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Virologic and immunologic response to HAART, by age and regimen class

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Abstract

Objective—To determine the impact of age and initial HAART regimen class on virologic and immunologic response within 24 months after initiation.

Design—Pooled analysis of data from 19 prospective cohort studies in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).

Methods—Twelve thousand, one hundred and ninety-six antiretroviral-naïve adults who initiated HAART between 1998 and 2008 using a boosted protease inhibitor-based regimen or a nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimen were included in our study. Discrete time-to-event models estimated adjusted hazard odds ratios (aHOR) and 95% confidence intervals (CIs) for suppressed viral load (≤ 500 copies/ml) and, separately, at least 100 cells/ μ l increase in CD4 cell count. Truncated, stabilized inverse probability weights accounted for selection biases from discontinuation of initial regimen class.

Results—Among 12 196 eligible participants (mean age = 42 years), 50% changed regimen classes after initiation (57 and 48% of whom initiated protease inhibitor and NNRTI-based regimens, respectively). Mean CD4 cell count at initiation was similar by age. Virologic response to treatment was less likely in those initiating using a boosted protease inhibitor [aHOR = 0.77 (0.73, 0.82)], regardless of age. Immunologic response decreased with increasing age [18–<30: ref; 30–<40: aHOR 0.92 (0.85, 1.00); 40–<50: aHOR = 0.85 (0.78, 0.92); 50–<60: aHOR = 0.82 (0.74, 0.90); ≥ 60 : aHOR=0.74 (0.65, 0.85)], regardless of initial regimen.

Conclusion—We found no evidence of an interaction between age and initial anti-retroviral regimen on virologic or immunologic response to HAART; however, decreased immunologic response with increasing age may have implications for age-specific when-to-start guidelines.

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Keywords

age; CD4 lymphocyte count; HAART; HIV; viral load

Introduction

The proportion of Americans who are HIV-infected and older than 50 is growing. By 2015, more than 50% of all adults with HIV in the United States will be age at least 50 years [1,2]. It is believed this increasing proportion of HIV-infected individuals who are age at least 50 years is driven by increased survival owing to HAART [3]. New infections also contribute to the increase in HIV-infected adults aged at least 50 years, occurring at an estimated rate of 6.5 per 100 000 population [2].

Although it is generally thought that older HIV-infected individuals initiating HAART will have a decreased immunological response [4–7,13–16] and an increased virologic response [4–12] compared with younger individuals, published data regarding immunologic and virologic response by age to HAART has been mixed. Some studies have demonstrated a smaller increase in CD4 cell count in older compared with younger adults [4–7,13–16], whereas others have been equivocal [10,12,17–19]. Some studies have demonstrated increased virologic suppression in older compared with younger adults [4–12] (which was hypothesized to be adherence-driven [5,20]), whereas one study reported the reverse [21], and many other studies have reported no differences [13,15–17,19]. Current guidelines recommend the initiation of HAART using either ritonavir-boosted protease inhibitors or nonnucleoside reverse-transcriptase inhibitors (NNRTI) [22,23]. These guidelines do not differentiate the recommendations by age, but there were a limited number of older individuals who contributed data to the studies that informed these guidelines. Of the participants in the largest randomized trial of initial HAART regimen class on HIV-1 RNA viral suppression, only 12% were age at least 50 years [24]. Similarly, the largest randomized trial of initial HAART regimen class on immunologic response had a median age of 38 years (interquartile range 32–44) [25].

Given the increasing number of individuals aged at least 50 years with HIV, it is important to determine if HIV antiretroviral guidelines should reflect age differences in virologic and immunologic response to HAART by regimen class. No study has evaluated immunologic and virologic response to HAART by both initial regimen class and age. Thus, the objective of this study was to evaluate the short-term virological and immunologic response to HAART by age and initial regimen class.

Methods

Study population and design

Owing to the large sample size needed to determine the interaction of age and HAART regimen class, our study was nested in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), a collaboration of eight interval and 13 clinical prospective cohort studies of demographically heterogeneous HIV-infected adults from the United States and Canada. The NA-ACCORD is a regional group of the International Epidemiological Databases to Evaluate AIDS (IeDEA) project with over 60 study sites in the United States and Canada. Details of the collaboration have been described elsewhere [26]. Briefly, contributing cohorts have used standardized methods of data collection and have submitted demographic, treatment, clinical, laboratory, and vital status data on enrolled participants. Each cohort's participation in NA-ACCORD was approved by the respective local institutional review boards.

