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Trends in CD4 count response to first-line antiretroviral treatment in HIV-positive patients from Asia, 2003–2013: TAHOD-LITE

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Abstract

Introduction—Antiretroviral treatment (ART) guidelines have changed over the past decade, recommending earlier initiation and more tolerable regimens. The study objective was to examine the CD4 response to ART, depending on the year of ART initiation, in HIV-positive patients in the Asia-Pacific.

Methods—We included HIV-positive adult patients who initiated ART between 2003–2013 in our regional cohort from eight urban referral centres in seven countries within Asia. We used mixed-effects linear regression models to evaluate differences in CD4 response by year of ART initiation during 36 months of follow-up, adjusted *a priori* for other covariates.

Results—Overall, 16962 patients were included. Patients initiating in 2006–09 and 2010–13 had an estimated mean CD4 count increase of 8cells/μL and 15cells/μL, respectively, at any given time during the 36 month follow-up, compared to those in 2003–05. The median CD4 count at ART initiation also increased from 96 cells/μL in 2003–05 to 173 cells/μL in 2010–13.

Conclusions—Our results suggest that the CD4 response to ART is modestly higher for those initiating ART in more recent years. Moreover, fewer patients are presenting with lower absolute

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Competing Interests

The authors do not have any competing interests to declare.

Authors' contributions

NLD and ML contributed to the concept development. KN, PSL, OTN, KVN, TPM, TTP, MPL and JYC contributed data for the analysis. NLD performed the statistical analysis and wrote the first draft of the manuscript. All authors commented on the draft manuscript and approved of the final manuscript.

CD4 counts over time. This is likely to reduce their risk of opportunistic infections and future non-AIDS defining cancers.

Keywords

Asia; HIV; epidemiology; CD4 trends; immunological response; ART

Introduction

CD4 counts are used as prognostic markers of HIV disease progression [1, 2]. Untreated HIV-infected persons have a gradual depletion in CD4 cell levels, leading to increased risk of AIDS-defining illnesses and death [3–6]. Combination antiretroviral therapy (ART) has been highly effective in preventing HIV disease progression and restoring CD4 cell levels as well as reducing viral replication and lowering rates of HIV-associated morbidity and mortality [7–9].

Initial World Health Organization (WHO) treatment guidelines, released in 2002, recommended ART initiation for those in advanced stages of HIV or in asymptomatic stages with CD4 count <200 cells/μL [10]. Delayed ART initiation was earlier suggested in stable patients to reduce the risk of developing and transmitting drug resistant HIV caused by suboptimal adherence [11, 12]. However, recent research has shown strong evidence to support earlier ART initiation at higher CD4 cell levels is beneficial in preventing disease progression and transmission, and also prevents the incidence of opportunistic infections (OIs) [8, 13–15]. After subsequent guideline revisions steadily increased the CD4 threshold for ART, in 2015, WHO treatment guidelines recommended ART initiation among all adults, regardless of CD4 count [16].

Others changes to the WHO treatment guidelines have also occurred over time including the use of more tolerable and convenient ART regimens, increased support and counselling services for patients, and routine monitoring of CD4 count and HIV viral load [16, 17]. These changes have been accompanied by improvements in patient outcomes, with reduced mortality rates for patients receiving care in recent years [18–20]. Although part of these improvements has been attributed to earlier ART initiation at higher CD4 counts, year of ART initiation has also shown an independent association with improved overall survival [21, 22].

A greater CD4 count response has previously been associated with younger age, female sex, lower pre-ART HIV viral load and CD4 count [23–25]. Yet, there has been little exploration as to whether CD4 count response has improved in recent years of ART initiation [23, 26]. The changes to treatment guidelines and patient management over time could result in an improved CD4 count response for patients initiating ART in recent years. Specifically, the move towards newer ARV drugs, associated with fewer side effects, for patients receiving care in Asia could lead to greater patient adherence [21]. In addition, certain ARV drugs classes, such as protease inhibitor-based regimens, may also evoke an increased CD4 count response [26–28]. Our study objective was to examine the time trends in and factors associated with CD4 response to first-line ART, by calendar year of ART initiation, in HIV-positive patients receiving care in an Asian regional observational cohort study.

Methods

Data collection and Participants

The TREAT Asia HIV Observational Database Low Intensity Transfer (TAHOD-LITE) cohort is a sub-study of the TREAT Asia HIV Observation Database (TAHOD) and currently consists of eight sites from the Asia-Pacific region including Cambodia, Hong Kong, India, Indonesia, Singapore, South Korea and Vietnam. TAHOD collects detailed patient data on a subset of patients seen at 20 treatment sites in the Asia-Pacific region [29]. Conversely, TAHOD-LITE collects routine clinical data on all patients seen at the 8 participating treatment sites. Thus, TAHOD-LITE is representative of the entire clinical population within our participating sites. Data are collected routinely when patients attend care at the treatment sites and include patient demographics, hepatitis serology, HIV-related laboratory test results and ART history. A more detailed description of TAHOD-LITE has been described elsewhere [21]. After being anonymized, data are transferred electronically to the Kirby Institute, University of New South Wales and are subjected to quality control procedures. Data include patient follow-up until May 2014. TAHOD-LITE was granted ethical approvals from Institutional Review Boards (IRB) at each participating clinical site, the University of New South Wales and the coordinating center at TREAT Asia/amfAR. Written consent was not obtained unless required by the site-specific IRBs.

