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MAJOR ARTICLE

Contribution of Human Herpesvirus 8 and Herpes Simplex Type 2 to Progression of Carotid Intima-Media Thickness in People Living With HIV

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Background. Human herpesvirus 8 (HHV-8) is a lymphotropic and vasculotropic herpesvirus with potential pro-atherogenic effects. We explored the influence of coinfection with HHV-8 and other herpesviruses on the rate of progression of carotid intima-media thickness (cIMT) in virologically suppressed people living with HIV (PLWH).

Methods. Prospective cohort study including men who have sex with men (MSM) infected with HIV. At the baseline visit, IgG antibodies against HHV-8 and other herpesviruses, highly sensitive C-reactive protein (hsCRP) levels, and Framingham risk scores were measured. To evaluate the progression of cIMT, successive measurements with high-resolution carotid artery ultrasound were performed over an 8-year period. Adjusted general linear mixed models were used to assess factors associated with faster cIMT progression.

Results. One hundred forty-one participants with suppressed HIV-RNA (<200 copies/mL) at cIMT measurement during the study period were included. Forty-six (31.3%) were coinfected with HHV-8 and 76 (54%) with herpes simplex virus 2 (HSV-2). Factors associated with faster cIMT progression adjusting for CD4 cell counts, time between cIMT measurements, hepatitis C, varicella zoster virus, and cytomegalovirus coinfection were seropositivity for HHV-8 ($P = .059$), HSV-2+HHV-8 coinfection ($P = .027$), Framingham risk score ($P = .057$), and hsCRP ($P = .027$). Coinfection with HHV-8 was independently associated with higher levels of hsCRP (odds ratio, 1.09; 95% confidence interval, 1.02 to 1.17; $P = .016$). When hsCRP and HHV-8 were simultaneously included in the adjusted model, the relationship of HHV-8 with cIMT progression was attenuated.

Conclusions. HHV-8 might contribute to progression of cIMT with a more prominent role when it coinfects with HHV-2 in virologically suppressed PLWH, and this effect could be driven by systemic inflammation.

Keywords.: atherosclerosis progression; highly sensitive C-reactive protein; human herpesvirus 8; inflammation; intima-media thickness; subclinical atherosclerosis.

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality in people living with HIV (PLWH) [1]. Compared with the general population, PLWH are at increased risk of cardiovascular events, to which different causes including traditional cardiovascular risk factors, antiretroviral therapy (ART), and HIV-associated chronic inflammation and immune activation have been implicated [2, 3].

Chronic immune activation and inflammation are main factors involved in the pathogenesis of atherosclerosis [4]. Despite successful ART, persistent residual inflammation does occur in PLWH [5], and infection with co-pathogens is one of the suggested contributing mechanisms. *Herpesviridiae* are highly prevalent among PLWH. This family of viruses has been particularly implicated in the pathogenesis of atherosclerosis [6]. Some of their members, including cytomegalovirus, herpes simplex virus type 2 (HSV-2), and varicella zoster virus, have been linked with subclinical atherosclerosis in PLWH in cross-sectional studies [7–9]. To date, only cytomegalovirus, through induction of cytomegalovirus-specific T cells, has been demonstrated in longitudinal studies to be associated with progression of atherosclerosis within this population [10].

Among *Herpesviridiae*, human herpesvirus 8 (HHV-8) stands out as an attractive candidate to be involved in atherosclerosis. HHV-8 is a lymphotropic and vasculotropic herpesvirus linked with Kaposi's sarcoma, and possibly with pulmonary hypertension in PLWH [11]. Because of the ability of HHV-8-infected vascular endothelial cells to induce the expression of growth factors that cause angiogenesis, endothelial cell proliferation, enhanced vascular permeability, and cytokine production, it

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had been suggested that HHV-8 could be involved in atherogenesis, but data are very limited [12]. In a previous study, we found that coinfection with HHV-8 was associated with increased inflammation and immune activation in virologically suppressed PLWH [13]. In the current investigation, we explored whether HHV-8 coinfection, as well as coinfection with other herpesviruses, was associated with faster progression of subclinical atherosclerosis, as assessed by longitudinal measurements of carotid intima-media thickness (cIMT).

METHODS

Study Population

The study was carried out in a cohort of adult PLWH cared for in the outpatient clinic of Elche University Hospital in Spain. Consecutive HIV-infected adult MSM, because of their increased risk for HHV-8 infection, willing to enroll in a longitudinal investigation including serial cIMT ultrasound measurements were prospectively invited to participate in the study. To avoid the confounding effect of HIV replication, only participants with virological suppression at cIMT measurement, defined as a viral load <200 copies/mL, were analyzed. Participants with a history of coronary heart disease were excluded. The study was approved by the local ethics committee (Comité Ético del Hospital General Universitario de Elche), and all included subjects signed an informed consent.

