Comparison of Single and Boosted Protease Inhibitor Versus Nonnucleoside Reverse Transcriptase Inhibitor–Containing cART Regimens in Antiretroviral-Naïve Patients Starting cART After January 1, 2000

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Background: Few published studies have considered both the short- and long-term virologic or immunologic response to combination antiretroviral therapy (cART) and the impact of different cART strategies. **Purpose:** To compare time to initial virologic (<500 copies/mL) or immunologic (>200/mm^3 cell increase) response in antiretroviral-naïve patients starting either a single protease inhibitor (PI; n = 183), a ritonavir-boosted PI regimen (n = 197), or a nonnucleoside reverse transcriptase inhibitor (NNRTI)–based cART regimen (n = 447) after January 1, 2000, and the odds of lack of virologic or immunologic response at 3 years after starting cART. **Method:** Cox proportional hazards models and logistic regression. **Results:** After adjustment, compared to patients taking an NNRTI-regimen, patients taking a single-PI regimen were significantly less likely to achieve a viral load (VL) <500 copies/mL (relative hazard [RH] 0.74, 95% CI 0.54–0.84, p = .0005); there was no difference between the boosted-PI regimen and the NNRTI regimen (p = .72). There were no differences between regimens in the risk of >200/mm^3 CD4 cell increase after starting cART (p > .3). At 3 years after starting cART, patients taking a single-PI–based regimen were more likely to not have virologic suppression (<500 copies/mL; odds ratio [OR] 1.60, 95% CI 1.06–2.40, p = .024), while there were no differences in the odds of having an immunologic response (>200/mm^3 increase; p > .15). This model was adjusted for CD4 and VL at starting cART, age, prior AIDS diagnosis, year of starting cART, and region of Europe. **Conclusion:** Compared to patients starting an NNRTI-based regimen, patients starting a single-PI regimen were less likely to be virologically suppressed at 3 years after starting cART. These results should be interpreted with caution, because of the potential biases associated with observational studies. Ultimately, clinical outcomes, such as new AIDS diagnoses or deaths, will be the measure of efficacy of cART regimens, which requires the follow-up of a very large number of patients over many years. **Key words:** *combination therapy, immunologic success, virologic success*

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Current recommendations for the treatment of antiretroviral-naïve patients with HIV suggest first-line therapy should be based on treatment with a single or ritonavir-boosted protease inhibitor (PI) regimen or alternatively with a nonnucleoside reverse transcriptase inhibitor (NNRTI)–based regimen.[1] Results from clinical trials comparing these strategies tend to be based on the short-term virologic response (i.e., to 24 or 48 weeks) and have provided conflicting results. Some have shown that a boosted-PI regimen has a superior response compared to a single-PI–containing regimen,[2] that an NNRTI-based regimen has a better outcome compared to a single-PI–based regimen,[3–5] or that there is no difference between different cART strategies.[6–8] Within cART strategies, some differences between antiretrovirals belonging to the same drug class have been shown.[1] The results from observational studies, where patients are not randomized, have suggested that a single-PI–based regimen may have a poorer short-term virological outcome.[9,10] Few published studies have considered the long-term immunologic response, despite this being one of the best markers for clinical disease progression,[11–13] and there are few comparative data of the virologic or immunologic outcome at 3 years after starting combination antiretroviral therapy (cART). Clinical experience of treating patients with cART, management of toxicities, and the availability of specific antiretrovirals increased markedly from 1996–2000, which makes comparisons of clinical trials performed at different calendar times difficult. Treatment guidelines for starting cART have changed considerably[1,14] over time, taking into account not only differences in efficacy but also various toxicities associated with specific regimens and difficulties with adherence.

The aims of this analysis were therefore to compare both the short-term and long-term immunologic and virologic response to cART in antiretroviral-naïve patients starting either a single-PI–based, a ritonavir-boosted PI regimen, or an NNRTI-based cART regimen after January 1, 2000. In addition, we sought to describe discontinuation and the reasons for discontinuation among patients starting cART for the first time.