The data selected for this analysis included all patients who were aged over 18 years when they initiated an ART regimen, consisting of three or more drugs, between 01 January 2003 and 31 December 2013, and had at least one subsequent visit after the date of ART initiation. There were also site-based exclusions where patients were excluded if they had initiated ART prior to: 2006 for Singapore; 2010 for Vietnam; and 2004 for Cambodia. Prior to these years, sites were unable to provide data on all patients that had been seen at the clinic.

Statistical analyses

The primary study objective was to evaluate CD4 count changes and factors associated with CD4 count change over 36 months of ART. A pseudo intention-to-treat approach was taken whereby any changes to treatment after ART initiation, including treatment interruptions were ignored. All patients were censored at the last clinic visit or date of death or 36 months from ART initiation, whichever occurred earlier. Pre-ART laboratory measurements, including CD4 count and HIV viral load, were defined as those within 6 months prior, and closest to or on the date of ART initiation.

Data were modelled using repeated-measures, random-intercept linear regression using generalized least squares estimation to evaluate differences in the CD4 response between the year periods of ART initiation (2003–05, 2006–09, 2010–13). Covariates, selected *a priori*, included clinical site, age at ART initiation, sex, mode of HIV exposure, pre-ART HIV viral load (copies/mL), pre-ART CD4 count (cells/μL), first ART regimen, hepatitis B and hepatitis C co-infection, time from ART initiation and squared time from ART initiation. These covariates were selected based on previous literature and available patient data collected in TAHOD-LITE. Continuous variables, including age at ART initiation, pre-ART

HIV viral load and pre-ART CD4 count, were categorized in the model. First ART regimen was categorized based on the drug classes included. The squared time from ART initiation was included to allow for the predicted CD4 count to be modelled as a quadratic curve from ART initiation. We also evaluated whether there was an interaction between the year period of ART initiation and time from ART initiation in a sensitivity analysis. This model was selected for the analysis as it includes all CD4 count measurements during the 36 months of follow-up and determines whether certain factors influence the CD4 response over the entire follow-up time rather than at one time point (eg. 12 months from ART initiation). As we modelled the CD4 count change from ART initiation, patients without a CD4 count result within 6 months prior to ART initiation (i.e. without a pre-ART CD4 count) were excluded from the model.

CD4 count response was also summarized by the median CD4 count, with interquartile range (IQR), and the proportion of patients within each CD4 count category (≤50, 51–100, 101–200, 201–350, 351–500 and ≥501 cells/μL) every 6 months up to 36 months from ART initiation, by year of ART initiation, overall and for each country. For these crude summaries, we only included CD4 count measurements that were closest to and within ±3 months of the given time point.

Data were analysed using Stata version 12 (Stata Corporation, College Station, Texas, USA) and SAS (version 9.4 for Windows).

Results

A total of 18 441 patients aged over 18 years had initiated ART between 1 January 2003 and 31 December 2013. Of these, 777 patients were excluded for not attending the clinic after ART initiation and 702 patients were excluded due to site-based exclusions (see Methods; Singapore, n=70; Vietnam, n=568; Cambodia, n=64). The remaining 16 962 were included in the analysis.

Patient Characteristics

A summary of the patient characteristics across all countries by year of ART initiation is given in Table 1. Briefly, the majority of patients were male (2003–05: 75%; 2006–09: 69%; 2010–13: 66%), reported heterosexual mode of HIV exposure (2003–05: 88%; 2006–09: 85%; 2010–13: 73%), initiated in recent years (2003–05: 17%; 2006–09: 37%; 2010–13: 46%) and had a first ART regimen consisting of nucleoside reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI) (2003–05: 92%; 2006–09: 97%; 2010–13: 98%). The median age at ART initiation was relatively consistent between periods of ART initiation (2003–05: 35 years, IQR: 30–40; 2006–09: 36 years, IQR: 31–42; 2010–13: 36 years, IQR: 30–43). Over 80% of the patients had a pre-ART CD4 count measurement, regardless of year of ART initiation. A minority of patients had a pre-ART HIV viral load measurement (2003–05: 14%; 2006–09: 15%; 2010–13: 29%) and the median pre-ART HIV viral load increased from 106 000 copies/mL (IQR: 32 000–261 000 copies/mL) in 2003–05 to 110 564 (IQR: 30 563–402 000 copies/mL) in 2010–13.

