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Hepatitis C Seropositivity and Kidney Function Decline Among Women With HIV: Data From the Women's Interagency HIV Study

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Abstract

Background—How co-infection with hepatitis C virus (HCV) impacts on the trajectory of kidney function among HIV-infected patients is unclear. This study examined the effect of HCV on kidney function over time among women infected with HIV.

Study Design—Retrospective observational cohort

Setting and Participants—Study sample included participants from the Women's Interagency HIV Study who were HIV-infected and had received HCV antibody testing and serum creatinine measurement at baseline.

Predictor—HCV seropositivity

Outcomes and Measurement—Estimated glomerular filtration rate (eGFR) calculated from semi-annual serum creatinine measurements using the 4-variable Modification of Diet in Renal Diseases (MDRD) Study equation. Linear mixed models were used to evaluate the independent effect of being HCV seropositive on eGFR over time, adjusting for demographic factors, co-morbid conditions, illicit drug use, measures of HIV disease status, use of medications, and interactions with baseline low eGFR (<60 mL/min/1.73m²).

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Results—Of the 2,684 HIV-infected women, 952 (35%) were found to be HCV seropositive. For 180 women with CKD at baseline (eGFR <60 mL/min/1.73m²), being HCV seropositive was independently associated with a fully-adjusted net decline in eGFR of about 5% per year (95% CI: 3.2 to 7.2%), relative to women who were seronegative. In contrast, HCV was not independently associated with decline in eGFR among women without low eGFR at baseline (p<0.001 for interaction).

Limitations—The MDRD Study equation has not been validated as a measure of GFR among persons with HIV or HCV. Proteinuria was not included in the study analysis. Because the study is observational, the effects of residual confounding cannot be excluded.

Conclusions—Among HIV-infected women with CKD, co-infection with HCV is associated with a modest, but statistically significant decline in eGFR over time. More careful monitoring of kidney function may be warranted for HIV-infected patients with CKD who are also co-infected with HCV.

Keywords

hepatitis C virus; HIV; kidney diseases; women

Infection with chronic hepatitis C virus (HCV) has been associated with various types of glomerulonephritis (in particular membranoproliferative glomerulonephritis) in HIV-uninfected populations.¹ These diseases are difficult to treat and often result in poor outcomes.² Approximately 15–30% of HIV-infected individuals are also infected with HCV.³ Treatment for HCV among HIV-infected individuals is problematic because of treatment toxicities and poor response rates.⁴ As a result, co-infected HIV/HCV patients may be at risk for HCV-related kidney disease.

Although research is limited, it appears that co-infection with HCV among HIV-infected populations may confer additional risk for adverse kidney-related outcomes. In the setting of HIV, HCV has been associated with proteinuria⁵, and risk for developing acute renal failure⁶ as well as end-stage renal disease requiring renal replacement therapy.⁷ However, the exact impact of HCV on kidney function trajectories over time in HIV patients has not been fully characterized. One prior study of HIV-infected women found that creatinine clearance tended to be lower among women co-infected with HCV, however results were not statistically significant, perhaps because of a relatively short follow-up time.⁸ Precisely how HCV impacts the rate of kidney function decline over time is important to clinicians and policy makers in order to anticipate the burden of chronic kidney disease among HIV-infected patients.

The purpose of this study was to examine the associations between HCV infection and kidney function over time, adjusting for potential confounders. HCV seropositivity was hypothesized to be independently associated with a greater decline in kidney function over time among HIV-infected women.

Methods

Study participants

Women in this study were participants in the Women's Interagency HIV Study (WIHS), a multi-center, prospective cohort study of the natural history, including treatment, of HIV infection. Full details of recruitment and baseline cohort characteristics have been described previously.^{9 10} The WIHS enrolled women who were either infected with HIV (Western blot confirmed) or were at risk for HIV between October 1994 and November 1995, and again between October 2001 and September 2002 from six clinical consortia in the United

States: Chicago, Los Angeles, New York City (Bronx and Brooklyn), San Francisco Bay Area, and Washington D.C. This analysis included HIV-infected WIHS participants who had baseline HCV antibody screening test results and serum creatinine measured. Participants were evaluated every 6 months with physical exam and questionnaires: data from follow-up visits through September 30, 2006 was included in the analysis. Informed consent was obtained from all participants in accordance with the US Department of Health and Human Services guidelines and the institutional review boards of participating institutions.

