Adherence and Viral Exposure Were Similar Between Treatment Groups Among Subjects with Genotypic Data

- Factors potentially related to the development of resistance include the exposure to viral replication and adherence.
- Viral load data were examined to explore whether differences in exposure to viral replication may have accounted for the observed differences in the incidence of resistance (Table 5).
- Figure 5 provides an illustration of the variables examined in the comparison of the exposure to viral replication.
- Adherence among subjects with genotypic data was similar (Table 6).
- No statistically significant differences between the treatment groups were observed using any of the measurements of exposure to viral replication, suggesting that the difference in the emergence of protease inhibitor resistance was not due to differing degrees of overall viral replication between the treatment groups. Results of the analyses are summarized in Table 6.

Figure 5. Viral Exposure Illustration

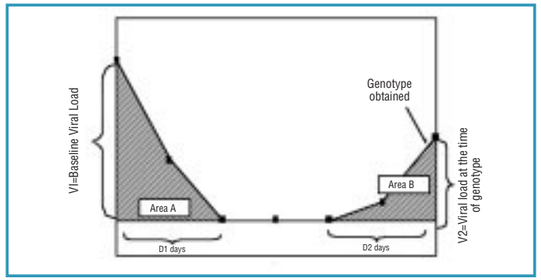

Table 6. Adherence of Subjects with Genotype Data Through 96 Weeks*

	Subjects with Genotype Data Through 96 Weeks		
Adherence Category	LPV/r (N=51)	NFV (N=95)	Overall p-value
<80%	10%	14%	
80%-90%	25%	15%	
>90%	65%	72%	0.258

* Overall adherence rate for this analysis was defined as the adherence rate over the first 96 weeks of the study or until discontinuation. Study visits at which bottles were not returned were not included in the calculation of adherence rate. The p-value for this analysis was computed using Pearson's chi-square test on the 2x3 table. There was no pill count data for one of the NFV subjects.

Adherence Was Higher in Responders Than in Non-responders

- For this analysis, a total of 187 subjects (74 LPV/r-treated subjects and 113 NFV-treated subjects) were classified as non-responders (VL >400 copies/mL at least once at Week 24 through Week 96), and 401 subjects were classified as responders (VL <400 copies/mL on all values obtained from Week 24 up to Week 96).
- Adherence was statistically significantly higher in responders than in non-responders (Table 7).

Table 7. Analysis of Adherence Through Week 96*

Adherence Category	Responders (N=401)	Non-responders (N=186)	Overall p-value
<80%	4%	9%	
80%-90%	11%	17%	
>90%	86%	75%	0.004

* The p-value for this analysis was computed using Pearson's chi-square test on the 2x3 table. There was no pill count data for one of the non-responders.

Analysis of Exposure to Viral Replication and the Emergence of 3TC Resistance

- The emergence of 3TC resistance in the subset of NFV-treated subjects without primary resistance to NFV was related to the duration of time with VL >400 copies/mL.
- The emergence of 3TC resistance in LPV/r-treated subjects was not related to any analyzed measure of viral replication (Table 8).

Table 8. Comparison of Exposure to Viral Replication Between Subjects Without 3TC Resistance and Subjects with 3TC Resistance, but No Resistance in Protease

	NFV			LPV/r		
Analysis	No 3TC (N=18)	3TC, but no PI (N=37)	p-Value	No 3TC (N=32)	3TC, but no PI (N=19)	p-Value
Baseline HIV RNA	4.98	5.13	0.428	5.04	5.19	0.437
VL at the time of genotype	3.57	3.66	0.696	3.70	3.56	0.576
Consecutive days since VL<400 copies/mL	84	129	0.018	132	115	0.573
Total days with VL>400 copies/mL	183	193	0.710	187	202	0.615
VL AUC from nadir to genotype	819	751	0.539	831	697	0.295
VL AUC from baseline to genotype	1,044	966	0.488	1,087	1,004	0.512

CONCLUSIONS

- Despite similar exposure to viral replication and adherence, protease inhibitor resistance was observed markedly less frequently in LPV/r-treated subjects than in NFV-treated subjects in this analysis (0% vs. 43%, p<0.001).
- Resistance to 3TC was also observed significantly less frequently in LPV/r-treated subjects than in NFV-treated subjects (37% vs. 81%, p<0.001).
- The difference in the rate of PI resistance development may reflect the higher IQ observed with LPV/r-treated subjects than in NFV-treated subjects.
- These findings confirm initial observations from phase II studies of LPV/r in ARV-naïve adults (M97-720 n=100) through 144 weeks and in children (M98-940 n=44) through 60 weeks where resistance to LPV/r has not been observed.

