Effect of age on immunological response in the first year of antiretroviral therapy in HIV-1-infected adults in West Africa

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Abstract

Objective—To assess the effect of aging on the immunological response to antiretroviral therapy (ART) in the West African context.

Methods—The change in CD4 T-cell count was analysed according to age at the time of ART initiation among HIV-infected patients enrolled in the International epidemiological Database to Evaluate AIDS (IeDEA) Collaboration in the West African region. CD4 gain over 12 months of ART was estimated using linear mixed models. Models were adjusted for baseline CD4 cell count, sex, baseline clinical stage, calendar period and ART regimen.

Results—The total number of patients included was 24 107, contributing for 50 893 measures of CD4 cell count in the first year of ART. The baseline median CD4 cell count was 144 cells/μl [interquartile range (IQR) 61–235]; median CD4 cell count reached 310 cells/μl (IQR 204–443) after 1 year of ART. The median age at treatment initiation was 36.3 years (10th–90th percentiles=26.5–50.1). In adjusted analysis, the mean CD4 gain was significantly higher in younger patients ($P < 0.0001$). At 12 months, patients below 30 years recovered an additional 22 cells/μl on average [95% confidence interval (CI) 2–43] compared to patients at least 50 years.

Conclusion—Among HIV-infected adults in West Africa, the immunological response after 12 months of ART was significantly poorer in elderly patients. As the population of treated patients is likely to get older, the impact of this age effect on immunological response to ART may increase over time.

Keywords

age; antiretroviral treatment; HIV/AIDS; immunological response; linear mixed models; West Africa

Introduction

Effective antiretroviral therapy (ART) has significantly increased the life expectancy of HIV-infected patients [1–5] in developed and resource-limited countries. Ageing of the general population and large-scale access to ART in resource-limited countries have both contributed to the overall ageing of the HIV population. A study estimated at 3 million the number of people aged at least 50 years and living with HIV in 2007 in sub-Saharan Africa [6].

Medical care addressing the specific needs of this ageing HIV population is needed [7]. Data from Europe and the USA reported a lower immune response to ART in older patients [8–19]. This age effect, which remained moderate with no obvious threshold effect [19,20], was partly explained by the decreased thymic output over age [20,21]. Other studies, with smaller sample size, did not find any effect of age on the immune response to ART [22,23].

The effect of age on the response to ART in sub-Saharan Africa has not been well documented so far. And yet, due to several immunological and demographic specificities of sub-Saharan Africa, the effect of age on immune restoration may differ from that observed

in high-income countries. On one hand, HIV-infected patients in Africa are presenting a higher level of T-cell activation compared to those in high-income countries [24]; whereas an increased T-cell activation has been related to a lower CD4 gain after ART initiation [25]. Hence, a decrease of de-novo production of CD4 (potentially related to age) might have a greater impact when the loss of CD4 is accelerated by a persistent immune activation. On the other hand, life expectancy being far lower in sub-Saharan Africa compared to high-resource settings (e.g. 57 years in Cote d'Ivoire compared to 81 years in France in 2009), HIV patients who survive beyond 50 years may be selected patients presenting specific characteristics of a slower progression of the infection.

The objective of this analysis was to estimate the impact of age on the immunological response to ART 12 months after treatment initiation, in HIV-infected adults followed in the West-African context.

Methods

The IeDEA West Africa collaboration

To better describe the current epidemiology of HIV infection and especially care patterns and treatment, a prospective and observational multicohort collaboration located in West Africa was established in 2006 within the International epidemiologic Database to Evaluate AIDS (IeDEA) Collaboration of the US National Institutes of Health (http://www.iedeawestafrica.org/) [26]. Fifteen HIV/AIDS adult clinics located within seven countries – Benin (n=1), Burkina Faso (n=1), Côte d'Ivoire (n=6), Gambia (n=1), Mali (n=2), Nigeria (n=2) and Senegal (n=2) – participated in this analysis. Every 18 months, each cohort submits information to the central coordinating centre in Abidjan, Côte d'Ivoire, using a standardized data format. The data collected capture demographic, therapeutic, clinical and biological information.

