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Prognosis of patients treated with cART from 36 months after initiation, according to current and previous CD4 cell count and plasma HIV-1 RNA measurements

The antiretroviral therapy cohort collaboration (ART-CC)*

Abstract

Objectives—CD4 cell count and plasma viral load are well known predictors of AIDS and mortality in HIV-1-infected patients treated with combination antiretroviral therapy (cART). This study investigated, in patients treated for at least 3 years, the respective prognostic importance of values measured at cART initiation, and 6 and 36 months later, for AIDS and death.

Methods—Patients from 15 HIV cohorts included in the ART Cohort Collaboration, aged at least 16 years, antiretroviral-naïve when they started cART and followed for at least 36 months after start of cART were eligible.

Results—Among 14 208 patients, the median CD4 cell counts at 0, 6 and 36 months were 210, 320 and 450 cells/ μ l, respectively, and 78% of patients achieved viral load less than 500 copies/ml at 6 months. In models adjusted for characteristics at cART initiation and for values at all time points, values at 36 months were the strongest predictors of subsequent rates of AIDS and death. Although CD4 cell count and viral load at cART initiation were no longer prognostic of AIDS or of death after 36 months, viral load at 6 months and change in CD4 cell count from 6 to 36 months were prognostic for rates of AIDS from 36 months.

Conclusions—Although current values of CD4 cell count and HIV-1 RNA are the most important prognostic factors for subsequent AIDS and death rates in HIV-1-infected patients treated with cART, changes in CD4 cell count from 6 to 36 months and the value of 6-month HIV-1 RNA are also prognostic for AIDS.

Keywords

cART; CD4 cell count; mortality; plasma HIV-1 RNA; prognosis of AIDS

Introduction

CD4 cell count is the dominant prognostic factor for progression to AIDS and death at the time patients start combination antiretroviral therapy (cART), with pretreatment levels of plasma HIV-1 RNA being only modestly prognostic after accounting for other factors [1]. In contrast, current levels of both CD4 cell count and HIV-1 RNA are strongly prognostic for the short-term risk of AIDS and death in patients on cART [2,3]. A number of studies have shown that between-patient differences in CD4 cell count at the time of starting cART are maintained for some years after starting cART, even in patients maintaining virological

suppression [4–8]. In previous analyses [9] we showed that baseline CD4 cell count and HIV-1 RNA were not prognostic for AIDS or death from 6 months after starting cART, after accounting for 6-month CD4 cell count and plasma HIV-1 RNA. It is unclear whether, in patients treated for some years, there is additional prognostic value in CD4 cell count and plasma HIV-1 RNA measurements at initiation of treatment and after initial response, after accounting for current values of these factors.

We used data from the Antiretroviral Therapy Cohort Collaboration (ART-CC) to establish the relative prognostic importance for new AIDS events and for death, from 36 months after starting cART, of CD4 cell count and HIV-1 RNA at 0, 6 and 36 months.

Patients and methods

The ART-CC is an international collaboration between the investigators of cohort studies of HIV-1-infected patients from Europe and North America which was established in 2000 to estimate prognosis of HIV-1-infected, treatment-naïve patients initiating cART. The collaboration has been described in detail elsewhere [1,9] and further information is available at <http://www.art-cohort-collaboration.org>. Prospective cohort studies were eligible for participation if they had enrolled at least 100 HIV-1-infected patients aged 16 years or more who had not previously received antiretroviral treatment, started cART with a combination of at least three antiretroviral drugs after 1996, and been followed for a median duration of at least 1 year after ART initiation. The dataset analysed here was assembled during 2007 and included data from 15 cohorts: the AIDS Therapy Evaluation Project [10], Netherlands (ATHENA) [11], the Agence Nationale de la Recherche sur le SIDA et les hépatites virales (ANRS) CO3 Aquitaine Cohort [12], the British Columbia Center for Excellence in HIV (HOMER) [13], Collaborations in HIV Outcomes Research (CHORUS) [14], the EuroSIDA study [3], the Frankfurt HIV Cohort [15], the ANRS CO4 French Hospital Database on HIV (FHDH) [16], the Italian Cohort of Antiretroviral-Naïve Patients (ICONA) [17], the Köln/Bonn Cohort [18], the Proyecto para la Informatización del Seguimiento Clínico-epidemiológico de la Infección por HIV y SIDA (PISCIS) cohort [19], the Royal Free Hospital Cohort [20], the South Alberta Clinic Cohort [21], the Swiss HIV Cohort Study (SHCS) [22], the 1917 Clinic Cohort from the University of Alabama [23], and the Veterans Aging Cohort Study (VACS) [24,25]. At all sites, institutional review boards had approved the collection of data. All cohorts provided anonymized data on a predefined set of demographic, laboratory, and clinical variables, which were then pooled and analysed centrally.

