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HIV Infection, Antiretroviral Therapy Initiation and Longitudinal Changes in Biomarkers of Organ Function§

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Abstract

Background—HIV is associated with end-organ diseases of aging *via* unclear mechanisms. Longitudinally assessing how HIV infection and ART initiation affect biomarkers of end organ function/disease could clarify these mechanisms. We investigated longitudinal changes in clinical biomarkers following 1) HIV infection and 2) ART initiation with evidence of viral suppression.

Methods—Cohort: Veterans Aging Cohort Study Virtual Cohort (VACS VC). VACS VC is a longitudinal cohort of HIV infected (HIV+) and race-ethnicity, sex, age, and clinical site-matched uninfected Veterans enrolled in the same calendar year. Inclusion criteria: a negative and successively positive (>six months) HIV antibody test. We used Wilcoxon signed-rank tests to analyze 1) the effect of HIV infection on lipids, renal, hepatic and hematologic/cardiovascular biomarkers and 2) whether ART initiation with HIV-1 RNA<500 cpm reverts any changes back to pre-HIV levels

Results—422 Veterans had at least 1 biomarker measurement available prior to HIV infection and prior to ART initiation. 297 had at least 1 biomarker measurement available prior to HIV infection and after ART initiation with evidence of viral suppression. Mean age prior to HIV infection was 43 years. HIV infection was associated with reduction in total cholesterol, HDL cholesterol, LDL cholesterol, serum albumin, ALT, platelet count, hemoglobin and elevation of FIB-4 score and triglycerides. These changes occurred without significant changes in BMI. ART initiation (with HIV-1 RNA<500cpm) did not reverse alteration in triglycerides, LDL cholesterol, hemoglobin, or FIB-4 to pre-HIV infection levels.

Conclusions—HIV infection is associated with longitudinal changes in serum levels of several biomarkers of end-organ function/disease and mortality. Multiple biomarkers (triglycerides, LDL cholesterol, hemoglobin, and FIB-4) remain altered from levels prior to HIV infection levels even following initiation of ART and evidence of viral suppression. These results give insights into

underlying mechanisms of increased risk for aging-related chronic diseases in the context of HIV infection.

Keywords

Clinical biomarkers; chronic diseases of aging; HIV infection; lipids

INTRODUCTION

HIV infection has been linked to several end organ diseases associated with aging (e.g., coronary heart disease, cancer, liver and kidney diseases [1–5] *via* mechanisms not fully understood. Longitudinally analyzing the association between HIV infection and biomarkers [6] associated with end-organ dysfunction or disease could provide insights into these mechanisms. However, prior studies have been cross-sectional and/or focused on biomarker changes associated with antiretroviral therapy (ART) initiation or regimen [7–9]. Few studies have examined the changes associated with HIV infection itself or compared biomarker levels before HIV infection to those after ART initiation [10–13]. These studies were often limited by small sample sizes, a narrow scope of biomarkers examined, and inconsistent results. Improving our understanding of how HIV infection itself impacts end organ diseases requires longitudinal assessment of biomarkers spanning multiple organ systems from time points before HIV infection and after ART initiation. Determining whether ART can return biomarker levels to those present prior to HIV infection remains a central question with important clinical and scientific implications for those aging with HIV.

Our objectives, therefore, were to compare multiple biomarkers of and risk factors for end organ disease (e.g., lipids, glucose, liver, hematologic, and renal function tests) before and after two important events: 1) HIV infection and 2) ART initiation with evidence of viremia reduction.

METHODS

Study Sample

The Veterans Aging Cohort Study Virtual Cohort (VACS VC) has been described in detail elsewhere [14]. Briefly, the VACS VC is a cohort (longitudinal, prospective) of HIV infected and sex, age, race-ethnicity, and geographic region-matched uninfected Veterans enrolled in the same calendar year [14]. For the current study, Veterans in the VACS VC were included if they had a documented negative and successively (greater than six months later) positive HIV antibody test.

Data for this cohort were extracted from the Immunology and Clinical Case Registries, National Pharmacy Benefits Management database, Veteran's Administration (VA) Decision Support System, Corporate Data Warehouse, Corporate Franchise Datacenter, National Patient Care Database, and patient treatment files.

Baseline was defined as the date of the biomarker measurement immediately preceding the date of last negative HIV antibody test. Data were obtained at three time points (Fig. 1): the date closest to but before the date of the last negative HIV antibody test (pre-HIV infection),

2) the date closest to but before the date of first ART prescription (pre-ART), 3) the date closest to but after the date of first ART prescription with evidence of HIV-1 RNA reduction (HIV-1 RNA <500 copies/mL; post-ART). These specific time points were selected to enable comparison to prior work [11]. For all participants who seroconverted but did not initiate ART, the pre-ART date was the date of last follow up in the VA health care system.

