APPENDIX

Additional details on study setting

The Women's Interagency HIV Study (WIHS) was initiated in 1994 and has enrolled over 4,000 women at six U.S. sites: Bronx, New York; Brooklyn, New York; Chicago, Illinois; Los Angeles, California; San Francisco, California; and Washington, D.C. Recruitment in the WIHS occurred in three waves (1994-1995, 2001-2002, and 2010-2012) from HIV primary care clinics, hospital-based programs, community outreach, support groups, and other locations.

The Multicenter AIDS Cohort Study (MACS) was initiated in 1984, and has enrolled approximately 7,000 gay or bisexual men from four U.S. sites: Baltimore, Maryland; Chicago, Illinois; Los Angeles, California; and Pittsburgh, Pennsylvania. MACS recruitment also occurred in three waves (1984-1985, 1987, and 2001-2003).

Additional details on study design are published.(1-4) Briefly, each study has semi-annual follow-up visits, during which participants undergo similar detailed examinations, specimen collection, and structured interviews assessing health behaviors, medical history, and medication use.

Additional details on inclusion and exclusion criteria

All WIHS participants were eligible for participation in the vascular substudy at the time of recruitment; MACS participation was restricted to men reporting no history of coronary heart disease (CHD). Additional exclusion criteria for MACS participants were age <40 years and weight >300 pounds, because the MACS vascular substudy also included coronary artery

calcium measurements,(5, 6) which provide little information among younger individuals and, for technical reasons, are difficult to perform in the morbidly obese.

For the present analyses, we excluded WIHS participants with a reported history of CHD (N=138) for consistency with the MACS. We also excluded 10 individuals who acquired HIV during the study period, 2004-2013.

Additional details on participant retention

The WIHS and MACS studies are documented to have excellent retention (7, 8). In the vascular disease study, all participants in this analysis contributed at least two study visits, with a maximum of 3 (MACS) or 4 (WIHS) visits. Our use of linear mixed models for the analysis of progression of CCA-IMT allows for missing visits, assuming that these visits are missing at random. The analysis of new focal plaque formation excluded any participant who did not attend the final study visit. We addressed the possibility that this exclusion affected effect estimates for focal plaque formation in two ways: first, we compared demographic and clinical characteristics of patients in the vascular follow-up study who did (N=1,313) and did not (N=512) complete the last visit. 17% of the latter group died in the interim. Demographic and clinical characteristics were generally similar by study completion status, although those who did not complete the last visit were more likely to have detectable HIV RNA levels (66% vs. 55% in the WIHS; 45% vs. 37% in the MACS). WIHS women who did not complete the last visit had slightly lower BMI (median 27.2 vs. 28.3) and total cholesterol levels (median 166 vs. 175 mg/dL). Among MACS men, those who did not complete the last visit were less likely to be on lipid-lowering therapy (20% versus 30%). All other cardiometabolic risk factors assessed were similar by study completion status, including smoking, HDL-cholesterol, use of anti-hypertensive medication, and history of diabetes.

To further examine the robustness of our findings, we conducted sensitivity analyses by conservatively assuming that HIV-infected and uninfected participants who did not complete the last visit had the same event rate, and this rate varied from 0% to 20%, a range observed in the WIHS and MACS. In these sensitivity analyses, the association between HIV infection and formation of plaque was attenuated with higher event rates but remained statistically significant (e.g., assuming a 10% event rate among those who did not complete the last visit, the relative risk for HIV infection was 1.44, 95% CI 1.05, 1.98). In summary, while we cannot completely rule out all possible bias, we do not have a strong basis to believe that those not completing the last visit are likely to change our inference with respect to the association of HIV infection and new plaque formation.

References

1. Barkan SE, Melnick SL, Preston-Martin S, et al. The Women's Interagency HIV Study. Epidemiology **1998**; 9: 117-125.
2. Bacon MC, von Wyl V, Alden C, et al. The Women's Interagency HIV Study: An observational cohort brings clinical sciences to the bench. Clin Diagn Lab Immunol **2005**; 12: 1013-1019.
3. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR, Jr. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. Am J Epidemiol **1987**; 126: 310-318.
4. Silvestre AJ, Hylton JB, Johnson LM, et al. Recruiting minority men who have sex with men for HIV research: results from a 4-city campaign. Am J Public Health **2006**; 96: 1020-1027.