Nineteen NA-ACCORD cohorts contributed the necessary data and agreed to participate in this study. Participants who were at least 18-year-old from these cohorts were included in our study if they initiated HAART using a boosted protease inhibitor-based or NNRTI-based regimen in combination with two or more NRTIs between January 1 1998 and December 31 2008. Those initiating HAART using only nucleoside analogues, nonboosted protease inhibitors, or dual protease inhibitor-NNRTI regimens were excluded from the study. Individuals were required to have at least one follow-up visit; those who discontinued or changed regimens in the first month following HAART initiation were excluded. Further, all participants had a pre-HAART CD4 cell count and HIV-1 RNA measured at, or within 6 months prior to, HAART initiation. Lastly, to most appropriately examine the impact of the initial HAART regimen on our immunologic and virologic outcomes of interest, individuals with a record of treatment prior to HAART initiation, or an HIV-1 RNA at least 500 copies/ml at HAART initiation were excluded.

Outcomes: immunologic and virologic response

Virologic and immunologic responses were measured up to 24 months following HAART initiation. Virologic response was measured using plasma HIV-1 RNA concentrations. Because of differences in HIV-1 RNA assays used in contributing cohorts over time, we defined an HIV-1 RNA measure of 500 copies/ml or less ('suppressed') as the virologic endpoint of interest. If a viral load result was reported as undetectable with an assay that used a lower limit of detection more than 500 copies/ml that measurement was discarded (<1% of all viral load measurements). Immunologic response was measured by CD4 cell count as reported by the cohorts. Time to an increase of 100 cells/ μ l relative to CD4 cell count at, or within 6 months prior to HAART initiation, was used in analyses as a clinically important response. If an individual had more than one HIV-1 RNA or CD4 cell count measurement within a month, the lowest HIV-1 RNA measurement and the arithmetic mean of the CD4 cell measurements were used.

Exposures: age at HAART initiation and initial HAART regimen class

Age at HAART initiation was calculated using the year of birth and the date of HAART initiation and was stratified into five groups 18–<30 years, 30–<40 years, 40–<50 years, 50–<60 years and at least 60 years. HAART was defined as a regimen containing at least three antiretroviral drugs from two or more classes including a boosted protease inhibitor and/or NNRTI. Initial HAART regimen class was specified as the class used at initiation of HAART (boosted protease inhibitor or NNRTI).

Other covariates of interest

Demographic and variables related to HIV disease progression were measured as possible confounders. Demographic variables included sex and race (White, Black, Latino or other/unknown). HIV transmission risk factor was categorized as men who have sex with men (MSM), history of injection drug use (IDU), heterosexual, or other/unknown. Individuals reporting IDU and either male-to-male sexual risk or heterosexual risk were classified as IDU. Other potential confounders included pre-HAART clinically diagnosed AIDS-defining illness (according to the 1993 criteria of the Centers for Disease Control and Prevention (CDC) excluding CD4 cell count less than 200 cells/ μ l), year of HAART initiation, sex and cohort. Data regarding time from HIV seroconversion and nadir CD4 cell count were not available.

Statistical analysis

Differences in means and proportions by age were tested using the chi-squared test statistics and ANOVA, respectively.

Using observational data, we conducted analyses that mimic 'as-treated' analyses in clinical trials with imperfect compliance [27]. To accomplish this aim, we followed individuals from the time of HAART initiation in monthly intervals until the outcome of interest, 'regular' censoring consisting of the date of the last CD4 cell measurement, death, or December 31, 2008; or 'discontinuation' censoring reflecting the date discontinuation of, or switch from, the initial HAART regimen class.

Discontinuation censoring may induce a selection bias because only those individuals who do not discontinue or change from their regimen remain in the study population [28]. To correct this bias, weights were used to allow for influence of those who are censored owing to discontinuation, thus reducing the selection bias [28,29]. Details regarding the estimation and use of published methods [28] are provided in the Appendix, <http://links.lww.com/QAD/A71>. Adjusted hazards odds ratios (aHOR) and 95% confidence intervals were estimated for the initial HAART regimen classes using weighted pooled logistic regression models with month as the interval of time. Kaplan–Meier estimates of the cumulative incidence of each outcome by age group were calculated, incorporating discontinuation and censoring weights [30]. To complement this analysis, we also conducted an 'intention-to-treat' analysis that did not censor at discontinuation or incorporate weights.

