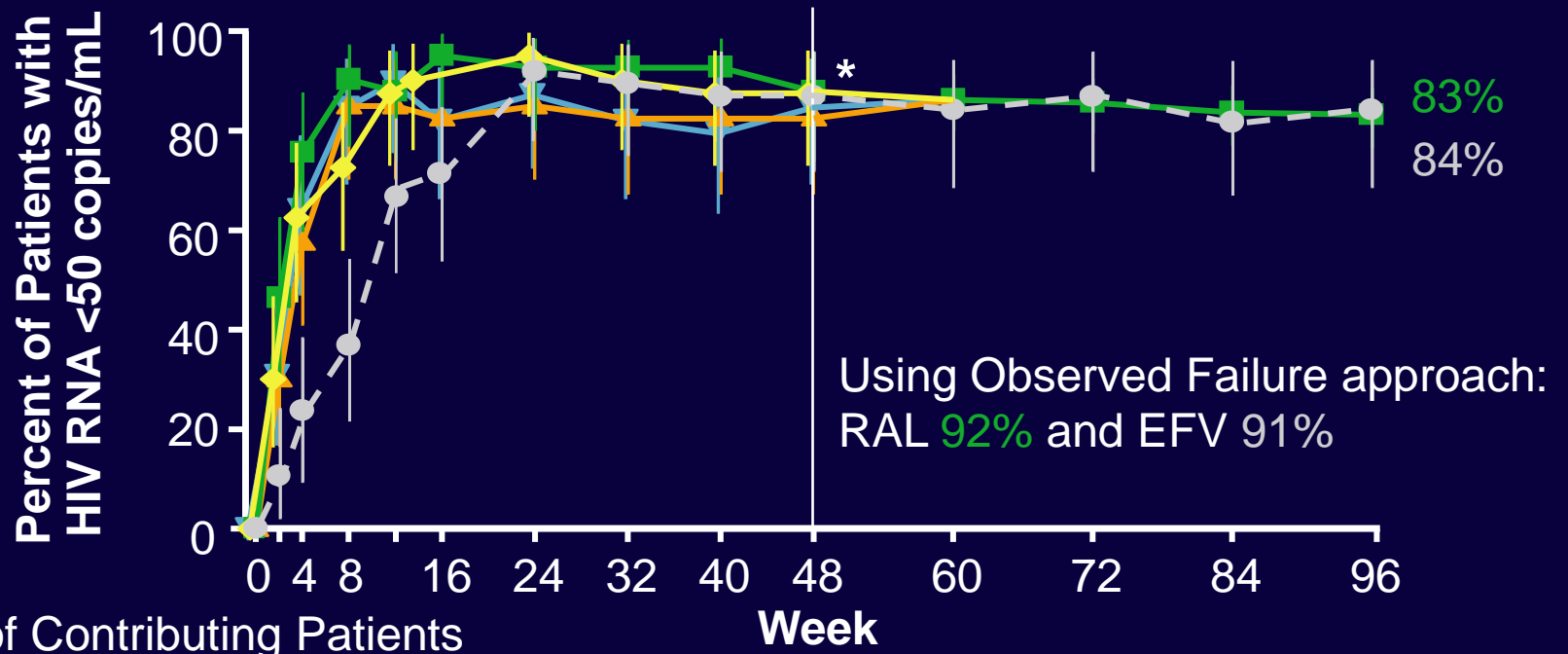


- Significantly shorter time to virologic response with RAL vs EFV ( $P < .001$ )
- Significantly greater CD4+ cell count increase with RAL vs EFV
  - +189 vs +163 cells/mm<sup>3</sup>; Δ 26 cells/mm<sup>3</sup> (95% CI: 4-47)

# STARTMRK: Virologic Outcome at Week 48 by BL Factors

Subgroup		Patients with HIV-1 RNA < 50 c/ml, % (Observed-Failure)	
		Raltegravir	Efavirenz
<b>Overall</b>		92	89
<b>Baseline Plasma HIV-1 RNA</b>	<100,000 copies/mL	93	89
	>100,000 copies/mL	91	89
<b>Baseline CD4+ Cell Count</b>	≤ 50 cells/mm <sup>3</sup>	84	86
	> 50 to ≤ cells/mm <sup>3</sup>	89	86
	> 200 cells/mm <sup>3</sup>	94	92
<b>Hepatitis B/C Coinfection</b>	B or C positive	94	88
	Both B and C negative	91	89
<b>Sex</b>	Male	91	88
	Female	96	93
<b>Race/Ethnicity</b>	White	92	93
	Black	89	91
	Asian	91	87
	Hispanic	93	85

# Protocol 004: 96-Week Results of RAL 400mg bid vs. EFV in Treatment-Naive Pts (NC = F)



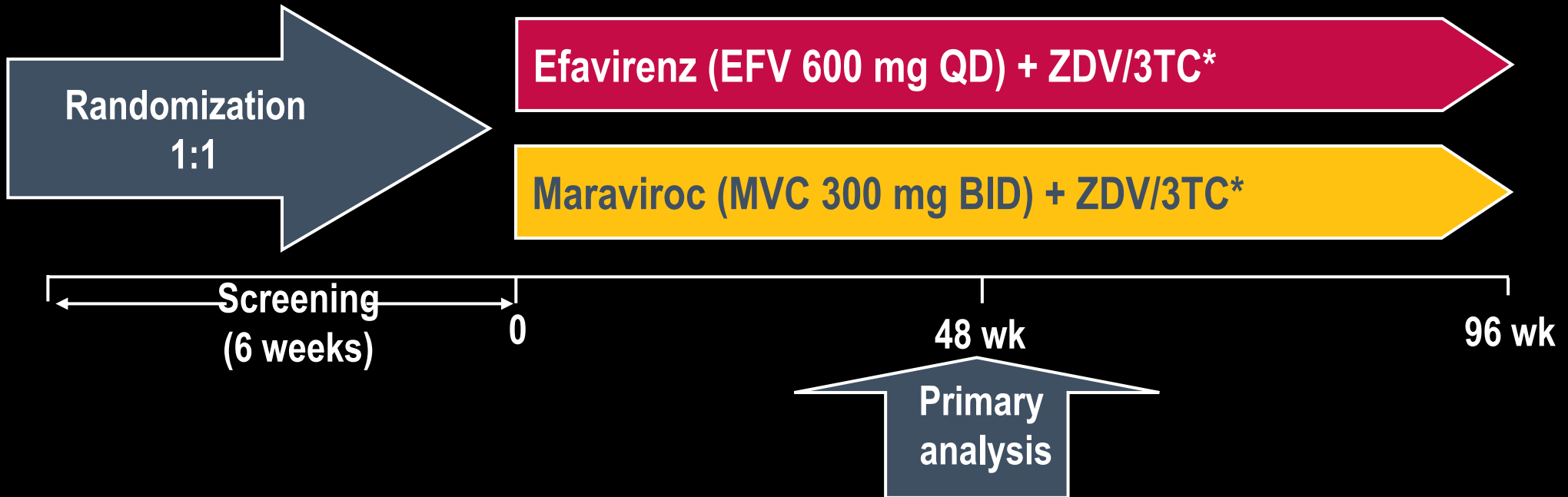
	Number of Contributing Patients		Week				
—▼— Raltegravir 100 mg bid.	39	39	39				
—▲— Raltegravir 200 mg bid.	40	40	40				
—■— Raltegravir 400 mg bid.	41	41	41	160	160	159	160
—◆— Raltegravir 600 mg bid.	40	40	40				
- - ● - - Efavirenz 600 mg qd	38	37	38	38	38	38	38

\*After Week 48, patients in all RAL groups continued at 400 mg bid  
All patients received TDF/3TC

# Raltegravir Once Daily

- Phase III randomized double blind placebo controlled trial
  - N =750
- RAL 800 mg once daily with TDF/FTC vs. RAL 400 mg twice daily with TDF/FTC
- Actively enrolling – lead cohort for safety

# Maraviroc Treatment Naïve MERIT Study: Phase 3 Trial Design



## Patient eligibility criteria:

- R5 HIV-1 infection
- No evidence of resistance to EFV, ZDV, or 3TC

MVC QD arm discontinued at end of Phase 2b (week 16)  
Due to evidence of decreased activity compared to EFV)

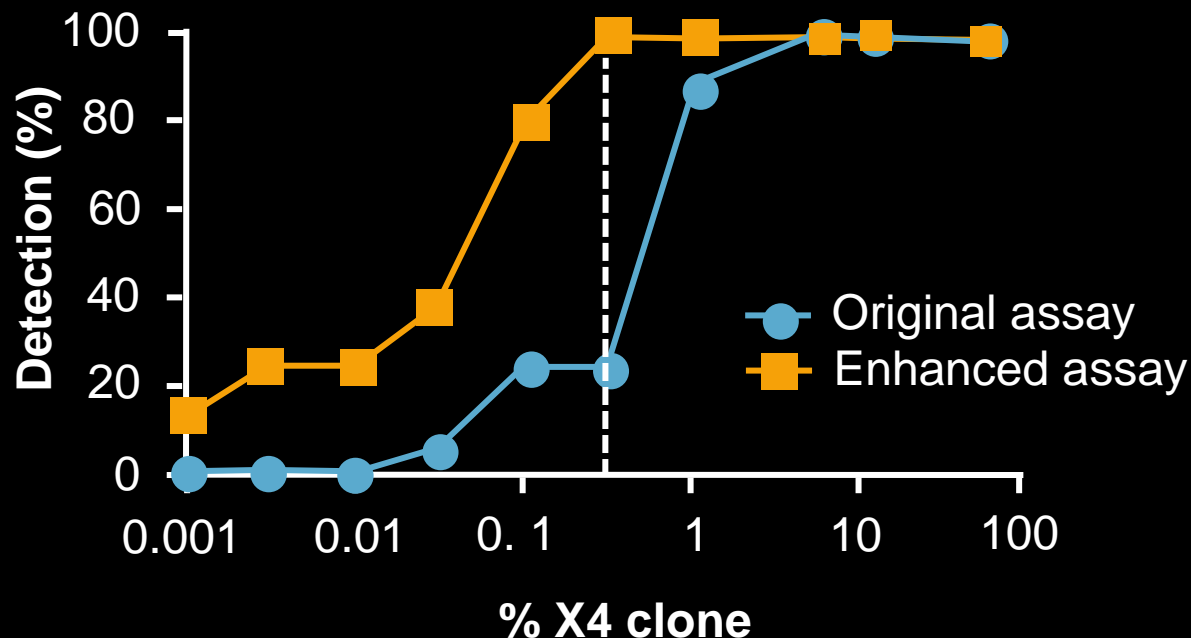
# CCR5 Inhibitor Virologic Failure

- Two mechanisms
  - Emergence of pre-existing X4 or dual tropic variants
    - MOTIVATE 1 wk 48, ~ 50% of patients in QD arm and ~ 63% of BID arm with virologic failure had D/M or X4 virus
    - “Cross resistant” by definition
    - No immunologic consequences observed so far
  - HIV remains R5 but uses receptor with compound bound
    - Difficult to detect without phenotype
    - Analysis of MVC resistance in 36 patients with R5 virus at failure
      - 43% had evidence of MVC resistance
    - Cross resistance btwn R5 inhibitors may or may not occur



