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CD4⁺ T-cell counts and plasma HIV-1 RNA levels beyond 5 years of highly active antiretroviral therapy (HAART)

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Abstract

Background—The heterogeneity of CD4⁺ T-cell counts and HIV-1 RNA at 5-12 years after the initiation of highly active antiretroviral therapy (HAART) remains largely uncharacterized.

Methods—In the Multicenter AIDS Cohort Study, 614 men who initiated HAART contributed data 5-12 years subsequently. Multivariate regression was used to evaluate the predictors of CD4⁺ counts and HIV-1 RNA levels.

Results—At 5-12 years post-HAART, the median CD4⁺ T-cell count was 586 (inter quartile range (IQR): 421-791) cells/μl and 78% of the HIV-1 RNA measurements were undetectable. Higher CD4⁺ T-cell counts 5-12 years post-HAART were predicted by higher CD4⁺ T-cell counts and higher total lymphocyte count pre-HAART, lack of hepatitis B or C virus co-infections, and greater CD4⁺ T-cell change as well as suppressed HIV-1 RNA in the first 5 years after starting HAART. Older men (≥50 years) with 351-500 CD4⁺ cells/μl at HAART initiation had adjusted mean CD4⁺ T-cell count of 643 cells/μl at 10-12 years post-HAART, which was similar to the adjusted mean CD4⁺ T-cell count (670 cells/μl, $p=0.45$) in this period for younger men starting HAART with lower CD4⁺ T-cell counts. HIV-1 RNA suppression in the first 5 years post-HAART predicted subsequent viral suppression.

Conclusion—Immunological and virological responses in the first five years post-HAART predicted subsequent CD4⁺ T-cell counts and HIV-1 RNA levels. The association between age and subsequent CD4⁺ T-cell count supports incorporating age in guidelines for use of HAART.

Keywords

CD4⁺ T-cells; HIV-1 RNA; HAART; response; age effects

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Introduction

It has been more than 15 years since the introduction of the highly active antiretroviral therapy (HAART). By reducing HIV-related morbidity and mortality¹⁻³, HAART has transformed HIV-1 infection to a manageable chronic condition⁴. In developed countries, over 70% of HIV-infected individuals have received HAART⁴⁻⁶. CD4⁺ T-cell counts (CD4⁺ counts) and plasma HIV-1 RNA (RNA) concentration after HAART initiation strongly predicts AIDS and death⁷⁻¹¹, highlighting the importance of characterizing these biomarkers post-HAART. Most published reports have studied CD4⁺ counts and RNA in the first 5 years after HAART initiation^{7, 10, 12-14} and the few that have studied these markers after 5 years of HAART¹⁵⁻¹⁸ have not delineated the factors related to their heterogeneity with long-term HAART use.

Here we describe the CD4⁺ count and plasma RNA distributions, and identify factors associated with these two biomarkers, at 5-12 years after HAART initiation in the Multicenter AIDS Cohort Study (MACS). We hypothesized that age, HIV-1 disease stage before HAART initiation, immunological and virological responses to HAART in the first five years after HAART, and types of HAART regimens would significantly affect later CD4⁺ count and RNA levels among long-term HAART users.

Methods

Population and Study Design

The MACS is an ongoing prospective study of HIV-1 infection among men who have sex with men (MSM) in the United States¹⁹⁻²¹. A total of 6,972 men were recruited: 5,622 before 1991 and 1,350 in 2001-2003 in Baltimore, MD; Chicago, IL; Los Angeles, CA; and Pittsburgh, PA. Study questionnaires are available at <http://www.statepi.jhsph.edu/macsf/forms.html>. MACS study protocols were approved by institutional review boards at each center, and informed consent was obtained from all participants.

