8th International Congress on Drug Therapy in HIV Infection Glasgow 2006

Comparison of single and boosted-protease-inhibitor versus non-nucleoside reverse transcriptase inhibitor containing cART regimens in antiretroviral naïve patients starting cART after 1/1/2000

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Members of the study group are listed in the appendix

BACKGROUND

- Current treatment recommendations for HIV-1-infection suggests first line therapy based on a single or ritonavir-boosted PI-regimen, or alternatively with a NNRTI-based regimen.
- Results from clinical trials comparing these strategies tend to be based on the short term virologic response (i.e. 24 or 48 weeks) and have provided conflicting results.
- Results from observational studies have suggested that a single PI-based regimen may have a poorer short-term virological outcome.
- It is crucial to consider not only 24 or 48 week response, but also longer-term virologic or immunologic response.
- Few published studies have considered the long-term immunologic response, despite this being one of the best markers for clinical disease progression.

OBJECTIVES

- To compare both the short-term and long-term virologic and immunologic response to cART in previously ART naïve patients according to the regimen.
- To describe treatment discontinuation rates among patients starting cART for the first time.

METHODS

- EuroSIDA is a prospective observational cohort study of › 11.000 HIV-patients from 90 clinics in 30 European countries, Israel and Argentina.
- All treatment-naïve patients who started cART after 1/1/00 [cART: 2 NRTIs + i) one PI, ii) a boosted PI (i.e. ritonavir boosted) or iii) an NNRTI].
- Patients with a CD4 count and VL prior to starting cART were included in these analyses.
- Patients with no follow-up after starting cART were excluded.
- All analyses used forward selection with entry criterion p‹0.1 to identify variables associated with each of the outcomes.
- Model selection was confirmed using backward selection. CD4 count nadir, CD4 and VL at starting cART, age, prior AIDS diagnosis, region of Europe, year of starting cART, exposure group, HBV and HCV status, gender and origin were included as potential explanatory variables in all analyses.

ANALYSES

- *A1 (n=827)* Logistic regression to determine odds of starting a PI-regimen (single or boosted).
- *A2 (n=827)* Time to discontinuation of initial cART regimen according to initial cART regimen (FU from date of starting cART to discontinuation or last FU).
- *A3 (n=789 [‹500 copies/ml])* Time to virologic response (VL‹500) according to the cART regimens (FU to first VL‹500, or until last VL).
- *A4 (n=827)* Time to immunologic response (a 100/mm³ increase in CD4 count) (FU to first CD4 ≥ 100/mm³ above baseline, or until last CD4).
- A2-A4: Kaplan-Meier estimates and Cox models, stratified by centre .
- *A5 (n=558)* Odds of a lack of virologic response (VL‹500 copies/ml) or immunologic response (›200/ mm³ increases in CD4 cells) at 3 years after starting cART was determined using logistic regression. VL and CD4 count closest to yr3 was determined, and patients were categorised as virologic or imunologic success, or not (no measurement equal failure). Patients without the potential for at least 3 years FU were excluded (n=269).

RESULTS

- Patient characteristics are listed in **table 1.** Two factors were independently associated with the odds of starting a PI-based regimen compared to starting an NNRTI-based regimen: *Region:* OR (North v. other regions)=0.45 (0.30–0.66), p‹0.0001, and *Nadir CD4:* OR (per doubling of CD4 nadir)=0.71 (0.64–0.66), p‹0.0001.
- In total, 408 patients (49.3%) discontinued their initial cART regimen. There was a significant difference in the time to discontinuation between the 3 treatment groups (p‹0.0001, log-rank test). At 12 months after starting cART, 32.0% of those taking a single-PI regimen were estimated to have discontinued this regimen (95% CI 25.1-38.9%), compared to 27.9% of patients taking a boosted-PI regimen (95% CI 21.5-34.3%) and 20.8% in patients taking the NNRTI-regimen (95% CI 17.0-24.6%). In an adjusted Cox model, the following parameters were independently associated with risk of discontinuing the initial cART regimen: *regimen:* RH for single-PI v. NNRTI: 1.83 (1.37–2.43), p‹0.0001, and RH for boosted-PI v. NNRTI: 1.50 (1.12–2.02), p=0.0071, *intravenous drug use:* RH (IVDU v others) =1.58 (1.14–2.19), p=0.0055, and *gender:* RH (female v. male)=1.37 (1.08–1.74), p=0.0092.
- Median time to virologic and immunologic response as well as relative hazards for short-term outcomes are listed in **table 2.**
- Finally, results of logistic regression models of lack of virologic and immunologic response after 3 years are shown in **figure 1.**

