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Original article

Estimated average annual rate of change of CD4+ T-cell counts in patients on combination antiretroviral therapy

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Background: Patients receiving combination antiretroviral therapy (cART) might continue treatment with a virologically failing regimen. We sought to identify annual change in CD4+ T-cell count according to levels of viraemia in patients on cART.

Methods: A total of 111,371 CD4+ T-cell counts and viral load measurements in 8,227 patients were analysed. Annual change in CD4+ T-cell numbers was estimated using mixed models.

Results: After adjustment, the estimated average annual change in CD4+ T-cell count significantly increased when viral load was <500 copies/ml (30.4 cells/mm^3, 95% confidence interval [CI] 26.6–34.3), was stable when viral load was 500–9,999 copies/ml (3.1 cells/mm^3, 95% CI -5.3–11.5) and decreased when viral load was ≥10,000 copies/ml (-14.8 cells/mm^3, 95% CI -4.5– -25.1). Patients taking a boosted protease inhibitor (PI) regimen had more positive annual CD4+ T-cell count changes than patients taking other regimens for any given viral load strata: 30.9 cells/mm^3 (95% CI 27.7–34.1) when viral load was <500 copies/ml, 14.2 cells/mm^3 (95% CI -2.1–30.4) when viral load was 500–9,999 copies/ml and -19.9 cells/mm^3 (95% CI -36.6– -3.3) when viral load was ≥10,000 copies/ml. By contrast, among patients taking a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, the CD4+ T-cell count significantly decreased when the viral load was 500–9,999 copies/ml (-18.6 cells/mm^3, 95% CI -33.8– -3.5) and decreased at a faster rate when the viral load was ≥10,000 copies/ml (-44.4 cells/mm^3, 95% CI -62.0– -26.9; *P*=0.0012, test for interaction).

Conclusions: On average, CD4+ T-cell counts did not significantly decrease until the viral load exceeded 10,000 copies/ml in patients treated with a boosted PI-containing cART regimen, but decreased in patients taking an NNRTI-based cART regimen when viral load was 500–9,999 copies/ml.

Introduction

The decrease in CD4+ T-cell counts has been extensively described prior to the introduction of combination antiretroviral therapy (cART) in 1996–1997, and was estimated to be between 50 and 80 cells/mm^3 per year in the absence of therapy [1–3], with a strong dependence on the HIV viral load [4,5]. Antiretroviral treatment guidelines recommend that the viral load should be maintained at as low a level as possible [6]. Some patients are maintained on a stable cART regimen despite having detectable levels of viraemia

[7], perhaps partly because of the limited number of available antiretrovirals for them to switch to. The Pursuing Later Treatment Options (PLATO) study considered CD4+ T-cell count changes in patients with triple-class failure during periods with stable viral load [8], defined as no more than 0.5 $\log_{10}$ copies/ml variation in viral load over the period in which CD4+ T-cell count slope or rate of change was estimated. However, information on CD4+ T-cell count changes in patients on cART but without triple-class treatment failure is currently lacking.

Patients on a virologically failing regimen can change treatment if they have treatment options remaining, but some have no remaining treatment options or choose to remain on a well-tolerated regimen. For these patients, information on CD4+ T-cell count changes will be important. Such patients can be monitored more closely for viral load increases and CD4+ T-cell count decreases in order to detect early clinical disease progression. Studies on patients starting primarily a protease inhibitor (PI)-based cART have reported a stable CD4+ T-cell count whilst cART was maintained, with a viral load of 1,000–10,000 copies/ml [7], and a significant decrease in CD4+ T-cell count when the viral load at virological failure was >10,000 copies/ml [9]. Although up to 90% of patients in developed countries treated with cART currently achieve virological suppression [10], the majority of patients currently treated with cART live in resource-limited settings and many patients are left on a virologically failing regimen. This regimen can often include a non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimen [11] and information on CD4+ T-cell count changes at different levels of viraemia in these patients is less well described. It is unknown whether similar CD4+ T-cell count changes can be expected for a given level of viraemia in patients taking an NNRTI-based regimen compared with a PI, triple-nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) abacavir-based cART regimen.

The aim of this study was to describe changes in CD4+ T-cell counts in patients who maintain a stable cART regimen with both detectable and undetectable levels of viraemia and to determine the level of viraemia at which CD4+ T-cell counts are expected to significantly decrease in patients on cART.