For this analysis, patients with a baseline HIV-1 RNA level less than 1000 copies/ml at initiation of therapy were excluded, because of concern they might not in fact have been treatment-naïve. Patients had to start cART after 1 January 1998, because early cART regimens were less effective than those currently available, and because both protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been available since that date. Only patients initiating therapy at least 3 years prior to the closing date of each cohort and who survived at least 3 years were included. They also had to have CD4 cell count and HIV-1 RNA measurements in the 6 months prior to cART initiation (described as ‘baseline’ values hereafter) and at months 6 and 36 (within ± 3 months). These time points were chosen so that previous work evaluating response at 6 months [9] could be extended by considering prognosis after an extended treatment period. The Kaplan–Meier estimates of cumulative probability of AIDS and of death from 36 months after initiating cART were estimated by CD4 cell count and HIV-1 RNA measured at 36 months. We used Cox proportional hazards models to estimate hazard ratios for new AIDS events (clinical part of the 1993 US Centers for Disease Control and Prevention revision of the AIDS case definition, [26]) and for death from any cause from 36 months after initiation of cART,

according to CD4 cell count and HIV-1 RNA at 0, 6 and 36 months. CD4 cell count was fitted in seven categories: less than 25, 25–49, 50–99, 100–199, 200–349, 350–499, or at least 500 cells/ μ l and HIV-1 RNA level in four categories: less than 500, 500–10 000, 10 000–100 000, or at least 100 000 copies/ml. We used the limit of 500 copies/ml to overcome the heterogeneity of the assays' detection levels within techniques and over time. All analyses were adjusted for sex, age (16–29, 30–39, 40–49, $\geq$ 50 years of age), presumed transmission group [men who have sex with men, injection drug use (IDU), heterosexual, others] and clinical AIDS before initiation (yes or no). Analyses accounting for values of CD4 cell count and HIV-1 RNA at 6 and 36 months were also adjusted for occurrence of a new AIDS event between start of cART and 6 months or between 6 months and 36 months in those without AIDS at initiation of cART. In all analyses, we used an intent-to-continue-treatment approach, and thus ignored changes to treatment regimen, including treatment interruptions and terminations. All analyses were stratified by cohort. Patients who remained alive were censored at their last visit and 50% of the average time between visits for each cohort. For example, if a cohort had, on average, 6 months between follow-up visits, patients who did not die would be censored at last visit and 3 months. This censoring method ensures that follow-up time is allocated in an unbiased way to those who did not die since the average time from last follow-up to death in those who died would be approximately 50% of the interval between scheduled visits.

Results

Baseline characteristics

Of 49 040 patients included in the ART-CC data set, 27 451 started cART after 1 January 1998, at least 3 years prior to their cohort closing date and 26 202 survived at least 3 years. Of these, 14 208 had CD4 cell count and HIV-1 RNA measurements in the 6 months prior to cART initiation and at month 6 and 36 post-cART initiation, and were included in this analysis. The excluded patients ($N = 13\,243$, including 5422 without 6-month measurements and 11 140 without 36-month measurements) were more likely to be infected via IDU, were less likely to be women and had lower viral load. The median CD4 cell count at start of cART was the same in both groups (data not shown).

Table 1 shows patient characteristics at baseline, at 6 months and at 36 months after starting cART. Median age was 38 years [interquartile range (IQR) 32–45] and the median calendar month at initiation of cART was January 2000 (IQR December 1998–May 2001).

Heterosexual transmission was the most frequent presumed mode of transmission (5654, 40%), and 10 581 patients (74%) were men. At baseline, 3375 patients (24%) had already had an AIDS event, whereas 404 (3%) had an AIDS event between start of cART and 6 months and 332 (2%) between 6 months and 36 months. The median baseline CD4 cell count was 210 cells/ μ l (IQR 80–350) and the median HIV-1 RNA 90 242 copies/ml (IQR 28 530–268 017).

