

Current Antiretroviral Therapy: New Drugs, New Classes, New Challenges

C. Bradley Hare, MD

Assistant Clinical Professor of Medicine, UCSF
Medical Director, Positive Health Program, SFGH



Approval of Antiretrovirals: 1987-2006

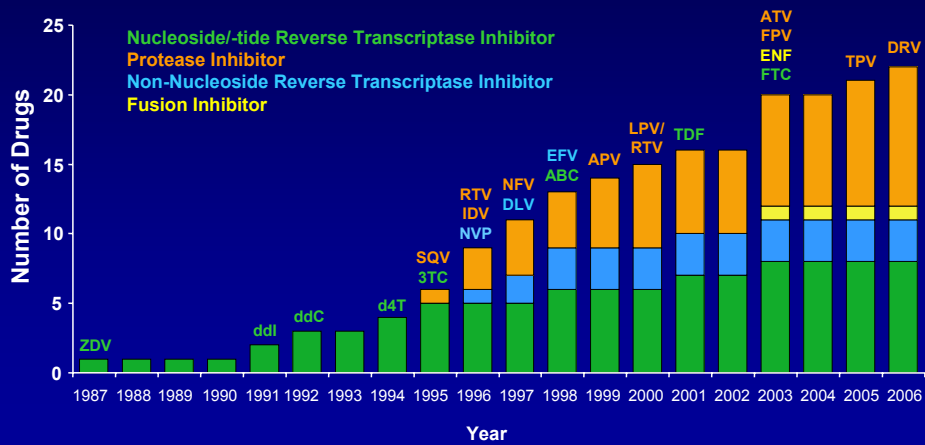


Figure does not include fixed-dose combinations.

FDA-Approved Drugs for HIV Therapy (when last we met)

NRTIs

Abacavir (ABC)
 Didanosine (ddl)
 Emtricitabine (FTC)
 Lamivudine (3TC)
 Stavudine (d4T)
 Tenofovir (TDF)
 Zalcitabine (ddC) *withdrawn 2005*
 Zidovudine (ZDV)
 3TC/ABC
 3TC/ABC/ZDV
 3TC/ZDV
 FTC/TDF

NNRTIs

Delavirdine (DLV)
 Efavirenz (EFV)
 Nevirapine (NVP)

PIs

Amprenavir (APV) *discontinued 2004*
 Atazanavir (ATV)
 Darunavir (DRV)
 Fosamprenavir (FPV)
 Indinavir (IDV)
 Lopinavir/ritonavir (LPV/RTV)
 Nelfinavir (NFV)
 Ritonavir (RTV)
 Saquinavir (SQV hgc)
 Tipranavir (TPV)

Fusion Inhibitors (FIs)

Enfuvirtide (ENF)

Multiple Class Combinations

EFV/FTC/TDF

Select Investigational ARVs

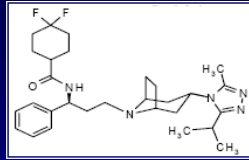
Drug	Target	Phase
Apricitabine	NRTI	I
Fosalvudine	NRTI	I
Etravirine (TMC-125)	NNRTI	III
Rilpivirine (TMC-278)	NNRTI	II/III
UK-453,061	NNRTI	I
Maraviroc (UK-427,857)	CCR5	Approved
Vicriviroc (SHC 417690)	CCR5	II/III
INCB009471	CCR5	I
PRO 140	CCR5	I
Raltegravir (MK-0518)	Integrase	Approved
Elvitegravir (GS-9137)	Integrase	II
Bevirimat (PA 457)	Maturation	I

Select Investigational ARVs

Drug	Target	Phase
Apricitabine	NRTI	I
Fosavudine	NRTI	I
Etravirine (TMC-125)	NNRTI	III
Rilpivirine (TMC-278)	NNRTI	II/III
UK-453,061	NNRTI	I
Maraviroc (UK-427,857)	CCR5	Approved
Vicriviroc (SHC 417690)	CCR5	II/III
INCB009471	CCR5	I
PRO 140	CCR5	I
Raltegravir (MK-0518)	Integrase	Approved
Elvitegravir (GS-9137)	Integrase	II
Bevirimat (PA 457)	Maturation	I

PIVOTAL STUDIES / EFFICACY

Maraviroc (MVC)



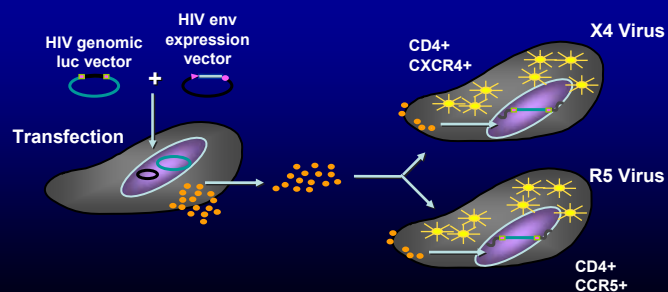
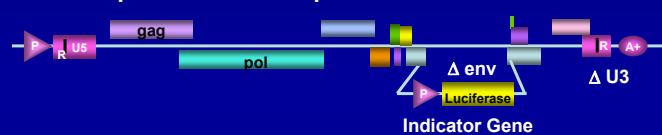
- Orally bioavailable inhibitor of CCR5 coreceptor
 - First drug in class
- Approved by the FDA on August 6, 2007 for patients who have
 - (1) Detectable HIV RNA
 - (2) Evidence of resistance to multiple antiretrovirals
 - (3) Infection with CCR5-tropic virus by viral tropism assay

Tropism Assay

Envelope Expression Vector: pHIVenv



HIV-1 Expression Vector: pHIVlucΔU3



Tropism Assay

Tropotype Result

R5

D/M

X4

Virus uses CCR5 co-receptors to enter the CD4+ cell.

R5

Activity of CCR5 antagonist anticipated?

YES

NO

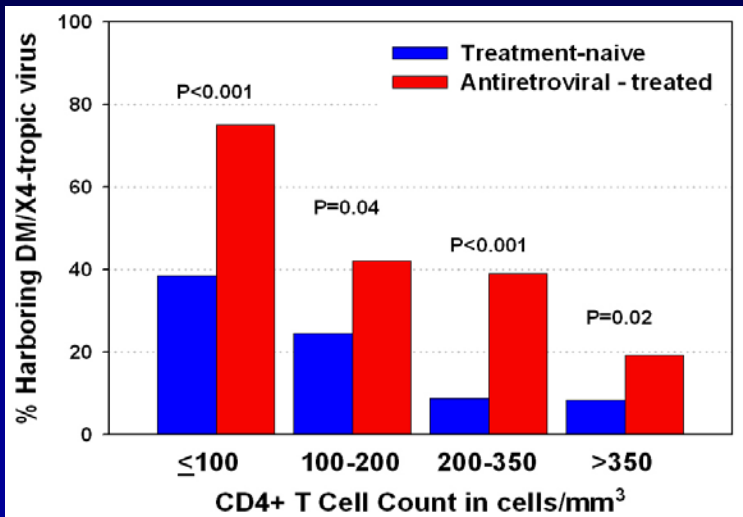
ABOUT TROPISM

WHAT IS TROFILE™?
Trofile is a CLIA-validated*, cell-based approach to determine an individual's HIV co-receptor tropism (or "tropotype™"). Co-receptor tropism is defined as an interaction of a virus with a specific co-receptor on the target cell. To gain entry to the CD4+ cell (host), HIV must bind to the cell surface CD4 receptor and to one of two chemokine co-receptors (CCR5 or CXCR4) also present on the cell surface.