Inclusion criteria

All naive HIV-infected patients aged 16 years or older at ART starting date, with documented sex, date of birth, date of ART initiation and CD4 T-cell count measured at ART initiation (or 6 months before) were eligible for this analysis.

Statistical analysis

Analyses were performed on an intent-to-continue basis; ART modifications were not taken into account. Baseline was defined as the date of ART initiation and the end point of the study was 12 months after baseline. The CD4 change from baseline was analysed with linear mixed models. The effect of age on CD4 change was adjusted for sex, baseline HIV clinical stage (Centers for Disease Control (CDC) or WHO), the year of ART initiation, ARTregimen and baseline CD4 cell count. A linear effect of age was compared to a class effect (5-year categories). Fixed effects on CD4 change were estimated using Wald tests. Residual homoscedasticity and normality were checked graphically. Robustness analyses were conducted using absolute CD4 cell count (after square root transformation). We considered a patient as lost to follow-up if he/she was not known to have died and was not seen at least 3 months prior to the cohort closure date. Results of the primary analysis were confirmed by performing a sensitivity analysis excluding patients who died or were lost to follow-up within the first 12 months.

Results

Population characteristics

The IeDEA West Africa database included a total of 33 815 patients as of January 2010. One thousand nine hundred and twenty-two patients with missing data were excluded (ART initiation after closure date, unknown date of ART initiation, missing demographic data), 1756 patients were previously under ART and 6030 patients (17.8%) had no baseline CD4 measurement available. In the present study 24 107 patients were finally eligible (Fig. 1) and the number of patients enrolled per site ranged between 216 and 3769.

The characteristics of the study sample and of the excluded patients are described in Table 1. In the study sample, the median age at ART initiation was 36.3 [interquartile range (IQR) 30.5–43.2], 63.6% of the patients were women and the baseline clinical stage was WHO stage I or II, or CDC stage A or B for 44.1% of the patients. Most patients started ART in 2004 or later (93.0%). Most patients (86.9%) initiated a non-nucleoside reverse transcriptase inhibitor (NNRTI) ART-based regimen. The most common ART combinations were stavudine + lamivudine + nevirapine for 7663 patients (31.8%), zidovudine + lamivudine + efavirenz for 3696 patients (15.3%) and zidovudine + lamivudine + nevirapine for 3496 patients (14.5%). Baseline median CD4 cell count was significantly lower ($P < 0.0001$) in the study sample compared to excluded patients [144 cells/µl (IQR 61–235) and 183 cells/µl (IQR 82–336), respectively]. Within the study sample, the baseline median CD4 cell count was 117 cells/µl (IQR 43–212) for patients lost to follow-up, 55 cells/µl (IQR 15–143) for deceased patients and 156 cells/µl (IQR 73–245) for patients who remained alive.

CD4 response to treatment

Within the study sample, the median number of CD4 measurements available during the study period was 2 (IQR 1–3). The median CD4 cell count was 277 cells/µl (IQR 177–403) and 310 cells/µl (IQR 204–443) 6 and 12 months after starting ART, respectively. At baseline, the median CD4 cell count was 150 cells/µl (IQR 64–241) for patients under 30 years and 150 cells/µl (IQR 69–240) for those at least 50 years. Twelve months after starting ART 42.3% of the patients had a CD4 cell count available, the median CD4 cell count was 332 cells/µl (IQR 216–473) for those aged 16–30 years and 305 cells/µl (IQR 208–416) for patients aged at least 50 years.

Table 2 presents adjusted estimates of mean CD4 change after 12 months of ART for the following reference group of patients: women who started a NNRTI-based ART regimen within the year 2004 or later, who initiated the treatment at clinical stage A, B or WHO I, II, with an initial CD4 cell count equal to 180 cells/µl and were aged between 16 and 30 years. The mean CD4 changes were adjusted for initial CD4 cell count, ART regimen, sex, initial clinical stage and year of ART initiation.