Study variables

The outcome of interest was estimated glomerular filtration rate (eGFR), which was calculated using the 4-variable Modification of Diet in Renal Diseases (MDRD) study equation (non-IDMS traceable).^{11 12} Although this equation was not developed in cohorts with HIV, it is commonly used in clinical practice, and its use has been recommended in chronic kidney disease (CKD) screening guidelines for HIV- infected patients.¹³ Estimated GFR was used both as a continuous variable, and was also dichotomized at a threshold of $<60 \text{ mL/min/1.73m}^2$ to define participants with baseline CKD based on low eGFR.¹⁴ Because the distribution of eGFR was skewed, and also because the MDRD Study equation is known to be less accurate at higher values, the outcome was transformed using the natural logarithmic transformation (logGFR). This normalized the distribution, and also served to down-weight changes in eGFR that occurred in the lower versus the upper ranges, which in effect “de-emphasized” changes in the upper ranges of eGFR, which are less informative. With the outcome natural log transformed, regression coefficients estimates, multiplied by 100, are approximately interpretable as the percentage change in the average value of the outcome per unit increase in the predictor.¹⁵

The predictor of interest was baseline HCV serostatus, which was determined by HCV antibody testing (Ortho-Clinical Diagnostic, Raritan, NJ, USA). Demographic covariates used in the analysis were: age, race (African American v. non-African American), income (annual income $\leq$ v. $\geq$ \$12,000), and education (non-graduate v. graduate from high school). Clinical (not HIV-related) covariates included self-reported diagnosis of hypertension or diabetes, systolic and diastolic blood pressure, presence of hepatitis B surface antigen (HBsAg), liver enzymes (alanine and aspartate aminotransferases), recent (previous 6 months) illicit drug use and injection drug use. HIV-related variables included CD4 cell count (cell/mm^3 , analyzed in units of 100), log-transformed HIV viral load, diagnosis of AIDS, and use of highly active anti-retroviral therapy (HAART). Use of angiotensin-converting enzyme (ACE) inhibitors and potentially renal toxic medications were evaluated, including: adefovir, cidofovir, tenofovir, foscarnet, indinavir, acyclovir, gancyclovir, sulfamethoxazole/trimethoprim, amphotericin B, and pentamidine. Information on ACE inhibitor use was based on an open-ended question to participants, asking them to describe other non-HIV related medications, and review of pill bottles when patients brought them to study visits (as they were encouraged to do at later visits). Data on all variables, including medications, were collected every 6 months, with the exception of HCV antibody and HBsAg (baseline only).

Statistical Analysis

Demographic, clinical and laboratory parameters at baseline were compared by HCV serostatus using t- and chi-square tests as appropriate. Multivariate logistic regression was used to estimate the relative odds of having $\text{eGFR} < 60 \text{ mL/min/1.73m}^2$ at baseline by HCV serostatus, adjusting for other covariates.

Linear mixed models with participant-specific random intercepts and slopes were used to estimate the relationship between HCV seropositivity and decline in logGFR. These models take into account the correlation of outcome by subject, and allow for differing numbers of observations across participants arising from missed visits and variable patterns of creatinine measurement. Normality of the residuals as well as linearity of covariate effects on logGFR were examined using graphical methods. To account for underlying secular trends in mean logGFR common to all participants, time trends were modeled using linear, quadratic and cubic terms. The additional effect of HCV seropositivity on decline in logGFR, net of any underlying trend, was modeled by the interaction of time since study entry with baseline HCV serostatus; exploratory analyses revealed no substantial departure from linearity in this effect. To determine whether the effect of HCV on decline in logGFR was different in the subset of women low eGFR (<60 mL/min/1.73m²) at baseline, we tested for a difference in HCV (and other covariate) effects by baseline eGFR status by including interaction terms for all covariates in a model which only included post-baseline logGFR values. Because the interaction with HCV was statistically significant, we subsequently estimated the effects of HCV (and all other covariates) on decline in post-baseline logGFR using linear mixed models stratified by baseline eGFR less than or greater than mL/min/1.73m². We evaluated for the significance for all covariate interactions with low baseline eGFR by using a Wald test to test for the equality of slope coefficients. We also performed sensitivity analysis of the final linear mixed models substituting an interaction between HCV and baseline eGFR as a continuous variable.

