CD4 cell count response to first-line combination antiretroviral treatment in HIV-2 compared to HIV-1 positive patients - A Multinational Multicohort European Study.

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Abstract:

Background: CD4 cell recovery following first-line combination antiretroviral treatment (cART) is poorer in HIV-2 than in HIV-1 positive (+) patients. Only large comparisons may allow adjustments for demographic and pretreatment plasma viral load (pVL).

Methods: ART naïve HIV-positive (HIV+) adults from two European multi-cohort collaborations, COHERE (HIV-1 alone) and ACHIeV2e (HIV-2 alone), were included, if they started first-line cART (without non-nucleoside reverse transcriptase inhibitors or fusion inhibitors) between 1997 and 2011. Patients without at least 1 CD4 cell count before start of cART, without a pretreatment pVL and with missing a priori defined covariables were excluded. Evolution of CD4 cell count was studied using adjusted linear mixed models.

Results: We included 185 HIV-2+ and 30,321 HIV-1+ patients, median age of 46 (IQR: 36; 52) and 37 (IQR: 31; 44) years, respectively. Median observed pretreatment CD4 cell counts/mm^3 were 203 (95%CI: 100; 290) in HIV-2+ and 223 (95%CI: 100; 353) in HIV-1+ patients. Mean observed CD4 cell count changes from start of cART to 12 months were +105 (95%CI: 77; 134) in HIV-2+ and +202 (95%CI: 199; 205) in HIV-1+patients, an observed difference of 97 cells/mm^3 in one year. In adjusted analysis, mean CD4 cell increase was overall 25 CD4 cells/mm^3/year lower (95% CI: 5; 44; P=0.0127) in HIV-2+ compared with HIV-1+ patients.

Conclusions: Poorer CD4 cell increase during first-line cART was observed in HIV-2+ patients even after adjusting for pretreatment pVL and other potential confounders. Our results underline the need to identify more potent therapeutic regimens or strategies against HIV-2.

Background

HIV-2 is less prevalent than HIV-1 and HIV-2 positive (+) individuals live mainly in West Africa, followed by Angola, Mozambique, Europe (primarily Portugal and France). [1] HIV-2 infection is characterized by a lower plasma viral load (pVL) and a slower clinical progression. [2-7] Antiretroviral therapy options for HIV-2 are restricted due to its natural resistance to NNRTIs and fusion inhibitors, and because some PIs have shown lower efficacy. [8-11]

The 2013 WHO guidelines for treatment of HIV-2 infection recommended either triple NRTIs or two NRTIs combined with a ritonavir-boosted PI (PI/r) as first-line combination ART (cART), with a lopinavir-containing regimen as preferred option. [12, 13] In Europe, recommended first line cART regimen for HIV-2 infection consisted of two NRTIs and one PI or one PI/r since 2010. [14, 15] Of note, the conduct of a randomized clinical trial designed to inform about optimal cART strategies for HIV-2 therapy is not feasible in Europe due to the low prevalence of HIV-2 infection, but is ongoing in West Africa.

CD4 cell recovery in HIV-2+ patients receiving first-line cART has been reported to be lower and slower than in HIV-1+ patients. [16-18] Two observational studies have reported a better immunological response in HIV-2+ patients with a PI/r based regimen compared to a triple NRTI regimen. [19, 20]

Comparative studies between HIV-1 and HIV-2 are often hampered by the small number of patients infected with HIV-2 under similar standardized follow-up. [3, 21] Contradictory results regarding CD4 cell recovery have been reported when pre-treatment pVL was taken into account. [3, 21, 22] The lower replication rate of HIV-2 has been hypothesized as one possible explanation leading to a poorer CD4 response to therapy. We compared immunological outcome in HIV-2- and HIV-1+ patients under standard follow-up in Europe, by adjusting for pretreatment plasma viral load levels at initiation of first cART, and other potential confounders.

