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Long-term patterns in CD4 response is determined by an interaction between baseline CD4 cell count, viral load and time: the Asia Pacific HIV Observational Database (APHOD)

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Abstract

Background—Random effects models were used to explore how the shape of CD4 cell count responses after commencing combination antiretroviral therapy (cART) develop over time, and in particular the role of baseline and follow-up covariates.

Methods—Patients in APHOD who first commenced cART after January 1, 1997, and who had a baseline CD4 cell count and viral load measure and at least one follow-up measure between 6 and 24 months, were included. CD4 cell counts were determined at every 6-month period following the commencement of cART for up to 6 years.

Results—1638 patients fulfilled the inclusion criteria with a median follow up time of 58 months. Lower post-cART mean CD4 cell counts were found to be associated with increasing age ($p<0.001$), pre-cART hepatitis C co-infection ($p=0.038$), prior AIDS ($p=0.019$), baseline viral load ≤ 100,000 copies/ml ($p<0.001$), and the Asia-Pacific region compared with Australia ($p=0.005$). A highly significant 3-way interaction between the effects of time, baseline CD4 cell count and post-cART viral burden ($p<0.0001$) was demonstrated. Higher long-term mean CD4 cell counts were associated with lower baseline CD4 cell count and consistently undetectable viral loads. Among patients with consistently detectable viral load CD4 cell counts appeared to converge for all baseline CD4 levels.

Conclusion—Our analyses suggest that the long-term shape of post-cART CD4 cell count changes depends only on a 3-way interaction between baseline CD4 cell count, viral load response and time.

Keywords

antiretroviral therapy; long-term CD4 response; viral load response

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INTRODUCTION

The introduction of combination antiretroviral therapy (cART) has been effective in decreasing morbidity and mortality rates due to HIV infection in Australia [1,2] and other developed countries [3,4]. Similar rate reductions have also been observed in HIV patients treated with cART in developing countries [5–7]. The use of cART has proven to effectively reduce viral replication, enabling increases in CD4 cell count and restoration of immune function[8]. The extent of immunological response following the initiation of cART has significant clinical implications.

Pre-treatment predictors of higher mean CD4 cell counts following the commencement of cART have been reported previously, and include younger age [9–13], female sex [12], higher pre-cART viral loads [11,14] and mode of HIV exposure other than injecting drug use [12]. In addition, the effect of pre-cART (baseline) CD4 cell counts on subsequent CD4 cell counts has been extensively studied [10–24]. Some of these studies have found that baseline CD4 cell counts influence subsequent CD4 cell count increments [20,21], whilst others reported either little or no evidence of such an association [22–24].

Previous research has demonstrated greater increases in mean CD4 cell counts if post-cART viral load suppression is completely or even partially sustained [16,25] However, opinion remains divided as to the extent of long term immune system restoration in the presence of sustained virological suppression. A number of studies have reported a plateau in the growth of mean CD4 cell counts within 2 to 3 years of the commencement of cART in the presence of sustained virological suppression [11,12,15,16,18], whilst others have shown continued increases well beyond 3 years of effective cART [10,14].

The objective of this paper was to use random effects models to explore statistically how the shape of CD4 cell count responses after commencing cART develop over time, and in particular the role of baseline and follow-up covariates.