Summary of the CD4 count response

Of the 14 448 patients with pre-ART CD4 count measurements, ART was initiated in 2003–05 for 2 421 patients, in 2006–09 for 5 281 patients and in 2010–13 for 6 746 patients. The median follow-up time for patients initiating in 2003–05 was 2.6 years, in 2006–09 was 2.5 years and in 2010–13 was 1.6 years.

The median CD4 count increases from ART initiation were: in 2003–05, from 96 cells/μL (IQR: 45–171 cells/μL) at ART initiation to 374 cells/μL (IQR: 237–561 cells/μL) at 36 months; in 2006–09, from 128 cells/μL (IQR: 52–201 cells/μL) at ART initiation to 401 cells/μL (IQR: 263–575 cells/μL) at 36 months; and in 2010–13, from 173 cells/μL (IQR: 53–286 cells/μL) at ART initiation to 418 cells/μL (IQR: 274–577 cells/μL) at 36 months (Figure 1). Overall, there was an increasing trend where those initiating in 2010–13 had a higher median CD4 count at ART initiation follow-up compared to prior year periods. However, this was not found be significant in the Kruskal-Wallis median test (p value = 0.368). Similar trends were observed when examined by country (Appendix 1).

The proportion of patients within each CD4 count category (≤50, 51–100, 101–200, 201–350, 351–500 and ≥501 cells/μL) up to 36 months from ART initiation is summarized in Figure 2. Largely as a result of ART initiation at higher CD4 counts, there was an increasing trend where those initiating in 2010–13 had a greater proportion of patients at higher CD4 counts than in previous year periods. The proportion of patients with CD4 count ≥201 cells/μL increased for patients initiating: in 2003–05, from 16% at ART initiation to 81% at 36 months; in 2006–09, from 25% at ART initiation to 85% at 36 months; and in 2010–13, from 44% at ART initiation to 85% at 36 months. This trend was also apparent by country (Appendix 2).

Modelling the CD4 count response up to 36 months

The model indicated that several factors were significantly associated with the CD4 count response over time (Table 2). In the univariate analysis, year period of ART initiation was significantly (p value <0.001) associated with the CD4 cell response. Those initiating in 2006–09 and 2010–13 had a mean CD4 count that at any given time during follow-up, was 8 cells/μL (95% CI: 3 to 13 cells/μL) and 13 cells/μL (95% CI: 8 to 19 cells/μL) higher than those initiating in 2003–05. In the multivariate model, the year period of ART initiation remained significant while adjusting for clinical site and other relevant covariates (p value <0.001). Here, the mean CD4 cell count was higher at any given time during follow-up, for those initiating in 2006–09 and 2010–13 by 8 cells/μL (95% CI: 3 to 13 cells/μL) and 15 cells/μL (95% CI: 9 to 20 cells/μL), respectively, compared to those initiating in 2003–05.

We conducted several sensitivity analyses to evaluate the robustness of our results. First, we evaluated whether there was an interaction between the year period of ART initiation and time from ART initiation. This interaction term was significant for those initiating in 2006–09 compared to 2003–05 (p value=0.002). The estimated mean CD4 count difference was not significantly higher for those initiating 2006–09 compared to 2003–05 from ART initiation, except at 3 months (Appendix 3). There was little evidence to suggest an interaction between time from ART initiation and those initiating in 2010–13, compared to

2003–05 (p value=0.527). The estimated mean CD4 count difference was significantly higher for those initiating in 2010–13, compared to 2003–05, up to 15 months and 27 to 36 months from ART initiation (Appendix 3). Second, we evaluated whether the inclusion of pre-ART CD4 count in the model biased our estimated CD4 count change. Using a mixed model approach with random intercept and random slope for time from ART initiation, we found minimal differences in the parameter estimates when pre-ART CD4 count was excluded (Appendix 4). We also found excluding other covariates with large proportions of missing data, such as pre-ART HIV viral load, HBV and HCV status, did not significantly affect the estimated mean CD4 count change for the covariates (Appendix 5). Third, we evaluated whether a mixed linear model with random intercept and random slope for time from ART initiation produced significantly different parameter estimates. The parameter estimates from this model was not substantially different from the primary analysis. The mean CD4 count difference was significantly higher, at any given time during follow-up, for those initiating in 2006–09 (p value=0.001) and 2010–13 (p value <0.001) compared to those initiating in 2003–05 (Appendix 5).

Other factors in the multivariate model significantly associated with a higher CD4 count response, at any given time during follow-up, included younger age, female gender, homosexual contact (compared to heterosexual contact), higher pre-ART HIV viral load, lower pre-ART CD4 count, and HBV or HCV negative (compared to positive).