Follow-up characteristics

Overall, 11 068 patients (78%) achieved a 6-month viral load of 500 copies/ml or less and 11 083 (78%) at 36 months. The initial cART regimen contained exclusively nucleoside reverse transcriptase inhibitors (NRTIs) in 1294 patients (9%), NRTIs and protease inhibitor(s) in 7969 patients (56%), NRTIs and NNRTI in 4519 patients (32%), NRTIs, NNRTI and protease inhibitors in 391 patients (3%). The 35 remaining patients received potent dual therapy. At 6 months, 12 951 patients (91%) were still receiving cART with 9526 (67%) still receiving the same regimen. Median 6-month CD4 cell count was 320 cells/ μ l (IQR 179–490) with the median increase in CD4 cell count from baseline being 101 cells/

μl (IQR 36–187). At 36 months median CD4 cell count was 450 cells/μl (IQR 301–644), with median increase from baseline 235 cells/μl (IQR 107–378). Of the patients 3583 (25%) had baseline CD4 cell count at least 350 cells/μl, rising to 6453 (45%) at 6 months and 9566 (68%) at 36 months.

During 32 689 person-years of follow-up from 36 months after starting cART, 345 patients developed at least one new AIDS event and 323 died. The rates of AIDS and of death per 100 person-years of follow-up were 1.06 [95% confidence interval (CI) 0.95–1.17] and 0.96 (95% CI 0.86 to 1.08), respectively. Moreover, Kaplan–Meier estimates of cumulative probability of death from 36 months after initiation of cART varied by 36-month CD4 cell count and viral load: the lower the CD4 cell count, the higher the probability of death and the higher the viral load, the higher the probability of death (Fig. 1). The pattern for AIDS was similar to that for death (Fig. 2). The 10 most common AIDS events occurring after 36 months were oesophageal or pulmonary candidiasis (55), *Pneumocystis jirovecii* (carinii) pneumonia (38), tuberculosis (33), wasting syndrome (28), Kaposi's sarcoma (24), HIV-related encephalopathy (23), non-Hodgkin lymphoma (20), CMV disease (16), recurrent bacterial pneumonia (13) and toxoplasmosis of the brain (11). Seventy deaths (36% of 192 classified deaths) were due to AIDS-defining causes.

Impact of baseline CD4 cell count on CD4 cell count at 6 and 36 months

Figure 3 (upper panel) shows that patients with higher baseline CD4 cell count tended to have higher CD4 cell counts at 36 months, although there is substantial between-patient variability. Median CD4 cell counts at 36 months were 277 cells/μl (IQR 175–401) in patients with baseline CD4 cell count less than 25 cells/μl, rising to 789 cells/μl (590–1006) in patients with baseline CD4 cell count at least 500 cells/μl. In patients with CD4 cell count less than 200 cells/μl at baseline, 80 and 43% of patients achieved 36-month CD4 cell count greater than 200 and 500 cells/μl, respectively (lower panel of Fig. 3).

Impact of baseline HIV-1 RNA on HIV-1 RNA at 6 and 36 months

At 36 months, 78% of patients were virologically suppressed (HIV-1 RNA <500 copies/ml). Virological suppression at 36 months differed slightly according to the baseline HIV-1 RNA: the proportions with HIV-1 RNA less than 500 copies/ml were 72, 78 and 79% for baseline HIV-1 RNA less than 10 000, 10 000–100 000 and greater than 100 000 copies/ml, respectively ($P < 0.001$). Levels of HIV-1 RNA 6 months after cART initiation were, however, strongly associated with HIV-1 RNA at 36 months: only 54% of patients with HIV-1 RNA greater than 500 copies/ml at 6 months were virologically suppressed at 36 months, compared with 84% of patients who were virologically suppressed at 6 months ($P < 0.001$).

