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Poor baseline immune function predicts an incomplete immune response to combination antiretroviral treatment despite sustained viral suppression

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Abstract

Objectives—To determine the prevalence and predictors of an incomplete immune response in patients with sustained viral suppression following their first or second combination antiretroviral treatment (cART) regimen.

Methods—All patients were recruited to the Australian HIV Observational Database (AHOD) by March 2006. Data were analysed to assess the prevalence of an incomplete immune response (<350 cells/μL) in the 12–24 months after starting the first or second cART regimen. Factors associated with an incomplete immune response were assessed using logistic regression and time to AIDS/death was assessed using survival analysis.

Results—Of the 2493 patients recruited to AHOD by March 2006, 590 were eligible for the analysis. Twenty eight percent of patients with a baseline CD4 count <350 cells/μL had an incomplete immune response 12–24 months after starting their first or second cART regimen. Lower baseline CD4 count prior to starting the cART regimen was predictive of an incomplete immune response. There was a non-significant trend towards faster AIDS or death in incomplete immune responders.

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Conclusions—An incomplete immune response in patients with sustained viral suppression is associated with poorer immune function prior to starting cART. Type of cART or individual antiretroviral drugs was not associated with an incomplete immune response.

Keywords

HIV; immune response; viral suppression; observational; Australia

Introduction

Combination antiretroviral treatment (cART) has led to significant reductions in morbidity and mortality associated with HIV infection.¹⁻⁴ Typically, HIV viral load decreases and peripheral CD4 T cells increase following cART initiation.⁵ CD4 T cell counts have been shown to increase for 3-7 years after starting cART⁵⁻¹⁰. However, patients starting cART at lower, compared to higher, baseline CD4 T cell counts generally reach lower CD4 T cell thresholds over similar follow up periods.^{5-8, 10} Whether patients with advanced immunodeficiency at the time of initiating cART have the potential to achieve better immune recovery remains controversial because of conflicting findings from short to medium term studies published to date.

One of the largest observational HIV cohort studies, EuroSIDA, recently reported ongoing immune recovery up to six years after starting cART in patients with maximal viral suppression, across all baseline CD4 T cell count strata.⁹ Ongoing immune recovery was also reported in a small study of patients with sustained viral suppression following six years of a lopinavir-ritonavir based treatment regimen.¹¹ There have been other reports, however, of a plateau in immune recovery after three or more years of cART, despite viral suppression.^{7, 10, 12} In addition, approximately one third of patients with viral suppression in the Swiss Cohort Study did not achieve CD4 T cell counts above the lower limit of normal (500 cells/ μ L) after 5 years of cART.¹² While normalisation of CD4 T cell counts remains a possibility with longer treatment duration, the finding that patients with baseline CD4 T cell counts <350 cells/ μ L experience lower absolute levels of immune recovery on average than patients with baseline CD4 T cell counts $\geq$ 350 cells/ μ L is consistent across a number of short to medium term cohort studies.^{7, 9, 10}

The objective of this paper is to assess the prevalence of, and risk factors for, an incomplete immune response, despite sustained viral suppression, in patients with baseline CD4 T cell counts <350 cells/ μ L. Therefore, we analysed data from the Australian HIV Observational Database (AHOD) to describe how common an immune response below the threshold of 100, 200 and 350 cells/ μ L was in patients with sustained viral suppression in the 12-24 months after starting a cART regimen, and to investigate predictors of an incomplete immune response. We also examined the clinical relevance of this phenomenon in terms of AIDS and/or death over the duration of follow up.

Methods

Participants and eligibility criteria

The Australian HIV Observational Database (AHOD) is a longitudinal, observational cohort study of patients with HIV in Australia, which has been described elsewhere in detail.¹³ The study population for this analysis included all patients enrolled in AHOD between July 1999 and March 2006. Patients were eligible for inclusion in this analysis if they: 1) started their first cART regimen (defined as a combination of three or more antiretroviral drugs) after June 1, 1996; 2) remained on their first cART regimen for at least 12 months; 3) had a CD4 T cell count and HIV viral load measure within the six month period prior to starting the first cART

regimen (baseline) and a CD4 T cell count 9-15 months after starting the same regimen; and 4) achieved virologic suppression within six months of starting the first cART regimen, sustained for a minimum of 12 months (determined by two or more consecutive undetectable viral load measures). Patients starting their first cART regimen may have had prior monoantiretroviral or dual ART experience. We defined viral suppression as <400 copies/mL because more sensitive assays were not uniformly available throughout the study period. Patients who were not eligible based on the above criteria were then considered for inclusion in the analysis by applying the same criteria from the start of their second cART regimen. Throughout this paper, "inclusion regimen" refers to the cART regimen that satisfied the inclusion criteria above.