Discussion

In this analysis consisting of 16 962 HIV-positive patients receiving care in the Asia-Pacific region, our findings have shown that long-term CD4 response to ART is greater in those initiating in 2010–13 and 2006–09 compared to those initiating in 2003–05, regardless of CD4 count at ART initiation. There was an increasing trend with those initiating in more recent years having a greater CD4 response compared to previous years. Over the follow-up period, the median CD4 count was also consistently higher, and the proportion of patients with higher CD4 counts increased in more recent years.

Similar temporal trends in CD4 count at ART initiation has been shown in other studies. A large multiregional comparison of HIV-positive adults initiating ART between 2002 and 2009 found a steady increase in the median CD4 count at ART initiation in most countries. This trend was apparent regardless of the income status of the country, although the greatest increases were seen in low-income and middle-income countries rather than in high-income countries and, was also higher in females than males [30]. In contrast, a meta-analysis of 44 studies did not find a significant increasing trend in the mean CD4 count at presentation for newly presenting HIV-positive adults. The annual estimated change in CD4 count at presentation was 1.6 cells/μL (95% CI: −4.4 to 5.4 cells/μL) which was not significant (p>0.05), adjusting for study inclusion criteria, data type and study location [31].

Overall, there were few studies that explored whether the year of ART initiation influenced the CD4 count response in HIV-positive patients. One study based in a London hospital showed an association between calendar year of ART initiation and CD4 response from ART initiation [23]. During the first 3 months of ART initiation, this association was not

significant. However, beyond 3 months, patients initiating from 1997 to 2003 had a yearly CD4 count increase that was 84 cells/μL (95% CI: −48 to −120 cells/μL) higher than those initiating in 1996 and before.

It is also difficult to ascertain which factors of patient care have contributed to the improved CD4 count response in recent years. A move towards greater adherence in patients, either due to physician advice, support services, or more tolerable and convenient regimens, could have played an important role [17, 32]. Previous studies have highlighted that patients who are more adherent have greater and more sustained gains in CD4 count than non-adherent patients [33–35]. Other predictors significantly associated with improved CD4 count recovery are also consistent with former studies, including older age, female sex, pre-ART HIV viral load, HBV and HCV co-infection [36–38].

The clinical implications of our findings are fairly limited as those initiating in 2010–13 were only 15 cells/μL higher compared to those in 2003–05. But, our analysis has highlighted that the proportion of patients at high range CD4 counts has drastically increased over time, in particular, at ART initiation but also through to 36 months follow-up. Therefore, over time, fewer patients are being exposed to lower CD4 counts where they are at higher risk of OIs [39] and non-AIDS defining cancers (NADCs) [40, 41]. Patients are also experiencing shorter durations at lower CD4 counts, which leads to a better overall prognosis [42].

An advantage of our study was the large patient sample size yet, our patient data were limited to a few variables. As such, we were unable to explore other important trends relating to lower CD4 counts, including the occurrence of NADCs or OIs. In addition, HIV viral load was not routinely collected at the clinical sites and had large proportions of missing data. Hence, we could not expand the scope of our analysis to also examine the HIV viral load response by year of ART initiation. Our model estimates for the pre-ART HIV viral load may also be bias and caution is advised when interpreting these findings.

We used observational data on CD4 counts collected during routine clinic visits for HIV-positive adults presenting between 2003 and 2013. Patients lost to follow-up (LTFU) can introduce potential bias that can impede on the analysis because it is unclear how many remain in care elsewhere or have died. The LTFU rate previously reported in TAHOD-LITE was relatively low and consistent between the years of ART initiation (2003–05: 2.1 per 100 person-years; 2006–09: 2.9 per 100 person-years; 2010–13: 2.8 per 100 person-years) [21]. We also had 8 clinical sites represent 7 countries across the region, and hence, our results are reflective of trends occurring within the clinical sites rather than their respective countries. The presence of country-level differences in when patients present for care, the available treatment options and the patient care provided, as well as other unmeasured confounding factors could have also contributed to heterogeneity. However, our analysis by clinical site has shown similar trends to the overall analysis where there is an increasing trend in CD4 response over time by the year of ART initiation. Furthermore, the model used in our analysis is adjusted for clinic site to account for these differences between sites.

In summary, we found that the CD4 response to ART is greater in those initiating in 2010–13 and 2006–09 compared to those in 2003–05, with greater proportions of patients starting treatment at higher CD4 counts in recent years. Patients initiating in more recent years spend less time exposed in lower CD4 count ranges, reducing their risk for serious OIs and future NADCs that are associated with lower CD4 count. As guidelines recommending immediate ART are more widely implemented, it will be important to monitor their impact on immediate and long-term clinical outcomes.

