

Rio Update

3rd International AIDS Society Conference
on HIV Pathogenesis and Treatment*



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Report Back for Community Consortium
August 17, 2005



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CLINICAL CARE OPTIONS
HIV

Novel Antiretroviral Agents

Bill Owen, M.D.

New Antiretrovirals in Development

■ NRTIs/NtRTIs

- SPD 754 (DOTC)
- Amdoxovir (DAPD)
- D-d4FC
- Racivir (\pm FTC)
- SN1212
- Compound X

■ Protease inhibitors

- TMC114
- GW0385

■ NNRTIs

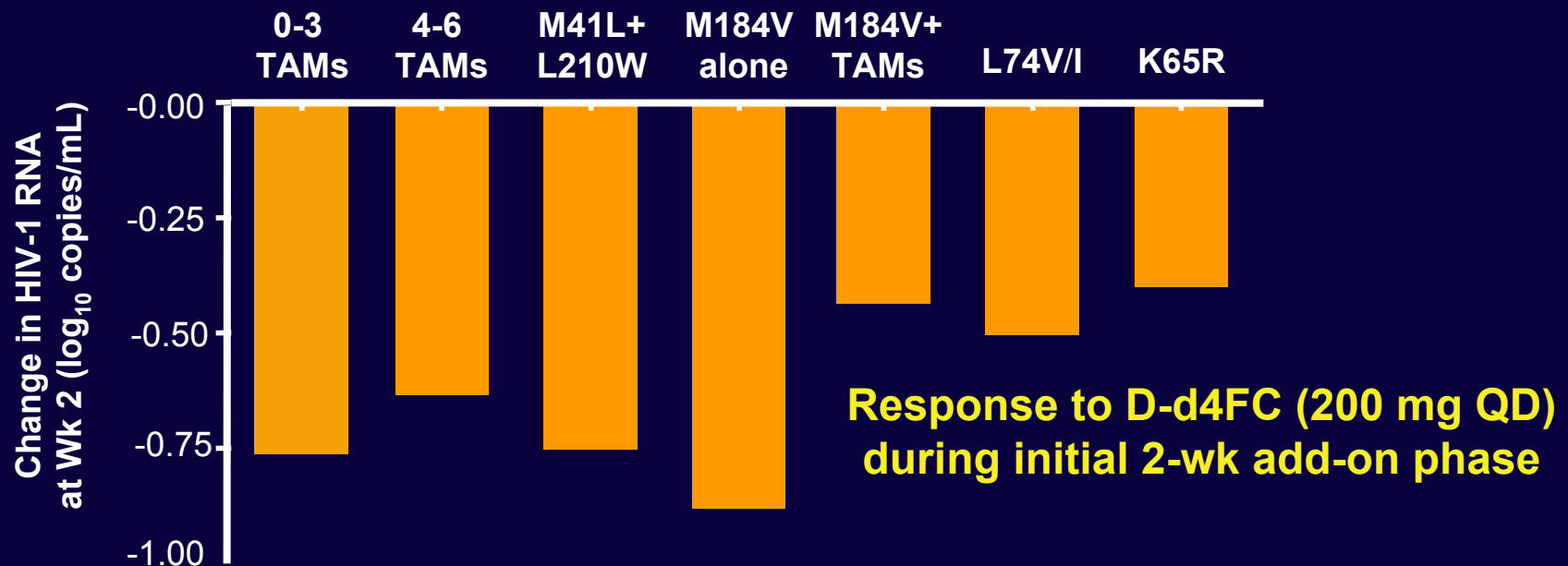
- TMC125
- GW678248
(prodrug = GW695634)
- TMC278
- BILR 355 BS
- CSIC
- DAPY/DATA
- UC781
- TMC120 (as
microbicide)

■ Entry inhibitors

- Aplaviroc
- Maraviroc
- Vicriviroc
- BMS-488043
- TNX-355
- NB-2, NB-64

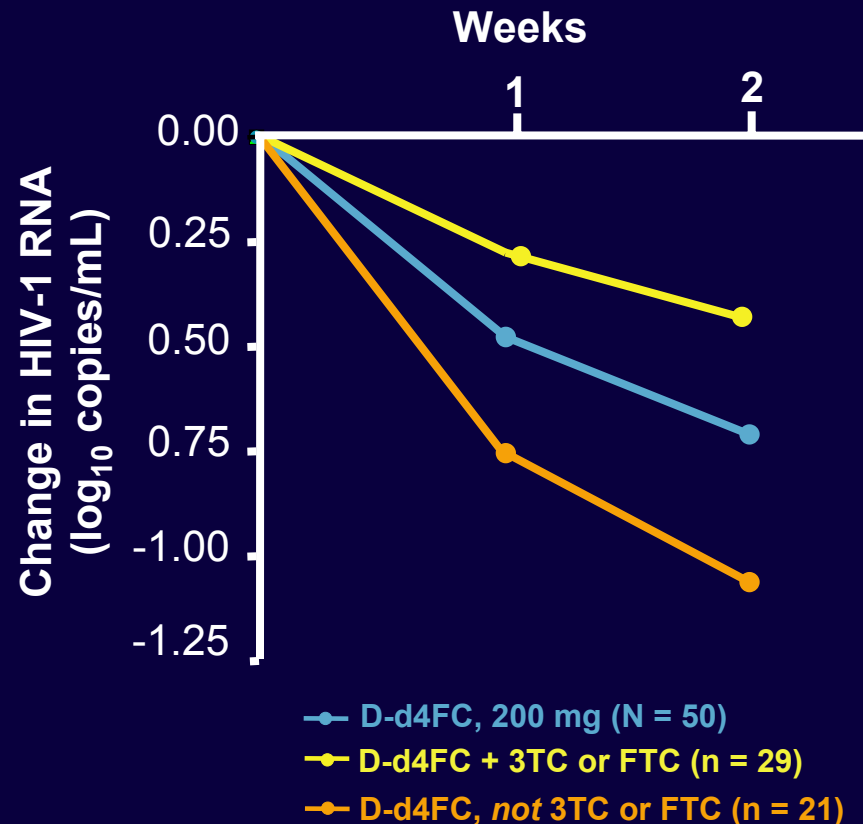
Virologic Response to D-d4FC

- Randomized, dose-ranging trial of D-d4FC vs placebo in 199 experienced pts with VL > 2000 copies/mL
- D-d4FC active against NRTI-resistant viruses