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Poster #1768

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Comparison of the Emergence of Resistance in a Blinded Phase III Study with Kaletra™ (lopinavir/ritonavir) or Nelfinavir plus d4T/3TC from Week 24 Through Week 96

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BACKGROUND

Study M98-863 was a multi-center, multinational, blinded, randomized, prospective study that compared the antiviral activity and safety of lopinavir/ritonavir (LPV/r) plus d4T and 3TC to that of nelfinavir (NFV) plus d4T and 3TC in ARV-naïve subjects. A total of 653 subjects were enrolled in the study (LPV/r N=326, NFV N=327). Study subjects were unblinded to their randomized treatment arms after all active subjects had reached Week 60. After Week 60, subjects were given the opportunity to remain on their randomized treatment arm or switch treatment from NFV to LPV/r.

The primary efficacy analyses included:

- The proportion of subjects with HIV RNA level <400 copies/mL at Week 24
- Time to loss of virologic response through Week 48.

Through Week 60, significantly more LPV/r-treated subjects experienced viral suppression to HIV RNA levels less than 50 copies/mL than NFV-treated subjects (Figure 1 and Figure 2).

Figure 1. Proportion <400 copies/mL (ITT NC=F)

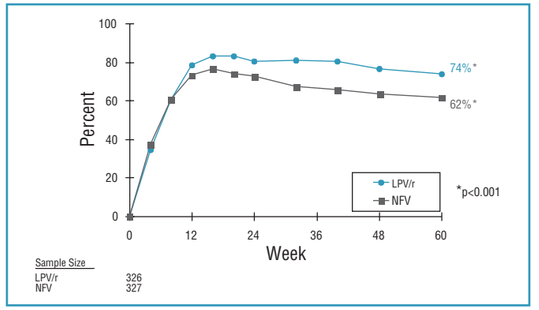
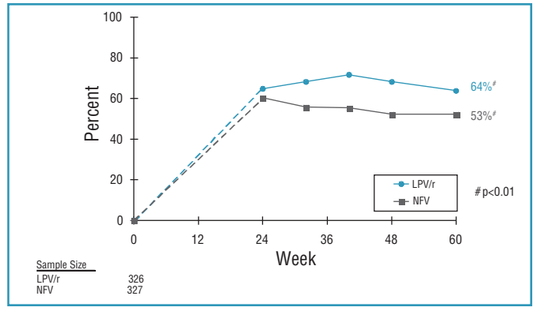


Figure 2. Proportion <50 copies/mL (ITT NC=F)



The differences in efficacy observed in this study may reflect the substantially different Inhibitory Quotient (IQ, C_{trough}/IC_{50} ratio) achieved with LPV/r versus NFV. A high IQ may also provide a pharmacologic barrier to the development of drug-resistance. The objective of this analysis was to evaluate differences in the incidence of protease inhibitor (PI) and reverse transcriptase inhibitor (RTI) resistance between the two arms of this study.

METHODS

Genotypic/Phenotypic Resistance

Genotypic resistance to NFV was defined as the development of a D30N and/or an L90M mutation in protease. Genotypic resistance to LPV was defined as the development of any primary or active site mutation in protease (amino acids 8, 30, 32, 46, 47, 48, 50, 82, 84 and 90) that was not present prior to the initiation of LPV/r treatment. Phenotypic analyses were performed on all samples obtained from LPV/r-treated subjects. Resistance to 3TC was defined as the presence of an M184V and/or M184I mutation in reverse transcriptase. Genotype (GenSeq™) and phenotype (PhenoSense™) were performed by ViroLogic, Inc. Secondary mutations were previously defined by Hirsch et al. in *JAMA* 1998.[3]

Adherence

Overall adherence was measured by pill counts of protease inhibitor (non-placebo), and was computed as the proportion of pills consumed relative to the expected number consumed.