METHODS

The Asia-Pacific HIV Observational Database (APHOD) is part of the National Institutes of Health (NIH) International Epidemiological Databases Evaluating AIDS (IeDEA) collaboration. APHOD consists of two adult cohorts, the Australian HIV Observational Database (AHOD) and the Treat Asia HIV Observational Database (TAHOD), and one paediatric cohort, the Treat Asia Paediatric HIV Observational Database (TApHOD). The current analyses include patients recruited to the adult cohorts AHOD and TAHOD. AHOD collects data from 27 sites throughout Australia and TAHOD currently collects data from 17 sites throughout 10 countries in the Asia-Pacific Region. Ethics approval for the two cohorts was granted to all participating sites by relevant institutional review boards (IRB). Written informed consent was obtained for all AHOD patients at recruitment. Unless required by local IRBs, written informed consent was wavered for TAHOD patients. Study methodologies are similar for AHOD and TAHOD. Data are transferred electronically to the National Centre in HIV Epidemiology and Clinical Research (NCHECR), and updated every six months. Core data variables collected include: sex, date of birth, date of most recent visit, HIV exposure category, HBV surface antigen status (HBV), anti-HCV antibody status (HCV) (note: missing equals negative), CD4 and CD8 T lymphocyte counts, HIV viral load measurements, antiretroviral and opportunistic infection prophylaxis treatments, AIDS defining illness and date and cause of death. Detailed descriptions of these cohorts have been provided elsewhere [26,27].

Inclusion Criteria

Analyses include patients who commenced cART (defined as 3 or more antiretroviral drugs) after January 1 1997, and who have a baseline CD4 cell count and viral load measurement within 6 months prior to and up to 1 month after commencing cART. The measurements that were nearest to the date cART commenced were chosen as the baseline values. Patients were also required to have at least one follow-up CD4 cell count measurement and viral load measurement between six months and 24 months after the commencement of cART. Only CD4 cell measurements with a corresponding viral load measurement were used in the analysis. The recorded time at each CD4 cell count measurement after the commencement of cART was rounded to the nearest bi-annual anniversary date of the commencement of cART. Where patients had more than one CD4 cell count measurement within a six month period, the measurement closest to the bi-annual anniversary date was chosen. An intention to treat approach (ITT) was used in all the analyses. This assumes that once patients have commenced cART then all analyses include all patients with follow-up data regardless of their treatment status at each time-point.

Statistical Analysis

Linear random effects models were used to investigate the predictors of long-term changes in CD4 cell counts up to 6 years after the commencement of cART. Random effects models were chosen to analyse these data specifically because these models are relatively robust to missing value bias when the probability of an observation being missing depends only on the surrounding responses and/or covariates included in the model (i.e. missing at random (MAR) data) [28]. In the full multivariate model, post-cART CD4 cell count was defined as the dependent variable, and baseline CD4 cell count was treated as a continuous covariate and not included in the dependent variable, so as to determine predictors adjusted for baseline CD4 cell count. Categorical covariates included sex (male versus female), cohort (TAHOD versus AHOD), pre-cART viral load (≤ 100,000 versus >100,000 copies/ml), pre-cART HBV and/or HCV co-infection (yes versus no), prior AIDS (yes versus no), and reported mode of HIV exposure (homosexual, heterosexual, injecting drug use, other). Other continuous covariates included age at the commencement of cART and time after the commencement of cART. The proportion of time from 6 months after the commencement of cART that a subject's viral load was above 400 copies/ml was included as a continuous time-dependent covariate (referred to hereafter as 'post-cART viral burden'). Viral burden levels were categorised into the following groups: continuously sustained viral suppression (burden level =0), intermittent viral suppression (burden level=0.5) and continuous viral load greater than 400 copies/ml (burden level=1), representing 0%, 50% and 100% of post-cART viral load measurements > 400 copies/ml. Post-cART viral burden was updated using each new viral load measurement regardless of whether there was a corresponding CD4 cell count measurement.

Based on exploratory analyses, the following potential interactions were tested by adding interaction terms one at a time to the full random effects model. The interaction terms that were assessed (at the α =0.01 level) were cohort with a) time b) baseline CD4 cell count and c) post-cART viral burden, and time with a) age, b) sex, c) pre-cART HCV co-infection, d) pre-cART HBV co-infection, e) pre-cART HIV-1 RNA load and f) the reported mode of HIV exposure. The effects of significant covariates that did not interact with time were, by implication of the modelling structure, deemed to have occurred in the first six months, and therefore described as set predictors. The covariance structure for the full model was also chosen using Akaike's information criterion. A reduced multivariate model was then obtained from the full model by eliminating non-significant covariates (p>0.05 for main effects, p>0.01 for interaction effects) that were not substantial confounders of other effects (<20% change in other effects). The covariance structure chosen for the full model was retained for the reduced model. All analyses were performed using SAS version 9.1 and STATA version 10.