TROFILE VIRAL CLASSIFICATION
CCR5 (R5) Virus = Virus uses CCR5 chemokine co-receptor to enter the CD4+ cell.
DUAL/MIXED (D/M) Virus = Dual-tropic viruses can use either the CXCR4 or CCR5 co-receptors to enter the CD4+ cell. Mixed-tropic is a mixed population of both CCR5 and CXCR4 tropic viruses.
CXCR4 (X4) Virus = Virus uses CXCR4 chemokine co-receptor to enter the CD4+ cell.
Non-reportable = Your patient's tropotype could not be determined by the Trofile assay. Common causes of failure of the assay are viral load <1,000 copies/mL, reduced viral fitness, or compromised sample collection/handling.

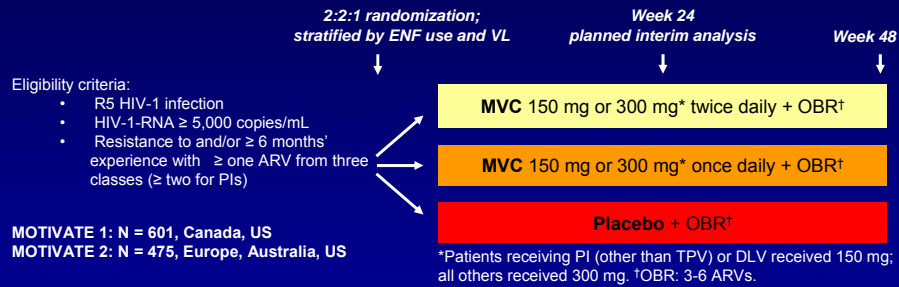
CO-RECEPTOR ANTAGONISTS
A new class of drugs – co-receptor antagonists – provides a novel mechanism to inhibit the HIV viral replication cycle. These drugs work by binding to a specific chemokine receptor (CCR5 or CXCR4) and block the virus' ability to bind these co-receptors and initiate its entry into the host cell. Trofile can help determine whether a CCR5 antagonist or a CXCR4 antagonist may be an appropriate drug for your patient. Several clinical trials on CCR5 antagonists have demonstrated the positive and negative predictive value of Trofile in clinical settings.

Prevalence of DM/X4 Tropism by Treatment Status and CD4 Count



MOTIVATE: Maraviroc in Treatment-Experienced Patients With R5 Virus

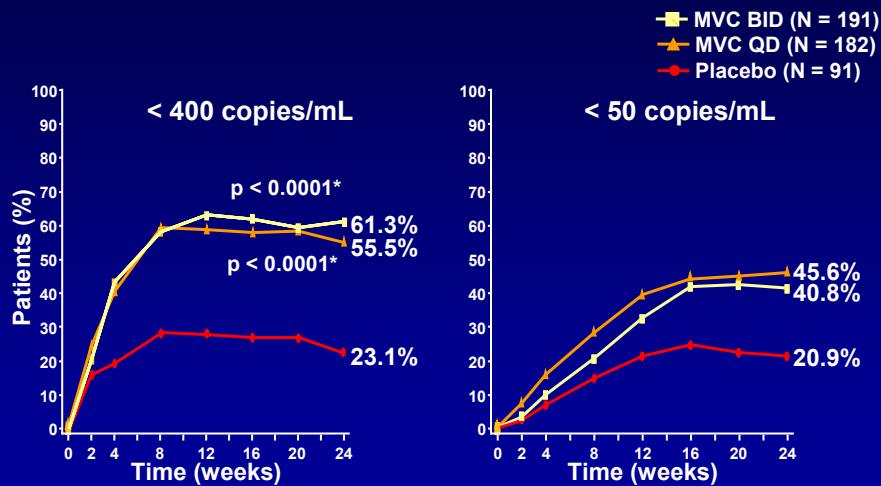
- Randomized, double-blind, placebo-controlled, parallel phase IIb/III studies
- 44% failed screening with X4 or dual/mixed virus detected
- Primary endpoint: mean change in HIV-1 RNA at Week 24



Baseline Data (MOTIVATE 2)	MVC BID + OBR (N = 191)	MVC QD + OBR (N = 182)	Placebo + OBR (N = 91)
Mean CD4+ count, cells/mm ³ (range)	182 (3-820)	174 (1-966)	174 (2-545)
Mean HIV-1 RNA, log ₁₀ copies/mL (range)	4.84 (2.96-6.22)	4.87 (2.49-6.33)	4.89 (3.75-7.07)
ENF in OBR, %	39	37	45
≤ 2 active drugs in OBR, %	62	63	66

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

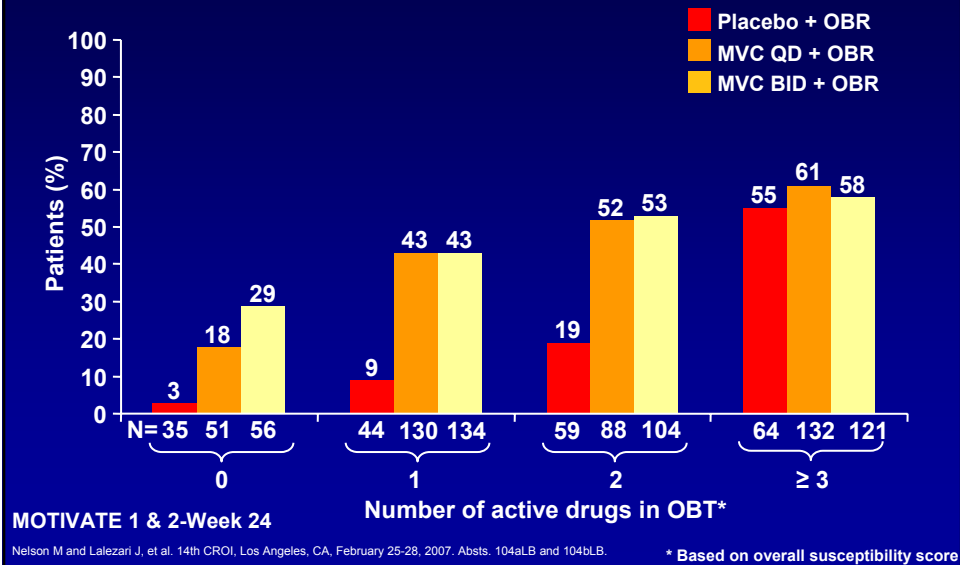
MOTIVATE 2*: Percentage of Patients with Undetectable HIV-1 RNA



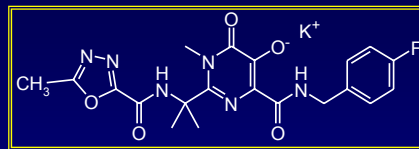
*Results from MOTIVATE 1 were comparable

Nelson M and Lalezari J, et al. 14th CROI, Los Angeles, CA, February 25-28, 2007. Absts. 104aLB and 104bLB.