Analyses were performed using SAS 9.2 (Cary, North Carolina, USA) and a *P*-value of less than 0.05 was used to identify statistically significant variables.

Results

Nineteen NA-ACCORD cohorts participated in our study, contributing 116 619 possible participants. Of these, 25 449 participants initiated HAART with a boosted protease inhibitor-based or NNRTI-based regimen between January 1, 1998 and December 31, 2008. Eight thousand, one hundred and eighty-five participants were excluded owing to lack of HIV-1 RNA or CD4 cell measurement at, or within 6 months prior to, HAART initiation and 2903 participants were excluded owing to an HIV-1 RNA 500 copies/ml or less at, or within 6 months prior to HAART initiation. Eleven participants were excluded because they were less than 18-years-old at HAART initiation. Finally, 1541 were excluded for failing to maintain their initial regimen for at least one month and 613 were excluded for not having at least one visit in 24 months after HAART initiation and prior to the date of administrative censoring (December 31 2008), resulting in 12 196 eligible participants in our study population.

The mean age of the study population was 42 years (range 18, 83). The participants were predominantly male, and the proportion of males increased with increasing age (Table 1). The proportion of participants who had a history of IDU was greatest among the 40–59 year-old (21%). Mean CD4 and HIV-1 RNA levels at HAART initiation ranged between 205–250 cells/ μ l and 4.66–4.73 $\log_{10}$ copies/ml, respectively, across age groups. The proportion of adults with a clinical AIDS diagnosis prior to HAART ranged from 14–17% across the age groups. Overall, 29% of participants initiated HAART on a boosted protease inhibitor-based regimen and 71% on an NNRTI-based regimen.

Half (50%) (6134/12 196) of individuals did not remain on their initial therapy regimen class 24 months after initiation; 25% (3100/12 169) changed regimen class and 25% (3034/12 196) discontinued treatment. Of all the individuals who did not remain on their initial therapy regimen for 24 months after initiation, 43% (2645/6134) changed regimen class or discontinued treatment in the first 6 months after HAART initiation. Those initiating HAART at the oldest ages had the smallest proportion that changed regimen classes or discontinued treatment (18–<30 years: 51%; 30–<40 years: 50%; 40–<50 years: 52%; 50–

<60 years: 50%; ≥60 years: 44%; P -value <0.01) and a greater proportion of individuals who initiated HAART using a boosted protease inhibitor-based regimen changed regimen class or discontinued treatment (57%) compared with individuals initiating using an NNRTI-based regimen (48%, P -value<0.01).

The cumulative incidence of HIV-1 RNA 500 copies/ml or less did not differ by age, even after stratifying by initial regimen (Fig. 1). The cumulative incidence of an increase of at least 100 cells/ μ l differed by age with older individuals less likely to achieve this immunologic response (Fig. 2). The difference in immunologic response by age was seen among both boosted protease inhibitor and NNRTI initiators.

The results of the pooled logistic regression models are shown in Table 2. The occurrence of HIV-1 RNA suppression increased with increasing age, however, these estimates were not statistically significant. Immunologic response decreased with increasing age and the estimates were statistically significant. Those who initiated using a boosted protease inhibitor had a decrease in the hazard odds of virologic response compared with those who initiated using an NNRTI; additionally, there was not a significant increase in the likelihood of immunologic response on those initiating with boosted protease inhibitors compared with NNRTIs. Those with higher HIV-1 RNA levels at HAART initiation, Blacks, those in HIV risk groups other than MSM, and those initiating HAART in the late 1990s and early 2000s had a decrease in the hazard odds of HIV-1 RNA 500 copies/ml or less. Males, those with a lower HIV-1 RNA level at HAART initiation, those in HIV risk groups other than MSM, and those initiating HAART in the late 1990s and early-to-mid 2000s had a decrease in the hazard odds of immunologic response.