Independent Variable

Independent variables were constructed to describe two intervals between three time points: 1) pre-HIV infection to pre-ART initiation and 2) pre-HIV infection to post-ART initiation with evidence of HIV-1 RNA reduction (Fig. 1).

Dependent Variables

Dependent variables were defined as the change in levels of biomarkers associated with morbidity and mortality in the period 1) pre-HIV infection and pre-ART initiation and 2) pre-HIV infection and after ART initiation and HIV-1 RNA <500 copies/mL. We selected the following biomarkers: body mass index (BMI), high and low density lipoprotein (HDL, LDL) cholesterol, total cholesterol, triglycerides, non-HDL-cholesterol (total cholesterol minus HDL cholesterol), albumin, alanine transaminase (ALT), aspartate transaminase (AST), AST/platelet ratio (APRI = (AST[U/L]/AST upper limit of normal (40 U/L))/platelets [$10^9/L$])[15], liver fibrosis index 4 (FIB-4 = age (years) $\times$ AST [U/L]/(platelets [$10^9/L$] $\times$ (ALT [U/L])^{1/2})[16], bilirubin, blood glucose, hemoglobin A1c (HbA1c), blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), systolic and diastolic blood pressure (SBP, DBP), heart rate, hemoglobin, and platelet counts.

ART initiation was determined based on pharmacy prescription data. Prior work in the VACS demonstrates that 96% of Veterans receive all of their ART medications from the VA.¹⁴ Age, sex, and race/ethnicity were obtained from administrative data. BMI was obtained from Health-Factors data, which are collected in a standardized form within the VA. Blood pressure (BP) was calculated using the average of three outpatient (routine) clinical BP measurements. Lipids, hepatic, renal, and hematologic biomarkers were obtained from clinical laboratory data.

Covariates

We collected data on relevant comorbidities for lipids (HMG CoA reductase inhibitor and gemfibrozil prescription, diabetes mellitus) hepatic markers (hepatitis C, alcohol abuse or dependence, diabetes), and renal markers and blood pressure (antihypertensive therapy, diabetes).

HMG CoA reductase inhibitor, gemfibrozil and antihypertensive therapy use were assessed using pharmacy prescription data. Cardiovascular disease was present if there was 1 inpatient and/or 2 outpatient ICD-9 codes for coronary heart disease (410.xx–414.xx), congestive heart failure (428.XX, 429.3, 402.01, 402.11, 402.91, 425.XX), or stroke (433.X1, 434.X1, 436 (inpatient), 438.X (outpatient.)). Diabetes was diagnosed using a previously validated metric incorporating glucose measurements, anti-diabetic agent use, and/or 2 outpatient and/or 1 inpatient ICD-9 codes for this diagnosis [17]. Hepatitis C

infection (HCV) was present given a positive HCV antibody test or 2 outpatient and/or 1 inpatient ICD-9 code [18]. Alcohol dependence or abuse was determined using ICD-9 codes [19].

Analysis

We compared median changes in biomarkers 1) from pre-HIV infection to pre-ART initiation (analysis 1) and 2) from pre-HIV infection to post-ART initiation with evidence of HIV-1 RNA reduction (analysis 2), separately, using the Wilcoxon signed-rank test. To determine whether changes in biomarkers associated with analysis 1 occurred soon after infection, we examined the participants who were in the first tertile of duration of time between last negative HIV antibody date and pre-ART biomarker measurement date (median time 1.8 years). The percentage changes in median biomarker levels in analysis 1 were calculated as the difference between pre-HIV and pre-ART biomarker levels divided by pre-HIV biomarker levels. We performed additional sensitivity analyses limiting the sample to participants with biomarker data available at all three time points (pre-HIV infection, pre-ART and post-ART). To minimize confounding in our assessment of lipid changes, we conducted secondary analyses restricting the sample to participants without a prescription for HMG-CoA reductase inhibitors/gemfibrozil, or diabetes at any of the time points being compared. Similarly, for liver related biomarkers, we restricted the sample to those without diabetes, alcohol abuse or hepatitis C.