SUMMARY AND DISCUSSION

- This study included more than 800 ART naïve patients who started cART after January 2000.
- Compared to patients starting a NNRTI-cART regimen,
  - patients starting a *single* PI-cART regimen were less likely to achieve virologic suppression and were more likely not to have a VL‹ 500 cp/ml at 3 years after starting cART.
- Compared to patients starting a NNRTI-cART regimen,
  - patients starting a *boosted* PI-regimen had similar short and long-term virologic responses. They were more likely to achieve a short-term immunologic response, whereas there were no significant differences in risk of not achieving an increase of at least 200 CD4 cells/mm³ after 3 years.
- These results should be interpreted with caution because of the potential biases associated with observational studies.
- But, it is reassuring to see that the results from an observational setting are consistent with those from INITIO, a randomised trial.
- Ultimately, clinical outcomes, such as new AIDS diagnoses or death, will be the measure of the efficacy of cART regimens, which requires the follow-up of a very large number of patients over many years.

Table 1

Characteristics of the patients at initiation of cART

		Single PI		Boosted PI		NNRTI		
		N	%	N	%	N	%	p-value
All		183	22.1	197	23.8	447	54.1	-
Gender	Male	131	71.6	140	71.1	296	66.2	0.29
	Female	52	28.4	57	28.9	151	33.8	
Race	White	167	91.3	171	86.8	399	89.3	0.37
	Other	16	8.7	26	13.2	48	10.7	
Exposure group	Homosexual	58	31.7	78	39.6	152	34.0	0.44
	IDU	40	21.9	40	20.3	86	19.2	
	Heterosexual	73	39.9	62	31.5	178	39.8	
	Other	12	6.6	17	8.6	31	6.9	
Region	South/ Argentina	48	26.2	58	29.4	116	26.0	<0.0001
	Central	19	10.4	30	15.2	61	13.6	
	North	14	7.7	33	16.8	100	22.4	
	East	102	55.7	76	38.6	170	38.0	
Prior Hepatitis C Status	AIDS	53	29.0	49	24.9	69	15.4	0.0002
	Negative	78	42.6	103	52.3	243	54.4	0.11
	Positive	42	23.0	36	18.3	77	17.2	
	Unknown	63	34.4	58	29.4	127	28.4	
Hepatitis B Status	Negative	89	48.6	111	56.3	218	48.8	0.41
	Positive	6	3.3	8	4.1	18	4.0	
	Unknown	88	48.1	78	39.6	211	47.2	
		Median	IQR	Median	IQR	Median	IQR	
CD4 nadir		180 146	73 – 318 59 – 274	140 125	50 – 252 50 – 236	230 210	141 - 356 136 – 305	<0.0001 <0.0001
Viral load		4.99	4.39 – 5.65	5.05	4.66 – 5.60	4.89	4.37 – 5.31	0.0050
Age		35.5	29.3 – 42.7	37.6	30.4 – 45.3	36.8	30.0 – 44.4	0.35
Date of started cART		06-01	9/00 – 1/03	03-02	5/01 – 8/03	11-01	3/01 – 3/03	<0.0001

PI; protease inhibitor. NNRTI; non-nucleoside reverse transcriptase inhibitor. IDU; intravenous drug use reported as probably route of transmission.

