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Interruption of antiretroviral therapy is associated with increased plasma cystatin C

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Abstract

Background—Cystatin C has been proposed as an alternative marker of renal function. We sought to determine if participants randomized to episodic use of antiretroviral therapy guided by CD4+ count (drug conservation; DC) had altered cystatin C levels compared to those randomised to continuous antiretroviral therapy (viral suppression; VS) in the Strategies for Management of Antiretroviral Therapy Trial, and to identify factors associated with increased cystatin C.

Methods—Cystatin C was measured in plasma collected at randomization, 1, 2, 4, 8 and 12 months after randomization in a random sample of 249 and 250 participants in the DC and VS groups respectively. Logistic regression was used to model the odds of ≥ 0.15 mg/dl increase in cystatin C (1 standard deviation [SD]) in the first month after randomisation, adjusting for demographic and clinical characteristics.

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Amanda Mocroft helped develop the project, performed statistical analyses and drafted the manuscript, Christina Wyatt contributed to the development of the project, interpretation of analyses and contributed to writing the manuscript. Lynda Szczech, Wafaa El-Sadr, Russell Tracy, Lewis Kuller, Michael Shlipak, Brian Angus and Hartwig Klinker provided input into analyses and contributed to writing the manuscript. Jacquie Neuhaus supported statistical analyses, provided initial exploratory analyses and contributed to writing the manuscript. Michael Ross proposed the project, provided input into analyses and interpretation of data, contributed to writing the manuscript and supervised the project.

Conflict of Interest

None reported

Results—At randomisation, mean (SD) cystatin C level was 0.99 (0.26 mg/dl) and 1.01 (0.28 mg/dl) in the DC and VS arms respectively ($p=0.29$). In the first month after randomisation, 21.8% and 10.6% had ≥ 0.15 mg/dl increase in cystatin C in the DC and VS arm respectively ($p=0.0008$). The difference in cystatin C between the treatment arms was maintained through 1 year after randomisation. After adjustment, participants in the VS arm had significantly reduced odds of ≥ 0.15 mg/dl increase in cystatin C in the first month (OR 0.42; 95% CI 0.23–0.74, $p=0.0023$).

Conclusions—These results demonstrate that interruption of antiretroviral therapy is associated with an increase in cystatin C, which may reflect worsened renal function.

Introduction

The introduction of effective antiretroviral therapy (ART) for the treatment of HIV-1 infection has led to a dramatic decline in mortality and morbidity^{1, 2}. As patients survive longer, renal disease has become an important contributing factor to morbidity and mortality³. While ART has been demonstrated to reduce the incidence and severity of HIV-associated nephropathy (HIVAN)^{4–6}, specific antiretrovirals may be associated with nephrotoxicity, or with increased rates of hypertension and diabetes, which in turn may increase the risk of kidney disease^{7, 8}. Several studies have considered the impact of ART on serum creatinine, proteinuria, estimated glomerular filtration rate (GFR), and progression of kidney disease^{9–12}. Cystatin C, a non-glycosylated basic protein secreted by all nucleated cells and freely filtered by the glomerulus, has been considered as a prognostic marker for mortality and morbidity¹³ and also proposed as an alternative marker of GFR¹⁴. Serum cystatin C levels correlate well with GFR in patients without HIV^{15–17}, and may be more sensitive than serum creatinine in the detection of early renal insufficiency^{18, 19}. Serum cystatin C levels are not affected by muscle mass, which may be decreased in patients with advanced HIV disease²⁰. Further, serum cystatin C levels have been correlated with renal function in HIV-infected patients and have been noted to be higher in HIV-1 infected patients compared to uninfected individuals^{21, 22}. To our knowledge changes in cystatin C associated with starting or stopping ART have not been previously described.