Sample Selection for Analysis

Samples from all subjects with HIV RNA ≥500 copies/mL once during the period from Week 24 through Week 96 while on their assigned-treatment were submitted for analysis. A total of 74 LPV/r-treated and 113 NFV-treated subjects had at least one sample submitted for resistance testing. For subjects with multiple VLs ≥500 copies/mL during this period, the latest sample for which the genotypic sequence was available was used for this analysis, unless PI resistance had been identified at an earlier timepoint. Through Week 96, more LPV/r-treated subjects remained on their randomized treatment than subjects on NFV (Figure 3). A summary of time of sample selection is provided in Figure 4.

Figure 3. Number of Subjects on Study Through 96 Weeks

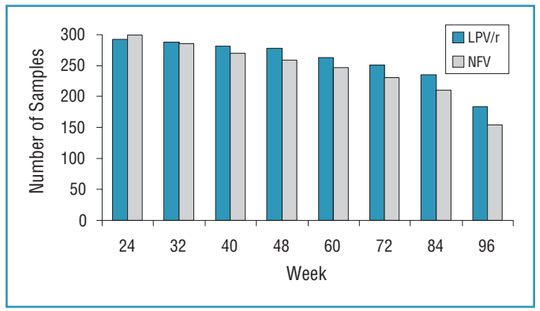
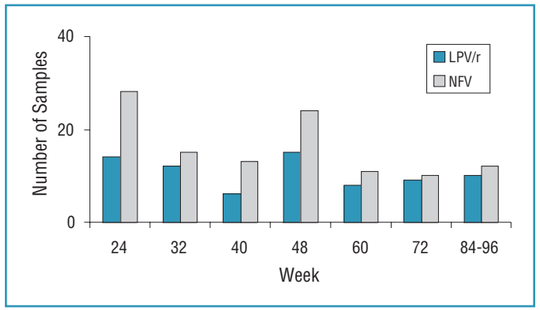


Figure 4. Sample Selection for Genotype Data Through 96 Weeks



RESULTS

LPV/r-Treated Subjects Demonstrated a Significantly Lower Level of Resistance Than NFV-Treated Subjects

- Viral isolates from 51/74 LPV/r-treated subjects and 96/113 NFV-treated subjects through Week 96 while on treatment could be amplified for resistance testing.
- None of the 51 LPV/r-treated subjects with available genotype demonstrated genotypic resistance to LPV (Table 1).
- The absence of resistance to LPV was confirmed by phenotype in all LPV/r-treated subjects for whom a phenotype result was available (46/51 samples).
- Forty-one of the 96 NFV-treated subjects with available genotypes demonstrated genotypic resistance to NFV.
- Baseline genotype was available for 35/41 NFV-treated subjects whose rebound sequence displayed resistance. The D30N or L90M mutation was not present in the baseline isolates from any of the 35 subjects.
- 3TC resistance was noted significantly more frequently in NFV-treated subjects than in LPV/r-treated subjects (81% vs. 37%, p<0.001)

Table 1. Incidence of Resistance in Viral Isolates up to Week 96

Category	LPV/r	NFV	p-value
Genotypic resistance detected in protease	0/51 (0%)	41/96 (43%)	<0.001
Number of subjects with a D30N mutation	N/A	28/41	—
Number of subjects with L90M mutation	N/A	12/41	—
Number of subjects with both L90M and D30N mutations	N/A	1/41	—
3TC resistance detected	19/51 (37%)	78/96 (81%)	<0.001

Appearance of Other Mutations in NFV-Treated Subjects Who Developed D30N and/or L90M Mutation

- Coincident with the D30N and/or L90M, 19/35 of the rebound isolates (among subjects with baseline data) also contained at least one primary or secondary mutation that was not present at baseline. These included L10F/I/V, M36I, M46I, L63P, A71T/V, G73S, V77I, V82A/T, I84V and N88D (Tables 2 and 3).[3]
- New secondary mutations appeared in 15 rebound isolates containing the D30N and 4 rebound isolates containing the L90M mutation.