RESULTS

Demographic and pre-cART clinical characteristics

A total of 1638 patients fulfilled the inclusion criteria; 917 (56%) were from AHOD and 721 (44%) were from TAHOD. The median follow-up time was 58 months. Overall there were proportionally more males (86%) and patients whose exposure category was male homosexual contact (54%); and the majority of patients had no prior AIDS related illness reported (73%), and pre-cART viral load was ≤ 100,000 copies/ml (65%) (Table 1). TAHOD had a higher proportion of female patients (24% versus 6%), patients with a prior AIDS related illness (44% versus 13%) and patients with pre-cART HIV viral load greater than 100,000 copies/ml (40% versus 32%). The distribution of reported mode of HIV exposure also differed considerably between these cohorts. A greater proportion of patients in TAHOD reported mode of HIV exposure as heterosexual contact (58% versus 10%), while the reported mode of HIV exposure for the majority of patients in AHOD was homosexual contact (73% versus 28%). TAHOD patients were significantly younger at the time of commencing cART (37.6 versus 40.1 years) and had a lower mean baseline CD4 cell count (173 versus 386 cells/μL). The proportions of patients with pre-cART HCV coinfection were similar for both cohorts (TAHOD: 3%; AHOD 4%). Figure 1 shows the observed mean CD4 cell counts (cells/μL) over time for TAHOD and AHOD separately. Patients in TAHOD commenced cART at substantially lower CD4 cell counts (<200 cells/μL) compared to AHOD patients. However, both cohorts demonstrate increasing mean CD4 cell counts for up to 6 years.

Set predictors of post-cART mean CD4 cell counts

The set predictors of post-cART mean CD4 cell counts were covariates that did not significantly interact with time, including cohort, age, sex, pre-cART HCV and HBV status, pre-cART viral load and HIV exposure. Interactions between cohort and baseline CD4 cell count or post-cART viral burden were also assessed and were not significant. Table 2 presents the estimated effects from the full and reduced random effects models for the set predictors. Lower post-cART mean CD4 cell counts were found to be associated with increasing age (−14 cells/μL per 10-year increase in age 95%CI [−21, −7], $p<0.001$), pre-cART HCV co-infection (−41 cells/μL 95% CI [−79,−2], $p=0.038$), prior AIDS (−23 cells/μL 95%CI [−42, −2], $p=0.019$) and pre-cART HIV viral load ≤ 100,000 copies/ml (−40 cells/μL 95%CI [−56, −25], $p=0.000$). There was no evidence that either sex or pre-cART HBV co-infection affected post-cART CD4 cell counts ($p=0.56$ and $p=0.36$ respectively). Reported mode of HIV exposure was also not associated with post-cART CD4 cell counts overall ($p=0.27$). However, the exposure covariate was kept in the final model as the removal of this covariate produced a 28% change in the estimated effect of cohort primarily as a result of the larger proportion of heterosexuals in TAHOD. The final model indicated that, when adjusted for all other predictors (including time, post-cART viral burden and baseline CD4 cell count), patients from TAHOD had a mean post-cART CD4 cell count 27 cells/μL (95%CI [8, 46], $p=0.005$) lower than AHOD patients.