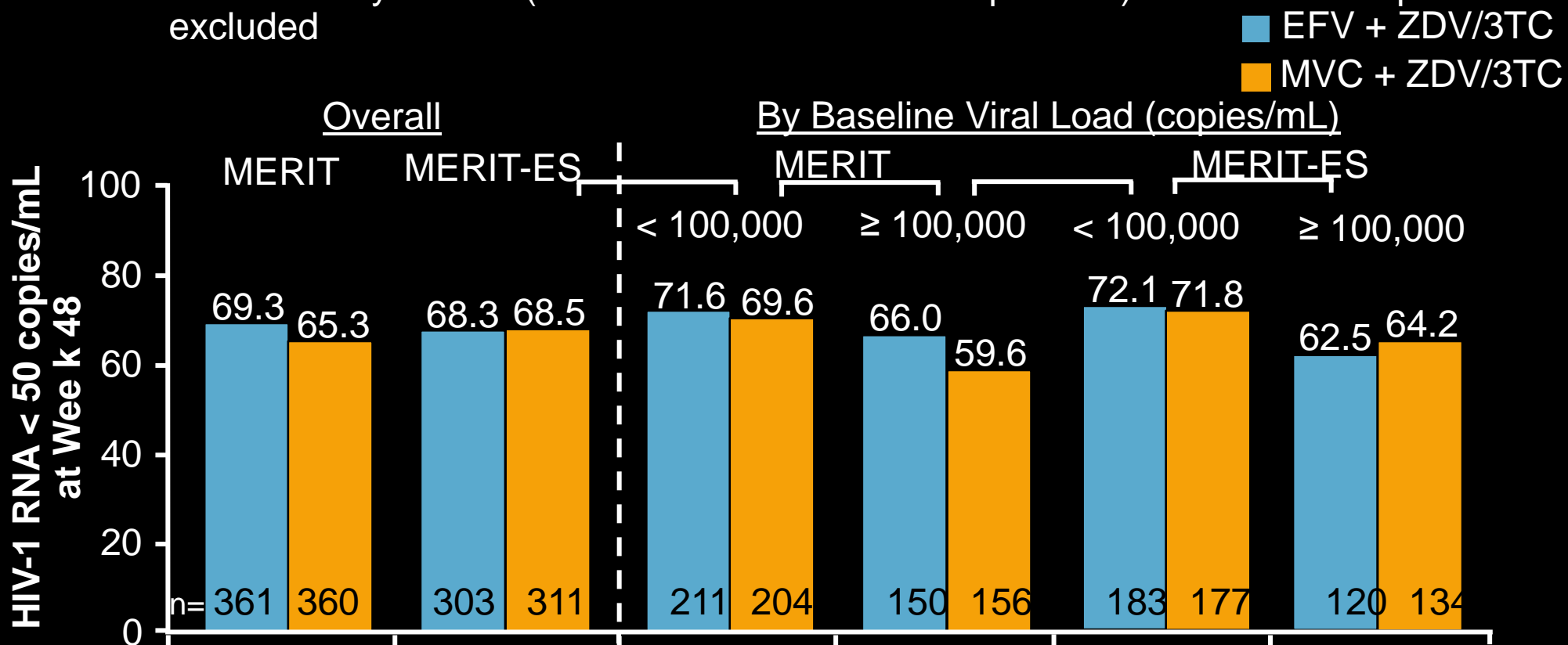
# Enhanced Phenotypic Tropism Assay Detects Low Levels of X4-Using Virus

- Enhanced assay highly sensitive in detecting CXCR4-using HIV variants comprising 0.3% of viral populations
  - Detection improved approximately 30-fold over original assay



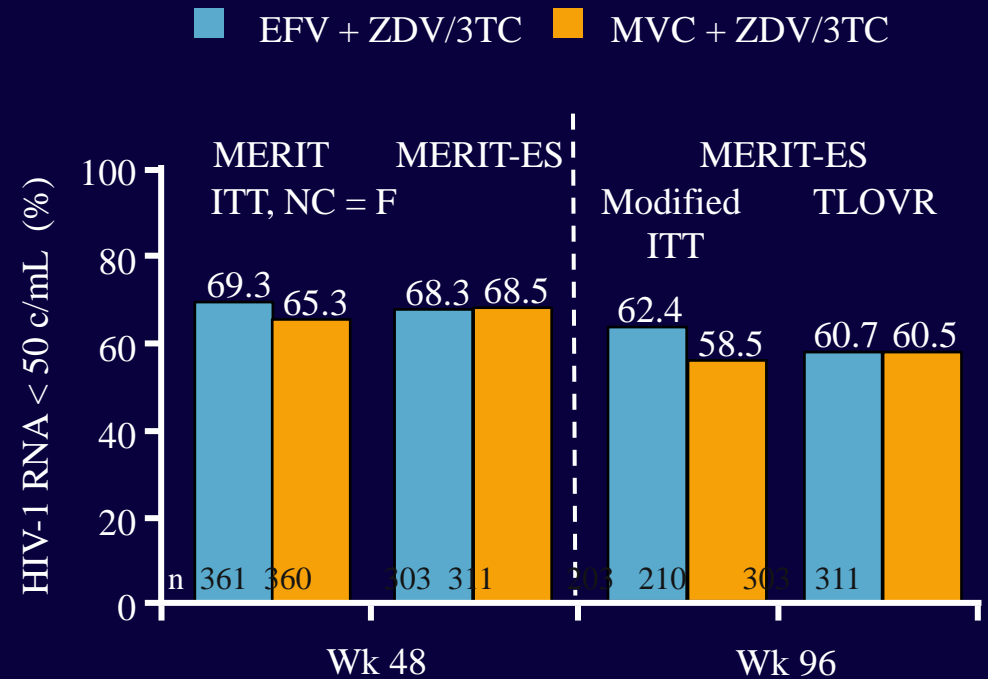
# Reanalysis of Virologic Efficacy in MERIT With Enhanced Tropism Assay

- Enhanced phenotypic tropism assay resulted in reclassification of 15% of patients from R5 to D/M at screening
  - Noninferiority criteria (rates of HIV-1 RNA < 50 copies/mL) met when D/M patients excluded



# MERIT: Wk 96 Response With MVC vs EFV in Naive Pts

- MERIT-ES: reanalysis of MERIT trial using enhanced phenotypic tropism assay suggested noninferiority of MVC to EFV when additional pts with D/M-tropic virus identified by enhanced assay excluded<sup>[1]</sup>
- Wk 96 efficacy analysis included only MERIT-ES population<sup>[2]</sup>
- Similar proportions in MVC and EFV with VL < 50 copies/mL at Wk 96
- CD4+ increase at Wk 96 greater with MVC vs EFV (+212 vs +171 cells/mm<sup>3</sup>)
- EFV more likely discontinued for AEs: 15.5% vs 6.1% on MVC
- MVC more likely discontinued for insufficient response: 12.5% vs 5.9% on EFV



- Higher levels of dyslipidemia on EFV
- 5/15 pts who discontinued EFV for tolerability developed NNRTI mutations in follow-up<sup>[3]</sup>

1. Saag M, et al. ICAAC/IDSA 2008. Abstract 1232a. 2. Heera J, et al. IAS 2009. Abstract TUAB103. 3. Nelson M, et al. IAS 2009. Abstract MOPEB040.

# Alternatives to Ritonavir

- PK enhancers with HIV activity
- Co-formulation in FDC

# GS-9350: A Pharmacoenhancer Without Anti-HIV Activity

AA Mathias, P German, M Lee, C Callebaut, L Xu, L Tsai, B Murray, H Liu,  
K Yale, D Warren and BP Kearney