Impact of CD4 cell count at baseline, 6 and 36 months on rates of AIDS and death from 36 months

Table 2 shows associations of CD4 cell count and HIV-1 RNA at baseline, 6 and 36 months with rates of AIDS and death from 36 months after starting cART. The first and third columns show that, after adjusting for sex, transmission group, age and Centers for Disease Control and Prevention (CDC) stage at cART initiation, CD4 cell counts at each time point predicted rates of AIDS and of death from 36 months after cART initiation. There was a strong and graded association of CD4 cell count at 36 months with subsequent rates of AIDS and of death [hazard ratios 32.6 (95% CI 21.7–49.0) for AIDS and 26.4 (95% CI 17.3–40.2)] comparing participants with 36-month CD4 cell count less than 25 with those with at least 500 cells/μl. There were also graded associations of baseline and 6-month CD4 cell count with post-36-month rates of AIDS and of death, but the strength of associations declined as the time before 36 months increased.

Impact of HIV-1 RNA at baseline, at 6 and 12 months, on rates of AIDS and death from 36 months

There was a strong and graded association of the level of HIV-1 RNA at 36 months with subsequent rates of AIDS and of death, whereas 6-month HIV-1 RNA was also, though less strongly, prognostic. In contrast, baseline HIV-1 RNA was not prognostic for rates of AIDS or death from 36 months after cART initiation.

Impact of adjusting for CD4 cell count and HIV-1 RNA at other time points

The second and fourth columns of Table 2 show hazard ratios for the baseline, 6 and 36-month measurements of CD4 cell count and HIV-1 RNA, adjusting for both baseline characteristics and the measurements made at other time points. Thirty-six-month CD4 cell count and HIV-1 RNA were strongly associated with subsequent rates of AIDS and of death, although associations were attenuated after adjusting for each other and for previous measurements. In the mutually adjusted analyses, neither baseline CD4 cell count nor baseline HIV-1 RNA appeared prognostic for rates of AIDS or of death from 36 months after cART initiation (Table 2). There was a weak positive association of 6-month HIV-1 RNA with rates of AIDS, but the adjusted association of 6-month CD4 cell count was negative. This implies that, after accounting for 36-month measurements, greater increases in CD4 cell count between 6 and 36 months are associated with lower subsequent rates of AIDS.

Discussion

In this large cohort collaboration, we showed that in patients who survive and are followed up for longer than 36 months there is a strong relationship between the CD4 cell count at cART initiation and the CD4 cell count at 6 and 36 months. Viral suppression at 36 months is associated with levels of HIV-1 RNA at 6 months, but only weakly associated with pretreatment levels. HIV-1 RNA at cART initiation is not prognostic for new AIDS events or death after 36 months. Associations of baseline CD4 cell count with rates of AIDS and death from 36 months are abolished once subsequent values are adjusted for. CD4 cell counts and HIV-1 RNA at 6 months after initial treatment response remain prognostic for new AIDS events but not the risk of death, after adjusting for 36-month values. CD4 cell count and HIV-1 RNA at 36 months were the strongest predictors of subsequent rates of AIDS and death.

Limitations and strengths

We excluded patients who had not been followed up beyond 36 months or who did not have measurements of CD4 cell count and HIV-1 RNA at 6 and 36 months, therefore the results presented here are only applicable to patients who survived for longer than 36 months after starting cART. Factors associated with exclusion – infection via IDU, male sex and lower viral load – have been linked to loss to follow-up and missing values in previous studies [27,28]. However, even though the exclusion of such patients will lead to less precise estimates of progression rates and associations, it is unlikely to bias estimates from the prognostic model since measured characteristics that differed between included and excluded patients were included in the models [1].

We were not able to assess the effects of some risk factors for death and new AIDS events, for example, adherence to antiretroviral treatment and concentration of haemoglobin, because they were either not collected or not collected in all the cohorts. However, adherence to antiretroviral treatment in naive patients is largely reflected by the success rate at 6 months and thereafter, which has been captured in our model. Haemoglobin concentration, which was not collected in all cohorts participating in ART-CC, has been

shown to be prognostic for AIDS and death [2,29,30] but its omission from the models presented here is unlikely to change the qualitative conclusions about the relative importance of CD4 cell count and HIV-1 RNA at different times for prognosis from 36 months.

Strengths of our study include its large size and the broad range of patients included: from different industrialized countries with different settings of care and with wide variation in relevant clinical characteristics such as mode of transmission, age and extent of immune suppression before starting cART. Therefore, our results should be applicable to patients with HIV infection followed in clinical centres in industrialized countries who survived for longer than 36 months after starting cART. As for previous prognostic models from this collaboration [1], the presented models have high discriminatory power.

