Abstract 108

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Exploring the Effects of Adherence on Resistance: Use of Local Linear Regression to Reveal Relationships Between Adherence and Resistance in Antiretroviral-Naive Patients Treated with Lopinavir/ritonavir or Nelfinavir

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BACKGROUND

The relationship of adherence to virologic response has been well documented for protease inhibitor-based therapy, with lower adherence consistently resulting in higher viral loads or higher probability of virologic failure (Haubrich 1999, Bangsberg 2000, Paterson 2000, e.g.) In contrast, the relationship between adherence and the development of viral resistance is less well-understood. The study of this relationship requires access to both reliable adherence data and a complete characterization of the emergence of resistance to each drug in the regimen of study.

Previously, the superior antiviral activity of lopinavir/ritonavir (LPV/r), compared to nelfinavir (NFV), in a phase 3, randomized, double-blind study in antiretroviral-naive patients has been documented (Walmsley 2002). In that trial, the emergence of both primary and secondary protease inhibitor resistance mutations as well as the rates of emergence of NRTI mutations were lower for LPV/r-treated patients than for NFV-treated patients. Among patients with genotype data, compared to LPV/r-treated patients, NFV-treated patients had higher rates of primary PI mutations (48% vs. 0%), secondary PI mutations (53% vs. 14%), and 3TC resistance (82% vs. 37%). Among all patients, Kaplan-Meier estimates of resistance emergence through 2 years were 29% (3TC resistance, NFV group), 20% (primary PI mutations, NFV group), 7% (3TC resistance, LPV/r group), and 0% (primary PI mutations, LPV/r group) (Kempf 2003). In this analysis, we have assessed the relationship of resistance emergence and adherence in this randomized study.

METHODS

Design

Study 863 was a randomized, double-blind, double-dummy, phase 3 clinical trial comparing LPV/r to NFV in 653 antiretroviral-naive patients. All patients also received stavudine (d4T) and lamivudine (3TC). Patients were followed for up to 2 years. Patients with HIV RNA levels above 400 copies/mL at Week 24 or later visits had samples sent for genotypic resistance testing. Patients who did not reach Week 24 were excluded from the analysis.

Resistance

Primary PI resistance was defined as the emergence of a D30N or L90M mutation in protease or M46I/L plus confirmed phenotypic resistance for NFV-treated patients or any primary or active site mutation (8, 30, 32, 46, 47, 48, 50, 54, 82, 84, and 90) for LPV (Hirsch 2000). Secondary PI mutations were defined as those appearing at positions 10, 20, 33, 53, 71, 73, 77, and 88, plus positions 46 and 54 for NFV. 3TC resistance was defined as the presence of the M184V/I/T mutation in reverse transcriptase.

Adherence

At each study visit, pill counts of returned study drug were conducted. Adherence was calculated as the number of pills consumed relative to the number expected to be consumed. Between any two visits, adherence was censored at a maximum of 100%. Overall protease inhibitor adherence and overall 3TC adherence were computed. For protease inhibitor adherence, only the active protease inhibitor (not placebo) was used in the assessment of adherence.

Adherence vs. Virologic Response

The relationship of adherence to the probability of having one or more HIV RNA values above 400 copies/mL any time at or after Week 24 was analyzed using logistic regression.

Adherence vs. Resistance

The relationship of adherence to the probability of resistance development (through approximately two years of therapy) was assessed by local linear regression. To conduct the local linear regression, patients with resistance were assigned a value of 1 and patients without resistance were assigned a value of 0.

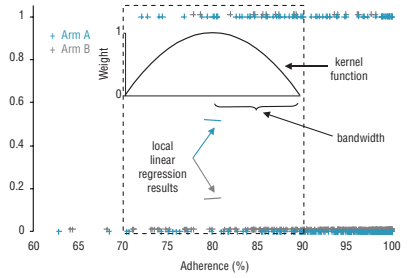
Then, a weighted linear regression was conducted at each adherence level. The analysis is *local* because it includes only data within a specified *neighborhood* of the given adherence level.

An example of local linear regression is shown in Figure 1. To estimate the probability of resistance at 80% adherence for Arm A and Arm B, the size of the local neighborhood (dashed box) is determined by the *bandwidth* (in this case, 10). A *kernel* function ($1-x^2$) determines the weights to use (values closer to 80% receive higher weight). The process is repeated across the range of adherence values. Larger bandwidths result in larger local neighborhoods and hence smoother estimates because more data are included in the analysis at each adherence level.

Two types of analyses were conducted

- Probability of resistance among all enrolled patients on study for at least 24 weeks.
- Probability of resistance only among patients with genotype data (viremic patients).

Figure 1. Concepts of Local Linear Regression

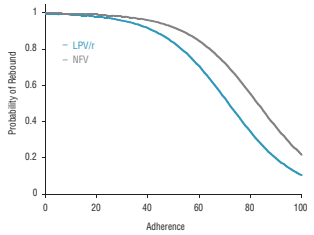


RESULTS

Probability of Virologic Rebound

- For NFV-treated patients, the maximal risk of 3TC resistance was approximately 50%, compared to approximately 15% for LPV/r-treated patients.