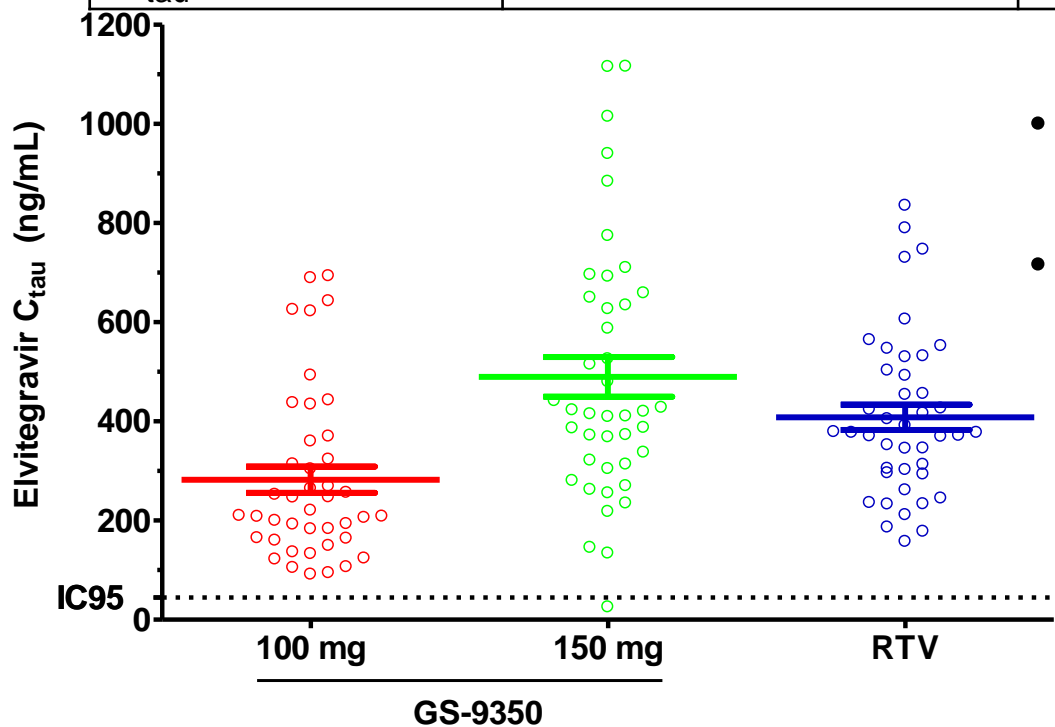
Gilead Sciences  
Foster City, CA, USA

## **GS-9350: A Pharmacoenhancer Without Anti-HIV Activity**

- Potent, irreversible (mechanism-based) inhibition of CYP3A
- No anti-HIV activity
- Greater CYP450 enzyme inhibition specificity
- Less induction of drug metabolizing enzymes and transporters
- Reduced potential for lipid abnormalities
- Improved physicochemical properties

# Elvitegravir PK

Mean (CV%) EVG PK (n = 42)	GS-9350 100 mg FDC	GS-9350 150 mg FDC	EVG + RTV 100 mg
AUC <sub>tau</sub> (ng.hr/mL)	21100 (25.4)	27000 (29.4)	22500 (23.4)
C <sub>max</sub> (ng/mL)	2250 (26.3)	2660 (27.6)	2500 (32.1)
C <sub>tau</sub> (ng/mL)	282 (60.4)	490 (52.9)	409 (40.5)



Bars represent geometric mean ( $\pm$  95% CI)

- GS-9350 effectively boosts EVG within FDC tablet
- High EVG trough concentrations maintained w/ GS-9350 150 mg
  - 11-fold above the protein binding-adjusted IC<sub>95</sub> (44.5 ng/mL)
  - Low within-subject variability (15% CV)

# QUAD Study

- GS 9350/elvitegravir/TDF/FTC (QUAD – fixed dose combination) vs. EFV/TDF/FTC (fixed dose combination).
- Phase II randomized double blind
- 75 patients with 2:1 randomization
- Actively recruiting.
- Studies comparing ATV/r with ATV/9350 are planned

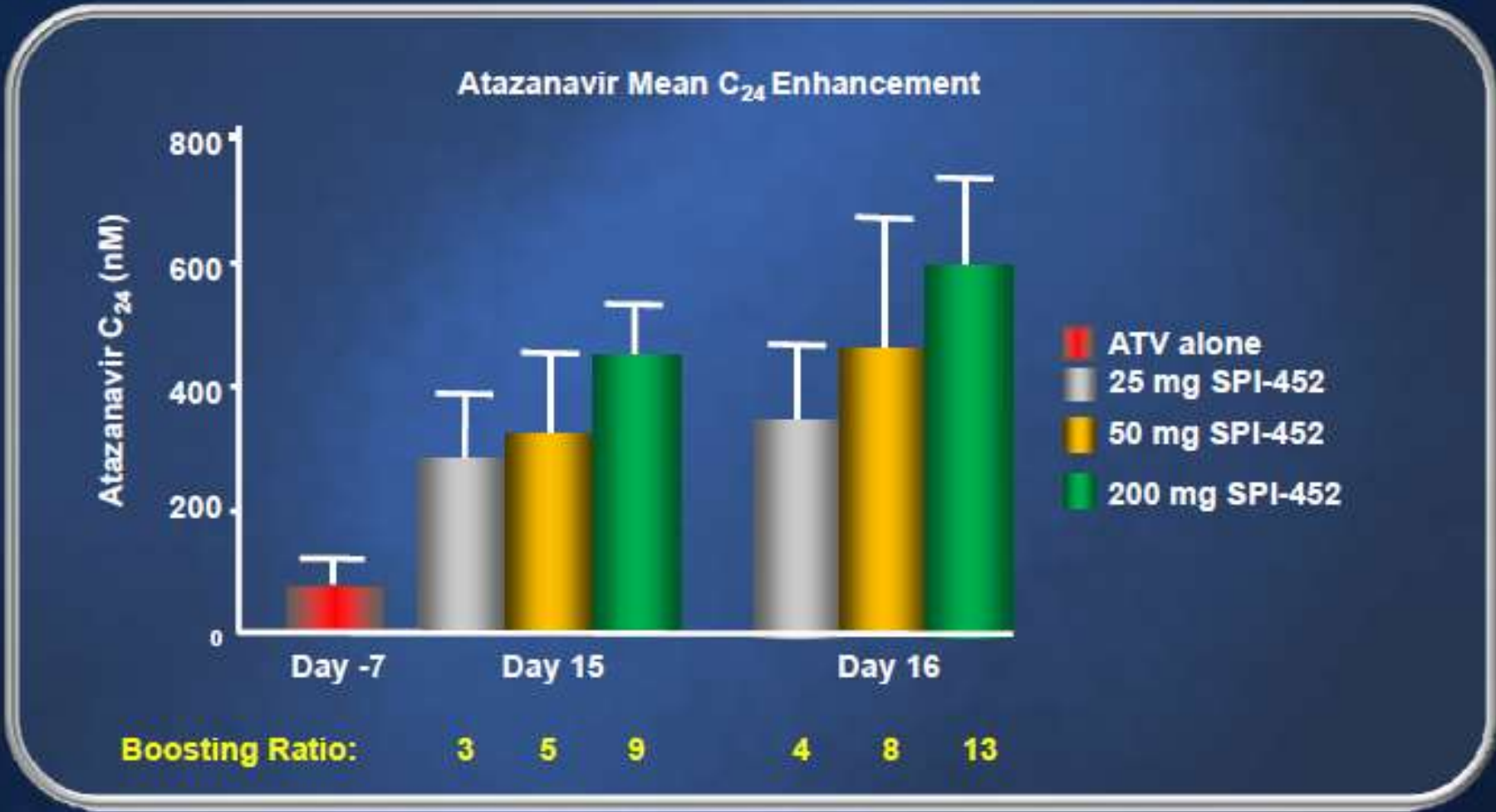


# Preclinical and Early Clinical Evaluation of SPI-452, a New Pharmacokinetic Enhancer (PKE)

S. Gulnik, M. Eissenstat, E. Afonina, D. Ludtke,  
J. Erickson, R. Dagger, B. Wynne, R. Guttendorf \*

# Study 0452-002: Proof of Clinical Concept

## SPI-452 Enhances Atazanavir Exposure ( $C_{24}$ )



# Alternatives To NRTI in first and second line treatment

- Resistance
- Mitochondrial toxicity
- Lactic acidosis

# Alternatives to NRTI in Naïve Patients or 2<sup>nd</sup> Line when NRTI resistance is HIGH

- LPV/r plus raltegravir (vs. LPV/r plus TDF/FTC)
  - Open-label study fully enrolled (N = 206)
- DRV/r plus raltegravir
  - Single arm pilot in ACTG
  - Small comparative study on-going
  - Large comparative study planned in Europe.
- Atazanavir plus raltegravir (no ritonavir)
- CCR5 plus boosted PI (e.g. Vicriviroc + ATV/r)

# ATV BID + RAL BID pharmacokinetics

- 3 step PK study: RAL 400 BID, then ATV 300 BID, then both
- N=22, healthy volunteers

**Table 2: Summaries and Statistical Analyses for Atazanavir Pharmacokinetic Parameters**

Pharmacokinetic Parameter	Treatment		Ratios of Adjusted Geometric Means (ATV+RAL/ATV BID) Point Estimate (90% CI)
	ATV BID Day 12 (N=22)	ATV+RAL BID Day 26 (N=19)	
C <sub>max</sub> (ng/mL) – Geometric Mean (%CV) Range	5434 (19) (3150 – 7690)	4817 (21) (2780 – 6290)	0.887 (0.835, 0.941)
AUC(0-12) (ng•h/mL) – Geometric Mean (%CV) Range	30906 (21) (19539 – 45957)	25579 (25) (12065 – 39179)	0.830 (0.777, 0.886)
C <sub>min</sub> (ng/mL) – Geometric Mean (%CV) Range	1166 (34) (495 – 2130)	817 (36) (250 – 1550)	0.710 (0.647, 0.779)
C <sub>0</sub> (ng/mL) – Geometric Mean (%CV) Range	1468 (34) (668 – 2810)	1148 (37) (469 – 2160)	0.779 (0.716, 0.846)
T <sub>max</sub> (h) – Median (Min, Max)	2.0 (2.0, 4.0)	2.0 (1.0, 4.0)	–



# ATV BID + RAL BID

## Pharmacokinetics

**Table 3: Summary and Statistical Analyses for Raltegravir Pharmacokinetic Parameters**

Pharmacokinetic Parameter	Treatment		Ratios of Adjusted Geometric Mean (ATV+RAL/RAL) Point Estimate (90% CI)
	RAL BID Day 5 (N=22)	ATV+RAL BID Day 26 (N=19)	
<b>C<sub>max</sub> (ng/mL) – Geometric Mean (%CV) Range</b>	634 (169) (252 – 9429)	952 (120) (254 – 6298)	1.394 (0.990 – 1.964)
<b>AUC(0-12h) (ng•h/mL) – Geometric Mean (%CV) Range</b>	2728 (129) (890 – 24871)	4539 (98) (1394 – 19186)	1.536 (1.135 – 2.081)
<b>C<sub>min</sub> (ng/mL) – Geometric Mean (%CV) Range</b>	60.2 (128) (14.5 – 566)	97.8 (154) (30.4 – 1219)	1.479 (1.083 – 2.020)
<b>C<sub>0</sub> (ng/mL) – Geometric Mean (%CV) Range</b>	135 (70) (41.0 – 523)	158 (114) (33.1 – 1266)	1.134 (0.782 – 1.645)
<b>T<sub>max</sub> (h) – Median (Min, Max)</b>	3.0 (1.0, 6.0)	4.0 (2.0, 8.0)	–

# ATV plus RAL Pilot

- ATV 300 BID with RAL 400 BID in treatment naïve patients
- Phase II randomized open label compared to ATV/r plus TDF/FTC
- 90 patients with 2:1 randomization
- Actively recruiting.
- Simplification study – with different dose – recently reported

# Vicriviroc plus ATV/r

- Vicriviroc 30 mg QD plus ATV/r (300/100) QD in treatment naïve patients with R5 virus
  - $CD4 \geq 200$  cells/mm<sup>3</sup>
- Phase II randomized open label compared to ATV/r plus TDF/FTC
- 200 patients with 1:1 randomization
- Actively recruiting.