Methods

Data collection

COHERE (HIV-1+ patients) and ACHIeV2e (HIV-2+ patients) are prospective, multinational, observational cohort collaborations. Data were pooled in the COHERE in EuroCoord 2011 and ACHIEV2E 2011 data merger. COHERE is a collaboration of 40 cohorts from across Europe [23] and is part of the EuroCoord network (www.**EuroCoord**.net). The 23 cohorts participating in the present study through the COHERE network and the 9 cohorts participating through the ACHIeV2e network [24, 25] (listed in the Acknowledgments) submitted a defined dataset (patient demographics, current cART, CD4 counts and HIV RNA values, clinical status and events) to their network-specific Coordination Centre, using the HIV Cohort Data Exchange Protocol (HICDEP). [26] The final data set was merged at the Bordeaux Regional Coordinating Centre for COHERE and ACHIeV2e adhering to strict quality-assurance guidelines and performing data quality checks.

Study population

Adult patients aged 18 or older infected either with HIV-2 or HIV-1 (dual seropositive and dual infected patients were excluded), who started a first-line cART regimen from 1997 to 2011 were included in the analysis. HIV-2+ and HIV-1+ patients receiving a NNRTI- or fusion inhibitor containing regimen were not included because of the natural resistance of HIV-2 to these drug classes. [11] Observations were excluded if patients presented without one pretreatment CD4 cell count in a window of 6 months before start of cART [27] and without a pretreatment pVL based on quantification methods with a detection limit of 500 copies/mL or lower. We used a cut-off of 500 copies/mL (2.7 $\log_{10}$ copies/mL) to define undetectable pVL, as a consensus shared by the majority of contributing centers in the dataset. [24, 25] Only patients with complete data for potential confounders (listed below) were included in all analyses (Figure S1). Criteria used to initiate therapy of HIV-2 infection were those fitting the national treatment guidelines of each contributing center effective at the time of cART start. The choice of antiretroviral combination was at the physician's discretion based on these treatment guidelines.

Follow-up began at initiation of the first cART regimen (baseline). Follow-up was censored when the ART combination was modified for whatever reason, at death or at the last available CD4 cell counts whichever occurred first.

Virological data and CD4 cell count

All serological results, pVL values and CD4 cell count were obtained from laboratories of participating centers. HIV-1 and HIV-2 infection were diagnosed by ELISA tests confirmed by Western Blot. Quantification of HIV-2 viral load was assessed by in house methods; [25] the quality control assessments of quantification assays used by the ACHIeV2e network showed heterogeneity which improved from 2006 to 2011. [24, 25] Pre-treatment pVL and pre-treatment CD4 cell counts were defined as the closest measurement in a window of 6 months before cART start.

Statistical analysis

We studied the effect of the HIV-type on CD4 cell count at initiation of first cART (intercept) and on CD4 cell count change cells/mm3/year (slope) using linear mixed effect models with a random intercept and a random slope. The correlation between individual baseline CD4 value(s) and the subsequent CD4 slope(s) was handled through an unstructured covariance matrix of random effects. We checked the underlying model assumptions (normality and homoscedasticity of residuals). [28]

We studied the effect of the following a priori defined covariables on CD4 cell count at cART initiation and on CD4 cell count change by introducing an interaction term with the slope: HIV-type (HIV-2 versus HIV-1 – main exposure variable), pVL as a continuous covariable ($\log_{10}$ copies/mL with imputation of the limit of detection for undetectable pVL), age (per 10-year increase), sex, geographic origin (Europe, Africa, Asia, other/unknown), HIV transmission route (heterosexual, homosexual, drug use, other /unknown), prior AIDS diagnosis, cART regimen (two NRTIs + 1 ritonavir-boosted PI (other than lopinavir/r and darunavir/r), two NRTIs + lopinavir/r or darunavir/r, three NRTIs, other ART combinations

(mainly two or three NRTIs + an unboosted PI or combinations with integrase inhibitors), period of cART initiation (1998-1999, 2000-2001, 2002-2003, 2004-2005, 2006-2007, 2008-2009, 2010-2011) and time between HIV diagnosis and cART start. The slope was additionally adjusted for pre-treatment CD4 cell count (per 100 cells/mm^3 increase).

