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Lower Adherence to HAART Observed Prior to Transient HIV-1 Viremia ("Blip")

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Background

- Transient increases in plasma HIV-1 RNA, or "blips," are frequently observed in HIV-infected individuals receiving antiretroviral therapy.
- The relationship between adherence and blips remains ambiguous. An absence of reliable and continuous adherence measures preceding and following a blip may limit statistical power to identify such a relationship.
- Electronic monitors that record and store dosing histories may improve adherence assessment and better define the relationship between adherence and blips.

Methods

Studies M99-056 and M02-418 were prospective, randomized, open-label, multicenter, parallel arm clinical trials evaluating the safety, tolerability, antiviral efficacy and pharmacokinetics of lopinavir/ritonavir (LPV/r) soft-gel capsules, administered QD (800/200 mg) or BID (400/100 mg), in combination with nucleoside reverse transcriptase inhibitors (stavudine [d4T] and lamivudine [3TC] BID in M99-056, tenofovir disoproxil fumarate [TDF] and emtricitabine [FTC] QD in M02-418) in antiretroviral-naïve, HIV-1 infected subjects. For the purpose of these studies, subjects were considered antiretroviral-naïve if they had received less than 7 days of prior antiretroviral therapy. In addition, subjects were required to have plasma HIV-1 RNA >1,000 copies/mL at screening. However, there was no CD4+ T-cell count restriction.

Blood collection for quantitation of plasma HIV-1 RNA was conducted at baseline, weeks 4, 8, 16 and 24, every 8 weeks thereafter until week 48, and every 12 weeks thereafter until week 96. For this analysis, a blip was defined as one plasma HIV-1 RNA value between 50–1000 copies/mL immediately preceded and immediately followed by plasma HIV-1 RNA measurements <50 copies/mL.[1] In case of multiple episodes of transient viremia for a given subject, only the first episode was included in the evaluation.

For M99-056, resistance to LPV was defined as the presence of any primary or active site mutation in protease (at positions 8, 30, 32, 46, 47, 48, 50, 82, 84 and 90). 3TC resistance was defined as the emergence of the M184V/I mutation in reverse transcriptase. For study M02-418, resistance to LPV was defined conservatively as the development of any mutation in protease at positions 8, 30, 32, 46, 47, 48, 50, 82, 84 and 90, with a corresponding decrease in phenotypic susceptibility to LPV of at least 2.5-fold compared to wild-type HIV-1. Resistance to TDF was defined as the emergence of any new mutation in reverse transcriptase at positions 41, 65, 67, 70, 210, 215, 219 or an insertion mutation in the vicinity of codon 69. FTC resistance was defined as the emergence of the M184V/I mutation in reverse transcriptase.

Treatment compliance was assessed through the use of MEMS® monitors, which electronically recorded and stored LPV/r bottle openings for subjects enrolled throughout these studies. Each subject's dosing history pattern was summarized using a daily binary adherence sequence: on each consecutive day, adherence was defined as "correct" if the subject took **at least the prescribed number of LPV/r doses.** This coding retains much of the temporal structure in the individual dosing.

Correct dosing adherence was summarized and depicted graphically in both daily and weekly intervals. For subjects who experienced transient HIV-1 viremia (or "blip"), correct dosing adherence during a period of time around the blip was compared with correct dosing compliance for the same subject during a period of time in which a blip did not occur.

The average number of days with correct dosing adherence was compared between blip and non-blip episodes using generalized estimating equation (GEE) methodology. The association between blip occurrence and virologic failure was assessed using a chi-squared test. All statistical tests were considered significant at the 5% level.

Results

- Subjects receiving LPV/r QD or LPV/r BID had comparable virologic efficacy, rates of resistance and immunologic improvement in studies M99-056 and M02-418.[2,3]
- Of 228 subjects enrolled, 223 (98%) have MEMS data available (92 LPV/r BID, 131 LPV/r QD). Baseline demographics for subjects with MEMS data available are shown in Table 1.

Table 1. Demographic Characteristics of Subjects with MEMS Data Available

	LPV/r QD (N=131)	LPV/r BID (N=92)
Gender		
Male	105 (80.2%)	69 (75.0%)
Female	26 (19.8%)	23 (25.0%)
Race/Ethnicity		
White	71 (54.2%)	43 (46.7%)
Black	36 (27.5%)	34 (37.0%)
Hispanic	15 (11.5%)	9 (9.8%)
Asian	8 (6.1%)	5 (5.4%)
Other*	1 (0.8%)	1 (1.1%)
Age (years)		
Mean ± SD	39.5 ± 11.19	37.2 ± 8.83
Range	19 – 75	19 – 75
Time Since HIV-1 Diagnosis (years)		
Mean ± SD	2.3 ± 4.11	1.9 ± 3.38
Range	0.1 – 18.5	0.1 – 16.7
Baseline Plasma HIV-1 RNA (log_{10} copies/mL)		
Mean ± SD	4.85 ± 0.737	4.72 ± 0.728
Range	3.44 – 6.44	1.70 – 6.18
Baseline CD4+ T-cell Count (cells/mm^3)		
Mean ± SD	264.7 ± 206.75	248.3 ± 192.79
Range	3 – 990	5 – 1006

* Includes 1 "American Indian/Alaska Native" (QD) and 1 "Other" (BID).