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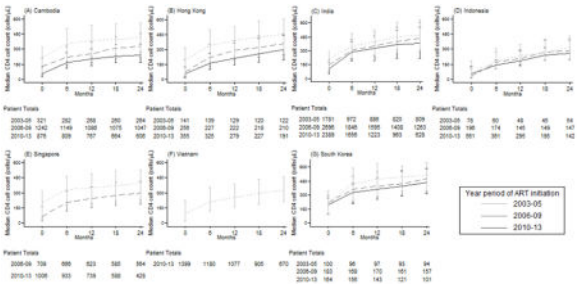
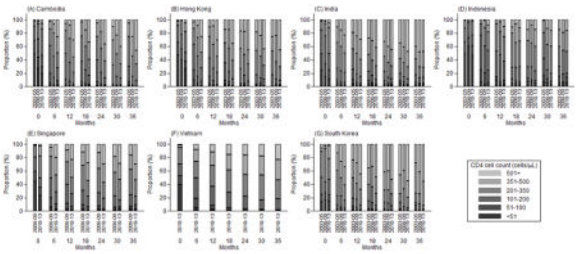
Appendix 1. The median CD4 count (cells/μL) and patient totals over the time since ART initiation, by the year period of ART initiation and country



Appendix 2. The proportion of patients in each CD4 count (cells/μL) category over time since ART initiation, by country and year period of ART initiation



Appendix 3. Estimated mean CD4 count (cells/μL) change when considering an interaction between year period of ART initiation and follow-up time from ART initiation

Month of follow-up	Year period of ART initiation	Mean Diff.	95% CI	p value
3	2003–05	ref		
	2006–09	**10**	**(4, 15)**	**0.001**
	2010–13	**18**	**(12, 24)**	**<0.001**
6	2003–05	ref		
	2006–09	5	(−1, 11)	0.093
	2010–13	**15**	**(9, 22)**	**<0.001**
9	2003–05	ref		
	2006–09	2	(−4, 9)	0.497
	2010–13	**13**	**(6, 19)**	**<0.001**
12	2003–05	ref		
	2006–09	1	(−6, 7)	0.856
	2010–13	**10**	**(4, 16)**	**0.002**

Month of follow-up	Year period of ART initiation	Mean Diff.	95% CI	p value
15	2003–05	ref		
	2006–09	0	(−6, 6)	0.979
	2010–13	**8**	**(1, 14)**	**0.017**
18	2003–05	ref		
	2006–09	0	(−6, 6)	0.888
	2010–13	6	(0, 12)	0.067
21	2003–05	ref		
	2006–09	1	(−5, 8)	0.666
	2010–13	5	(−2, 12)	0.132
24	2003–05	ref		
	2006–09	3	(−4, 9)	0.425
	2010–13	5	(−2, 12)	0.126
27	2003–05	ref		
	2006–09	4	(−3, 10)	0.233
	2010–13	**7**	**(0, 14)**	**0.046**
30	2003–05	ref		
	2006–09	5	(−1, 11)	0.128
	2010–13	**10**	**(3, 18)**	**0.004**
33	2003–05	ref		
	2006–09	6	(−2, 13)	0.150
	2010–13	**16**	**(7, 24)**	**<0.001**
36	2003–05	ref		
	2006–09	5	(−6, 17)	0.354
	2010–13	**23**	**(10, 36)**	**<0.001**

Note: Multivariate model adjusts for age at ART initiation, gender, HIV mode of exposure, pre-ART HIV viral load, pre-ART CD4 count, first ART regimen, hepatitis B co-infection, hepatitis C co-infection and clinical site.

Appendix 4. Comparison of estimated mean CD4 count (cells/μL) change up to 36 months from ART initiation using a mixed linear model, with random intercept and random slope for time from ART initiation

	Model 1			Model 2		
	Mean Diff.	**95% CI**	**p value**	**Mean Diff.**	**95% CI**	**p value**
Year of ART Initiation			<0.001			<0.001
2003–2005	ref			ref		
2006–2009	6	(2, 10)	0.001	7	(3, 11)	0.001

	Model 1			Model 2		
	Mean Diff.	**95% CI**	**p value**	**Mean Diff.**	**95% CI**	**p value**
2010–2013	9	(5, 13)	<0.001	11	(7, 15)	<0.001
Time from ART initiation (per month)	16	(15, 16)	<0.001	16	(15, 16)	<0.001
Age at ART initiation (years)			<0.001			
≤30	ref			ref		
31–40	−5	(−8, −2)	0.003	−5	(− −9, −2)	0.001
41–50	−11	(−15, −7)	<0.001	−12	(−16, −8)	<0.001
51+	−7	(−12, −2)	0.004	−8	(−13, −3)	0.001
Sex						
Male	ref			ref		
Female	1	(−2, 4)	0.445	1	(−2, 5)	0.332
Mode of HIV Exposure			<0.001			<0.001
Heterosexual contact	ref			ref		
Homosexual contact	11	(5, 16)	<0.001	11	(6, 16)	<0.001
Injecting drug use	−17	(−24, −10)	<0.001	−17	(−24, −10)	<0.001
Other/unknown	4	(−1, 9)	0.111	4	(−1, 9)	0.111
Pre-ART CD4 cell count (cells/μL)						
≤50				ref		
51–100				11	(7, 16)	0.000
101–200				9	(5, 13)	0.000
201+				−3	(−6, 1)	0.169
First ART regimen			0.009			0.013
NRTI[1]+NNRTI[2]	ref			ref		
NRTI[1]+PI[3]	−4	(−10, 3)	0.263	−3	(−9, 3)	0.374
Other/unknown	20	(6, 35)	0.007	20	(5, 35)	0.007