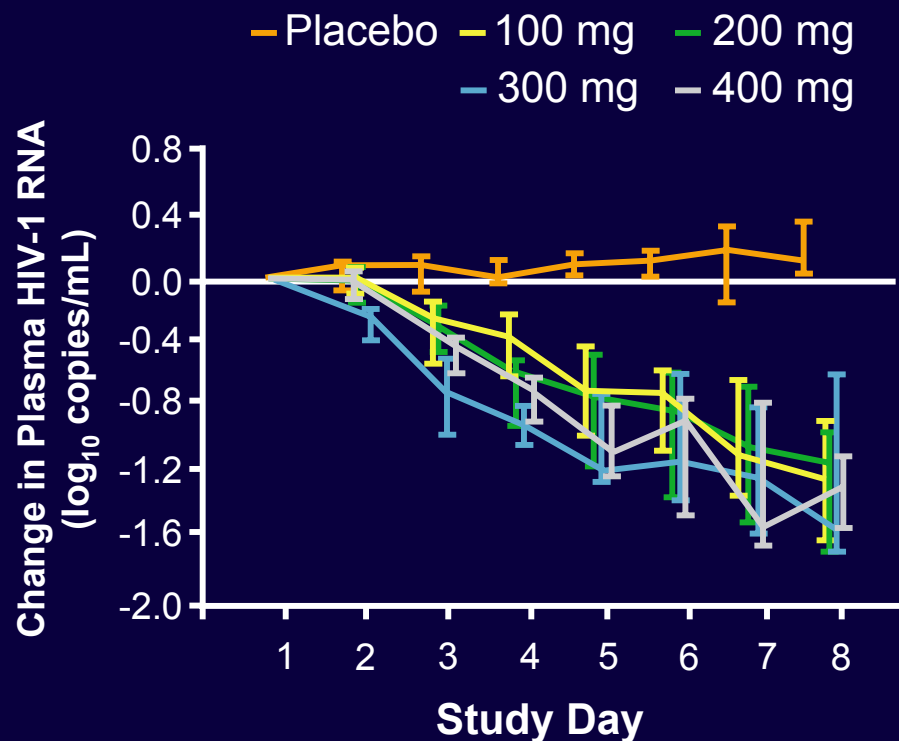
Limitations on Use of D-d4FC With Other NRTIs

- ↓ response in pts on 3TC/FTC
 - Result may be due to an intracellular PK interaction similar to that observed with SPD754
- ↑ incidence of hyperlipasemia when used with ddl
 - 3 cases of pancreatitis



Activity of Novel NNRTI GW695634

- Multicenter, double blind, randomized 7-day add-on study
- N = 44 NNRTI-exp pts
- 27 \geq 1 NNRTI mutation at BL
- Remaining 17 had history of NNRTI mutations
 - Most common NNRTI mut: K103N, V108I, Y181C
- BL VL, 4.4-4.6 log
- BL CD4+, 230-345



POWER1: Efficacy and Safety of TMC114/r in PI-Experienced Patients

- Ongoing 96 week randomized trial of 3-class experienced pts ^[1]
 - ≥ 1 primary PI mutation
 - BL HIV-1 RNA:
TMC114/r 4.5 vs Control 4.4
 - BL CD4+:
TMC114/r 204 vs Control 233
- Pooled interim results for POWER 1 & POWER 2 presented at CROI 2005
- Planned 24-wk analysis of POWER 1 trial presented at IAS
 - Less advanced than pooled cohort

Treatment Arms

TMC114 400 mg QD
Ritonavir 100 mg QD
(n = 64)