Data collection

Ethical approval was obtained from all relevant institutional review boards and all study procedures were in accordance with the revised, 1975 Helsinki Declaration. Written, informed consent is obtained on enrolment to the cohort. Data is collected from 27 clinical sites throughout Australia, including hospitals, sexual health clinics and general medical practices. Prospective data collection for the cohort commenced in 1999, with retrospective data provided where available. Data are transferred electronically to the National Centre in HIV Epidemiology and Clinical Research (NCHECR) every six months. Core variables collected include: date of birth, sex, date of first positive HIV test result, date of most recent clinic visit, HIV exposure category, hepatitis B virus (HBV) and hepatitis C virus (HCV) status, CD4 and CD8 T cell counts, HIV viral load, antiretroviral and prophylactic treatment histories (including start and stop dates), AIDS defining illness history and cause of death.

Data analysis

The primary endpoint was the recovery of the CD4 T cell count 12-24 months after starting the first or second cART regimen. Patients were censored at the first of: 1) the stop date of the same regimen; 2) the date 24 months after starting the same regimen; or 3) the date of the last undetectable viral load measure. Consequently, patients were not followed up past the end of the period of sustained viral suppression in this analysis. We defined complete and incomplete immune responses as CD4 T cell counts of ≥ 350 cells/ μ L and <350 cells/ μ L, respectively. We also examined lower thresholds of CD4 T cell recovery (i.e. <100 cells/ μ L and <200 cells/ μ L) to determine the proportion of patients with more impaired immune recovery 12-24 months after starting their inclusion regimen. Only patients with a CD4 T cell count of <350 cells/ μ L at the time of starting the inclusion regimen (baseline) were included in the logistic regression and survival analyses. Patients were classified as incomplete immune responders if all their available CD4 T cell counts were <350 cells/ μ L between the date nine months after starting the inclusion regimen and the date their data were censored. All other patients were classified as complete immune responders. We also performed sensitivity analyses that defined an incomplete immune response as one or more CD4+ T cell count <350 cells/ μ L between 9-15 months post-cART initiation, or that did not restrict the sample to patients with a CD4+ T cell count <350 cells/ μ L at baseline.

Data analyses were performed using Stata version 8 (StataCorp LP, College Station, Texas, USA). Logistic regression analysis was used to assess factors associated with an incomplete immune response in patients with sustained viral suppression. Covariates assessed for inclusion in the multivariate model were sex, age, HIV exposure, year of HIV infection, prior AIDS, prior HBV, prior HCV, prior antiretroviral treatment (ART), mono/dual therapy prior to first cART, year inclusion regimen started, first or second cART regimen, antiretroviral drug classes included in the regimen, zidovudine/stavudine containing regimens, baseline HIV viral load and CD4 T cell count, nadir CD4 T cell count and CD4 T cell count slope in the 24 months prior to start of the inclusion regimen. Linear regression was used to estimate the CD4 slope.

A median of six (IQR 2-9) CD4 counts were available in the 24 months prior to starting the inclusion regimen. CD4 slope was classified into two subgroups for the logistic regression analysis: 1) positive slope (increasing CD4 count); and 2) negative slope (decreasing CD4 count). Covariates were entered into the model if they had a p value of <0.10 in the univariate analysis. The forward step-wise method was used, using the log-likelihood ratio statistic to assess contribution to the model. $P < 0.05$ was considered statistically significant.

Kaplan-Meier methods were used to assess time to the first AIDS event or death following the start of the inclusion regimen in complete and incomplete immune responders. Data for each patient were censored at the last date of follow up, defined as the most recent of the following: clinic visit date, CD4 T cell count or HIV viral load test date, antiretroviral or prophylactic treatment start or stop dates. Cox proportional hazards models were used to assess predictors of the first AIDS event or death in complete and incomplete immune responders, following the start of the inclusion regimen.