PATIENTS AND METHOD

EuroSIDA is a prospective, European study of 11,928 patients with HIV-1 infection in 80 centers across Europe (including Israel and Argentina as non-European representatives; see Appendix). Details of the study have been published.[15] Six cohorts have been recruited to date, the first in May 1994, of 3,117 patients, and the latest recruited in December 2003, of 2,121 patients. At recruitment, in addition to demographic and clinical information, a complete antiretroviral history was collected, together with the eight most recent CD4 counts and viral load (VL) measurements. Patients are seen within their clinics as required, but at 6 monthly intervals relevant data are extracted from patient clinical charts onto follow-up forms. This analysis includes data to August 2005 and includes details on all CD4 lymphocyte counts and viral loads measured since last data collection, the date of starting and stopping each antiretroviral drug, the use of drugs for prophylaxis against opportunistic infections, and all AIDS-defining illnesses using the clinical criteria from 2003. cART was defined as treatment with two nucleosides with one PI, a boosted PI (i.e., ritonavir boosted), or an NNRTI.

Members of the coordinating office visited all centers to ensure correct patient selection and that accurate data were provided by checking the information provided against case notes for all reported clinical events and a random sample of 10% of all other patients.

Statistical Analysis

All patients from the EuroSIDA study who started cART after January 1, 2000, without prior antiretroviral treatment (i.e., antiretroviral naïve) and with a CD4 count and viral load measured prior to starting cART were included in these analyses. This date was selected to ensure that patients included in analyses were starting contemporary and the most effective cART regimens. Patients with no follow-up after starting cART were excluded. Patients were included in analyses as indicated in **Figure 1** and in the following discussion; the numbers refer to the number of patients included for each specific endpoint. All analyses used forward selection, with entry criterion $p < .1$ to identify variables associated with each of the outcomes. Model selection was confirmed using backward selection. CD4 count nadir, CD4 and viral load at starting cART, age, prior AIDS diagnosis, region of Europe, year of starting cART, exposure group, hepatitis B and C status, gender, and

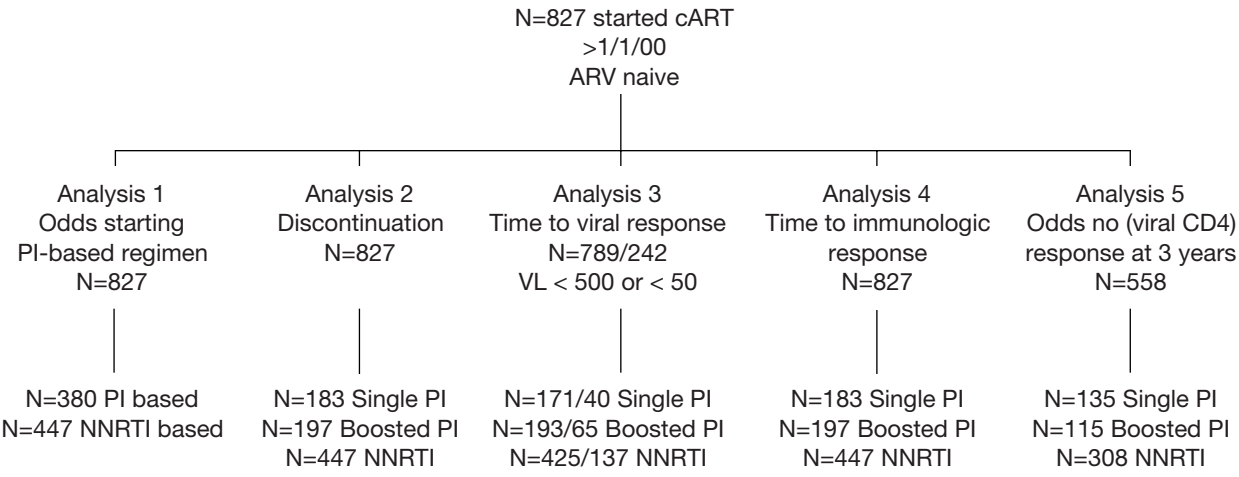


Figure 1. Patients included in analysis.

ethnic origin were included as potential explanatory variables in all analyses.

Analysis 1 (n = 827)

Logistic regression was used to determine the odds of starting a PI-containing regimen (single or boosted).

Analysis 2 (n = 827)

Discontinuation was defined as the first date when the patient was no longer taking that regimen. Reasons for discontinuation were classified as previously described in the EuroSIDA study.[16,17] Patients taking a single PI with two nucleosides were classified as discontinuing at the first date of taking either no PI or more than one PI or less than two nucleosides or more than two nucleosides. Thus a discontinuation may also be a switch to a second cART regimen. Kaplan-Meier estimates and Cox proportional hazards models, stratified by center, were used to compare the probability of discontinuation or relative hazard of discontinuation according to initial cART regimen. Patients were followed from the date of starting cART to discontinuation or last follow-up; patients who did not discontinue their regimen were censored at last follow-up. The second cART regimen was classified as a distinct regimen from the first regimen (e.g., a NNRTI-based regimen followed by a boosted-PI regimen), as restarting a cART regimen within the same category (i.e., single-PI regimen followed by a single-PI regimen), as starting an "other" regimen (≥3 antiretrovirals but not single-PI, boosted-PI, or NNRTI-based regimen), or as no second regimen (i.e., patients stopped cART without restarting a regimen during follow-up).