# Switching Therapy in Suppressed Patients

- Simplification
- Lessen toxicity
- Improve tolerability
- Decrease cost?

# SwitchMRK 1 and 2: Randomized Comparison of Continued LPV/r vs. switch to RAL in suppressed Patients

Joseph Eron\*<sup>1</sup>, Jaime Andrade<sup>2</sup>, Roberto Zajdenverg<sup>3</sup>, Cassy Workman<sup>4</sup>,  
David A. Cooper<sup>5</sup>, Benjamin Young<sup>6</sup>, Xia Xu<sup>7</sup>,  
Bach-Yen Nguyen<sup>7</sup>, Randi Leavitt<sup>7</sup>, and Peter Sklar<sup>7</sup>

<sup>1</sup>University of North Carolina, Chapel Hill, NC, USA; <sup>2</sup>Anting Hospital Civil de Guadalajara, Guadalajara, Mexico; <sup>3</sup>Hospital Escola Sao Francisco de Assis, Rio de Janeiro, Brazil; <sup>4</sup>AIDS Research Initiative, Darlinghurst, Australia; <sup>5</sup>University of New South Wales, Sydney, Australia; <sup>6</sup>Denver Infectious Disease Consultants, Denver, CO, USA; and <sup>7</sup>Merck Research Laboratories, West Point, PA, USA

# SWITCHMRK 1 and 2 (P032 & 033)

## Study Design

- Identical, multicenter, double-blind, randomized, active-controlled studies
- Study population
  - Well controlled on a stable LPV/r regimen (b.i.d.) in combination with at least 2 NRTIs (and no other active PI) for  $\geq 3$  months
    - HIV RNA  $<50$  copies/mL (US PCR) or  $<75$  copies/mL (bDNA)
    - Patients were not required to be intolerant of LPV/r
    - Patients with prior virologic failure were not excluded
      - No limit on number of prior ART regimens
  - No lipid lowering therapy for at least 12 weeks
- Randomized (1:1) to continue LPV/r or switch to RAL

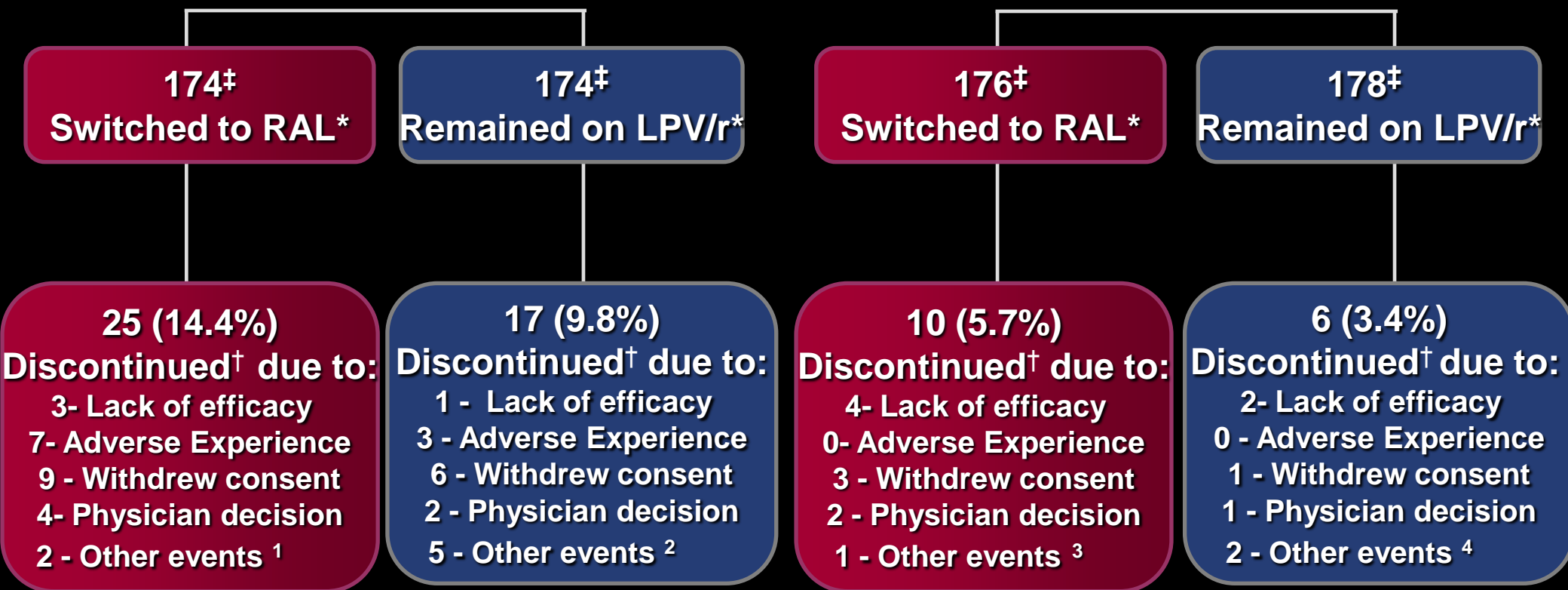
# SWITCHMRK 1 and 2 (P032 & 033)

## Study Design (2)

- Primary endpoints
  - Mean % change in lipids at week 12
    - Total-C, Triglycerides, non-HDL-C, and LDL-C
  - Proportion of patients with viral load <50 copies/mL at Wk 24
    - Non-completer = Failure approach (NC=F)
    - Noninferiority hypothesis with 12% margin
  - Safety and tolerability

# Protocols 032, 033

## Patient Disposition



<sup>1</sup>RAL: Deviation from protocol (1), Other (1)

<sup>2</sup>LPV/r: Lost to follow-up (4), Deviation from protocol (1)

<sup>3</sup>RAL: Deviation from protocol (1)

<sup>4</sup>LPV/r: Lost to follow-up (1), Deviation from protocol (1)

\*In combination with background antiretroviral therapy

‡Randomized and treated

# Protocols 032, 033

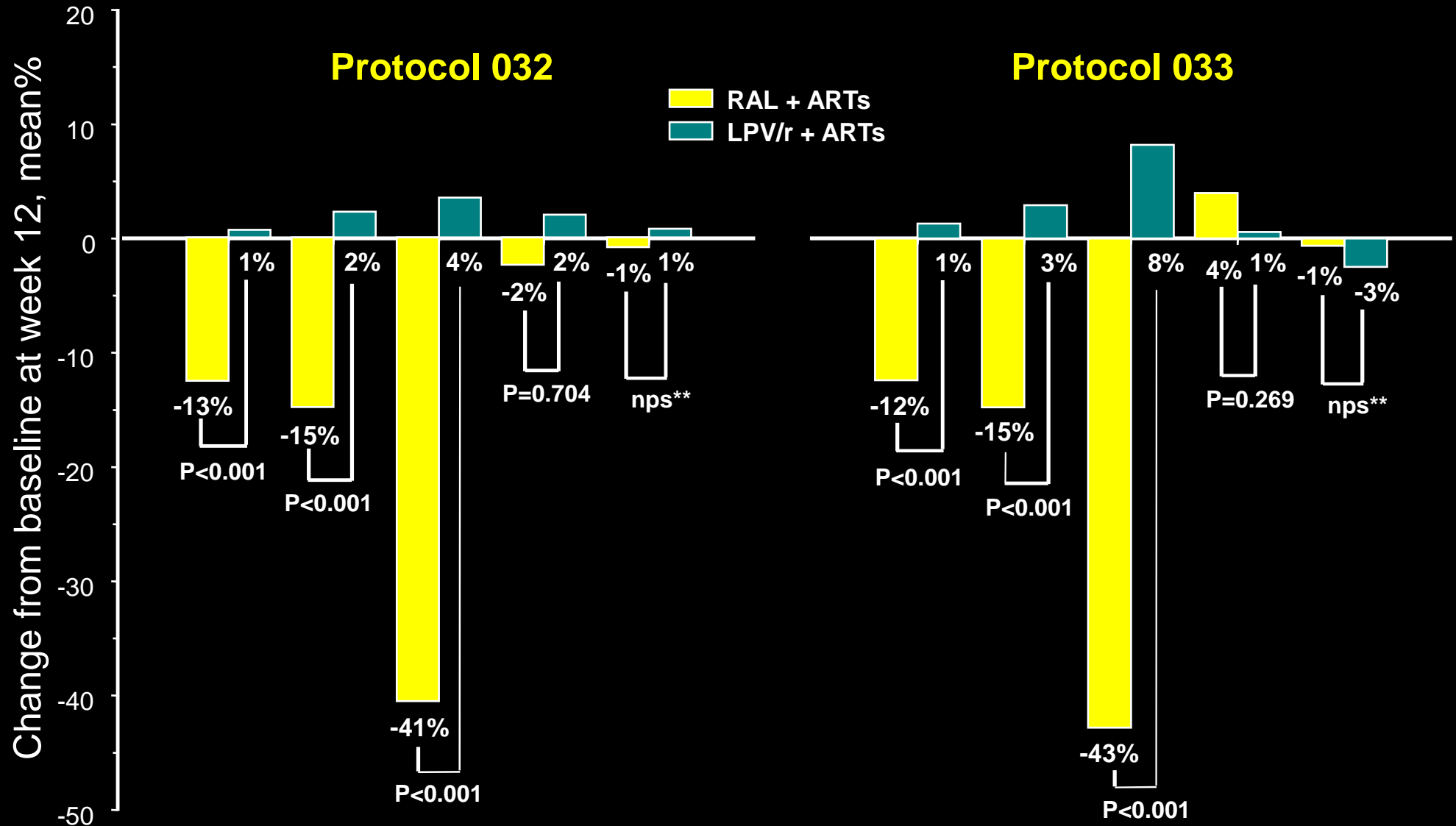
## Patient Baseline Characteristics (2)

	Protocol 032		Protocol 033	
	RAL*	LPV/r*	RAL*	LPV/r*
# Patients Treated	N = 174	N = 174	N = 176	N = 178
% with vRNA ≤ 50 copies/mL	94.3	92.5	96.0	95.5
Mean CD4 count (cells/μl)	478	508	471	482
% on LPV/r ≤ 1 yr	16.7	17.8	17.6	18.5
Median yrs of prior ART (min, max)	3.3 (0.3, 22.3)	3.6 (0.5, 20.2)	3.7 (0.5,19.2)	4.6 (0.6,16.3)
Median # of prior ART (min, max)	5.0 (4.0, 16.0)	5.0 (2.0,15.0)	5.5 (3.0,13.0)	6.0 (4.0,14.0)

\*In combination with background antiretroviral therapy.