The Strategies for Management of Antiretroviral Therapy (SMART) trial was a randomized controlled clinical trial which compared the episodic use of ART (drug conservation, or DC arm) guided by CD4+ cell counts with continuous therapy aimed at virologic suppression (VS arm)²³. The study demonstrated that the DC strategy was associated with inferior outcomes with regards to development of opportunistic disease or death and the composite endpoint of cardiovascular, hepatic and renal disease²³; an increased risk of fatal or non-fatal renal disease was described in the DC arm compared to the VS arm. In another study from SMART²⁴, plasma biomarkers of inflammation (IL-6, high sensitivity C-reactive protein [hsCRP], amyloid A, amyloid P), coagulation (D-dimer, prothrombin fragments 1+2), and lipids (total cholesterol, HDL, LDL, triglycerides) were measured to determine whether they were associated with all cause mortality and cardiovascular disease.

The aims of the current study were to describe changes in plasma cystatin C in SMART participants included in the previous biomarker substudy, and to investigate the factors associated with increase in cystatin C levels after randomisation. Since many of the previously measured biomarkers are also associated with renal disease, we sought to determine whether these biomarkers were associated with cystatin C.

SMART Study Participants and Treatment Protocol

Between January 2002 and January 2006, 5,472 HIV-infected participants were enrolled in SMART by 318 sites in 33 countries. Participants were eligible if they had a CD4+ count >350 cells/mm³ and were willing to initiate, modify or stop ART as per study guidelines²³. SMART participants were randomized to one of two ART strategies. For the VS group, ART was used

in an uninterrupted manner with the goal of maximal suppression of HIV replication. The experimental drug conservation (DC) strategy entailed episodic use of ART for periods defined by CD4⁺ count thresholds. ART was stopped (or deferred) until the CD4⁺ count dropped to <250 cells/mm³, at which time ART was to be (re-)initiated and continued until the CD4⁺ count rose to >350 cells/mm³. Upon confirmation that the CD4⁺ count was >350 cells/mm³, ART was to be stopped and resumed again when the CD4⁺ count was <250 cells/mm³. During periods of ART use, the goal was to achieve maximal viral suppression. As previously reported, on January 11, 2006, investigators and participants were notified of a safety risk in the DC group, enrollment was stopped, and participants in the DC group were advised to restart ART²³.

Specimens Collected for Biomarker Substudy

In SMART, follow-up study visits occurred at month 1, month 2, then every 2 months for the first year, and every 4 months thereafter. 5151 participants (94%) had blood stored for future use. Plasma specimens were collected using EDTA (lavender top) tubes, aliquoted, and shipped frozen to a central repository. Only specimens obtained prior to January 11, 2006 were used for the biomarker analyses described in this paper. Plasma specimens collected at randomisation and one month after randomisation were identified for participants who consented to specimen storage for future research. A random sample of 250 participants without a pre-existing history of cardiovascular disease from each treatment group was chosen from 1286 participants with available samples. One participant in the DC group who did not have an adequate specimen at randomisation was subsequently excluded.

Measurement of Cystatin-C and inflammatory markers

Cystatin-C was measured on plasma samples that were stored at -70°C. A BNII nephelometer (Dade Behring Inc., Deerfield, Ill) that utilized a particle-enhanced immunonephelometric assay (N Latex Cystatin-C) was used. The assay range is 0.195 to 7.330 mg/dl. The reference range for young, healthy individuals is 0.53 to 0.92 mg/dl. The inflammatory markers were measured by the Laboratory for Clinical Biochemistry Research at the University of Vermont.

Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula²⁵ and the Cockcroft-Gault formula²⁶

Statistical methods

Descriptive statistics were used to demonstrate the change in cystatin C in the first year after randomisation in the DC versus VS arm. Pearson correlation coefficients were used to determine the correlation between (a) values of cystatin C and markers of inflammation, coagulation and lipids at randomisation, (b) marker values at randomisation and change in cystatin C between randomisation and month 1, (c) marker values and cystatin C at month 1 and (d) changes in marker and cystatin C values between randomisation to month 1. Logistic regression, using forward selection with $p > 0.2$ inclusion criteria, was used to model the odds of ≥ 1 SD increase in cystatin C, 0.15 mg/dl, in the first month after randomisation. Variables included in multivariate models were gender, age, race, mode of HIV infection, hepatitis B and C status, prior AIDS, HIV-RNA ≤ 400 copies/ml at randomisation, current and prior smoking status, diabetes, treatment with blood pressure or lipid lowering therapy, previous antiretroviral experience, ART status at enrolment, and exposure to protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), or nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). Randomisation values for age, weight, body mass index, CD4⁺ count, HIV-RNA levels, total cholesterol, HDL, LDL, and triglycerides, as well as nadir CD4⁺ count were also included.