Data Collection

Demographic, clinical, and laboratory variables were collected at the baseline visit, occurring between January 2008 and April 2012. The last cIMT measurement occurred in October 2016. To evaluate the progression of subclinical atherosclerosis, successive cIMT measurements with high-resolution B-mode carotid artery ultrasound were performed to study participants using a standardized protocol, as previously described [14]. Three measures were taken from the right and left common carotid and bulb portions. Total cIMT at the common carotids and at the bulbs was calculated with the mean of all right and left measurements and analyzed as a continuous variable. The carotid bulbs were chosen to assess cIMT progression because of the higher progression rates described at this location in PLWH [15]. Carotid plaque was defined as a localized cIMT measure >1.5 mm. To minimize variability, all measurements were performed by the same investigator (M.M.), who was blinded to patients' clinical details and to previous scans. cIMT measurements were performed with approximately annual to biannual frequency.

At the baseline visit, a blood sample was collected for routine tests and serological and biomarker measurement. IgG antibodies against the majority of the herpesviruses were measured by commercial enzyme-linked immunosorbent assay test kits: FOCUS Diagnostics (Cypress, CA. U.S.A) for HSV-2; Vircell SL (Granada, Spain) for varicella zoster virus (VZV), and Siemens Healthcare Diagnostics (Barcelona, Spain) for cytomegalovirus (CMV). HHV-8 coinfection was assessed with the Indirect Fluorescent Assay (Advanced Biotechnologies Inc., MD, U.S.A). This latest test provided qualitative but not quantitative determination of IgG antibodies. Highly sensitive C-reactive protein (hsCRP) was measured with a chemiluminescent immunometric assay (Immulite 2000, Siemens, Madrid, Spain). Infection with hepatitis C virus (HCV) was defined by a positive serology plus a positive HCV RNA by polymerase chain reaction. CD4+ and CD8+ cell counts and HIV RNA were measured at baseline and every 6 months throughout the study period. Hypertension, diabetes, and dyslipidemia were defined by a previous diagnosis or by a current prescription of pharmacological therapy for any of the risk factors.

Cardiovascular risk factors were managed at the clinic according to a standard protocol. For lipid management, the therapeutic goal for low-density lipoprotein cholesterol was <130 mg/dL; lipid-lowering agents were initiated after dietary therapy failure. Blood pressure target goals were <140 mmHg for systolic and <90 mmHg for diastolic blood pressure. For patients with diabetes or renal disease, the target goals were <130/80 mmHg. To achieve blood pressure target goals, a predefined protocol was implemented, starting with lifestyle modifications and sequentially adding the following drugs at each visit: (i) an angiotensin receptor blocker, (ii) a thiazide diuretic, and (iii) a calcium channel blocker or a β-blocker. In patients with confirmed diabetes mellitus, the goal was reducing the hemoglobin A1c level to <7%. To achieve this objective, a predefined protocol starting with metformin was followed. In patients with very high triglycerides (≥500 mg/dL), the first priority was triglyceride lowering with diet and fenofibrate. The second priority was prevention of coronary heart disease with statins+ezetimibe. Weight loss and/or exercise were recommended, and smokers were strongly recommended to give up smoking.

Statistical Analyses

Differences in demographic and clinical characteristics between patients with and without HHV-8 coinfection were assessed using the chi-square or Fisher exact test for categorical variables, and the Student *t* or Mann-Whitney *U* tests for continuous variables.

To assess progression of cIMT, we examined the individual change in cIMT on each measurement at the far wall of the left and right carotid bulbs over time. Factors associated with cIMT progression were analyzed using a general linear mixed model, with the individual patient as a random effect. All cIMT increments were selected for multivariate analysis, and the models were adjusted for the variables significantly associated with cIMT progression in the univariate analysis, as well as for coinfection with other herpesviruses, CD4 cell count values at cIMT measurement, and antiretroviral regimen composition, because of their association with cardiovascular disease in PLWH [7–9, 16].

The closest CD4 cell counts within 6 months before or after cIMT determination were chosen for analysis. To avoid overadjustment, the Framingham risk score, as a summary variable comprising all the individual cardiovascular risk factors, was selected for inclusion in the models to predict cIMT progression. Missing data were handled through listwise deletion. Statistical significance for these models was defined by a 2-sided P value <.05.