Six-monthly visits include standardized interviews, physical examinations, and collection of blood for concomitant laboratory testing and storage. Positive enzyme immunoassays with confirmatory Western blot tests were used to determine HIV-1 seropositivity. RNA levels were determined using Roche Ultrasensitive RNA PCR assay (Hoffman-LaRoche, Nutley, NJ, U.S.A.) with a detection limit of 50 copies/ml, and CD4⁺ levels were quantified using standardized flow cytometry^{22, 23}. For 2001-03 recruits who initiated HAART prior to study entry, historical information on CD4⁺ counts, RNA measurements and use of antiretroviral therapy (ART) was abstracted from medical records. Hepatitis B virus (HBV) infection was determined by positive surface antigen or core antibody. Hepatitis C virus (HCV) infection was defined by positive antibody. Presence of an AIDS-defining illness (AIDS) was based on the clinical conditions listed in the 1993 CDC case definition²⁴ but did not include cases identified only by low CD4⁺ counts. Self-reported use of ART at each visit was summarized to define use of HAART according to the DHHS/Kaiser Panel guidelines²⁵. The date of HAART initiation was the midpoint between the last study visit without report of HAART use (last no-HAART) and the first visit at which HAART use was reported (first HAART). Adherence to HAART was dichotomized as 100% or less than 100% based on self-reported adherence to current medications over the last four days²⁶.

We used data collected up to September 30, 2009 (end of visit 51). Specifically, our study population was restricted to HIV-positive men who 1) initiated HAART on or after July 1, 1995, with ≤ 1 year between the last no-HAART and first HAART visits, 2) reported using HAART for $\geq 80\%$ of the visits post-HAART initiation, and 3) had $\geq$ one CD4⁺ count and

RNA measurement available at 5-12 years after HAART initiation. The measurements at visits where participants did not report using HAART (n=393 person-visits) were excluded from the analysis.

Outcome Variables

We examined three outcome variables: (1) continuous CD4⁺ count, (2) binary indicator of suppressed RNA (<50 copies/ml), and (3) log₁₀ (RNA) for those with detectable RNA measured at 5-12 years after HAART initiation. CD4⁺ counts above 1500 cells/μl (i.e., above the normal range) were set to 1500 to reduce variance.

Statistical Analysis

Linear regression analyses were conducted for the continuously distributed outcomes, and logistic regression was used for RNA suppression. Factors with *p*-value ≤ 0.1 were kept in final models. SAS GENMOD procedure (SAS Institute, Cary, North Carolina, USA) with generalized estimating equations was used to control for within-subject correlation.

For each outcome, two models were used. First, we examined pre-HAART factors including last known CD4⁺ count (≤200, 201-350, 351-500, or >500 cells/μl), RNA level (≤1,000, 1,001-10,000, 10,001-100,000, or >100,000 copies/ml), AIDS (yes /no), experience of any ART, HBV co-infection, and HCV co-infection. We also examined factors in the first five years on HAART, including CD4⁺ slope (per 50 cells/μl change per year), < 50 RNA copies/ml for ≥ 50% of measurements (yes / no), and total number of times regimens were switched (0, 1, 2+). Age at HAART initiation (<40, 40-49.9, or ≥50 years), race, cohort entry (pre-2001 or 2001-03), calendar year of HAART initiation, number of years since HAART initiation (each year treated linearly, centered at 8 years), and adherence to HAART (100% vs. <100%) in the 4 days before the study visit were also evaluated. MACS center was included to control for site variability. Because CD4⁺ measurements may be difficult to obtain in resource-limited settings, we also examined the effects of total lymphocyte count (TLC) below <1,200 cells/μl (yes / no) before HAART and its occurrence in the first five years on HAART²⁷. For this analysis, we excluded 2001-03 recruits who initiated HAART before study entry, because pre-therapy TLC was not available. For the analysis of TLC as predictor, we excluded the CD4⁺ count as a covariate.

