

# A Randomized Trial of 1 or 2 Protease Inhibitors in Combination with a Non-Nucleoside Reverse Transcriptase Inhibitor and Background Therapy in Patients with Virologic Failure on an Initial Protease-Inhibitor Containing Regimen (CPCRA 057)

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## BACKGROUND

- CPCRA 057 was a multi-center randomized trial conducted between August 1998 and June 2000. This report describes the randomized comparison of open-label regimens containing 1 vs. 2 PIs in combination with 1 NNRTI and NRTI background therapy for patients with inadequate viral suppression on their first PI-containing regimen.
- CPCRA 057 also investigated a second research question (immediate versus deferred NNRTI use) in a separate cohort. These results will be submitted elsewhere.

## STUDY DESIGN

### Entry Criteria:

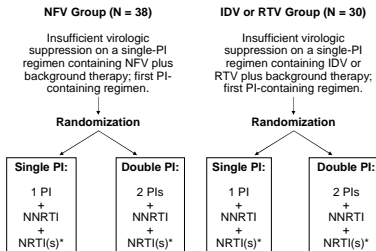
- On first PI-containing regimen for at least 16 weeks, single PI.
- Insufficient virologic suppression (> 400 cp/ml) after at least 16 weeks.
- No prior NNRTI experience.

Randomization was stratified by PI in failing regimen (NFV versus IDV or RTV), clinical unit, and whether viral load of <500 cp/ml had ever been achieved on the failing regimen (viral suppression (VS) stratum). Primary endpoint was percentage of patients with viral load > 10,000 cp/ml or death at Month 12.

All analyses are by intent-to-treat.

The study was designed to enroll 400 patients; due to slow accrual enrollment was stopped early (N=68).

Figure 1 – Study Design



\* May include NRTIs and/or other agents with anti-HIV activity (e.g. hydroxyurea, abefovir dipivoxil).

## BASELINE CHARACTERISTICS

- Between 10/98 and 3/00, 68 patients enrolled at 15 CPCRA units.
- In the 2 PI group, the following PI combinations were prescribed at randomization: RTV/SQV (400mg/800mg, 80%), RTV/IDV (400mg/400mg, 9%), SQV/NFV (1000mg/1250mg, 3%), Other (8%).
- In the 1 PI group, prescribed PIs included IDV (68%) and APV (21%) in the NFV group; and NFV (93%) or APV (7%) in the IDV or RTV group.
- The prescribed NNRTIs were EFV (88%) and NVP (12%).

Table 1 – Baseline Characteristics

	2 PI + NNRTI (N=35)	1 PI + NNRTI (N=33)
Age (mean)	41	42
Female	29%	27%
Race (% non-White)	66%	73%
Latino/Latina	17%	18%
African American	49%	54%
White	34%	27%
Male homosexual contact	37%	46%
History of injecting drug use	20%	15%
History of HIV disease progression	31%	30%
CD4 Count		
Mean ± S.D.	315 ± 190	319 ± 210
Median	255	267
Baseline HIV-RNA (log cp/mL)		
Mean ± S.D.	4.2 ± 0.7	4.1 ± 0.7
Median	4.2	4.1
Viral suppression (VS) stratum <sup>1</sup>	46%	54%
PI in failing regimen		
Nelfinavir	54%	58%
Indinavir	40%	39%
Ritonavir	6%	3%

<sup>1</sup>Ever achieved HIV RNA < 500 cp/mL on failing regimen

Table 2 – Selected Baseline Resistance Mutations

	2 PI + NNRTI (N=31)	1 PI + NNRTI (N=28)
PI Mutations		
30 N	7 (23%)	6 (21%)
46 I/L	5 (16%)	11 (39%)
48 V	0	0
82 A/F/T	4 (13%)	6 (21%)
84 V	0	1 (4%)
90 M	8 (26%)	10 (36%)
Any of the above	18 (58%)	20 (71%)
NRTI Mutations		
41 N	11 (36%)	12 (43%)
67 N	8 (26%)	5 (18%)
69 D	0	2 (7%)
70 R	7 (23%)	3 (11%)
184 V	27 (86%)	24 (86%)
215 F/Y	10 (32%)	16 (57%)
219 E/Q	4 (13%)	2 (7%)
Any of the above	28 (90%)	26 (93%)