5. Kingsley LA, Cuervo-Rojas J, Munoz A, et al. Subclinical coronary atherosclerosis, HIV infection and antiretroviral therapy: Multicenter AIDS Cohort Study. AIDS **2008**; 22: 1589-1599.
6. Post WS, Budoff M, Kingsley L, et al. Associations between HIV infection and subclinical coronary atherosclerosis. Ann Intern Med **2014**; 160: 458-467.
7. Hessol NA, Weber KM, Holman S, et al. Retention and attendance of women enrolled in a large prospective study of HIV-1 in the United States. J Women's Health **2009**; 1627-1637.
8. Dudley J, Jin S, Hoover D, Metz S, Thackeray R, Chmiel J. The Multicenter AIDS Cohort Study: Retention after 9½ years. Am J Epidemiol **1995**; 142: 323-330.

Appendix Table 1. Association between risk factors and change in right common carotid artery intima-media thickness (CCA-IMT), overall and by cohort.

	Women's Interagency HIV Study (WIHS) (N=3493 obs, 1011 women)		Multicenter AIDS Cohort Study (MACS) (N=2130 obs, 814 men)		Combined (N=5623 obs, 1825 people)	
	β (μm/year)	*P*	β (μm/year)	*P*	β (μm/year)	*P*
Year since baseline	1.3 (-3.8, 6.4)	0.61	-1.3 (-11.8, 9.1)	0.80	-0.3 (-5.0, 4.3)	0.89
HIV infection	0.0 (-1.1, 1.0)	0.94	0.7 (-0.8, 2.2)	0.38	0.2 (-0.7, 1.0)	0.67
Demographic risk factors						
Age (per year)	0.0 (-0.1, 0.1)	0.92	0.0 (-0.1, 0.1)	0.68	0.0 (-0.1, 0.1)	0.72
Race/ethnicity (ref = white or other)						
Black	2.0 (0.4, 3.6)	0.017	2.6 (0.7, 4.5)	0.007	2.3 (1.1, 3.4)	<0.001
Hispanic	1.6 (-0.1, 3.4)	0.065	3.3 (0.7, 5.9)	0.012	2.3 (1.0, 3.6)	0.001
Income (ref: income <$30,000/year)						
$30,000/year or more	1.7 (0.4, 3.0)	0.008	0.7 (-0.9, 2.3)	0.39	1.2 (0.3, 2.2)	0.014
Education (ref: did not complete high school)						
Completed high school	0.8 (-0.3, 1.9)	0.155	0.5 (-2.7, 3.7)	0.76	1.0 (-0.1, 2.1)	0.080
At least some college	0.3 (-0.8, 1.4)	0.62	-0.8 (-3.7, 2.2)	0.61	0.2 (-0.9, 1.3)	0.70
Behavior-related characteristics						
History of injection drug use	-0.5 (-2.0, 1.0)	0.54	0.0 (-2.8, 2.8)	0.99	0.1 (-1.2, 1.4)	0.89
Current crack/cocaine use	2.9 (1.2, 4.6)	0.001	1.8 (-0.4, 4.0)	0.113	2.3 (0.9, 3.6)	0.001
Current alcohol use (ref. = abstainer)						
Light (<3 drinks/week, WIHS; 1-3, MACS)	-0.3 (-1.3, 0.6)	0.51	0.9 (-1.0, 2.8)	0.35	-0.1 (-0.9, 0.8)	0.90
Moderate (3-13, WIHS; 4-13 MACS)	-1.8 (-3.4, -0.2)	0.026	1.2 (-1.0, 3.4)	0.28	-0.4 (-1.7, 0.8)	0.50
Heavier (14+ drinks/week)	-2.4 (-4.8, 0.1)	0.059	-0.3 (-3.4, 2.9)	0.88	-1.6 (-3.4, 0.3)	0.093

History of hepatitis C infection	0.9 (-0.6, 2.4)	0.23	-1.8 (-4.0, 0.4)	0.112	-0.2 (-1.4, 1.0)	0.79
Metabolic risk factors						
Current smoker at baseline	-0.3 (-1.2, 0.7)	0.57	-0.7 (-2.4, 1.0)	0.43	-0.4 (-1.3, 0.4)	0.34
Body mass index (per kg/m^2)	0.0 (0.0, 0.1)	0.40	0.0 (-0.2, 0.2)	0.93	0.0 (0.0, 0.1)	0.58
Systolic blood pressure (per 10 mm Hg)	0.1 (-0.1, 0.4)	0.33	0.5 (-0.1, 1.0)	0.095	0.2 (0.0, 0.5)	0.087
Use of anti-hypertensive medications	-2.1 (-3.4, -0.8)	0.002	-1.1 (-2.8, 0.6)	0.22	-1.6 (-2.7, -0.6)	0.002
Total cholesterol (per 10 mg/dL)	-0.1 (-0.2, 0.1)	0.40	0.0 (-0.2, 0.1)	0.91	0.0 (-0.1, 0.1)	0.61
HDL-cholesterol (per 10 mg/dL)	-0.1 (-0.4, 0.2)	0.39	-0.4 (-0.9, 0.1)	0.123	-0.2 (-0.5, 0.0)	0.090
Use of anti-cholesterol medications	1.2 (-0.9, 3.2)	0.26	-0.4 (-2.1, 1.2)	0.62	0.1 (-1.1, 1.3)	0.87
History of diabetes	-0.1 (-1.3, 1.0)	0.83	-0.6 (-3.0, 1.8)	0.63	-0.1 (-1.2, 1.0)	0.83