Analysis 3 (n=789 [<500 copies/mL] and n = 242 [<50 copies/mL])

Time to virologic response (VL <500 or <50 copies/mL) was calculated using Kaplan-Meier figures and the cART regimens were compared using Cox proportional hazards models, stratified by center. Thirty-eight or 585 patients were excluded because viral load at starting cART was <500 copies/mL or because the lower limit of detection was >50 copies/mL, respectively. Follow-up was calculated from the date of starting cART to first VL <500 or <50 copies/mL or until last viral load measurement. Patients whose VL <500 copies/mL at starting cART were excluded from the analysis of time to VL <500, similarly patients whose VL <50 copies/mL at starting cART were excluded from the analysis of time to VL <50 (as were patients where viral load had not been measured with sufficient sensitivity).

Analysis 4 (n = 827)

Time to immunologic response (a 100/mm^3 or 200/mm^3 increase in CD4 count) was calculated using Kaplan-Meier figures and the cART regi-

mens were compared using Cox proportional hazards models, stratified by center. Follow-up was calculated from the date of starting cART to first CD4 at least 100/mm^3 or 200/mm^3 higher than CD4 at starting cART or until last CD4 measurement.

Analysis 5 (n = 558)

Patients without the potential for 3 or more years follow-up were excluded (n = 269). The odds of a lack of virologic response (VL <500 copies/mL) or immunologic response (>200/mm^3 increases in CD4 cells) at 3 years after starting cART in the remaining 558 patients were determined using logistic regression. The viral load and CD4 count closest to 3 years was determined, with a 3-month window period on either side of this date. Patients were categorized as virologic or immunologic success or not. Thus patients with no measurement in this window were counted as failures.

All statistical analyses were performed using SAS version 9.1 (Statistical Analysis Software, Cary, North Carolina, USA).

RESULTS

Patient Characteristics

The patients are described in detail in **Table 1**. Patients were not randomized to treatment, and there were some differences in their characteristics. Of note, patients starting NNRTI-based cART had significantly higher CD4 counts at baseline compared to the single-PI or boosted-PI groups and a higher CD4 nadir prior to starting cART, while patients taking the single-PI–based cART started cART earlier in calendar time (p < .0001, all comparisons). In addition to the data presented in **Table 1**, the most commonly used nucleoside pairs were zidovudine/lamivudine (490, 59.3%), lamivudine/stavudine (122, 14.8%), and stavudine/didanosine (64, 7.7%). Of 183 patients taking a single-PI regimen, the most commonly used PI was nelfinavir (115, 62.8%); of 197 patients taking a boosted-PI regimen, lopinavir/ritonavir was the most frequently used (107, 54.3%); and among 447 patients taking an NNRTI-based regimen, efavirenz was the most commonly used (315, 70.5%). There were no differences between the three groups in the proportions of patients who started cART prior to recruitment to EuroSIDA (n = 544, 69.5%; p = .36).

Odds of Starting a PI-Based (Single or Boosted) cART Regimen

Only two factors were associated with the odds of starting a PI-based regimen compared to starting an NNRTI-based regimen. In an adjusted analysis, patients from Northern Europe had significantly lower odds of starting a PI-based regimen compared to patients from any other region of Europe (odds ratio [OR] 0.45, 95% confidence interval [CI] 0.30–0.66, p < .0001), as did patients with a higher CD4 count nadir (OR 0.71 per doubling of CD4 nadir, 95% CI 0.64–0.66, p < .0001).

