

HIV/AIDS Therapy: Adult Issues in the Inpatient and Outpatient Setting

An update on the pharmacotherapy management of HIV/AIDS

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The role of Integrase Inhibitors in HIV Management



Pommier Y, et al. Nat Rev Drug Discov. 2005;4:236-248.

Integrase Enzyme

- Viral enzyme essential to replication of both HIV-1 and HIV-2
- Integration
 - Follows reverse transcription, which synthesizes double-stranded DNA copy of HIV-1 RNA after infection
 - Essential step before viral DNA can be transcribed back into viral RNA
 - Incorporates or “integrates” viral DNA into host cell’s DNA

3 Domains of Integrase Enzyme

- Integrase enzyme: 32-kDa protein encoded by integrase portion of the viral *pol* gene
- 3 domains defined by x-ray crystallography or nuclear magnetic resonance imaging
 - N-terminal zinc finger domain enhances multimerization and promotes integration of the 2 ends of viral DNA into host cell chromosome
 - Dimeric central catalytic domain required for enzymatic activity of integrase
 - C-terminal domain directs metal- and sequence-independent DNA binding
- Current integrase inhibitors disrupt by binding to catalytic domain
 - Raltegravir, elvitegravir

Semenova E, et al. Adv Pharmacol. 2008;56:199-228.

4 Key Steps in Integration

- Assembly of a stable PIC after reverse transcription of viral DNA
- 3'-end processing
- Strand transfer
- Creation of intact double-stranded DNA

Integrase Strand Transfer Inhibitors

- Raltegravir (pyrimidinone analogue, formerly known as MK-0518)^[1]
 - First approved integrase inhibitor
 - First demonstrated clinical activity in Protocol 004 comparing 4 raltegravir doses vs placebo in 35 ARV-naïve patients
- Elvitegravir (diketo acid derivative of dihydroquinoline-3-carboxylic acid, formerly known as GS-9137)^[2]
 - In late-stage clinical development
 - First demonstrated clinical activity in GS 120-1101 comparing various doses of elvitegravir vs placebo in 40 antiretroviral-naïve patients

1. Markowitz M, et al. J Acquir Immune Defic Syndr. 2006;43:509-515.
2. DeJesus E, et al. J Acquir Immune Defic Syndr. 2006;43:1-5.

Introduction

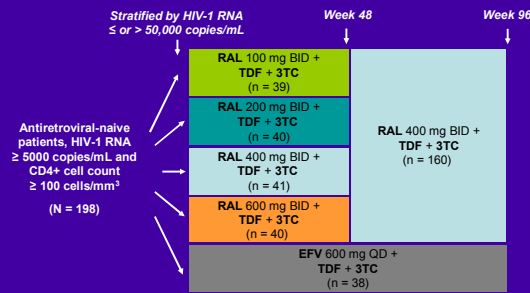
- **Raltegravir**
 - Efficacy and safety studied in both treatment-naive and treatment-experienced patients
 - Currently approved for treatment-experienced patients
- **Elvitegravir**
 - Efficacy and safety studied in both treatment-naive and treatment-experienced patients
 - Investigational

Protocol 004 Phase IIa: Key Conclusions

- 10-day monotherapy with RAL highly potent, safe, with favorable pharmacokinetic profile vs placebo in 35 treatment-naive patients
 - Significant reductions in HIV-1 RNA at all doses of RAL vs placebo: approximately 2.0 log reduction in HIV-1 RNA
 - No serious adverse events or grade 3/4 laboratory abnormalities
 - No treatment discontinuations due to adverse events

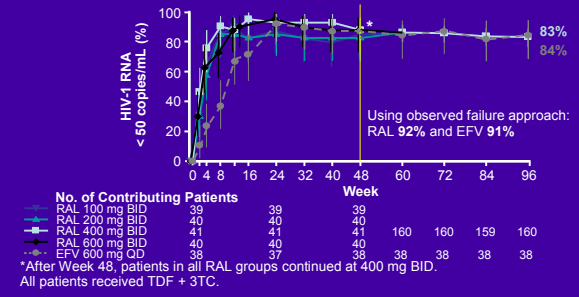
Markowitz M, et al. J Acquir Immune Defic Syndr. 2006;43:509-515.

