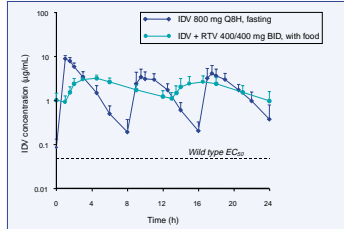


Norvir-Indinavir Combination Evaluation THE NICE STUDY

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Background

Effect of Norvir (RTV) on Indinavir (IDV) PK Profile in HIV-Negative Volunteers



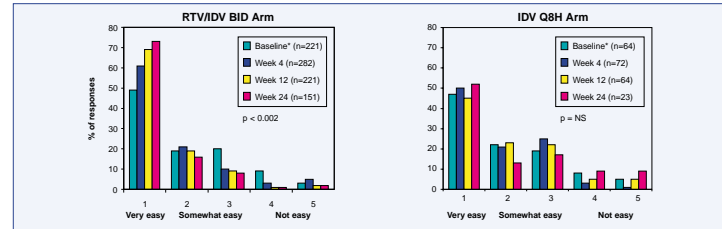
Hsu et al. Indinavir can be Taken with Regular Meals when administered with ritonavir. 12th World Conference on AIDS, Geneva, Switzerland, June, 1998.

Effect of RTV on IDV Pharmacokinetics

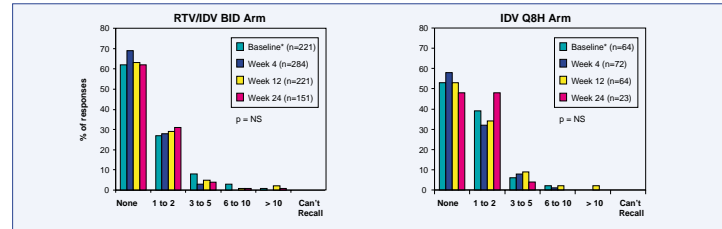
IDV Pharmacokinetics (relative to 800 mg Q8H)				
RTV Dose	IDV Dose	C _{min}	C _{max}	AUC
400	400	↑	↓	=
200	600	↑	=	↑
100	800	↑	↑	↑

Saah et al. Multiple-dose Pharmacokinetics (PK) and Tolerability of Indinavir (IDV) Ritonavir (RTV) Combination in Healthy Volunteers. 6th Conference on Retroviruses and Opportunistic Infections, Chicago, February 1999.

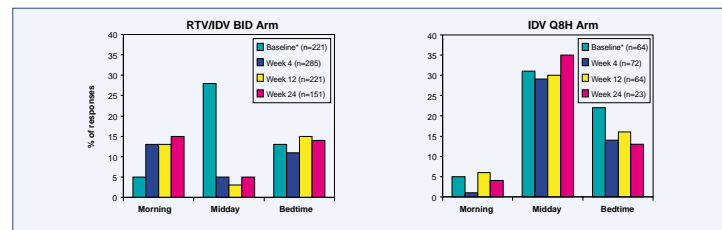
Question 1: In the past two weeks, on a scale of 1 to 5, how easy has it been for you to take your protease inhibitor medicine as prescribed?



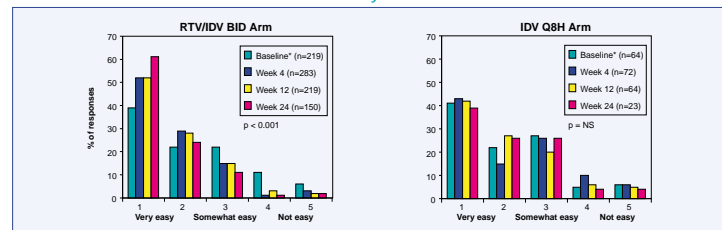
Question 2: In the past two weeks, how many times do you think you missed taking your protease inhibitor medication?