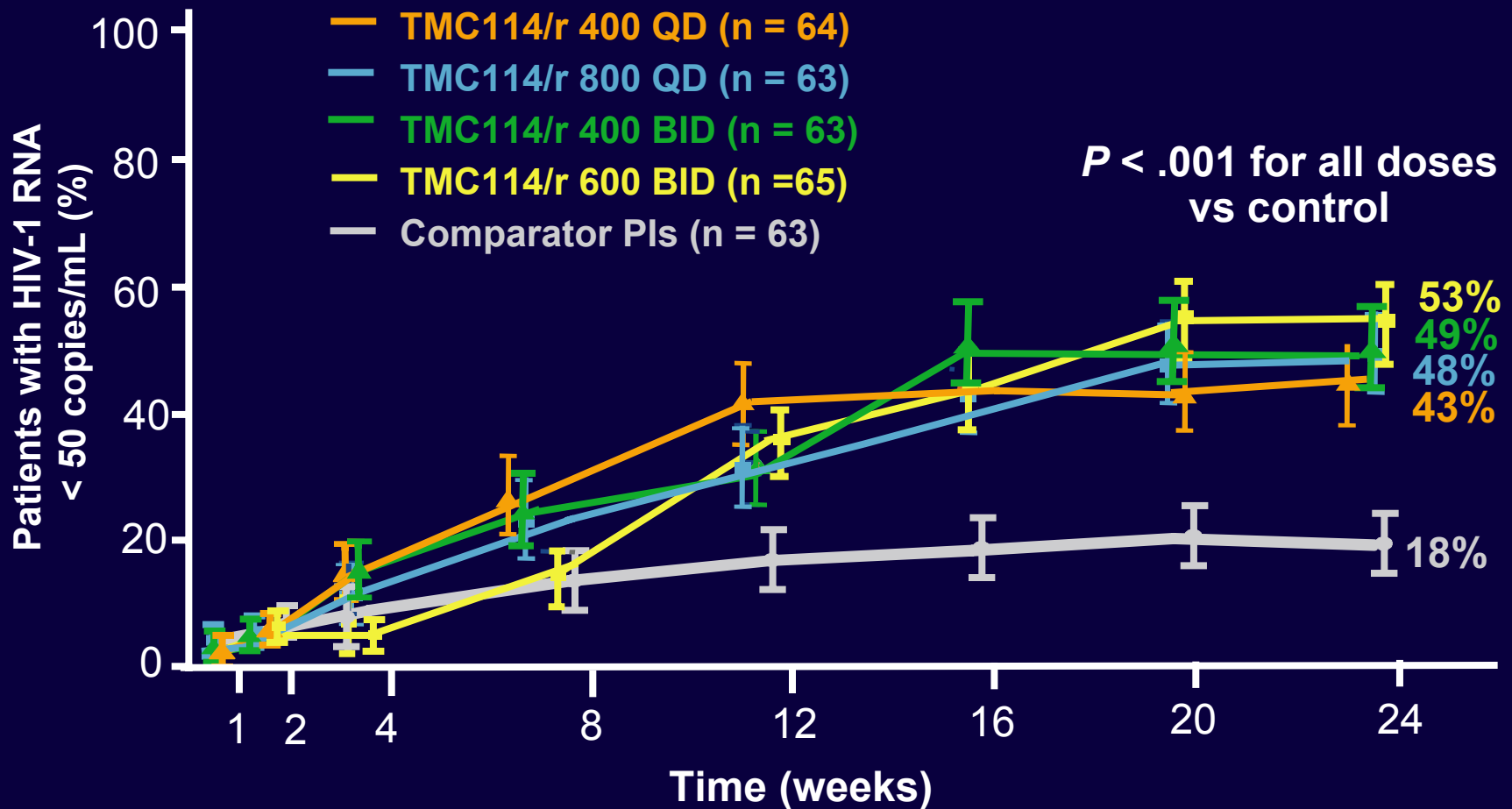
TMC114 800 mg QD
Ritonavir 100 mg QD
(n = 63)

TMC114 400 mg BID
Ritonavir 100 mg BID
(n = 63)

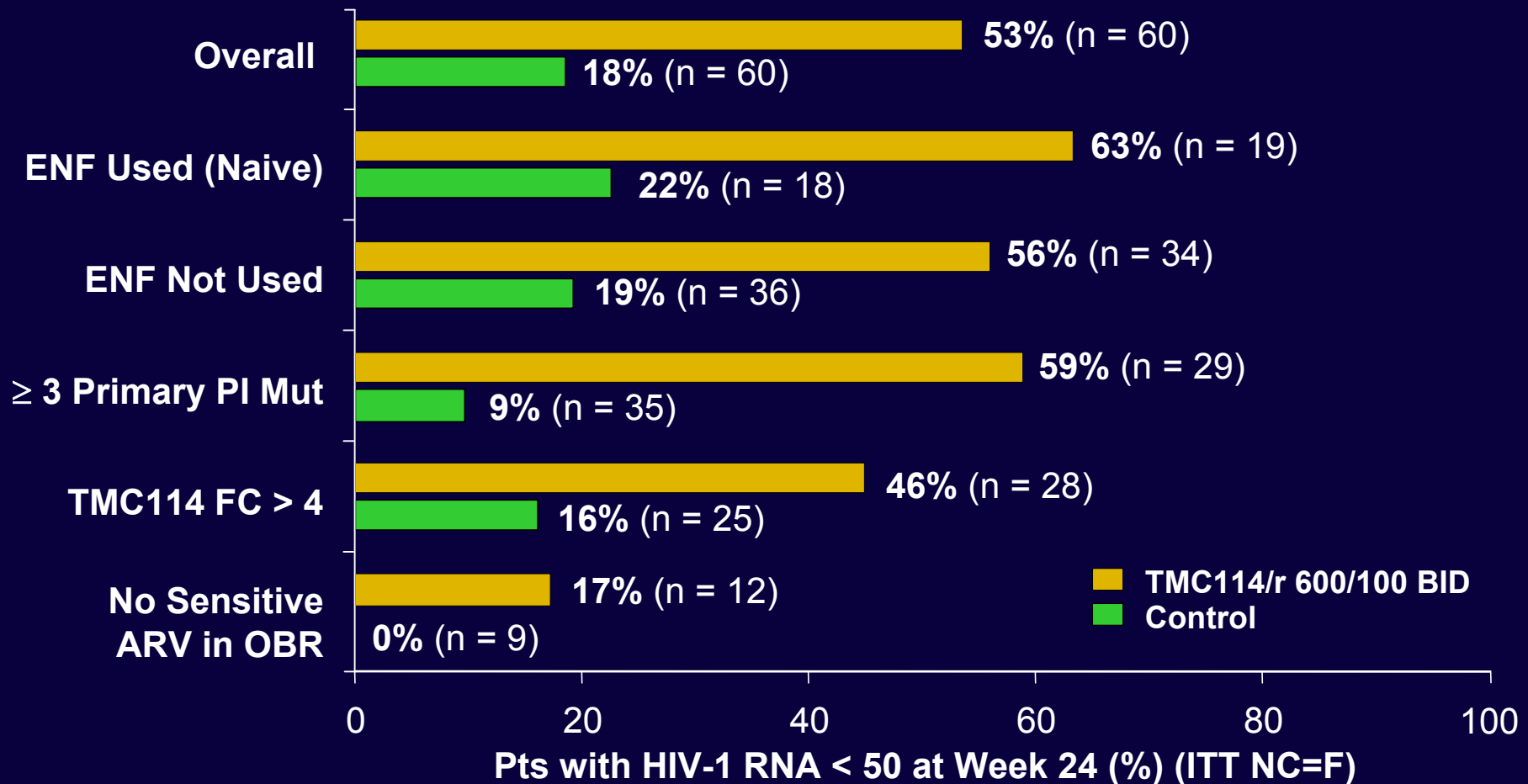
TMC114 600 mg BID
Ritonavir 100 mg BID
(n = 65)