The association of HHV-8 coinfection with inflammation was assessed with a binomial general linear mixed model using a complementary log–log link, which was adjusted for the factors associated with HHV-8 seropositivity in the univariate analysis. The associations between HHV-8 coinfection and the risk of new developing plaques and cardiovascular events were examined by means of generalized linear models using as an offset term the time to event development or to the end of the study observation period. Variables included in the analyses were cardiovascular risk at baseline, assessed by Framingham risk score, CRP, HIV-related factors, type of ART, and coinfection with herpesviruses.

RESULTS

Patients Characteristics

The study included 141 consecutive participants receiving ART who remained suppressed (HIV RNA < 200 copies/mL) at cIMT measurements during the study period; 9 participants with detectable HIV RNA levels at measurement were excluded. Baseline clinical data are shown in Table 1. Mean (±SD) age was 46 (±13) years, and median (Q1–Q3) CD4 cell count was 608.5 (391.8–847.5) cells/μL. The most frequent antiretroviral regimens were based on protease inhibitors (PIs; 38% participants) and non-nucleoside reverse transcriptase inhibitors (NNRTIs; 31%). Forty-three (30.5%) participants were coinfected with HHV-8, 76 (54%) with HSV-2, 135 (96%) with VZV, and 128 (94%) with CMV. Six patients developed vascular events during the study period: 5 coronary-related events and 1 peripheral artery disease.

Factors Associated With Human Herpesvirus 8 Coinfection

Coinfection with HHV-8 was associated with higher levels of hsCRP (median [Q1–Q3], 3.77 [1.34–7.31] vs 1.89 [0.91–3.94] mg/L, P = .003, in HHV-8-coinfected vs -noncoinfected, respectively), and there was a marginal association with higher Framingham score (median [Q1–Q3], 9% [4.25%–15.0%] vs 6.0% [2.0%–12.0%], respectively, P = .053), with lower CD8 cell counts (866 [619.5–1144] cells/μL vs 1024.5 [713.5–1574.5] cells/μL, respectively, P = .053) and a lower frequency of hepatitis C coinfection (2% vs 13%, P = .063) (Table 1). Median baseline cIMT was higher among HHV-8-infected individuals (median [Q1–Q3], 1.0 [0.75–1.30] mm in HHV-8-infected

Table 1. Baseline Characteristics of the Patients by Human Herpesvirus 8 Infection Serological Status

Variable	All Patients (n = 141)	HHV-8-Seropositive (n = 43)	HHV-8-Seronegative (n = 98)	*P* Value
Age, mean (SD), y	46 (13)	49.31 (14.74)	44.95 (12.50)	.090
CD4 cell count, cell/ μL	608.50 (391.75–847.50)	605 (383–803)	608 (424.50–854.75)	.675
CD8 cell count, cell/μL	989.50 (690.25–1446.25)	866 (619.50–1144)	1024.50 (713.50–1574.50)	.053
PI-including regimen	54 (38)	15 (35)	39 (40)	.707
NNRTI-including regimen	53 (31)	20 (47)	33 (34)	.186
INSTI-including regimen	36 (26)	10 (23)	26 (27)	.834
Antihypertensive agents	29 (21)	8 (19)	21 (21)	.822
Hypertension	42 (30)	14 (33)	28 (29)	.691
Dyslipidemia	62 (44)	23 (53)	39 (40)	.144
Lipid-lowering therapy	43 (30)	13 (30)	30 (31)	>.999
Diabetes	43 (30)	1 (10)	42 (31)	.097
Smoking	72 (51)	24 (56)	48 (49)	.471
Ex-smokers	19 (14)	5 (12)	14 (14)	.792
Framingham risk score, median (IQR), %	7 (2–3)	9 (4.25–15)	6 (2–12)	.053
Hepatitis C coinfection	14 (10)	1 (2)	13 (13)	.064
HSV-2 seropositivity	76 (54)	34 (79)	42 (46)	<.001
VZV seropositivity	135 (96)	41 (95)	94 (96)	>.999
Cytomegalovirus seropositivity	128 (91)	41 (95)	87 (89)	.105
hsCRP, mg/mL	2.16 (1.03–4.55)	3.77 (1.34–7.31)	1.89 (0.91–3.94)	.003
Baseline cIMT, mm	0.89 (0.738–1.19)	1 (0.75–1.29)	0.84 (0.70–1.10)	.054
Carotid plaques	40 (28)	14 (33)	26 (27)	.544
Time between measurements, y	1.67 (1.08–2.85)	1.60 (1.04–2.75)	1.70 (1.10–2.92)	.430
Duration of virological suppression, y	4.66 (2.70–6.82)	4.027 (2.61–6.82)	4.791 (3.92–6.48)	.135

Continuous variables are expressed as median (Q1–Q3), unless indicated. Categorical variables are expressed as No. (%).