Results

Study Cohort

The total cohort consisted of 2493 patients with HIV, with 1865 patients commencing their first cART regimen after June 1, 1996. Of these, 1086 had a baseline CD4 T cell count and HIV viral load, and a CD4 T cell count 9-15 months after starting their first cART regimen. Four hundred and seventy eight patients achieved viral suppression within six months of starting their first cART regimen and sustained this for at least 12 months. Of these, 336 patients remained on their first cART regimen for at least 12 months (first cART group). Of the 1529 patients excluded because they did not meet criteria on their first cART regimen, 1318 commenced their second cART regimen. Of these, 920 had a baseline CD4 T cell count and HIV viral load measure and a CD4 T cell count 9-15 months after starting their second cART regimen. Sustained viral suppression was achieved by 377 of these patients, and 255 remained on their second cART regimen for at least 12 months (second cART group). An additional patient was excluded because their first CD4 T cell count in the 9-15 months after starting their first cART regimen came after the stop date of the same regimen. Therefore, a total of 590 (24%) patients were eligible for analysis. The median number of viral load measures in the period of sustained virological suppression in this analysis was seven (IQR 6-8) and the median number of CD4+ T cell counts measured during the period of follow up was eight (IQR 6-9). CD4+ T cell counts were measured every 84 days (median, IQR 56-98) during the period of follow up.

Incomplete immune responses to combination antiretroviral treatment

A total of 292 patients had a baseline CD4 T cell count <350 cells/ μ L (Table 1). Of these, 83 (28%) had an incomplete immune response in the 9-24 months after starting the inclusion regimen. The median number of CD4 T cell counts available in the 9-24 months after starting the inclusion regimen was seven (interquartile range (IQR), 5-9 for complete immune responders and 6-9 for incomplete immune responders). The proportion of patients on their first or second cART regimen was similarly distributed across the outcome groups, with 129 (62%) of the complete immune responders on their first cART regimen compared to 57 (69%) of the incomplete immune responders ($p=0.266$).

We also examined incomplete immune responses at more advanced degrees of immunodeficiency. A total of 130 patients had a baseline CD4 T cell count <200 cells/ μ L (Table 1). Of these, 16 (12%) had an incomplete immune response defined as <200 cells/ μ L 9-24 months after starting the inclusion regimen. Only 60 patients had a baseline CD4 T cell count <100 cells/ μ L, with 3 (5%) of these having an incomplete immune response defined as

<100 cells/ μ L 9-24 months after starting the inclusion regimen. No further analysis was conducted on these more advanced immunodeficiency groups because of limited sample size.

Determinants of an incomplete immune response

Lower baseline and nadir CD4 T cell count strata, prior AIDS and HIV exposure other than homosexual contact were significantly associated with an incomplete immune response in patients with sustained viral suppression in the univariate analysis (Table 2). After adjusting for confounders, only baseline CD4 T cell count was significant in the multivariate model. Patients with a baseline CD4 T cell count of 100-199 cells/ μ L or 200-350 cells/ μ L were 77% and 96%, respectively, less likely to have an incomplete immune response than patients with a baseline CD4 T cell count <100 cells/ μ L. None of the treatment related variables, including treatment regimen (defined by either the drug classes or individual antiretroviral drugs contained in the regimen), time period when the regimen was started, prior ART, or whether the regimen was the first or second cART regimen, were associated with an incomplete immune response. Other demographic and clinical variables, including age, sex, HIV exposure, year of HIV infection, hepatitis B or C virus co-infection, baseline HIV viral load, nadir CD4 T cell count and CD4 slope prior to starting the regimen were not associated with an incomplete immune response in this study.

We also performed sensitivity analyses that defined an incomplete immune response as one or more CD4+ T cell count <350 cells/ μ L between 9-15 months post-cART initiation, or that did not restrict the sample to patients with a CD4+ T cell count <350 cells/ μ L at baseline. Immune function prior to cART was consistently found to be associated with an incomplete immune response in these analyses. Interestingly, the slope of CD4 count in the 24 months prior to starting the inclusion regimen was significant in addition to baseline CD4+ T cell count in both of these analyses. Type of cART and individual antiretroviral drugs were consistently not associated with an incomplete response.