CD4 cell count

These analyses show that CD4 cell count remains a dominant prognostic factor among HIV-infected patients as time on cART increases. The impact of the CD4 cell count at cART initiation on the CD4 cell counts at 6 and at 36 months confirm the importance of initiating cART before CD4 cell counts decline too far [31,32]. Although CD4 cell counts continue to increase after 36 months in our data, and up to 5 years after cART initiation according to previous work [6] among patients who initiate cART at CD4 cell count less than 200 cells/ μ l and maintain virological suppression, only 25% of such patients have CD4 cell count greater than 500 cells/ μ l at 36 months. In patients who started cART at CD4 cell count less than 200 cells/ μ l, normalization of CD4 cell count is unlikely to be achieved [7]. Coinfection by hepatitis viruses has been found to be associated with smaller CD4 cell count increases [33]. Our models could not take into account infection by hepatitis viruses. However, they included history of IDU, which is a risk factor for coinfection, especially HCV, and CD4 cell count at 6 months, which could reflect the impact of coinfection on CD4 cell count increases.

When values at 6 and 36 months are taken into account, the CD4 cell count at baseline does not influence the prognosis for AIDS events or death, whereas CD4 cell count at 6 months is prognostic for AIDS but not for death. Whereas it appears that the impact of immunosuppression on death is totally captured by the last measurement of CD4 cell count, the impact of CD4 cell count at 6 months on prognosis for AIDS from 36 months requires careful explanation. The counterintuitive negative association of 6-month CD4 cell counts with rates of AIDS after 36 months is seen only after adjusting for the 36-month values. It implies that patients who reached a particular CD4 cell count at 36 months by increasing their CD4 cell count from 6 months and therefore by improving their immunological status have a better prognosis than patients who reached the same CD4 cell count by decreasing their CD4 cell count from 6 months. Therefore, after allowing for their 36-month CD4 cell count, patients with lower CD4 cell counts at 6 months (hence higher increases between 6 and 36 months) have better prognosis than patients with higher CD4 cell counts at 6 months (hence lower increases between 6 and 36 months). The patients for whom CD4 cell count decreased between 6 and 36 months after cART initiation could have interrupted their treatment, which is not assessed in our study, or received a less potent cART regimen, or have failed to adhere to treatment [34].

HIV-1 RNA

The association of HIV-1 RNA at 6 months with HIV-1 RNA at 36 months and AIDS after 36 months confirms the importance of early response to cART and the deleterious effect of virological failure after starting cART, which can be induced by lack of adherence to treatment and/or resistance [35]. Therefore, the first 6 months under ART is a critical time in

the care and follow-up of patients treated with cART [36,37]. In models adjusted for measurements at 0 and 36 months, virological suppression at 6 months remains prognostic for AIDS: this finding confirms the importance of achieving an early virological response. In the same way, patients with detectable HIV-1 RNA at 36 months have higher subsequent rates of AIDS or death, probably because of both their lower subsequent increases in CD4 cell count and higher rates of non-AIDS death associated with continuing HIV replication [38].

Conclusion

Although current values of CD4 cell count and HIV-1 RNA are the most important prognostic factors for subsequent rates of AIDS and death, consistent with our previous results [1], changes in CD4 cell count from 6 to 36 months and the value of 6-month HIV-1 RNA are also prognostic for subsequent rates of AIDS. Physicians should be aware of the prognostic importance of immunological status at cART initiation, which continues to influence subsequent CD4 cell counts, and of the initial virological response to cART, reflected by 6-month HIV-1 RNA.

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Appendix

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Fig. 1. Kaplan–Meier estimate of cumulative probability of death after 36 months from start of cART by CD4 group (upper panel) and by HIV-1 RNA (lower panel)

cART, combination antiretroviral therapy.

Fig. 2. Kaplan–Meier estimate of cumulative probability of AIDS after 36 months from start of cART by CD4 group (upper panel) and by HIV-1 RNA (lower panel)
cART, combination antiretroviral therapy.

Fig. 3. Distribution of CD4 cell count (cells/μl)

(a) Distribution of CD4 cell count (cells/μl) at 36 months after cART initiation according to CD4 cell count at cART initiation. (b) Distribution of CD4 cell count (cells/μl) at 36 months after cART initiation according to CD4 cell count at 6 months. cART, combination antiretroviral therapy.