Second, we assessed the effects of HAART regimens used between visit_(i) and visit_(i+1) on the biomarkers at visit_(i+1). We examined the three backbones of HAART: (1) PI-HAART (HAART regimens containing any protease inhibitor (PI), taken as the reference group), (2) NNRTI-HAART (HAART regimens containing any non-nucleoside reverse transcriptase inhibitor (NNRTI) without PI), (3) triple-NRTI-HAART (HAART regimens containing only NRTIs). We then examined the 15 most frequently used HAART regimens by replacing the HAART backbones in the model with a HAART regimen variable (15 categories). We also included race, center, year of cohort entry (pre-2001, 2001-2003), pre-HAART HBV and HCV co-infections, calendar year of HAART initiation, and number of years since HAART initiation. Since current disease stage and adherence may predict regimen type, we also included time-varying covariates that were updated at each visit: age (<40, 40-49.0, or ≥50 years), CD4⁺ count and RNA detection at the prior visit, cumulative number of times regimens were switched between HAART initiation and the prior visit (0, 1, 2+), and adherence. We also repeated the analyses, with restriction to the men who were ART-naïve prior to HAART initiation.

Results

A flow chart of the study population is shown in Supplemental Figure 1; 614 MACS participants contributed 4,431 CD4⁺ and RNA measurements while using HAART for 5-12 years. At HAART initiation, 47% were <40 and 12% >50 years old. Before initiating HAART, 40% were ART-naïve and more than half had <350 CD4⁺ cells/μl and ≥10,000 RNA copies/ml. In the first five years on HAART, 70% had a positive CD4⁺ slope. The 614 men analyzed were similar to the men excluded due to missing data (n=188) or on HAART for < 80% of visits (n=200) in terms of the calendar year and age at HAART initiation, race, cohort entry, CD4⁺ and RNA levels, and proportion ART-naïve before HAART initiation.

Of the 4,431 person-visits with CD4⁺ counts and RNA measurements, 53% were classified as PI-HAART-related. Of those visits, ritonavir-boosted regimens were reported at 70%, with lopinavir/ritonavir (Kaletra) accounting for about one-third. The other boosted PIs were atazanavir (25%), indinavir (17%), and saquinavir (9%). Among the 42% NNRTI-based HAART person-visits, efavirenz was reported at 67% and nevirapine at 32%. Triple-NRTI-HAART regimens were reported at 5% of person-visits. Figure 1 shows the frequency of the most reported HAART regimens by calendar time.

CD4⁺ T-cell count at 5-12 years after HAART initiation

Sixty-three percent of the 614 men contributed at least five CD4⁺ counts 5-12 years after HAART initiation (Table 1). The unadjusted median CD4⁺ count during this interval was 585 (IQR: 412 - 791) cells/μl. Figure 2 shows the trajectories of median CD4⁺ count from pre-HAART to 12 years after HAART initiation and the overall adjusted mean CD4⁺ count in the 5-12 years by pre-HAART levels. In the first five years after HAART initiation, the CD4⁺ counts in each group increased significantly ($p<0.01$), but were stable at 5-12 years on HAART for those with >350 CD4⁺ cells/μl pre-HAART. Adjusting for factors shown in Table 2, men with ≤ 350 CD4⁺ cells/μl pre-HAART had a mean annual increase of 11 cells/μl ($p<0.01$) while on HAART for 5-12 years.

In multivariate analysis (Table 2), men with lower pre-HAART CD4⁺ counts or with HBV or HCV co-infections had lower counts at 5-12 years on HAART. CD4⁺ slope in the first five years on HAART predicted subsequent CD4⁺ counts only for those with <500 CD4⁺ cells/μl prior to starting HAART. Those who suppressed virus for ≥50% of when measured or remained on their initial or second regimen (compared to those who switched their HAART regimens ≥ two times) in the first five years on HAART had significantly higher CD4⁺ counts in the subsequent eight years.

Age at HAART initiation also affected long-term CD4⁺ counts. The adjusted mean CD4⁺ count for those ≥50 years at HAART initiation was significantly lower than that for participants younger than 40 years. Men younger than 40 years who started HAART with 201-350 CD4⁺ cells/μl (reference group) had an adjusted mean cell count of 670 cells/μl in the 10-12 years after HAART initiation as compared with 578 cells/μl in those aged ≥50 years with the same starting level of CD4⁺ cells ($p<0.01$). To achieve equivalent CD4⁺ counts as the younger men, those aged ≥50 years at HAART initiation needed to start HAART with 351-500 CD4⁺ cells/μl (adjusted mean CD4⁺ counts at 10-12 years post-HAART was 643 cells/μl, $p=0.45$ for comparing to the reference group). Restricting to men who were ART-naïve before HAART initiation, older men still had 60 fewer CD4⁺ cells/μl on average when compared to the younger men (Table 2). The lack of statistical significance for this difference most likely resulted from a reduced sample size. The average long-term CD4⁺ count (653 cells/μl) for men aged 40-49.9 years who initiated HAART with 201-350 CD4⁺ cells/μl did not differ significantly ($p=0.39$) from that of the younger men starting with the same cell count.