Clinical outcomes

There were 20 AIDS or death events reported during the 1575 person-years included in the survival analysis. Nine of these events occurred among incomplete immune responders, with seven being AIDS defining illness events. Five of the AIDS events in incomplete immune responders occurred in the first six months after starting the inclusion regimen, with four following the start of the first cART regimen. Baseline CD4 T cell counts were <200 cells/ μ L all of these patients.

Time to AIDS or death was shorter for incomplete immune responders (Figure 1), but was not statistically significant (HR=1.96; 95% CI, 0.82-4.76; p=0.132).

Discussion

In our study, almost one third of patients with a baseline CD4 T cell count <350 cells/ μ L did not achieve immune recovery $\geq$ 350 cells/ μ L in the 12-24 months after starting their first or second cART regimen, despite sustained viral suppression. A lower baseline CD4 T cell count was associated with an incomplete immune response 12-24 months after starting cART, perhaps partially reflecting the increased time required for CD4 counts to increase sufficiently to reach an absolute threshold. Treatment type was not associated with an incomplete immune response in our study. While AIDS-free survival was shorter among incomplete, compared to complete, immune responders in our study, the difference was not significant.

Baseline CD4 T cell count was predictive of immune recovery in patients with viral suppression in our study, which is consistent with prior studies^{10, 12, 14} despite the range of immunological

outcome definitions and duration of follow up used across studies. Nadir CD4 T cell count and CD4 slope prior to starting cART have previously also been associated with immune recovery in patients with viral suppression.¹⁵ In our study, CD4 slope prior to starting the cART regimen was only associated with an incomplete immune response in the sensitivity analyses. While it has previously been suggested that the naïve CD4 T cell count at the time of starting cART¹⁶ or particular *CCL3L1-CCR5* genotypes¹⁷ influence immunological recovery in patients with viral suppression, we were unable to confirm this in our study as we do not collect information on naïve or memory CD4 T cells.

Whether there is an association between the type of antiretroviral treatment and immune recovery in patients with viral suppression is controversial because of conflicting evidence from different studies. No association was found between immune recovery 5-6 years after starting cART and the individual antiretroviral drugs¹² or drug classes¹⁰ contained in the first cART regimen in some studies, while zidovudine/lamivudine based treatment regimens¹⁴ and the combination of protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the same regimen¹⁵ were associated with short term immune responses in other studies. Our study found no association between either the drug classes or individual antiretroviral drugs contained in the regimen and immune recovery. Older age,^{10, 12, 14} duration of infection¹², injecting drug use,¹⁰ baseline viral load^{14, 15} and poor adherence to therapy,¹⁴ have previously been associated with incomplete or slower rates of immune recovery in patients with viral suppression. However, none of these factors were significantly associated with an incomplete immune response in our study.

A prior population-based study of immunological and virological discordance six months after starting cART found higher mortality rates in patients with a <50 cell increase in CD4 T cell count compared to those with a ≥50 cell increase, in the context of early viral suppression.¹⁴ In our study, we were unable to detect a significant difference in AIDS-free survival between incomplete and complete immune responders with sustained viral suppression. The use of a threshold definition of immune response, compared to examining the rate of immune recovery, is an obvious difference between the two studies. However, more importantly, our survival analysis was limited in statistical power given the small sample size and the low clinical event rates of AIDS and death. The Swiss Cohort Study were also unable to detect any significant difference in the rate of CDC category B or C events between complete and incomplete immune responders (≥500 and <500 cells/μL after 5 years, respectively).¹² Much larger observational cohort studies are needed to confirm whether patients with incomplete immune recovery following cART initiation experience worse health outcomes in terms of AIDS and/or death, given the low frequency of these clinical events in the cART era.

Many of the clinical events in our study occurred early after starting the cART regimen, particularly in the incomplete immune responder group. Among incomplete immune responders, all clinical endpoints in the first six months after starting the cART regimen were AIDS defining illnesses and the majority of these patients were on their first cART regimen. Further, all of these patients had advanced immunodeficiency, indicated by their baseline CD4 T cell counts. This suggests that some of these patients may have experienced immune reconstitution syndrome after starting cART. However, more than half the AIDS events occurred at least one year after starting the first or second regimen. Our study was limited in its ability to accurately assess whether patients experienced immune reconstitution syndrome as only the first occurrence of each type of AIDS defining illnesses per patient is recorded and clinicians are not asked to record diagnosis of immune reconstitution syndrome.

