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Authors

Karris, Maile Y

Jain, Sonia

Bowman, Vi Q

et al.

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Nucleoside-Sparing Regimens with Raltegravir and a Boosted Protease Inhibitor: An Unsettled Issue

Maile Y. Karris¹, Sonia Jain¹, Vi Q. Bowman⁹, Gunter Rieg⁹, Miguel Goicoechea⁸, Michael P. Dube³, Shubha Kerkar⁴, Carol Kemper⁵, Catherine Diamond⁶, Xiaoying Sun¹, Eric S. Daar², Richard H. Haubrich⁷, and Sheldon Morris¹ for the California Collaborative Treatment Group (CCTG) 589 Study Team

¹University California San Diego, CA, USA

²Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center and the David Geffen School of Medicine at UCLA, CA, USA

³University of Southern California Keck School of Medicine, CA, USA

⁴Desert Regional Medical Center, CA, USA

⁵Santa Clara Valley Medical Center, CA, USA

⁶University California Irvine, CA, USA

⁷Gilead Sciences, CA, USA

⁸Scripps Health San Diego, CA, USA

⁹Kaiser Permanente, CA, USA

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The recent publication by Van Lunzen et al (HARNESS) evaluated the efficacy and safety of switching HIV infected adults from a stable regimen of 2 NRTIs with a third antiretroviral (ART) agent to either ritonavir boosted atazanavir (ATV/r) 300/100 mg plus tenofovir disoproxil fumarate and emtricitabine 300/200 mg once daily (ATV/r+TDF/FTC) or ATV/r plus raltegravir 400 mg twice daily (ATV/r+RAL)¹. Interestingly a lower proportion of participants in the ATV/r+RAL arm maintained viral suppression at weeks 24 and 48. There was no immunologic benefit or reduction in adverse events with switching. In fact,

Reprints or correspondence: Dr. Maile Young Karris, Antiviral Research Center, University of California, San Diego, 200 West Arbor Drive, mail code 8208, San Diego, CA 92103, USA, Telephone: (619) 543-8080; Fax: (619) 543-5066; m1young@ucsd.edu.

Clinical trials registry: NCT00752856 (<http://www.ClinicalTrials.gov>)

California Collaborative Treatment Group (CCTG) 589 Protocol Team Members: In addition to the authors, other members of the CCTG 589 protocol team included the following: M. Witt (HUCLA), J. Tilles (UCI), R. Larsen (USC); R. Thomas, F. Wang, and E. Seefried (University of California, San Diego).

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tolerability of the ATV/r+RAL arm was lower due to dyslipidemia and pill burden. We also performed a study evaluating an NRTI sparing regimen in treatment naïve HIV infected persons using a similar approach.

From October 2008 to November 2009, the California Collaborative Treatment Group (CCTG) performed a randomized, open-label 48 week, multicenter study comparing the efficacy, safety and tolerability of RAL + ritonavir boosted lopinavir (LPV/r) 400/100 mg twice daily to a fixed dose combination of efavirenz 600 mg (EFV)+ TDF/FTC daily (EFV/TDF/FTC) in HIV-infected, treatment naïve subjects (N=51). The study was approved by local institutional review boards and all participants underwent informed consent prior to enrollment. Fifty-one subjects were randomized (25 in EFV/TDF/FTC and 26 in RAL +LPV/r) and included in the analyses with documentation of baseline characteristics, HIV-1 RNA, CD4 cell counts and resistance testing. The primary efficacy analysis used a linear mixed effects model to assess the difference in the HIV RNA decay rates in the first 2 weeks between the treatment groups. Repeated HIV RNA Measured at baseline, day 2, 7, 10 and 14 were treated as the outcome. The fixed effects included time, treatment group, and treatment group-by-time interaction. The random effects included both intercept and slope. Secondary analysis also compared the proportion of subjects with undetectable RNA (HIV viral load < 50 copies/mL) at weeks 4, 8, 12, 16, 24, 36 and 48 between the two groups using Fisher's exact test.

The majority (96%) of participants were men; with a median age of 43 years (IQR: 31, 48). Eighty-four percent were White and 9.8% Black with 51% Hispanic. The median baseline viral load was 4.7 log₁₀ copies/mL (IQR: 4.1,4.9), the median CD4 count was 358 cells/mm³ (IQR: 176, 459). There were no statistically significant differences in the baseline characteristics between treatment arms.

Compared with those in the EFV/TDF/FTC arm, participants in the RAL+LPV/r group demonstrated significantly more rapid viral decay in the first two weeks (-0.16 vs -0.13 log₁₀/day, p=0.0007) and a higher proportion demonstrated an undetectable HIV RNA at week 4 (54% vs 12% p = 0.003). However, no differences in viral suppression between the two groups were observed and at week 8 and week 48 (86% vs 87.5%, p>0.99, figure 1). No differences were observed in the CD4 T cell dynamics between the arms over the 48 weeks. Unlike HARNESSE we did not observe the presence of integrase strand transfer inhibitor (INSTI) resistance in person failing RAL + LPV/r.

We also evaluated self-reported adherence (ACTG recall questionnaire) as the RAL+LPV/r arm necessitated a higher pill count and more frequent dosing than EFV/TDF/FTC. Overall assuming missing equals not adherent, the proportion of subjects with perfect adherence was low (25%) in this study with the EFV/TDF/FTC arm demonstrating a slightly higher but not significantly different proportion with adherence than the RAL+LPV/r arm (36% vs 15%, respectively, p=0.12). Frequency of all reported adverse events also showed no significant difference between the two arms (60% in the EFV/TDF/FTC arm vs. 50% in the RAL +LPV/r arm, p=0.58).