**Investigator-selected PI +
OBR**
(n = 63)

POWER1: Virologic Response to TMC114/r



POWER1: Subgroup Analyses of Response to TMC114/r 600/100 BID



Safety of TMC114/r and PK Data

- Safety and tolerability of TMC114/r similar to control [1]

Grade 3 or 4 AEs*, n (%)	TMC114/r (600/100) (n = 65)	Control PIs (n = 63)
ALT	1 (1.5)	2 (3.2)
AST	0	3 (4.8)
Total cholesterol	5 (7.7)	0
Triglycerides	7 (10.8)	5 (8.0)

* Enhanced ACTG-graded laboratory abnormalities (worst toxicity grades)

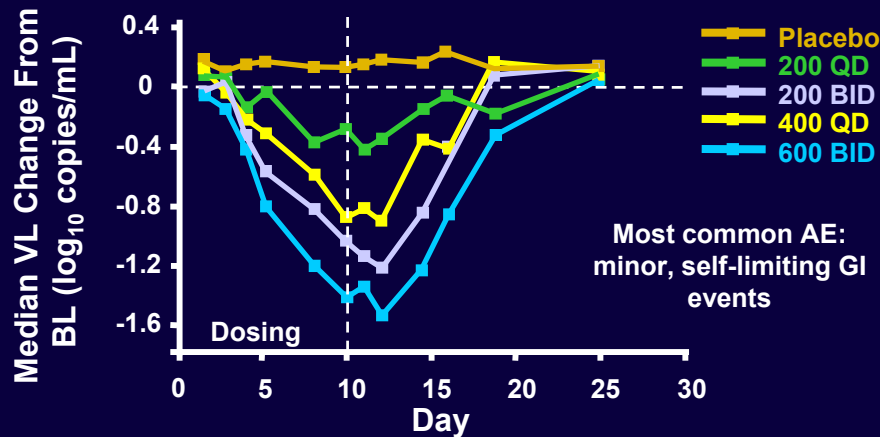
- No effect of 20 mg omeprazole or 150 mg BID ranitidine on TMC114 PK in separate study in HIV(-) volunteers [2]
 - Impact of 40 mg omeprazole unknown

1. Grinsztein B, et al. IAS 2005. Abstract WePeLB6.2C01.

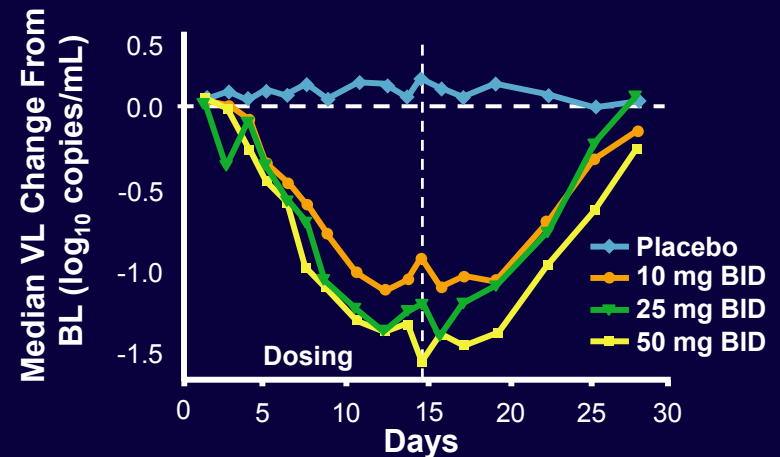
2. Sekar V, et al. IAS 2005. Abstract WePe3.3C13.

CCR5 Inhibitors in Development

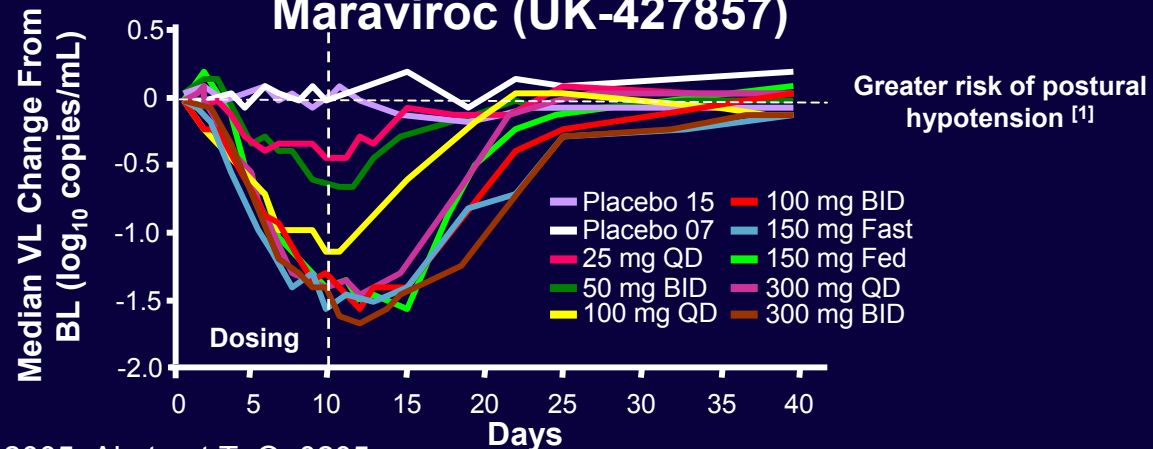
Aplaviroc (GW873140)