Discontinuation of an Initial cART Regimen

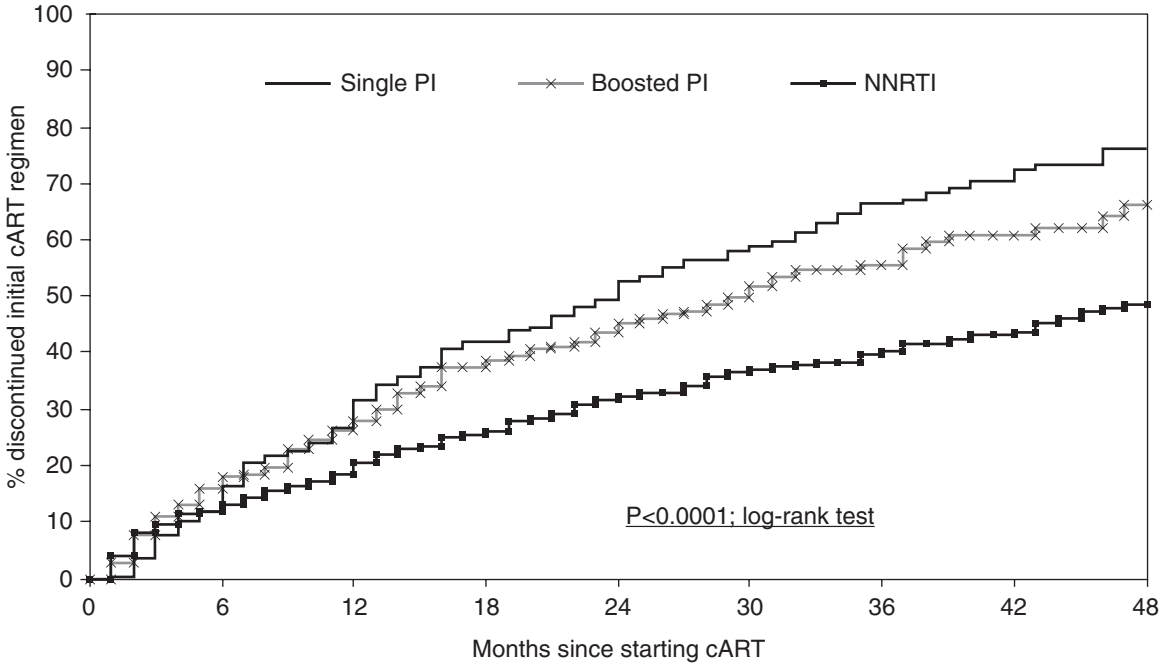
In total, 408 patients (49.3%) discontinued their initial cART regimen. There was a significant difference in the time to discontinuation among the three treatment groups, as shown in **Figure 2** (p < .0001, log-rank test). At 12 months after starting cART, 32.0% of those taking a single-PI regimen 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% of patients taking the NNRTI regimen (95% CI 17.0%–24.6%). In the multivariate forward-selection Cox proportional hazards model, compared to patients starting an NNRTI-based regimen, patients starting a single-PI regimen had a significantly higher risk of discontinuation (relative hazard [RH] 1.83, 95% CI 1.37–2.43, p < .0001), as did patients starting a boosted-PI regimen (RH 1.50, 95% CI 1.12–2.02, p = .0071). Intravenous drug users also had an increased risk of discontinuation of the initial cART regimen compared to all other exposure groups combined (RH 1.58, 95% CI 1.14–2.19, p = .0055), as did females (RH 1.37, 95% CI 1.08–1.74, p = .0092). There was no relationship between calendar year of starting cART and discontinuation (RH per year later 1.02, 95% CI 0.92–1.14, p = .66).

Of 408 patients who discontinued their initial cART regimen, 71 (17.4%) did not restart cART during a median follow-up of 8 months after discontinuation (interquartile range [IQR] 1–16 months), and 71 patients (17.4%) restarted a cART regimen within the same class as the one they had

Table 1. Characteristics of the patients at initiation of cART

		Single PI		Boosted PI		NNRTI		
		n	%	*n*	%	*n*	%	*p*
All		183	22.1	197	23.8	447	54.1	—
Gender	Male	131	71.6	140	71.1	296	66.2	.29
	Female	52	28.4	57	28.9	151	33.8	
Race	White	167	91.3	171	86.8	399	89.3	.37
	Other	16	8.7	26	13.2	48	10.7	
Exposure group	Homosexual	58	31.7	78	39.6	152	34.0	.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	<.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	AIDS	53	29.0	49	24.9	69	15.4	.0002
Hepatitis C status	Negative	78	42.6	103	52.3	243	54.4	.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	.41
	Positive	6	3.3	8	4.1	18	4.0	
	Unknown	88	48.1	78	39.6	211	47.2	
		n	%	*n*	%	*n*	%	*p*
		Median	IQR	Median	IQR	Median	IQR	
CD4		180	73–318	140	50–252	230	141–356	<.0001
CD4 nadir		146	59–274	125	50–236	210	136–305	<.0001
Viral load		4.99	4.39–5.65	5.05	4.66–5.60	4.89	4.37–5.31	.0050
Age		35.5	29.3–42.7	37.6	30.4–45.3	36.8	30.0–44.4	.35
Date started cART		June 2001	Sept 2000 to Jan 2003	March 2002	May 2001 to Aug 2003	Nov 2001	March 2001 to March 2003	<.0001