The effects of time, post-cART viral burden levels and baseline CD4 cell counts on post-cART mean CD4 cell counts

The final random effects model revealed a highly significant 3-way interaction between the effects of time, baseline CD4 cell count and post-cART viral burden ($p<0.0001$). The disadvantage of fitting a third order interaction model is that it does not provide a simple summary for the effects of the interacting covariates. To assist in the interpretation of these interaction effects, we present them graphically using selected estimates for the clinically relevant baseline CD4 cell count levels of 200, 350 and 500 cells/μL and post-cART viral burden levels of 0, 0.5, 1 (representing 0%, 50% and 100% of post-cART viral load measurements > 400 copies/ml). Figure 2a, b and c demonstrates this 3-way interaction by illustrating the shape of mean CD4 cell increase predicted by the final random effects model

for subjects with the following set predictor characteristics: 45 years old, AHOD cohort, no pre-cART HCV co-infection, pre-cART viral load ≤ 100,000 copies/ml, no prior AIDS and homosexual contact as the reported mode of HIV exposure. Whilst varying the values for the set predictors would produce a vertical shift in the curves from months 6 to 72, the rates of change during this period would remain the same, so overall shapes would not be altered.

For example, as shown in Figure 2a, a patient with the following set predictor characteristics: 45 years old, AHOD cohort, no pre-cART HCV co-infection, pre-cART viral load ≤ 100,000 copies/ml, no prior AIDS and homosexual contact as the reported mode of HIV exposure, and with viral load remaining below 400 copies/ml, will experience a continuous increase in CD4 cell counts beyond 6 years. This increase occurs across all baseline CD4 cell strata, and at year 6 the mean absolute CD4 cell count is above 500 cells/μL for all baseline CD4 cell strata. For viral burden levels of 0.5 (intermittently below 400 copies/ml), there is an initial increase in CD4 cell count for all baseline CD4 cell strata. After 4 years the mean absolute CD4 cell count begins to decrease for the higher baseline CD4 cell strata and plateau for patients whose baseline CD4 cell count was 200 cells/μL. However, for all groups at 6 years of follow-up mean absolute CD4 cell counts remain above baseline CD4 cell levels, and all greater than 300 cells/μL. For viral loads continuously above 400 copies/ml (viral burden=1), mean absolute CD4 cell count begins to decrease very soon after 6 months for the higher baseline CD4 cell strata, and for patients in the lowest baseline CD4 cell strata values begin to decrease after approximately 2 years. At year 6 mean CD4 cell count for all strata are below baseline values, yet remain around 200 cells/μL or greater (Figure 2c). Further, the mean absolute CD4 cell count for each baseline CD4 cell strata appear to converge by year 6.

DISCUSSION

In this study, patients with sustained virological response demonstrate increasing CD4 cell counts for up to 6 years following the commencement of cART, with mean absolute CD4 cell counts at year 6 above 500 cells/μL for all baseline CD4 cell strata. Patients with intermittent virological response also demonstrated increases in CD4 cell count for several years post cART, with CD4 cell increases continuing longer among patients in the lowest baseline CD4 cell strata. At year 6, mean absolute CD4 cell counts among patients with intermittent virological response were above 350 cells/μL for all baseline CD4 cell strata, and among patients with consistently detectable viral load (>400 copies/ml) mean CD4 cell counts at 6 years were approximately 200 cells/μL or greater.

Our results are broadly consistent with the literature demonstrating greater increases in mean CD4 cell counts if viral load suppression is sustained or partially sustained [16,21,24,25,29–31]. To our knowledge, this study is the first to qualitatively explore the shape of long-term CD4 cell responses by modelling the three way interaction between CD4 cell count, viral load and time. Several studies have reported a biphasic CD4 cell increase, demonstrated as a rapid increase in CD4 cell count change in the first few months with continued yet slower increase for up to several years of follow-up with a plateau by approximately the third year of follow-up [11,12,17,19,20,32,33], while other studies have shown continual increases in CD4 cell count response with sustained low viral loads; even after the fourth year following the commencement of cART [10,31,34–36]. Our study suggests that age, cohort, HCV status, baseline viral load and prior AIDS act as set predictors on CD4 cell count changes, producing a vertical shift in the long-term CD4 cell count response. The long-term shape of the CD4 cell count response was determined in our analyses by a 3 way interaction between baseline CD4 cell count, detectable viral load and time.