Stratified and subgroup analyses

For all stratified or subgroup analyses described below we used the linear mixed regression models adjusted for the same covariables described above. Our main hypothesis was related to the potential of differences in pVL which might explain the differences of CD4 cell count evolution between HIV-2 + and HIV-1+ patients. To explore the stability of estimations, we further restricted the analysis to patients with a baseline pVL measured by a test with a limit of 100 copies/mL or lower. We explored whether the effect of the virus type (HIV-2 or HIV-1) on CD4 cell response was modified by the level of baseline pVL by testing homogeneity of the association between HIV-type and CD4 cell count evolution across baseline pVL strata (pVL <500 and ≥500 copies/mL) by integrating an interaction term in the linear mixed model. We stratified the analyses of immunological response according to the type of cART received, i.e. three NRTIs, two NRTIs combined with a ritonavir-boosted PI (other than lopinavir/r and darunavir/r), and two NRTIs combined with either lopinavir/r or darunavir/r, to assess if the cART regimen had an effect on the association between HIV-type and CD4 cell response by testing homogeneity of the association HIV-type and CD4 cell count evolution across baseline cART regimen. The three categories of cART were chosen because these cART regimens were those recommended by WHO during the study period. [13]

Results are presented for 12 months of follow-up after cART initiation but analyses are based on all available CD4 cell counts after cART initiation up to 115 and 150 months in HIV-2+ and HIV-1+ patients. We described categorical variables with frequencies (%) and continuous variables with median (IQR). CD4 cell count changes were described with means and 95% confidence intervals after having assessed the normality assumption. Categorical variables were compared between HIV-2+ and HIV-1+ (included and excluded) patients using chi-

square tests or Fisher's exact test as appropriate. Quantitative variables were compared between groups using the Wilcoxon-Mann-Whitney test.

All analyses were performed with SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

Characteristics at cART start

In the ACHIeV2e dataset 243 HIV-2+ patients full-filled inclusion criteria; of those, 58 were excluded for a total of 185 HIV-2+ patients in the analyses (Figure S1). We observed no significant difference between included and excluded HIV-2+ patients (Table S1). In the COHERE dataset 66,483 HIV-1+ patients full-filled inclusion criteria; of these 36,162 were excluded for a total of 30,231 HIV-1+ patients in the analyses (Figure S1). Included HIV-1+ patients were less often of European origin, less often injection drug users, more often treated with two NRTIs combined with either lopinavir/r or darunavir/r than non-included patients (Table S1).

Baseline characteristics are presented in Table 1. At start of first-line cART, HIV-2+ patients were significantly older (median age 46 (IQR: 36; 52) years) compared with HIV-1+ patients (37 (32; 44) years; $P<0.0001$). The proportion of HIV-2+ patients with a pVL below 500 copies/mL was significantly higher compared with patients infected with HIV-1 (60% versus 12%, $P<0.0001$). Median pVL (IQR) was 3.2 $\log_{10}$ copies/mL (2.2; 4.2) and 4.8 $\log_{10}$ copies/mL (4.0; 5.4) in HIV-2+ and HIV-1+ patients, respectively. Median time between HIV diagnosis and cART start was significantly longer in HIV-2+ compared with HIV-1+ patients (1.0 years versus 0.6 years, $P=0.0390$). Two NRTIs plus lopinavir/r or darunavir/r was the most frequent cART regimen in HIV-2+ and HIV-1+ patients (43% and 36.5% respectively) followed by two NRTIs plus other boosted PIs (23.8% versus 22.6%). Three NRTIs were prescribed in 13% and 7.2% of HIV-2+ and HIV-1+ patients, respectively. Median pre-treatment CD4 cell count was similar in HIV-2+ versus HIV-1+ patients (203 cells/mm^3; IQR: 100; 290 versus 223; IQR: 100; 353) cells/mm^3, $P=0.1480$). After adjustment for a priori defined confounding covariables a significant difference in CD4 cell count at cART initiation

remained between HIV-2+ and HIV-1+ patients. HIV-2+ patients had 56 CD4 cells/mm3 less at cART initiation compared to HIV-1+ patients (*P*<0.0001).