Protocol 004 Phase IIb: Raltegravir in Treatment-Naive Patients



Markowitz M, et al. IAC 2008. Abstract TUAB0102.

Protocol 004 Phase IIb: 96-Wk Results of RAL vs EFV in Tx-Naive Pts (NC = F)



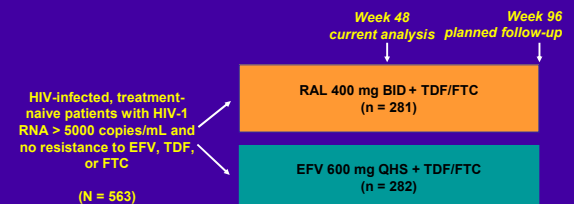
Copyright © 2008 Merck & Co., Inc., Whitehouse Station, New Jersey, USA. All Rights Reserved. Markowitz M, et al. IAC 2008. Abstract TUAB0102.

Adverse Events With RAL

- **Protocol 004^[1]**
 - Adverse events similar in both study arms
 - Grade 3/4 creatinine kinase elevations more frequent with RAL vs EFV: 6.3% vs 2.6%
 - Neuropsychiatric symptoms more frequent with EFV vs RAL: 29% vs 13% by Week 48 and 32% vs 16% by Week 96, respectively
- **Response rates and resistance mutations developing at failure similar in clade B and non-clade B viruses^[2]**

1. Markowitz M, et al. IAC 2008. Abstract TUAB0102.
2. Danovich R, et al. IAC 2008. Abstract TUAA0302.

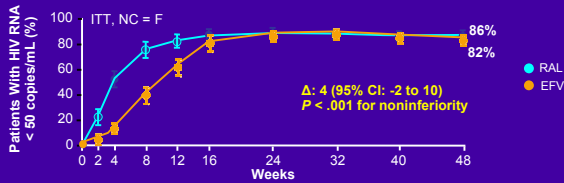
STARTMRK Phase III: RAL vs EFV in Treatment-Naive Patients



- Primary endpoint: HIV-1 RNA $<$ 50 copies/mL at Week 48
- Secondary endpoints: CD4+ cell count, safety, and tolerability
- 53% of patients had HIV-1 RNA $>$ 10⁶ copies/mL; 47% of patients had CD4+ cell counts $<$ 200 cells/mm³ at baseline

Lennox J, et al. ICAAC/IDSA 2008. Abstract 896a.

STARTMRK: Virologic and Immunologic Efficacy at Week 48



RAL n = 281 279 281 279 281 279 280 280 281 280
EFV n = 282 282 282 282 281 282 280 281 281 281

- 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/mm³; Δ: 26 cells/mm³ (95% CI: 4-47)

Lennox J, et al. ICAAC/IDSA 2008. Abstract 896a.
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STARTMRK: Adverse Events at Week 48

- Moderate/severe drug-related clinical adverse events more frequent in EFV vs RAL arm (32% vs 16%; $P < .001$)
 - Serious clinical adverse events in 10% of patients in both arms
- Fewer patients experienced CNS events by Week 8 with RAL vs EFV (10.3% vs 17.7%, respectively; $P = .015$)
 - Difference significant at Week 8; persisted through Week 48
- Malignancies developed in 1 patient in RAL arm vs 9 patients in EFV arm
 - 2/9 in EFV arm considered drug-related

Lennox J, et al. ICAAC/IDSA 2008. Abstract 896a.

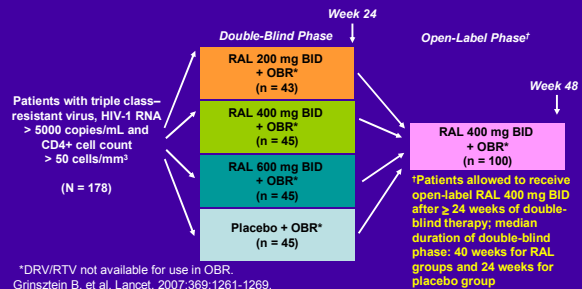
Protocol 004 Phase IIb: Second-Phase Viral Decay

- RAL-treated patients significantly more likely to achieve HIV-1 RNA < 50 copies/mL from Day 15-57 ($P \leq .047$)
 - Difference no longer evident by Weeks 16-24 and no difference observed at primary endpoint or at Week 96
- Plasma HIV-1 RNA significantly lower at start of second-phase decay in RAL groups vs EFV group ($P < .0001$)
 - Possible explanations
 - Greater intrinsic antiviral activity of RAL
 - More widespread distribution of RAL to sites and cells capable of producing HIV-1 particles
 - Mechanistic differences between inhibition of reverse transcriptase enzyme alone vs reverse transcriptase plus integrase enzymes

Murray JM, et al. AIDS. 2007;21:2315-2321.