Note: cART = combination antiretroviral therapy; PI = protease inhibitor; NNRTI = nonnucleoside reverse transcripase inhibitor; IDU = intravenous drug use



N under follow-up					
Single PI	183	112	68	36	17
Boosted PI	197	130	78	44	15
NNRTI	447	331	239	154	73

Figure 2. Time to discontinuation of specific cART regimens. Discontinuation was defined as the first date when the patient was no longer taking a specific regimen; this definition included intensification, switches, or stopping cART.

discontinued. **Table 2** illustrates the changes made to the initial cART regimen and the reasons for discontinuation.

Short-Term Virologic Response

There were no differences between treatment groups in terms of the time between viral load measures (median for all groups; 3 months, IQR 2–4 months, $p = .50$ for comparison). The results are summarized in **Table 3**. The median time to achieve a VL <500 copies/mL was significantly longer in the single-PI group (5.3 months) versus the boosted-PI group (3.0 months) or the NNRTI group (3.2 months, $p < .0001$). After stratification by center and adjustment, patients in the single-PI group were significantly less likely to achieve a VL <500 copies/mL (RH 0.74, 95% CI 0.59–0.92, $p = .0081$) compared to patients in the NNRTI group, while patients in the boosted-PI group had a similar chance of virologic success. There was a 20% increase in the chance of virologic suppression per year later of starting cART (RH 1.20, 95% CI 1.12–1.29, $p < .0001$). Although the number of patients known to have viral load measured with a lower limit of detection of <50 copies/mL was considerably smaller, a highly consistent pattern was seen.

Short-Term Immunologic Response

There were no differences between treatment groups in terms of the time between CD4 counts (median for all groups; 3 months, IQR 2–4 months, $p = .27$ for comparison). These results are also summarized in **Table 3**. Patients taking a boosted regimen had a significantly shorter median time to achieve a CD4 increase of more than 100/mm^3 ($p = .0076$). Similarly, after adjustment they were significantly more likely to achieve a CD4 response greater than 100/mm^3 compared to patients taking an NNRTI-regimen (RH 1.30, 95% CI 1.05–1.62, $p = .017$). There was a 17% increased chance of immunologic response per year later of starting cART (RH 1.17, 95% CI 1.09–1.25, $p < .0001$). In contrast,

Table 2. Discontinuation of an initial cART regimen

	Initial cART regimen		
	Single PI (*n* = 183)	Boosted PI (*n* = 197)	NNRTI (*n* = 447)
Patients stopping their first cART regimen (*n*, %)	117 (63.9)	105 (53.3)	186 (41.6)
Second cART regimen (*n*, %)[a]			
Single PI	0 (0)	13 (12.4)	33 (17.7)
Boosted PI	45 (38.5)	0 (0)	44 (23.7)
NNRTI	33 (28.2)	36 (34.3)	0 (0)
Restarted initial regimen	12 (10.3)	13 (12.4)	46 (24.7)
Started other cART regimen	14 (12.0)	24 (22.9)	24 (12.9)
Not started	13 (11.1)	19 (18.1)	39 (21.0)
Patients starting 2nd regimen with no treatment break (*n*, %)	50 (48.1)	25 (29.1)	31 (21.1)
% starting 2nd regimen by 12 months after starting cART	15.7	12.7	7.1
Reasons for stopping (*n*, %)			
Treatment failure	19 (16.2)	7 (6.7)	24 (12.9)
Toxicities	29 (24.8)	34 (32.4)	52 (28.0)
Patient/physician choice	30 (25.6)	39 (37.1)	52 (28.0)
Other	15 (12.8)	11 (10.5)	31 (16.7)
Unknown	24 (20.5)	14 (13.3)	27 (14.5)

Note: cART = combination artiretroviral therapy; PI = protease inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor.

[a]Second cART regimen was classified as a distinct regimen to first (e.g., a NNRTI-based regimen followed by a boosted-PI regimen), as restarting a cART regimen within the same category (i.e., single-PI regimen followed by a single-PI regimen), as starting an "other" regimen (≥3 antiretrovirals but not single-PI, boosted-PI, or NNRTI-based regimen) or as no second regimen (i.e., patients stopped cART without restarting a regimen during follow-up).

there were few differences when comparing regimens in the time to, or relative hazard of, a CD4 increase of more than 200/mm^3.

