

PRELIMINARY RESULTS FROM INDINAVIR (IDV) AND RITONAVIR (RTV) IN A ONCE-DAILY REGIMEN (MERCK 103/104)

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INTRODUCTION

Previously reported pharmacokinetic (PK) studies have demonstrated a favorable IDV profile using IDV/RTV once-daily. Merck Protocol 089, a pharmacokinetic study in healthy volunteers, showed that a regimen of IDV/RTV 1200/100 once-daily resulted in a C_{max} 19.8 μM (90% CI 15.9, 24.6), AUC_{24h} 130.3 $\mu\text{M}\cdot\text{hr}$ (90% CI 108.8, 156.1), C_{min} 273 nM (90% CI 233, 320). The regimen IDV/RTV 1200/200 mg once-daily was selected to study its pharmacokinetic and anti-retroviral effects in patients with HIV infection. The indinavir IC_{95} in wild-type virus is 25 to 50 nM in the ViroLogic assay.

METHODS

This is an open-label, phase II, 48-week study of IDV/RTV 1200/200 once-daily with d4T + 3TC b.i.d. in treatment-naïve patients who have plasma viral load ≥ 5000 copies/mL and $CD4^+$ lymphocyte count ≥ 50 cells/mm³. Preliminary results from the first 24 weeks are presented.

Statistical Analysis

Proportions were analyzed by three approaches:

1. Observed data up to 24 weeks were analyzed.
2. GEE Model based analyses: the proportions of patients with virological responses (HIV RNA <400 and less than <50 copies/mL) at all time points are estimated simultaneously by the Generalized Estimating Equation method.
3. NC=F (Non-Completers Equal Failures).

In Methods 2 and 3, patients who discontinued prematurely due to an adverse experience or to either lack or loss of virological efficacy are treated as virological failures for all subsequent time points.

Changes in HIV RNA plasma concentrations and $CD4^+$ lymphocyte counts from baseline were analyzed by two methods:

- Observed data up to 24 weeks, and
- Mixed-effects model using restricted maximum likelihood (REML) estimator to estimate the change from baseline at each time point was used.

RESULTS

Table 1. Baseline characteristics of the population enrolled in the study (N=40)

Characteristic	Value	95% CI
Age, yrs	median	32
	(range)	(21 - 46)
Gender	Male	52.5%
	Race	
	White	60%
	African-American	25%
	Other	15%
CD4 ⁺ lymphocyte count cells/mm ³	median	329
	(range)	(38 - 964)
HIV RNA log ₁₀ copies/mL	median	4.91
	(range)	(3.54 - 6.53)
	mean	4.84
	(std dev)	(0.60)

Table 2. Patient accounting

Number of patients enrolled	40
Discontinuations	8
Reasons	
- Lost to follow-up	5
- Patient withdrew	1
- Patient non-adherence	1
- Other	1

Table 3. Percentage of Patients with HIV RNA suppression by method of analysis at Week 24

Results at Week 24	RNA (Amplicor) Below 400 copies/mL				RNA (Ultrasensitive) Below 50 copies/mL			
	N	n	%	95% CI	N	n	%	95% CI
Observed Data	32	28	87.5	(76.0, 99.0)	32	21	65.6	(49.2, 82.1)
GEE Model-based	--	--	85.4	(69.9, 93.6)	--	--	64.8	(47.4, 78.9)
NonCompleter = Failure	--	--	71.8	(57.7, 85.9)	--	--	53.8	(38.2, 69.5)

N = Number of patients with viral RNA measurements.
n = Number of patients with viral RNA below limit.

