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Introduction

- IDV/RTV 800/100mg used BID instead of IDV 800mg TID removes the need for dietary restriction and provides a PK profile that may lead to greater efficacy and reduced toxicity.
- Despite clinical use of IDV/RTV bid there is limited data on its efficacy, safety and tolerability

Objectives

- Primary**
- To compare the efficacy of the two drug regimens with respect to HIV-1 viral load response
- Secondary**
- To compare the efficacy of the two drug regimens with respect to CD4+ T cell response
 - To compare the two drug regimens with respect to safety and tolerability

Methods

- A randomised, open label clinical trial
- Patients were randomised to receive either indinavir 800mg TID or indinavir/ritonavir 800/100mg BID in combination with AZT 300mg/3TC 150mg BID. All patients must have received at least 3 months of AZT prior to entry. Ritonavir liquid was used in the study until capsules became available 6 months after study commencement.
- HIV RNA was quantified to 50 copies/ml (Chiron bDNA assay v3)
- Analysis (Mann-Whitney, Student's t, Chi-square and Fischer's exact tests) is by intention to treat ('missing = failure' [m=f] for dichotomous variables and a 'last observation carried forward' [LOCF] imputation for continuous variables)

Results

- 106 patients enrolled of whom 104 started treatment (54 tid arm; 50 bid arm).
- The baseline characteristics were well matched. The lower CD4 count and higher incidence of CDC class C events in the TID arm did not differ significantly from the BID arm (table 1).
- Median overall duration of therapy prior to study entry was 29 months. All patients had been exposed to AZT (most commonly at a dose of 200mg BID) in combination with either ddl or ddC as dual therapy. 39% of patients had been treated with AZT monotherapy.

Results

- Median log₁₀ HIV RNA (IQR) at entry was 4.0 (3.3-4.5). Median CD4+ count (IQR) was 168 (40-319).
- At Week 112 no significant differences were found in:
 - Decrease of log₁₀HIV-RNA (-1.63 logs TID, -1.41 logs BID; p=0.28) (figure 1).
 - Mean CD4 count rise from baseline (140 cells/mm³ TID, 92 cells/mm³ BID; p=0.19) (figure 2).
 - Percentage of patients with VL < 50 copies (59% TID, 64% BID; p=0.86) (figure 3).
- Permanent study discontinuation data is presented in table 2.
- Drug interruption and dose reduction data is presented in table 3.
- Grade 3 and 4 adverse event data is presented in table 4.
- Laboratory adverse event data is presented in table 5.
- Clinical nephrolithiasis data is presented in table 6.

Table 1. Baseline characteristics

	IDV/AZT/3TC TID (n=54)	IDV/RTV/AZT/3TC BID (n=50)
Sex n (%)		
Male	35 (65)	32 (64)
Female	19 (35)	18 (36)
Age (years)		
Mean (SD)	34.9 (6.1)	35.4 (6.2)
Body Weight (kg)		
Mean (SD)	58.0 (10.3)	59.3 (10.0)
N (%) > 60kg	22 (40.7)	21 (42)
CD4 cells/mm³		
Median (IQR)	143 (33-324)	191 (53-312)
HIV-1 RNA (log₁₀ c/ml)		
Median (IQR)	4.2 (3.4-4.4)	4.0 (3.2-4.4)
CDC n (%)		
A	15 (28)	10(20)
B	23 (42)	31 (62)
C	16 (30)	9 (18)
Risk Group n (%)		
Heterosexual	45 (83)	43 (86)
Homosexual	8 (15)	7 (14)
IDU	1 (2)	1 (0)

Figure 1. Mean log₁₀ HIV-RNA change from baseline ITT analysis (LOCF)

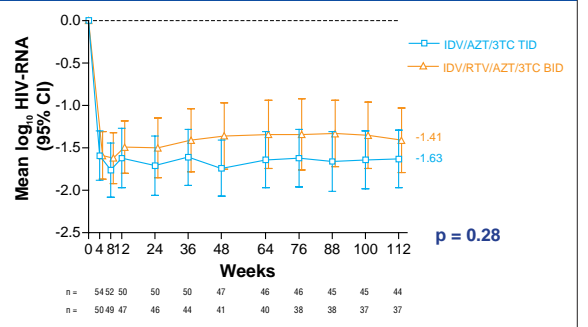


Figure 2. Mean CD4+ increase from baseline ITT analysis (LOCF)

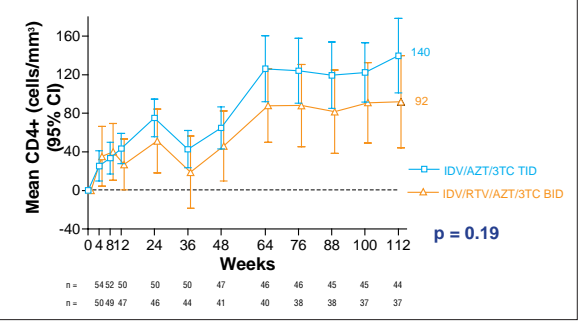


Figure 3. Percentage of patients with HIV-RNA <50 copies/ml ITT analysis (m = f)