Long-Term Virologic Response

There was a higher proportion of patients taking the single-PI regimen without virological response (VL <500 copies/mL) at 3 years after starting cART (54.8%) compared to the boosted-PI group (40.9%) or the NNRTI-group (43.2%, p = .041). As illustrated in **Figure 3**, after adjustment for CD4 and viral load at starting cART, age, prior AIDS diagnosis, year of starting cART, and region, patients taking a single-PI regimen had significantly increased odds of lack of virological response at 3 years after starting cART (OR 1.60, 95% CI 1.08–2.59, p = .023) compared to patients taking the NNRTI regimen. There were no significant differences in the odds of lack of virological response when comparing patients taking the NNRTI regimen with patients taking the boosted-PI regimen. There were 36% decreased odds of lack of virologic response per year later of starting cART (OR 0.64, 95% CI 0.50–0.83, p = .0006).

Long-Term Immunologic Response

There were some differences in the proportion of patients without immunologic response (CD4 increase >200/mm^3) at 3 years after starting cART; the proportion was lower in the boosted-PI group

Table 3. 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*	RH	95% CI	*p*
Virologic response										
VL <500 copies/mL[a]	Single PI	5.3	4.0–6.3	—	0.67	0.54–0.84	.0005	0.74	0.59–0.92	.0081
	Boosted PI	3.0	3.0–3.7	—	1.03	0.84–1.28	.75	1.04	0.84–1.29	.72
	NNRTI	3.2	3.0–3.9	<.0001	1.00	—	—	1.00	—	—
VL <50 copies/mL[b]	Single PI	5.7	3.3–8.0	—	0.69	0.42–1.13	.14	0.63	0.38–1.04	.065
	Boosted PI	4.5	3.4–6.2	—	0.83	0.56–1.25	.38	0.87	0.57–1.31	.49
	NNRTI	4.0	3.8–4.9	.11	1.00	—	—	1.00	—	—
Immunologic response										
CD4 increase >100/mm^3[c]	Single PI	7.0	5.9–9.0	—	0.90	0.74–1.15	.49	0.93	0.74–1.17	.53
	Boosted PI	5.9	4.1–6.4	—	1.32	1.07–1.63	.011	1.30	1.05–1.62	.017
	NNRTI	7.0	6.0–8.0	.019	1.00	—	—	1.00	—	—
CD4 increase >200/mm^3[d]	Single PI	15.0	13.4–18.1	—	0.90	0.71–1.16	.43	0.91	0.71–1.17	.47
	Boosted PI	12.2	10.5–14.0	—	1.13	0.90–1.42	.30	1.12	0.88–1.42	.35
	NNRTI	15.9	14.0–18.2	.054	1.00	—	—	1.00	—	—

Note: cART = combination antiretroviral therapy; CI = confidence interval; RH = relative hazard; VL = viral load; PI = protease inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor. Multivariate model adjusted for [a]viral load at date of starting cART, date started cART, gender, race, and hepatitis C status; [b]viral load, race, and date started cART; [c]date started cART, CD4, viral load and CD4 nadir at starting cART, and prior AIDS diagnosis; [d]viral load, CD4 and CD4 nadir at starting cART, age, and date of starting cART.