MOTIVATE 1 and 2: Effect of OBR on Outcome



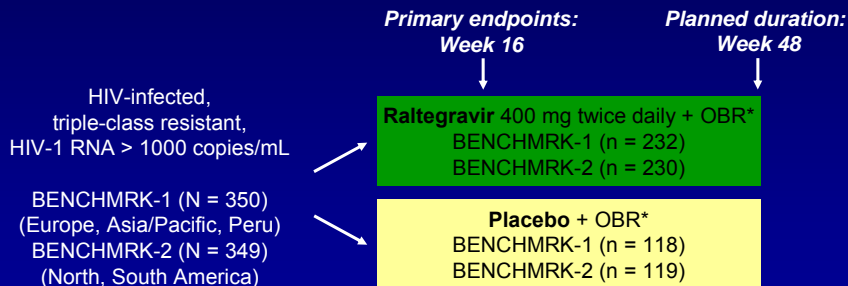
Raltegravir (RAL, MK-0518)



- Orally bioavailable inhibitor of the HIV integrase enzyme
 - First drug in class
 - Inhibits strand transfer step of integration process
- Terminal half-life ~9h, requiring BID dosing
 - Relatively high PK variability after single dose
 - Approved dose 400 mg BID, without regard to food
- Metabolised by glucuronidation
 - Not affected by CYP 3A inducers or inhibitors (e.g, not ritonavir boosted)
- Approved by FDA on October 12, 2007

BENCHMRK 1 and 2: Raltegravir in Treatment-Experienced Pts

- Randomized, double-blind, placebo-controlled, parallel phase III studies
- Primary endpoints: HIV-1 RNA, CD4+ cell counts, and adverse events at Week 16



*Selected investigational antiretrovirals permitted in OBR.

Cooper D, et al. CROI 2007. Abstract 105aLB. Steigbigel R, et al. CROI 2007. Abstract 105bLB.

BENCHMRK 1 & 2

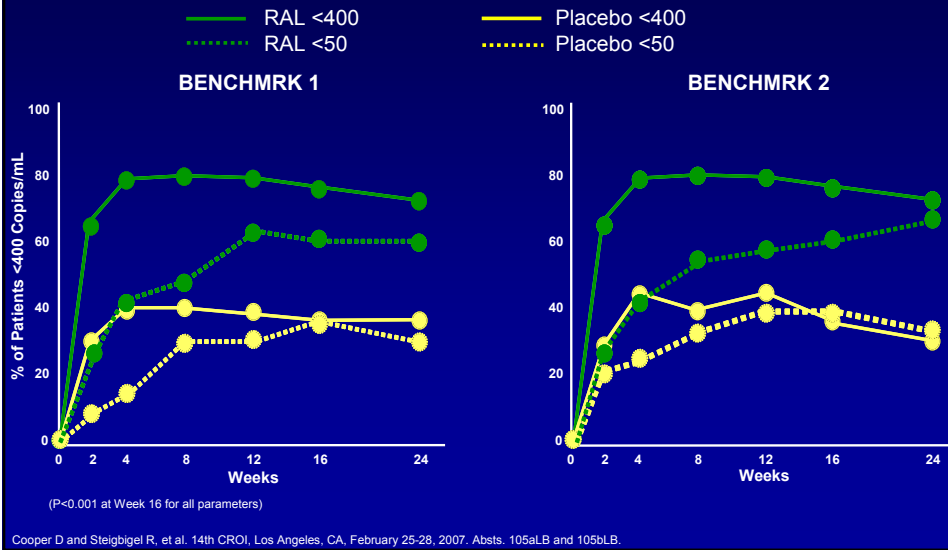
Baseline Patient Characteristics

	BENCHMRK-1		BENCHMRK-2	
	RAL (n = 232)	Placebo (n = 118)	RAL (n = 230)	Placebo (n = 119)
Mean Age, yrs (SD)	46 (9)	44 (8)	45 (9)	46 (8)
% Male	84	87	91	90
% Caucasian	75	81	55	65
Mean CD4 Count, cells/mm ³	156	153	146	163
GM Viral Load, copies/mL (log ₁₀ HIV RNA)	40519 (4.6)	31828 (4.5)	48366 (4.7)	47789 (4.7)
% AIDS	94	90	91	92
Median Yrs of Prior ARTs (median # ART)	11 (12)	10 (12)	10 (12)	10 (12)
% Hep B+/% Hep C+	8/15	4/20	10/3	3/4
% GSS [§] 0/1	30/33	29/41	20/44	26/40
% PSS [§] 0/1	19/29	18/33	10/34	19/27
% new enfuvirtide in OBT	21	20	19	20
% new darunavir in OBT	27	25	45	50

§ GSS/PSS = total ART in OBT to which pt's virus showed geno/phenotypic sensitivity by Phenosense GT assay. Enfuvirtide and darunavir use in naïve patients were each counted as + 1 active agent and added to GSS/PSS

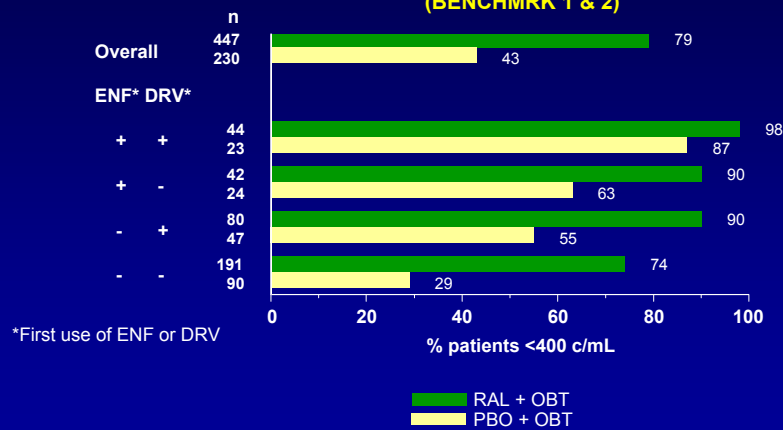
Cooper D and Steigbigel R, et al. 14th CROI, Los Angeles, CA, February 25-28, 2007. Absts. 105aLB and 105bLB.

Percent <400 and <50 Copies/mL (ITT, NC=F)



BENCHMRK 1 & 2: Secondary analyses

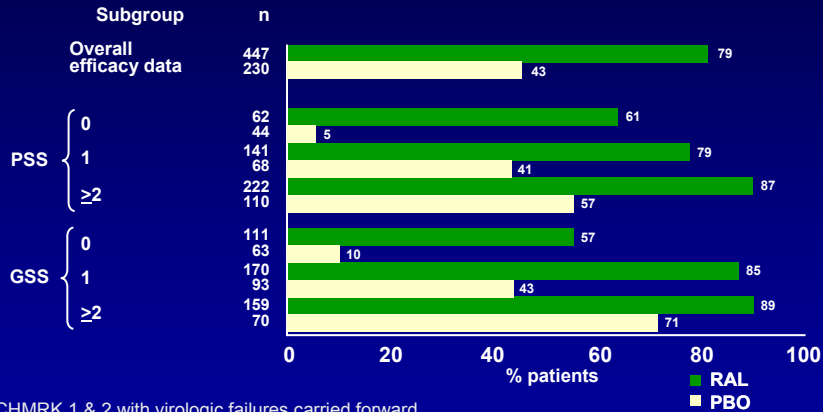
Effect of background regimen (BENCHMRK 1 & 2)



1 Cooper D, et al. 14th CROI, Los Angeles 2007, #105aLB; 2 Steigbigel R, et al. *ibid*, #105bLB

BENCHMRK 1 & 2: Secondary analyses

% Patients with HIV RNA <400 c/mL at Week 16 by PSS/GSS of OBT*

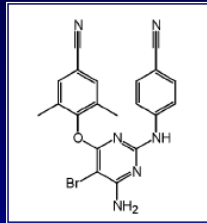


* BENCHMRK 1 & 2 with virologic failures carried forward

GSS = genotypic sensitivity score
PSS = phenotypic sensitivity score

1 Cooper D, *et al.* 14th CROI, Los Angeles 2007, #105aLB; 2 Steigbigel R, *et al. ibid.*, #105bLB

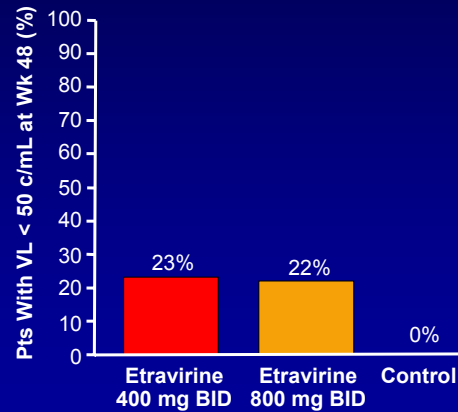
Etravirine (ETR)