Note: Global p-values for year of ART initiation, pre-ART CD4 count and age are test for trend. Other global p-values are test for heterogeneity.

[1]NRTI = nucleoside reverse transcriptase inhibitor.

[2]NNRTI = nonnucleoside reverse transcriptase inhibitor.

[3]PI = protease inhibitor.

Appendix 5. Comparison of estimated mean CD4 count (cells/μL) change up to 36 months from ART initiation using a mixed linear model, with random intercept and random slope for time from ART initiation

	Model 1			Model 2		
	Mean Diff.	**95% CI**	**p value**	**Mean Diff.**	**95% CI**	**p value**
Year of ART Initiation			**<0.001**			**<0.001**
2003–2005	ref			ref		
2006–2009	**6**	**(2, 10)**	**0.001**	**6**	**(2, 10)**	**0.002**
2010–2013	**9**	**(5, 13)**	**<0.001**	**9**	**(5, 13)**	**<0.001**
Time from ART initiation (per month)	**16**	**(15, 16)**	**<0.001**	**16**	**(15, 16)**	**<0.001**
Age at ART initiation (years)			**<0.001**			**<0.001**
≤30	ref			ref		
31–40	**−5**	**(−8, −2)**	**0.003**	**−6**	**(−9, −3)**	**<0.001**
41–50	**−11**	**(−15, −7)**	**<0.001**	**−13**	**(−17, −9)**	**<0.001**
51+	**−7**	**(−12, −2)**	**0.004**	**−9**	**(−14, −4)**	**<0.001**
Sex						
Male	ref			ref		
Female	1	(−2, 4)	0.445	2	(−1, 5)	0.319
Mode of HIV Exposure			**<0.001**			**<0.001**
Heterosexual contact	ref			ref		
Homosexual contact	**11**	**(5, 16)**	**<0.001**	**11**	**(6, 16)**	**<0.001**
Injecting drug use	**−17**	**(−24, −10)**	**<0.001**	**−11**	**(−19, −2)**	**0.011**
Other/unknown	4	(−1, 9)	0.111	3	(−1, 8)	0.168
First ART regimen			**0.009**			**0.030**
NRTI[1]+NNRTI[2]	ref			ref		
NRTI[1]+PI[3]	−4	(−10, 3)	0.263	−4	(−10, 3)	0.252
Other	**20**	**(6, 35)**	**0.007**	**17**	**(2, 31)**	**0.026**
Pre-ART HIV viral load (copies/mL)						
≤100000				ref		
>100000				**30**	**(25, 35)**	**<0.001**
Not tested				6	(1, 10)	0.014
Pre-ART CD4 (cells/μL)						0.724
≤50				ref		
51–100				**12**	**(8, 16)**	**<0.001**
101–200				**10**	**(6, 14)**	**<0.001**
201+				0	(−4, 3)	0.895
Hepatitis B co-infection						0.086

	Model 1			Model 2		
	Mean Diff.	**95% CI**	**p value**	**Mean Diff.**	**95% CI**	**p value**
Negative				ref		
Positive				**−6**	**(−11, −1)**	**0.042**
Not tested				−3	(−8, 2)	0.291
Hepatitis C co-infection						**0.016**
Negative				ref		
Positive				**−10**	**(−16, −3)**	**0.005**
Not tested				1	(−4, 7)	0.601

Note: Global p-values for year of ART initiation, age at ART initiation, pre-ART HIV viral load and pre-ART CD4 count are test for trend. Other global p-values are test for heterogeneity.

[1] NRTI = nucleoside reverse transcriptase inhibitor.

[2] NNRTI = nonnucleoside reverse transcriptase inhibitor.

[3] PI = protease inhibitor.