Vicriviroc (SCH-417690)



Maraviroc (UK-427857)



1. Schuermann D, et al. IAS 2005. Abstract TuOa0205.

2. McHale M, et al. IAS 2005. Abstract TuOa0204.

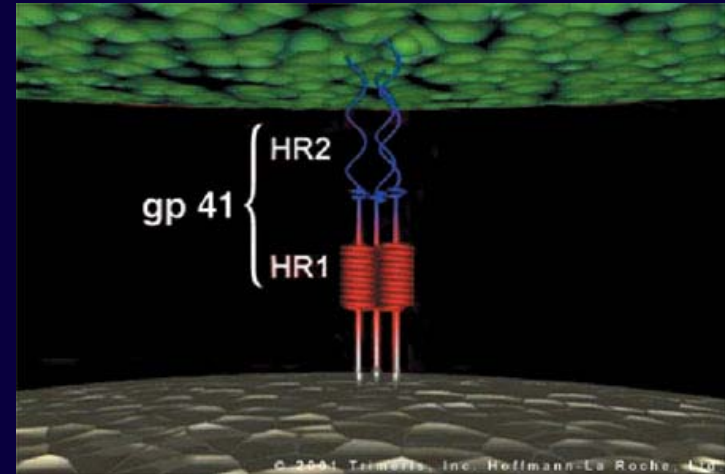
Interactions Between Vicriviroc and Other Antiretrovirals

Coadministered Antiretroviral	Effect on Vicriviroc* Levels	C _{max} (ng/mL)	AUC (ng*hr/mL)
Tenofovir	↔	+5%	-6%
Zidovudine/lamivudine	↔	-8%	-9%
Ritonavir	↑	+254%	+528%
Lopinavir/ritonavir ^[1]	↑	+238%	+417%
Efavirenz	↓	-67%	-81%
Efavirenz + ritonavir	↑	+196%	+384%

* *Vicriviroc* = SCH417690

Oral Fusion Inhibitors NB-2 & NB-64

- Both inhibited HIV-1 replication, cell-cell fusion, virus entry by inhibiting
 - formation of gp41 fusion-active core
 - gp41 6-helix bundle formation
 - alpha-helical conformation
- Compounds demonstrated antiviral activity against
 - Range of R5-tropic, X4-tropic laboratory and clinical HIV-1 isolates
 - Clades A to G, Group O
- inhibited HIV-1 p24 production in vitro
- 20 similar compounds now identified with stronger activity



Metabolic Complications and Other Adverse Events

Bill Owen, M.D.

High Prevalence of Osteopenia

- Aquitaine cohort is a large French database
- BMD performed on 400 consecutive HIV+ patients
 - 73% male
 - Median age 43
- DEXA revealed
 - osteopenia in 54.5% (t-score -1 to -2.5)
 - osteoporosis in 25.1% (t-score <-2.5)
- Increased risk for OP: males, AIDS dx, lipodystrophy

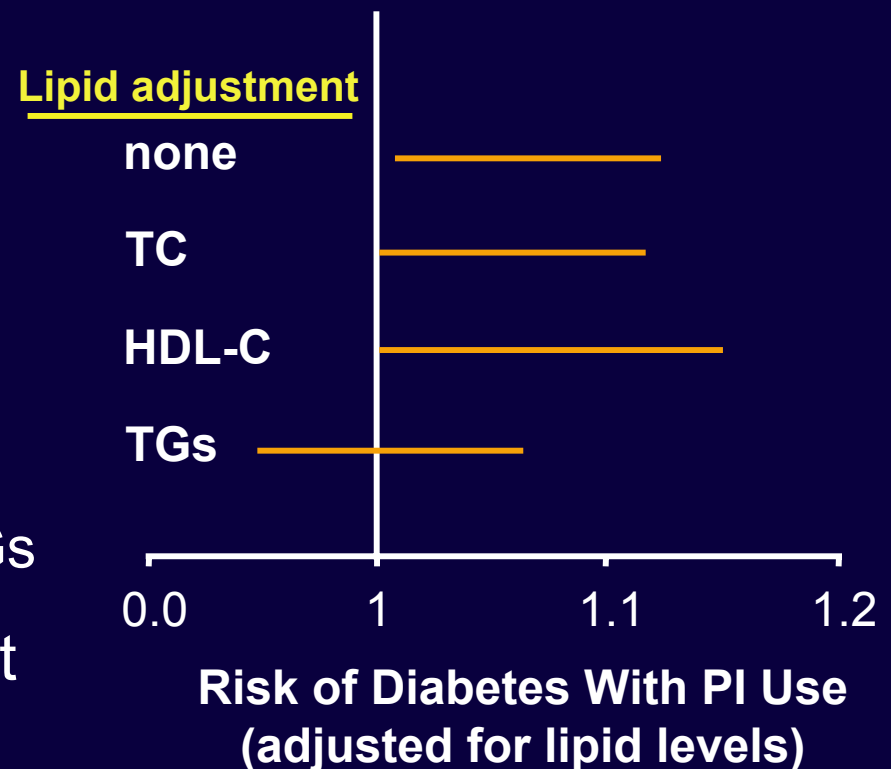
Prevalence of Metabolic Syndrome in MACS Cohort

- HIV-positive men (n=646) more likely to have metabolic syndrome than HIV-negative men (n=397)
 - Low HDL, elevated TGs, elevated glucose more likely in HIV+
 - Increased waist circumference less likely in HIV+