Methods

The EuroSIDA study is a prospective observational cohort of 16,599 HIV type-1 (HIV-1)-infected patients in 102 centres across Europe, Israel and Argentina. The study has been described in detail previously [12]. In order to compare cART regimens, cART was classified into four groups (single PI, boosted PI, NNRTI and triple-nucleoside); each regimen included exactly two NRTIs plus either a PI, ritonavir-boosted PI, NNRTI or abacavir.

Three viral load strata were defined: <500 copies/ml (this cutoff was used as there are a wide range of viral load assays, with variable lower limits of detection, in routine use across the EuroSIDA study), 500–9,999 copies/ml and ≥10,000 copies/ml, to reflect previous studies and commonly used cutoffs [7–9]. Patients were eligible for inclusion in the analysis as soon as they started cART and when they had three consecutive viral load measurements within any of the viral load strata, provided there had not been a change in cART regimen between the four treatment groups. For example, a change in the nucleoside pairs was allowed, as was a change from a single PI-containing regimen to another (providing the viral load stayed within the same strata), but the episode would end when a patient started a cART regimen that was not based on a single PI. For patients with >1 viral load measurement within a 28-day period, the maximum value during the 28-day period was calculated and assigned to the median date. A similar procedure was used for patients with >1 CD4+ T-cell count measured within a 28-day period; the median CD4+ T-cell count was assigned to the median date [13]. For each viral load included in the analysis, the corresponding CD4+ T-cell count measured at the same date was used to estimate the annual change in CD4+ T-cell count for each viral load strata. For example, a patient with 11 consecutive viral loads that measured <500 copies/ml whilst on NNRTI-based cART would have the annual change in CD4+ T-cell count estimate based on 11 CD4+ T-cell counts, and that annual change in CD4+ T-cell count would be allocated to the <500 copies/ml viral load in NNRTI strata. The median date of last follow-up was October 2008.

Baseline was defined as the date each patient was first included in the analysis and mixed models were used to estimate the annual change in CD4+ T-cell count. Models were adjusted for gender, HIV exposure group (homosexual, intravenous drug user, heterosexual or other), ethnic origin (White versus other), region (southern Europe/Argentina, central Europe, northern Europe and eastern Europe), hepatitis B and C status, prior AIDS diagnosis, duration of cART (<6 months, 6 months–3 years and >3 years) [13], nucleoside pairs (zidovudine/lamivudine, lamivudine/stavudine, didanosine/stavudine, any two nucleosides including tenofovir, any two nucleosides including abacavir [but not tenofovir] or any other two nucleosides [13]), whether the patient was antiretroviral-naive at starting cART, age, peak viral load prior to baseline, CD4+ T-cell nadir prior to baseline and the development of extensive triple-class failure. The dependant variable was CD4+ T-cell count, the key independent variables were viral load strata and cART treatment group, enabling the average

differences in annual change in CD4+ T-cell count to be estimated within viral load strata and cART treatment groups. Within-patient correlation was modelled using an autoregressive (first order) covariance structure, using repeated measurements. Failure of an antiretroviral was defined as a viral load >500 copies/ml after ≥4 months of continuous treatment. Extensive triple-class failure was defined as failure of ≥2 NRTIs, a boosted PI and an NNRTI [14].

All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). Sensitivity analyses included modelling the change in CD4+ T-cell count and the intercept for each patient as a random effect, using a square root or logarithmic transformation of CD4+ T-cell count, using least squares regression based on each successive set of three CD4+ T-cell counts to estimate the annual change in CD4+ T-cell count and comparing the estimates of these CD4+ T-cell count changes between strata of interest using generalized estimating equations.

Results

A total of 8,227 patients were included in these analyses, as described in Table 1. There were some differences between the baseline characteristics when comparing the three viral load strata.