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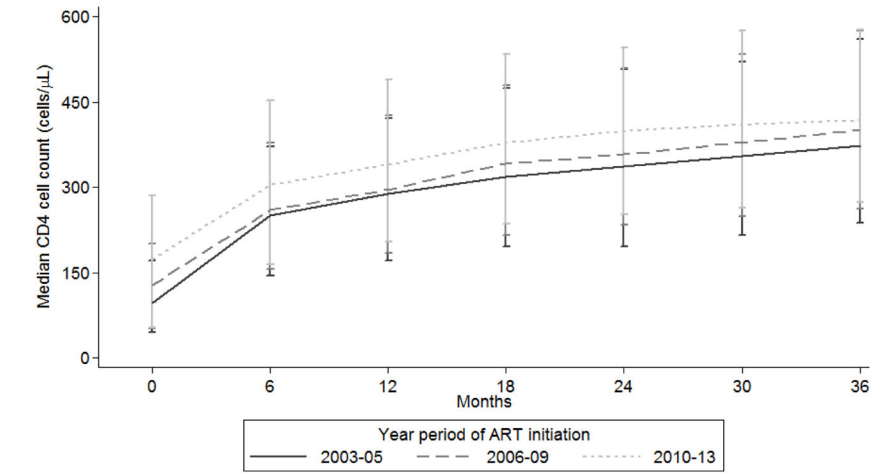

Patient Totals

2003-05	2421	1556	1439	1339	1349	1304	783
2006-09	5282	4246	3859	3603	3404	3261	1763
2010-13	6750	5439	4554	3667	2784	2076	869

Figure 1.

The median CD4 count (cells/μL) and patient totals over the time (months) since ART initiation, by the year period of ART initiation.

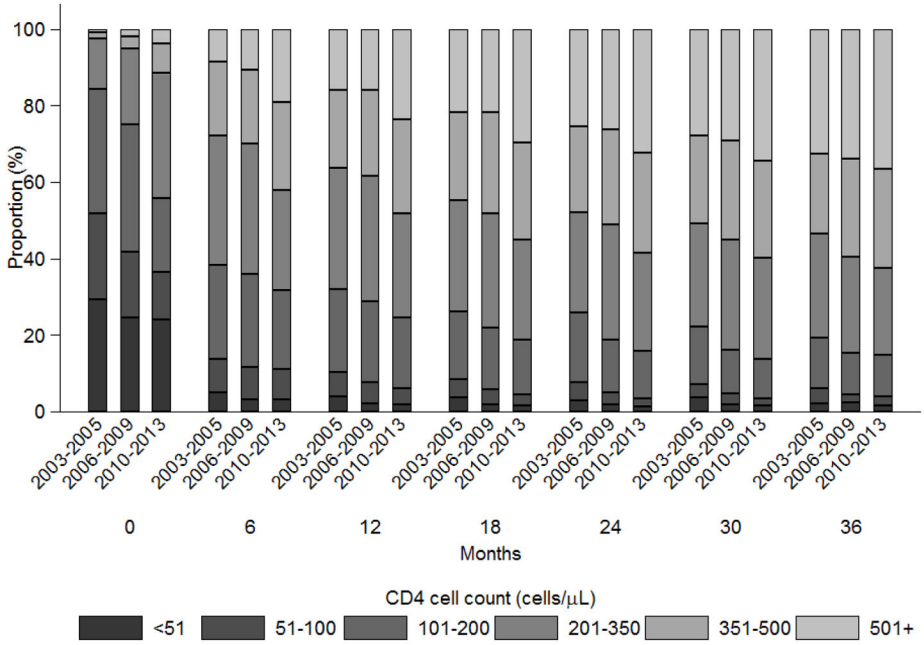

Figure 2.

The proportion of patients in each CD4 count (cells/μL) category over time since ART initiation, by year period of ART initiation.

Table 1

Summary of the patient characteristics across all countries.

	2003–05 n (%)	2006–09 n (%)	2010–13 n (%)
Total	2874	6248	7840
Age			
≤30	736 (25)	1505 (24)	2087 (26)
31–40	1440 (50)	2865 (46)	3343 (43)
41–50	508 (18)	1272 (20)	1555 (20)
51+	190 (7)	606 (10)	855 (11)
Median [IQR]	35 [30, 40]	36 [31, 42]	36 [30, 43]
Sex			
Male	2149 (75)	4312 (69)	5176 (66)
Female	721 (25)	1931 (31)	2657 (34)
Transgender	4 (<0.2)	5 (<0.1)	7 (<0.1)
Mode of HIV exposure			
Heterosexual	2529 (88)	5272 (85)	5748 (73)
Homosexual	111 (4)	405 (6)	784 (10)
Injecting drug user	84 (3)	125 (2)	571 (7)
Other/Unknown	150 (5)	446 (7)	737 (10)
HCV (ever)			
Negative	754 (26)	2609 (42)	4093 (52)
Positive	80 (3)	171 (3)	776 (10)
Not tested	2040 (71)	3468 (55)	2971 (38)
HBV (ever)			
Negative	939 (33)	2869 (46)	4702 (60)
Positive	108 (4)	305 (5)	473 (6)
Not tested	1827 (63)	3074 (49)	2665 (34)
Pre-ART CD4 (cells/μL)			
≤50	708 (25)	1295 (21)	1620 (21)
51–100	543 (19)	915 (15)	833 (10)
101–200	793 (27)	1748 (28)	1307 (17)
>200	377 (13)	1325 (21)	2990 (38)
Not tested	453 (16)	967 (15)	1094 (14)
Median [IQR]	96 [45, 171]	128 [52, 201]	172 [53, 286]
Pre-ART viral load (copies/mL)			
$\leq 10^5$	191 (7)	458 (7)	1073 (14)
$>10^5$	204 (7)	518 (8)	1154 (15)
Not tested	2479 (86)	5272 (85)	5613 (71)
Median [IQR]	106 000 [32 000, 261 000]	114 000 [29 785, 351 500]	110 564 [30 563, 402 000]
First ART regimen			
NRTI+NNRTI	2719 (95)	5930 (95)	7381 (95)