All analyses were performed using SAS version 9.1 (Statistical analysis Software, Cary, NC USA). All tests of significance were 2-sided.

Results

Characteristics at randomisation of participants assigned to the DC and VS arm in this substudy of SMART were well balanced with no significant differences ($p>0.1$ for all comparisons) (Table 1). At randomisation, 73.1% and 75.2% of DC and VS participants, respectively, were on ART. At randomisation, mean (SD) cystatin C level was 0.99 (0.26 mg/dl) and 1.01 (0.28 mg/dl) in the DC and VS arms, respectively ($p=0.29$). 90 participants in the DC arm (36.3%) had a cystatin C level > 1.0 mg/dl, compared to 101 participants in the VS arm (41.2%, $p=0.26$, chi-squared test).

The difference in cystatin C levels between the DC and VS arms, together with the proportion of participants having a ≥ 0.15 mg/dl rise in cystatin C in the DC and VS arms is shown in Figure 1. Six participants with cystatin C levels > 5 mg/dl at randomisation were excluded from this analysis (1 DC, 5 VS); inclusion of these participants did not alter our findings (data not shown). In the first month after randomisation, there was a small rise in cystatin C (mean 0.05, SD 0.18 mg/dl) in the DC arm and a small decrease in cystatin C in the VS arm (mean -0.02 , SD 0.17 mg/dl; $p<0.0001$ for difference). The proportion of participants who experienced a ≥ 0.15 mg/dl increase in cystatin C was significantly higher in the DC arm (21.8%) compared to the VS arm (10.6%; $p=0.0008$, chi-squared test). Cystatin C remained higher in the DC arm than the VS arm from month 1 through month 12 (Figure 1). Highly consistent results were seen censoring the analysis at the date of restarting ART in the DC arm (data not shown). There were no significant differences between the treatment arms in the proportion of participants with a cystatin-C level of > 1.0 mg/dl at months 1, 4, 8 and 12 ($p>0.1$, chi-squared test).

Other markers of kidney function were measured in a subset of participants at randomisation, month 4 and month 12 of follow-up. There was no significant difference in serum creatinine or MDRD eGFR between participants in the DC and VS arms at any time point (Table 2), or when comparing participants from different races within the DC and VS arm (data not shown). In addition, there was no change in weight or albumin from randomisation to month 4 or month 12, or from month 4 to month 12 in either treatment arm ($p>0.25$, all comparisons). Among all participants, there was a significant correlation between cystatin C and MDRD eGFR at months 0, 4 and 12 (correlation coefficients -0.41 , -0.22 , -0.35 , $p<0.0001$, $p=0.092$, $p<0.0001$ respectively) and between cystatin C and serum creatinine at months 0, 4 and 12 (correlation coefficients 0.234, 0.308, 0.665, $p<0.0001$ for all). Consistent results were seen between the DC and VS arms when GFR was estimated using the CG equation (data not shown).

Figure 2 shows the unadjusted odds ratio of > 1 SD increase in cystatin C comparing the VS arm to the DC arm within subgroups of patients. For example, in patients with a CD4 count of $\leq 500/\text{mm}^3$ at randomisation, 5.2% of participants in the VS arm had ≥ 0.15 mg/dl increase in cystatin C compared to 22.2% in the DC arm (odds ratio [OR] 0.19; 95% confidence interval [CI] 0.07 – 0.53, $p=0.0015$). The corresponding proportions in participants with a CD4 > 500 cells/ mm^3 at randomisation were 14.1% and 21.5% (OR 0.60, 95% CI 0.33 – 1.10, $p=0.098$, p -value for interaction=0.059). The odds ratio of > 1 SD increase in cystatin C comparing the VS arm to the DC arms was similar in patients who were on or off antiretrovirals at baseline and in patients with undetectable plasma HIV-RNA (< 400 copies/ml) compared to those with plasma HIV-RNA ≥ 400 copies/ml.