## RESULTS

Figure 2 – Time to First Follow-up HIV RNA > 10,000 cp/mL or Death

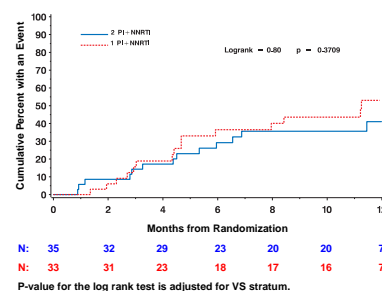
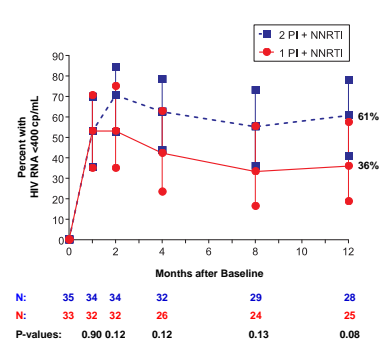
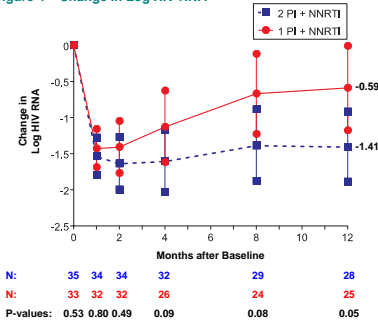


Figure 3 – Percent by Month with HIV RNA <400 cp/mL



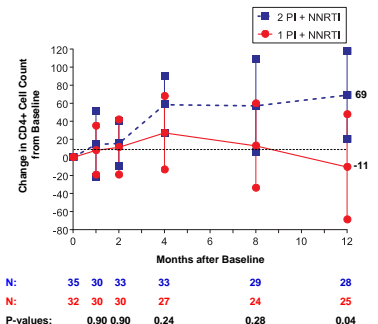
Tests are adjusted for PI in failing regimen (NFV versus IDV or RTV) and VS stratum. There is no adjustment for multiple comparisons.

Figure 4 – Change in Log HIV RNA



P-values are for pointwise t-tests adjusted for PI in failing regimen (NFV vs. IDV or RTV) and VS stratum. There is no adjustment for multiple comparisons.

Figure 5 – Change in CD4+ Cell Count



P-values are for pointwise t-tests adjusted for PI in failing regimen (NFV vs. IDV or RTV) and VS stratum. There is no adjustment for multiple comparisons.

## RESULTS

- There was no significant difference between the treatment groups for HIV-RNA >10,000 cp/ml or death at 12 months (primary endpoint, p=0.37, see Figure 2).
- There were no deaths or disease progression events by 12 months.
- Collectively, the data support a trend toward better virologic control and greater CD4+ cell increase in the 2 PI group compared to the 1 PI group.
- Subgroup analyses within the NFV and IDV or RTV groups showed similar CD4+ and HIV RNA trends as the pooled analysis, although differences in CD4+ and log HIV RNA were not statistically significant.
- There were 7 patients who experienced Grade 4 Adverse Events (3 in the 1 PI arm and 4 in the 2 PI arm). In the 2 PI arm these were pancreatitis, sepsis, hypertriglyceridemia, and elevated liver enzymes. In the 1 PI group, these were hypertriglyceridemia, mucosal fungal infection, and seizures.

## CONCLUSIONS

- In patients with virologic failure on their first PI, the NNRTI-containing salvage regimens with 2 PIs provided better virologic and immunologic responses than the regimens with 1 PI.
- In part, the improved virologic response in the 2 PI arm may have been due to the pharmacological boosting of the second PI with RTV in the presence of an NNRTI.
- However, RTV may also have acted as another potent drug in the 2 PI regimen since it was used at a dose of 400 mg twice daily.
- Suboptimal response in the 1 PI treatment group may be due to lack of pharmacological boosting or to preexisting resistance.

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