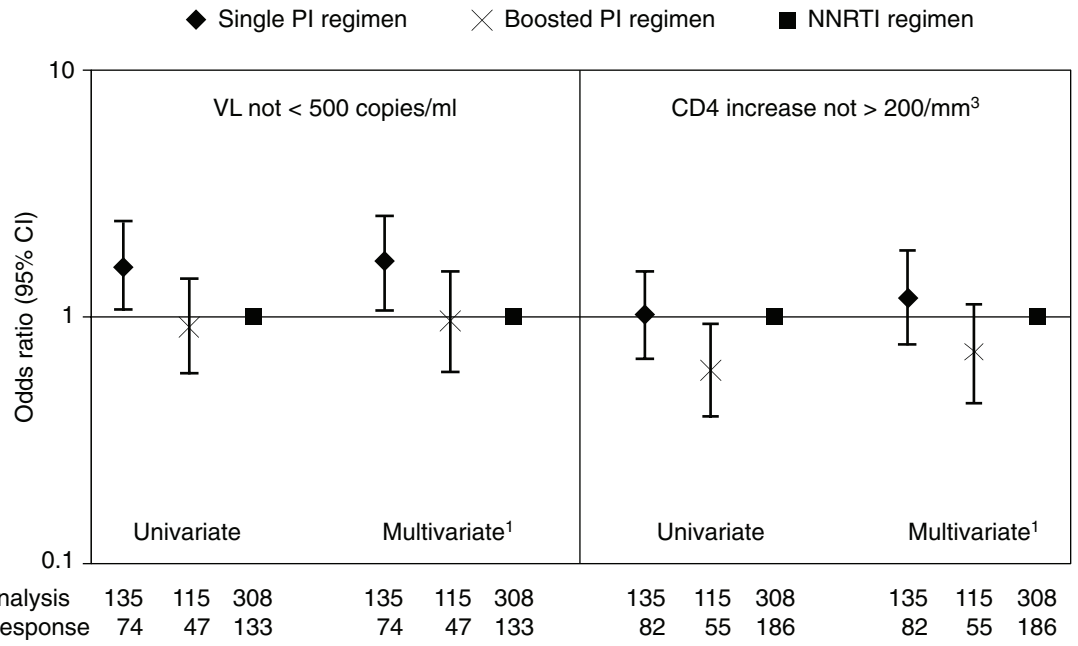


Figure 3. Univariate and multivariate odds of lack of virologic or immunologic response at 3 years after starting cART. [1]Multivariate analyses were adjusted for date of starting cART, CD4 and viral load at starting cART, and prior AIDS diagnosis.

(47.8%) compared to the single-PI group (60.7%) or the NNRTI group (60.4%; $p = .049$). However, as illustrated in **Figure 3**, after adjustment for CD4 and viral load at starting cART, age, prior AIDS diagnosis, year of starting cART, and region, there were no statistically significant differences in the odds of lack of immunologic response when comparing the NNRTI group with either the single-PI group ($p = .42$) or the boosted-PI group ($p = .16$). There were 26% decreased odds of lack of immunologic response per year later of starting cART (OR 0.74, 95% CI 0.57–0.96, $p = .014$).

DISCUSSION

This study has analyzed data from over 800 antiretroviral-naïve patients who started a contemporary cART regimen after January 2000. We have shown that, compared to patients starting an NNRTI-based cART regimen, patients starting a single-PI–based cART regimen were less likely to achieve virologic suppression and were more likely not to have a viral load <500 copies/mL at 3 years after starting cART.

Current treatment guidelines state that one of the goals of antiretroviral therapy is to maximally and durably suppress HIV viremia,[1] thus it is crucial to consider not only 24- or 48-week response, as in most clinical trials, but also longer term virologic or immunologic response. This study has considered both of these outcomes. Two thirds of the patients contributed data to this analysis, and some caution is required because of the smaller sample size. However, it is useful to confirm the generalizability of clinical trials in less selected patient groups who are taking cART as part of routine clinical care. Our results are highly consistent with the INITIO trial,[5] a randomized trial comparing virologic and immunologic outcomes at 3 years in patients starting efavirenz, nelfinavir, or efavirenz plus nelfinavir (with didanosine and stavudine). This trial, analyzed by intention-to-treat, reported a better virologic outcome at 3 years in antiretroviral-naïve patients starting efavirenz compared to nelfinavir but no differences in immunologic response. Previous clinical trials have shown no difference in virologic response at 48 weeks between a PI-based or an NNRTI-based regimen[6,8] or, consistent with our study at 3 years, a favorable response for the NNRTI-based regimen at 48 weeks,[3,4,18,19] particularly when considering virologic suppression to <50 copies/mL.[15] Patients

in this analysis were not randomized to treatment, and there were some differences in their characteristics at the date of starting cART. Although we have adjusted for these differences in multivariate analyses, the differences in virologic or immunologic response could reflect differences between patients that we either do not know or cannot adjust for.[20]

Fewer clinical trials have compared boosted-PI regimens with single-PI regimens. Walmsley et al. demonstrated a better virological response at 48 weeks for a boosted-PI regimen of lopinavir-ritonavir compared to a single-PI regimen based on nelfinavir,[2] whereas fos-amprenavir was demonstrated to have superior virologic efficacy at 48 weeks compared to a single-PI regimen containing nelfinavir.[21] The CD4 count at recruitment to these clinical trials was quite variable but tended to be higher than the CD4 count of patients starting cART in this observational study. Various clinical trials have found nelfinavir to have an inferior virologic effect compared to lopinavir/ritonavir, efavirenz, or fos-amprenavir[2,4,21]; in a post hoc analysis excluding patients taking a single-PI regimen containing nelfinavir, there was no significant difference between a single-PI or an NNRTI regimen. However, this was a post hoc analysis, with a wide confidence interval around the odds ratio, and the result should be interpreted with caution. Genotypic resistance with the selection of the D30N or the multiple-PI–resistant L90M mutation has been reported in patients taking nelfinavir with virologic rebound,[22,23] the latter of which might limit future treatment options.