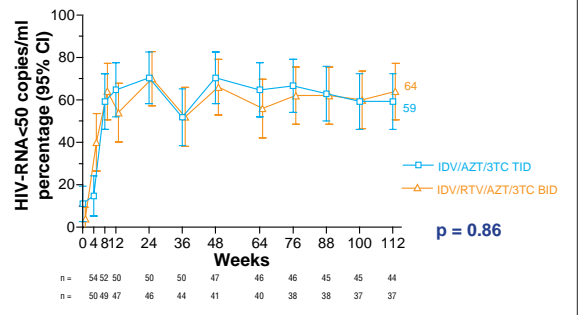


Table 2. Permanent discontinuations from study medication

	IDV/AZT/3TC TID (n=54)	IDV/RTV/AZT/3TC BID (n=50)	p-value
Death n (%)	2 (4)	1 (2)	>0.1
Drug intolerance n (%)	4 (7)	3 (6)	>0.1
Patient choice n (%)	2 (4)	0	>0.1
Investigator choice n (%)	1 (2)	0	>0.1
Non compliance n (%)	1 (2)	2 (4)	>0.1
Lost to follow up n (%)	3 (6)	4 (8)	>0.1
Total patients n (%)	13 (24)	10 (20)	>0.1

Table 3. Drug interruptions and dose reductions from study medication

	IDV/AZT/3TC TID (n=54)	IDV/RTV/AZT/3TC BID (n=50)	p-value
GI intolerance n (%)	7 (13)	12 (24)	> 0.1
Myelotoxicity n (%)	4 (7)	6 (12)	> 0.1
Clinical nephrolithiasis n (%)	3 (6)	3 (6)	> 0.1
CNS Intolerance n (%)	0	1 (2)	> 0.1
Allergic Reaction n (%)	4 (7)	3 (6)	> 0.1
Intercurrent illness/hospitalization n (%)	5 (9)	2 (4)	> 0.1
Hyperbilirubinaemia n (%)	0	2 (4)	> 0.1
Non compliance with protocol n (%)	1 (2)	5 (10)	> 0.1
Total patients n (%)	17 (31)	24 (48)	> 0.1

Table 4. Grade 3 and 4 adverse events at least possibly related to study medication

	IDV/AZT/3TC TID (n=54)	IDV/RTV/AZT/3TC BID (n=50)	p-value
Hyperbilirubinemia n (%)	15 (28)	20 (40)	> 0.1
Anemia n (%)	2 (4)	4 (8)	> 0.1
Elevated triglycerides n (%)	-	4 (8)	> 0.1
Allergic reaction n (%)	1 (2)	2 (4)	> 0.1
Neutropenia n (%)	1 (2)	1 (2)	> 0.1
Diarrhea n (%)	1 (2)	1 (2)	> 0.1
Eosinophilia n (%)	1 (2)	-	> 0.1
Fever n (%)	-	1 (2)	> 0.1
Fatigue n (%)	-	1 (2)	> 0.1
Headache n (%)	-	1 (2)	> 0.1
Total patients n (%)	20 (37)	28 (56)	> 0.1

Table 5. Laboratory adverse events

	IDV/AZT/3TC TID (n=54)	IDV/RTV/AZT/3TC BID (n=50)	p-value
Total bilirubin > 1.0 mg/dl n (%)	47 (87%)	45 (90%)	>0.1
Creatinine > 1.4 mg/dl n (%)	18 (33%)	20 (40%)	>0.1
SGPT > 120 u/l n (%)	3 (6%)	2 (4%)	>0.1
Glucose > 110 mg/dl n (%)	12 (22%)	12 (24%)	>0.1
Triglycerides > 400 mg/dl n (%)	5 (9%)	14 (28%)	0.03
Total Cholesterol >240 mg/dl n (%)	10 (19%)	29 (58%)	<0.01

Table 6. Clinical nephrolithiasis

	IDV/AZT/3TC TID (n=54)	IDV/RTV/AZT/3TC BID (n=50)	p-value
Back pain +/- haematuria n (%)	5 (9)	10 (20)	>0.1
Renal calculus n (%)	4 (7)	2 (4)	>0.1
Macroscopic haematuria +/- dysuria n (%)	1 (2)	3 (6)	>0.1
Total patients n (%)	10 (19)	15 (30)	>0.1

Conclusions

- Patients in both arms responded well to therapy despite past nucleoside exposure
- No statistically significant difference in virological or immunological response between TID and BID arms.
- Trends towards more drug interruptions, dose reductions and adverse events in the BID arm.
- Clinical nephrolithiasis and nephrotoxicity observed in both arms with a trend towards more events in the BID arm.
- Lipid levels in the BID arm were significantly raised compared to TID dosing.

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