Follow-up data

Median follow-up from first-line cART start until treatment modification, death or last available CD4 cell count was 10 (IQR: 1; 27) and 8 months (IQR: 2; 21) in HIV-2+ and HIV-1+ patients (*P*=0.0412). A median of 3 (2; 8) and 4 (2; 8) CD4 cell counts per HIV-2+ and HIV-1+ patient were available, respectively (*P*=0.1555). Among HIV-2+ and HIV-1+ patients, 4.3% and 5.4% were lost to follow up (P=0.5017) and 1.1% and 1.7% died (P=0.5344), respectively.

CD4 cell count evolution

In patients still followed at 12 months, median observed CD4 cell counts at 12 months were 265 (IQR: 182; 420) in HIV-2+ and 404 (IQR: 262; 571) in HIV-1+ patients (Figure 1). Mean observed change in CD4 cell count from start of cART to M12 was +105 (95%CI: 77 to 134] in HIV-2+ and +202 (95%CI: 199 to 205) in HIV-1+ patients which is an observed difference of 97 CD4 cells/mm^3 in CD4 cell increase in one year.

After adjusting for pre-treatment pVL only, the mean CD4 cell count increase remained significantly lower in HIV-2+ compared with HIV-1+ patients (difference of -41 CD4 cells/mm^3/year (95% CI: -20 to -61); *P*<0.0001). This difference persisted (difference of -25 CD4 cells/mm^3/year (95% CI: -44 to -5); *P*=0.0127) after adjustment for pre-treatment pVL and the other potential confounders (Table 2). All a priori defined covariables were significantly and independently associated with CD4 cell count change. Of note, irrespectively of the HIV type and all other variables included in the model, patients receiving three NRTIs had on average a significantly lower CD4 cell increase when compared with patients receiving a boosted PI based cART regimen (difference in slope of -34 cells/mm^3/year; 95% CI: -40 to -26; *P*<0.0001; Table 2).

All subgroup and stratified analyses showed stable results. When considering only patients with a baseline pVL measured by an assay with a detection limit of 100 copies/mL or lower (HIV-1 n=27,594; HIV-2 n=129), CD4 cell increase was lower in HIV-2+ patients in adjusted analysis (difference of -29 CD4 cells/mm^3/year (95% CI: -4 to -53); *P*=0.0227). The effect of HIV type on CD4 cell count response was not modified by baseline pVL, thus the effect of HIV on CD4 cell count response did not differ in those with a baseline pVL of 500 copies/mL or more (HIV-1 n=26,602; HIV-2 n=75) and those with a baseline pVL below 500 copies/mL (HIV-1 n=3,719; HIV-2 n=110) (*P*=0.1711). Differences in CD4 cell increase between HIV-2+ and HIV-1+ patients were not modified by the initial cART regimen (interaction test: *P*=0.9093).

Discussion

The reasons for the previously reported poorer immunological response to first line cART in HIV-2+ patients are still poorly understood. Using data from two large European observational cohort collaborations, we found a significantly lower CD4 cell increase after starting first-line cART between HIV-2+ compared with HIV-1+ patients (i.e. observed difference of 97 CD4 cells/mm3). The difference in CD4 cell count increase between HIV-2+ and HIV-1+ patients remained significant after adjusting for pre-treatment pVL, cART regimen and other main confounders (i.e. difference of 25 cells/mm^3/year). Furthermore, the difference between HIV-2 and HIV-1 was not modified by the cART regimen.