Overall, the majority of the patients were male (*n*=6,313, 76.7%), of White ethnic origin (*n*=7,045, 85.6%) and belonged to the homosexual HIV exposure group (*n*=3,646, 44.3%). A total of 1,630 patients (19.8%) were infected with HIV via intravenous drug use. At baseline, 2,496 (30.3%) patients had a prior diagnosis of AIDS, median age was 39.0 years (interquartile range [IQR] 33.8–46.0) and the median baseline date was November 1999 (IQR January 1998–August 2003). At baseline, 2,277 (27.7%) patients had a CD4+ T-cell count ≤200 cells/mm^3 and 3,574 (43.4%) had a CD4+ T-cell count >350/mm^3. At baseline, almost half of the patients (*n*=3,785, 46.0%) were using a single PI-based regimen, 1,922 (23.4%) were taking a boosted PI regimen and 2,189 (26.6%) patients were using an NNRTI-based regimen.

The 8,227 patients contributed 111,371 viral load CD4+ T-cell count measurements with a median of 11 (IQR 6–18) measurements per patient, measured a median time apart of 3.2 months (IQR 2.8–4.6). The majority of the viral load measurements during follow-up were <500 copies/ml (*n*=98,910, 88.8%); of these, almost 40% were measured in patients taking an NNRTI-based regimen, as shown in Figure 1. Over the same time period, >40% of the CD4+ T-cell counts were >500 cells/mm^3 (*n*=48,672, 43.7%) and <15% were ≤200 cells/mm^3 (*n*=13,205, 11.9%). The most common single PI regimen contained indinavir (*n*=15,042, 48.4%) or nelfinavir (*n*=8,886, 28.6%), whereas lopinavir was the most commonly used boosted PI (*n*=11,224, 35.3%) and efavirenz the most common NNRTI (*n*=23,169, 57.0%). The most common NRTI backbones (pairs) in use were zidovudine and lamivudine (*n*=39,801, 35.7%), followed by lamivudine and stavudine (*n*=24,538, 22.0%), any tenofovir-containing pair (*n*=18,314, 16.4%) and an NRTI backbone containing abacavir (in patients not taking an abacavir-based triple-nucleoside regimen; *n*=13,263, 11.9%).

After adjustment, the CD4+ T-cell count significantly increased in patients with viral load <500 copies/ml (average estimated annual change 30.4 cells/mm^3, 95% CI 26.6–34.3), was not significantly different from zero in patients with viral loads of 500–9,999 copies/ml (average estimated annual change 3.1 cells/mm^3, 95% CI -5.3–11.5) and significantly decreased in patients with viral load ≥10,000 copies/ml (average estimated annual change -14.8 cells/mm^3, 95% CI -4.5–-25.1). In addition, there was a significant interaction between cART treatment regimen and viral load strata, suggesting that the annual change in CD4+ T-cell count differed in different viral load strata depending on the cART regimen in use (*P*=0.0012, test for interaction).

The adjusted average estimated annual changes in CD4+ T-cell count, stratified by viral load group and cART regimen are shown in Figure 2; they were most favourable in patients using a boosted PI regimen and less favourable in patients using an NNRTI-based cART regimen. In patients treated with a boosted PI regimen, the average estimated annual change in CD4+ T-cell count was 30.9 cells/mm^3 (95% CI 27.7–34.1) when the viral load was <500 copies/ml. The change in CD4+ T-cell count was not significantly different from zero when the viral load was 500–9,999 copies/ml (average estimated annual change 14.2 cells/mm^3, 95% CI -2.1–30.4) and significantly decreased when the viral load was ≥10,000 copies/ml (average estimated annual change -19.9 cells/mm^3, 95% CI -36.6–-3.3). By contrast, the CD4+ T-cell count increased at a slower rate in patients taking an NNRTI-based regimen with a viral load <500 copies/ml (average estimated annual change 23.4 cells/mm^3, 95% CI 21.1–25.6), significantly decreased when the viral load was 500–9,999 copies/ml (average estimated annual change -18.6 cells/mm^3, 95% CI -33.8–-3.5) and decreased at a faster rate when viral load ≥10,000 copies/ml (average estimated annual change -44.4 cells/mm^3, 95% CI -62.0–-26.9). In each viral load strata, there was a significantly greater increase in CD4+ T-cell count in patients taking a boosted PI compared with an NNRTI-based regimen. When the viral load was <500 copies/ml, the difference was 11.0 cells/mm^3 (95% CI 8.2–13.8; *P*<0.0001). When the viral load was 500–9,999 copies/ml, the difference was

32.8 cells/mm^3 (95% CI 12.8–52.7; *P*=0.0013). When the viral load was ≥10,000 copies/ml, the difference was 24.5 cells/mm^3 (95% CI 4.6–44.5; *P*=0.016). The changes in CD4$^+$ T-cell count within each viral load strata were similar in patients taking a single PI-based cART regimen and abacavir (Figure 2). The CIs were wide for the estimates in CD4$^+$ T-cell count changes for triple-NRTI-containing regimens, particularly at higher viral loads, reflecting a lower number of viral load measurements in this group.