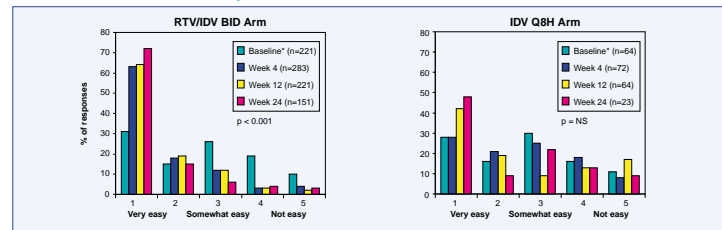
Question 3: In the past two weeks when did you miss at least one dose of your protease inhibitor medication? (check all that apply)



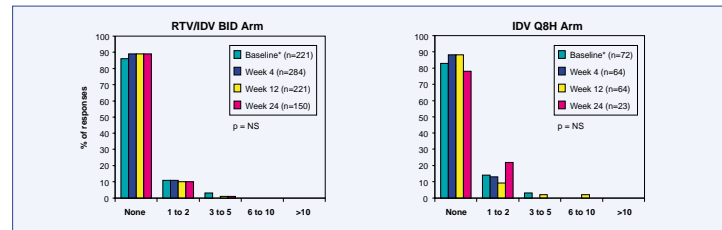
Question 4: In the past two weeks, on a scale of 1 to 5, how easy has it been for you to take your protease inhibitor doses about the same time each day?



Question 5: In the past two weeks, on a scale of 1 to 5, how easy has it been for you to schedule your protease inhibitor medicine and your meals?



Question 6: In your view, how many times do you think it is OK to miss taking your protease inhibitor medication in a two-week period?



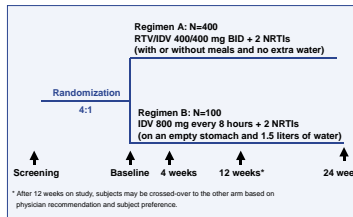
Study Description

- Multicenter, randomized, controlled, open-label study
- Primary Objective:
 - Evaluate the medication taking habits and preference of study subjects for RTV/IDV BID regimen compared with IDV Q8H
- Entry Criteria:
 - >18 years of age
 - HIV-positive subjects currently receiving triple therapy with IDV 800 mg Q8H + 2 NRTIs
 - HIV RNA < Lower limit of quantitation using an assay performed at a local laboratory

RTV Dose Escalation

- 200 mg BID for 2 days
- 300 mg BID for 3 days
- 400 mg BID thereafter
- This escalation schedule can be increased to 10 days to improve tolerability
- Dosing with food may improve tolerability
- Telephone contact from study site to each subject prior to initiating regimen to review correct dosing and escalation schedule

Study Design



Methods

- Analyses presented are based on data entered as of December 13, 2000
- For the analyses of MTS-6
 - Baseline presents subjects with Week 12 data, which is similar to baseline for all randomized subjects
 - For the most conservative analysis, the maximum p-value for the RTV/IDV arm and minimum p-value for the IDV arm observed at all timepoints are presented

Subject Disposition ITT Analysis

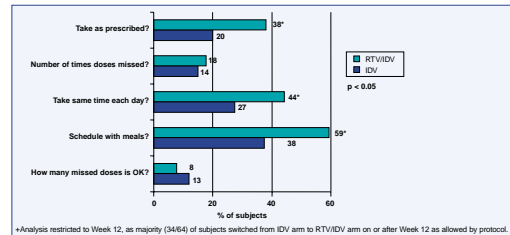
	RTV/IDV	IDV
Subjects randomized*	345	84
Discontinuations – total	121 (35%)	26 (31%)
Discontinuations due to adverse events	75 (22%)	10 (12%)
Serious adverse events	14 (4%)	2 (2%)
Subjects who switched regimens on or after 12 weeks	9	34

Baseline Data All Subjects

	RTV/IDV	IDV
Total (N)*	332	83
Gender (%)		
Male	92	84
Female	8	16
Race (%)		
African-American	16	24
Caucasian	67	61
Other	17	15
Age (yrs)		
Mean	42	41
Range	21-66	24-59
CD ₄ Count (cells/μL)		
Mean	571	544
Range	20-1913	40-1320