- Orally bioavailable “second generation” NNRTI
- Designed to be effective against HIV containing K103N mutation
- Currently in expanded access

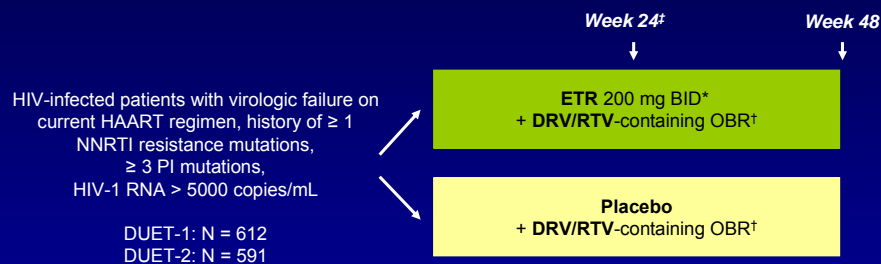
TMC125-C223: Virologic Response to Etravirine at Week 48

- N = 199 HIV-infected patients with NNRTI resistance and ≥ 3 primary PI mutations
 - Median fold NNRTI resistance
 - NVP: 61.3
 - EFV: 41.4
 - Etravirine: 1.6
- Patients randomized to
 - Etravirine (400 mg BID) + NRTIs \pm LPV/RTV \pm ENF
 - Etravirine (800 mg BID) + NRTIs \pm LPV/RTV \pm ENF
 - Active control: best available regimen from licensed agents (NNRTIs excluded)



Cohen C, et al IAC 2006. Abstract TUPE0061.

DUET 1 and 2: Etravirine + DRV/RTV-Containing OBR Phase III Trials



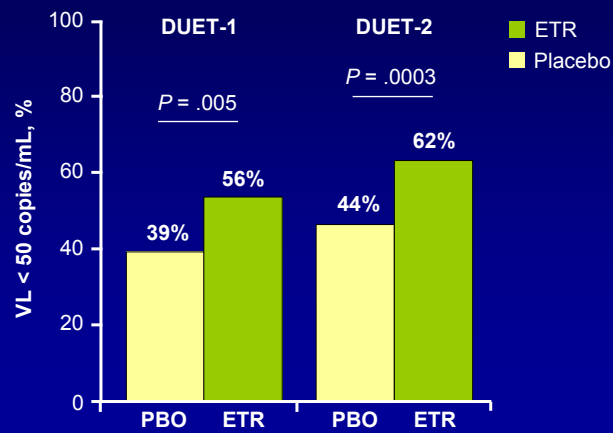
*New formulation equivalent to 800 mg BID with old formulation.

[†]Investigator-selected OBR to consist of DRV/RTV (600/100 mg/mL) + ≥ 2 NRTIs \pm enfuvirtide.

[‡]Planned Week 24 analysis: primary endpoint HIV-1 RNA < 50 copies/mL (TLOVR)

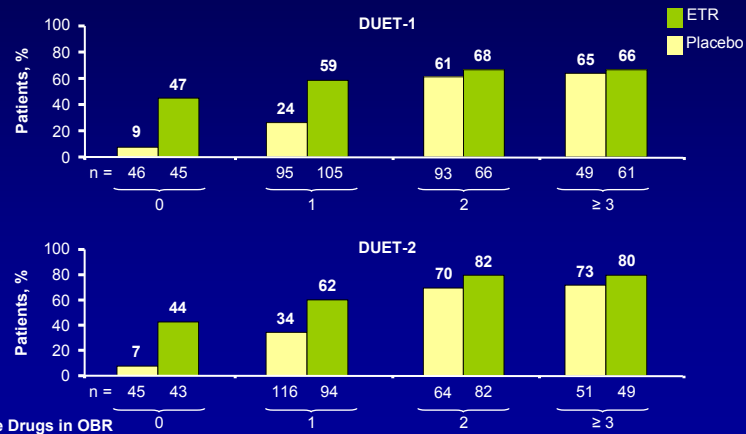
Madruga JV, et al. Lancet. 2007;370:29-38. Lazzarin A, et al. Lancet. 2007;370:39-48.
Katama C, et al. IAS 2007. Abstract WESS204.2. Mills A, et al. IAS 2007. Abstract WESS204.1.

DUET 1 and 2: <50 copies/mL at Week 24 (TLOVR Analysis)



Madruga JV, et al. Lancet. 2007;370:29-38. Lazzarin A, et al. Lancet. 2007;370:39-48.
 Katlama C, et al. IAS 2007. Abstract WESS204.2. Mills A, et al. IAS 2007. Abstract WESS204.1.

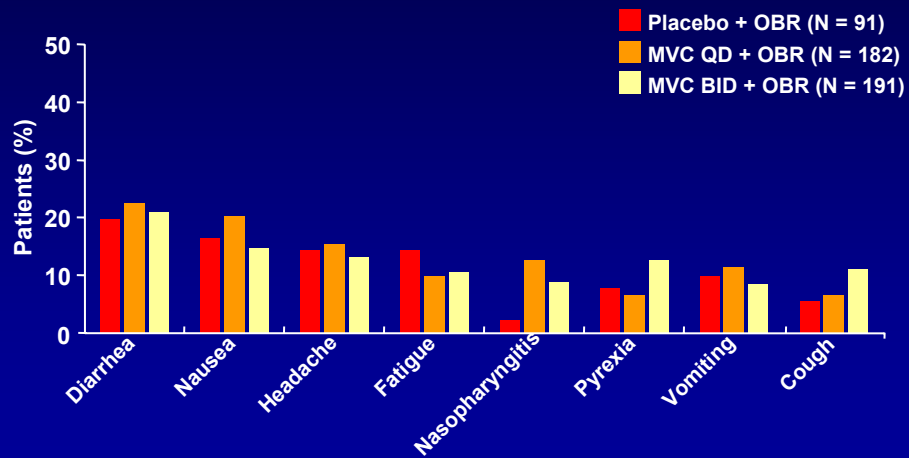
DUET 1 and 2: VL < 50 copies/mL by Active Drugs in OBR



Madruga JV, et al. Lancet. 2007;370:29-38. Lazzarin A, et al. Lancet. 2007;370:39-48.
 Katlama C, et al. IAS 2007. Abstract WESS204.2. Mills A, et al. IAS 2007. Abstract WESS204.1.

SAFETY / TOLERABILITY

Maraviroc: Incidence of Adverse Events Occurring in $\geq 10\%$ of Patients



MOTIVATE 2-Week 24

Nelson M and Lalezari J, et al. 14th CROI, Los Angeles, CA, February 25-28, 2007. Absts. 104aLB and 104bLB.