Table 2 shows the same results, but the differences in the adjusted average estimated annual change in CD4$^+$ T-cell count for the different cART regimens are compared with a single PI-containing regimen within each viral load strata. For example, when the viral load was <500 copies/ml, patients taking an NNRTI-containing regimen had significantly lower increases in CD4$^+$ T-cell count than those taking a single PI-containing regimen (average estimated annual difference -7.5 cells/mm^3, 95% CI -10.5–-4.6; *P*<0.0001). Patients taking

Table 1. Patient characteristics at baseline[a]

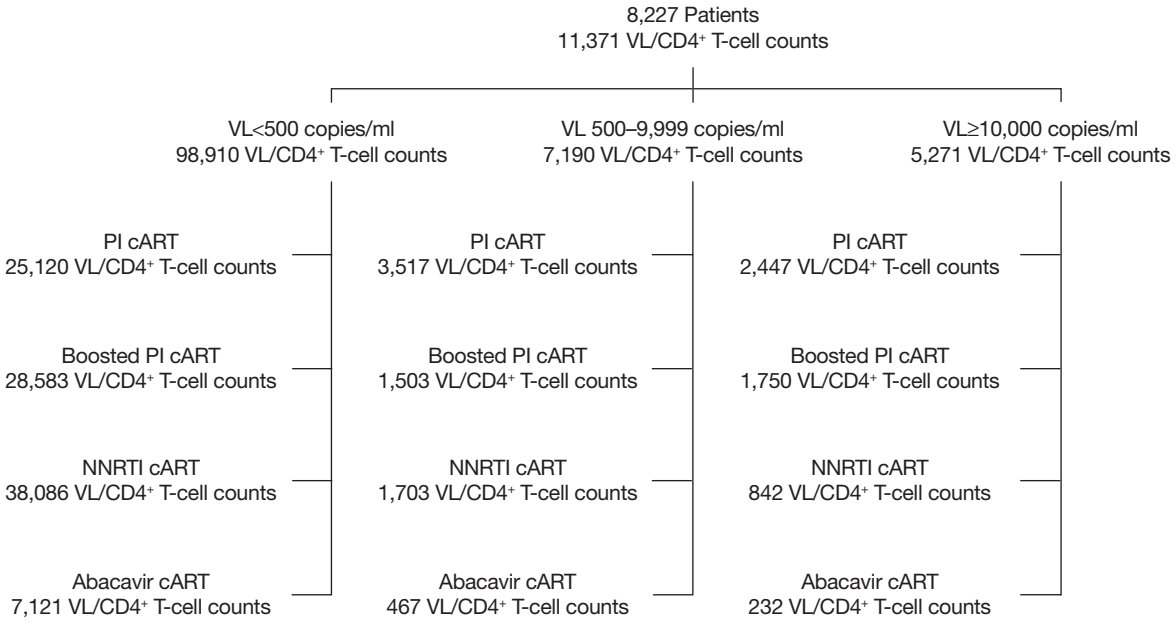
Characteristic	All	VL<500 copies/ml	VL 500–9,999 copies/ml	VL≥10,000 copies/ml	*P*-value
All, *n* (%)	8,227 (100)	6,543 (79.5)	901 (11.0)	783 (9.5)	–
Gender					0.013
Male, *n* (%)	6,313 (76.7)	4,993 (76.3)	686 (76.1)	634 (81.0)	
Female, *n* (%)	1,914 (23.3)	1,550 (23.7)	215 (23.9)	149 (19.0)	
Race					0.64
White, *n* (%)	7,045 (85.6)	5,615 (85.8)	766 (85.0)	664 (84.8)	
Other, *n* (%)	1,182 (14.4)	928 (14.2)	135 (15.0)	119 (15.2)	
HIV exposure					0.86
Homosexual, *n* (%)	3,646 (44.3)	2,884 (44.1)	400 (44.4)	362 (46.2)	
IDU, *n* (%)	1,630 (19.8)	1,291 (19.7)	182 (20.2)	157 (20.1)	
Heterosexual, *n* (%)	2,310 (28.1)	1,852 (28.3)	254 (28.2)	204 (26.0)	
Other, *n* (%)	641 (7.8)	516 (7.9)	65 (7.2)	60 (7.7)	
Region					<0.0001
Southern Europe/Argentina, *n* (%)	2,660 (32.3)	2,034 (31.1)	361 (40.1)	265 (33.8)	
Central Europe, *n* (%)	2,214 (26.9)	1,718 (26.3)	247 (27.4)	249 (31.8)	
Northern Europe, *n* (%)	2,288 (27.8)	1,852 (28.3)	231 (25.6)	205 (26.2)	
Eastern Europe, *n* (%)	1,065 (13.0)	939 (14.4)	62 (6.9)	64 (8.2)	
Prior AIDS, *n* (%)	2,496 (30.3)	1,856 (28.4)	277 (30.7)	363 (46.4)	<0.0001
Hepatitis B status					0.12
Uninfected, *n* (%)	5,835 (70.9)	4,663 (71.3)	628 (69.7)	544 (69.5)	