	Estimated Odds Ratio for HIV+ vs HIV- Pts (95% CI)	P Value
Metabolic syndrome	1.50 (1.14-1.98)	.004
■ Elevated fasting triglycerides	2.81 (2.25-3.52)	< .001
■ Elevated fasting glucose	1.81 (1.38-2.38)	< .001
■ Increased waist circumference	0.38 (0.28-0.53)	< .001
■ Low HDL cholesterol	3.15 (2.53-3.92)	< .001
■ High blood pressure	1.04 (0.84-1.29)	.715

Impact of Lipids on Relationship Between PIs & Diabetes in D:A:D

- Longer PI use associated with \uparrow onset of diabetes
 - 5-6% \uparrow in diabetes per yr of PI use
- TGs also associated with diabetes
 - 7.07 RR per 2-fold \uparrow in TGs
- PI-diabetes association lost when adjusted for TGs

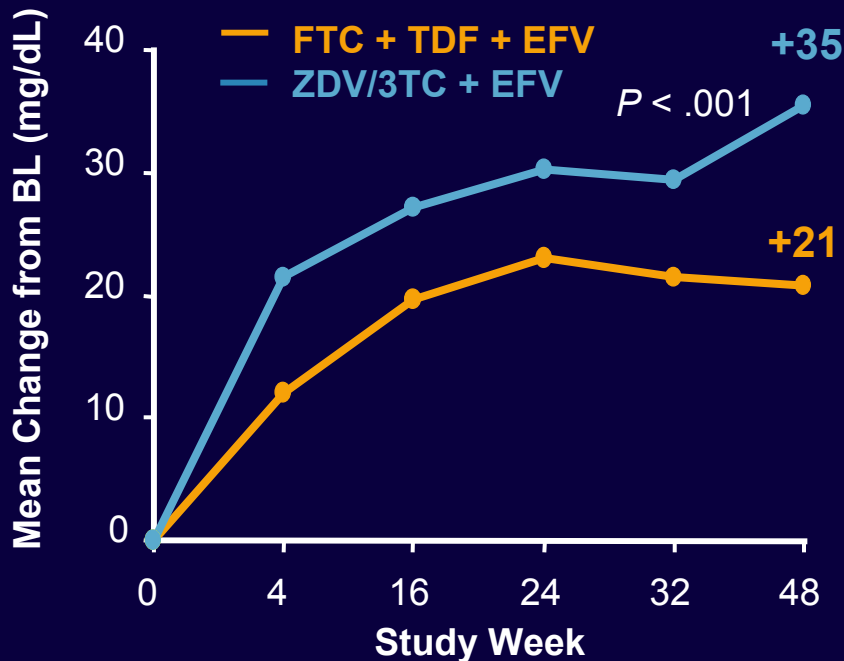


Lipid Effects of First-line Regimens

- Swiss HIV Cohort Study (N = 1065; FU 17-18 mos)
 - ↑ cholesterol with either PIs (+7 mg/dL/yr) or NNRTIs (+8 mg/dL/yr)
 - Patients primarily on LPV/r, IDV/r, or NFV
 - IDV/r had the greatest increase (+25 mg/dL/yr)
 - ↑ triglycerides with PIs (+19 mg/dL/yr), particularly with RTV regimens, vs NNRTI (-12 mg/dL/yr)
 - ↑ HDL-C with NNRTIs (+4 vs +0.4 mg/dL/yr for PI)