In a separate model to examine the effect of TLC on long-term CD4⁺ counts, those with pre-HAART TLC <1,200 cells/μl had an adjusted mean CD4⁺ count of 514 cells/μl at 10-12 years on HAART, which was 122 cells/μl lower than that of those with ≥1,200 cells/μl ($p<0.01$). Similarly, those with a nadir TLC <1,200 cells/μl in the first five years after HAART initiation had an adjusted mean of 522 CD4⁺ cells/μl at 10-12 years on HAART, 134 cells/μl lower than those whose TLC was always above 1,200 cells/μl in the first five years. The effects of the other factors examined persisted in this model except that the effect of having switched regimens ≥2 times was smaller (-11 cells/μl with $p=0.74$, as compared to the reference group).

When examining the effects of recently used HAART regimens on CD4⁺ counts, we controlled for potential confounding by including time-varying age, CD4⁺ counts, detection of RNA, cumulative number of times switched regimen from HAART initiation to the prior visit, and adherence. Race, study center, year of cohort entry, and pre-HAART HBV and HCV co-infection status were also included. The adjusted CD4⁺ counts did not differ significantly for those reporting PI-, NNRTI-, or triple-NRTI-based HAART regimens. Furthermore, specific HAART regimens did not differentiate the CD4⁺ counts at 5-12 years after HAART initiation (data not shown).

Since follow-up times varied across the cohort and individuals followed for 10 years may have differed from those with less follow-up, we repeated the above analyses with restriction to the 314 men who were followed for at least 10 years under HAART and observed similar findings (supplemental Table 1). Specifically, differences in the estimates of the effects on the CD4⁺ count shown in Table 2 between the full and the restricted analysis were all less than 50 cells/mm³ and within the confidence limits of the estimates. Furthermore, the median CD4⁺ counts over time in Figure 2 did not differ significantly when using the restricted sample (supplemental Figure 2).

Factors associated with suppressed RNA at 5-12 years after HAART initiation

Overall, 78% of RNA measurements in 5-12 years after HAART were undetectable (<50 copies/ml) and this percentage increased over time (bottom of Figure 2). Age, center, pre-HAART CD4⁺ counts, RNA levels, and AIDS status had little to no effect on this proportion after accounting for RNA in the first five years following initiation. Recent HAART initiators were more likely to suppress RNA (Table 3). After including this variable, the effect of being ART-naïve when starting HAART was no longer significant. Participants enrolled in 2001-3 also were more likely to suppress RNA when compared to the pre-2001 recruits (Table 3). However, among men who were ART-naïve at HAART initiation, cohort entry year did not affect long-term RNA suppression, and the effect of switching regimens also attenuated. As shown in Table 3, the RNA response to HAART in the first five years following initiation predicted subsequent viral suppression, as did the number of times regimens were switched in those five years and current adherence to HAART. Non-Caucasians were less likely to suppress RNA, significantly so for the African-American group (OR=0.42, $p<0.01$). RNA suppression was more likely with increased time on HAART (OR=1.28 per year increase, $p<0.01$).