The interaction of age and initial HAART regimen class was not statistically significant for our virologic outcome ($P=0.40$) or immunologic outcome ($P=0.19$). The increase in the hazard odds of viral suppression comparing NNRTI to boosted protease inhibitor was seen across all age groups (Table 3). The decrease in the hazard odds of immunologic response with increasing age was seen after stratification by initial regimen.

An intention-to-treat analysis that did not censor individuals at discontinuation or incorporate weights demonstrated similar findings, but, as expected, were attenuated. For example, those initiating on boosted protease inhibitors had a 21% decrease in the likelihood of viral suppression compared with those initiating on an NNRTI [HOR=0.79 (0.75, 0.83)] and immunologic response decreased with increasing age [18–<30 years: ref; 30–<40 years: aHOR=0.91 (0.84, 0.98); 40–<50 years: aHOR=0.86 (0.80, 0.93); 50–<60 years: aHOR=0.90 (0.82, 0.99); ≥60: aHOR=0.81 (0.71, 0.92)]. Age did not modify the effect of initial regime on virologic or immunologic response ($P=0.11$ and $P=0.35$, respectively).

Discussion

This is the largest study of the impact of age and regimen class on virologic and immunologic response to HAART to date. Our study has several important findings. First, half (50%) of individuals who initiated therapy discontinued or changed their initial regimen within the first 2 years. Individuals initiating using an NNRTI-based regimen were more likely to achieve virologic suppression (HIV-1 RNA ≤500 copies/ml) than those initiating using a boosted protease inhibitor-based regimen; however, we did not see a significant increase in virologic suppression with increasing age. In contrast to the virologic outcome, the immunologic outcome did not differ by regimen class, but was clearly impacted by age with older individuals less likely to have an increase in of at least 100 cells/ μ l. Age at HAART initiation did not modify the effect of the initial regimen on virologic or immunologic response.

The estimation of 50% of individuals discontinuing or changing their initial HAART regimen is an underestimation of the proportion that discontinues, or changes, his/her initial HAART regimen in the first 2 years because our inclusionary criteria required that an individual must continue their initial regimen for at least 1 month. Notably, 25% changed regimen class, suggesting potential side-effect or toxicity, whereas 25% discontinued treatment for at least 1 month suggesting potential nonadherence. We found a greater proportion of individuals who initiated HAART using a boosted protease inhibitor-based regimen changed regimen class or discontinued treatment compared with individuals initiating using an NNRTI-based regimen (57 and 48%, respectively). Similarly, in a randomized trial with immunologic outcomes, the proportion that discontinued or changed from their initial HAART regimen class was 43 and 32% for those who initiated using protease inhibitor and NNRTI regimens, respectively [25]. This could be because protease inhibitors are more difficult to tolerate than NNRTIs with side-effects including diarrhea, hyperlipidemia and glucose dysmetabolism. Studies examining time to toxicity outcomes by age and HAART regimen class are needed to further assess the need for age-specific treatment guidelines.

Our data did not show improved virologic response in older patients compared with younger age groups, as been previously shown [4–12]. Previous studies concluded improved virologic response among older adults was owing to better adherence to HAART, and Silverberg *et al.* [5], found that controlling for adherence mitigated the differences in virologic responses between age groups [5,20]. Although we were unable to measure and directly account for adherence in our study, our inclusionary criteria and censoring at the time of discontinuation of, or change from, initial HAART regimen resulted in a study population that is more likely to be adherent, regardless of age. Our study criteria for participation and our methods to account for changes in initial HAART regimen were necessary to achieve our objective of estimating the average causal effect of initial HAART regimens on immunologic and virologic response by age. Our findings were similar to the findings of a randomized-controlled trial of viral suppression by initial ART regimen at 96 weeks, with those initiating using NNRTIs more likely to suppress compared with those initiating using boosted protease inhibitors [24].

CD4 cell recovery has been shown to be inversely associated with age and other groups have also found a depressed immunologic response in older patients [12,31,32]. Several mechanisms may account for the suboptimal immunologic response in older individuals, including reduced T-cell regenerative capacity owing to either thymic dysfunction and/or the exhaustion of stem cells, naive T cells or central memory T cells. Chronic inflammation may also affect T-cell regeneration. The fact that our findings did not differ by regimen class provides additional evidence for a more broadly defined mechanism for the impact of age on immunologic response to HAART. Although further research is needed to determine if guidelines for when to start HAART should differ by age, our observation that older individuals are less likely to have a robust immunologic response suggest that the optimal time to start HAART might differ by age.