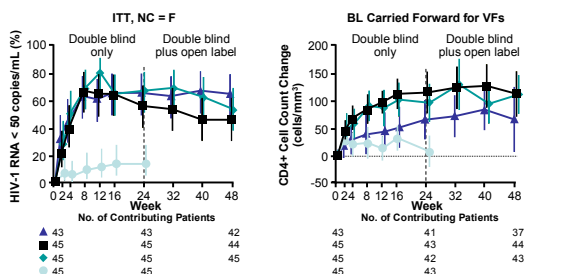
Protocol 005 Phase IIb: RAL in Treatment-Experienced Patients

- Randomized, double-blind, placebo-controlled, dose-ranging, phase IIb study



Protocol 005 Phase IIb: 48-Week Results

▲ Raltegravir 200 mg BID ■ Raltegravir 400 mg BID ◆ Raltegravir 600 mg BID ● Placebo



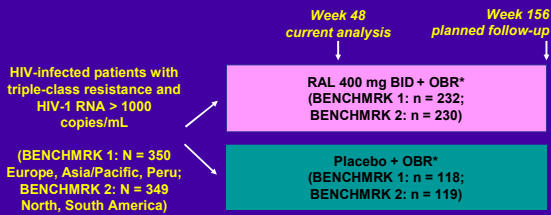
Grinsztejn B, et al. ICAAC 2007. Abstract H-713. Adapted with permission of Merck & Co., Inc., Whitehouse Station, New Jersey, USA. Copyright © 2007. Merck & Co., Inc., All Rights Reserved.

Protocol 005 Phase IIb: Most Frequent Week 24 AEs

AEs Occurring in ≥ 5% of Pts, n	RAL 200 mg (n = 43)	RAL 400 mg (n = 45)	RAL 600 mg (n = 45)	Placebo (n = 45)
Diarrhea	5	1	0	7
Nausea	3	2	5	5
Vomiting	3	2	1	1
Fatigue	4	0	2	1
Headache	4	0	2	3
Pruritus	1	2	3	0
Increased bilirubin	3	4	2	2

Grinsztejn B, et al. Lancet. 2007;369:1261-1269.

BENCHMRK 1 & 2 Phase III: RAL in Treatment-Experienced Patients



*Investigator-selected OBR based on baseline resistance data and history; DRV and TPV use permitted.

Steigbigel RT, et al. N Engl J Med. 2008;359:339-354.

BENCHMRK 1 & 2: Baseline Characteristics

Characteristic	RAL + OBR (n = 232)	Placebo + OBR (n = 118)
Mean HIV-1 RNA, log ₁₀ copies/mL	4.6	4.6
Median CD4+ cell count, cells/mm ³	151	158
AIDS diagnosis, %	92	91
Median duration of ARV exposure, yrs	10	10
GSS 0, %	25	28
GSS 1, %	39	41
PSS 0, %	15	19
PSS 1, %	31	30
First-time use of DRV in OBR, %	36	38
First-time use of ENF in OBR, %	20	20

BENCHMRK 1 & 2: HIV-1 RNA and CD4+ Cell Count Results at Week 48

Outcome at Week 48	RAL + OBR (n = 443)	Placebo + OBR (n = 228)	P Value*
HIV-1 RNA < 50 c/mL,† %	64	34	< .001
HIV-1 RNA < 400 c/mL,† %	72	37	< .001
Mean change in HIV-1 RNA vs BL, log ₁₀ c/mL	-1.7	-0.8	< .001
Mean change in CD4+ cell count vs BL, cells/mm ³	109	45	< .001

*P value derived from a logistic regression model adjusted for BL HIV-1 RNA level (log₁₀), first ENF use in OBR, first DRV use in OBR, active PI in OBR.
†Virologic failures carried forward.

Steigbigel RT, et al. N Engl J Med. 2008;359:339-354.