As reported previously by others we also observed greater increases in CD4 cell counts for patients in the lowest baseline CD4 cell strata in the continuous or intermittent virological

response groups (Figures 2a and 2b). In the MACS study, long term significant increases in CD4 cell count were observed among ART naïve patients whose baseline CD4 cell count was below 400 cells/μl, and among intermittent antiretroviral users, with baseline CD4 cell counts below 200 cells/μL [37]. In contrast, another study found no significant difference in response to highly active antiretroviral therapy among those patients with higher pre-treatment CD4 cell counts once adjusted for age and nadir CD4 cell count [38]. Further, our study showed that patients who commenced cART at CD4 cell counts greater than 350 cells/μL achieved CD4 cell levels similar to HIV negative patients. This has been reported by Mocroft et al (2007), who also proposed that with longer period of time with suppressed viral load, similar levels may also be achieved among patients commencing cART at lower CD4 cell counts. Our results broadly concur with this as we also have shown that despite the lower absolute CD4 cell counts at year 6 for patients commencing cART at lower CD4 cell counts, if viral load suppression is sustained, these patients continue to experience CD4 growth. Also suggesting that with longer duration of time with suppressed viral load, CD4 levels may also normalise for these patients [36]. Moore and Keruly (2007) have also reported normalised CD4 cell levels after 6 years of sustained virological response, but only among patients with baseline CD4 cell counts above 350 cells/μl [12].

Post-cART mean CD4 cell counts were not found to be significantly associated with sex, prior HBV co-infection or the reported mode of HIV exposure. Whilst we are not aware of any studies finding a significant effect for pre-cART HBV co-infection, there have been other studies that have found that injecting drug use as the mode of HIV infection was associated with lower post-cART mean CD4 cell counts [12,39]. Yet with only 42 of the 1638 patients in this study having injecting drug use as the mode of HIV infection, there was low statistical power to detect a small to moderate effect. However, consistent with the findings of a number of other studies, we found that lower post-cART mean CD4 cell counts were associated with increasing age at commencement of cART [9–13], and prior AIDS [14]. Pre-treatment (baseline) viral load of 100,000 copies/ml or less [11,14] was also associated with lower post-cART mean CD4 response. Although this may seem counter-intuitive initially, these findings demonstrate that among subjects with equal pre-treatment CD4 counts, those with higher baseline viral loads will have a greater absolute CD4 response following the initiation of effective treatment. These findings have also been reported in at least two other studies [11, 14]. We also found that pre-cART HCV co-infection was associated with lower mean CD4 cell counts. Whist this association is consistent with the findings of 2 studies that we are aware of [18,40], others have not found such a link [10–12].

The long-term trends in CD4 cell counts were consistent for both the AHOD and TAHOD cohorts, despite the small, and questionably clinically relevant, benefit for AHOD in terms of mean CD4 cell counts post cART. The lower mean CD4 cell response observed in TAHOD compared with AHOD may be due to Asian versus primarily Caucasian populations. In a previous study comparing TAHOD patients with patients from the French Aquitaine cohort, patients from TAHOD had lower absolute CD4 cell count at every level of CD4% [41]. Reduced circulating CD4 cells counts have also been shown in African American versus Caucasian American populations [42]. However, this cohort difference between AHOD and TAHOD may also reflect differences in antiretroviral availability between the cohorts with some resource limited sites in TAHOD having reduced access to second and third line antiretrovirals [43].