Maraviroc: Number of Category C Events

Event, n	Placebo (n = 91)	MVC QD (n = 182)	MVC BID (n = 191)
Total exposure; patient-years	41	106	112
Herpes virus infection	2	9	2
Esophageal candidiasis	2	6	2
Cytomegalovirus (CMV) infection*	0	0	1
Mycobacterium avium	2	0	1
Recurrent bacterial pneumonia	3	0	0
<i>Pneumocystis jiroveci</i> pneumonia	0	0	1
Mycobacterial infection	0	0	1
Cryptosporidium enteritis	1	0	0
Kaposi's sarcoma	1	1	2
Lymphoma	0	1	1
Total number of events	11	17	11
Patients (% of patients)	9 patients (9.9%)	16 patients (8.8%)	11 patients (5.8%)

* Includes CMV infection, CMV gastrointestinal infection, and CMV retinitis

Lalezari J, et al. 14th CROI, Los Angeles, CA, February 25-28, 2007. Abst. 104bLB.

Maraviroc: Change in CD4 Cell Count from Baseline by Tropism Result at Time of Failure

Tropism result, Baseline → Treatment Failure	Mean change in CD4 count from baseline, cells/mm ³ in patients with treatment failure		
	Placebo + OBR N = 209	MVC QD + OBR N = 414	MVC BID + OBR N = 426
All treatment failures	+14 (n = 97)	+49 (n = 68)	+71 (n = 77)
R5 → R5	+15 (n = 80)	+61 (n = 18)	+138 (n = 17)
R5 → D/M or X4	+67 (n = 4)	+37 (n = 31)	+56 (n = 32)

MOTIVATE 1 & 2-Week 24

Data excludes patients who had no tropism result at time of failure and patients with non-R5 virus at baseline

Nelson M and Lalezari J, et al. 14th CROI, Los Angeles, CA, February 25-28, 2007. Absts. 104aLB and 104bLB.

Raltegravir: Grade 2-4 Drug Related Clinical Adverse Events (%)

	BENCHMRK-1		BENCHMRK-2	
	RAL (n = 232)	Placebo (n = 118)	RAL (n = 230)	Placebo (n = 119)
Mean Exposure (Wks)	26.0	23.0	25.3	22.5
Abdominal Distension	0.4	3.4	3.9	0.8
Abdominal Pain	1.3	3.4	4.3	0
Diarrhea	6.5	11.0	12.2	9.2
Nausea	3.9	6.8	9.1	8.4
Headache	2.6	6.8	7.8	4.2
Fatigue	1.7	0	4.3	2.5

Cooper D and Steigbigel R, et al. 14th CROI, Los Angeles, CA, February 25-28, 2007. Absts. 105aLB and 105bLB.

Raltegravir: Laboratory Abnormalities (%) (≥1 % in at least one treatment group)

Test	Toxicity Criteria*	BENCHMRK-1		BENCHMRK-2	
		RAL (n = 232)	Placebo (n = 118)	RAL (n = 230)	Placebo (n = 119)
ANC	<750 c/uL	2.6	1.7	4.8	5.1
Hgb	<7.5 gm/dL	1.3	0.8	0.4	0
LDL-C**	≥190 mg/dL	6.0	2.8	1.4	0.9
Chol**	>300 mg/dL	6.5	3.4	2.2	4.2
TG**	>750 mg/dL	5.6	2.5	3.9	7.5
Creatinine	≥1.9 x ULN	0	0	1.7	2.5
Panc. Amylase	≥2.1 x ULN	3.0	2.5	3.4	2.5
AST	2.6 – 5.0 x ULN (Gr 2)	9.9	2.5	8.3	7.6
	≥5.1 x ULN	2.2	2.5	2.1	3.3
ALT	2.6 – 5.0 x ULN (Gr 2)	6.9	8.5	6.5	9.2
	≥5.1 x ULN	5.6	2.5	1.3	1.6

*Grade 3 or 4 per DAIDS toxicity criteria for all tests except grade 2-4 for AST and ALT
**Fasting

Cooper D and Steigbigel R, et al. 14th CROI, Los Angeles, CA, February 25-28, 2007. Absts. 105aLB and 105bLB.

Etravirine: Adverse Events

- Incidence of adverse events and lab abnormalities similar to placebo
 - Higher rate of rash in ETR (17% vs 9%)
 - 2% discontinued due to rash

Parameter	DUET-1		DUET-2	
	TMC125 + BR (n=304)	Placebo + BR (n=308)	TMC125 + BR (n=295)	Placebo + BR (n=296)
Any AE (any cause)	93	93	92	92
Grade 3/4 AE	21	28	28	27
Discontinuation due to AE, %	5	5	6	4
Serious AE, %	12	20	15	17
Death (any cause), n (%)	4 (1.3%)	8 (2.6%)	4 (1.4%)	7 (2.4%)
Most common AEs*				
Rash (any type), %	20	10	14	9
Nausea, %	14	12	14	10
Diarrhoea, %	12	20	18	20
Headache	10	13	9	11
Injection site reaction	7	7	13	15
AEs of interest				
Nervous system disorders	15	20	15	17
Psychiatric disorders	10	14	16	17
Hepatic AEs	5	7	5	4

No deaths in the TMC125 group were considered at least possibly related to trial medication;
*In >10% patients in TMC125 group in either trial

Madruga JV, et al. Lancet. 2007;370:29-38. Lazzarin A, et al. Lancet. 2007;370:39-48.
Katama C, et al. IAS 2007. Abstract WESS204.2. Mills A, et al. IAS 2007. Abstract WESS204.1.

FAILURE / RESISTANCE

Maraviroc Phase 2b Dual / Mixed-Tropic HIV Study

	N	Viral Load	CD4 Change	HIV RNA < 400	HIV RNA < 50
OBR	58	-0.97	36	24%	11%
MVC 150mg (QD) + OBR	57	-0.91	60	25%	21%
MVC 150mg (Bid) + OBR	52	-1.20	62	31%	27%

- Experienced patients with dual / mixed tropic virus
- No superiority in either MVC arm compared to the OBT arm in terms of VL declines from baseline.
- A greater increase in CD4 count occurred in both MVC groups versus the placebo group (but no change in CD4%) – requires further investigation.

Mayer, H. et al., XVI International AIDS Conference, Toronto, Canada, 13th-18th August 2006, Abstract THLB0215

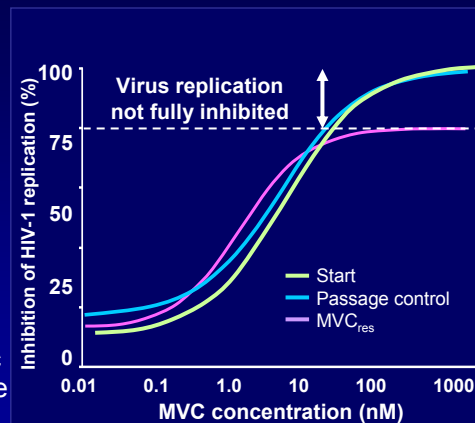
Maraviroc: CCR5 antagonist resistance

Phenotypic resistance¹

- Shift in IC₅₀ in PBMC
- Decreased maximum percentage inhibition in U87 cells (eg, Monogram assay¹)
- *In vitro* selected resistant virus often cross-resistant to other CCR5 inhibitors