RESULTS

Seven hundred and twenty eight people had a negative and successively (greater than six months later) positive HIV antibody test. We excluded 164 participants because they did not have at least one pre-HIV infection biomarker measurement and one pre-ART or post-ART biomarker measurement. Of the remaining 564 participants, 422 had 1 biomarker measured prior to HIV infection and prior to ART initiation and 297 had 1 biomarker measured prior to HIV infection and after ART initiation and HIV-1 RNA reduction. The characteristics of our study sample prior to HIV infection as well as those who were excluded are presented in Table 1. Just over 60% of the participants were African-American, one-third was white and 96% were male (Table 1). Comorbidities such as alcohol abuse/dependence, smoking, and hepatitis C were common whereas cardiovascular disease and diabetes were not (Table 1). For participants in analysis 1, the median time of HIV infection was 3.5 years. For participants in analysis 2, the median number of years of ART exposure was 1.3 years. Median CD4+ T-cell count during the pre-ART period was 315 cells/mm³ and in the post-ART period (with HIV RNA<500), it was 477 cells/mm³ among participants who had available CD4+ T-cell count data in both periods.

HIV infection without ART initiation was associated with significant changes in lipids, hepatic and hematologic biomarkers ($p<0.01$ for all; Table 2). Specifically, HDL-cholesterol, LDL-cholesterol, total cholesterol, albumin, ALT, platelet count and hemoglobin decreased while triglycerides, and liver scores (APRI and FIB-4) increased. These alterations occurred without significant BMI changes in the cohort (Table 2). Analyzing tertiles of duration of time between last negative HIV antibody date and pre-ART

biomarker measurement date, we observed that changes in HDL-cholesterol, triglycerides, ALT and hemoglobin were present within 1.8 years of HIV infection i.e. among those in the first (shortest duration) tertile (Fig. 2). For these participants, median HIV-1 RNA level and CD4 cell counts closest to the time of the biomarker measurement were 36000 copies/ml and 371 cells/mm³, respectively.

HIV infection followed by ART initiation and a reduction in HIV-1 RNA to less than 500 copies/ml did not result in a complete normalization of all biomarkers (i.e. biomarkers did not return to pre-HIV levels), (Table 3). Compared with pre-HIV infection levels, LDL cholesterol and hemoglobin remained significantly lower and FIB-4 and serum triglycerides remained significantly higher even after ART initiation with viral suppression (<500 copies/mL) (Table 3).

In secondary analyses, similar biomarker changes occurred among participants with biomarker data available at all three time points (i.e., pre-HIV infection, pre-ART and post-ART) though sample sizes were reduced (Appendix 1). When we excluded participants with relevant comorbid diseases (diabetes, hepatitis C, alcohol abuse and dependence) or medications (HMG CoA reductase inhibitors, gemfibrozil, antihypertensive medication), significant changes in biomarker levels associated with recent HIV infection remained except for LDL, total cholesterol and ALT (Appendix 2).

DISCUSSION

HIV infection without ART initiation is associated with decreased LDL-cholesterol, HDL-cholesterol, total cholesterol, albumin, ALT, hemoglobin and platelet count, and increased triglycerides, APRI and FIB-4 score. The majority of these changes were evident within 1.8 years of infection, without significant BMI changes in the cohort, and with a median CD4 cell count of 371 cells/mm³. HIV infection followed by ART initiation and viral suppression to <500 copies/mL was associated with normalization (i.e. return to pre-HIV infection levels) of some but not all of the altered biomarkers.

Our finding that HIV infection is associated with significant changes in lipid, albumin and hematologic biomarker levels is consistent with prior studies [10, 13, 20, 21, 29, 30]. However, none of these earlier studies specifically focused on triglycerides and hepatic biomarkers, nor did they examine multiple biomarkers spanning multiple organ systems. Looking simultaneously across multiple organ systems, particularly prior to ART initiation encourages more unified hypotheses about the intersection between HIV pathogenesis and co-morbid diseases. Moreover, this study also provides new evidence that 1) changes in these biomarkers can happen relatively quickly (i.e., < 2 years), 2) these changes can occur with moderate reduction in median CD4 cell count, and 3) ART combined viral suppression to <500 copies/mL is associated with a normalization (i.e. return to pre-HIV infection levels) of some but not all biomarkers. We cannot say definitively from these data whether alterations that begin within 1.8 years, worsen over time in the same untreated individual since our study only examined 1 time point per person during the untreated phase of HIV infection.