	2003–05 n (%)	2006–09 n (%)	2010–13 n (%)
NRTI+PI	148 (5)	290 (5)	381 (5)
Other	7 (<0.3)	28 (<0.5)	78 (1)
Previous mono/dual therapy			
No	2632 (92)	6053 (97)	7680 (98)
Yes	242 (8)	195 (3)	160 (2)

Table 2

Estimated mean CD4 count (cells/μL) change up to 36 months from ART initiation.

	Univariate			Multivariate		
	Mean Diff.	**95% CI**	**p value**	**Mean Diff.**	**95% CI**	**p value**
Year of ART Initiation			<0.001			**<0.001**
2003–2005	ref			ref		
2006–2009	8	(3, 13)	0.003	**8**	**(3, 13)**	**0.002**
2010–2013	13	(8, 19)	<0.001	**15**	**(9, 20)**	**<0.001**
Time from ART initiation (per month)	16	(15, 16)	<0.001	**16**	**(16, 17)**	**<0.001**
Age at ART initiation (years)			<0.001			**<0.001**
≤30	ref			ref		
31–40	−11	(−15, −6)	<0.001	**−9**	**(−13, −5)**	**<0.001**
41–50	−21	(−26, −16)	<0.001	**−20**	**(−25, −15)**	**<0.001**
51+	−19	(−25, −13)	<0.001	**−17**	**(−24, −11)**	**<0.001**
Sex						
Male	ref			ref		
Female	18	(14, 22)	<0.001	**17**	**(13, 21)**	**<0.001**
Mode of HIV Exposure			<0.001			**<0.001**
Heterosexual contact	ref			ref		
Homosexual contact	16	(9, 23)	<0.001	**18**	**(11, 25)**	**<0.001**
Injecting drug use	−21	(−30, −12)	<0.001	−7	(−18, 3)	0.186
Other/unknown	6	(0, 13)	0.061	4	(−2, 11)	0.167
Pre-ART HIV viral load (copies/mL)						
≤100000	ref			ref		
>100000	41	(34, 47)	<0.001	**38**	**(32, 45)**	**<0.001**
Not tested	7	(1, 13)	0.024	5	(−1, 11)	0.117
Pre-ART CD4 (cells/μL)			<0.001			**<0.001**
≤50	ref			ref		

	Univariate			Multivariate		
	Mean Diff.	**95% CI**	**p value**	**Mean Diff.**	**95% CI**	**p value**
51–100	10	(4, 15)	0.001	**9**	**(3, 14)**	**0.002**
101–200	5	(1, 10)	0.040	3	(−2, 8)	0.230
201+	−8	(−13, −4)	<0.001	**−15**	**(−20, −10)**	**<0.001**
First ART regimen			0.031			0.109
NRTI[1]+NNRTI[2]	ref			ref		
NRTI[1]+PI[3]	−4	(−12, 4)	0.331	−5	(−13, 3)	0.246
Other	24	(4, 44)	0.020	16	(−4, 36)	0.108
Hepatitis B co-infection						
Negative	ref			ref		
Positive	−12	(−20, −5)	0.001	**−11**	**(−18, −4)**	**0.003**
Not tested	−5	(−10, −1)	0.033	−5	(−12, 2)	0.134
Hepatitis C co-infection						
Negative	ref			ref		
Positive	−20	(−28, −12)	<0.001	**−12**	**(−21, −3)**	**0.008**
Not tested	−4	(−9, 1)	0.145	3	(−5, 10)	0.478

Note: Global p-values for year of ART initiation, age and pre-ART CD4 count are test for trend. Other global p-values are test for heterogeneity.

[1]NRTI = nucleoside reverse transcriptase inhibitor.

[2]NNRTI = nonnucleoside reverse transcriptase inhibitor.

[3]PI = protease inhibitor.