The overall mean effect of age on the CD4 gain was significant ($P<0.0001$). Compared to patients below 30 years [251 cells/µl; 95% confidence interval (CI) 239; 263], the average CD4 change was not significantly different ($P=0.7017$) in patients between 30 and 34 years (254 cells/µl, 95% CI 242; 266). For patients aged at least 35 years, the mean CD4 change at 12 months was significantly lower compared to patients aged below 30 years (−17 cells/µl, 95% CI −33; −2 for 35–40 years; −20 cells/µl, 95% CI −37; −3 for 40–45 years; −34 cells/µl, 95% CI −54; −15 for 45–50 years and −22 cells, 95% CI −43; −2 for patients aged 50 years).

The average CD4 gain was significantly higher among women than men (+30 cells/µl, 95% CI +21; +39), for patients with a nonadvanced clinical stageat baseline (A, B, I, II) compared to advanced (AIDS, III, IV; +17 cells/µl, 95% CI +6 +28), for patients who

initiated ART in 2004 or later compared to patients starting prior 2004 (+48 cells/μl, 95% CI +31; +64) and for patients treated with NNRTI ART-based regimen compared to protease inhibitor ART-based regimen (+36 cells/μl, 95% CI +18; +54). The effect of initial CD4 cell count on mean CD4 change was also significant (P<0.0001), +19 cells/μl (95% CI +18; +20) for each 50 cells/μl CD4 cell count lower at baseline.

As a robustness analysis, the linear mixed model was also conducted by removing patients lost to follow-up (n=5690) and deceased patients (n=779) during the first year of ART. Fig. 2 illustrates the mean CD4 change estimated on these two subsets. Although the average CD4 gain was slightly higher when considering lost to follow-up and deceased patients, the overall results were similar. Also, a continuous linear effect of age led to a similar fit of the data (AIC linear 614759 vs. AIC categories 614767).

Discussion

In a large collaboration of observational cohorts of HIV-infected patients in West Africa, we found a significant impact of age on the immune response during the first 12 months of ART with a −20 to −34 cells/μl reduction in CD4 gain among patients older than 40 compared to patients younger than 30 years. This impairment in CD4 gain may have serious clinical and public health consequences, life expectancy being related to the time spent with higher CD4 cell counts [27].

Data on the effect of age in Africa are very scarce but always showed a poorer ART response in older patients [2,3,28]. We confirmed the effect of age on CD4 responses in sub-Saharan Africa; however, we were not able to explore the possible causal factors. Thymic output may be compromised by malnutrition and infections [29] and higher level of T-cell activation [24] may also participate to an increased turnover of T cells. A poor immunological response in older patients is particularly problematic in this context where HIV RNA viral load measurement and new line of ART are rarely available [30]. Therefore, an improvement in the CD4 response among older patients should be achieved by improving modifiable risk factors of poor immunological response such as HIV replication, concomitant infections or malnutrition.

An interesting result is related to the absence of clear threshold effect of age in our study. It is difficult to conclude on the existence of a clear threshold from results published so far because the cut-points varied [9,18,28] and the justification of a nonlinear effect was often lacking. Our interpretation is that there is a continuous effect of age (following thymic atrophy) that has a substantial impact on CD4 response as early as from 40 years.

Our study presents several limitations that need to be discussed. No adjustment on virological response could be performed in the present study because HIV-RNA viral load was not widely available in the study clinics like in most settings in resource-limited countries. However, older patients are known to show a better virological response [18] even after adjustment for time from seroconversion [31] that could be linked to treatment adherence. By not taking into account a better virological response in older patients we may have in fact underestimated the deleterious effect of age on the CD4 response and the observed relationship may be minimal. A methodological drawback regularly encountered in cohorts established in resource-limited countries is the high rate of losses to follow-up [32]. The consequence may be a biased estimate of the CD4 gain. Statistical approaches have been proposed to correct this type of bias [33]. However, these approaches also have their limitations and one of them is the common assumption that patients lost to follow-up are homogeneous. For instance, one can assume that they are all in a poorer health status than those followed [34]. A recent active survey performed in East Africa [35] reported that

actually one-third of lost-to-follow-up patients were dead but others had been transferred or had travelled because they had an improved health status. In our study, we observed a trend towards a better immunological response when including patients lost to follow-up in the analyses, which may be due to a better outcome in these patients. Although our conclusions were robust to the inclusion/exclusion of patients lost to follow-up and deceased, additional information on these patients would lead to more accurate estimates.