Table 2. Incidence of Secondary Mutations in Conjunction with D30N and/or L90M

Number of subjects with:	
1 secondary mutation	7
2 secondary mutations	8
3 secondary mutations	2
4 secondary mutations	2
Total	19

Table 3. Appearance of Secondary Mutations in Conjunction with D30N and/or L90M

L10F, I ,or V	4	G73S	1
M36I	7	V77I	3
M46I	3	V82 A or T	1
L63P	4	I84V	1
A71 V	8	N88D	5

Appearance of Secondary Mutations in LPV/r-Treated Subjects

- Isolates were examined for the presence of any of the following secondary mutations: 10, 20, 24, 33, 36, 53, 54, 63, 71, 77 and 88.
- Baseline genotype was available for 42/51 subjects with rebound genotype. Genotype data for all 51 subjects are provided in Table 4.
- The latest rebound sequences for 34/42 (81%) subjects did not demonstrate any new secondary mutations.
- The remaining 8/42 sequences demonstrated one single polymorphism/secondary mutation at rebound that was not present at baseline, including L10F (1), M36I/L(5), L63P (1), and A71T (1).
- At rebound, one subject no longer had a secondary mutation that had been present at baseline.

Table 4. Comparison of Baseline and Rebound Genotype for LPV/r-Treated Subjects Through Week 96

Subject	Days on Study	Days Since VL Determination <400	Baseline Sequence	New Mutations	Lost Mutations
1	370	66	E35D, N37N/T, R57R/K, L63P	I72I/V	R57R/K
2	619	113	R57R/K, L63P, I72IV, V77V/I	–	–
3	609	266	E35D, M36I, N37D, R41R/K, R57K L63P, I64V, A71V, V771, I93L	– I72I/T	– R41R/K
4	227	58	K14R, I15V, G16E, L63T, H69K, V77I	–	–
5	164	*	W42R, I64V	–	W42R
6	541	125	N37E, P39S/T, I62I/V, L63P/T, A71T, V77I, I93L	–	I62I/V
7	187	*	L10I, E35D, R57K, I62V, L63P, I64I/L, I72L, I93L	–	–
8	552	98	Not Available	①	①
9	539	107	Not Available	②	②
10	505	*	N37D, R57R/K, L63L/P, A71T, I72I/A/T/V	–	R57R/K, I72A/T
11	169	28	L33V, E35E/D, M36M/I, N37A/T, R41K, I64V, I93L	**L10L/F**, M36L, N37N/D, I72I/V	–
12	226	56	T12T/A, I13V, K14R, E35D, M36I, R41K K45R, R57K, L63P, H69K, L89M	–	T12T
13	185	56	E35D, R41K, L63P, I93L	–	–
14	170	29	T12T/S, I15V, L19L/I, D60E, I62V, L63P/S	T12A, I13V, I62I, **A71T**	T12T/S I15V, L19L/I, D60E, L63S
15	246	186	T12T/R, K14K/R, I15I/V, G16G/E, L19I, R41K, I64I/V, V77V/I	–	T12T/R, I15I/V, G16G/E
16	371	92	L10I/V, M36M/I, L63C	H69H/Y	–
17	165	22	Not Available	③	③
18	674	85	Not Available	④	④
19	279	*	I62I/V, L63A, I64M, V77V/I	I13I/V	–
20	352	71	E35D, N37E, R57R/K, D60E, L63L/P, I64V, V77I, I93L	–	R57R, L63L
21	220	70	T12S, I15V, L19I, M36I, R41K, L63L/P, H69K, L89M, I93L	–	L63L
22	666	447	T12S, I15V, L19T, M36I, G40G/V, R41K, L63V, H69K, L89M, I93L	–	G40G/V
23	651	217	Not Available	⑤	⑤
24	336	56	N37N/S, L63Q, I64V, V77I	K70T	N37N
25	280	*	T12T/S	L19L/V, **M36M/I**	–
26	299	77	Q2Q/K, T12T/K, K20R, E35D, N37D, R41R/K, L63P, A71T	N37N, D60D/E, I62I/V, A71A	Q2Q/K T12T/K, R41R
27	336	56	Not Available	⑥	⑥
28	360	122	I15I/V, L19L/I, N37A/T, R41K, I62I/V, V77I, I93L	–	I15I/V
29	497	118	K43K/R, I62I/R, L63P	**M36M/L**	I62I/R
30	200	59	N37N/D, D60E, Q61E, L63P, I72I/T, V77I	R57K, L63T	N37N/D, Q61E, L63P, I72I/T
31	337	112	E35D	I13I/V, N37N/S, E35E	–
32	452	117	I15V, N37A/T, V82I, I93L	–	–
33	280	56	E35D/N, N37D, L63P, K70R, V77I	**M36M/I**, V77V	–
34	535	365	L19Q, V77I	**L63L/P**	–
35	361	225	I64V, I72V	–	–
36	175	31	L10I, I13V, G16E, E21E/K, N37N/D, I62V, L63S, I64M, I72T	–	E21E/K, N37N/D
37	581	162	I13V, K14R, K20I, E35D, M36I, R41K, L63P, H69K, L89I/M	K43K/R	L89I
38	399	371	R41K, D60E, I64V	**M36M/I**	–
39	189	102	K14K/R, I15V, M36I, N37N/D, R41K, L63S	–	K14K, N37N
40	162	37	N37N/S, I62V, L63P, I64L	I66I/T	–
41	561	224	L19I	–	–
42	543	106	Not Available	⑦	⑦
43	343	62	I13I/V, E35D, N37N/S, I62I/V, L63P	E35E, N37C/Y	I62I/V
44	363	61	P39T, R41R/K, D60E, I62V, L63P, V77V/I	I62I	–
45	534	104	Not Available	⑧	⑧
46	173	56	E35D, N37E, D60E, I64V, I72T	N37D	–
47	229	56	T12T/A, I13V, K14K/R, I15I/V L19L/I, L63P, H69Q, I72I/V, V77I	–	T12T/A, K14K I15I/V, L19L/I
48	185	51	R41R/K, Q61E, L63P, V77I	**M36M/I**	–
49	505	224	Not Available	⑨	⑨
50	331	110	N37D, L63P	–	–
51	511	343	I15V, G16A, N37D, L63L/I, A71T, I72T, I93L	L63T	L63L