# Protocols 032, 033

## Lipids-Mean Percent Change from Baseline at Week 12

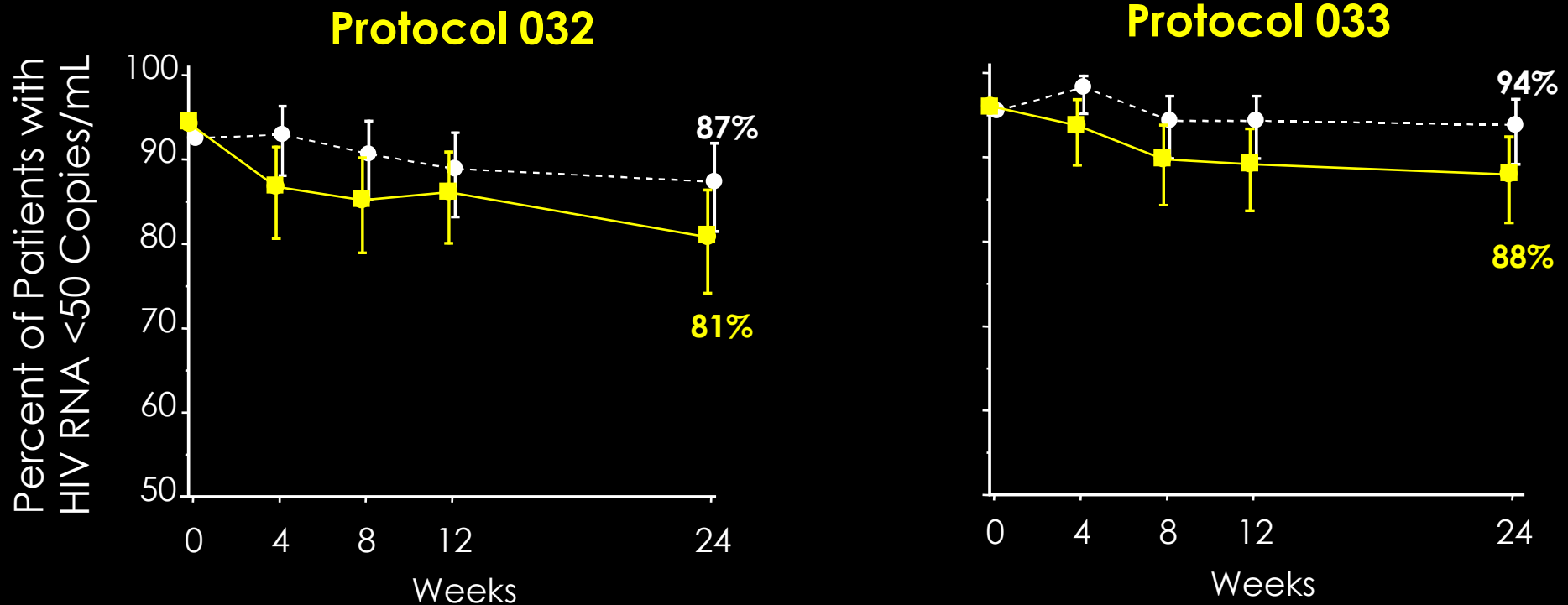


Mean mg/dL:	Fasting Cholesterol	Non-Fasting HDL-C	Fasting Triglycerides*	Fasting LDL-C	Fasting HDL-C
At Baseline	217 205	166 158	190 164	116 105	49 47
At Week 12	186 205	138 159	113 172	109 103	47 46

Mean mg/dL:	Fasting Cholesterol	Non-Fasting HDL-C	Fasting Triglycerides*	Fasting LDL-C	Fasting HDL-C
At Baseline	214 211	168 164	210 219	104 104	46 48
At Week 12	183 212	138 166	125 237	103 104	45 46

\*Median Percent Change    \*\*Not prespecified for test

# Percent of Patients (95% CI) With HIV RNA <50 Copies/mL (NC = F)



## Number of Contributing Patients

	0	4	8	12	24	0	4	8	12	24
■ <b>RAL + ARTs</b>	174	166	169	173	172	176	176	176	176	175
● <b>LPV/r + ARTs</b>	174	171	171	171	174	178	178	177	177	178

In P032,

- ★ 149 patients on RAL had HIV RNA < 50 copies/mL at Week 12; 134/149 (90%) remained suppressed (< 50 copies/mL) at Week 24.
- ★ 152 patients on LPV/r had HIV RNA < 50 copies/mL at Week 12; 145/152 (95%) remained suppressed (< 50 copies/mL) at Week 24.

In P033,

- ★ 157 patients on RAL had HIV RNA < 50 copies/mL at Week 12; 148/157 (94%) remained suppressed (< 50 copies/mL) at Week 24.
- ★ 167 patients on LPV/r had HIV RNA < 50 copies/mL at Week 12; 161/167 (96%) remained suppressed (< 50 copies/mL) at Week 24.



# Protocols 032, 033

## Confirmed Virologic Failures

	Protocol 032		Protocol 033	
	RAL <sup>†</sup>	LPV/r <sup>†</sup>	RAL <sup>†</sup>	LPV/r <sup>†</sup>
>400 copies/mL*	3	2	9	2
>50 copies/mL*	13	10	19	7

<sup>†</sup>In combination with background antiretroviral therapy

\*Virologic failure required confirmed viral rebound at least 1-week apart

Based upon post-hoc data collection:

- 84% (27/32) of patients with confirmed VF (>50 c/mL) in the RAL group reported that their regimen at study entry was not their 1<sup>st</sup> ART regimen
  - 66% (18/27) reported a history of VF on prior regimen(s)

# Protocol 033:Resistance Summary

## PN033 Confirmed Failures

Study Drug	Virologic Failures (>400/ml)	Study drug mutations (InSTI or PI*)	RTI mutations†
RAL	9	G140G/S, Q148R, Q148Q/H, N155N/H	D67D/G, M184V, T215T/I; Y181C
		N155H	M184M/V; K103R
		N155H, Q148Q/R, Y143Y/C	D67D/N, K70K/R, M184V, K219Q
		Q148H, G140S	M184V; K103N, P225H
		G140G/S, Q148R, Q148Q/H, N155N/H, Q148Q/R	None
		N155H	None
		Y143Y/S, Q148Q/R	None
		None	None
		Not done	Not done
LPV/r	2	L10I, K20R, M36I, M46L, I54V, L63P, A71V, V82A, L90M	K65R, D67N, K219E; K103R, Y181C
		V11V/I, L63P, V77I	None

\*Data derived by population sequencing. All amino acid changes from baseline observed in any of multiple independent PCR reactions are listed without regard to linkage.