In conclusion, CD4 gain after ART initiation was significantly poorer in elderly patients in this West African setting. As the population of treated HIV-infected patients in this part of the world is likely to get older, thanks to the overall effectiveness of ART and considering that the scaling-up of ART will continue, the impact of this age effect on patients' immunological response is likely to increase over time.

Acknowledgments

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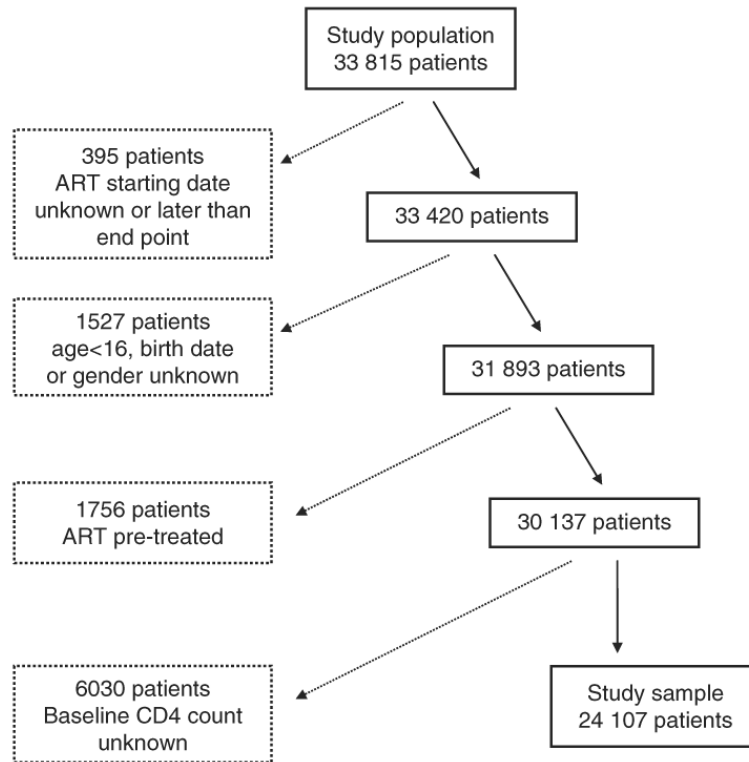
Fig. 1.
Flow diagram of the selection of the study sample (IeDEA West Africa Collaboration).
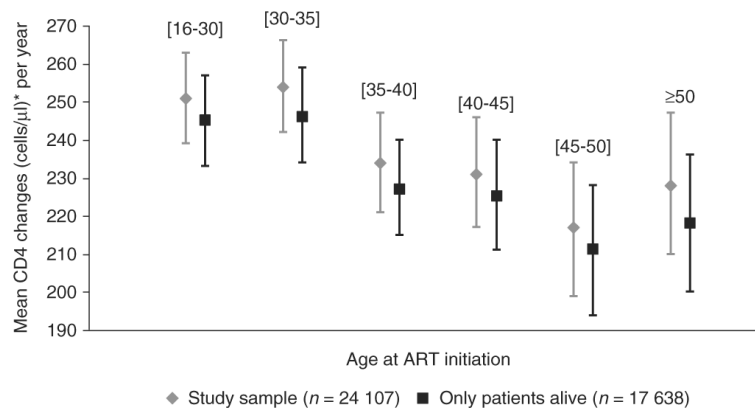
Fig. 2.
Mean CD4 changes with 95% confidence intervals (cells/µl) after 12 months of ART according to age, estimated by adjusted linear mixed models in the study population, with and without deceased and lost to follow-up patients ($n = 24\,107$ and $n = 17\,638$, respectively) (IeDEA West Africa Collaboration). *For the reference group: women, initiating NNRTI regimen after 2003 at Centers for Disease Control clinical stage A, B or WHO I, II and with 180 CD4 cells/µl at baseline.