In a multivariate model adjusted for treatment arm, HIV exposure route, exposure to blood-pressure lowering medication and previous treatment to protease inhibitors, participants in the

VS arm had less than half the odds of ≥ 0.15 mg/dl increase in cystatin C in the first month after randomisation to SMART compared to participants in the DC arm (adjusted OR 0.42; 95% CI 0.23 – 0.74, $p=0.0023$). There was a significantly higher odds of increased cystatin C in participants treated at randomisation with blood pressure lowering medications (adjusted OR 1.91; 95% CI 1.06 – 3.44, $p=0.038$) and those who had been treated previously with protease inhibitors (adjusted OR 2.17; 95% CI 1.07 – 4.40, $p=0.030$). Participants infected with HIV through intravenous drug use had marginally significantly increased odds of an increase in cystatin C (adjusted OR 2.07; 95% CI 0.91 – 4.71, $p=0.077$). There was no significant association between race and increase in cystatin C in univariate ($p=0.57$) or multivariate analyses ($p=0.43$). In addition, there was no relationship between exposure to specific NRTIs and change in cystatin C, although the power for this analysis was limited. These analyses were repeated modelling the change in cystatin C rather than the proportion with a ≥ 0.15 mg/dl increase with highly consistent results (data not shown). Multivariate analyses were also performed separately for the DC and VS arms. There was no qualitative difference in the association of variables with change in cystatin C at month 1 between the treatment groups (data not shown). In the subset of patients with cystatin C levels measured at 12 months after randomisation ($n=283$; 150 DC versus 133 VS), participants in the VS arm had lower odds of a ≥ 0.15 mg/dl increase in cystatin C at 12 months after adjustment for the same factors as shown in table 3 (OR 0.38, 95% CI 0.13 – 1.10, $p=0.075$), although this was of marginal significance.

The lowest and highest quintiles of cystatin C at randomization were 0.81 and 1.14 respectively; the correlation between cystatin C and serum creatinine at randomization in the lowest quintile was 0.27 ($n=57$ observations, $p=0.045$) and in the highest quintile was 0.71 ($n=57$ observations, $p<0.0001$). Additional correlations between cystatin C, inflammatory, coagulation and lipid biomarkers are shown in Table 3. The increase in cystatin C at 1 month after randomisation was correlated with an increase in hsCRP, IL-6, amyloid A, and D-dimer, and a decrease in HDL and total cholesterol between randomisation and month 1. Biomarker values at randomization were added to the logistic regression model described above. After adjustment, none of the biomarkers were independently associated with a ≥ 0.15 mg/dl increase in cystatin C at 1 month after randomisation. Further analyses detected no correlation between randomisation values of cystatin C and HIV-RNA in the DC arm (Table 3, column (a); correlation coefficient 0.037, $p=0.57$), but there was a weak correlation in the VS arm (correlation coefficient 0.195, $p=0.0021$). The correlation coefficients were similar in the DC and VS arms when considering the correlation between HIV-RNA at randomisation and change in cystatin C over the first month (Table 3, column (b)), and change in HIV-RNA versus change in cystatin C over the first month (Table 3, column (d)). In addition, there was a weak correlation between HIV-RNA at 1 month after randomisation and change in cystatin C in the DC arm (correlation coefficient -0.141 , $p=0.027$), which was not apparent in the VS arm (correlation coefficient 0.061, $p=0.034$).

Discussion

The increased risk of kidney disease demonstrated in the DC arm of SMART²³ motivated the current study of changes in plasma cystatin C, a proposed early marker of subclinical kidney damage. In the subset of SMART participants evaluated in this study, those who discontinued or deferred ART (DC arm) had a rapid small, but significant, increase in plasma cystatin C compared to participants who were treated with continuous ART (VS arm), and were significantly more likely to have cystatin C levels higher than the level at randomisation. The difference in cystatin C levels between the DC and VS arms of SMART were maintained through 1 year of follow-up.