ART regimens have been mainly developed for and validated in HIV-1+ patients; their potency is likely to be different in HIV-2+ patients. Lower potency of several PIs, such as nelfinavir, fosamprenavir, and atazanavir has been reported by phenotypic studies. [8] The replication cycle of HIV-2 is clearly different from that of HIV-1. HIV-2 pVL is more often below the threshold of detectability, and lower when quantified, compared to HIV-1 pVL, even at advanced disease stages. Total pro-viral DNA is very similar in HIV-1- and HIV-2 infection after adjustment for CD4 cell count. [29-32] This suggests at least a blockade of HIV-2 replication at the post-integration level and may explain the differences between HIV-1 and

HIV-2 with regard to the potency of PIs. Of note, the difference in CD4 increase between HIV-2 and HIV-1 was smaller (i.e. difference of 25 cells/mm^3/year) after adjusting for pre-treatment pVL, cART regimen and other main confounders but remained significant. Furthermore, our results were robust after adjustement for pVL as a time-dependent covariable.

The time between HIV-diagnosis and cART initiation, known to contribute to a poorer immunological response to cART, was longer in HIV-2+ compared to HIV-1+ patients. This longer delay is probably due to the slower CD4 cell decrease and the longer asymptomatic stage distinguishing natural history of HIV-2 infection. [3] Nonetheless, CD4 cell increase remained significantly lower in HIV-2+ patients in our analysis adjusted for this delay between HIV-diagnosis and cART initiation. For both HIV-1 and HIV-2 infections initiation of cART was recommended at more advanced stages during the study period than currently is the case. Criteria used to initiate antiretroviral therapy in HIV-2+ patients were those fitting the national guidelines of each contributing center effective at the time of cART start. These guidelines were consistent across Europe and included CDC stages B and C, CD4 lymphopenia and HIV-2 RNA levels above the detection limit of the quantification assay; the level of CD4 lymphopenia defined for cART indication in HIV-2 infection was lower than that defined for HIV-1 infection, and may also explain the difference observed in pre-treatment CD4 cell counts. Of note, median CD4 cell count was 203 cells/mm^3 in HIV-2+ patients at cART start, lower than in HIV-1+ patients, similar to that reported at ART start in the IeDEA-West Africa HIV-2 cohort study (i.e. 166 cells/mm^3). [33] It has since been demonstrated that earlier treatment of HIV-1 infection is the best strategy for successful immune restoration.[34] Long term non-progressors account for 6% of the whole asymptomatic HIV-2 population, applying the same methodology as used to determine their proportion in HIV-1 infected patients.[35] Among the remaining 94% there are patients with slightly progressive infection, who might benefit from earlier treatment leading to a better immune restoration.

We found an overall significantly lower CD4 cell increase in patients receiving a three NRTIs regimen compared with those receiving a ritonavir-boosted PI based regimen. These findings

obviously confirm the results of a European observational study which partly included the same HIV-2 infected patients,[20] but also those of a recent West African study. [19] Direct comparisons of different treatment regimens in observational studies are challenging and the gold standard design for such analyses and for evidence-based conclusions are randomized clinical trials. Such trials are not realisable in Europe due to the restricted size of potentially eligible HIV-2 infected patients living there. However, we report for the first time a comparison of CD4 cell response to first line cART in a large population of HIV-2 and HIV-1 infected patients under standardized routine follow-up in Europe allowing us to adjust the comparison for initial pVL levels, cART regimen, region of origin, and other patients' characteristics such as pre-treatment CD4 cell count and previous AIDS diagnosis, and for calendar periods of cART initiation.

Chronic immune activation and inflammation markers have been linked to disease progression in HIV-1+ [36, 37] and HIV-2+ patients. [38-40] Differences in CD4 cell count response to first cART may be linked to differences in the underlying pathogenicity of these two viruses regarding immune activation. However, chronic immune activation is directly linked to pVL [39, 41] and in our comparison of immune response we controlled for pVL in various ways. Of note, it has been shown that HIV-2 non-progression is associated with better immune response to the virus, less immune activation, broad neutralizing antibody response; nevertheless we do not know what came first: the particularities of HIV-2 replication or the immune response.