Table 1

Characteristics of the 14208 patients at start of cART, 6 and 36 months, with number of events and deaths during follow-up from 36 months after start of cART.

	Number of patients	Percentage	Events from 36 months	
			AIDS	Deaths
	14 208		345	323
Sex				
Male	10 581	74	284	279
Female	3627	26	61	44
Exposure group				
Men who have sex with men	4844	34	76	58
Heterosexual	5654	40	84	81
IDU	1840	13	94	92
Other	1870	13	91	92
Age at cART initiation (years)				
16–29	2154	15	34	14
30–39	6140	43	154	107
40–49	3740	27	92	103
≥50	2174	15	65	99
CDC disease stage				
C at 0 months	3375	24	111	110
A/B at 0 months C at 6 months	404	3	11	11
A/B at 0 and 6 months C at 36 months	332	2	27	29
A/B at 0, 6 and 36 months	10 097	71	196	173
CD4 cell count at 0 months (cells/μl)				
0–24	1606	11	58	53
25–49	997	7	35	34
50–99	1523	11	42	47
100–199	2669	19	74	65
200–349	3830	27	74	66
350–499	2058	14	37	33
≥500	1525	11	25	25
HIV-1 RNA at 0 months (copies/ml)				
<10 000	1571	11	41	34
10 000–100 000	5884	41	132	117
≥100 000	6753	48	172	172
CD4 cell count at 6 months (cells/μl)				
0–24	184	1	16	17
25–49	285	2	15	20
50–99	967	7	37	39
100–199	2640	19	68	71
200–349	3679	26	103	75

	Number of patients	Percentage	Events from 36 months	
			AIDS	Deaths
350–499	3036	21	52	51
≥500	3417	24	54	50
HIV-1 RNA at 6 months (copies/ml)				
<500	11 068	78	172	190
500–10 000	1783	13	58	55
10 000–100 000	884	6	76	49
≥100 000	473	3	39	29
CD4 cell count at 36 months (cells/μl)				
0–24	142	1	48	42
25–49	85	1	17	16
50–99	270	2	39	26
100–199	1086	8	47	46
200–349	3059	21	66	71
350–499	3489	24	65	57
≥500	6077	43	63	65
HIV-1 RNA at 36 months (copies/ml)				
<500	11 083	78	121	159
500–10 000	1401	10	49	43
10 000–100 000	1199	8	86	63
≥100 000	525	4	89	58

cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; IDU, injection drug use.

Table 2

Hazard ratios for AIDS and for death from 36 months after initiation of cART, by CD4 cell count and HIV-1 RNA at 0, 6 and 36 months.