Plasma cystatin C levels are determined by the net balance of secretion of cystatin C into plasma and clearance by glomerular filtration²⁷. The increased cystatin C levels found in the DC arm compared to the VS arm must therefore reflect either a reduction in GFR in the DC group that was not detected by changes in serum creatinine or eGFR, and/or increased secretion of cystatin C from cells into the plasma. The latter explanation seems unlikely as research has shown that cystatin C levels do not increase in the setting of acute stress²⁸. Systemic levels of cystatin C have been shown to be independent of several characteristics, including age²⁹, gender^{29, 30} and muscle mass³¹. There are conflicting data in the literature regarding whether systemic inflammation can influence cystatin C levels independent of renal function. Knight et al. reported that cystatin C levels were independently associated with C reactive protein (CRP) levels in a cohort of healthy subjects, nearly all of whom were Caucasians with normal renal function³². However, another study by Singh et al., which included a more racially diverse population with a higher prevalence of chronic kidney disease, found that the association of cystatin C with inflammatory markers was not independent of GFR³³. The latter study suggested that impaired renal function is associated with inflammation and that levels of cystatin C are reflective of decreased GFR even in the presence of systemic inflammation. In this study, there was a strong correlation between randomisation levels of cystatin C and serum creatinine in the upper quintile of cystatin C at randomisation. One explanation for this observation is that at higher levels, cystatin C and creatinine are well correlated and reflect impaired renal function, whereas at lower levels, cystatin C and/or creatinine are more prone to the influence of other factors such as inflammation and muscle mass, respectively. Although we identified weak correlations between levels of inflammatory markers and cystatin C, there was no independent association between hsCRP or IL-6 and change in cystatin C after adjustment for other variables. We therefore hypothesise that the increase in cystatin C observed in the DC arm of SMART upon interruption of ART reflected systemic inflammation that was concurrent with and may have contributed to renal injury.

We also found that an increase in cystatin C from randomisation to month 1 correlated with the value of D-dimers and HDL levels at 1 month after randomisation and with the change in these markers from randomisation to month 1. Increased D-dimers and decreased HDL are associated with increased risk of cardiovascular disease in the general population and can be induced by systemic inflammation³⁴. D-dimers and HDL are also more likely to be elevated and decreased respectively in participants with chronic kidney disease, possibly contributing to the increased risk of cardiovascular mortality in that population^{35, 36}.

There are several mechanisms by which interruption or deferral of ART may have resulted in an increase in cystatin C. While it is possible that the increase in cystatin C could reflect systemic inflammation rather than a decrease in renal function, we hypothesize that the inflammation was concurrent with and may have contributed to renal injury. Renal glomerular and tubular epithelial cells are susceptible to infection by HIV, and infected cells have been detected in the kidney, even in persons receiving ART with undetectable plasma HIV-RNA levels^{37,38}. HIV infection of human renal tubular epithelial cells induces apoptosis and production of inflammatory mediators³⁹⁻⁴². Studies have demonstrated that ART can induce marked improvement in functional and histological abnormalities in some patients with HIV-associated nephropathy after a reduction in viral load^{38, 43, 44}. Participants in the DC arm of SMART who were previously taking ART had a marked increase in plasma HIV-RNA levels after discontinuation or deferral of ART following randomisation. Moreover, participants in the DC arm were more likely to have an increase in cystatin C if they had an HIV-RNA level ≤ 400 copies/ml at randomisation before ART discontinuation. It is therefore plausible that withdrawal of ART resulted in increased HIV replication in renal epithelial cells, resulting in local inflammation and renal injury.

Our study has several limitations. Although there was a statistically significant difference in cystatin C levels between the DC and VS arms at month 1 after randomisation, the magnitude of the difference was small, and the clinical significance and relationship of this difference with renal disease are unclear. Since serum creatinine measurements were only available on a subset of participants, we cannot exclude the possibility that the lack of difference in creatinine and creatinine-based estimates of GFR between DC and VS arms was a result of ascertainment bias. Finally, since we did not use a “gold standard” to measure GFR (such as iothalamate or inulin clearance), we cannot be certain that the rise in cystatin C reflects a decline in GFR. However, cystatin C has been shown to be a better marker of GFR than serum creatinine in several disease settings, and creatinine itself has never been validated as a marker of GFR in HIV-infected patients using a “gold standard”. Prospective, well-designed studies are therefore urgently needed to explore the accuracy of cystatin C and creatinine as markers of GFR in patients with HIV infection.

