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Timing Error Analysis of Data on Adherence to Lopinavir/Ritonavir Provides Superior Explanatory Power for Virologic Response

H. Knobel[1], A. Guelar[1], G. Vallecillo[1], B. Vrijens[2], E. de Klerk[2], E. Cabrero[3a], E. Salmeron[3a], K. Niemi[3b], S. Mayer[3b]
[1]Servicio Medicina Interna-Infecciosas, Hospital del Mar, Barcelona; [2]AARDEX Ltd, Zug CH; [3]Abbott Laboratories, [a]Madrid, [b]Abbott Park, IL

BACKGROUND

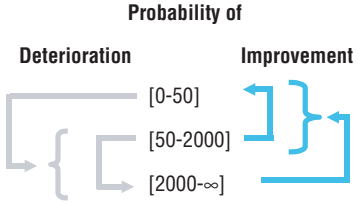
- It has been well documented that patient adherence to antiretroviral (ARV) therapy is critical in the treatment of HIV-1 infection and is directly associated with virologic success or failure. Paterson and colleagues explored the relationship between adherence and ARV therapy and found that adherence of 95% or greater was significantly associated with successful virologic outcome and CD4 T-lymphocyte increases.[1]
- Lopinavir/ritonavir (Kaletra®, LPV/r) is a protease inhibitor approved for use in combination with other ARVs for the treatment of HIV infection. Lopinavir, co-formulated with a low dose of ritonavir, takes advantage of the cytochrome P450 CYP3A inhibition of ritonavir, which results in substantially increased (plasma) lopinavir exposure.
- The inhibitory quotient (IQ) for lopinavir, defined as the ratio of the pre-dose concentration to its protein-binding adjusted EC_{50} for wild-type virus, is on average >75 at the 400/100 mg BID dose.[2] This high IQ potentially contributes to the durability of response by providing a pharmacologic barrier to the emergence of viral resistance and may allow for less restrictive adherence margins to obtain maximum treatment benefit.

INTRODUCTION

- Study M99-046 was an open-label, worldwide early access program designed to provide LPV/r to patients who were failing on, or intolerant to, available ARV agents and who had limited remaining treatment options.
- A single centre sub-study was offered to all patients enrolled in M99-046 at the centre and explored the relationship between patient adherence to LPV/r-based ARV therapy and corresponding efficacy using electronic adherence monitoring ("Medication Event Monitoring System" [MEMS®], AARDEX Ltd.).
- Patients who provided separate informed consent for this adherence sub-study received LPV/r in the same bottles that were used in M99-046; however, a MEMS monitor (cap) was used in place of the original medication cap. The MEMS cap recorded the exact date and time the bottle was opened, allowing for objective quantification of the patient's dosing pattern over time.
- Patients received LPV/r 400/100 mg BID in combination with other ARV agents as selected by the investigator. The dose of LPV/r was to be increased to 533/133 mg BID if dosed concurrently with either efavirenz or nevirapine.

METHODS

- Patients enrolled in the adherence sub-study were followed using the MEMS cap for 6 months. Subsequent to study completion and the discontinuation of MEMS, patients continued to be followed as part of their standard of care.
- During the adherence sub-study, monthly visits were scheduled to collect limited safety information including serious adverse events and reasons for discontinuations. In addition, patients' HIV-RNA and CD4 measurements were obtained as part of their standard of care during the sub-study and follow-up period.
- Virologic response, as defined by the percentage of patients with plasma HIV-RNA <50 copies/mL, was summarized at the end of the sub-study, and the end of the follow-up period.
- Quantitative dosing information was measured at Months 1, 3 and 6 using the MEMS cap and a patient self-report questionnaire.
- The following adherence variables were assessed using data collected from the MEMS caps:
  - Taking Compliance: percentage of prescribed number of doses taken
  - Timing Compliance: percentage of doses taken within prescribed intervals
  - Correct Dosing Compliance: percentage of days with correct number of doses
  - Timing Error: a 'new' compliance parameter related to the degree of skewness (or asymmetry) in the distribution of interdose intervals.[3]
- The relationship between plasma viral load and patient adherence to therapy was evaluated by modeling the probability that a patient's future viral load would fall from, or rise to, a defined category, given the current viral load and an assumption that patient adherence continues unchanged. For the purpose of this analysis, viral load categories of <50, 50-2000, and >2000 copies/mL were taken to represent virologic response, partial virologic response, and virologic failure, respectively.