Table 2

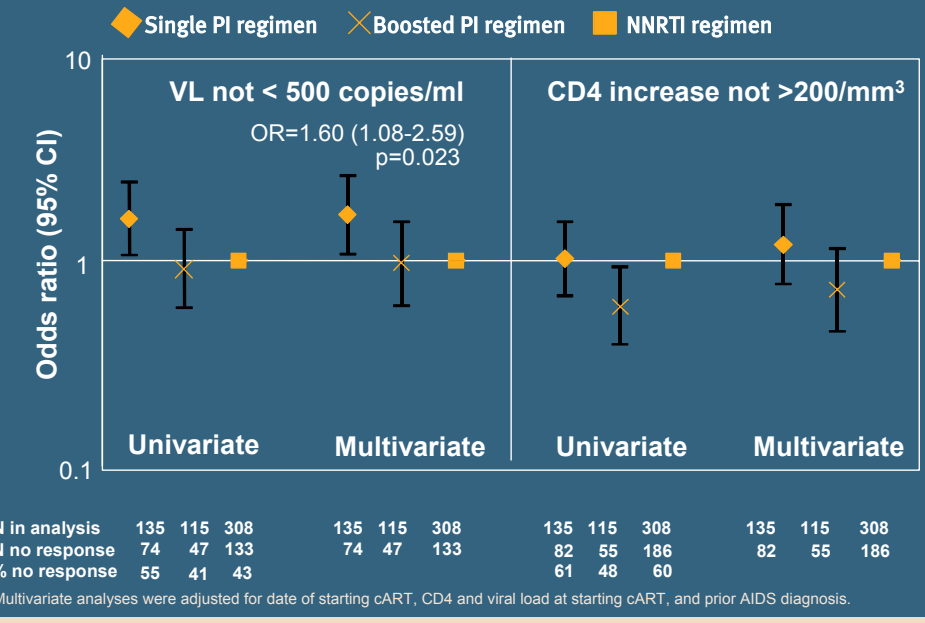
Short term virologic or immunologic response to cART regimens

		Median time to response (months)			Univariate Relative Hazard of Outcome			Multivariate Relative Hazard of Outcome		
		Median	95% CI	P	RH	95% CI	p-value	RH	95% CI	p-value
Virologic response										
VL < 500 copies/ml[1]	Single PI	5.3	4.0 – 6.3	-	0.67	0.54 – 0.84	0.0005	0.74	0.59 – 0.92	0.0081
	Boosted PI	3.0	3.0 – 3.7	-	1.03	0.84 – 1.28	0.75	1.04	0.84 – 1.29	0.72
	NNRTI	3.2	3.0 – 3.9	<0.0001	1.00	-	-	1.00	-	-
VL < 50 copies/ml[2]	Single PI	5.7	3.3 – 8.0	-	0.69	0.42 – 1.13	0.14	0.63	0.38 – 1.04	0.065
	Boosted PI	4.5	3.4 – 6.2	-	0.83	0.56 – 1.25	0.38	0.87	0.57 – 1.31	0.49
	NNRTI	4.0	3.8 – 4.9	0.11	1.00	-	-	1.00	-	-
Immunologic response										
CD4 increase >100/mm³[3]	Single PI	7.0	5.9 – 9.0	-	0.90	0.74 – 1.15	0.49	0.93	0.74 – 1.17	0.53
	Boosted PI	5.9	4.1 – 6.4	-	1.32	1.07 – 1.63	0.011	1.30	1.05 – 1.62	0.017
	NNRTI	7.0	6.0 – 8.0	0.019	1.00	-	-	1.00	-	-
CD4 increase >200/mm³[4]	Single PI	15.0	13.4 – 18.1	-	0.90	0.71 – 1.16	0.43	0.91	0.71 – 1.17	0.47
	Boosted PI	12.2	10.5 – 14.0	-	1.13	0.90 – 1.42	0.30	1.12	0.88 – 1.42	0.35
	NNRTI	15.9	14.0 – 18.2	0.054	1.00	-	-	1.00	-	-

CI; confidence interval. RH; relative hazard. Multivariable model adjusted for: [1]viral load at date of starting cART, date started cART, gender, race and hepatitis C status; [2]viral load and race; [3]date started cART, CD4, viral load and CD4 nadir a starting cART and prior AIDS diagnosis; [4]viral load, CD4, and CD4 nadir at starting cART, age and date of starting cART

Figure 3

Univariate and multivariate odds of lack of virologic or immunologic response at 3 years after starting cART



N in analysis	135	115	308	135	115	308	135	115	308	135	115	308
N no response	74	47	133	74	47	133	82	55	186	82	55	186
% no response	55	41	43				61	48	60			

Multivariate analyses were adjusted for date of starting cART, CD4 and viral load at starting cART, and prior AIDS diagnosis.

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