In summary, in this randomised comparison, an increase in cystatin C levels was demonstrated after stopping ART in the DC arm of SMART. Cystatin C levels in the DC arm were consistently higher than the levels seen in the VS arm, and these increases were associated with increased production of inflammatory and coagulation-related biomarkers. These data demonstrate that discontinuation of ART was associated with an increase in cystatin C, which may be attributable to activation of inflammatory mediators. The reasons for this increase and the association with other biomarkers of inflammation and kidney function and with clinical renal disease require further investigation.

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Appendix

Strategies for Management of Antiretroviral Therapy (SMART) Study Group

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SMART was initiated by the Terry Bein Community Programs for Clinical Research on AIDS (CPCRA) and implemented in collaboration with international coordinating centers in Copenhagen (Copenhagen HIV Programme), London (Medical Research Council, Clinical Trials Unit), Sydney (National Centre in HIV Epidemiology and Clinical Research) and Washington (CPCRA). Participating staff are listed below.

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*Increase in cystatin C defined as ≥ 0.15 mg/l increase; *Adjusted for baseline cystatin C;

Figure 1.
Cystatin C after randomisation in SMART

Figure 2.
Odds ratio of >1 SD (0.15 mg/dl) increase in cystatin C by 1 month after randomisation to SMART

Table 1

Characteristics at randomisation in the subset of participants in SMART with measured cystatin-C
 Characteristics of participants from SMART with measured cystatin-C: Comparison of DC and VS arms; all factors measured at randomisation

	Drug conservation N=249		Virologic suppression N=250	
	N	%	N	%
Gender	Female	72	74	29.6
Race				
	Black	131	121	48.4
	White	86	93	37.2
	Other	32	26	14.4
Mode of Infection ¹				
	Same sex	110	113	45.2
	Opposite sex	132	132	52.8
	IDU	29	25	10.0
	Blood	13	13	5.2
	Other	15	17	6.8
Hepatitis				
	B positive	11	8	3.2
	C positive	50	44	17.6
Prior AIDS	71	28.5	68	27.2
HIV RNA ≤ 400	142	57.0	136	54.4
Cardiovascular Disease risk Factors				
	Smoker	103	111	44.4
	Diabetes	22	24	9.6
	Prior cardiovascular disease	0	0	0
	Blood pressure treatment	60	76	30.4
	Lipid lowering treatment	41	45	18.0
Antiretroviral History				
	Naïve	16	15	6.0
	Protease-inhibitor exposed	170	158	62.8
	Non-nucleoside exposed	158	159	63.2

	Drug conservation		Virologic suppression	
	N	%	N	%
ART at Randomisation ²	182	73.1	188	75.2
	77	42.3	89	47.3
	99	54.4	90	47.9
	11	6.0	13	6.9
	On antiretrovirals			
	Protease inhibitor			
	Non-nucleoside			
	Protease inhibitor+non-nucleoside			

	Drug conservation		Virologic suppression	
	Median	IQR	Median	IQR
Age	44	38-52	44	38-50
CD4	532	432-720	550	430-743
CD4 nadir	250	133-350	267	167-386
HIV RNA viral load	2.60	1.70-4.00	2.60	1.88-3.75
Total cholesterol	181	156-208	183	157-213
HDL cholesterol	40	32-47	41	31-50
LDL cholesterol	103	85-126	107	86-131
Triglycerides	153	93-246	157	106-258
Cystatin-C	0.94	0.83-1.09	0.97	0.84-1.11