Observational studies have also compared cART regimens. Observational studies tend to have more power than clinical trials and can follow a larger number of patients for a longer duration, but they also include a number of inherent biases and the results should always be interpreted with caution. To date, observational studies have focused on short-term response in the same way as clinical trials. Some have shown a better short-term virological response in antiretroviral patients starting an NNRTI regimen compared to a either a single-PI (in agreement with our findings[24–26]) or boosted-PI regimen,[24] whereas others have reported no such differences in both antiretroviral-naïve patients[27] or in a cohort with antiretroviral-experienced patients.[28] Our analyses demonstrated an improvement in both immunologic and virologic response over time, consistent with reports from other observational studies.[29,30] All analyses included this variable in forward selection models, and it was adjusted for whenever appropriate.

Compared to patients taking the NNRTI-based cART regimen, there was some evidence that patients taking the boosted-PI regimen were more likely to have a CD4 cell increase of more than 200/mm^3, but this was not significant after adjustment. The immunologic response tends to be a secondary endpoint in clinical trials. Data variously suggest an inferior immunologic response at 96 weeks in patients taking an NNRTI-based regimen (nevirapine) compared to a single-PI regimen containing indinavir[6] and no differences between various NNRTI, single-PI, or boosted-PI regimens[4,19] or between various single-PI regimens and NNRTI regimens.[2,3,5,8] In contrast to our data, Ghani et al. found no difference in the time for a CD4 cell rise of 100/mm^3 or more after starting cART when comparing PI (single or boosted regimens) or NNRTI regimens but some evidence of a less sustained response in patients taking NNRTIs[31]; others have not found any difference between regimens.[24,25,27,28,32] One possible explanation for these discrepancies is the relatively short duration of follow-up in studies and the time it takes for differences in CD4 count to appear.

We found high rates of discontinuation, as previously reported from ourselves and other observational cohorts.[17,33–35] We have used a combined definition for discontinuation that included intensification, switches, or stopping cART. The factors related to discontinuation may vary if each type of discontinuation was investigated separately, but there was limited power for this analysis. It was reassuring to note that the majority of patients who stopped a cART regimen subsequently restarted. Patients taking either the boosted-PI or single-PI regimen were significantly more likely to discontinue their regimen, most commonly due to toxicities or patient/physician choice or treatment failure. NNRTI-based regimens are a popular choice for initial cART regimen and tend to have a lower pill burden and fewer toxicities than PIs.[1] Dosing frequency, food and fluid requirements, pill burden, drug interaction potential, baseline hepatic function, and toxicity profile all need to be taken into account when starting any PI-based regimen, and a number of metabolic abnormalities, including dyslipidemia, fat maldistribution, and insulin resistance, have been associated with PI use.[1]

There are several points to note in interpreting this data. We selected a priori the time point at which to compare cART regimens to determine longer term responses, and it is possible that different results would be seen at different time points. These analyses were not performed to reduce testing at multiple time points. It is possible that there are differences in CD4 cell gain between cART strategies among those patients who achieve maximal virological suppression after starting cART.[36] The results are only generalizable to a class level to some extent as there may be substantial differences in virologic or immunologic responses within cART strategies depending on the antiretrovirals used. There was not sufficient power in this study to look at antiretrovirals used within each cART strategy. In addition, there are a number of ongoing randomized trials in antiretroviral-naïve patients comparing NNRTI regimens with boosted-PI regimens, and the results from these trials will address both immunologic outcome and toxicities in patients randomized to treatment. A final point for consideration is that we used forward selection to identify variables associated with immunologic or virologic suppression. This methodology can introduce bias, particularly with a small sample size.[37] Although most sophisticated analyses could be performed, we have tried to balance practical clinical considerations with statistical analyses.

In conclusion, compared to antiretroviral-naïve patients starting an NNRTI-based regimen, patients starting a single-PI–based cART regimen have a poorer virologic response at 3 years after starting cART. These results should be interpreted with caution because of the potential biases associated with observational studies. 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.

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APPENDIX

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