†RTI mutations do not necessarily reflect concurrent OBT

# Protocols 032, 033

## Combined Analyses of the Subgroups (OF)

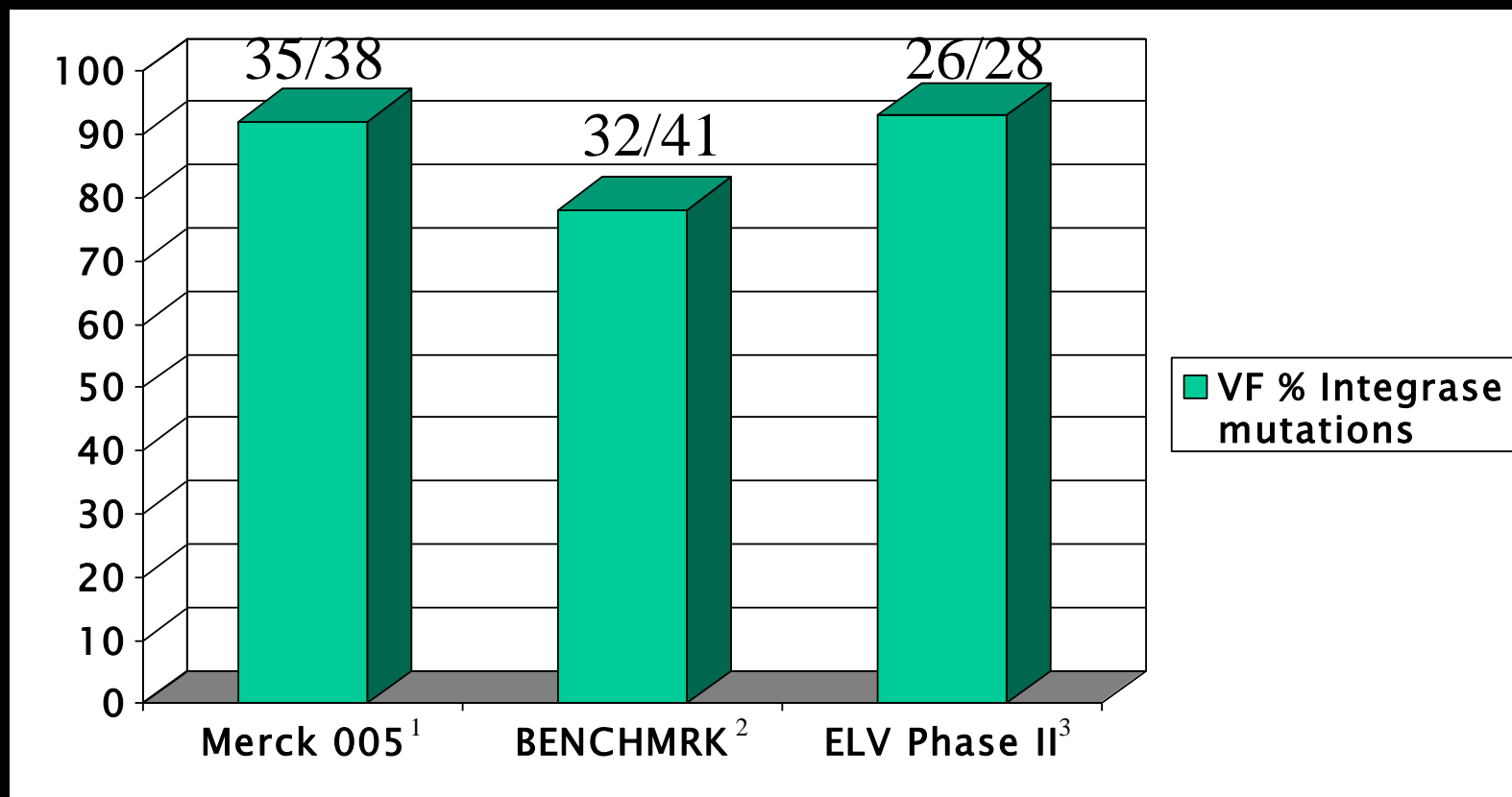
Subpopulation	Response (% with HIV RNA < 50 copies/mL)				Difference in Percent Response <sup>†</sup> % (95% CI)
	n/N	RAL % (95% CI)	n/N	LPV/r % (95% CI)	
<b>Total</b>	293/327	89.6 (85.8, 92.7)	319/338	94.4 (91.4, 96.6)	-4.8 (-9.1, -0.7)
<b>Gender</b>					
<b>Female</b>	60/62	96.8 (88.8, 99.6)	74/80	92.5 (84.4, 97.2)	4.3 (-4.4, 12.8)
<b>Region</b>					
<b>Africa</b>	24/25	96.0 (79.6, 99.9)	19/20	95.0 (75.1, 99.9)	1.0 (-15.6, 20.5)

<sup>†</sup> The 95% CIs were calculated using Miettinen and Nurminen's method.

N = Number of patients in each treatment group; n = Number of patients in each subcategory.

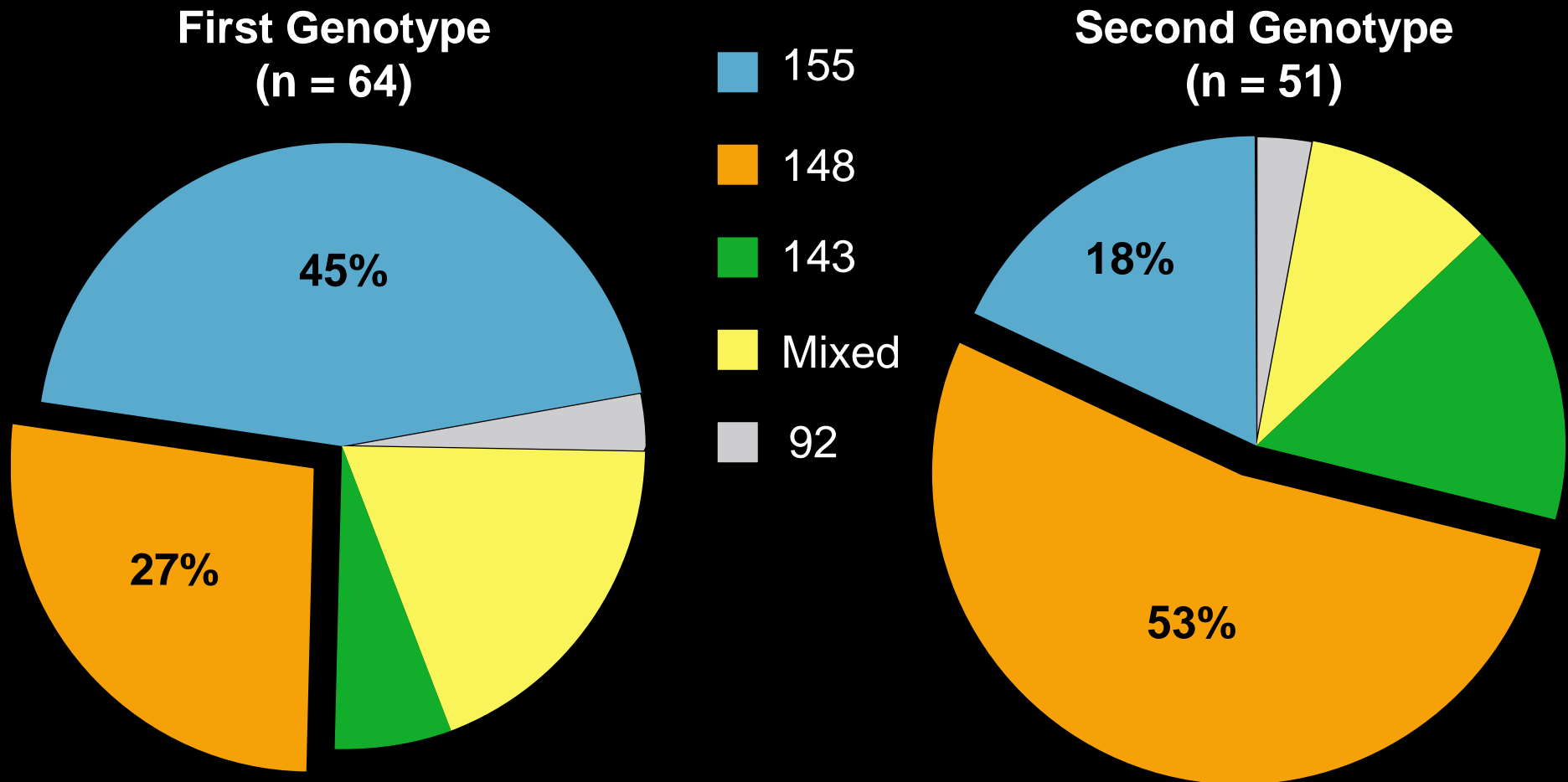
# Integrase Inhibitor Resistance

- Raltegravir:
  - Resistance occurs thru mutation in the enzyme – in and round active site
  - Two major pathways (N155 or Q148):*Q148H/G140S* most common.
  - Most have multiple mutations

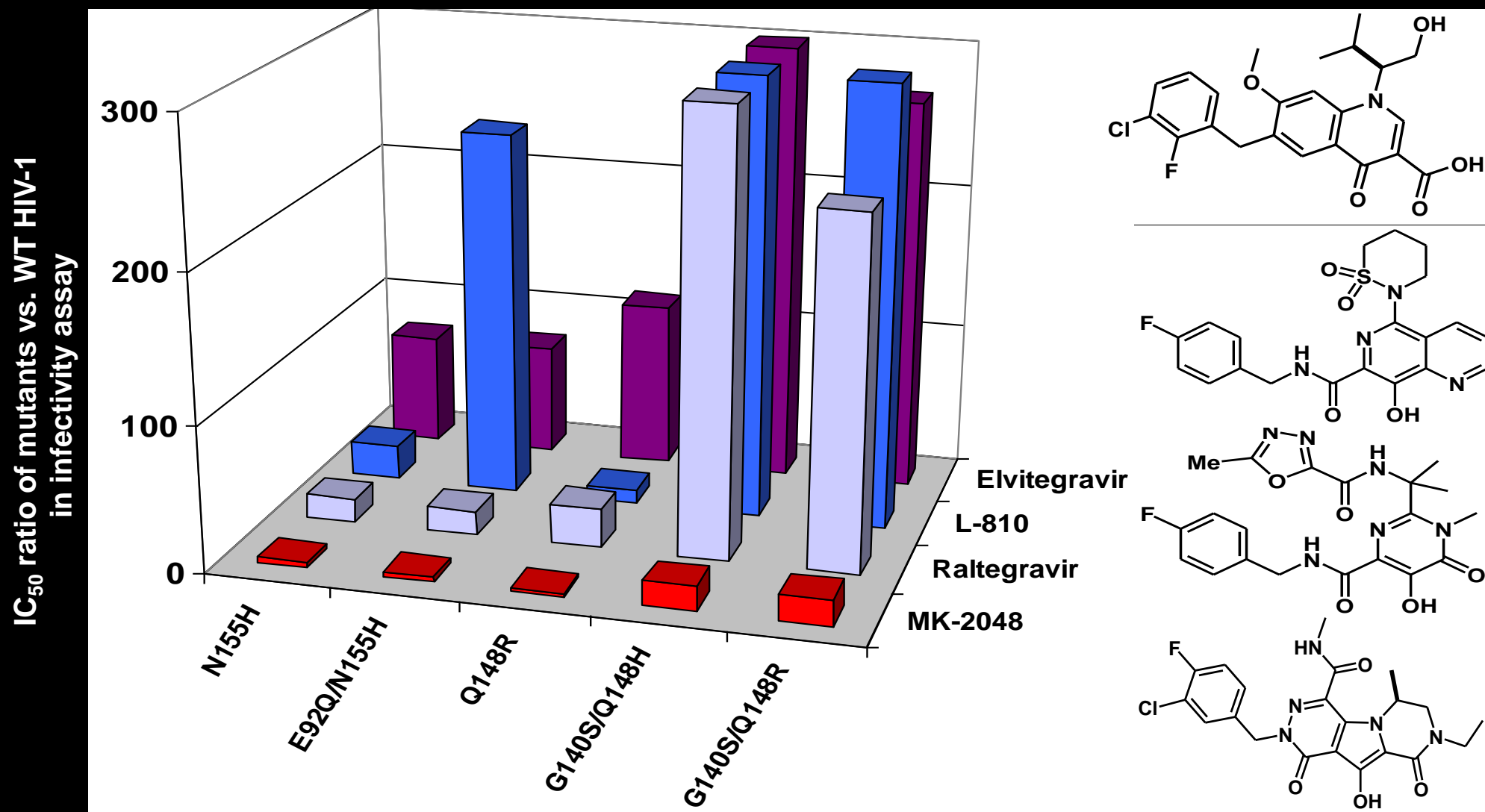


<sup>1</sup>Hazuda DRW 2007; Grinsztejn *et al. Lancet* 2007; **369**: 1261-69, <sup>2</sup>Steigbigel CROI 2007 LB 105b, <sup>3</sup>McColl *et al* DRW 2007

# BENCHMARK 1 & 2: Evolution From N155 to Q148 Mutations Over Time



# Mutations can confer cross resistance to structurally diverse integrase inhibitors



# Options for Second-line Therapy

- LPV/r and 2 NRTI
- Darunavir/r and 2 NRTI
- Boosted protease inhibitor alone
  - Data from Lilongwe on second line
- Boosted PI plus an alternative to NRTI
  1. etravirine
  2. maraviroc
  3. Raltegravir
  4. More than one agent?