¹ Patients can be classified as belonging to more than one risk group

² % of those on antiretrovirals at randomisation

Table 2

Markers of renal function

	Month	DC		VS		p-value ¹
		N with data	Mean $\pm$ SD	N with data	Mean $\pm$ SD	
Estimated GFR ²	0	141	97.6 $\pm$ 23.2	135	93.4 $\pm$ 24.0	0.15
	4	107	98.7 $\pm$ 20.8	108	95.3 $\pm$ 23.2	0.92
	12	82	96.4 $\pm$ 21.5	91	94.8 $\pm$ 25.4	0.90
Creatinine	0	141	0.96 $\pm$ 0.24	135	1.05 $\pm$ 0.76	0.19
	4	107	0.93 $\pm$ 0.19	108	0.97 $\pm$ 0.23	0.63
	12	82	0.95 $\pm$ 0.20	91	1.00 $\pm$ 0.35	0.59
Albumin	0	133	4.14 $\pm$ 0.43	118	4.17 $\pm$ 0.41	0.52
	4	107	4.01 $\pm$ 0.44	94	4.01 $\pm$ 0.62	0.17
	12	73	4.09 $\pm$ 0.46	81	4.10 $\pm$ 0.49	0.33
Cystatin C	0	248	0.99 $\pm$ 0.26	245	1.01 $\pm$ 0.28	0.31
	4	205	0.86 $\pm$ 0.23	202	0.84 $\pm$ 0.31	0.026
	12	150	0.91 $\pm$ 0.32	133	0.91 $\pm$ 0.44	0.081

¹ Adjusted for values at randomisation

² GFR estimated by MDRD equation. Results were similar when GFR was estimated by Cockcroft-Gault.

Table 3

Pearson correlation coefficients for (a) marker values and cystatin C at randomisation; (b) marker values at randomisation and change in cystatin C between randomisation and month 1; (c) marker values at 1 month after randomisation and change in cystatin C between randomisation and month 1 and (d) change in marker values between randomisation and month 1 and change in cystatin C (randomisation to month 1)

Marker	(a) marker values and cystatin C at randomisation			(b) marker values at randomisation and change in cystatin C (randomisation to month 1)			(c) marker values 1 month after randomisation and change in cystatin C (randomisation to month 1)			(d) change in marker values (randomisation to month 1) and change in cystatin C (randomisation to month 1)		
	N	Correlation	p	N	Correlation	P	N	Correlation	p	N	Correlation	p-value
CD4 (cells/mm ³)	493	-0.035	0.43	493	0.090	0.045	488	-0.060	0.18	488	-0.125	0.0058
Log HIV-RNA (copies/ml)	493	0.116	0.0099	493	-0.128	0.0044	487	0.143	0.0015	487	0.277	<0.0001
HDL (mg/dl)	492	-0.220	<0.0001	492	0.029	0.52	491	-0.240	<0.0001	490	-0.196	<0.0001
LDL (mg/dl)	493	-0.040	0.37	493	-0.032	0.47	490	0.014	0.76	490	-0.016	0.72
Total Cholesterol (mg/dl)	493	0.029	0.51	493	0.029	0.51	492	0.063	0.16	492	-0.093	0.040
Log triglycerides (mg/dl)	493	0.181	<0.0001	493	0.057	0.21	492	0.213	<0.0001	492	-0.081	0.073
Log D-dimer (µg/mL)	490	0.124	0.0061	490	-0.105	0.020	493	0.168	0.0002	490	0.254	<0.0001
Log prothrombin fragment 1+2 (pmol/L)	483	-0.014	0.76	483	-0.064	0.16	489	-0.005	0.91	479	0.079	0.083
Log Amyloid A (mg/L)	493	0.046	0.31	493	-0.005	0.92	493	0.072	0.11	493	0.148	0.0010
Log hsCRP (µg/mL)	493	0.085	0.089	493	-0.034	0.45	493	0.133	0.0030	493	0.192	<0.0001
Log Amyloid P (µg/mL)	491	0.017	0.70	491	-0.029	0.52	492	0.075	0.099	490	0.064	0.16
Log IL-6	492	0.255	<0.0001	492	-0.033	0.46	491	0.285	<0.0001	490	0.121	0.0072