There are important limitations to our analyses. First is survivorship bias, that is, the possible selective drop out of patients with poorer immunological responses. The group investigated may be biased toward being inherently better responders and therefore more likely to remain in follow-up than non-responding or non-adherent patients. However, we did not restrict our investigation to those with poor CD4 cell count at commencing cART or just patients with a

sustained viral load below detection. We were able to describe CD4 response for all levels of baseline CD4 cell count and among those with and without sustained viral suppression. Further, random effects models were used in this study to minimise potential bias arising from missing at random data. Second, these analyses were in essence exploratory and not hypothesis testing. We considered many interaction terms in the random effects models, which may raise concerns about multiple comparisons. To limit false positive interactions, these were only considered if p-values were less than 0.01. Third, our analyses ignored ARV changes, assuming that ARV effects on CD4 cell count responses are entirely predicted by viral load response. Our modelling approach, using proportion of viral loads detectable, though simple, may not completely capture the relationship between viral load and CD4 cell count changes. However, specifically analysing ART regimens is notoriously difficult, and we preferred an intention to treat approach in this analysis. This approach also has the advantage that results are likely broadly applicable to all cART regimens.

In summary, our data have shown that patient's with continuously or intermittently sustained virological response experience ongoing CD4 cell increases for several years after commencing cART, with higher increases among patients with lower baseline CD4 cell counts. Our findings illustrate the effect of baseline CD4 cell count, post-cART viral load and time on the shape of long-term CD4 cell response. The long-term CD4 cell increase observed in this study was similar for both the AHOD and TAHOD cohorts, despite the slightly lower overall absolute CD4 cell response in TAHOD over the six years. Future analyses should aim to investigate whether the potential regional differences in CD4 cell count responses identified in our study are clinically important.

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Appendix

The Australian HIV Observational Database

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Health and HIV Clinic, Penrith; K Brown, N Skobalj, Illawarra Sexual Health Clinic, Warrawong; L Wray, H Lu, Sydney Sexual Health Centre, Sydney; Dubbo Sexual Health Centre, Dubbo; P Canavan*, National Association of People living with HIV/AIDS; C Lawrence*, National Aboriginal Community Controlled Health Organisation; I Zablotska*, National Centre in HIV Social Research, University of NSW; B Mulhall*, Department of Public Health and Community Medicine, University of Sydney; M Law*, K Petoumenos*, K Falster*, Sadaf Marashi Pour*, C Bendall National Centre in HIV Epidemiology and Clinical Research, University of NSW.

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Western Australia: **D Nolan, S Mallal, C Forsdyke, J Skett, S Bulgannawar, Department of Clinical Immunology, Royal Perth Hospital, Perth.**

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The TREAT Asia HIV Observational Database

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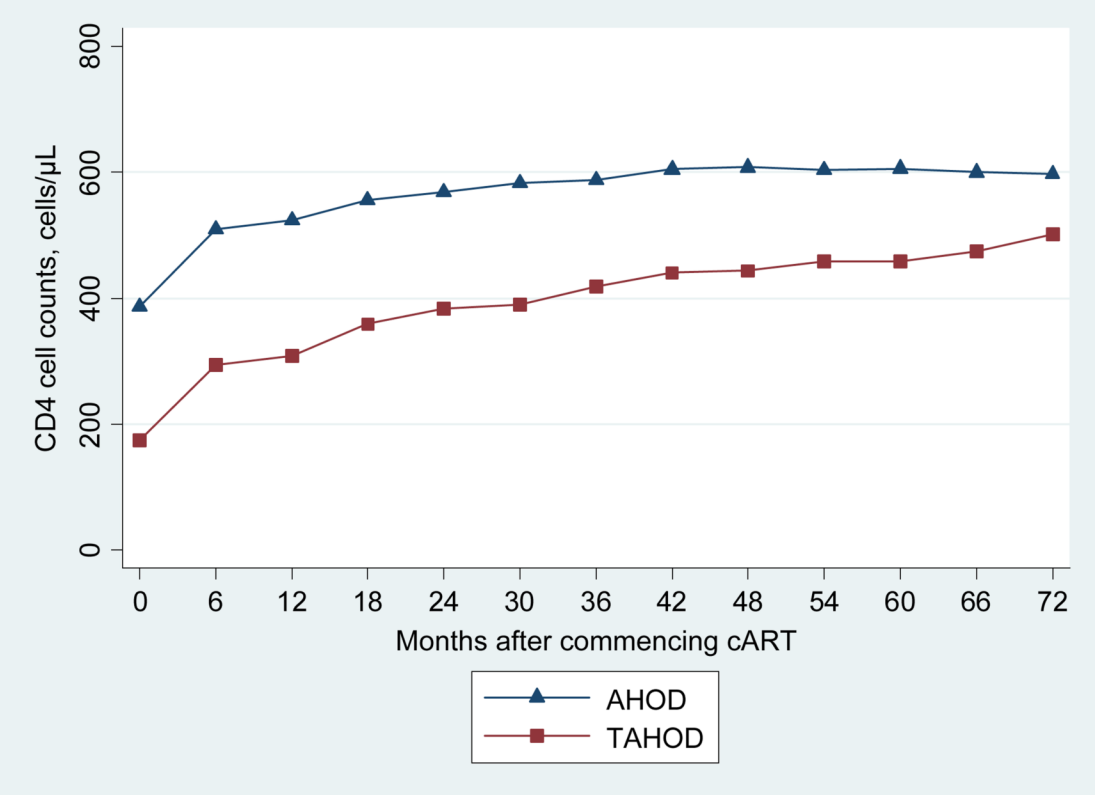

