Letter to the Editor

Journal of the International Association of Physicians in AIDS Care
Volume 7 Number 6
November/December 2008 281-282

10.1177/1545109708327489
http://jiapac.sagepub.com
hosted at
http://online.sagepub.com

No Residual Activity of Raltegravir After Development of 148 Complex Mutations In Vivo

To the Editor:

Some antiretroviral (ARV) medications, such as protease inhibitors (PIs), do have residual antiviral activity after development of mutations.[1] In contrast, others do not, that is, the first generation nonnucleoside reverse transcriptase inhibitors (NNRTIs). Whether this applies to raltegravir (RAL), a new HIV-integrase inhibitor, is not known.[2,3] Atazanavir (ATV) is a moderate booster of RAL.[4] Because the antiviral activity of some agents can be augmented by enhancing their pharmacokinetics (eg improvement of indinavir [IDV] levels with ritonavir [RTV] boosting),[5] we sought to investigate whether boosted RAL with ATV might affect HIV-RNA levels in RAL-resistant patients. Three 5-class experienced patients currently failing an RAL-containing regimen of tenofovir, emtricitabine, and RTV-boosted darunavir (DRV) added ATV 150 mg orally twice a day to their regimen. Raltegravir genotypic assay was performed by Merck & Co, the manufacturer of RAL, as it was not available somewhere else. CD4 counts and HIV-RNA levels were monitored up to 24 weeks. At week 2, trough concentrations (Ct) of RAL were obtained. Table 1 summarizes the findings.

Despite achieving adequately elevated RAL trough levels, there was no significant change in the HIV-RNA levels up to 24 weeks, indicating that once RAL resistance has developed through 148 K/R/H complex, even increasing RAL exposure may not enhance its antiviral activity.

Homayoon Khanlou
Department of Medicine
AIDS Healthcare Foundation
Los Angeles, California

Shilpa Sayana
Department of Medicine
AIDS Healthcare Foundation
Los Angeles, California

Edward Acosta
Department of Pharmacology
University of Alabama
Birmingham, Alabama

Table 1. Summary of the Data

	Baseline				Week 2	Week 12		Week 24	
n	CD4	VL $\log_{10}$	RAL Mutations	Tropism	RAL Ct (ng/mL)	CD4	VL $\log_{10}$	CD4	VL $\log_{10}$
1	88	4.36	148 complex	X4+	411	93	4.4	119	4.57
2	179	5.6	148 complex	X4+	833	73	5.5	27	5.5
3	171	4.5	148 complex	X4+	346	125	4.93	73	5.2

Abbreviations: Ct, trough concentration; RAL, raltegravir; VL, viral load (HIV-RNA levels).

References

1. Kempf DJ, Isaacson JD, King MS, et al. Identification of genotypic changes in human immunodeficiency virus protease that correlate with reduced susceptibility to the protease inhibitor lopinavir among viral isolates from protease inhibitor-experienced patients. *J Virol*. 2001;75: 7462-7469.
2. Steigbigel RT, Cooper DA, Kumar PN, et al, and BENCHMRK Study Teams. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med*. 2008;359:339-354.
3. Cooper DA, Steigbigel RT, Gatell JM, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 infection. *N Engl J Med*. 2008;359:355-65.
4. Iwamoto M, Wenning LA, Mistry GC, et al. Atazanavir modestly increases plasma levels of raltegravir in healthy subjects. *Clin Infect Dis*. 2008;47:137-140.
5. Acosta EP, Henry K, Baken L, Page LM, Fletcher CV. Indinavir concentrations and antiviral effect. *Pharmacotherapy*. 1999;19:708-712.