RESULTS

Summary of Patient Disposition/Demographics and Baseline Characteristics

Table 1. Patient Disposition

Total enrollment (patients dosed)	27
Excluded from analysis	
Transferred to clinics not participating in this sub-study	2
Discontinued (adverse event)	1
Did not return MEMS cap	1
Included in analysis	23

Study Duration/Follow-up

- A total of 23 patients completed the adherence sub-study and were treated for an average of 213 days [range: 172-287].
- After completion of the sub-study, patients continued to be followed for an average of 131 additional days [range: 0-463].

Table 2. Demographics/Baseline Characteristics (n=23)

Gender	
Male	78% (18/23)
Race	
Caucasian	100% (23/23)
Age (years)	
Mean (range)	37 (27-55)
HIV-1 Subtype "B"	100% (23/23)
Previous ARV Use (mean #)	
NRTIs (range)	3.0 (1-7)
PIs (range)	1.8 (0-4)
NNRTI (range)	0.7 (0-2)
Mutations in Protease (n=22)*	
Mean	4.5
Median	5.0
Range	0-8

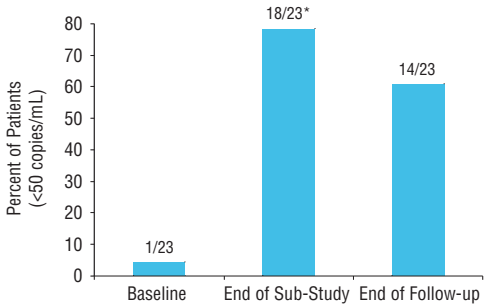
* One patient entered the sub-study with a viral load <50 copies/mL and resistance testing could not be performed.

Summary of Virologic Response and Safety

Table 3. Viral Load and CD4 Outcomes

	Baseline	End of Sub-Study	End of Follow-up
Viral Load (copies/mL)			
Mean	37,020	1,236	5,548
Median	23,000	<50	<50
Range	<50-140,000	<50-13,000	<50-72,000
CD4 T-lymphocytes (cell/mm^3)			
Mean	272	400	465
Median	206	409	447
Range	13-775	112-810	118-1,053

Figure 1. Percent of Patients with Viral Load <50 copies/mL



* 3 additional patients had a viral load <50 copies/mL at some time during the adherence sub-study; these patients were found to be non-adherent to their ARV regimens (using MEMS) and had lost virologic control by the end of the sub-study.

Adverse Events

- Adverse events that resulted in premature study discontinuation or met the definition of "serious" were collected.
  - One subject prematurely discontinued the study on Day 5 due to an adverse event of "gastrointestinal intolerance."
  - Two subjects experienced serious adverse events during the study: hospitalization for "cryptococcal meningitis" (n=1) and hospitalization for "toxic psychosis" (n=1). Neither of the events was judged to be related to LPV/r by the investigator and neither resulted in discontinuation from the study.

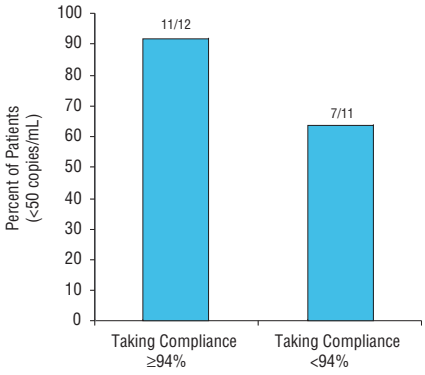
Summary of Adherence Variables and Association with Virologic Response

Table 4. Adherence Variable Outcomes

	Taking Compliance	Correct Dosing	Timing Compliance
Mean	91%	81%	71%
Median	94%	84%	81%
Range	50-100%	2-100%	2-100%

RESULTS

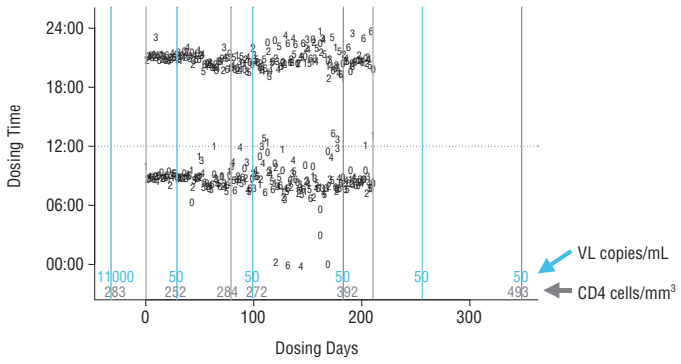
Figure 2. Percent of Patients with a Viral Load <50 copies/mL at the End of the Sub-Study Stratified by Median Taking Compliance



Modeling the Association Between Viral Load and Dosing Histories

- A total of 113 viral load measurements were reported for the 23 patients included in this analysis.
  - 53% (60/113) were <50 copies/mL
  - 22% (25/113) were 50-2000 copies/mL
  - 25% (28/113) were >2000 copies/mL
- As shown in Figure 3, the relationship between viral load, CD4 count and patient adherence can be summarized over time for an individual patient. In this example, the horizontal axis displays the dosing days relative to study entry with the viral load and CD4 measurements displayed immediately above the horizontal axis. The vertical axis gives the time of drug intake (bottle opening) on a 24-hour clock. The digits plotted correspond with the days of the week (0=Sunday, 1=Monday, 2=Tuesday... and 6=Saturday).