There are several limitations to our analyses. Differences in immunological outcome between HIV-1 and HIV-2 may have been observed due to unmeasured confounding factors. We cannot completely rule out a selection bias as we did not analyze pretreatment slopes of CD4 cells decrease in HIV-1 and HIV-2 populations. We were neither able to adjust for hepatitis B and/or hepatitis C co-infection, although we adjusted for geographical origin and transmission risk group which are closely linked to hepatitis B and C seroprevalences. Furthermore, follow-up was quite short and may hamper the extrapolation of our results to the long term.

Our study has several strengths. This is a large study comparing CD4 cell dynamics between HIV-2+ and HIV-1+ patients after start of first-line cART. The data quality was assured through two large European collaborative networks adhering to strict quality control checks which allowed us to adjust our comparative analysis for the major confounding variables. Furthermore, we could confirm our main findings in subgroup and stratified analyses showing the robustness of the results and the absence of effect modification by initial pVL and cART regimen.

Differences in CD4 cell dynamics between HIV-2 and HIV-1 were consistent in all analyses with a poorer CD4 cell increase after start of treatment in HIV-2+ patients, even after adjustment on plasma viral load. Our results underline the need to identify other factors contributing to this lower CD4 cell response such as more potent drugs against HIV-2, adapted to the particularities of the virus replication when compared with HIV-1, in order to improve case management.

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Figure Legends

Figure 1: Median observed CD4 cell counts after first line cART initiation in HIV-2 and HIV-1 infected patients up to 12 months of follow-up. Legend: vertical bars represent the interquartile range (IQR).

Table 1: Characteristics of patients at initiation of first cART

Characteristics	HIV-1 (n=30,231)		HIV-2 (n=185)		P-value
Median age in years (IQR)	37	(31;44)	46	(36;52)	<0.0001
Female, n (%)	8179	(27.1)	88	(47.6)	<0.0001
Region of origin, n (%)					<0.0001
Europe	16517	(54.6)	47	(25.4)	
Africa	2495	(8.3)	130	(70.3)	
Asia	413	(1.4)	2	(1.1)	
Unknown/Other[a]	10806	(35.7)	6	(3.2)	
Transmission risk group, n (%)					<0.0001
Heterosexual	10783	(35.7)	154	(83.2)	
Homo/bisexual male	11825	(39.1)	7	(3.8)	
Injecting drug user	4887	(16.2)	2	(1.1)	
Mother-to-child	26	(0.1)			
Unknown/other	2710	(9.0)	22	(11.9)	
Prior AIDS diagnosis n (%)	7169	(23.7)	42	(22.7)	0.7471
First line cART regimen, n (%)					0.0002
2 NRTIs + 1 PI/rtv (not LPV or DRV)	6823	(22.6)	44	(23.8)	
2 NRTIs + LPV/rtv or DRV/rtv	11039	(36.5)	79	(42.7)	
3 NRTIs	2180	(7.2)	24	(13)	
Other combinations	10189	(33.7)	38	(20.5)	
Period of treatment initiation, n (%)					<0.0001
1998-1999	6292	(20.8)	13	(7.0)	
2000-2001	3708	(12.3)	19	(10.3)	
2002-2003	3810	(12.6)	32	(173)	
2004-2005	4613	(15.3)	34	(18.4)	
2006-2007	5557	(18.4)	44	(23.8)	
2008-2009	5102	(16.9)	30	(16.2)	
2010-2011	1149	(3.8)	13	(7.0)	
Pretreatment HIV RNA viral load					
<500 copies /ml, n (%)	3719	(12.3)	110	(59.5)	<0.0001
Median $\log_{10}$ copies/mL (IQR)*	4.8	(4.0;5.4)	3.2	(2.2;4.2)	<0.0001
Median pretreatment CD4 cell count cells/mm3 (IQR)	223	(100;353)	203	(100;290)	0.1480
Median delay beween first HIV seropositivity and cART start (years) (IQR)**	0.61	(0.11;3.79)	0.97	(0.21;5.25)	0.0390