Although a few studies have looked at the effect of regimen on clinical response by age group [5,12], no study has examined the effect of regimen type on clinical response in a population this large or heterogeneous. Bartlett *et al.* [33], suggested NNRTI-based regimens were associated with improved virologic suppression compared with protease inhibitor-based regimens, but did not comment on how this effect might vary with age. Patterson *et al.* [11], found immune reconstitution and viral suppression did not vary by treatment regimen when stratified by age. Our results demonstrate an increase in virologic response with NNRTI-based regimens compared with protease inhibitor-based regimens, regardless of age. Although this may suggest that NNRTIs might be preferred in this older

group, efavirenz, the current guideline-preferred NNRTI, has known CNS adverse effects that also might cause it to be a less desirable drug in some older patients. Studies examining time to side-effect and comorbidity events by age and initial HAART regimen class are needed to further assess the need for age-specific treatment guidelines.

Strengths of this study include the large study population of antiretroviral therapy naïve adults coupled with modern analytical methods to account for the possible selection biased induced by censoring individuals once they discontinued or changed their initial HAART regimen. We did not have data on time from seroconversion to distinguish those who were infected recently from those who have aged with HIV. Survival is suspected to be the driver of the greater proportions of HIV-infected individuals who are older, but it is not the only mechanism. Theoretically, older individuals with HIV infection may have had their infection longer than younger individuals, and these differences may have contributed to the age-related effects on immunologic response. Another limitation was using a definition of viral suppression (<500 copies/ml) that is higher than current standards (<200 copies/ml); however, owing to the changes in the lower limit detection of HIV-1 RNA assays during our study time period, using a lower limit of detection cut-off of 200 copies/ml resulted in omitting 115 050 (8%) viral load measurements, creating a bias by removing many of the participants from the earlier years of our study. Additionally, we did not have data on the reason for the switch or discontinuation. Reasons for switching are important for future studies that could examine differences in toxicity by age and regimen. Lastly, we did not have a direct measurement of adherence, such as drug plasma levels; however, we suspect our study criteria and design restricted the study population to the more adherent HIV-infected individuals.

HIV is a chronic disease that requires life-long therapy and optimizing initial HAART regimen is important. Although future studies will need to evaluate the impact of toxicity and non-AIDS-related comorbidities on virologic and immunologic outcomes, our data do not currently support the use of specific HAART regimens for specific age groups. However, given the impact of CD4 cell count on long-term survival, initiating HAART at higher CD4 cell counts for older individuals may be useful given the decreased likelihood of a robust (≥ 100 cells/ μ l) CD4 cell response with increasing age.

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NA-ACCORD participating cohorts (representatives):

- (1) AIDS Link to the IntraVenous Experience (Gregory D.Kirk)
- (2) Adult AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (Constance A. Benson, Ronald J. Bosch, Ann C. Collier)
- (3) HAART Observational Medical Evaluation and Research (Robert S. Hogg, Richard Harrigan, Julio Montaner)
- (4) HIV Outpatient Study (John T. Brooks, Kate Buchacz)

- (5) HIV Research Network (Kelly A. Gebo)
- (6) Johns Hopkins HIV Clinical Cohort (Richard D. Moore)
- (7) John T. Carey Special Immunology Unit Patient Care and Research Database, Case Western Reserve University (Benigno Rodriguez)
- (8) Kaiser Permanente Northern California (Michael A. Horberg, Michael J. Silverberg)
- (9) Longitudinal Study of Ocular complications of AIDS (Jennifer E. Thorne)
- (10) Multicenter Hemophilia Cohort Study-II (James J. Goedert)
- (11) Multicenter AIDS Cohort Study (Lisa P. Jacobson)
- (12) Montreal Chest Institute Immunodeficiency Service Cohort (Marina B. Klein)
- (13) Ontario HIV Treatment Network Cohort Study (Sean B. Rourke, Anita R. Rachlis)
- (14) Southern Alberta Clinic Cohort (M. John Gill)
- (15) Studies of the Consequences of the Protease Inhibitor Era (Steven G. Deeks, Jeffery N. Martin)
- (16) University of Alabama at Birmingham 1917 Clinic Cohort (Michael S. Saag, Michael Mugavero, James Willig)
- (17) University of North Carolina, Chapel Hill HIV Clinic Cohort (Joseph J. Eron, Sonia Napravnik)
- (18) University of Washington HIV Cohort (Mari M. Kitahata and Heidi M. Crane)
- (19) Veterans Aging Cohort Study (Amy C. Justice, David Fiellin)
- (20) Vanderbilt-Meharry CFAR Cohort (Timothy R. Sterling, Sam Stinette, Peter Rebeiro, David Haas)
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Fig. 1. Cumulative incidence of HIV RNA at least 500 copies/ml in the first 2 years after HAART initiation, by age group and initial HAART regimen class