Figure 2. Probability of Viral Rebound by Adherence in Study 863



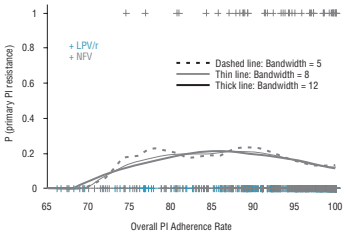
Variable	Odds Ratio (95% CI)
Treatment Group	2.4 (1.6, 3.6)
Adherence (per % increase)	0.93 (0.91, 0.95)

Probability of Resistance Among All Patients

Primary PI Resistance

- For NFV-treated patients, a bell-shaped relationship between adherence and the probability of the emergence of primary PI mutations was observed (Figure 3). The maximal probability of resistance was approximately 20%, occurring at an adherence level of 85-90%.
- The bandwidths of 5, 8, and 12 shown in the figure demonstrate that smaller bandwidths give more variable estimates while larger bandwidths result in smoother estimates.
- No LPV/r-treated patient demonstrated the emergence of primary PI mutations, so the estimated probability was zero at all adherence levels.

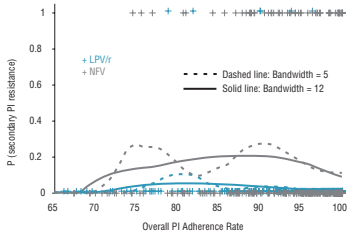
Figure 3. Probability of Primary PI Resistance by Adherence: All Patients



Secondary PI Resistance

- For NFV-treated patients, the maximal risk of secondary PI mutations was approximately 20%, at 85-90% adherence (Figure 4).
- Since relatively few LPV/r-treated patients (n=7) demonstrated new secondary PI mutations, the shape of the secondary resistance/adherence curve could not be precisely defined. The maximal risk was approximately 5%, at an adherence level of 80-85%.

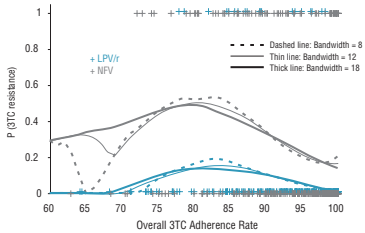
Figure 4. Probability of Secondary PI Resistance by Adherence: All Patients



3TC Resistance

- For both NFV and LPV/r, a bell-shaped relationship between adherence and the probability of 3TC resistance was observed (Figure 5).
- For NFV-treated patients, the maximal risk of 3TC resistance was approximately 50%, occurring at an adherence level of 75-85%.
- For LPV/r-treated patients, the maximal risk of 3TC resistance was approximately 15%, occurring at an adherence level of 80-85%.

Figure 5. Probability of 3TC Resistance by Adherence: All Patients



RESULTS *continued*

Probability of Resistance Among Viremic Patients with Genotype Data

Primary or Secondary PI Resistance

- Among viremic NFV-treated patients with genotype data (n=96), the probability of the emergence of primary PI resistance mutations increased with increasing adherence, reaching a maximum of approximately 65% at 100% adherence (Figure 6).
- Likewise, for NFV-treated patients, the probability of secondary PI mutations increased with increasing adherence, reaching a maximum of approximately 60% at 100% adherence (Figure 7).
- For viremic LPV/r-treated patients with genotype data (n=51), the probability of secondary mutations remained relatively stable across all adherence levels, generally between 10-15% at adherence levels between 75-95% but lower outside that adherence range (Figure 7).

Figure 6. Probability of Primary PI Mutations by Adherence: Viremic Patients with Genotype

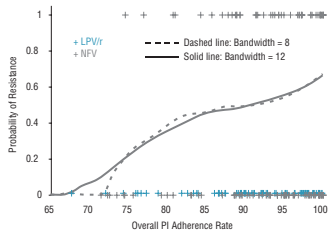
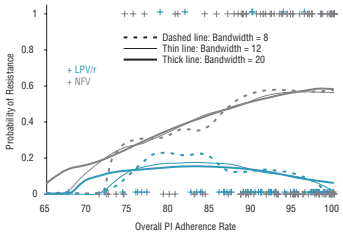


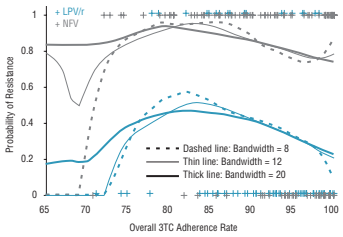
Figure 7. Probability of Secondary PI Resistance by Adherence: Viremic Patients with Genotype



3TC or Secondary PI Resistance

- Among viremic NFV-treated patients with genotype data, probability of 3TC resistance generally remained between 75-95% at all adherence levels above 75% (Figure 8).
- Among viremic LPV/r-treated patients with genotype data, probability of 3TC resistance generally ranged from 30-50% at adherence levels of 75% or higher, dropping to 10-20% at 100% adherence.