Infected, *n* (%)	451 (5.5)	350 (5.3)	44 (4.9)	57 (7.3)	
Unknown, *n* (%)	1,941 (23.6)	1,530 (23.4)	229 (25.4)	182 (23.2)	
Hepatitis C status					0.40
Uninfected, *n* (%)	4,321 (52.5)	3,454 (52.8)	450 (49.9)	417 (53.3)	
Infected, *n* (%)	1,539 (18.7)	1,227 (18.7)	167 (18.5)	145 (18.5)	
Unknown, *n* (%)	2,367 (28.8)	1,862 (28.5)	284 (31.5)	221 (28.2)	
cART regimen					<0.0001
Single PI, *n* (%)	3,785 (46.0)	2,761 (42.2)	558 (61.9)	466 (59.5)	
Boosted PI, *n* (%)	1,922 (23.4)	1,603 (24.5)	130 (14.4)	189 (24.1)	
NNRTI, *n* (%)	2,189 (26.6)	1,915 (29.3)	172 (19.1)	102 (13.0)	
Triple-nucleoside, *n* (%)	331 (4.0)	264 (4.0)	41 (4.6)	26 (3.3)	
Median viral load, $\log_{10}$ copies/ml (IQR)	2.3 (1.7–2.7)	2.0 (1.7–2.5)	3.3 (3.0–3.7)	4.7 (4.4–5.1)	<0.0001
Median CD4$^+$ T-cell count, cells/mm^3 (IQR)	315 (188–475)	334 (207–494)	308 (179–452)	176 (78–304)	<0.0001
Median nadir CD4$^+$ T-cell count, cells/mm^3 (IQR)	153 (62–252)	166 (72–264)	145 (60–235)	67 (18–144)	<0.0001
Median age, years (IQR)	39 (34–46)	39 (34–47)	38 (34–44)	38 (33–44)	<0.0001
Median baseline, month/year (IQR)	11/99 (1/98–8/03)	7/00 (4/98–2/04)	10/98 (9/97–4/00)	2/98 (4/97–2/00)	<0.0001
Median time from cART, years (IQR)	0.9 (0.3–2.4)	0.9 (0.3–2.4)	1.1 (0.5–2.1)	1.1 (0.4–2.5)	<0.0001

[a]Baseline was defined as the first date that each patient was included in the analysis. Patients might switch between categories after baseline (see *Methods* section). cART, combination antiretroviral therapy; IDU, intravenous drug user; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VL, viral load.

a boosted PI-containing regimen with a viral load ≥10,000 copies/ml had significantly greater increases in CD4+ T-cell count compared with those taking a single PI-containing regimen (average estimated annual difference 20.4 cells/mm^3, 95% CI 3.3–37.5; P=0.019).