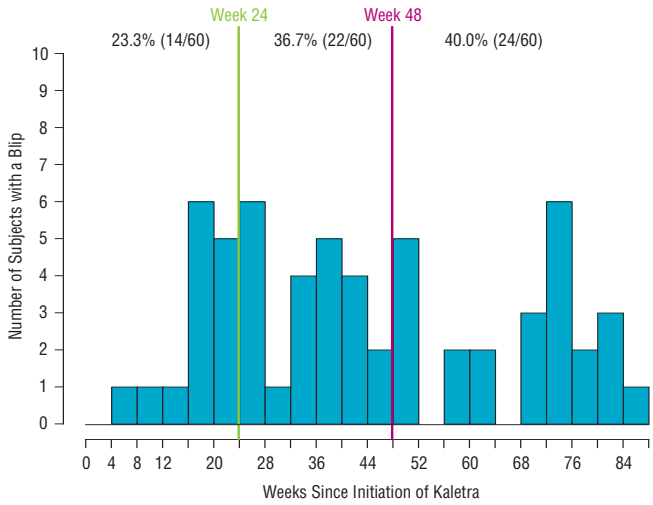
The number of subjects in each study experiencing a transient increase in the plasma HIV-1 RNA ("blip") is summarized in Table 2.

Table 2. Number of Subjects Who Experienced Transient Plasma HIV-1 RNA Viremia ("Blips")

	LPV/r QD (N, %)	LPV/r BID (N, %)	Magnitude of Blip Median (range) copies/mL
M99-056 (N=18 LPV/r QD, 17 LPV/r BID)	6 (33%)	7 (41%)	85 (51–858)
M02-418 (N=113 LPV/r QD, 75 LPV/r BID)	33 (29%)	14 (19%)	82 (51–563)
Total (N=131 LPV/r QD, 92 LPV/r BID)	39 (30%)	21 (23%)	82 (51–858)

Transient viremia was identified in 60 (27%) subjects (39 LPV/r QD, 21 LPV/r BID). A similar number of subjects experienced transient viremia ("blips") on LPV/r QD compared to LPV/r BID (30% vs. 23%; p=0.212 [Cochran-Mantel-Haenszel test]). The median blip was 82 copies/mL (range: 51–858). One subject experienced transient viremia with HIV-1 RNA >1000 copies/mL and was not included in the analysis. Neither baseline viral load nor baseline CD4+ T-cell count was associated with the occurrence of blips. Figure 1 summarizes the time to first blip.

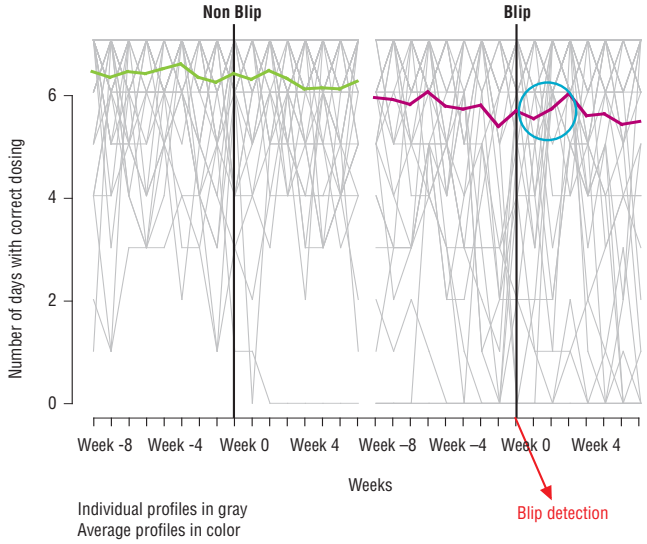
Figure 1. Time to Occurrence of the First Blip



Median (IQR) time to the first blip was 282 (169–448) days. Moreover, 23.3% of the blips occurred prior to week 24, 36.7% between weeks 24 and 48, and 40.0% after week 48. The Kaplan-Meier estimated median time of follow-up for the study was 673 days (95% CI: 670–676 days, approximately 96 weeks).

Figure 2 shows the mean number of days per week of correct dosing adherence during blip and non-blip episodes.