In a separate model, persons using NNRTI-based regimens were as likely to suppress RNA as those on PI-based regimens, controlling for current age (OR=1.47, $p=0.04$ for comparing age ≥50 vs. <40), race, CD4⁺ counts and RNA detectability at the prior visit, adherence and number of years after HAART initiation. Participants using triple-NRTI-HAART were significantly less likely to suppress RNA than those using PI-HAART (OR=0.42, $p<0.01$) or NNRTI-HAART (OR=0.40, $p<0.01$). Similar results were observed among those who were ART-naïve at HAART initiation (data not shown). Compared to the reference regimen (tenofovir + emtricitabine + efavirenz), some regimens containing nevirapine were

associated with a greater likelihood of detectable RNA. We then restricted the analyses to those using NNRTI-regimens (without any PIs) and observed a lower odds of viral suppression for those using nevirapine compared to efavirenz (OR=0.67, $p=0.08$). Not surprisingly, a higher percentage (80%) of undetectable RNA was observed among those with complete adherence, compared to 70% for those with less adherence (adjusted OR was 1.34, $p<0.01$).

Restricting the analysis to those 314 men who were followed for ≥ 10 years under HAART, most of the odds ratios for suppressed HIV RNA were further from null but all were in the same direction as for the full population (supplemental Table 2).

Factors associated with level of detectable RNA

Among the 22% ($n=970$) of person-visits with detectable RNA while on HAART for 5-12 years, the median RNA was 958 (IQR: 149 – 9,180) copies/ml. RNA level prior to HAART initiation affected long-term RNA level; adjusted median RNA at 5-12 years were 955 and 330 copies/ml for those with pre-HAART RNA of $>10,000$ and $\leq 1,000$ copies/ml, respectively ($p<0.01$). The effect of RNA while under HAART in the first 5 years on subsequent RNA levels was also significant; adjusted median RNA at 5-12 years after HAART initiation were 1,181 and 223 copies/ml for those with $<50\%$ and $\geq 50\%$ undetectable RNA measurements, respectively ($p<0.01$).

Discussion

In this study, several factors were found to be associated with lower CD4⁺ counts in men who had received HAART for 5-12 years. Important modifiable factors were older age (>50 years) and lower CD4⁺ counts at the time of HAART initiation. Other significant factors were the annual change in CD4⁺ count in the first 5 years of HAART (for those who initiated HAART with < 500 CD4⁺ cells/ μ l), the number of switches in HAART regimens in the first 5 years, and hepatitis B and C virus infections.

The importance of age and baseline CD4⁺ count at HAART initiation in the immunological response to HAART 5-12 years later extends the findings of Kaufmann et al that these parameters were significantly associated with CD4⁺ count at 5 years after HAART¹². In the present study, we show that to have an equivalent long-term immunological response as younger men, older men needed to start HAART at higher CD4⁺ counts. Specifically, those 50 years or older who initiated HAART with 351-500 CD4⁺ cells/ μ l had equivalent CD4⁺ counts at 10-12 years after HAART to those younger than 40 years who started HAART with 201-350 T-cells/ μ l. Adjusting for age, we also show that long-term CD4⁺ counts in men who started HAART at different CD4⁺ count levels follow almost parallel trajectories. MACS investigators also reported similar parallel trajectories over the 3 ½ years after HAART initiation³, and in a joint analysis with the Women's Interagency HIV-1 Study (WIHS) up to 7 years post-HAART¹⁵. In the present study, we show that CD4⁺ counts increased during the years 5 to 12 on HAART among men who started HAART with ≤ 350 CD4⁺ cells/ μ l, consistent with the earlier report from the MACS and WIHS¹⁵ and with a recent report¹⁶ that showed that those with lower pre-HAART CD4⁺ counts took longer to reach CD4⁺ >500 cells/ μ l than those with higher counts. Age also was negatively associated with CD4⁺ count increases after 4 years of HAART¹⁶. The association of older age with lower CD4⁺ count might be due to diminution of thymic T cell production with age²⁸.

Older age is associated with a more rapid progression to AIDS and a shorter survival both in the absence of HAART^{29, 30} and in the presence of HAART^{2, 31-34}. It is also well known that immune function declines with age. Therefore, initiating HAART at relatively high CD4⁺ counts might be of more benefit in older HIV-1-infected individuals than in younger

ones. In Europe, but not in the U.S.²⁵, age >50 years is included in the guidelines³⁵ for initiation of HAART at CD4⁺ counts >350 cells/μl. Age may explain some of the heterogeneity in response to HAART among those starting treatment at relatively high CD4⁺ counts, and the data from this study support the inclusion of age in treatment guidelines.