Figure 1. Proportions (95% CI) of patients with HIV RNA <400 copies/mL over time using the Amplicor Standard Assay

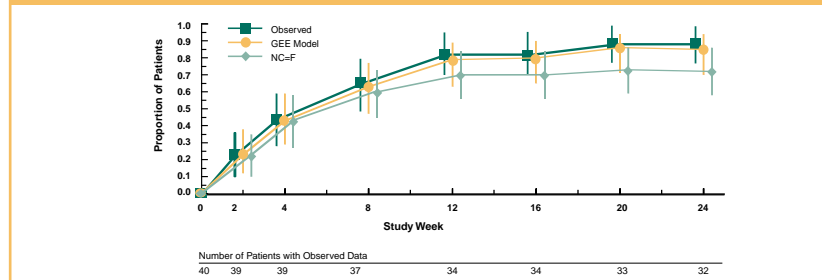


Figure 2. Proportions (95% CI) of Patients with HIV RNA <50 copies/mL over time using the Ultrasensitive Amplicor Assay

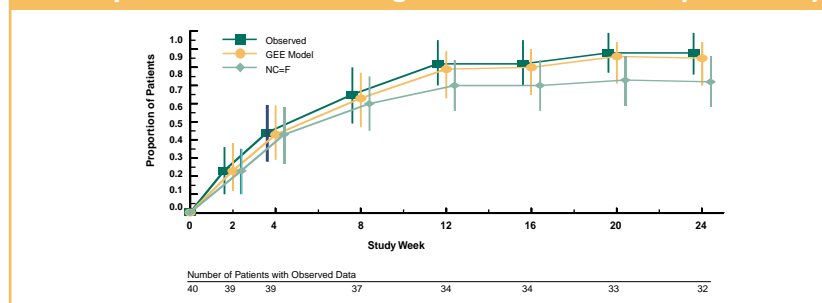
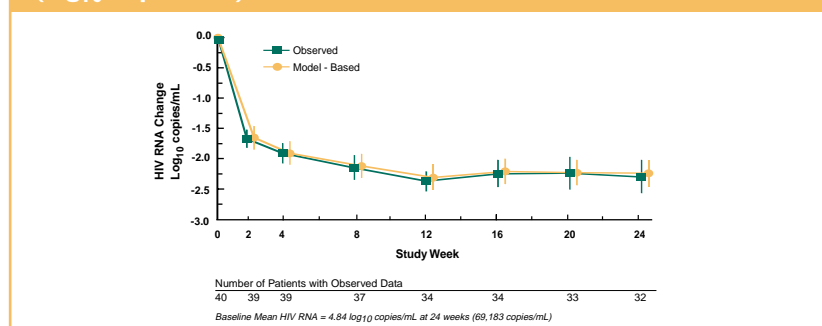
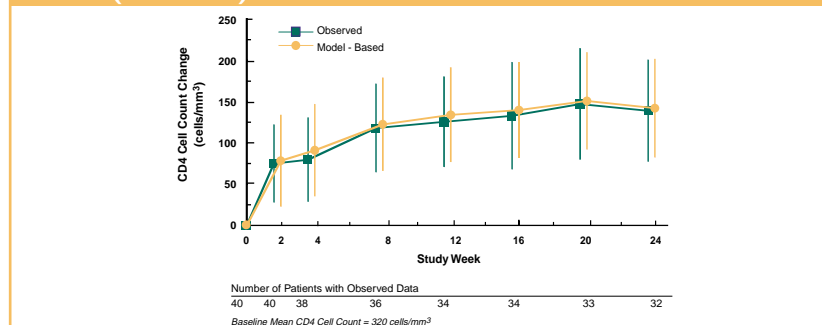


Figure 3. Mean (95% CI) change from baseline in HIV RNA (log₁₀ copies/mL) over time



The observed mean HIV RNA was 2.54 log₁₀ copies/mL at 24 weeks (SD 0.65 log₁₀).

Figure 4. Mean (95% CI) change from baseline in CD4 cell count (cells/mm³) over time

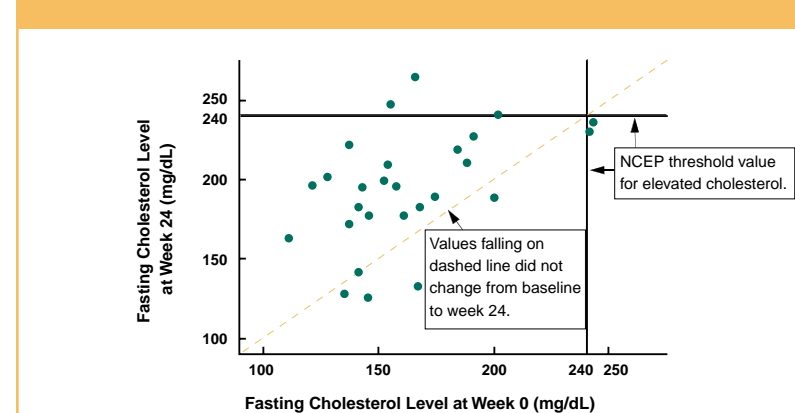


The observed mean CD4⁺ lymphocyte count at 24 weeks was 450 cells/mm³ (SD 208).