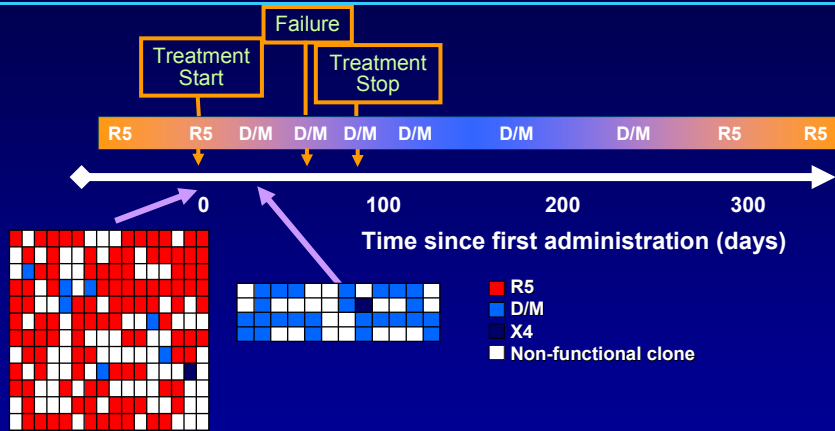
MOTIVATE 1 and 2 MVC failures²

- ~65% with dual/mixed (D/M) tropic virus without phenotypic resistance
- 4/12 who had R5 only at failure had phenotypic resistance
 - No specific amino acid pattern changes



1. Moore J, et al. 4th IAS, Sydney 2007, #TUBA102; 2. Mori J, et al. XVI IHHVDRW, Barbados 2007, #10

Maraviroc: Emergence of D/M tropic virus on CCR5 antagonist therapy



- Clonal and phylogenetic analyses suggest emergent D/M tropic virus on CCR5 antagonists predominantly from pre-existing population
- Clinical implications of emerging D/M virus remain to be fully defined

Lewis M, et al. XVI IHIVDRW, Barbados 2007, #56

Raltegravir: Cross-resistance between integrase inhibitors

- *In vitro* patterns of resistance suggest cross-resistance between elvitegravir (EVG) and raltegravir (RAL)

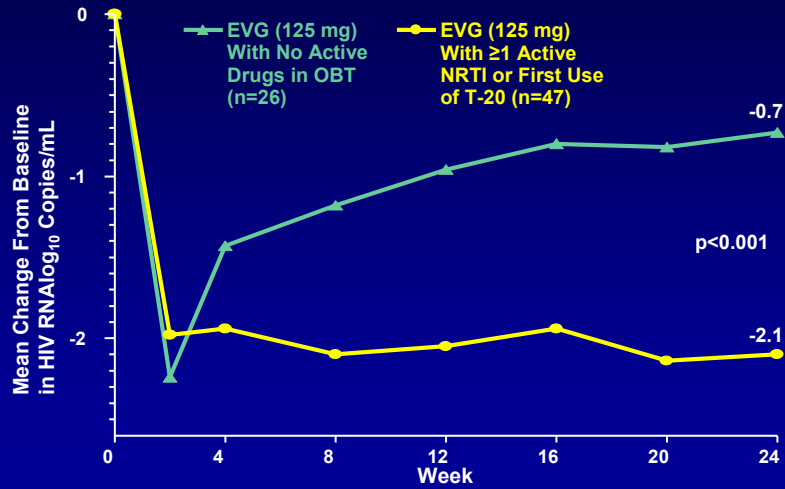
Drug	H51Y	E138K	S142G	Q148R	E138K S147G Q148R	N155H
EVG	4.0	0.7	8.0	118	175	38
RAL	0.9	0.9	1.0	20	34	23

■ FC ≤ 2.5 ; ■ FC 2.5-10; ■ FC ≥ 10

- Study of patients viremic on EVG study \Rightarrow cross over to RAL
 - One week mono-substitution, then optimized regimen
- Results: 2 patients enrolled; study stopped due to $<0.3 \log_{10}$ decline at Day 7 after switch in both
 - Major BL GT mutations: (1) N155H; (2) H51Y / E138K / S147G / Q148R
- Conclusion: While some isolates may allow successful sequencing, cross-resistance risk is significant concern

DeJesus E, et al. 4th IAS, Sydney 2007, #TUPEB032

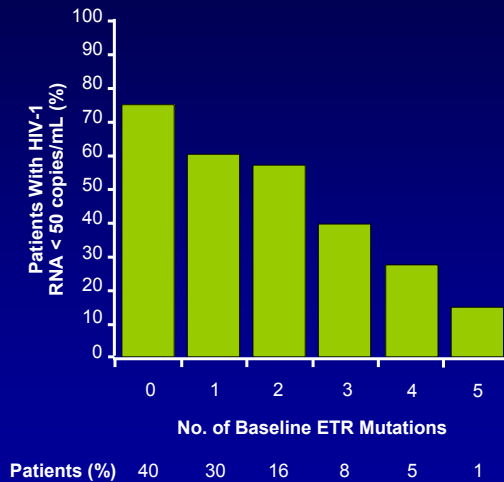
Elvitegravir: Change in HIV RNA With EVG



Etravirine: Baseline ETR Mutations and Virologic Response in DUET 1 and 2

- 13 mutations associated with ETR resistance:

V90I	A98G
L100I	K101E/P
V106I	V179D/F
Y181C/I/V	G190A/S
- Presence of ≥ 3 ETR mutations associated with response similar to placebo + OBR
 - 70% of patients had 0 or 1 ETR resistance mutations at BL
 - 14% of patients had ≥ 3 ETR resistance mutations at BL

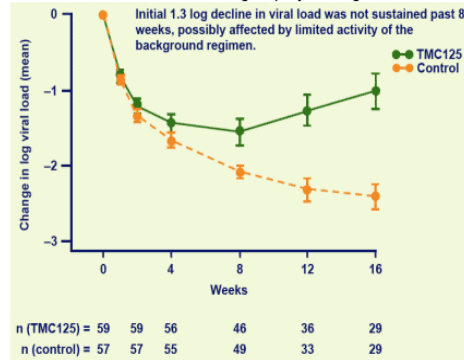


Katlama C, et al. IAS 2007. Abstract WESS204.2.

Etravirine in NNRTI Failures: Use Carefully

- Phase II study of 116 NNRTI first failures
- Randomized to etravirine 200 mg bid equivalent + NRTIs vs. comparator PI + NRTIs
- Well tolerated
 - 10% mild rash
- Rebound after 8 weeks in ETR arm likely due to inadequacy of NRTI backbone

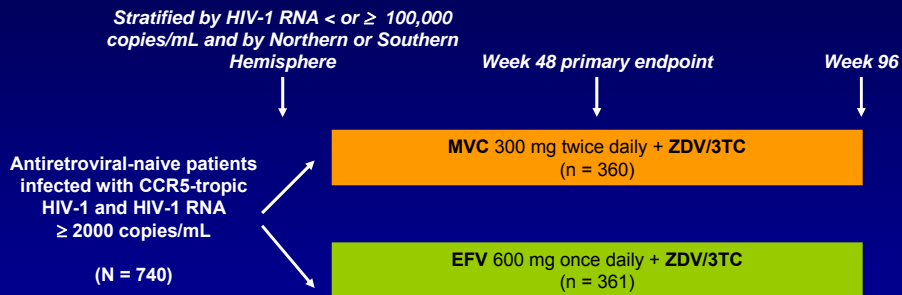
TMC125-C227: Change in viral load (observed)
Viral load declined in TMC125 group by 1.3 log at week 8 & then rebounded.