In the present study, the median CD4⁺ count was 585 cells/μl, and RNA was undetectable (<50 copies/ml) in 78% of the measurements that occurred 5-12 years under HAART. Among the 22% with detectable RNA, the median was 958 copies/ml. Given that more than half of the men had <350 CD4⁺ cells/μl and almost 90% had ≥ 1,000 RNA copies/ml when HAART was initiated, this study shows that the effectiveness of HAART persists for up to 12 years.

Immunological and virological responses in the first 5 years following HAART initiation strongly influenced these responses in the subsequent 5-7 years. Also, individuals who responded well to the first or second HAART regimens maintained higher CD4⁺ counts and lower HIV RNA than those who switched regimens at least twice. This may reflect a suboptimal response to HAART, the presence of drug-resistance viral strains, and/or adverse effects of HAART that limit therapy³⁶.

Total lymphocyte count (TLC), stratified as greater or less than 1200 cells/μl, was evaluated as a surrogate for CD4⁺ count and a lower TLC was also associated with lower CD4⁺ counts at 5-12 years on HAART. This finding supports inclusion of TLC in HIV treatment guidelines, as in the UNAID guidelines, and may be useful for regions where measurement of CD4⁺ counts is not available. However, factors that can affect TLC such as infectious diseases and nutritional deficiencies^{37, 38} may not be present in the MACS. Therefore, optimal cutoff values for use of TLC in treatment guidelines might vary regionally.

We did not observe significant differences in long-term CD4⁺ counts by race, although African-Americans were approximately 50% less likely than Caucasians to suppress RNA. Virologic and immunologic responses to HAART did not significantly differ by race in the WIHS³⁹. However, we and others have reported racial differences in adherence to HAART^{26, 40} which predicts better RNA suppression⁴¹⁻⁴³. It is notable that decreased achievement of viral suppression in African-Americans in the present study did not translate into an effect on long-term CD4⁺ counts. Similarly, consonant with the literature and guidelines, we observed that triple-NRTI therapy^{25, 44, 45} and nevirapine relative to efavirenz⁴⁶⁻⁴⁸ were less likely to suppress HIV RNA.

The data on which the present study is based, including characteristics before HAART was initiated, were obtained using standardized longitudinal methods. That is, they were collected without bias that may arise when disease progression may direct the frequency of measurements that are obtained^{49, 50}. Insufficient numbers and follow-up time limit our ability to evaluate new HAART regimens.

The results presented here were obtained after those with the fastest progression of HIV disease after initiating HAART were removed, because our analysis did not begin until 5 years after HAART initiation. The goal of this study was to describe the experience of the subgroup of HAART initiators who are long-term users. Thus, the current results are generalizable only to such people. This restriction should represent a conservative bias since CD4⁺ count at HAART initiation strongly predicts progression in the first 5 years following HAART initiation^{3, 7-10}, that is, if they had been included, the effect of CD4⁺ count at HAART initiation on immunological response should be even stronger. The removal of those who progressed within the first five years after HAART initiation may explain why this study did not observe the plateauing of CD4⁺ count after 2 years that was previously reported in the MACS.⁴ The results presented here may not be generalizable to those who

have started HAART in the last 5 years. Our population started HAART early in the HAART era with a variety of initial regimens that are different from the regimens most commonly started today. A further limitation is that our population had largely received mono- or dual-therapy before initiating HAART. However, this is probably not a major limitation because restriction of the present analysis to the 40% men who were ART-naïve HAART initiation yielded similar trends as those observed in the overall population. To evaluate the long-term effects of new HAART regimens, analyses similar to the present study should be performed with each new cohort of HAART initiators, keeping in mind that the results of these analyses will always be limited to historical initiators likely to be unrepresentative of recent initiators.