(a) Overall cumulative incidence of HIV RNA 500 copies/ml or less in the first 2 years after HAART initiation. (b) Cumulative incidence of HIV RNA 500 copies/ml or less in those initiating HAART with a boosted PI-based regimen. (c) Cumulative incidence of HIV RNA 500 copies/ml or less in those initiating HAART with an NNRTI-based regimen. HAART highly active antiretroviral treatment, NNRTI nonnucleoside reverse transcriptase inhibitor, PI protease inhibitor.

Fig. 2. Cumulative incidence of an increase in CD4 cells of at least 100 cells/ml in the first 2 years after HAART initiation, by age group and initial HAART regimen class

(a) Overall cumulative incidence of at least 100 cells/ml in the first 2 years after HAART initiation. (b) Cumulative incidence of an increase of at least 100 cells/ml in those initiating HAART with a boosted PI-based regimen. (c) Cumulative incidence of an increase of at least 100 cells/ml in those initiating HAART with NNRTI-based regimen. NNRTI nonnucleoside reverse transcriptase inhibitor, PI protease inhibitor.

Characteristics of participants ($N = 12196$) at antiretroviral therapy initiation, by age, NA-ACCORD 1998–2008.

Table 1

Characteristic	Age group					
	18–29 years $n = 1342$	40–49 years $n = 3930$	50–59 years $n = 4292$	50–59 years $n = 2034$	≥60 years $n = 598$	
Male, n %	1022	3163	3594	1786	548	91.6%
Race and ethnicity, n %						
White	391	1266	1465	697	248	41.5%
Black	478	1236	1531	774	202	33.8%
Hispanic	181	494	355	136	42	7.0%
Other/Unknown	292	934	941	427	106	17.7%
HIV transmission risk group						
MSM	513	1394	1163	406	95	15.9%
Injection drug use	104	482	915	433	54	9.0%
Heterosexual contact	313	808	770	315	96	16.1%
Other/Unknown	412	1246	1445	880	353	59.0%
CD4 cell count, mean (SD)	250 (188)	213 (177)	211 (183)	205 (165)	206 (164)	
Log ₁₀ HIV viral load, mean (SD)	4.66 (0.77)	4.73 (0.76)	4.69 (0.77)	4.68 (0.78)	4.66 (0.80)	
Viral suppression (≤500 copies/ml) within 6 months of HAART initiation, n %	1065	2907	2993	1385	401	67.1%
Clinical AIDS diagnosis, n %	216	556	682	339	100	16.7%
Year of HAART initiation, mean	2003	2003	2003	2003	2003	
First HAART regimen, n %						
Boosted PI-based	354	1123	1326	630	159	26.6%
NNRTI-Based	988	2807	2966	1404	439	73.4%

NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 2

Adjusted^a hazard odds ratios (aHOR) and 95% confidence intervals (95% CI) of virologic and immunologic response to HAART within 24 months following HAART initiation, NA-ACCORD, 1998–2008.