Statistically significant alterations in some biomarkers may have been more clinically relevant (e.g. lipids changes) than others (e.g. platelets) therefore looking beyond individual biomarker alterations may be informative. Presently, the exact mechanism underlying the association between HIV infection and many aging-related chronic diseases remains unknown. However, our findings suggest that HIV infection prior to ART initiation is not only associated with changes in individual risk factors (e.g., serum lipids) but perhaps more importantly, that the changes in multiple biomarkers across several organ systems may be indicative of a pro-inflammatory response. For example, we observed decreases in the negative acute phase reactants, HDL-cholesterol [22] and albumin [23]. Serum triglycerides, which increased following infection in this study, have been correlated with interferon α , a pro-inflammatory cytokine [24]. Anemia and dyslipidemia, which are both independently associated with acute myocardial infarction [25] and mortality [26], are also strongly correlated with biomarkers of inflammation (e.g., interleukin-6, D-dimer, and soluble CD14) in this population [27]. Thrombocytopenia, which has previously been associated with HIV infection [28] as well as other viral infections, may represent an auto-immune platelet destruction [21], impaired platelet production and/or altered platelet activation and consumption [29, 30]. Alternatively, many of these changes could be linked with impairment in hepatic function. In this study, although liver biomarkers were in the normal range, HIV infection was associated with increases in levels of APRI and FIB4, derived biomarkers of hepatic fibrosis.

While the results from this study should be interpreted cautiously given the relatively small sample sizes for certain biomarkers, our findings do provide new insights, which may be relevant to an important clinical question. Observational data suggest that an excess risk of serious non-AIDS events, including acute myocardial infarction, exists among HIV infected people with sustained low levels of HIV-1 RNA over time compared with uninfected people [25, 31]. Our results are consistent with these observations because ART initiation and a reduction of HIV-1 RNA levels to less than 500 copies/mL did not normalize all biomarkers of end organ disease (i.e. return to pre-HIV levels), many of which are associated with non-AIDS events. If the changes in these biomarkers associated with HIV infection are indicative of an underlying pro-inflammatory state, it is possible that successful ART may not completely eliminate the excess risk of end organ disease that is associated with HIV infection.

This study has limitations that warrant comment. Biomarker availability was not uniform for each participant across study time intervals because these biomarkers were ordered as part of clinical care. Selection bias may have been introduced if participants with more extreme biomarker changes between periods were more likely to have biomarker data available than those with less extreme biomarker changes. Fasting status was not ascertainable, which may affect interpretation of certain metabolic biomarkers. However, it is the practice of the VA and other clinical centers to recommend fasting to patients who are undergoing metabolic panel evaluations. Moreover we focus on changes in biomarker levels over time and not absolute biomarker levels. We do not have reason to believe that majority of subjects had a fasting status that differed from one biomarker measurement to the next. The fact that many of the changes we observed were consistent with prior work is also reassuring. Assay sensitivity limitations did not permit the use of lower HIV-1 RNA thresholds (<40

copies/mL) to define HIV suppression. It is unlikely, that ART use during the pre-ART phase was not captured since prior work in the VACS demonstrates that 96% of Veterans receive all of their ART medications from the VA [14]. FIB-4 changes with infection may have been attributable to age though APRI findings support the FIB-4 data. Biomarkers of immune activation and inflammation, which were not obtained as part of routine clinical care, were not available for analysis in this study. Our sample was largely male. Thus our observations may not generalize to female HIV seroconverters. Likewise, this cohort is likely more generalizable to that portion of the US HIV population that is minority and has a high burden of comorbid diseases.

In conclusion, HIV infection was associated with changes in lipids, albumin, ALT, APRI, FIB-4, platelets, and hemoglobin in a sample in which substantial weight loss was uncommon. The majority of these changes were evident within 1.8 years of infection. HIV infection followed by ART initiation and HIV-1 RNA of less than 500 copies/mL was associated with normalization (i.e. return to pre-HIV infection levels) of some but not all of the altered biomarkers. LDL cholesterol and hemoglobin remained significantly lower and FIB-4 and serum triglycerides remained significantly higher. If confirmed in other studies, these data contribute to our understanding of potential mechanisms linking HIV infection and the increased risk of aging-related chronic diseases.

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APPENDICES

Appendix 1

Effects of HIV infection and ART initiation on biomarkers of organ function among participants with available biomarkers measured during all three time points (pre-HIV, pre-ART, post-ART with HIV-1 RNA<500 copies/mL).