In summary, over half of the men in this study who reported HAART use for more than 5 years had >500 CD4⁺ cells/ μ l and three-fourths had undetectable plasma RNA. Our data support using age in the guidelines for initiating HAART, such that persons who are older than 50 years should start treatment at higher CD4⁺ counts, e.g., 350 – 500 cells/ μ l. This interaction of age and immunological stage when starting treatment and the effects of specific regimens on long-term response to treatment should be further evaluated by large collaborative observational cohorts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Frequency of the most reported HAART regimens used according to calendar year of follow-up. Numbers in the parenthesis after each regimen in legend are the total number of person-visits and percentage on that regimen overall in the 5-12 years on HAART. Blank section (complement to color) represents percent of other regimens which were individually reported by less than 1% of HAART users. abc- abacavir, atz - atazanavir, azt - zidovudine, efv – efavirenz, ftc – emtricitabine, idv - indinavir, lam – lamivudine, lpv - Kaletra (lopinavir + ritonavir), nfv - nelfinavir, nvp – nevirapine, rtv – ritonavir, tdf - tenofovir disoproxil fumarate (DF)

Figure 2.

Trajectories of median CD4⁺ count in the 12 years after initiation of highly active antiretroviral therapy (HAART), according to CD4⁺ count levels before HAART initiation among 614 HIV-positive men who contributed data after five years from HAART initiation. The dots are median CD4⁺ count in each time interval from HAART initiation. Horizontal dotted lines are reference lines plotted at the CD4⁺ count of 200, 350, 500 cells/μl. The middle vertical dotted line shows the cutoff at five years after HAART initiation. The numbers below the labels of the x-axis are the percentages with undetectable HIV-1 RNA and total number of men in each time interval. The numbers at the end of each line are adjusted mean CD4⁺ count at 5-12 years after HAART initiation for each pre-HAART CD4⁺ count category from the main effects multivariate model.

Table 1

Characteristics of 614 men who had CD4⁺ T-cell counts or HIV RNA measurements at 5-12 years after HAART initiation in the MACS.

Characteristics	N (%)
Age at HAART initiation (years)	
<40	288 (47)
40-49.9	251(41)
≥ 50	75 (12)
Race	
Caucasian	369 (60)
African American	151 (25)
Latino	84 (14)
Other	10 (2)
Center	
Baltimore	140 (23)
Chicago	159 (26)
Pittsburgh	133 (22)
Los Angeles	182(30)
Cohort	
Pre-2001	327 (53)
2001-2003	287 (47)
Calendar year of HAART initiation	
Median (IQR)	1998 (1997, 2000)
Had AIDS before HAART	48 (8)
Used ART before HAART	368 (60)
Pre-HAART CD4 ⁺ T-cell count (cells/μl)	
≤ 100	80 (13)
101-200	106 (17)
201-350	188 (31)
351-500	121 (20)
>500	119 (19)
Pre-HAART HIV-1 RNA(copies/ml)	
≤1,000	74 (12)
1,001-10,000	121 (20)
10,001-100,000	252 (41)
>100,000	167(27)
Pre-HAART Hepatitis B virus infection	434 (71)
Pre-HAART Hepatitis C virus infection	64 (10)
CD4 ⁺ T-cell count change per year in 0-4.9 years after HAART(cells/μl)	
Median (IQR)	34 (−1, 67)
Suppressed HIV RNA(<50 copies/ml) at ≥ 50% of study visits in 0-4.9 years after HAART	294 (48)
Total number of times regimens were switched in 0-4.9 years after HAART	

Characteristics	N (%)
0	119 (19)
1	143 (23)
2	122 (20)
3	126 (21)
4+	104 (17)
Follow-up time after HAART initiation (years)	
Median (IQR)	10.2 (7.3, 12.2)
Number of CD4 ⁺ T-cell measurements contributed 5-12 years after HAART	
1-2	119 (19)
3-4	106 (18)
5-6	63 (10)
≥ 7	326 (53)

ART: Antiretroviral therapy; HAART: highly active antiretroviral therapy; IQR: interquartile range

Table 2

Factors (other than HAART-regimens) associated with CD4⁺ T-cell count 5-12 years after HAART initiation from multivariate analysis