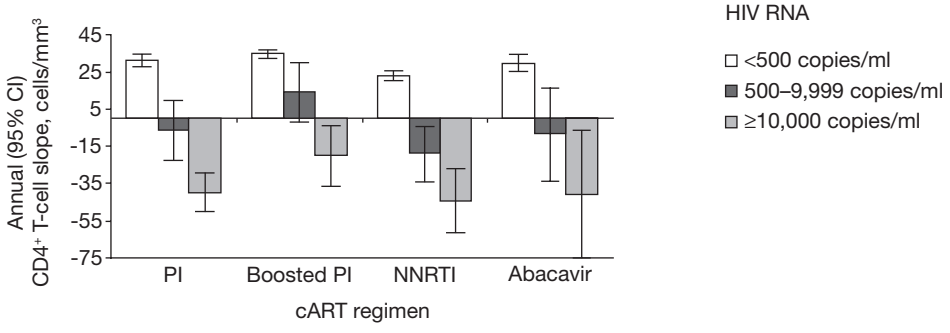
A number of sensitivity analyses were performed. Analyses were repeated using a square root and logarithmic transformation of the CD4+ T-cell count to make the data more normally distributed and to reduce some of the variation in changes in CD4+ T-cell counts. In addition, different covariance structures were investigated, as was allowing each patient to have a random change in CD4+ T-cell counts and intercept (that is, using random effects), all with consistent results. A

Figure 1. Follow-up and inclusion of patients



cART, combination antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VL, viral load.

Figure 2. Adjusted[a] average annual change in CD4+ T-cell counts in patients on a stable cART regimen



[a]Adjusted for CD4+ T-cell count at baseline, current viral load, extensive triple-class failure, minimum CD4+ T-cell count and maximum viral load recorded prior to baseline, exposure group, hepatitis B and C status, region, ethnic origin, HIV exposure category, prior AIDS, age, time since first starting combination antiretroviral therapy (cART) and nucleoside pair. CI, confidence interval; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 2. Adjusted[a] annual change in CD4+ T-cell count in patients on stable cART regimens compared with a single PI cART regimen

	VL<500 copies/ml			VL 500–9,999 copies/ml			VL≥10,000 copies/ml		
Regimen	Estimate	95% CI	*P*-value	Estimate	95% CI	*P*-value	Estimate	95% CI	*P*-value
Single PI	0	–	–	0	–	–	0	–	–
Boosted PI	3.5	0.1–6.9	0.045	19.8	0.5–39.2	0.044	20.4	3.3–37.5	0.019
NNRTI	-7.5	-10.5–-4.6	<0.0001	-13.0	-29.1–3.2	0.12	-4.1	-23.2–14.9	0.67
Abacavir	-1.3	-6.1–3.5	0.60	-2.5	-29.3–24.3	0.85	-0.7	-35.6–34.2	0.97

[a]Adjusted for CD4+ T-cell count at baseline, current viral load, extensive triple-class failure, minimum CD4+ T-cell count and maximum viral load (VL) recorded prior to baseline, exposure group, hepatitis B and C status, region, ethnic origin, HIV exposure category, prior AIDS, age, time since first starting combination antiretroviral therapy (cART) and nucleoside pair. CI, confidence interval; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

completely alternative method of analysis using least squares regression analysis with generalized estimating equations also confirmed our findings, although the variability around the changes in CD4+ T-cell counts was considerably higher in this analysis.

Discussion

To our knowledge, this is one of the first studies to specifically address CD4+ T-cell count changes in patients on a stable cART regimen that has sufficient power to compare cART regimens and viral load strata. Although overall CD4+ T-cell counts did not significantly decrease in patients on cART unless the viral load was >10,000 copies/ml, there were some differences according to cART regimen used. CD4+ T-cell counts did not significantly decrease until the viral load was >10,000 copies/ml in patients treated with a boosted PI-containing cART regimen, but decreased in patients taking an NNRTI-based cART regimen when viral load was 500–9,999 copies/ml.