	AIDS		Death	
	Adjusted only for other variables measured at start of cART ^a	Adjusted for variables at start of cART and at other time points ^b	Adjusted only for other variables measured at start of cART ^a	Adjusted for variables at start of cART and other time points ^b
CD4 cell count at 0 month	<i>P</i> -trend <0.001	<i>P</i> -trend 0.34	<i>P</i> -trend <0.001	<i>P</i> -trend 0.062
0–24	2.22 (1.35,3.64)	1.37 (0.67,2.77)	1.89 (1.14–3.13)	0.52 (0.25–1.08)
25–49	2.45 (1.44,4.18)	1.95 (0.97,3.94)	2.15 (1.26–3.67)	0.99 (0.48–2.01)
50–99	1.97 (1.19,3.27)	1.43 (0.75,2.75)	1.90 (1.15–3.12)	0.87 (0.45–1.68)
100–199	2.08 (1.31,3.29)	1.61 (0.90,2.89)	1.60 (1.00–2.55)	0.98 (0.54–1.76)
200–349	1.44 (0.91,2.28)	1.27 (0.75,2.17)	1.22 (0.77–1.93)	0.97 (0.57–1.66)
350–499	1.24 (0.74,2.06)	1.11 (0.66,1.89)	1.05 (0.62–1.77)	0.91 (0.53–1.56)
≥500	1	1	1	1
CD4 cell count at 6 months	<i>P</i> -trend <0.001	<i>P</i> -trend 0.017	<i>P</i> -trend <0.001	<i>P</i> -trend 0.65
0–24	4.64 (2.60,8.26)	0.42 (0.19,0.96)	5.67 (3.20–10.05)	1.23 (0.54–2.79)
25–49	3.14 (1.74,5.66)	0.55 (0.25,1.19)	4.14 (2.42–7.09)	1.31 (0.62–2.77)
50–99	2.31 (1.50,3.57)	0.54 (0.29,1.00)	2.38 (1.54–3.68)	0.86 (0.45–1.64)
100–199	1.61 (1.11,2.33)	0.54 (0.31,0.91)	1.68 (1.16–2.45)	0.81 (0.47–1.41)
200–349	1.93 (1.38,2.69)	1.00 (0.64,1.57)	1.41 (0.98–2.03)	0.91 (0.56–1.47)
350–499	1.15 (0.79,1.69)	0.86 (0.56,1.33)	1.20 (0.81–1.77)	1.00 (0.65–1.56)
≥500	1	1	1	1
CD4 cell count at 36 months	<i>P</i> -trend <0.001	<i>P</i> -trend <0.001	<i>P</i> -trend <0.001	<i>P</i> -trend <0.001
0–24	32.61 (21.73,48.96)	11.12 (5.99,20.62)	26.37 (17.30–40.18)	16.65 (8.60–32.23)
25–49	16.57 (9.54,28.80)	5.83 (2.90,11.71)	13.87 (7.89–24.37)	8.80 (4.25–18.21)
50–99	14.60 (9.68,22.02)	5.83 (3.39,10.01)	7.66 (4.81–12.22)	5.52 (3.07–9.94)
100–199	3.92 (2.67,5.77)	2.55 (1.57,4.13)	3.14 (2.14–4.61)	2.86 (1.75–4.67)
200–349	2.14 (1.50,3.03)	1.61 (1.07,2.42)	2.02 (1.43–2.84)	1.97 (1.30–2.97)
350–499	1.92 (1.36,2.72)	1.52 (1.04,2.22)	1.54 (1.08–2.20)	1.47 (0.99–2.17)
≥500	1	1	1	1
HIV-1 RNA at 0 month	<i>P</i> -trend 0.31	<i>P</i> -trend 0.53	<i>P</i> -trend 0.07	<i>P</i> -trend 0.45
<10 000	1	1	1	1
10 000–100 000	0.99 (0.69,1.41)	0.81 (0.56,1.16)	1.04 (0.70–1.52)	0.88 (0.59–1.30)
≥100 000	1.13 (0.80,1.61)	0.83 (0.57,1.21)	1.29 (0.88–1.89)	1.04 (0.70–1.56)
HIV-1 RNA at 6 months	<i>P</i> -trend <0.001	<i>P</i> -trend <0.001	<i>P</i> -trend <0.001	<i>P</i> -trend 0.78
<500	1	1	1	1
500–10 000	1.80 (1.33,2.43)	1.10 (0.81,1.51)	1.49 (1.09–2.03)	0.96 (0.70–1.33)
10 000–100 000	4.62 (3.49,6.10)	1.89 (1.38,2.58)	2.69 (1.95–3.71)	1.07 (0.74–1.55)
≥100 000	4.50 (3.15,6.42)	1.58 (1.06,2.38)	3.05 (2.05–4.53)	1.02 (0.65–1.61)
HIV-1 RNA at 36 months	<i>P</i> -trend <0.001	<i>P</i> -trend <0.001	<i>P</i> -trend <0.001	<i>P</i> -trend <0.001

	AIDS		Death	
	Adjusted only for other variables measured at start of cART ^a	Adjusted for variables at start of cART and at other time points ^b	Adjusted only for other variables measured at start of cART ^a	Adjusted for variables at start of cART and other time points ^b
<500	1	1	1	1
500–10 000	2.67 (1.91,3.74)	2.07 (1.46,2.95)	1.84 (1.30–2.59)	1.54 (1.08–2.20)
10 000–100 000	5.95 (4.47,7.93)	3.47 (2.49,4.84)	3.42 (2.53–4.62)	2.05 (1.44–2.92)
≥100 000	15.11 (11.39,20.05)	5.31 (3.65,7.72)	7.24 (5.31–9.86)	2.39 (1.59–3.61)

cART, combination antiretroviral therapy.

^a Adjusted for sex, transmission group, age and CDC stage at start of cART.

^b Adjusted for sex, transmission group, age, CDC stage at start of cART, between start of cART and 6 months and between 6 months and 36 months as well as CD4 cell counts and HIV-1 RNA at 0, 6 and 36 months.