Biomarkers	N	Median (IQR)		
		Pre-HIV	Pre-ART (Analysis 1 Cohort)	Post-ART HIV RNA<500 (Analysis 2 Cohort)
Average median duration, years				
BMI	38	23.8 (4.5)	24.5 (4.5)	25.1 (4.5)
Lipids (mg/dL)				
HDL cholesterol	22	40.5 (31.0)	37.0 (16.0)	39.0 (11.0)
Non-HDL cholesterol	21	120 (68.0)	109.0 (43.0)	131.2 (51.0)
LDL cholesterol	23	96.2 (61.0)	79.0 (29.6)	89.0 (53.0)

Biomarkers	N	Median (IQR)		
		Pre-HIV	Pre-ART (Analysis 1 Cohort)	Post-ART HIV RNA<500 (Analysis 2 Cohort)
<i>Triglycerides</i>	22	105.5 (104.0)	120.0 (122.0)	124.0 (135.0)
<i>Total cholesterol</i>	27	178.0 (69)	161.0 (57.0)	182.0 (54.0)
Hepatic				
<i>Albumin (g/dL)</i>	23	4.1 (0.6)	3.9 (1.1)	3.9 (0.8)
<i>ALT (IU/L)</i>	44	38 (50.0)	31.0 (15.0)	26.7 (23.5)
<i>AST (IU/L)</i>	44	34.5 (28.5)	30.0 (16.0)	27.5 (17.1)
<i>APRI</i>	44	0.4 (0.3)	0.3 (0.2)	0.3 (0.2)
<i>FIB-4</i>	44	1.0 (0.7)	1.3 (0.8)	1.2 (0.7)
<i>Bilirubin (mg/dL)</i>	25	0.6 (0.5)	0.6 (0.3)	0.6 (0.4)
<i>Glucose (mg/dL)</i>	43	97.0 (27.0)	94.0 (23.0)	99.0 (23.0)
<i>HbA1c (%)</i>	3	5.9 (1.2)	6.0 (0.8)	5.5 (5.2)
Renal				
<i>BUN (mg/dL)</i>	43	13.0 (5.0)	13.0 (5.0)	14.0 (7.0)
<i>Creatinine (mg/dL)</i>	44	1.0 (0.2)	1.0 (0.3)	0.9 (0.3)
<i>eGFR (mL/min/1.73m²)</i>	44	99.0 (29.6)	93.3 (32.8)	97.5 (43.5)
Cardiovascular/Hematologic				
<i>SBP (mmHg)</i>	62	125.8 (24.3)	131.2 (19.7)	126.5 (13.3)
<i>DBP (mmHg)</i>	62	77.3 (16.7)	78.7 (11.0)	76.3 (15.3)
<i>Heart rate (beats/second)</i>	68	75.5 (20.5)	79.0 (23.0)	80.0 (16.5)
<i>Hemoglobin (g/L)</i>	40	14.5 (2.3)	13.6 (1.9)	13.9 (2.0)
<i>Platelets (count/mL)</i>	44	227.0 (79.5)	236.5 (70.5)	242.5 (82.5)

HIV-human immunodeficiency virus; ART-antiretroviral therapy; BMI-body mass index; HDL-high density lipoprotein; LDL-low density lipoprotein; ALT-alanine transaminase; AST-aspartate transaminase; FIB-4-liver fibrosis index-4; HbA1c-hemoglobin A1c; BUN-blood urea nitrogen; eGFR-estimated glomerular filtration rate; SBP-systolic blood pressure; DBP-diastolic blood pressure.

Post ART data represent closest biomarker measurement after HIV-1 RNA <500 copies/mL.

Appendix 2

Effects of HIV infection on biomarkers of organ function accounting for medications and comorbid disease status (Analysis 1 cohort).

Biomarkers	N	Median (IQR)		Median Difference (IQR)	P-Value
		Pre-HIV	Pre-ART	Pre-HIV vs Pre-ART	
BMI	90	24.1 (5.0)	24.2 (5.9)	0.0 (3.0)	0.60
Lipids (mg/dL)					
HDL cholesterol	54	43.6 (21.0)	34.7 (17.0)	-9.8 (18.0)	<0.01
Non HDL cholesterol	54	117.0 (38.0)	124.5 (28.1)	1.5 (40.1)	0.25
LDL cholesterol	52	97.0 (35.6)	98.2 (34.7)	-0.5 (28.3)	0.73
Triglycerides	63	95.0 (55.0)	116.0 (91.0)	22.0 (110.0)	0.03
Total cholesterol	75	168.0 (44.0)	160.0 (37.0)	-1.0 (37.0)	0.16

