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The "95% adherence rule" may not apply to lopinavir/ritonavir (LPV/r) based HAART regimens

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Introduction

The prevailing dogma holds that very high rates of adherence to antiretroviral therapy, on the order of 95% or more, are necessary to achieve complete virologic suppression.[1] This belief is based largely on findings in a cohort of patients receiving primarily unboosted protease inhibitor (PI) therapy in the 1990s. Lopinavir/ritonavir (LPV/r, Kaletra) offers an improved pharmacokinetic profile and higher genetic barrier to resistance, when compared to the PIs used in this earlier study. These advantages suggest that LPV/r based regimens may be more forgiving of non-adherence than other regimens.

Methods

Setting: Montefiore Medical Center's Center for Positive Living/Infectious Diseases (CPL/ID) Clinic. Enrollment began in March 2004.

Study design: Prospective, open-label. Subjects meeting enrollment criteria and providing informed consent were trained in the proper use of medication event monitoring system (MEMS®, Aardex, Ltd.) caps and underwent monitoring of LPV/r dosing for 24 weeks. Demographic and clinical information were collected for all subjects, and HIV-1 viral load (VL) was measured at enrollment and at study completion. MEMS data were uploaded to the Aardex secure server at each follow-up visit. An interim analysis was conducted on the first 53 of a planned 70 study completers. Investigators and providers were blinded to the MEMS data until the interim analysis was performed.

Enrollment criteria:

- HIV infection documented serologically or virologically
- Receipt of an antiretroviral regimen containing LPV/r soft-gel capsules (133mg/33mg) at a dosage of either three of four capsules twice per day. Equivalent dosage of LPV/r tablets (200mg/50mg), once available, was permitted.
- Expectation that LPV/r therapy would continue for 24 weeks
- Willingness to use a MEMS cap properly for each dose of LPV/r (i.e. precludes the use of pillboxes, pocket doses, etc.)

Subjects were questioned about proper use of MEMS caps at each study visit (four follow-up study visits in total). Adherence was defined as (number of bottle openings/number of doses prescribed)x100. Time intervals during which subjects were receiving ART from a source other than their own bottles (e.g. hospitalization) were eliminated from both the numerator and denominator.

All aspects of the study were reviewed and approved by the Montefiore Medical Center Institutional Review Board.

Results

Data from an interim analysis of the first 53 study completers are presented in Tables 1-3 and Figure 1. All patients except for one received LPV/r soft-gel caps at a dosage of 3 capsules twice per day. One patient received 4 capsules twice per day.

The mean duration of MEMS cap adherence monitoring was 160±25.4 days. The mean adherence rate was 72.7%±22.8%. Adherence rates ranged from 23.5% to 100% with a median of 80.2%. Rates of virologic suppression according to adherence quartile are presented in Table 3. Rates of virologic suppression according to the adherence strata presented in the original study by Paterson et al. are depicted in Figure 1. There was no significant correlation between adherence level and proportion of subjects achieving virologic suppression <400 copies/ml (Spearman's rho=0.11, P=0.44) or <75 copies/ml (Spearman's rho=0.11, P=0.43).

Table 1. Characteristics of study cohort

Demographic or clinical characteristic	N (%)
Gender	
Female	22 (41%)
Male	30 (57%)
Transgender	1 (2%)
Mean age±S.D.	45.5±7.7
Ethnicity	
Latino/a	28 (53%)
Black	21 (40%)
White	4 (7%)
HIV risk behavior	
Heterosexual contact	28 (53%)
Injection drug use	17 (32%)
Male sex with male	8 (15%)
CDC defined AIDS	
Yes	44 (83%)
No	9 (17%)
Mean years since HIV diagnosis±S.D.	10.1±4.9
Mean lowest documented CD4+ count±S.D. (cells/ul)	168±173
Mean highest documented $\log_{10}$VL	5.05±0.76
Mean enrollment CD4+ count±S.D. (cells/ul)	459±281
Mean enrollment $\log_{10}$VL	2.67±1.18

Table 2. Antiretroviral treatment background of study cohort

	N (%)
Cumulative time on ART	
<1 year	2 (4%)
1-3 years	11 (21%)
3-5 years	5 (9%)
5-7 years	7 (13%)
>7 years	28 (53%)
# of prior ART agents (mean±S.D.)	4.8±2.7
# of prior PIs (mean±S.D.)	1.5±1.2
ART regimen	
2 NRTIs+LPV/r	39 (74%)
3 NRTIs+LPV/r	8 (15%)
4 NRTIs+LPV/r	3 (6%)
Other*	3 (6%)

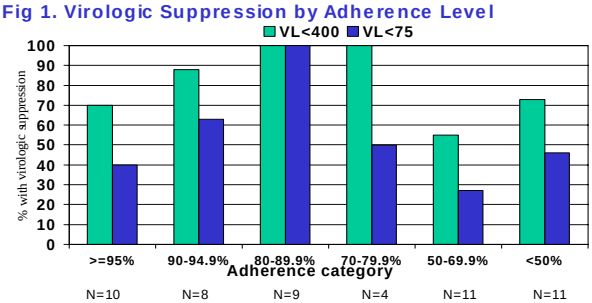
*Includes one patient each receiving NRTI+NNRTI+LPV/r, NRTI+Fusion Inhibitor+Additional PI+LPV/r, Fusion Inhibitor+LPV/r

Table 3. Virologic suppression by adherence quartile

Adherence rate	N	# with VL<400 (%)*	# with VL<75 (%)†
23.5%--50.6%	14	10 (71.4%)	7 (50%)
50.7%--80.2%	13	9 (69.2%)	4 (30.8%)
80.3%--92.8%	13	13 (100%)	12 (92.3%)
92.9%--100%	13	9 (69.2%)	5 (38.5%)

*P=0.17 for difference between groups
†P=0.008 for difference between groups

Fig 1. Virologic Suppression by Adherence Level



Discussion

The original study that gave rise to the "95% rule" showed that 95% adherence to antiretrovirals was necessary to achieve satisfactory rates of virologic suppression below 400 copies/ml.[1] The results of the present study suggest that the "95% rule" may not apply to LPV/r based regimens. The sharp dropoff in virologic suppression at adherence rates below 95% observed in the original study was not seen in the present study. Surprisingly high levels of virologic suppression occurred across a wide range of adherence rates. In fact, virologic suppression rates were remarkably similar in the lowest and highest quartiles of adherence. While these data require confirmation in follow-up studies, they strongly suggest that acceptable rates of virologic suppression occur at adherence rates above 80% and perhaps at adherence rates even lower.

These results were obtained in an urban, HIV infected population with substantial antiretroviral experience, low nadir CD4 counts, and high maximum documented viral loads. While MEMS cap monitoring is not foolproof, numerous studies, including the original study by Paterson et al., have demonstrated its value in predicting virologic outcomes. In the present study, the likelihood of improper MEMS cap usage was minimized by initial training and by detailed questioning at each follow-up visit. It is likely that the improved pharmacokinetic profile of LPV/r, combined with its high genetic barrier to resistance renders LPV/r based regimens more forgiving of non-adherence than other regimens.

Conclusions

Relatively high levels of virologic suppression <400 copies/ml were observed across a wide range of antiretroviral adherence levels.

The improved pharmacokinetic profile of LPV/r and its high genetic barrier to resistance likely confer increased forgiveness of sub-optimal adherence.

Additional studies are necessary to better understand the relationship between adherence to LPV/r and virologic suppression.

Reference

1. Paterson DL, Swindells S, Mohr J, *et al*. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Int Med* 2000;133:21-30.

Acknowledgements

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