In CCTG 589 initiation of RAL+LPV/r did result in a higher proportion of participants achieving an undetectable HIV VL at week 4, as would be expected with an INSTI based regimen. However the difference in virologic suppression between arms was not sustained over time and did not result in immunologic benefit. There were no differences noted in terms of side effects, but persons on RAL+LPV/r did report lower rates of adherence.

The use of an INSTI combined with a protease inhibitor (PI) offers possible therapeutic advantages over nucleoside reverse transcriptase inhibitors combined with non-nucleoside reverse transcriptase in relation to: (1) antiviral potency given the combination of both late (PI) and mid-cycle (INSTI) viral target inhibitors allowing for more efficient termination of viral replication from cellular reservoirs and more rapid early plasma viral decay^{2,3}, and (2) immune recovery⁴⁻⁷. Studies of combination therapy with INSTI+PI in HIV infected persons who are naive to therapy have demonstrated rapid early plasma viral decay, which may be beneficial in that it minimizes onward HIV transmissions⁸. This may have benefit in select patients where the goal is rapid virologic suppression such as in pregnant women with a detectable HIV viral load. Additionally, studies evaluating INSTI + PI therapy do not document long term virologic or immunologic benefit⁸⁻¹⁰, but some studies (a switch study and an NRTI and ritonavir sparing study) did demonstrate a higher risk for development of INSTI resistance mutations^{1,9} and in at least one study in ART-naïve showed a higher failure rate in subjects with low CD4 and HIV viral loads > 100,000 copies/mL⁸. These observations have led to the recommendations from multiple guideline panels that inclusion of NRTIs in patients who are ART naïve or switching ART is the preferred treatment approach¹¹. The interpretation of the results of CCTG 589 and HARNESS was limited by small sample sizes and adherence issues. Yet our experiences highlight that the use of a twice daily INSTI (RAL is the only INSTI evaluated in all the studies to date) combined with a PI is not an ideal regimen for routine care. It remains unknown if combinations of a PI with a daily INSTI confers additional virologic or immunologic benefits to people living with HIV and would benefit from further evaluation. However this question may be less relevant with the recent approval of the novel NRTI, tenofovir alafenamide which exhibits potent viral suppression and reduced toxicity.

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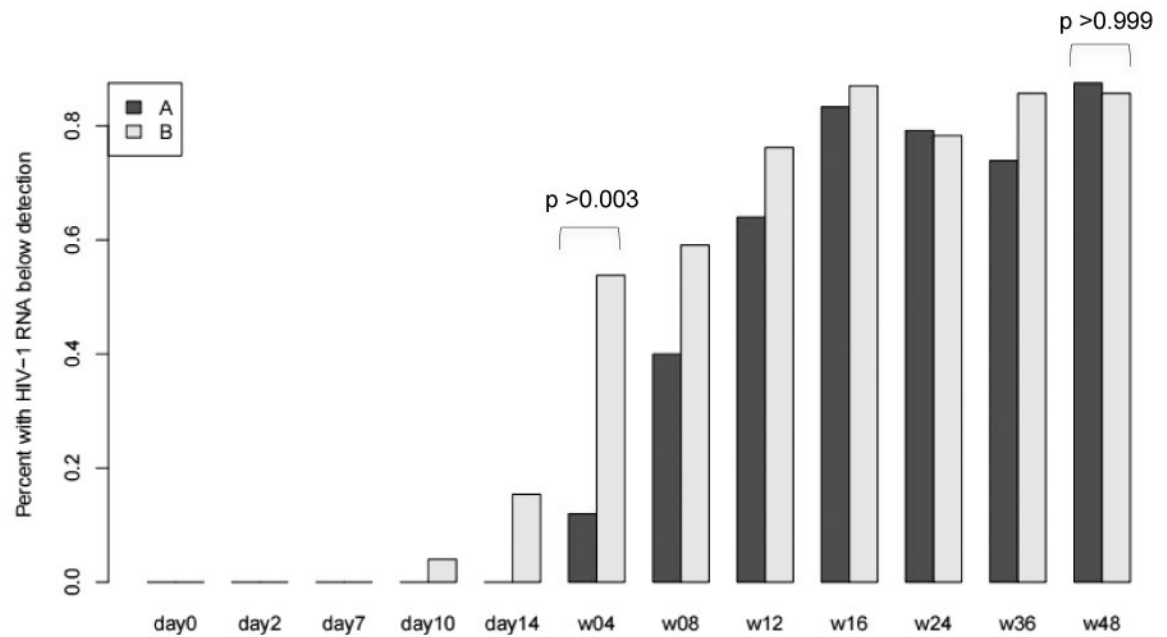


Figure 1.

Proportion of study participants (A-dark gray EFV/FTC/TDF and B-light gray RAL+LPV/r) with an undetectable HIV viral load over time ignoring the missing RNA measurements due to early study discontinuation between week 4 and week 48. Significant difference are noted between arms at week 4 (with a higher proportion of persons in the RAL+LPV/r arm achieving an undetectable HIV viral load) but no difference is observed at week 48.