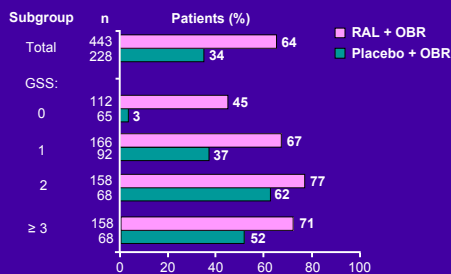
BENCHMRK 1 & 2: Efficacy by BL HIV-1 RNA and CD4+ Cell Count

Patient Group, %	HIV-1 RNA < 50 copies/mL at Week 48*	
	RAL + OBR (n = 443)	Placebo + OBR (n = 228)
HIV-1 RNA at BL,		
• > 100,000	48 (n = 156)	16 (n = 76)
• ≤ 100,000	73 (n = 287)	43 (n = 152)
CD4+ cell count at BL,		
• ≤ 50	50 (n = 139)	20 (n = 75)
• > 50 to ≤ 200	67 (n = 167)	39 (n = 82)
• > 200	76 (n = 136)	44 (n = 71)

*Virologic failures carried forward.

Cooper DA, et al. N Engl J Med. 2008;359:355-365.

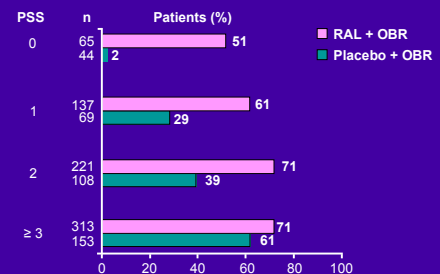
BENCHMRK 1 & 2: HIV-1 RNA < 50 c/mL at Week 48, Overall and by GSS*



*Virologic failures carried forward.

Cooper DA, et al. N Engl J Med. 2008;359:355-365.

BENCHMRK 1 & 2: HIV-1 RNA < 50 c/mL at Week 48 by BL PSS*



*Virologic failures carried forward.

Cooper DA, et al. N Engl J Med. 2008;359:355-365.

BENCHMRK 1 & 2: AEs Through Week 48

- ❑ Clinical AEs
 - ❑ RAL groups: 89%
 - ❑ Placebo groups: 87%
 - ❑ Considered treatment related: 54% in each group
- ❑ Laboratory abnormalities
 - ❑ RAL groups: 23%
 - ❑ Placebo groups: 22%
 - ❑ Considered treatment related: 14% and 13%, respectively
- ❑ Most common drug-related clinical AEs in both treatment groups
 - ❑ Diarrhea, nausea, headache
- ❑ Most common drug-related laboratory abnormalities
 - ❑ Increased serum lipid, aminotransferase, creatinine levels

Steigbigel RT, et al. N Engl J Med. 2008;359:339-354.

BENCHMRK 1 & 2: Risk of Malignancies at Week 48

Rate, per 100 person-years	RAL + OBR	Placebo + OBR	Relative Risk
Total	3.5 (n = 462)	2.3 (n = 237)	1.5 (0.5 – 6.3)
BENCHMRK-1	3.4 (n = 232)	1.2 (n = 232)	
BENCHMRK-2	3.6 (n = 230)	3.3 (n = 230)	

Cooper DA, et al. CROI 2008. Abstract 788.

BENCHMRK 1 & 2: Risk of Myopathy and Rhabdomyolysis

- Creatine phosphokinase grade 4 elevations (> 20-fold)
 - RAL: 2.2%
 - Placebo: 0.7%
- Caution suggested in using RAL in patients receiving concomitant medications known to cause this condition

Raltegravir [package insert].