Table 1

Baseline and follow-up characteristics for study sample ($n = 24\,107$) compared to patients not included in the analysis ($n = 9708$).

Variables	Patients excluded	Study sample
Total number of patients	9708	24107
Baseline CD4 cell count (cells/µl)		
Median (IQR)	183 (82–336)	144 (61–235)
Unknown (%)	7288 (75.1)	–
Age at baseline (years)		
Median (IQR)	36.7 (30.7–43.7)	36.3 (30.5–43.2)
Unknown (%)	1714 (17.7)	–
<25 years (%)	558 (5.8)	1486 (6.2)
25–29	1166 (12.0)	3885 (16.1)
30–34	1621 (16.7)	5192 (21.5)
35–39	1716 (17.7)	4939 (20.5)
40–45	1184 (12.2)	3716 (15.4)
45–50	835 (8.6)	2459 (10.2)
50–54	490 (5.1)	1370 (5.7)
55	424 (4.4)	1060 (4.4)
Sex (%)		
Women	5804 (59.8)	15322 (63.6)
Men	3457 (35.6)	8785 (36.4)
Unknown	447 (4.6)	–
Baseline clinical stage (%)		
CDC stage A, B, WHO I, II	3796 (39.1)	10637 (44.1)
AIDS stage, WHO III, IV	3036 (31.3)	9702 (40.2)
Unknown	2876 (29.6)	3768 (15.7)
Year of ART initiation (%)		
Prior to 2004	847 (8.7)	1683 (7.0)
2004 to 2009	8521 (87.8)	22424 (93.0)
Unknown	340 (3.5)	–
Initial ART regimen (%)		
NNRTI-based	7804 (80.4)	20938 (86.9)
PI-based	700 (7.2)	1331 (5.5)
Others	750 (7.7)	1739 (7.2)
Unknown	454 (4.7)	99 (0.4)
Follow-up characteristics		
Died (%)	188 (1.9)	779 (3.2)
Lost to follow-up (%)	2602 (26.8)	5690 (23.6)
Number of CD4 measurements	8915	50893
Median number of CD4 measurements (IQR)	0 (0–2)	2 (1–3)

IeDEA West Africa Collaboration.

ART, antiretroviral treatment; CDC, Centers for Disease Control; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 2

Mean CD4 change (cells/µl) after 12 months of ART, estimated by multivariable linear mixed model.

	Mean CD4 change estimated (cells/µl)	95% Confidence interval	*P* value
Age at baseline[a] (years)			<0.0001
[16–30]	+251[b]	+239; +263	
[30–35] vs. [16–30]	+3	−12; +18	
[35–40] vs. [16–30]	−17	−33; −2	
[40–45] vs. [16–30]	−20	−37; −3	
[45–50] vs. [16–30]	−34	−54; −15	
[50–81] vs. [16–30]	−22	−43; −2	
Baseline[a] CD4 cell count			<0.0001
For 50 cells/µl lower	+19	+18; +20	
Sex			<0.0001
Women vs. men	+30	+21; +39	
Baseline[a] clinical stage			<0.0001
A, B/I, II vs. AIDS/WHO III, IV	+17	+6; +28	
Year of ART initiation			<0.0001
Prior to 2004 vs. up to 2003	−48	−64; −31	
Initial ART regimen			<0.0001
PI-based vs. NNRTI-based	−36	−54; −18	
Others regimen vs. NNRTI-based	−45	−60; −30	

IeDEA West Africa Collaboration.

ART, antiretroviral treatment; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a]Baseline: initiation of ART.

[b]For the reference group: 16–30-year-old women, initiating NNRTI regimen after 2003 at Centers for Disease Control clinical stage A, B or WHO I, II and with 180 CD4 cells/µl at baseline.