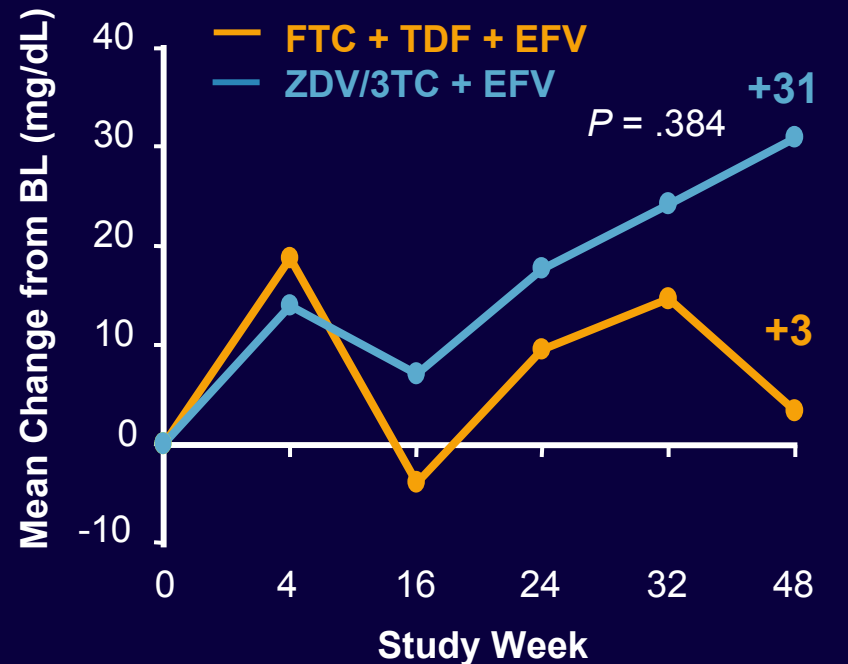
GS934: Effect of NRTIs on Lipids

Total Cholesterol



—	256	239	232	226	217	205
—	250	233	225	202	195	178

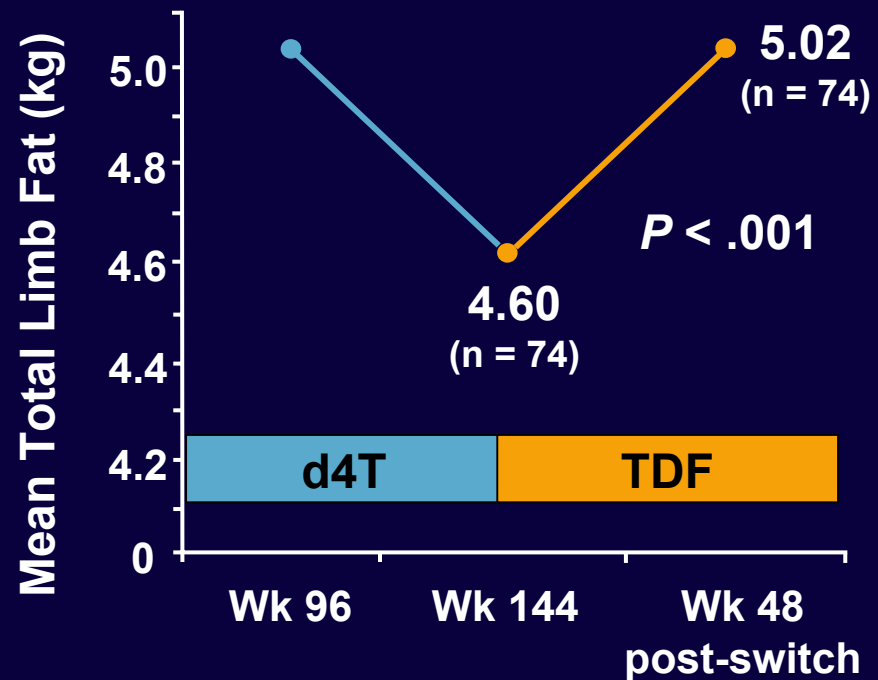
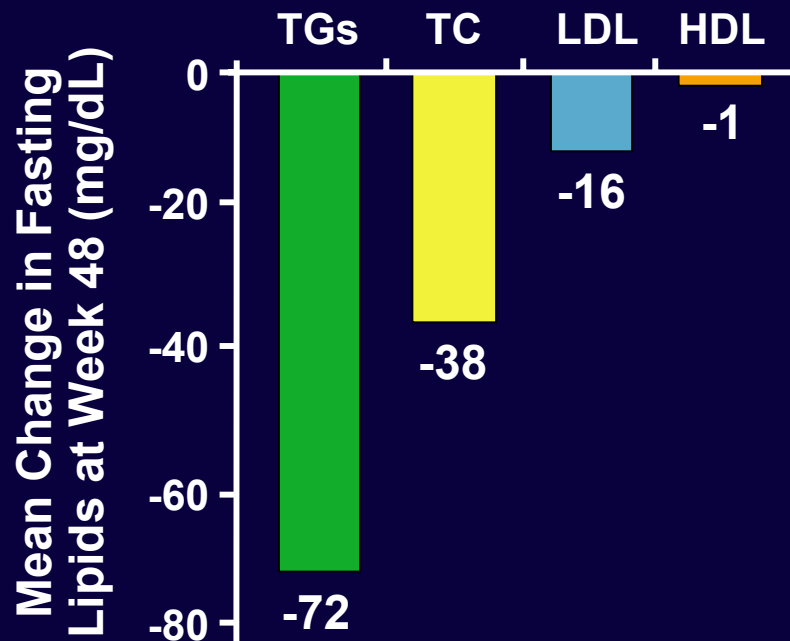
Triglycerides



—	256	239	232	226	217	205
—	250	233	225	202	195	178

Impact of Switching From d4T on Lipids and Limb Fat

- 96-week open-label extension phase of 903 study
 - Data from subgroup of pts given d4T for 144 weeks who switched to open-label TDF for 48 weeks



Switching Thymidine NRTI to Abacavir or Tenofovir Improves Facial Lipoatrophy

- RAVE study at CROI 2005 reported improvement in limb fat with replacement of TNRTI by TDF or ABC
- 24 patients (71% d4T, 29% AZT) switched to ABC
- 23 patients (83% d4T, 17% AZT) switched to TDF
- Historical controls for 3-D surface laser imaging of face using 17 patients receiving collagen +3150 mm³