Our study had several strengths, including the use of multiple HIV viral load measures to define a period of sustained viral suppression of minimum 12 months duration. Similarly, we used all CD4 T cell count measures recorded in the 9-24 months after starting the first or second

cART regimen to classify patients as either incomplete or complete immune responders. In doing so, we reduced misclassification bias that may have arisen if patients were classified on the basis of one low CD4 T cell count.

Our study also had some limitations. First, we did not limit our study to antiretroviral naïve patients starting their first cART regimen. The inclusion of patients who met eligibility criteria on their second cART regimen, in addition to those eligible on their first, as well as patients who may have received prior mono- or dual- antiretroviral treatment (ART), was a trade-off for larger sample size. While this introduced more variability into the sample, we included prior ART and first/second cART regimen as covariates in the logistic regression analysis to enable adjustment for potential confounding. Second, we had relatively limited power to detect any difference in survival between incomplete and complete immune responders. Third, we used a fairly broad definition of an incomplete immune response in our study, although we did obtain consistent results on sensitivity analyses. Finally, our analyses are limited by relatively short follow up in the data available to us. Ideally analyses would be based on longer durations of follow-up, which would allow longer term assessments of incomplete immune recovery in patients with undetectable viral load to be evaluated.

Despite average CD4 T cell count increases continuing for at least 6 years after starting cART, ^{7, 9, 10} a small proportion of patients with good viral load outcomes have modest or poor CD4 T cell responses. Our study suggests that this is not associated with the type of cART regimen. While longer treatment duration may eventually improve the average immune recovery of patients commencing cART with a CD4 T cell count < 350 cells/μL, there is some suggestion that patients with extended advanced to moderate immune suppression, both prior to and during the early years of treatment, experience worse long term health outcomes. In the context of mounting evidence that these patients might also be higher risk of serious non-AIDS morbidity or mortality,^{18, 19} it seems that further study of the long term morbidity and mortality outcomes in these patients is warranted.

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Appendix

Appendix 1: The Australian HIV Observational Database

Asterisks indicate steering committee members in 2006-2007.

New South Wales

D Ellis, General Medical Practice, Coffs Harbour; M Bloch, T Franic, S Agrawal, Holdsworth House General Practice, Darlinghurst; D Allen, Holden Street Clinic, Gosford; D Smith, C Mincham, Lismore Sexual Health & AIDS Services, Lismore; D Baker*, R Vale, 407 Doctors, Surry Hills; C O'Connor; Royal Prince Alfred Hospital Sexual Health, Camperdown; E Jackson, D Hunter, K McCallum, Blue Mountains Sexual Health and HIV Clinic, Katoomba; M Gotowski, S Taylor, L Stuart-Hill, Bligh Street Clinic, Tamworth; D Cooper, A Carr, M Lacey, K Hesse, St Vincent's Hospital, Darlinghurst; R Finlayson, I Prone, Taylor Square Private Clinic, Darlinghurst; MT Liang, Nepean Sexual Health and HIV Clinic, Penrith; K

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Figure 1. Time to AIDS or death after commencing the first or second cART regimen among complete and incomplete immune responders

Table 1
Frequency and percentage of patients with an incomplete immune response (<100, <200 and <350 cells/ μ L), despite sustained viral suppression, 9-24 months after starting a CART regimen

Endpoint threshold	Total patients ¹ N	Incomplete immune response ² N (%)
<350 cells/ μ L	292	83 (28)
<200 cells/ μ L	130	16 (12)
<100 cells/ μ L	60	3 (5)

¹Total number of patients with a baseline CD4 T cell count below the endpoint threshold.

²All available CD4 T cell counts in the 9-24 months after starting the inclusion regimen were below the endpoint threshold.