In order to estimate the independent effect of HCV, we adjusted for age, race, poverty, diabetes, hypertension, measured blood pressure, HIV-related factors (AIDS, CD4 cell count, HIV viral load), HBsAg, use of nephrotoxic medications (as defined previously) and ACE inhibitors, and illicit drug use, updating time-dependent covariates as appropriate. In addition, to fully address confounding by other influences on decline in logGFR, we included interactions of time with race, diabetes, hypertension, illicit drug use, poverty, AIDS, and medications (HAART, renal toxic medications and ACE inhibitors). For diabetes, hypertension, and AIDS, the time-dependent interaction term was calculated as time since onset of the condition, while for illicit drug use and medication use, it was calculated as the current duration of use; for women currently free from a given exposure, the corresponding interaction term was set equal to zero. In order to create summary estimates of individual slopes, we also calculated rates of logGFR decline for each participant using the fixed and random effects estimated by the linear mixed model. This method borrows information across participants, efficiently shrinking the slope estimates for those with relatively sparse or noisy logGFR values toward the average slope for other participants with similar covariate values. Stata version 9.0 (College Station, TX, USA) was used for all analyses. A p-value of 0.05 was considered statistically significant.

Results

Of the 2,791 HIV+ women in WIHS, 2,702 (97%) had HCV serology results (Figure 1). Of those 2,702 women, 18 (0.7%) were missing baseline serum creatinine measurement and were also excluded from the analysis, leaving a final study population of 2,684 women. Women who were missing HCV serology or baseline serum creatinine ($n=107$, or 3.8% of the the original 2,791) were slightly older (mean age ($\pm$ SD): $37(\pm 8)$ v. $35(\pm 8)$, p -value=0.008) and more likely to use injection drugs (47 v. 33%, p -value=0.002) and were less likely to be on HAART at baseline (8% v. 14%, p -value=0.02). However, there were no significant differences in mean ALT, serum creatinine, or the proportion with $eGFR < 60$ mL/min/1.73m² between the women who were and were not excluded for missing data.

Of the 2,684 women in the final cohort, 945 (35%) were HCV seropositive. HIV/HCV co-infected women were more likely to be older, African American, poor, and drug users at baseline, and were less likely to report being on HAART (Table 1). Among the women with $\text{eGFR} \geq 60 \text{ mL/min/1.73m}^2$, those who were HCV seropositive were more likely to have a higher HIV viral load, have had an AIDS-defining illness, and have hypertension. Diabetes was not significantly more common among women with HCV. At baseline, 180 (6.7%) of the women in the sample had an $\text{eGFR} < 60 \text{ mL/min/1.73m}^2$. At baseline there was a higher prevalence of CKD among women who were HCV seropositive: 9.8% (93/945) versus 5% (87/1,739) ($p\text{-value} < 0.01$). Before adjustment, women with HCV appeared to be twice as likely to have prevalent CKD based on eGFR (unadjusted OR=2.07 [95% CI: 1.53 to 2.81]; $p\text{-value} < 0.001$). After adjustment for age, the relative odds was attenuated to 1.47 (95% CI: 1.07 to 2.01, $p\text{-value} = 0.017$), and after full adjustment for all the covariates (age, African American ethnicity, education, low income, diabetes, hypertension, AIDS, CD4 cell count, log HIV viral load, HAART, use of renal toxic medications, injections drug use and any illegal drug use) the estimate was further attenuated and no longer significant (OR=1.35 [95% CI: 0.93 to 1.97], $p\text{-value} = 0.11$).

The median follow-up time was 4.8 years (first and third quartiles: 3.5, 11 years) for women without CKD at baseline (based on eGFR), 4.5 years (first and third quartiles: 1, 11) for women with CKD. The median number of creatinine measurements was 9 (first and third quartiles: 4, 16) for women without baseline CKD, 6 (first and third quartiles: 2, 14) for women with CKD. There were no missing follow-up creatinine data for 2,429 (91%) of the women in the study; 100 (3%) were missing only one measurement, 155 (4%) were missing ≥ 2 measurements. The linear mixed models allowed for differing numbers of observations across participants arising from missed visits.

Based on calculation of individual slopes from the linear mixed models, the majority of HIV infected women had either improvement or no change, or only mildly decreased eGFR over time, regardless of HCV status (Figure 2). However, the women who were also HCV seropositive were more likely to experience a decline in eGFR over time, and experience higher rates of decline.