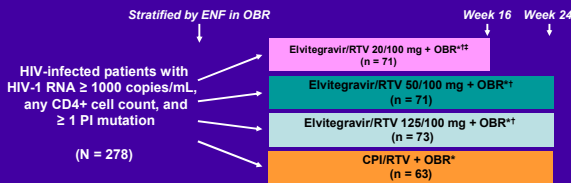
GS 120-1101 Phase IIa: ELV Monotherapy Proof-of-Concept Study

- ❑ Phase IIa, 10-day monotherapy study of elvitegravir vs placebo
 - ❑ N = 40 infected patients
 - ❑ Naive or off treatment ≥ 90 days
- ❑ Mean BL VL 4.75 log₁₀ c/mL
- ❑ Mean BL CD4+ 442 cells/mm³
- ❑ Elvitegravir dosing
 - ❑ 200, 400, 800 mg BID
 - ❑ 800 mg QD
 - ❑ 50 mg + RTV 100 mg QD
- ❑ Dose-dependent response
 - ❑ RTV boosting allowed lower, QD elvitegravir dosing
- ❑ Reductions in HIV-1 RNA (ELV 400 or 800 mg BID or ELV 50/100 mg QD)
 - ❑ ≥ -1.91 log₁₀ copies/mL
 - ❑ ≥ -2.00 log₁₀ copies/mL in 50% of patients
 - ❑ Maximum reductions on Days 10 or 11 in all but 1 patient
- ❑ No serious AEs

DeJesus E, et al. J Acquir Immune Defic Syndr. 2006;43:1-5.

GS 183-0105 Phase IIb: ELV in Treatment-Experienced Patients

- Randomized, active-control, partially-blinded (dose of elvitegravir), phase IIb dose-finding study



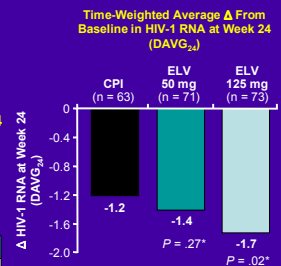
*OBR = NRTIs ± ENF (NNRTIs excluded). **TPV and DRV permitted after Week 16. †Discontinued at Week 16 by DSMB.

Zolopa A, et al. CROI 2007. Abstract 143LB.

GS 183-0105 Phase IIb: Primary Endpoint Analysis

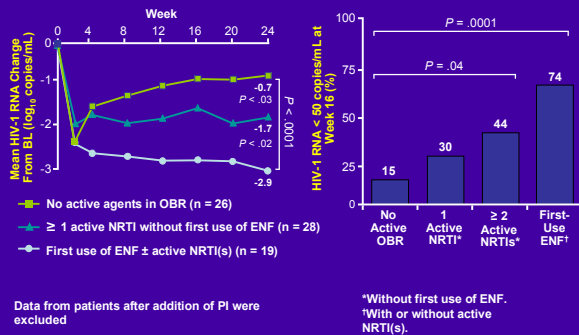
- ❑ ELV 50-mg and 125-mg arms met noninferiority criteria for DAVG₂₄ vs CPI
- ❑ ELV 125-mg arm demonstrated significantly greater mean decrease in VL at Weeks 16 and 24 vs CPI
- ❑ AEs comparable to comparator PI arm

Week 16 HIV-1 RNA < 50 copies/mL, %	
CPI	30
Elvitegravir 50 mg	38
Elvitegravir 125 mg	40



*Pairwise comparison vs CPI/RTV.

GS 183-0105 ELV/RTV 125/100 mg: Response by Active Agents in OBR



GS 183-0105 Phase IIb: AEs and Discontinuations

- No evidence of increased grade 2, 3, or 4 AEs in ELV groups vs comparator PI group
- 11% to 13% discontinued in each arm
 - 3% to 4% due to issues of safety, tolerability, or efficacy

Zolopa A, et al. CROI 2007. Abstract 143LB.

Pharmacology of Elvitegravir: Implications for Dosing & Interactions

- Elvitegravir / ritonavir 150/100 mg being studied in ongoing clinical trials^[1]
- Elvitegravir metabolized via cytochrome P450 3A4^[2]
 - Elvitegravir exposure enhanced by coadministration with low-dose ritonavir
 - Allows QD dosing
 - Ritonavir associated with numerous drug-drug interactions
 - Significant interactions with PIs reported
 - If coadministered with ritonavir-boosted atazanavir or lopinavir, elvitegravir dose reduced to 85 mg.

1. Mathias A, et al. ICAAC 2007. Abstract A-1417. 2. Mathias A, et al. ICAAC 2007. Abstract A-1418.

Conclusions

- Strand transfer inhibitors of HIV integrase have been found to be potent and durable suppressors of HIV replication in vivo
 - Predictable activity in the integrase inhibitor-naïve patient
- To date tolerability profile appears highly favorable
- Resistance and cross-resistance require further study