Among all patients, the lack of a substantial decrease in CD4+ T-cell counts in patients on a stable cART regimen with stable viraemia (500–10,000 copies/ml) might be a result of the limited capacity of the virus to reproduce itself (because of resistance mutations) or residual antiretroviral activity [15,16]. We planned *a priori* to test whether the CD4+ T-cell count changes were similar in different cART regimens for a given level of viraemia. We found evidence that patients taking a boosted PI regimen had a slower decrease in CD4+ T-cell counts at viral loads ≥10,000 copies/ml compared with other cART regimens. Furthermore, in patients with a viral load of 500–9,999 copies/ml, patients on NNRTI-based regimens experienced significant decreases in CD4+ T-cell counts, but those treated with a boosted PI had stable CD4+ T-cell counts. These results should, of course, be interpreted with caution. As this was a non-randomized comparison, confounding by indication cannot be ruled out and although the statistical test for interaction was significant, the analyses had more limited power in patients with viral loads >500 copies/ml. Our results are based on a heterogeneous patient population taking one of the currently recommended first-line cART regimens; only a minority of patients had experienced extensive triple-class failure. However, our results are similar to those of PLATO [8], where lower CD4+ T-cell increases in patients taking an NNRTI-based regimen were seen when compared with a regimen containing a boosted PI. This is consistent with the hypotheses that PI-based regimens can lead to a reduction in the replicative capacity of HIV [17,18], that PIs are more potent for down-regulation of apoptosis [19] or that use of PI-containing regimens are associated with residual antiviral activity, whereas a single resistance mutation in NNRTIs can lead to complete resistance [6,20].

In resource-limited settings, the most commonly prescribed regimen is nevirapine, lamivudine and stavudine, used in almost 50% of patients [21]. A public health approach to using cART is often used [22], which is designed to have the maximum clinical benefit on a population level by using cART, without necessarily providing individualized optimized treatment. For example, a lack of resources and infrastructure means that few patients on cART are monitored with regular viral load testing and patients might remain on a virologically failing regimen as a consequence. For such patients, in those settings where CD4+ T-cell counts are used to monitor patients, maintaining the CD4+ T-cell levels to reduce the risk of clinical disease progression despite virological failure becomes of utmost importance. In the absence of viral load measurements, one approach would be to continue a treatment regimen that includes lamivudine, which has been demonstrated to have a positive effect on CD4+ T-cell counts despite almost complete resistance [23]. Furthermore, the results from our study would suggest that better CD4+ T-cell count increases might be obtained by using a ritonavir-boosted PI-based regimen rather than by using an NNRTI-based regimen. When considering other drug classes for introduction in resource-limited settings, antiviral activity, cost, toxicities and genetic barrier are all important considerations, in addition to

the ability to increase CD4+ T-cell counts when patients are viraemic, where the findings of our study might be an additional relevant consideration.

There are some limitations of this study that should be noted. There is a degree of variability associated with the CD4+ T-cell count because of biological variation, exercise, the presence of other illnesses, pharmacological agents, diurnal and seasonal variations and a high underlying variability in total lymphocyte counts [24–26], although our various sensitivity analyses demonstrated the results were robust using different assumptions and models. Current treatment guidelines state that treatment should be changed if the patient fails virologically [6] and we were not able to determine why patients were maintained on a failing regimen. Data on adherence was not available on the majority of patients and it is possible that there was some variability in adherence in patients with viraemia >500 copies/ml, which could be related to changes in CD4+ T-cell count. We categorized the viral load into three strata, reflecting previous studies and commonly used cutoffs [7–9]. The analysis of larger data sets would allow more viral load categories to be analysed. Treatment guidelines recommend maintaining viral load <50 copies/ml [6]; however, we chose to group together all viral loads <500 copies/ml to reflect the range of lower limits of detection for viraemia used across Europe and over time and because there is little evidence that low-level viraemia (50–500 copies/ml) affects immunological response [27,28]. Analyses were also performed excluding periods within viral load strata where the viral load varied by >0.5 $\log_{10}$ copies/ml as in the PLATO study [8]. This is most likely to occur when patients are starting and stopping cART regimens rather than being on stable therapy. This additional sensitivity analysis showed similar results.

To conclude, there was some evidence that boosted PI-based cART regimens were associated with greater increases in CD4+ T-cell counts at low viral loads and smaller decreases in CD4+ T-cell counts at high viral loads when compared with other cART regimens. The possibility of a difference in the change in CD4+ T-cell count within antiretroviral drug classes for a given level of viraemia is intriguing, although larger studies with more power are urgently required.

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Disclosure statement

The authors declare no competing interests.

Additional file

Additional file 1: A list of members of the EuroSIDA Study Group can be found at http://www.intmedpress.com/uploads/documents/AVT-09-OA-1435_Mocroft_Add_file1.pdf

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