AIDS = acquired immunodeficiency syndrome, CI, confidence interval, HDL = high-density lipoprotein, HIV = human immunodeficiency virus, ref = reference group.

Models are adjusted for all covariates listed.

Appendix Table 2. Characteristics of HIV-infected participants who were consistently ART-treated and persistently virologically suppressed[a].

	Women's Interagency HIV Study (WIHS)		Multicenter AIDS Cohort Study (MACS)	
	HIV+, persistently suppressed (N=122)	HIV+, not persistently suppressed (N=625)	HIV+, persistently suppressed (N=164)	HIV+, not persistently suppressed (N=366)
Characteristic	% or median (IQR)	% or median (IQR)	% or median (IQR)	% or median (IQR)
Demographic characteristics				
Age, years (median, IQR)	42 (37-47)	40 (35-46)	50 (45-54.5)	47 (44-53)
Race/ethnicity				
Black (non-Hispanic)	36.9	26.6	9.2	7.4
Hispanic	36.9	64.3	15.2	36.9
White (non-Hispanic)	21.3	6.9	75.0	54.4
Other	4.9	2.2	0.6	1.4
Income				
<$30,000 per year	80.3	84.2	41.7	51.6
$30,000+ per year	19.7	15.8	58.3	48.4
Education (at study entry)				
Did not complete high school	37.7	41.3	5.5	8.5
Completed high school	28.7	30.6	12.2	14.2
Some college or completed college	30.3	26.9	54.9	53.6
Attended/complete graduate school	3.3	1.3	27.4	23.8
Behavior-related characteristics				
History of injection drug use	27.1	28.0	4.9	10.1
Current crack/cocaine use	2.5	7.2	9.8	16.5
Current alcohol use				

Abstainer	64.8	52.0	19.5	20.7
Light (<3 dks/week, WIHS; 1-3, MACS)	27.1	36.0	62.2	51.4
Moderate (3-13, WIHS; 4-13 MACS)	8.2	9.4	13.4	22.7
Heavier (14+ drinks/week)	0.0	2.6	4.9	5.3
History of hepatitis C infection	31.2	31.8	11.0	20.2
Metabolic risk factors				
Current smoker	27.9	48.0	26.8	37.6
Body mass index, kg/m^2 (median, IQR)	27.2 (24.0-31.5)	27.5 (24.0-32.1)	25.2 (22.4-27.6)	24.8 (22.6-27.7)
Systolic blood pressure, mmHg (median, IQR)	116 (105-124)	115 (107-128)	125 (116-131)	123 (115-131)
Total cholesterol, mg/dL (median, IQR)	186 (160-220)	170 (145-197)	200 (171-236)	187 (157-211)
HDL cholesterol, mg/dL (median, IQR)	48 (40-61)	44 (34-54)	44 (36-53)	42 (35-51)
Current use of anti-hypertensive medications	18.9	19.5	26.2	19.4
Current use of lipid lowering medications	9.0	5.4	36.6	21.6
History of diabetes	23.8	18.9	6.7	10.1
HIV-specific characteristics				
Baseline CD4+ T-cell count, cells/mm^3 (median, IQR)	568 (419-739)	418 (259-616)	591 (438-748)	466 (310-681)
History of clinical AIDS	38.5	35.2	9.8	14.2
Potent ART use in past 6 months	100.0	62.4	100.0	75.1
Nadir CD4+ T-cell count before ART use[b], cells/mm^3 (median, IQR)	219 (115-403)	286 (173-412)	272 (157-363)	286 (155-400)

AIDS = acquired immunodeficiency syndrome, ART = antiretroviral therapy, HIV = human immunodeficiency virus, IQR = interquartile range.

All characteristics assessed at baseline unless otherwise noted. [a]Persistently suppressed viral load (<50 copies/mL for MACS, <80 copies/mL for WIHS) and consistently on ART throughout study period. [b]Among those using ART at baseline.