In the combined data, we found that the effect of HCV on net decline in eGFR differed significantly by baseline eGFR status, so the linear mixed model analyses were stratified by $\text{eGFR} < 60 \text{ mL/min/1.73m}^2$. Among the women with CKD at baseline, HCV seropositivity was statistically significantly associated with a net decrease in eGFR of 5.6% per year after adjustment for other covariates (Table 2). This effect was greater than the effect observed for hypertension, and slightly less than the effect for diabetes. In contrast, for women with a baseline $\text{eGFR} \geq 60 \text{ mL/min/1.73m}^2$, HCV did not appear to have a significant effect in change in eGFR over time. Results from the sensitivity analysis using an interaction term for HCV and eGFR as a continuous variable (as opposed to dichotomous) were also significant.

Discussion

In this study of HIV-infected women, HCV seropositivity was associated with a slightly lower eGFR over time in the women who had $\text{eGFR} < 60 \text{ mL/min/1.73m}^2$ at baseline. In contrast, it did not appear to be associated with a lower eGFR over time among women whose had a baseline $\text{eGFR} \geq 60 \text{ mL/min/1.73m}^2$. The association between HCV seropositivity and decline in renal function remained statistically significant even after adjusting for demographic factors, illicit drug use, diabetes, hypertension, parameters of HIV disease, and medication use (HAART, nephrotoxic medications and ACE inhibitors). This is the first study to our knowledge to find an association between HCV seropositivity and longitudinal eGFR among HIV infected women with CKD.

There are several possible explanations for the association between HCV infection and renal decline. Renal decline could be caused by HCV-induced glomerular disease. Studies support an association between HCV and various types of glomerulonephritis, (particularly membranoproliferative glomerulonephritis) and cryoglobulinemia.^{16–20} Alternatively, HCV could be accelerating renal disease associated with HIV, diabetes and hypertension. In non-HIV infected populations, HCV has been associated with more rapid decline in renal function in diabetics.²¹ Studies have linked HCV to atherosclerosis and atherosclerotic diseases both in HIV and non-HIV infected populations.^{22–25} It is unlikely that the decline in renal function could be related to hepatorenal syndrome in the setting of HCV-induced cirrhosis: only 1% of participants reported having cirrhosis during later years of the survey (question was not asked at baseline). And finally, given the observational nature of the study, it is still possible that the findings could be caused by residual confounding.

Our finding that HCV was associated with eGFR decline only in women with eGFR <60 mL/min/1.73m² is somewhat surprising, but also consistent with prior literature. A large study of veteran healthcare users found that being HCV seropositive was associated with increased risk for developing end-stage renal disease, but was not associated with prevalent CKD (defined as eGFR <60 mL/min/1.73m²).²⁶ The authors hypothesized that patients with HCV infection who reach CKD may experience a more rapid decline to end-stage renal disease (and renal replacement therapy) or death, and therefore fewer numbers are observed to have eGFR in the CKD range at any one time. This study appears to support this hypothesis by showing that among the HIV-infected women who had low eGFR at baseline, those who were HCV seropositive had significantly greater declines in eGFR over time compared with those who were seronegative.

A major limitation of this study is the use of the MDRD Study equation to estimate GFR. This equation has not been independently validated as a measure of GFR among persons with HIV nor HCV. However, the MDRD Study equation is widely incorporated into clinical care, and has been recommended in guidelines for screening for CKD in HIV populations.¹³ Since our study was based among all HIV-infected women, principle results could only be influenced if the MDRD Study equation were selectively inaccurate among participants with HCV, which is possible given muscle wasting associated with chronic liver disease. A number of studies comparing serum creatinine to direct GFR measurement in cirrhotic patients have shown that creatinine may overestimate true creatinine clearance (i.e. appear normal in the setting of diminished GFR).^{27–28} This should, in theory, bias our findings in the opposite direction. Regardless, research is needed to determine the accuracy of GFR estimating equations in the setting of HIV and HCV.