Woodfall, et al. 8th Intl Congress on Drug Therapy in HIV Infection, 2006, Abstract PL5.6

NAÏVE DATA

MERIT: Maraviroc vs Efavirenz in Treatment-Naive Patients

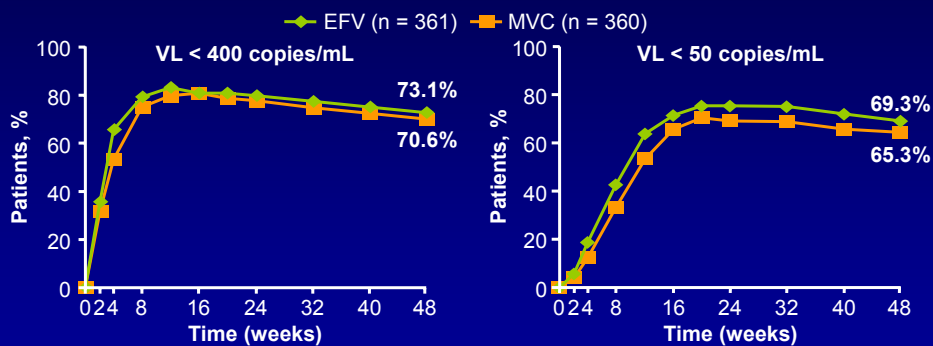


MVC 300-mg once-daily arm discontinued early due to failure to demonstrate noninferiority to efavirenz at end of phase IIB (Week 16)

- Stringent noninferiority margin: -10% for lower bound of 1-sided 97.5% CI

Saag M, et al. IAS 2007. Abstract WESS104.

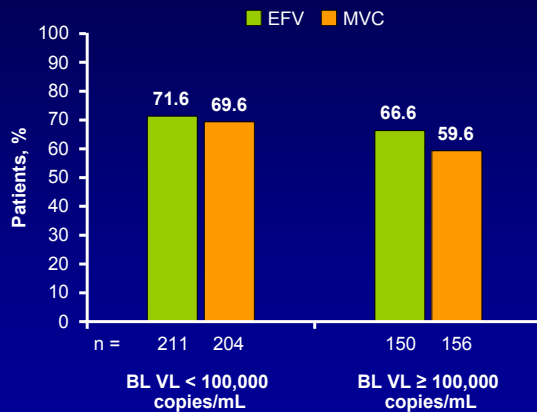
MERIT: Patients With VL < 400 and < 50 Copies/mL by Week 48 (ITT)



- MVC was noninferior to EFV *only* for < 400 copies/mL endpoint (70.6% vs 73.1%)
- CD4+ cell count increases were higher in patients receiving MVC vs EFV (+170 vs +144 cells/mm³)

Saag M, et al. IAS 2007. Abstract WESS104.

MERIT: Patients With VL < 50 Copies/mL by Baseline VL



Drug Discontinuations

	Total	AEs	Efficacy
EFV	25.2%	13.6%	4.2%
MVC	26.9%	4.2%	11.9%

Saag M, et al. IAS 2007. Abstract WESS104.

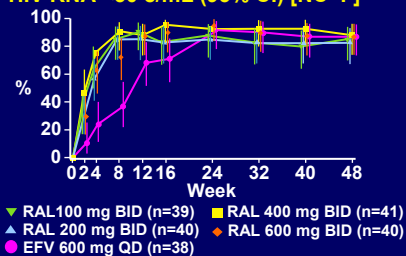
Raltegravir (RAL) with TDF and 3TC in treatment-naïve patients

- Patients randomized equally to TDF/3TC + EFV or RAL at 100, 200, 400 or 600 mg BID
 - Mean BL HIV RNA 4.6–4.8 log₁₀ c/mL
 - Mean BL CD4+ 271–338 cells/mm³
 - All susceptible at baseline
- AEs similar
 - More CNS AEs with EFV

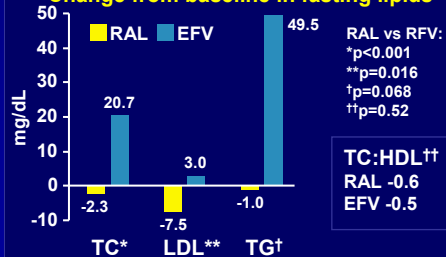
Virologic failures

- RAL, n=5 (3%)
 - Two with integrase mutations; both N155H, 1 with multiple mutations
 - 3TC resistance (n=4)
 - K65R (n=1)
- EFV, n=1 (3%)
 - K65R and G190E

HIV RNA <50 c/mL (95% CI) [NC=F]



Change from baseline in fasting lipids



Markowitz M, et al. 4th IAS, Sydney 2007, #TUAB104

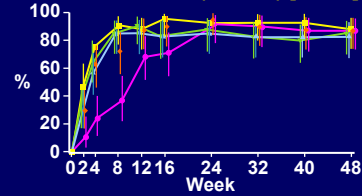
Raltegravir (RAL) with TDF and 3TC in treatment-naïve patients

- Patients randomized equally to TDF/3TC + EFV or RAL at 100, 200, 400 or 600 mg BID
 - Mean BL HIV RNA 4.6–4.8 log₁₀ c/mL
 - Mean BL CD4+ 271–338 cells/mm³
 - All susceptible at baseline
- AEs similar
 - More CNS AEs with EFV

Virologic failures

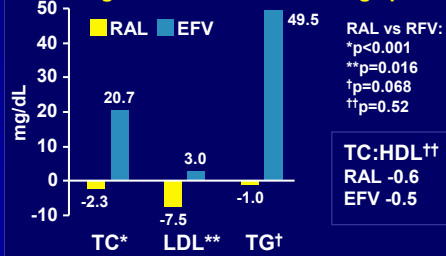
- RAL, n=5 (3%)
 - Two with integrase mutations: both N155H, 1 with multiple mutations
 - 3TC resistance (n=4)
 - K65R (n=1)
- EFV, n=1 (3%)
 - K65R and G190E

HIV RNA <50 c/mL (95% CI) [NC=F]



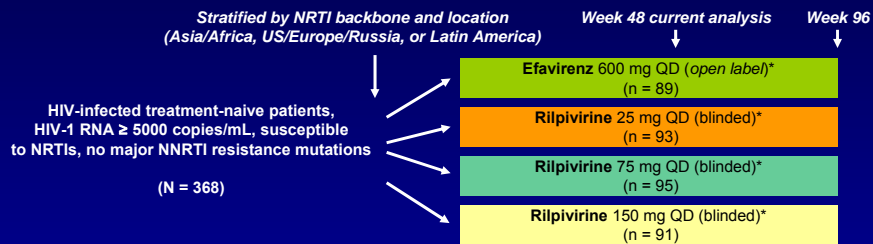
▼ RAL100 mg BID (n=39) ▲ RAL 200 mg BID (n=40)
 ■ RAL 400 mg BID (n=41) ◆ RAL 600 mg BID (n=40)
 ● EFV 600 mg QD (n=38)

Change from baseline in fasting lipids



Markowitz M, et al. 4th IAS, Sydney 2007, #TUAB104

TMC278-C204: Rilpivirine vs Efavirenz in Treatment-Naïve Patients

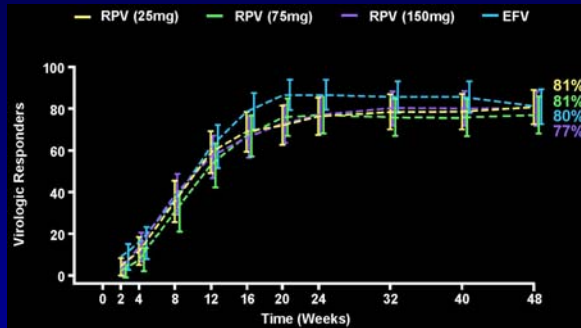


Results at 48 Weeks	Efavirenz 600 mg (n = 89)	Rilpivirine 25 mg (n = 93)	Rilpivirine 75 mg (n = 95)	Rilpivirine 150 mg (n = 91)
VL < 50 copies/mL, %	81	81	80	77
Mean Δ in CD4+ count, cells/mm ³ (SD)	127 (104)	125 (112)	148 (148)	143 (140)