Legend: cART: combination antitretroviral therapy; rtv, ritonavir boost; LPV, lopinavir; DRV, darunavir. Other regimens largely consisting of two or three NRTIs plus an unboosted PI or of combinations with integrase inhibitors (347 [1.1 %] HIV-1 infected and 7 HIV-2 [3.8%] infected patients were treated with an integrase inhibitor).[a]HIV-1: for 9,462 patients the geographical origin was reported as unknown and 1,344 were from other regions (Oceania-not Australia, Australia and New Zealand, America, North America, Central and South America and Middle East); HIV-2: for 2 patients the geographical origin was reported as unknown and 2 patients were from America and 2 patients from Central and South America. *For patients with a viral load below the detection limit of the test, the detection limit has been imputed for the calculation.

Table 2: Estimated mean CD4 cell count differences at first line cART start and CD4 cell count changes adjusted for all listed co-variables. For CD4 cell count changes, a negative value indicates a lower CD4 increase, and a positive value indicates a higher CD4 increase. (N=30,231 for HIV-1 infected patients and N=185 for HIV-2 infected patients)

	CD4 cell count at initiation of first cART (cells/mm^3)			CD4 cell count change (cells/mm^3/year)		
	Mean	**95% CI**	***P***	**Mean**	**95% CI**	***P***
Intercept/slope	533	518; 549	<0.0001	154	142; 166	0.0003
HIV type						
HIV-2 vs HIV-1	**-56**	**-86; -26**	**<0.0001**	**-25**	**-44; -5**	**0.0127**
Pretreatment plasma viral load (per additional 1 $\log_{10}$ copies/mL)	-26	-28; -24	<0.0001	9	8; 10	<0.0001
Age at treatment initiation (per additional 10 years)	-22	-25; -20	<0.0001	-9	-10; -7	<0.0001
Sex						
Female vs Male	26	19; 32	<0.0001	10	6; 15	<0.0001
Geographic origin			<0.0001			<0.0001
Europe (ref)						
Africa	-31	-40; -22		-25	-32; 19	
Asia	-53	-73; -33		-7	-21; 6	
Other or unknown	-18	-23; -13		-4	-8; -1	
Transmission group			<0.0001			<0.0001
Heterosexual (ref)						
Homo/bisexual male	53	47; 59		9	4; 13	
Injecting drug user	-25	-33; -18		-16	-21; -10	
Other or unknown	-9	-17; 0		-12	-18; -6	
Prior AIDS diagnosis						
Yes vs No	-126	-132; -121	<0.0001	6	2; 10	0.0047
cART regimen			<0.0001			<0.0001
2 NRTIs + 1 PI/rtv (ref)						
2 NRTIs + LPV/rtv or DRV/rtv	-9	-15; -3		4	-1; 8	
3 NRTIs	53	42; 63		-34	-40; -26	
Other combinations	24	17; 32		-5	-11; 0.5	
Period of cART initiation			<0.0001			<0.0001
1998-1999	-7	-16; 2		-53	-60; -46	
2000-2001	-26	-36; -17		-59	-66; -52	
2002-2003	-14	-23; -6		-56	-62; -49	
2004-2005	-17	-25; -9		-50	-57; -44	
2006-2007	3	-4; 11		-38	-44; -32	
2008-2009 (ref)						
2010-2011	-11	-24; 3		130	108; 153	
Delay beween first HIV seropositivity and cART start (per additional year)	-0.8	-1.4; -0.3	0.0039	-1.1	-1.5; -0.7	<0.0001
Pretreatment CD4 cell count (per additional 100 cells/mm^3)*	-	-	-	-2	-3; -1	<0.0001

Legend: ref: reference category; cART: combination antitretroviral therapy; rtv, ritonavir boost; LPV, lopinavir; DRV, darunavir. Other regimens largely consisting of two or three NRTIs plus an unboosted PI or of combinations with integrase inhibitors.* The reported difference in CD4 cell count change is for a difference of 100 CD4 cells/mm^3 at baseline, i.e. in a patient with 400 CD4 cells/mm^3 the increase is of 2 cells less than compared to a patient with 300 CD4 cells/mm^3.