Biomarkers	N	Median (IQR)		Median Difference (IQR)	P-Value
		Pre-HIV	Pre-ART	Pre-HIV vs Pre-ART	
Hepatic					
Albumin (g/dL)	46	4.2 (0.3)	4.0 (0.7)	−0.2 (0.8)	<0.01
ALT (IU/L)	78	30.5 (34.0)	27.5 (25.0)	1.0 (23.0)	0.52
AST (IU/L)	78	25.5 (18.0)	28.0 (20.0)	3.5 (15.0)	0.17
APRI	78	0.3 (0.2)	0.4 (0.2)	0.1 (0.2)	0.03
FIB-4	78	0.9 (0.8)	1.3 (0.9)	0.4 (0.8)	<0.01
Bilirubin (mg/dL)	49	0.7 (0.4)	0.6 (0.3)	0.0 (0.5)	0.26
Glucose (mg/dL)	70	96.0 (18.0)	94.0 (19.0)	−1.5 (21.0)	0.59
HbA1c (%)	1	--	--	--	--
Renal					
BUN (mg/dL)	54	13.0 (6.0)	12.0 (5.0)	−0.5 (8.0)	0.17
Creatinine (mg/dL)	55	1.0 (0.3)	1.0 (0.24)	−0.1 (0.3)	0.25
eGFR (mL/min/1.73m ²)	55	95.5 (20.6)	92.2 (33.2)	3.6 (29.8)	0.39
Cardiovascular/Hematologic					
SBP (mmHg)	71	124.3 (18.0)	125.3 (18.7)	2.0 (16.0)	0.56
DBP (mmHg)	71	74.3 (14.0)	76.0 (11.0)	2.7 (12.0)	0.06
Heart rate (beats/second)	70	76.5 (23.0)	80.0 (17.0)	4.0 (25.0)	0.15
Platelets (count/mL)	78	221.5 (63)	210.5 (73.0)	−18.0 (90.0)	0.26

p-value for Mann-Whitney U test comparing pre-HIV and pre-ART biomarker levels.

No HMG CoA reductase inhibitor/gemfibrozil prescription, diabetes (BMI & lipids); No diabetes, hepatitis C, alcohol abuse and dependence diagnosis (hepatic and platelets); No antihypertensive medication or diabetes (renal and heart rate); HIV-human immunodeficiency virus; ART-antiretroviral therapy; BMI-body mass index; HDL-high density lipoprotein; LDL-low density lipoprotein; ALT-alanine transaminase; AST-aspartate transaminase; FIB-4-liver fibrosis index-4; HbA1c-hemoglobin A1c; BUN-blood urea nitrogen; eGFR-estimated glomerular filtration rate; SBP-systolic blood pressure; DBP-diastolic blood pressure.

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Fig. (1).
Study design.

Fig. (2).

Median percentage changes in biomarkers from pre-HIV to pre-ART (Analysis 1 cohort) by tertiles of duration of ART-naïve HIV infection. Percentage change defined as: (pre-ART biomarker level minus pre-HIV biomarker level)/pre-HIV biomarker level * 100%. $P < 0.05$ for median differences in biomarkers among those in the first tertile (shortest ART-naïve HIV infection time) for HDL-cholesterol, triglycerides, ALT and hemoglobin; second tertile for HDL-cholesterol, total cholesterol, albumin, FIB-4, hemoglobin, platelets; third tertile for HDL-cholesterol, albumin, APRI, FIB-4, hemoglobin, platelets. HIV-human immunodeficiency virus; ART-antiretroviral therapy; BMI-body mass index; HDL-high density lipoprotein; LDL-low density lipoprotein; ALT-alanine transaminase; AST-aspartate transaminase; APRI-AST to platelet ratio; FIB-4-liver fibrosis index.

Table 1

Characteristics of HIV seroconverters prior to first positive HIV antibody test.

Unless Otherwise Stated, Data are N (%) of Column	Analysis 1 Cohort	Analysis 2 cohort	Excluded from Analyses
	Seroconverters with 1 Pre-HIV and Pre-ART Biomarkers	Seroconverters with 1 Pre-HIV and Post-ART Biomarkers	Seroconverters Not Represented in Analysis 1 or Analysis 2 Cohorts
N	422	297	164
Median (range) year of last negative HIV antibody test	2000 (1989–2009)	1997 (1987–2008)	1994 (1987–2009)
Median (range) year of first positive HIV antibody test	2004 (1989–2009)	2000 (1989–2009)	1998 (1990–2009)
Median (range) year of first ART prescription	2006 (1997–2010)	2002 (1992–2010)	1999 (1991–2010)
Mean age at last negative HIV antibody test (SD), yrs.	44.0 (9.4)	42.4 (8.8)	41.8 (8.9)
Mean age at first positive HIV antibody test (SD), yrs.	47.5 (9.5)	46.0 (9.0)	46.1 (9.4)
Mean age at first ART prescription, yrs.	50.5 (9.4)	47.2 (9.0)	47.9 (9.0)
Demographics			
Male	405 (96)	288 (97)	155 (95)
Race			
White	133 (32)	114 (38)	55 (34)
African American	265 (63)	168 (57)	97 (59)
Hispanic	16 (4)	12 (4)	7 (4)
Other	8 (2)	3 (1)	5 (3)
Comorbid Disease			
Cardiovascular disease	25 (6)	11 (4)	0 (0) **
Diabetes	13 (3)	7 (2)	0 (0)
Non-melanomatous cancer	11 (3)	5 (2)	3 (2)
Hepatitis C	76 (18)	33 (11)	5 (3) **
Substance Use			
Alcohol abuse and dependence diagnosis	145 (34)	63 (21)	10 (6) **
Smoking diagnosis or medication	90 (21)	31 (10)	3 (2) **
Cocaine abuse	110 (26)	45 (15)	7 (4) **
Medications			
Cholesterol lowering medication prescription	17 (4)	5 (2)	1 (0.6)
Antihypertensive medication prescription	76 (18)	23 (8)	6 (4) **