*Missing demographic data = 14

Percentage of Subjects Showing MTS-6 Improvement from Baseline to Week 12*



Medication Regimen Preference Survey

Randomization Arm	Prefers RTV/IDV	Prefers IDV	No Preference
RTV/IDV	87% ¹	7% ²	6%
IDV	57% ³	29% ⁴	14%

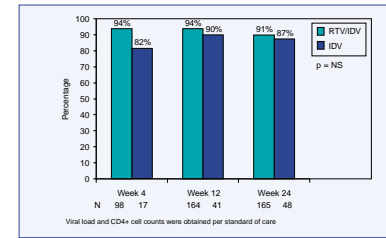
¹96% (182/190) of the RTV/IDV subjects who preferred RTV/IDV did so for convenience.
²80% (15/19) of the RTV/IDV subjects who preferred IDV did so for tolerability.
³97% (20/20) of the IDV subjects who preferred RTV/IDV did so for convenience.
⁴72% (13/18) of the IDV subjects who preferred IDV did so for tolerability.

Medication Regimen Preference Survey

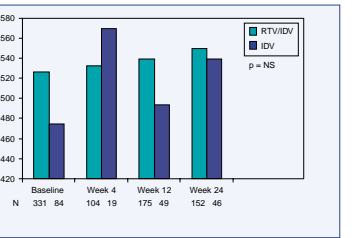
Randomization Arm	Prefers RTV/IDV	Prefers IDV	No Preference
RTV/IDV	86% ¹	6% ²	8%
IDV	62% ³	25% ⁴	13%

¹93% (175/188) of the physicians (of RTV/IDV subjects) who preferred RTV/IDV did so for tolerability.
²80% (10/12) of the physicians (of RTV/IDV subjects) who preferred IDV did so for efficacy.
³90% (37/41) of the physicians (of IDV subjects) who preferred RTV/IDV did so for convenience.
⁴63% (10/16) of the physicians (of IDV subjects) who preferred IDV did so for efficacy.

Proportion of Subjects with HIV RNA Load <400 copies/mL



Median CD4+ Cell Count (cells/mm³)



Grade 3/4 Lipid Toxicities

Laboratory Parameter	RTV/IDV (n=228)	IDV (n=61)	p Value
Fasting Triglycerides (>750 mg/dL)	27 (12%)	2 (3%)	p = 0.054
Cholesterol (>300 mg/dL)	51 (22%)	8 (13%)	p = 0.152

Results

- 87% of the subjects randomized to RTV/IDV 400/400 mg BID and 57% of the subjects randomized to IDV 800 mg Q8H preferred RTV/IDV BID regimen. Convenience was cited as the most frequent (96%) reason.
- Subjects randomized to RTV/IDV reported improvement from baseline in:
 - Ease of taking their protease inhibitor as prescribed; and
 - Ease with scheduling their protease inhibitor medication and meals.
- Overall compliance was similar between the RTV/IDV and IDV arms; however, 30% of subjects on IDV continued to miss their midday dose, over the six month observation period.
- A higher proportion of subjects randomized to RTV/IDV had viral load <400 copies/mL compared to those on IDV at Week 24 (92% vs. 88%), however this did not reach statistical significance.
- A higher proportion of subjects randomized to the RTV/IDV arm had increased triglycerides/cholesterol values.
- One case of nephrolithiasis was observed in the IDV Q8H arm during the follow-up period.
- Premature discontinuations for adverse events were more frequent (22%) in the RTV/IDV arm compared to the IDV arm (12%); however, subjects who remained on RTV/IDV preferred this regimen for improved adherence and convenience.
- These results suggest that it is safe to switch virologically suppressed subjects from IDV 800 mg Q8H to RTV/IDV 400/400 mg BID. Moreover, improvements in convenience, adherence and compliance may be observed.

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