# What about Third Line Therapy?

- Three class failure – NRTI, NNRTI, PI
- Aim for virologic suppress
-



# TRIO Study: RAL + ETR + DRV/RTV Highly Effective As 3 Active Agents

- Multicenter, phase II study of DRV/RTV plus ETR plus RAL (N = 103); addition of NRTIs, enfuvirtide at discretion of physician
  - Inclusion criteria included  $\leq 3$  DRV and  $\leq 3$  ETR RAM
  - 59% of patients had  $< 1$  active agent in OBR, as assessed by GSS
- 90% of patients attained HIV-1 RNA  $< 50$  copies/ml at Week 24 (95% CI: 85% to 96%)
- Median increase in CD4+ = 99 cells/mm<sup>3</sup> (IQR: 32-147)
- Of 10 patients with detectable HIV-1 RNA at Week 24, only 3 had confirmed HIV-1 RNA  $> 400$  copies/mol
- 2 possibly drug-related clinical grade 4 AEs; only 1 led to treatment discontinuation

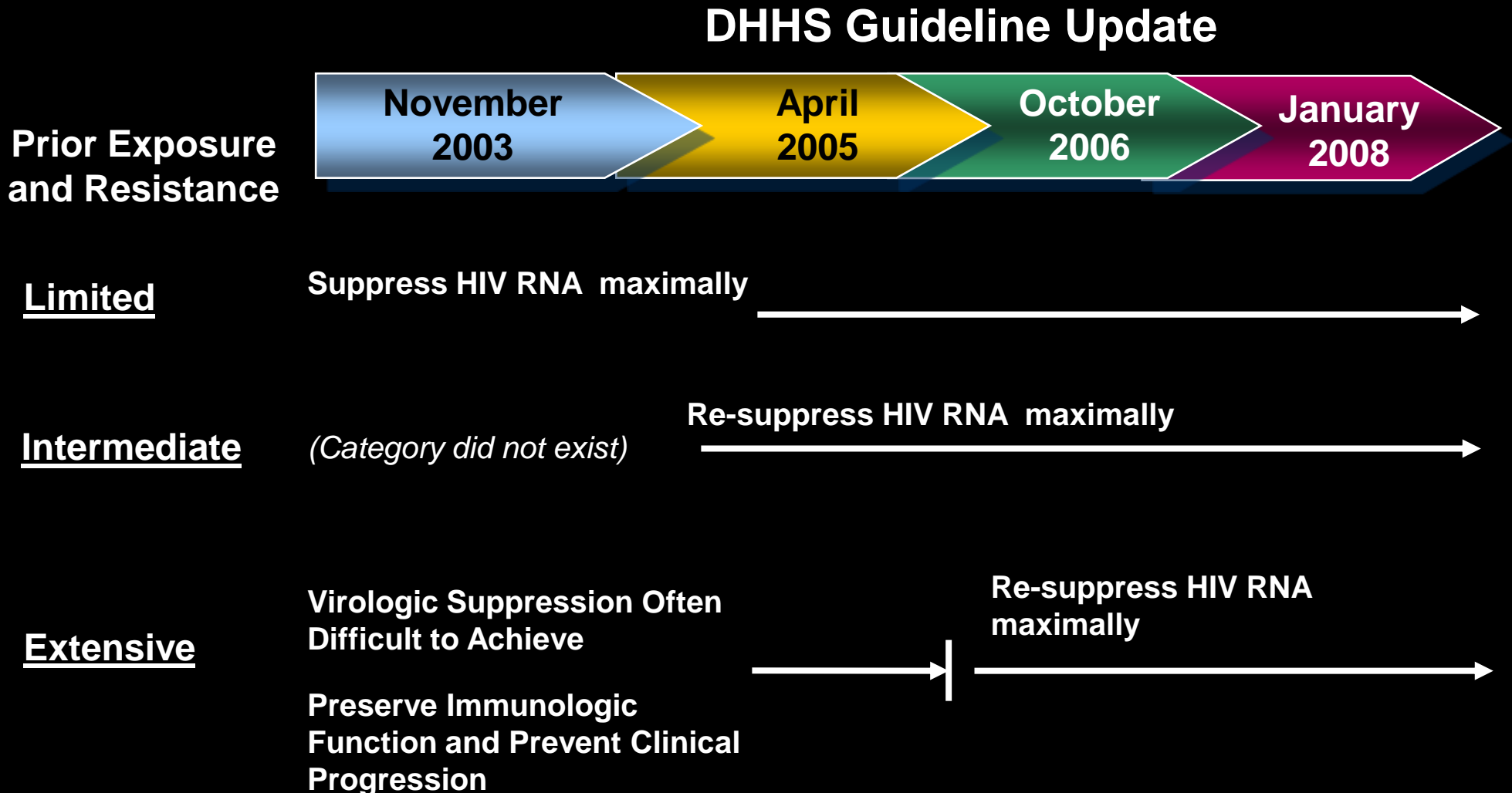
# Impact of New Agents on Treatment Strategy

- Treatment-naive patients
  - May improve tolerability and expand target populations
  - Novel combinations that spare nucleosides or ritonavir can be explored
- Second line therapy
  - Better options if high level NRTI resistance or no resistance testing
- Switch for complex or poorly tolerated regimens
  - opportunity for improvement?
- Third Line Therapy
  - High likelihood of success
  - When will new agents be available to you.

# Back up Slides

No Need to print out!

# Evolution of National HIV Treatment Guidelines: Appropriate Treatment Goals After Virologic Failure

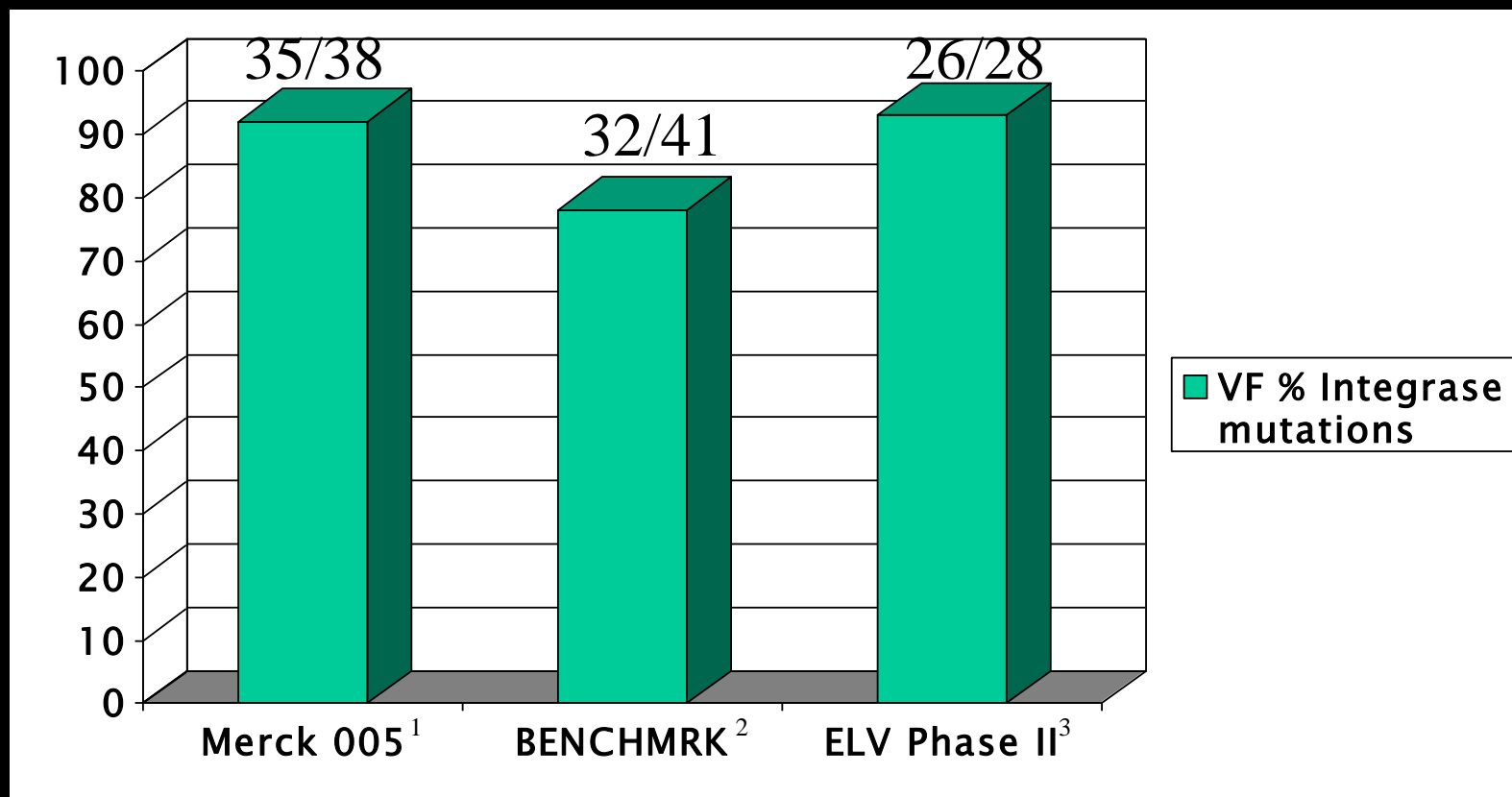


# CCR5 Inhibitor Virologic Failure

- Two mechanisms
  - Emergence of pre-existing X4 or dual tropic variants
    - MOTIVATE 1 wk 48, ~ 50% of patients in QD arm and ~ 63% of BID arm with virologic failure had D/M or X4 virus
    - “Cross resistant” by definition
    - No immunologic consequences observed so far
  - HIV remains R5 but uses receptor with compound bound
    - Difficult to detect without phenotype
    - Analysis of MVC resistance in 36 patients with R5 virus at failure
      - 43% had evidence of MVC resistance
    - Cross resistance btwn R5 inhibitors may or may not occur