Analysis cohorts are not mutually exclusive.

Age, demographics, comorbidity, substance use and medications presented as N (%) of total column.

HIV-human immunodeficiency virus; ART-antiretroviral therapy.

**
p<0.05; Chi square test for difference between analysis cohorts and excluded subjects.

Table 2

Effects of HIV infection on biomarkers of organ function (Analysis 1 cohort).

Biomarkers	N	Median (IQR)	Median (IQR)	Median Difference ^a (IQR)	Median % Difference	P-Value (Median Difference)
		Pre-HIV	Pre-ART	Pre-HIV vs Pre-ART		
Average median duration, years				3.5	--	--
BMI	125	24.5 (5.2)	24.4 (5.7)	0.0 (3.1)	6.9	0.85
Lipids (mg/dL)						
HDL cholesterol	94	43.1 (20)	34.7 (16)	−9.3 (15.0)	24.1	<0.01
Non-HDL cholesterol	92	130.0 (50.9)	122.5 (36.8)	−0.5 (55.5)	0.4	0.34
LDL cholesterol	88	103.4 (41.5)	97.0 (36.6)	−3.0 (34.9)	16.6	0.03
Triglycerides	106	99 (70)	121.0 (100.0)	22.0 (99.0)	43.7	<0.01
Total cholesterol	120	172.0 (51.5)	159.0 (45.0)	−7.0 (50.0)	15.4	<0.01
Hepatic						
Albumin (g/dL)	132	4.1 (0.7)	3.8 (0.8)	−0.2 (0.8)	10.4	<0.01
ALT (IU/L)	210	36.0 (41)	32.5 (23.0)	−5.0 (28.0)	39.1	<0.01
AST (IU/L)	210	31.5 (31)	34.0 (28.0)	2.0 (23.0)	34.6	0.63
APRI	210	0.34 (0.46)	0.39 (0.45)	0.05 (0.32)	48.6	0.04
FIB-4	210	1.1 (1.1)	1.5 (1.2)	0.4 (0.9)	52.5	<0.01
Bilirubin (mg/dL)	141	0.6 (0.5)	0.6 (0.4)	0.0 (0.4)	40.0	0.62
Glucose (mg/dL)	185	97 (20)	95.0 (21.0)	−1.0 (24.0)	12.2	0.30
HbA1c (%)	21	5.9 (3.1)	6.0 (1.2)	−0.2 (2.0)	14.0	0.31
Renal						
BUN (mg/dL)	183	13.0 (6)	12.3 (6.0)	0.0 (7.0)	28.6	0.49
Creatinine (mg/dL)	180	1.0 (0.3)	1.0 (0.3)	0.0 (0.2)	11.1	0.69
eGFR (mL/min/1.73m ²)	180	94.6 (30.8)	92.9 (31.7)	−1.4 (27.5)	13.2	0.62
Cardiovascular/Hematologic						
SBP (mmHg) ^e	176	127.7 (22.7)	129.3 (17.2)	1.7 (19.1)	7.7	0.62
DBP (mmHg) ^e	176	77.5 (15.5)	78.5 (12.2)	2.0 (12.8)	9.2	0.12
Heart rate (beats/second)	177	77.0 (20)	78.0 (20.0)	2.0 (24.0)	14.3	0.16
Hemoglobin (g/L)	185	14.8 (2)	13.8 (2.1)	−1.0 (2.3)	8.7	<0.01
Platelets (count/mL)	210	228.0 (78.0)	204.0 (95.0)	−18.0 (95.0)	19.9	<0.01

HIV-human immunodeficiency virus; ART-antiretroviral therapy; BMI-body mass index; HDL-high density lipoprotein; LDL-low density lipoprotein; ALT-alanine transaminase; AST-aspartate transaminase; APRI-AST to platelet ratio; FIB-4-liver fibrosis index-4; HbA1c-hemoglobin A1c; BUN-blood urea nitrogen; eGFR-estimated glomerular filtration rate; SBP-systolic blood pressure; DBP-diastolic blood pressure.