Table 2
Characteristics of patients with sustained viral suppression and baseline CD4 T cell count <350 cells/μL and determinants of an incomplete immune response (<350 cells/μL) 9-24 months after starting the first or second cART regimen

Baseline covariates		Complete immune responders (N=209)		Incomplete immune responders (N=83)		Univariate				Multivariate					
		N	%	N	%	OR	95%	CI	P-value	P- overall	AOR	95%	CI	P-value	P- overall
Age	<35	60	29	22	27	1.00				0.723					
	35-45	74	35	30	36	1.11	0.58	2.11	0.761						
	≥45	75	36	31	37	1.13	0.59	2.15	0.715						
Sex	Male	198	95	77	93	1.00				0.519					
	Female	11	5	6	7	0.71	0.26	1.99	0.519						
HIV Exposure	Homosexual contact	155	74	50	60	1.00				0.024	1.00				0.351
	Other	53	25	32	39	1.87	1.09	3.22	0.023		1.36	0.71	2.61	0.355	
	Missing	1	1	1	1	3.10	0.19	50.48	0.427		2.28	0.05	97.61	0.668	
Prior AIDS	No	179	86	51	61	1.00				<0.001	1.00				0.234
	Yes	30	14	32	39	3.74	2.08	6.74	<0.001		1.59	0.74	3.42	0.234	
1 st /2 nd cART regimen	First	129	62	57	69	1.00				0.266					
	Second	80	38	26	31	0.74	0.43	1.26	0.266						
Prior ART	ART naïve	92	44	37	45	1.00				0.931					
	Prior ART	117	56	46	55	0.98	0.59	1.63	0.931						
Year of HIV infection	<1996	114	55	44	53	1.00				0.367					
	1996-1999	58	28	27	32	1.21	0.68	2.14	0.522						
	≥2000	36	17	9	11	0.65	0.29	1.45	0.293						
	Missing	1	0	3	4	7.77	0.79	76.73	0.079						
		106	51	52	63	1.00				0.066	1.00				0.077
Year regimen started	1996-1999	103	49	31	37	0.61	0.36	1.03	0.066		0.57	0.31	1.06	0.077	
	≥2000	173	83	73	88	1.00				0.982					
Prior HBV	Negative	7	3	3	4	1.02	0.26	4.04	0.982						
	Positive	29	14	7	8	0.57	0.24	1.36	0.208						
	Missing	184	88	69	83	1.00				0.380					
Prior HCV	Negative	10	5	6	7	1.60	0.56	4.57	0.380						
	Positive	15	7	8	10	1.42	0.58	3.50	0.444						
	Missing														

Baseline covariates		Complete immune responders (N=209)			Incomplete immune responders (N=83)			Univariate			Multivariate				
		N	%	N	%	OR	95%	CI	P-value	P-value overall [/]	AOR	95%	CI	P-value	P-value overall [/]
Baseline viral load (copies/ml)	≤400	39	19	14	17	1.00				0.720					
	>400	170	81	69	83	1.13	0.58	2.21	0.720						
Baseline CD4+ T cell count (cells/μl)	<100	17	8	43	52	1.00				<0.001	1.00				<0.001
	100-199	44	21	26	31	0.23	0.11	0.49	<0.001		0.23	0.11	0.49	<0.001	
	200-350	148	71	14	17	0.04	0.02	0.08	<0.001		0.04	0.02	0.08	<0.001	
Nadir CD4+ T cell count (cells/μl)	<100	39	19	53	64	1.00				<0.001	1.00				0.092
	100-199	68	32	22	26	0.24	0.13	0.45	<0.001		0.44	0.17	1.25	0.127	
	200-350	102	49	8	10	0.06	0.03	0.13	<0.001		0.39	0.12	1.32	0.129	
CD4+ T cell slope	Positive	51	25	25	30	1.00				0.229					
	Negative	126	60	43	52	0.70	0.39	1.26	0.229						
	Missing	32	15	15	18	0.96	0.44	2.08	0.910						
Current cART regimen	NRTI +/-PI, not NNRTI	95	45	46	55	1.00				0.134					
	NRTI +NNRTI, not PI	113	54	37	45	0.68	0.41	1.13	0.134						
	PI + NNRTI	1	1	0	0	N/A									
AZT/d4T containing regimen	AZT	52	25	22	26	1.00				0.276					
	d4T	79	38	46	46	1.13	0.60	2.14	0.690						
	Neither AZT or d4T	78	37	23	28	0.70	0.35	1.37	0.299						
Mono/dual ART prior to 1 st cART regimen	No	141	67	52	63	1.00				0.434					
	Yes	68	33	31	37	1.24	0.73	2.10	0.434						

[/] P-values reported for test of homogeneity in nominal covariates and test for trend for ordinal covariates. Patients with missing data were not included. Covariates that were significant on the univariate, but not the multivariate, analysis are presented in the multivariate section of the table, adjusted for baseline CD4+ T cell count.