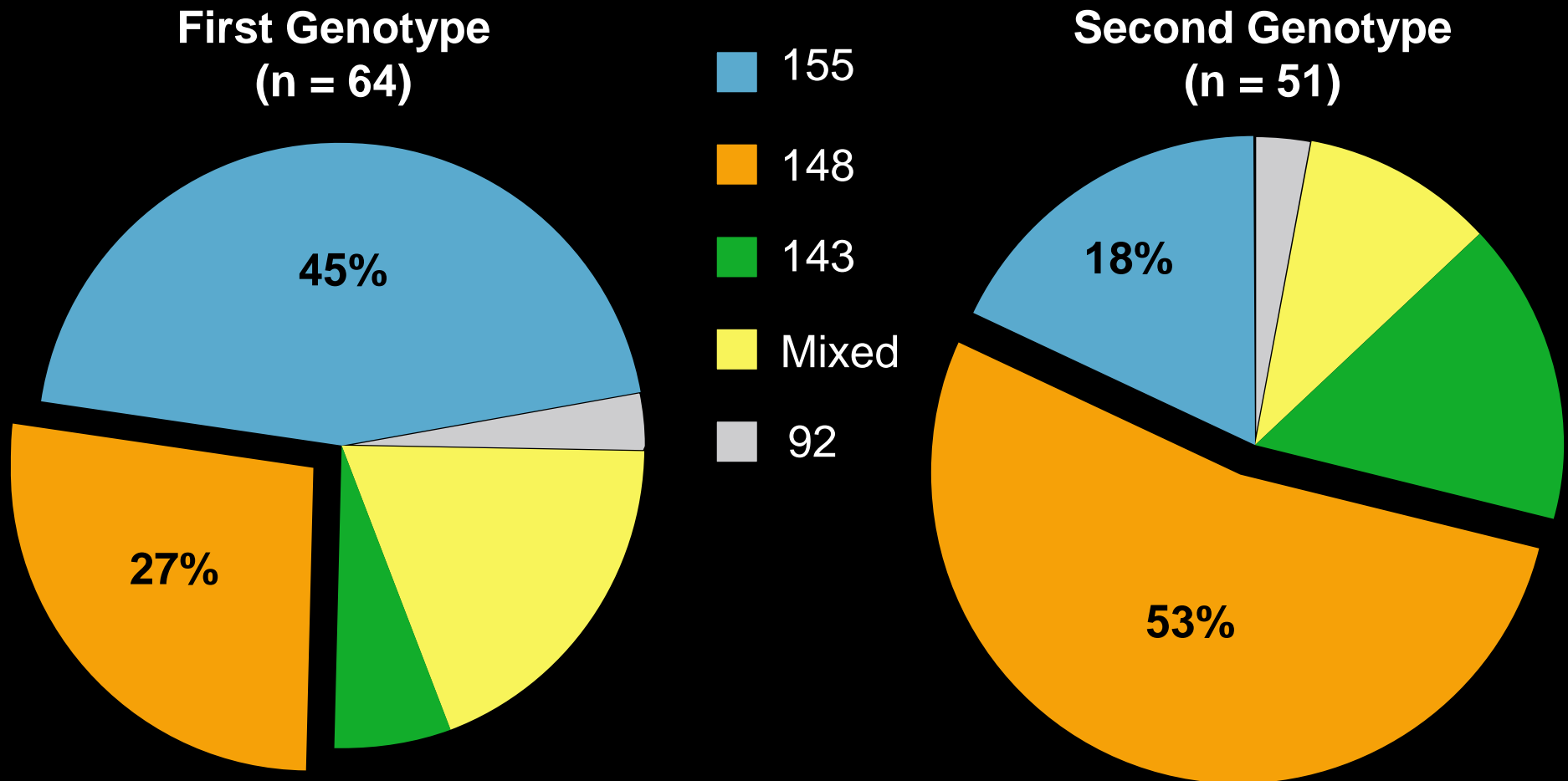
# Integrase Inhibitor Resistance

- Raltegravir:
  - Resistance occurs thru mutation in the enzyme – in and round active site
  - Two major pathways (N155 or Q148):*Q148H/G140S* most common.
  - Most have multiple mutations

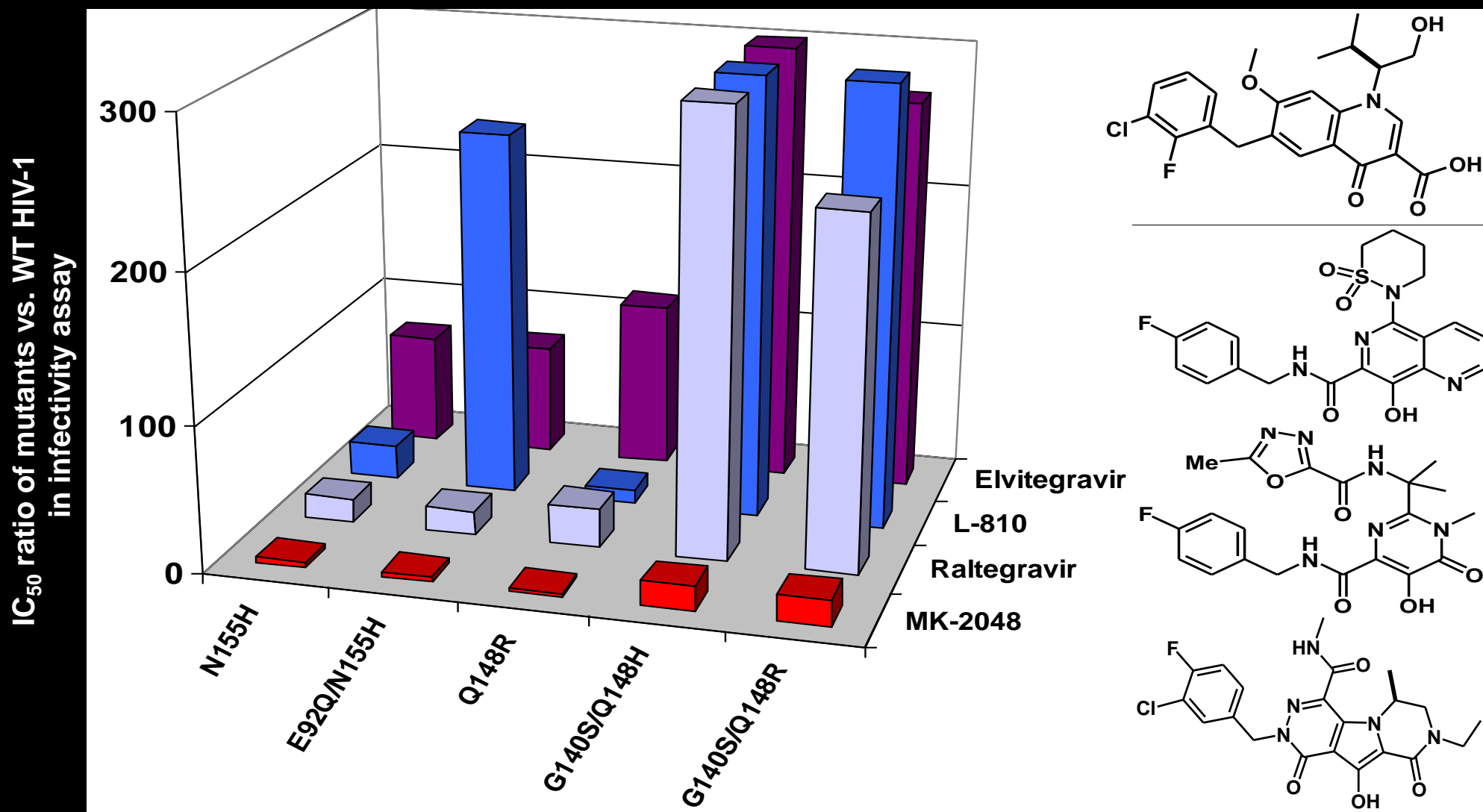


<sup>1</sup>Hazuda DRW 2007; Grinsztejn *et al. Lancet* 2007; 369: 1261-69, <sup>2</sup>Steigbigel CROI 2007 LB 105b, <sup>3</sup>McColl *et al* DRW 2007

# BENCHMARK 1 & 2: Evolution From N155 to Q148 Mutations Over Time



# Mutations can confer cross resistance to structurally diverse integrase inhibitors





# Integrase Inhibitors

- Raltegravir
  - Potent, rapid suppression; very well tolerated over 48 wks
    - 97% of subjects in BENCHMRK had initial response
  - High risk of resistance in treatment failure
  - Twice daily dosing with modest drug interactions
    - Metabolized by glucuronidation
- Elvitegravir
  - Potent in phase IIa and IIb studies
  - Phase III study started
  - Cross resistance likely with raltegravir
  - Once daily but requires RTV co-administration.

A high likelihood of success is dependent on additional active agents