Figure 3. Sample Adherence Data



Derivation of a New Compliance Parameter

- The timing error, which is a new compliance parameter used to assess the degree of skewness (or asymmetry) in the distribution of interdose intervals recorded by the MEMS cap, is defined as:

$$TE_i = \sqrt[3]{\frac{1}{n_i}\sum_k \left(\frac{\delta_{ik} - 12}{12}\right)^3}$$

TE_i = the timing error for patient i $\quad$ n_i = the number of interdose intervals for patient i $\quad$ δ_{ik} = the k^{th} dosing interval for patient i

- As indicated in Table 5, Timing Error was a better predictor (minimum p-value) of the deterioration or improvement in viral response when compared to the more traditional measures of adherence (i.e., timing compliance, correct dosing and taking compliance). Deviance numbers reflect the amount of unexplained variance in viral load data. A drop of 3.84 compared to the 'Null Model' represents a statistically significant reduction in unexplained variance.

RESULTS

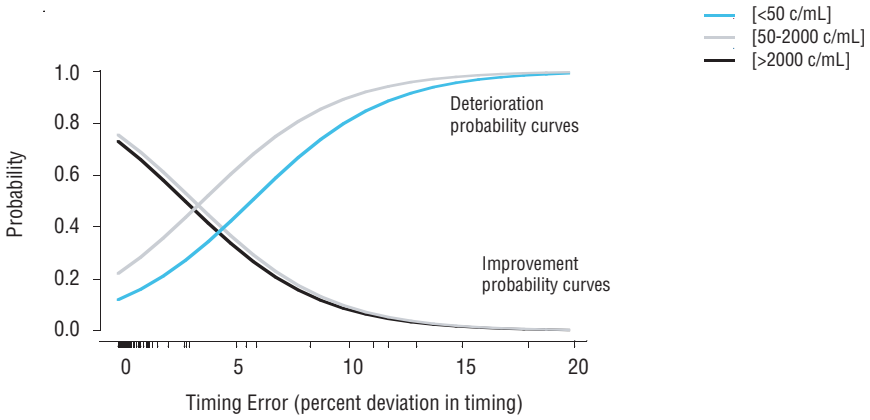
Table 5. Categorical Analysis of Viral Load as a Function of Patient Adherence to ARV Therapy*

	Deterioration		Improvement	
	Deviance	p-value	Deviance	p-value
Null model	112.7		107.6	
Timing compliance	109.6	0.078	106.9	0.403
Correct dosing	110.4	0.129	107.4	0.655
Taking compliance	106.8	0.015	105.5	0.147
Timing error	105.8	0.009	103.4	0.040

* Quantifies the proportion of variability in the transition probabilities explained by each of the variables. Each statistical test (deterioration or improvement) was performed at the α=0.05 level of significance.

- As shown in Figure 4, the probability of virologic improvement (success) decreases, while the probability of virologic deterioration (failure) increases, with increasing non-adherence or "deviation in timing." The plots represent the predicted probability of future success or failure for a given patient conditional to his/her most recent viral load category (i.e., <50, 50-2000, or >2000 copies/mL).

Figure. 4 Association Between Timing Error and Probability of Improvement/Deterioration in Viral Load



CONCLUSIONS

- In this adherence sub-study, LPV/r-containing therapy demonstrated effective viral suppression and appeared to be well tolerated, with only 3.7% (1/27) of these ARV-experienced patients discontinuing LPV/r therapy due to an adverse event.
- Electronic monitoring of drug intake may be an effective strategy in maintaining long-term adherence.
- Dose timing information increases the explanatory power of data on patient adherence and its effect on ARV treatment outcomes. The results suggest that avoidance of long interdose intervals, at least in this heavily pre-treated population, should be a priority in efforts to increase the probability of virologic suppression.
- Evaluation of baseline resistance data, in conjunction with dose timing information, may provide additional insight into treatment outcomes in ARV-experienced patients.

ACKNOWLEDGMENTS

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