Figure 1.
Observed mean CD4 cell counts (cell/µL) over time for TAHOD and AHOD.

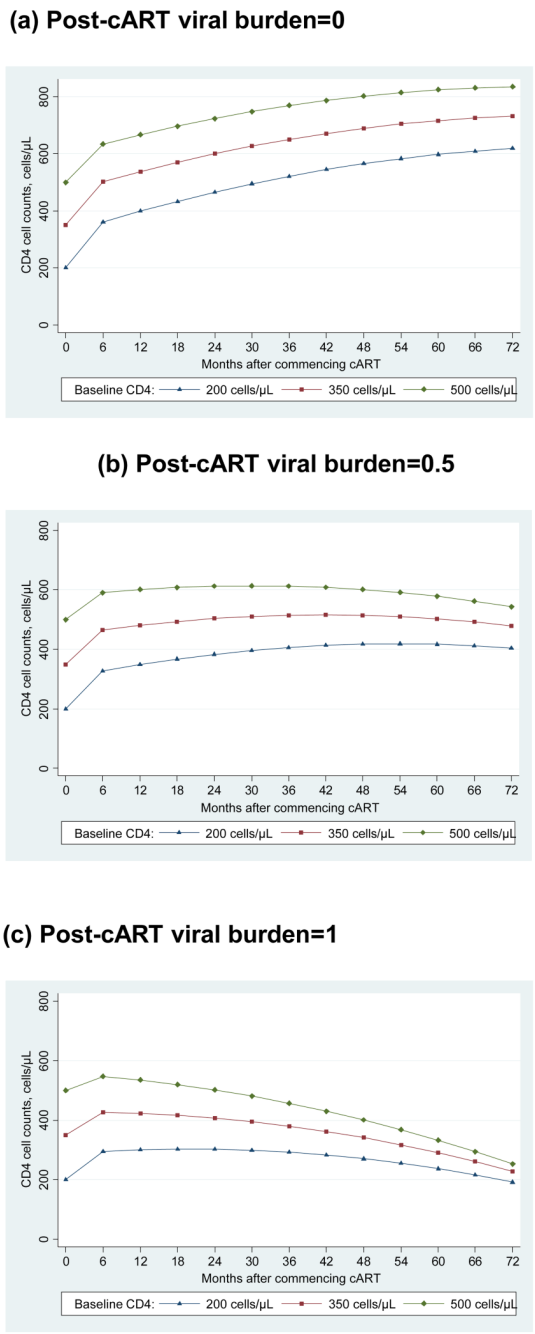

Figure 2.