An additional limitation is that HCV antibody status was used rather than HCV RNA testing. However, prior research has shown that the majority of HIV-infected individuals with a positive screening HCV antibody test will have chronic HCV by RNA testing²⁹, and seronegative HCV infection is relatively rare.³⁰ We did not adjust for current use of anti-HCV therapy, however prior analyses of this cohort have demonstrated that relatively few WIHS participants who tested positive for HCV antibody reported ever receiving treatment for HCV.³¹ The ascertainment of non-HIV related medication use (such as ACE inhibitors) was likely incomplete; however, misclassification should be non-differential with regards to HCV status. We did not include measures of diabetic control such as blood glucose or hemoglobin A1C in the analysis, however, a relatively small percentage of patients were diagnosed as having diabetes. Finally, a major limitation of our analysis was that it did not include proteinuria as it was not routinely tested on our sample, and therefore we cannot make broader inferences about the prevalence and incidence of true CKD.

In summary, this study found that among HIV-infected women with CKD (based on eGFR <60 mL/min/1.73m²), being HCV seropositive was associated with greater declines in eGFR over time, and that this association was independent of co-morbidities, substance abuse and use of renal-toxic medications. More research is needed to confirm these findings and to explore potential mechanisms underlying this association. Clinicians should be aware that HIV infected individuals with CKD may warrant more careful monitoring of their renal function over time if they are co-infected with HCV.

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Figure 1.
Flowchart of Study Population Selection

Figure 2.
Distribution of Rates of eGFR Decline by HCV Status (Based on Estimated Individual Slopes)

Table 1
Baseline Characteristics of Sample Population by Estimated Glomerular Filtration Rate and HCV Status

	eGFR $\geq$ 60 mL/min/1.73m ²			eGFR<60 mL/min/1.73m ²		
	HCV seronegative n=1,652 number (%) ^a or mean ($\pm$ SD)	HCV seropositive n=852 number (%) ^a or mean ($\pm$ SD)	p-value	HCV seronegative n=87 number (%) ^a or mean ($\pm$ SD)	HCV seropositive n=93 number (%) ^a or mean ($\pm$ SD)	p-value
Age	33 ($\pm$ 8)	39 ($\pm$ 6)	<0.001	39 ($\pm$ 9)	42 ($\pm$ 7)	0.008
African American	908 (55%)	513 (60%)	0.01	31 (36%)	44 (47%)	0.1
Non-high school graduate	580 (35%)	374 (44%)	<0.001	27 (31%)	37 (40%)	0.2
Income $\leq$ \$12,000/yr	868 (54%)	595 (72%)	<0.001	45 (52%)	65 (71%)	0.009
Injection drugs use	79 (5%)	707 (83%)	<0.001	7 (8%)	80 (86%)	<0.001
Any drug use	424 (26%)	437 (51%)	<0.001	21 (24%)	49 (53%)	<0.01
Diabetes diagnosis	64 (4%)	42 (5%)	0.2	8 (9%)	9 (10%)	0.9
Hypertension diagnosis	166 (10%)	180 (21%)	<0.001	29 (33%)	36 (39%)	0.5
Systolic blood pressure (mmHg)	114 ($\pm$ 14)	117 ($\pm$ 17)	<0.001	122 ($\pm$ 21)	122 ($\pm$ 22)	0.9
Diastolic blood pressure (mmHg)	73 ($\pm$ 10)	76 ($\pm$ 12)	<0.001	78 ($\pm$ 13)	80 ($\pm$ 13)	0.2
HBsAg ^b positive	42 (3%)	30 (4%)	0.2	2 (2%)	2 (2%)	0.9
AST ^c (IU/L)	31 ($\pm$ 32)	58 ($\pm$ 69)	<0.001	34 ($\pm$ 24)	58 ($\pm$ 56)	<0.001
ALT ^d (IU/L)	29 ($\pm$ 35)	47 ($\pm$ 51)	<0.001	30 ($\pm$ 30)	41 ($\pm$ 42)	0.03
CD4 cell count (cells/mm ³)	421 ($\pm$ 292)	417 ($\pm$ 332)	0.8	344 ($\pm$ 312)	362 ($\pm$ 276)	0.7
log HIV viral load (copies/mL)	3.9 ($\pm$ 1.2)	4.2 ($\pm$ 1.1)	<0.001	4.5 ($\pm$ 1.0)	4.2 ($\pm$ 1.1)	0.09
AIDS	325 (20%)	295 (35%)	<0.001	28 (32%)	38 (41%)	0.2
HAART ^e	330 (20%)	51 (6%)	<0.001	6 (7%)	2 (2%)	<0.01
Tenofovir Use	21 (1%)	3 (0.4%)	0.03	0	0	---
Foscarnet Use	2 (0.1%)	0 (0%)	0.3	0	0	---
Indinavir Use	17 (1%)	6 (0.7%)	0.4	1 (1%)	2 (2%)	0.6
Acyclovir Use	137 (8%)	76 (9%)	0.6	12 (14%)	5 (5%)	0.06
Gancyclovir Use	3 (0.2%)	1 (0.1%)	0.7	0	0	---
Bactrim Use	528 (32%)	375 (44%)	<0.001	41 (48%)	54 (59%)	0.1
Pentamidine Use (IV)	12 (0.7%)	8 (0.9%)	0.6	2 (2%)	0	0.1
ACE Inhibitor Use ^f	14 (0.7%)	3 (0.4%)	0.3	1 (1%)	2 (3%)	0.5