^aMedian differences are defined as: pre-ART biomarker level- pre-HIV biomarker level.

Table 3

Effect of HIV infection and ART initiation (HIV-1 RNA<500) on biomarkers of organ function (Analysis 2 cohort).

Biomarkers	N	Median (IQR)		Median Difference (IQR) ^a	Median % Difference	P-Value (Median Difference)
		Pre-HIV	Post-ART HIV RNA<500	Pre-HIV vs Post-ART HIV RNA<500		
Average median ART exposure, years				1.3	--	--
BMI	50	23.9 (4.9)	25.2 (4.7)	0.2 (3.3)	4.7	0.26
Lipids (mg/dL)						
HDL cholesterol	35	44.0 (31.0)	39.0 (16.0)	−4.0 (23.0)	25.0	0.09
Non-HDL cholesterol	36	121.0 (62)	132.1 (58.0)	−1.25 (66.5)	22.0	0.87
LDL cholesterol	34	102.0 (49.7)	90.5 (49.4)	−9.4 (42.6)	21.5	0.03
Triglycerides	34	105.5 (71.0)	124.0 (141.0)	28.5 (109.0)	49.4	<0.01
Total cholesterol	41	185.0 (61.0)	178 (54.0)	−8.0 (62.0)	15.8	0.55
Hepatic						
Albumin (g/dL)	29	4.1 (0.5)	3.9 (0.7)	0.0 (0.8)	10.0	0.97
ALT (IU/L)	54	32.5 (40.0)	26.0 (24.0)	−2.0 (33.0)	38.9	0.06
AST (IU/L)	54	31.5 (24.0)	26.5 (17.0)	−1.0 (16.0)	27.4	0.30
APRI	54	0.3 (0.3)	0.3 (0.2)	0.0 (0.2)	31.9	0.32
FIB-4	54	1.0 (0.7)	1.2 (0.7)	0.2 (0.5)	37.1	0.02
Bilirubin (mg/dL)	30	0.6 (0.5)	0.6 (0.4)	−0.05 (0.3)	31.7	0.67
Glucose (mg/dL)	54	97.0 (26.0)	98.5 (21.0)	3.0 (27.0)	15.3	0.80
HbA1c (%)	11	5.8 (0.9)	5.5 (4.7)	−0.2 (1.0)	8.6	0.86
Renal						
BUN (mg/dL)	53	13.0 (5.0)	14.0 (7.0)	0.0 (7.0)	27.2	0.94
Creatinine (mg/dL)	53	1.0 (0.2)	1.0 (0.3)	0.0 (0.4)	18.2	0.92
eGFR (mL/min/1.73m²)	53	93.4 (26.1)	95.1 (40.9)	−2.9 (37.0)	20.2	0.44
Cardiovascular/Hematologic						
SBP (mmHg) ^c	66	126.3 (24.3)	126.3 (15.5)	0.3 (22.7)	8.7	0.39
DBP (mmHg) ^c	66	77.3 (16.3)	76.2 (15.3)	−1.2 (14.7)	9.2	0.42
Heart rate (beats/second)	73	76.0 (20.0)	80.0 (18.0)	0.0 (19.0)	12.7	0.59
Hemoglobin (g/L)	52	14.7 (2.2)	13.9 (2.1)	−0.9 (2.0)	9.4	<0.01
Platelets (count/mL)	54	230.0 (78.0)	240.5 (85.0)	0.5 (70.0)	16.4	0.81

Median differences are defined as: post-ART biomarker level– pre-HIV biomarker level.

Data represent first biomarker measurement after ART initiation with HIV-1 RNA <500 copies/mL.

HIV-human immunodeficiency virus; ART-antiretroviral therapy; BMI-body mass index; HDL-high density lipoprotein; LDL-low density lipoprotein; ALT-alanine transaminase; AST-aspartate transaminase; APRI-AST to platelet ratio; FIB-4-liver fibrosis index-4; HbA1c-hemoglobin A1c; BUN-blood urea nitrogen; eGFR-estimated glomerular filtration rate; SBP-systolic blood pressure; DBP-diastolic blood pressure.