Table 4. The pharmacokinetic profile of IDV/RTV 1200/200 mg once-daily from 9 patients showing geometric means (90% CI)

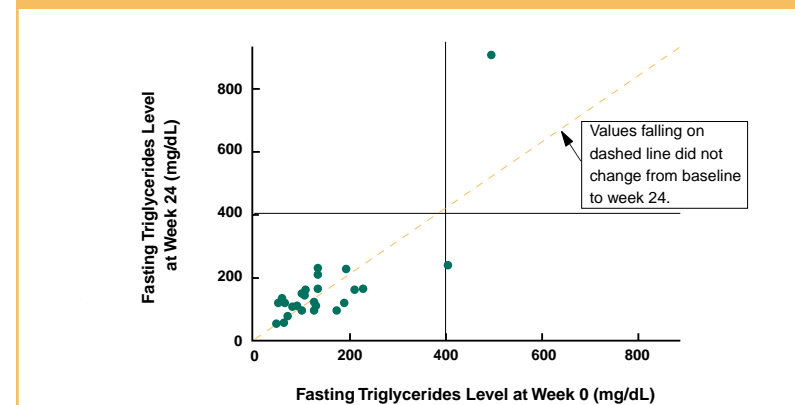
C_{max}	17.9 μM (16.2, 19.8)
AUC_{24h}	116 $\mu\text{M}\cdot\text{hr}$ (102, 131)
C_{24h}	156 nM (84, 292)

Figure 5. Change in serum cholesterol from baseline to Week 24



There were 27 patients who had both baseline and Week 24 fasting serum cholesterol data. The range of the change from baseline is [-35, 99] and the median change is 35 mg/dL. Values falling on the diagonal have a zero difference over the 24 week period. The National Cholesterol Education Program (NCEP) has set 240 mg/dL as the threshold value for elevated cholesterol.

Figure 6. Change in serum triglycerides from baseline to Week 24



There were 27 patients who had both baseline and Week 24 fasting serum triglycerides data. The range of the change from baseline is [-165, 404] and the median change is 14 mg/dL. Fasting serum triglycerides above 400 mg/dL are generally considered to be elevated.

Table 5. Adverse Experiences

Number of patients with:

Serious Adverse Experiences (AEs)	1
Serious drug-related AEs	0
Grade 2 or 3 AEs	16
Grade 2 or 3 drug-related AEs	6
Nephrolithiasis-related AEs	1

The serious adverse event was pneumonia (with fever and dyspnea) that resulted in hospitalization. The investigator felt the serious adverse event was definitely not related to study drug therapy.

Grade 2 drug-related AEs were alopecia (5 occurrences), nausea (2 occurrences), and fever (1 occurrence). The Grade 3 drug-related AE was gastric pain (1 occurrence).

The nephrolithiasis-related AE was renal colic. The patient did not have hematuria during the episode. A stone was not identified.

CONCLUSIONS

IDV/RTV 1200/200 mg once-daily in combination with d4T and 3TC, had both HIV RNA suppression and $CD4^+$ lymphocyte increases that were generally similar to historical data with indinavir standard therapy at Week 24.

The IDV/RTV/d4T/3TC combination was generally well-tolerated. One case of nephrolithiasis and modest increases in lipids were observed at 24 weeks.

Patients continue to be followed to assess longer term safety and durability.

A new arm of patients using IDV/RTV 1200/400 mg once-daily is being recruited to study further enhancement of the IDV pharmacokinetic profile and potential tolerability differences from the IDV/RTV 1200/200 arm.