Figure 8. Probability of 3TC Resistance by Adherence: Viremic Patients with Genotype



DISCUSSION

Bangsberg, et al. (2002) have demonstrated the bell-shaped relationship between adherence and resistance that was predicted by Friedland and Williams (1999). We believe our study to be the first randomized, controlled trial to confirm such a relationship.

Among patients on PI-based regimens who have detectable viral load, the risk or degree of resistance has been shown to increase with increasing adherence levels (Bangsberg 2000, Walsh 2002, Bangsberg 2002). Our results have corroborated such a relationship, especially for the development of PI mutations for nelfinavir-treated patients.

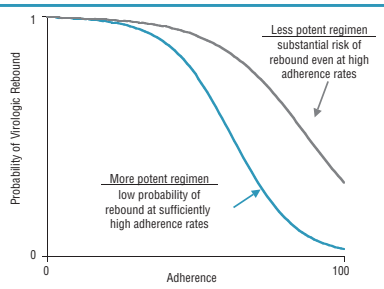
The relationship of adherence to virologic response has been well established (Haubrich 2000, Bangsberg 2000, Paterson 2000), with higher adherence resulting in better response rates.

Therefore, the bell-shaped relationship between adherence and the development of viral resistance appears to arise from the following:

- The probability of resistance is low at low adherence levels because while viral load is more likely to be detectable, selective pressure is absent because drug levels are low or nonexistent.
- The probability of resistance is also low at high adherence levels because viral replication is less likely, even though selective pressure is high for regimens with marginal pharmacokinetics.
- At intermediate adherence, patients are most likely to have ongoing viral replication while selective pressure is present, leading to a maximal probability of resistance development.

Thus, conceptually, the bell-shaped relationship between adherence and resistance can be broken into 2 components: the relationship of adherence to virologic response (Figure 9a) and the relationship of adherence to resistance among viremic patients (Figure 9b). The product of these two relationships results in the bell-shaped curves shown in Figure 9c.

Figure 9a. Model for Probability of Virologic Rebound by Adherence



DISCUSSION *continued*

Figure 9b. Model for Probability of Resistance in Viremic Patients by Adherence

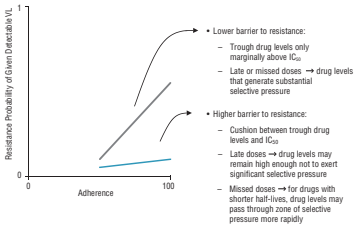


Figure 9c. Resulting Bell-Shaped Relationship Between Resistance and Adherence

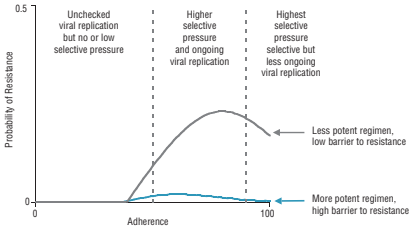
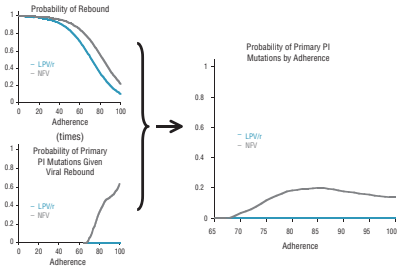


Figure 10 demonstrates the application of this model to the probability of primary PI mutations in our study. The plot in the upper left (same as Figure 2 above), when multiplied by the plot in the lower left (same as Figure 6 above), results in the third plot, which resembles Figure 3 above, as expected.

Figure 10. Model Applied to Study 863 Reproduces Bell-Shaped Relationship



A number of limitations apply to our results. Use of pill counts undoubtedly inflated the estimates of adherence in this study. However, results from other studies (Liu 2001, Bangsberg 2001) suggest that while pill counts overestimate adherence, they are generally correlated with electronic or composite measures of adherence. Thus, the shapes of the curves shown here are likely accurate, but they would be shifted toward lower adherence levels if a more precise adherence measure had been used. Also, we assumed patients with undetectable viral load or isolates that could not be genotyped did not have resistance mutations. If resistance mutations were present in those patients, the estimates of resistance would be higher than we showed, especially at higher adherence levels.

CONCLUSIONS

- When all patients were considered, local linear regression demonstrated a bell-shaped relationship between resistance and adherence.
- Among only viremic patients, PI resistance in NFV-treated patients increased with increasing adherence.
- At every adherence level, the risk of the emergence of PI mutations or 3TC resistance was lower for LPV/r-treated vs. NFV-treated patients.
- The risk of resistance development appears to be influenced by multiple factors:
  - Lower potency results in more patients with ongoing viral replication in the presence of drug.
  - A lower barrier to resistance leads to a greater risk of resistance development among patients without complete viral suppression.

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