Appendix Table 3. Association between HIV-specific risk factors and progression of right common carotid artery intima-media thickness (CCA-IMT), overall and by cohort.

	Women's Interagency HIV Study (WIHS)		Multicenter AIDS Cohort Study (MACS)		Combined	
HIV-related characteristic	**β (μm/year)**	***P***	**β (μm/year)**	***P***	**β (μm/year)**	***P***
Persistent virologic suppression						
HIV-uninfected	Ref.		Ref.		Ref.	
Persistently suppressed[a]	0.5 (-1.0, 2.1)	0.50	0.5 (-1.5, 2.4)	0.64	0.4 (-0.8, 1.5)	0.54
Not persistently suppressed	-0.2 (-1.2, 0.9)	0.76	0.8 (-0.8, 2.3)	0.35	0.1 (-0.8, 1.0)	0.79
Baseline CD4+ T-cell count		0.35[b]		0.56[b]		0.78[b]
HIV-uninfected	Ref.		Ref.		Ref.	
≥500 cells/μL	0.3 (-1.0, 1.5)	0.66	0.1 (-1.5, 1.8)	0.87	0.1 (-0.9, 1.1)	0.81
350-499 cells/μL	0.5 (-1.0, 1.9)	0.51	1.7 (-0.4, 3.9)	0.118	0.9 (-0.3, 2.1)	0.133
200-349 cells/μL	-0.3 (-1.8, 1.2)	0.71	1.3 (-1.1, 3.8)	0.29	0.2 (-1.1, 1.5)	0.74
<200 cells/uL	-0.9 (-2.7, 1.0)	0.36	-1.6 (-4.8, 1.7)	0.35	-1.0 (-2.6, 0.6)	0.23
Baseline HIV-1 viral load						
HIV-uninfected	Ref.		Ref.		Ref.	
Undetectable	1.2 (0.0, 2.5)	0.058	0.5 (-1.1, 2.1)	0.55	0.7 (-0.2, 1.7)	0.141
Detectable	-0.8 (-2.1, 0.4)	0.182	0.8 (-1.2, 2.7)	0.44	-0.4 (-1.5, 0.6)	0.43
Among HIV-infected						
Duration of ART use (per year)	0.1 (-0.1, 0.3)	0.39	0.0 (-0.2, 0.3)	0.79	0.1 (-0.1, 0.2)	0.35
History of clinical AIDS	-0.6 (-1.8, 0.7)	0.36	0.7 (-1.9, 3.3)	0.58	-0.3 (-1.4, 0.8)	0.59
Among HIV-infected on ART						
Nadir CD4+ T-cell count before ART		0.161[b]		0.39[b]		0.93[b]
≥500 cells/μL	Ref.		Ref.		Ref.	

350-499 cells/μL	1.3 (-1.3, 4.0)	0.32	-2.5 (-6.1, 1.0)	0.162	-0.7 (-2.8, 1.4)	0.50
200-349 cells/μL	2.8 (0.3, 5.4)	0.029	-2.1 (-5.5, 1.2)	0.21	0.3 (-1.7, 2.2)	0.81
<200 cells/μL	2.0 (-0.6, 4.6)	0.140	-2.3 (-5.7, 1.1)	0.190	-0.3 (-2.4, 1.7)	0.76
History of ART use						
Duration PI use (per year)	-0.1 (-0.5, 0.3)	0.77	0.0 (-0.5, 0.4)	0.82	-0.1 (-0.3, 0.2)	0.58
Duration NNRTI use (per year)	0.1 (-0.3, 0.5)	0.59	-0.2 (-0.6, 0.2)	0.35	-0.1 (-0.4, 0.2)	0.45
Duration NRTI use (per year)	-0.3 (-0.7, 0.1)	0.112	0.1 (-0.3, 0.5)	0.57	0.0 (-0.3, 0.2)	0.86

AIDS = acquired immunodeficiency syndrome, CI, confidence interval, HDL = high-density lipoprotein, HIV = human immunodeficiency virus, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, ref = reference group.

[a]Persistently suppressed viral load (<50 copies/mL for MACS, <80 copies/mL for WIHS) and consistently on ART throughout study period. [b]P for trend.

All analyses control for age, race/ethnicity, education, income, study site, history of injection drug use, crack/cocaine use, current smoking, current alcohol use, history of hepatitis C infection, body mass index, systolic blood pressure, total and HDL cholesterol, use of anti-hypertension medications, use of anti-cholesterol medications, history of diabetes. All models (except persistent suppression model) also control for history of AIDS.