Figure 2. Comparison of the Mean Number of Days Per Week with Correct Dosing Adherence during Blip and Non-Blip Episodes



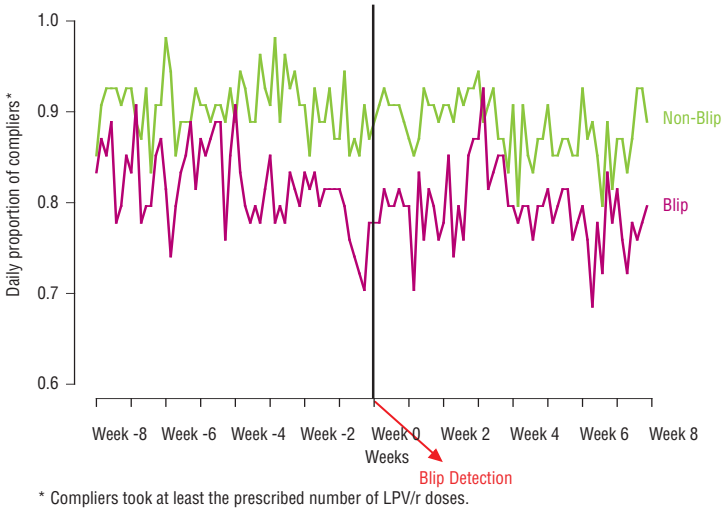
The mean number of days the subject administered the prescribed number of doses during the week prior to a blip was lower than during a matched period for the same subject during which a blip did not occur (5.55 vs. 6.22 days; p=0.007).

Of note, subjects who experienced plasma HIV-1 RNA levels above the level of quantitation were required by protocol to have the viral load result confirmed within 4 weeks. Subjects presented for the repeat viral load testing after a median (IQR) of 57 (36–79) days most likely corresponding to the next scheduled study visit.

Correct dosing adherence appeared to increase shortly following detection of the elevated viral load and subsequently returned to baseline levels.

When comparing the daily proportion of subjects with correct dosing adherence during blip and non-blip episodes (rather than the mean number of days per week with correct dosing compliance), a similar finding is noted as shown in Figure 3.

Figure 3. Comparison of the Daily Proportion of Subjects with Correct Dosing Adherence During Blip and Non-Blip Episodes



* Compliers took at least the prescribed number of LPV/r doses.

Once again, adherence is lower during a blip and appeared to improve shortly after the blip was detected.

Alternate definitions of virologic failure have been proposed and assessed for their relationship to blip occurrence.

1. a. two consecutive plasma HIV-1 RNA values >50 copies/mL or
   b. the last measured plasma HIV-1 RNA >50 copies/mL, with either occurring after initial suppression of HIV-1 RNA to ≤50 copies/mL
2. plasma HIV-1 RNA >1000 copies/mL at the end of the study or the last study visit after suppression to ≤50 copies/mL which was considered to be a more clinically meaningful endpoint
3. a. two consecutive plasma HIV-1 RNA values >200 copies/mL or
   b. the last measured plasma HIV-1 RNA >200 copies/mL, with either occurring after initial suppression of HIV-1 RNA to ≤50 copies/mL

Table 3 shows the association between blips and virologic failure.

Table 3. Association Between Blips and Virologic Failure

	Virologic Failure (1)			Virologic Failure (2)		Virologic Failure (3)		
Blip	**No**	**Yes (1a)**	**Yes (1b)**	**No**	**Yes**	**No**	**Yes (3a)**	**Yes (3b)**
No	110 (80.3%)	21 (15.3%)	6 (4.4%)	131 (95.6%)	6 (4.4%)	123 (89.8%)	11 (8.0%)	3 (2.2%)
Yes	45 (75.0%)	9 (15.0%)	6 (10.0%)	56 (93.3%)	4 (6.7%)	54 (90.0%)	3 (5.0%)	3 (5.0%)

The occurrence of blips was not associated with virologic failure using Definition 1 (p=0.33), Definition 2 (p=0.50), or Definition 3 (0.43).

No primary or active site mutation was observed in protease in either study. No significant difference was noted in the development of resistance in reverse transcriptase at position 184 between those who did or did not experience blips (5.0% [3/60] vs. 2.5% [4/163]; p=0.39).

Conclusions

- Blips defined by one plasma HIV-1 RNA between 50–1000 copies/mL immediately preceded and immediately followed by plasma HIV-1 RNA measurements <50 copies/mL are associated with decreased adherence.
- Patients may demonstrate short-term improvement in correct dosing compliance following detection of a blip. Whether this represents reinforcement of the need for adherence to antiretroviral medications at the study visit or possibly a behavioral response to notification of the subject regarding the elevated plasma HIV-1 RNA result is unclear.
- With a lopinavir/ritonavir-based regimen, blips do not appear to be associated with either virologic failure or the development of HIV-1 drug resistance.
- These results may be specific to lopinavir/ritonavir and may not reflect the relationships between adherence, blips and HIV-1 drug resistance that could occur with other drugs.

References

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3. Molina JM, Wilkin A, Domingo P, et al. Once-Daily versus Twice-Daily Lopinavir/ritonavir in Antiretroviral-Naïve Patients: 96-Week Results, Third IAS Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, Brazil, July 24–27 2005; Poster #WePe12.3C12.

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