Factors	Overall (n=4,431 person-visits)		ART-naïve before HAART (n=1,454 person-visits)	
	Difference in CD4 ⁺ T-cell count in cells/μl (95% CI)	p-value	Difference in CD4 ⁺ T-cell count in cells/μl (95% CI)	p-value
Pre-HAART CD4 ⁺ T-cell count (cells/μl)*				
≤ 200	-329 (-376, -282)	<0.01	-311 (-389, -232)	<0.01
201-350	-179 (-230, -128)	<0.01	-111 (-198, -24)	<0.01
351-500	-90 (-145, -36)	<0.01	-56 (-151, 39)	0.24
>500	Reference	-	Reference	-
Age (years) at HAART initiation				
<40	Reference	-	Reference	-
40-49.9	-17 (-55, 21)	0.39	-24 (-85, 36)	0.43
≥ 50	-92 (-140, -44)	<0.01	-59 (-137, 17)	0.13 CD4 ⁺
T-cells annual change in 0-4.9 years after HAART per 50 cells/μl/year increase if pre-HAART CD4 ⁺ ≤ 500	31 (8, 54)	<0.01	19 (3, 34)	0.02
HIV-1 RNA <50 copies/ml for ≥50% of HIV-1 RNA measurements in 0-4.9 years after HAART	95 (60, 131)	<0.01	115 (60, 171)	<0.01
Number of times switched regimen in 0-4.9 years after HAART				
0	Reference	-	Reference	-
1	34 (-18, 85)	0.19	25 (-46, 95)	0.49
2+	-51 (-95, -7)	0.03	-29 (-95, 37)	0.39
Pre-HAART Hepatitis B virus infection	-52 (-93, -11)	0.01	-64 (-126, -3)	0.04
Pre-HAART Hepatitis C virus infection	-49 (-108, 10)	0.10	-56 (-136, 24)	0.17
Years after HAART initiation (per 1 year increase)				
Pre-HAART CD4 ⁺ T-cell count ≤ 350 cells/μl	11 (7, 15)	<0.01	14 (6, 22)	<0.01
Pre-HAART CD4 ⁺ T-cell count > 350 cells/μl	2 (-4, 8)	0.51	1 (-11, 13)	0.88

HAART: Highly active antiretroviral therapy.

Estimates represent mean differences at 8 years after HAART initiation for those with annual change of 30 CD4⁺ cells/μl/year in the 0-4.9 years on HAART

Table 3

Factors (other than HAART-regimens) associated with undetectable (<50 copies/ml) HIV-1 RNA at 5-12 years after HAART initiation from multivariate analysis

Factors	Overall (n=4,431 person-visits)		ART-naïve before HAART (n=1,454 person-visits)	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Race				
Caucasian	Reference	-	Reference	-
African American	0.42 (0.28, 0.62)	<0.01	0.30 (0.16, 0.56)	<0.01
Latino	0.81 (0.49, 1.32)	0.39	0.88 (0.39, 1.95)	0.75
Other	0.31 (0.09, 1.10)	0.07	0.23 (0.03, 1.66)	0.14
Cohort				
Pre-2001	Reference	-	Reference	-
2001-2003	1.48 (0.99, 2.22)	0.06	0.96 (0.44, 2.10)	0.91
Calendar year of HAART initiation (per 1 year increase)	1.24 (1.13, 1.36)	<0.01	1.12 (0.95, 1.34)	0.20
HIV-1 RNA <50 copies/ml for ≥50% of HIV-1 RNA	5.41 (3.75, 7.81)	<0.01	3.80 (2.05, 7.05)	<0.01
Measurements in 0-4.9 years after HAART				
Number of times switched regimen in 0-4.9 years after HAART				
0	Reference	-	Reference	-
1	1.18 (0.69, 2.00)	0.56	1.19 (0.55, 2.56)	0.67
2+	0.66 (0.43, 1.02)	0.06	0.84 (0.45, 1.57)	0.58
Adherence 100% to HAART regimens in last 4 days	1.25 (1.03, 1.51)	0.03	1.37 (0.97, 1.93)	0.07

HAART: Highly active antiretroviral therapy.