* Subject never achieved VL<400.

① Rebound sequence: R41K, L63T, 164I/V
② Rebound sequence: I13V, E35D, N37N/S, R57K, L63P
③ Rebound sequence: T12E, M36I, I62V, L63P, I93L
④ Rebound sequence: T12S, L19I, M36I, R41K, D60E, Q61Q/E, L63P, H69K, L89M, I93L
⑤ Rebound sequence: T12T/P, K14R, E35D, N37D, R57K, L63P, V77I, I93L
⑥ Rebound sequence: H69Y
⑦ Rebound sequence: N37D, K43K/R, L63S/T, A71A/I/M/T/V, I93I/L
⑧ Rebound sequence: L10I, I13V, G16E, E35D, M36I, P39P/S, R41K, I62I/V, L63T, H69K, L89M
⑨ Rebound sequence: T12S, L19I, K20R, M36I, R41K, H69K, L89M, I93L

Table 5. Comparison of Exposure to Viral Replication Between Treatment Arms

Value (Figure 5)	Description	ABT-378/r Mean Value (n=51)	NFV Mean Value (n=96)	p-value
V1	Baseline HIV RNA (log_{10} copies/mL)	5.09	5.22	0.222
V2	HIV RNA value at the time of genotype (log_{10} copies/mL)	3.76	3.69	0.617
D2	Consecutive days since HIV RNA <400 copies/mL	138	162	0.206
D1+D2	Total days with HIV RNA >400 copies/mL	206	238	0.111
Area B	Viral load area under the curve (AUC) from nadir to time of genotype (days X log_{10} copies/mL)	833	902	0.387
Area A + Area B	Viral load AUC from baseline to time of genotype (days X log_{10} copies/mL)	1,108	1,131	0.767