^aNumbers and percentages may not sum perfectly due to missing data and rounding;

^b Hepatitis B virus surface antigen

^c Aspartate aminotransferase

^d Alanine aminotransferase

^e Highly active anti-retroviral therapy

^f Angiotensin-converting enzyme inhibitor use, results based on visit 5 data since no reports of ACE inhibitor use at baseline visit

Table 2

Longitudinal Differences in eGFR Associated with HCV and Other Covariates (Results of the Fully Adjusted Linear Mixed Models)^a

	eGFR $\geq$ 60 mL/min/1.73m ²			eGFR<60 mL/min/1.73m ²		
	%Δ/yr	95% CI	p-value	%Δ/yr	95% CI	p-value
HCV seropositive	-0.6	(-1.3 to 0.1)	0.08	-5.2	(-3.2 to -7.2)	<0.001
Age at cohort entry	0.01	(-0.04 to 0.05)	0.8	-0.1	(-0.3 to 0.01)	0.06
African American	-1	(-1.7 to -0.4)	0.002	0.1	(-2.4 to 2.6)	0.9
Non-high school graduate	0.5	(-0.2 to 1.1)	0.2	-2.2	(-4.9 to 2.6)	0.1
Income <\$12,000/year	0.5	(-0.3 to 1.2)	0.2	-1.1	(-1.6 to 3.8)	0.4
Diabetes diagnosis	-1.6	(-2.7 to -0.5)	0.004	-7.0	(-10.4 to -3.5)	<0.001
Hypertension diagnosis	-1	(-1.8 to -0.3)	0.008	-4.0	(-6.3 to -1.7)	0.001
Systolic blood pressure ^c	0.3	(-0.02 to 0.8)	0.2	0.1	(-1.8 to 2.0)	0.9
Diastolic blood pressure ^c	-0.5	(-1.2 to 0.3)	0.2	-0.2	(-3.0 to 2.6)	0.9
AIDS	-1	(-1.7 to -0.3)	0.003	2.4	(0.1 to 4.7)	0.04
CD4 cell count	-0.2	(-0.5 to 0.1)	0.2	0.9	(-0.4 to 2.2)	0.2
log HIV viral load	0.5	(-0.2 to 1.1)	0.2	1.1	(-1.6 to 3.8)	0.4
HAART	1.7	(0.9 to 2.5)	<0.001	-2.0	(-4.9 to 1.0)	0.2
HBSAg positive	-0.3	(-2.4 to 1.9)	0.8	-15.1	(-30.3 to 0.04)	0.05
Use of renal toxic medications	-2	(-2.8 to -1.2)	<0.001	-3.6	(-6.4 to -0.9)	0.009
ACE inhibitors	1.1	(-2.6 to 4.7)	0.6	-0.6	(-12.3 to 11.2)	0.9
Injection drug use	0.6	(-1.4 to 2.6)	0.6	9.1	(1.4 to 16.8)	0.02
Any drug use	-0.7	(-1.5 to 0.1)	0.1	-0.9	(-3.7 to 2.0)	0.5

^aTrend covariates (interactions with time) shown, with the exception of CD4 count, log HIV viral load, systolic and diastolic blood pressure which are treated as simple time-dependent covariates; all associations shown are net of underlying secular trends

^{**} Wald test for equality of slopes

[†] Analyzed in units of 10 mmHg

[‡] Analyzed in units of 100 cells/mm