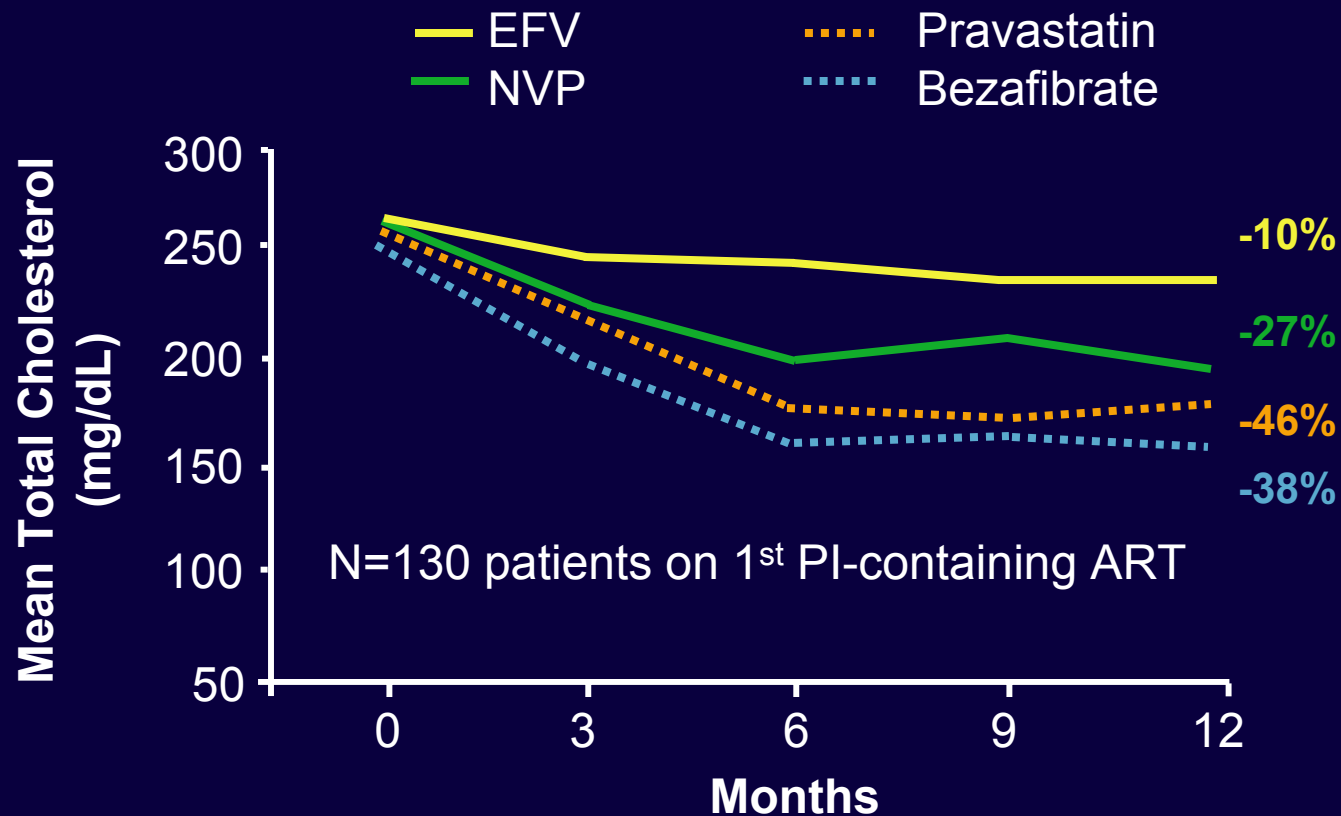
<i>Volume Change at Week 48, mm³</i>		
<i>Facial Feature</i>	<i>Abacavir (n = 24)</i>	<i>Tenofovir (n = 23)</i>
Forehead	-101	-169
Total cheek	2208	2812
• Left cheek	1031	1343
• Right cheek	1176	1469

Switch to Atazanavir Improves Lipids

- 33 HIV+ in Germany, 94% men, age 46, CD4 455, mean RNA 72, with severe hyperlipidemia
- Switch NNRTI or PI to either ATZ 400 or ATZ/r 300/100

<i>Lipid Parameter</i>	<i>Baseline, mg/dL</i>	<i>24 Weeks, mg/dL</i>	<i>Change, %</i>	<i>P Value</i>
Mean total triglycerides	528 ± 364	287 ± 236	46	.002
Mean total cholesterol	250 ± 74	205 ± 50	18	.001
Mean non-HDL chol	223 ± 74	174 ± 50	22	.003
Mean HDL & LDL chol				NS

Dyslipidemia: Lipid-Lowering Therapy vs PI to NNRTI Switch

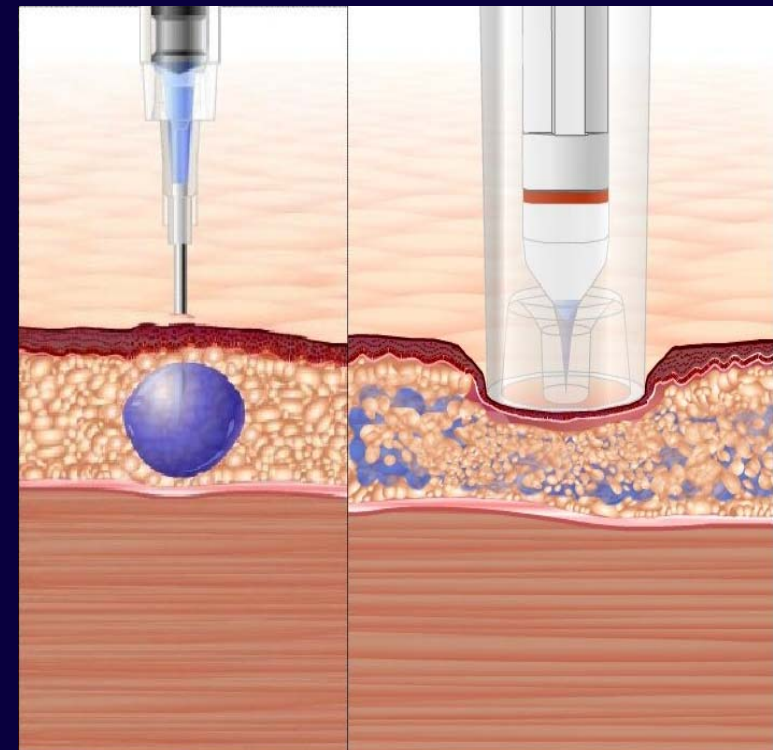


Atazanavir-induced Hyperbilirubinemia in HOPS cohort

- 1st follow-up measurement in 218 patients (147 boosted, 71 unboosted)
 - 12.9% grade 3-4 hyperbilirubinemia in boosted, 8.5% in unboosted
 - Clinical trials show as high as 53%
- Incidence and degree higher in certain patients
 - Ritonavir-boosted atazanavir
 - Higher baseline bilirubin
 - Neither factor could predict degree of elevation in individual
- Significant elevation NOT higher in chronic hepatitis patients

Needle-Free Injection System for Administration of Enfuvirtide

- Use of needle-free gas-powered injection system
 - Compared with standard needles and syringes
- No significant differences in ENF plasma levels
- ISR-related signs and symptoms significantly reduced
- 24 pts evaluated reported that needle-free injector was similar or easier to use than needles



Needle

Biojection
gas-powered
device