

technology, such as the need for ongoing training of site staff, the ability to manage a large volume of tests in clinics with a large patient population, and the potential lack of quality control,⁷ especially when used in more remote settings, where the technology could have the greatest impact.

Nevertheless, the prospect of a potentially simpler, cheaper, and more patient-centered care model is appealing, and studies looking at the implementation of Xpert HIV-1 VL and other point-of-care viral load assays to replace traditional care pathways should be prioritized.

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

To the Editors:

The recent publication by Van Lunzen et al¹ (HARNESS) evaluated

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

the efficacy and safety of switching HIV-infected adults from a stable regimen of 2 Nucleoside reverse transcriptase inhibitors (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). 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, tolerability of the ATV/r+RAL arm was lower because of dyslipidemia and pill burden. We also performed a study evaluating an NRTI-sparing regimen in treatment-naive 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-naive subjects (N = 51). The study was approved by local institutional review boards and all participants underwent informed consent before 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 per milliliter) at

weeks 4, 8, 12, 16, 24, 36, and 48 between the two groups using Fisher exact test.

Most of the (96%) participants were men; with a median age of 43 years [interquartile range (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 per milliliter (IQR: 4.1, 4.9), the median CD4 count was 358 cells per cubic millimeter (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 2 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, Fig. 1). No differences were observed in the CD4 T cell dynamics between the arms over the 48 weeks. Unlike HARNESS, 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

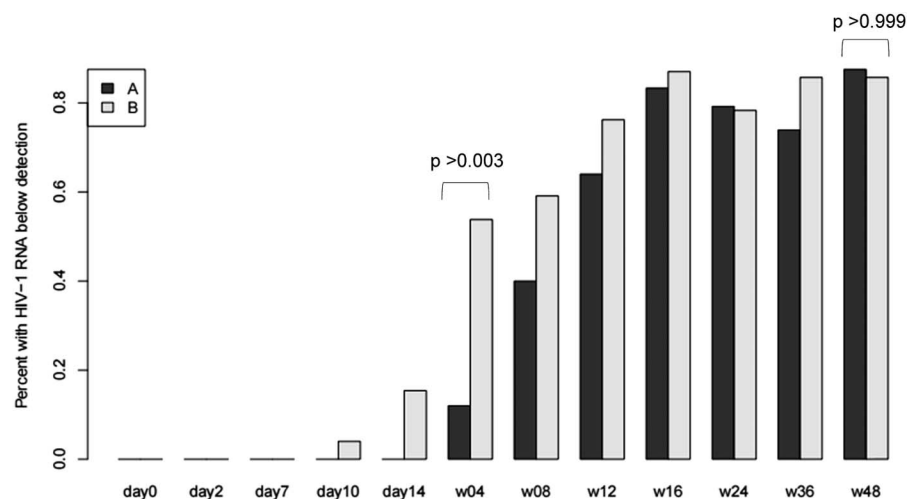
frequent dosing than EFV/TDF/FTC. Overall, assuming missing equals not adherent, the proportion of subjects with perfect adherence was low (25%) in this study with the EFV/TDF/FTC arm demonstrating a slightly higher but not significantly different proportion with adherence than the RAL+LPV/r arm (36% 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 initiations 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 nonnucleoside 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 recovery.⁴⁻⁷ 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 transmissions.⁸ 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. In addition, studies evaluating INSTI + PI therapy do not document long-term virologic or immunologic benefit,⁸⁻¹⁰ 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 1 study in ART naive showed a higher failure rate in subjects with low CD4 and HIV viral loads >100,000 copies per milliliter.⁸ These observations have led to the recommendations from multiple guideline panels that inclusion of NRTIs in patients who are ART naive or switching ART is the preferred treatment approach.¹¹ 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

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 because of early study discontinuation between week 4 and week 48. Significant differences 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.



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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Insights From Behavioral Economics to Design More Effective Incentives for Improving Chronic Health Behaviors, With an Application to Adherence to Antiretrovirals

To the Editors:

There is a growing recognition that many of today's health problems are not just medical in origin but also behavioral.¹ Unhealthy behaviors are responsible for an estimated 40% of premature deaths in the United States annually,² and adherence to long-term therapy for chronic diseases is only about 50%.³ For those living with HIV, the effectiveness of antiretroviral therapy (ART) drugs is hampered by suboptimal medication adherence: only about 60% of people with HIV and in treatment take their medication as prescribed, even among relatively affluent populations where structural barriers such as transport or medical costs likely play a minor role.⁴

Financial incentives have long been recognized as a tool for influencing behavior as evidenced by a large and established literature on contingency management (CM), which rewards desired behaviors with financial or other prizes. CM is typically rooted in traditional economic theory, the idea being that

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