	Outcomes HIV-1 RNA suppression (<500 copies/ml)		CD4 cell count increase of 100 cells/μl	
	aHOR ^a	95% CI	aHOR ^a	95% CI
Age (years)				
18–<30	REF	-	REF	-
30–<40	0.71	0.89–1.05	0.92	0.85–1.00
40–<50	0.66	0.89–1.04	0.85	0.78–0.92
50–<60	1.00	0.91–1.10	0.82	0.74–0.90
≥60	1.05	0.92–1.20	0.74	0.65–0.85
Initial HAART regimen class				
NNRTI	REF	-	REF	-
Boosted PI	0.77	0.73–0.82	1.03	0.98–1.09
CD4 cell count at HAART initiation				
<350 cells/μl	REF	-	REF	-
≥350 cells/μl	0.94	0.89–1.00	1.05	0.98–1.12
Log ₁₀ HIVRNA at HAART initiation	0.84	0.82–0.87	1.32	1.27–1.36
Sex				
Male	REF	-	REF	-
Female	0.98	0.92–1.05	1.13	1.05–1.21
Race and ethnicity				
White	REF	-	REF	-
Black	0.91	0.86–0.97	0.87	0.82–0.92
Hispanic	0.94	0.86–1.02	0.87	0.79–0.95
Other/Unknown	0.99	0.92–1.06	0.92	0.86–1.00
HIV transmission risk group				
MSM	REF	-	REF	-
Injection drug use	0.85	0.78–0.93	0.78	0.71–0.86
Heterosexual contact	0.92	0.85–0.99	0.86	0.79–0.93
Other/unknown	0.88	0.81–0.96	0.88	0.81–0.96
Clinical AIDS prior to HAART initiation				
No	REF	-	REF	-
Yes	1.04	0.97–1.11	0.94	0.88–1.01
Year of HAART initiation				
1998	REF	-	REF	-
1999	1.16	0.99–1.37	0.92	0.78–1.08
2000	1.21	1.03–1.42	0.93	0.79–1.09
2001	1.32	1.13–1.55	0.89	0.76–1.05
2002	1.15	0.98–1.34	0.91	0.78–1.07
2003	1.30	1.11–1.52	1.03	0.88–1.21

	Outcomes HIV-1 RNA suppression (<500 copies/ml)	CD4 cell count increase of 100 cells/μl		
2004	1.41	1.20–1.65	0.99	0.84–1.17
2005	1.43	1.22–1.68	1.13	0.96–1.34
2006	1.55	1.32–1.83	1.14	0.97–1.35
2007	2.02	1.70–2.40	1.21	1.02–1.44
2008	2.32	1.93–2.78	1.39	1.15–1.67

AIDS acquired immune deficiency syndrome, HAART highly active antiretroviral treatment, HIV human immunodeficiency virus, NNRTI nonnucleoside reverse transcriptase inhibitor, PI protease inhibitor.

^a Pooled logistic regression models weighted for the first change in ART regimen class (weights at the 1st and 99th percentile were truncated) and adjusted for cohort.

Table 3

Adjusted^a hazard odds ratios (aHOR) and 95% confidence intervals (95% CI) virologic and immunologic response to HAART within 24 months following HAART initiation, by regimen class and age, NA-ACCORD, 1998–2008.

	aHOR ^a NNRTI	95% CI	aHOR ^a Boosted PI	95% CI
Virologic response (HIV RNA ≤500 copies/ml)				
Age (years)				
18–<30	Ref	-	0.75	0.64–0.88
30–<40	0.98	0.89–1.07	0.71	0.64–0.79
40–<50	0.94	0.85–1.03	0.76	0.68–0.85
50–<60	0.98	0.88–1.09	0.79	0.69–0.90
≥60	1.06	0.91–1.24	0.77	0.63–0.94
Immunologic response (≥100 cells/μl increase in CD4 cell count)				
Age (years)				
18–<30	Ref	-	0.94	0.80–1.11
30–<40	0.90	0.82–0.99	0.96	0.86–1.07
40–<50	0.83	0.76–0.91	0.88	0.79–0.99
50–<60	0.80	0.72–0.90	0.84	0.73–0.96
≥60	0.73	0.63–0.85	0.76	0.60–0.97

AIDS acquired immune deficiency syndrome, HAART highly active antiretroviral treatment, HIV human immunodeficiency virus, NNRTI nonnucleoside reverse transcriptase inhibitor, PI protease inhibitor.

^aPooled logistic regression models weighted for the first change in HAART regimen class (weights at the 1st and 99th percentile were truncated) and adjusted for CD4 cell and HIV viral load at initiation, race and ethnicity, HIV transmission risk group, sex, cohort, clinical AIDS diagnosis prior to HAART initiation, year of HAART initiation and month from HAART initiation.