1. Pozniak A, et al. IAS 2007. Abstract WEPEA105. 2. Pozniak A, et al. CROI 2007. Abstract 144LB.

Rilpivirine (RPV; TMC278): 48-week primary analysis of trial TMC278-C204

% HIV RNA <50 c/mL at 48 weeks (TLOVR)



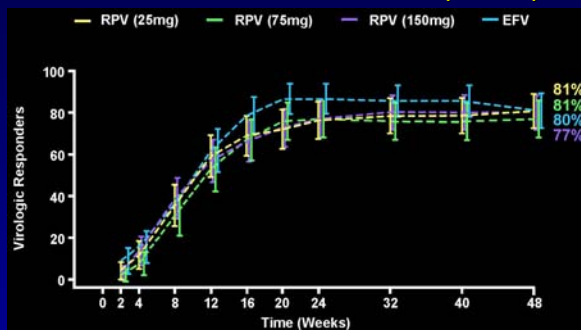
	RPV	EFV
TC (mg/dL)	+5	+31
LDL-C (mg/dL)	0	+16
HDL-C (mg/dL)	+5	+12
TC:HDL-C	-0.45	-0.30
TG (mg/dL)	-10	+18

- CD4 gains 125-150 for all groups
- Incidence of rash (5.6% vs 0.4%) and nervous system-related events (27% vs 5.4%) lower with RPV than with EFV
 - Caveat – open-label study makes tolerability compared to EFV difficult to assess

Pozniak A, et al. 14th CROI, Los Angeles 2007, #144LB

Rilpivirine (RPV; TMC278): 48-week primary analysis of trial TMC278-C204

% HIV RNA <50 c/mL at 48 weeks (TLOVR)



	RPV	EFV
TC (mg/dL)	+5	+31
LDL-C (mg/dL)	0	+16
HDL-C (mg/dL)	+5	+12
TC:HDL-C	-0.45	-0.30
TG (mg/dL)	-10	+18

- CD4 gains 125-150 for all groups
- Incidence of rash (5.6% vs 0.4%) and nervous system-related events (27% vs 5.4%) lower with RPV than with EFV
 - Caveat – open-label study makes tolerability compared to EFV difficult to assess

Pozniak A, et al. 14th CROI, Los Angeles 2007, #144LB

DOSING / DRUG INTERACTIONS

MVC Dosing

Maraviroc (MVC)¹

- Standard dose: 300 mg BID
- With boosted PIs (except TPV/r) and other CYP3A inhibitors, use MVC 150 mg BID
- With NNRTIs (including ETR) and other CYP3A inducers, use MVC 600 mg BID
- With both ETR and DRV+RTV, use MVC 150 mg BID (CYP3A inhibitor overrides inducer)

1. Pfizer "Dear Doctor" letter, 07/18/2007

Integrase Inhibitor Drug-Drug interactions

Elvitegravir (EVG)

- At studied doses, no significant interactions noted between EVG and TPV+RTV¹, DRV+RTV² or FPV+RTV³
- Cannot be simultaneously given with Maalox⁴
 - HIV integrase inhibitors form a complex with divalent cations (eg, Mg⁺⁺) at active site of integrase enzyme
 - Omeprazole did not alter EVG, thus this compound does not exhibit pH dependent absorption⁵

Raltegravir (RAL)

- No significant interaction with ETR⁶
- No significant interaction between ATV 400 mg (unboosted) with RAL 100 mg BID⁷ or ATV/r (300 mg/100 mg) with RAL 400mg BID

1. Mathias A, et al. 4th IAS, Sydney 2007, #TUBDB06; 2. Mathias A, *ibid*, #TUBDB03; 3. Ramanathan S, *ibid*, #WEPEB014; 4. Ramanathan S, et al. 8th IWCPHIV, Budapest 2007, #69; 5. Ramanathan S, et al. 8th IWCPHIV, Budapest 2007, #70; 6. Anderson J, et al. 4th IAS, Sydney 2007, #TUPDB02; 7. Mistry G, et al. *ibid*, #MOPEB109

NNRTI Drug-Drug interactions

Rilpivirine (TMC278)¹

- Famotidine reduces RIL levels by 85% due to decreased absorption
- Can give famotidine 12 hours before or 4 hours after RIL administration
- Expected with all acid reducing agents: pH dependent effect

Etravirine (ETR)²

- ETR decreased exposure of atorvastatin 40 mg by (37%)²

1. van Heeswijk R, et al. 4th IAS, Sydney 2007, #TUBDB01; 2. Schöller-Gyüre M, et al. *ibid*, #WEPEA106;

Drug Interactions: Etravirine and PIs

Drug*	Effect on Exposure	Dosing Recommendations
ATV ^(1,2)	ATV ↓ 14%, ETR ↑ 50%	Not recommended due to decrease in ATV C _{min}
ATV/RTV ⁽¹⁾	ATV ↓ 17%, ETR ↑ 30% [†]	No change in dosing
SQV/RTV ⁽²⁾	SQV ↔	No change in dosing; no data on ETV reported
FPV/RTV ⁽²⁾	APV ↑ 30% [†]	May require change in FPV dosing; no data on ETV
LPV/RTV ⁽²⁾	LPV ↔, ETR ↔	No change in dosing
DRV/RTV ⁽²⁾	DRV ↔, ETR ↓ 37% [†]	No change in dosing
TPV/RTV ⁽²⁾	TPV ↔, ETR ↓ 76%	Not recommended
IDV ⁽²⁾	IDV ↓ 46%, ETR ↑ 51%	Not recommended

*Drugs administered at standard doses.

[†]Not considered to be clinically relevant.

- Schöller-Gyüre M, et al. Glasgow 2006. Abstract P278.
- Kakuda T, et al. Glasgow 2006. Abstract PL5.2

ROLE OF NEW AGENTS IN TREATMENT

DHHS Guidelines 2007: Goals of Therapy in Antiretroviral-Experienced Patients

- **Prior treatment with no resistance identified**
 - Maximal viral suppression
- **Prior treatment and drug resistance**
 - The goals in this situation are to resuppress HIV RNA levels maximally (e.g., to <50 copies/mL) and to prevent further selection of resistance mutations
- **Extensive prior treatment and drug resistance**
 - The goal is to resuppress the HIV RNA levels maximally (e.g. to <50 copies/mL)

Adapted from DHHS Guidelines Dec 1, 2007. Available at: <http://AIDSinfo.nih.gov>. Accessed December 5, 2007.

IAS-USA Guidelines 2006: Updated Goals of Therapy in Experienced Patients

- Viral suppression to < 50 copies/mL is achievable and should be a goal of therapy in treatment-experienced patients
 - Consistent with current DHHS guidelines
- A crucial concept when initiating a new regimen after treatment failure is the **requirement of preferably 3, but at least 2, fully active agents** as determined by resistance test results and prior treatment history . . . if at least 2 drugs cannot be identified, *strong consideration should be given to **maintaining the current regimen until new drugs** become available, assuming immunologic and clinical stability.*

Hammer SM, et al. JAMA. 2006;296:827-843.

Three Principles to Salvage Therapy

1. Have a clear understanding of treatment goals

- Virologic suppression is possible in most of our patients
- Immunologic preservation
- Prevention of HIV disease progression
- Quality of life, minimize side effects and toxicities

2. Incorporate as much information as possible

- Use input from patient on dosing, side effects
- Treatment history
- Resistance testing – past and present

3. Use new agents wisely

- When possible, add at least 2 active new drugs
- Preferably at least one from a new class