Predicted mean CD4 cell counts (cell/μL) according to post-cART viral burden levels (a) 0 (b) 0.5 (c) 1 and baseline CD4 cell count levels 200, 350, 500 cells/μl for subjects with the following set predictor characteristics; 45 years old, AHOD cohort, no pre-cART hepatitis C coinfection, pre-cART viral load less than 100,000 copies/ml, no pre-cART AIDS related illness and with homosexual contact as the reported mode of HIV exposure.

Table 1

Demographic and pre-cART clinical characteristics of patients, by cohort.

Characteristic	AHOD N=917	TAHOD N=721	All Patients N=1638
Age, mean years [95% CI]	40.1[39.4, 40.7]	37.6[36.8, 38.4]	39.0[38.5, 39.5]
Sex			
Female	55 (6)	170 (24)	225 (14)
Male	862 (94)	551 (76)	1413 (86)
Pre-cART HCV coinfection			
No	876 (96)	700 (97)	1576 (96)
Yes	41 (4)	21 (3)	62 (4)
Pre-cART HBV coinfection			
No	898 (98)	680 (94)	1578 (96)
Yes	19 (2)	41 (6)	60 (4)
Pre-cART HIV-1 RNA load			
≤ 100,000 copies/ml	626 (68)	431 (60)	1057 (65)
> 100,000 copies/ml	291 (32)	290 (40)	581 (35)
Pre-cART AIDS related illness			
No	795 (87)	405 (56)	1200 (73)
Yes	122 (13)	316 (44)	438 (27)
Reported mode of HIV exposure			
Male Homosexual contact	676 (73)	200 (28)	876 (53)
Injecting drug use	26 (3)	16 (2)	42 (3)
Heterosexual contact	89 (10)	420 (58)	509 (31)
Other	126 (14)	85 (12)	211 (13)
Baseline CD4 cell count, mean cells/μl [95% CI]	386[369, 403]	173[162, 185]	292[281, 304]

Note: Data are frequencies and within cohort region percentages in parentheses, unless otherwise indicated

Table 2

Set predictors [a] on CD4 T-cell counts from linear mixed model analyses. Models are also adjusted for time, post-cART viral burden and baseline CD4 cell count.

		Full Model[b]			Reduced Model[c]		
	N	Difference in mean CD4 count cells/μL (95% CI)	p- value	p-trend	Difference in mean CD4 count, cells/μL (95% CI)	p-value	p-trend
Age at commencement of cART per 10 year increase	1638	−14(−21, −7)	0.000		−14(−21, −7)	0.000	
Cohort							
AHOD	917	Ref. group			Ref. group		
TAHOD	721	−26(−45, −7)	0.007		−27(−46, −8)	0.005	
Sex							
Female	225	Ref. group					
Male	1413	7(−17, 32)	0.564		…		
Pre-cART HCV coinfection							
No	1576	Ref. group			Ref. group		
Yes	62	−40(−77, −1)	0.043		−41(−79, −2)	0.038	
Pre-cART HBV coinfection							
No	1578	Ref. group					
Yes	60	−18(−58, 21)	0.357		…		
Pre-cART HIV-1 RNA load							
≤ 100,000 copies/ml	1057	Ref. group			Ref. group		
> 100,000 copies/ml	581	40(24, 56)	0.000		40(25, 56)	0.000	
Pre-cART AIDS related illness							
No	1200	Ref. group			Ref. group		
Yes	438	−23(−43,−4)	0.016		−23(−42,−2)	0.019	
Reported mode of HIV exposure							
Homosexual contact	876	Ref. group			Ref. group		
Injecting drug use	42	−22(−68, 24)	0.352	0.273	−22(−68, 24)	0.352	0.274
Heterosexual contact	509	−20(−41, 1)	0.065		−22(−42, −2)	0.030	
Other	211	−5(−29, 18)	0.636		−7(−30, 16)	0.544	

[a] Table omits parameter estimates corresponding to the interacting effects of the covariates- time after the commencement of cART, post-cART viral burden and baseline CD4 cell count.

[b] Model containing all covariates.

[c] Model containing significant covariates and/or substantial confounders of other effects.