Abbreviations: cIMT, carotid intima-media thickness; HHV-8, human herpesvirus 8; hsCRP, highly sensitive C-reactive protein; HSV-2, herpes simplex type 2; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VZV, varicella zoster virus.

and 0.83 [0.70–1.10] mm in HHV-8-uninfected, $P = .052$), and there was no difference in the number of baseline carotid plaques.

The association between HHV-8 and hsCRP was explored after adjustment for the Framingham risk score and for the factors linked with HHV-8 infection in the univariate analysis (Table 2). The results showed that individuals coinfected with HHV-8 continued to have significantly higher levels of hsCRP in the adjusted model (odds ratio [OR], 1.09; 95% confidence interval [CI], 1.02 to 1.17; $P = .016$). There were no significant differences between HHV-8-infected and -uninfected participants in the baseline cIMT after adjustment.

Factors Associated With Progression of Subclinical Atherosclerosis

Median (Q1–Q3) follow-up time per patient was 5.07 (4.38–6.03) years. All patients underwent at least 2 and 108 (76%) underwent 3 or more cIMT examinations, and the median (Q1–Q3) time between cIMT measurements was 1.67 (1.08–2.85) years. There were no significant differences in the cIMT between HHV-8-seropositive and -negative participants after the baseline visit (data not shown). The overall rate of progression of the cIMT at the bulb was +0.027 mm/y, 0.031 in HHV-8-coinfected and 0.024 in HHV-8-uninfected participants ($P = .872$). Factors associated with cIMT progression in univariate analysis were assessed through a general linear mixed model (Table 3). Results showed that positivity for HHV-8 infection ($P = .046$), for HSV-2 infection (0.049), dyslipidemia ($P = .024$), lipid-lowering therapy ($P = .015$), hypertension ($P = .035$), treatment with antihypertensive agents ($P = .026$), the Framingham risk score ($P = .005$), higher hsCRP levels ($P = .025$), and presence of a carotid plaque ($P < .001$) were associated with faster cIMT progression.

A multivariate model was fitted including seropositivity for HHV-8, HSV-2, CMV, VZV, CD4 cell counts at cIMT measurement, age, the Framingham risk score as a summary variable comprising all cardiovascular risk factors, hepatitis C coinfection, antiretroviral type, and time elapsed between cIMT measurements. The model showed that Framingham risk score ($P = .057$) and coinfection with HHV-8 ($P = .059$) were marginally associated with faster cIMT progression (Table 4, model A). Another model was constructed adding hsCRP. The model showed that hsCRP ($P = .031$) was associated with higher cIMT progression, but the relationship with HHV-8 seropositivity was much attenuated ($P = .182$) (Table 4, model B). Because of the association found with the 2 herpesviruses in the univariate analysis with cIMT progression, a third model was run adding the variable "coinfection with HHV-8 + HSV-2." The model showed that HHV-8 + HSV-2 seropositivity ($P = .028$) and Framingham risk score ($P = .025$) were significantly associated with faster cIMT progression (Table 4, model C). Framingham risk score at baseline was the only factor associated with both new developing plaques (adjusted OR, 1.126; 95% CI, 1.05 to 1.20; $P < .0001$) and either new developing plaques or cardiovascular events (adjusted OR, 1.073; 95% CI, 1.01 to 1.14; $P < .017$) during the study period.

Table 2. Adjusted General Linear Binomial Model With Complementary Link Log–Log Function Showing Factors Associated With Human Herpesvirus 8 Infection

Variable	OR (95% CI)	*P* Value
hsCRP, mg/mL	1.09 (1.02 to 1.17)	.017
Framingham risk score	1.0 (0.95 to 1.05)	.901
Hepatitis C coinfection	0.26 (0.01 to 1.25)	.188
CD8 cell count, cell/mm^3	1.0 (1.0 to 1.0)	.132
Baseline cIMT, mm	1.42 (0.70 to 2.68)	.316

Abbreviations: CI, confidence interval; cIMT, carotid intima-media thickness; HHV-8, human herpesvirus 8; hsCRP, highly sensitive C-reactive protein; OR, odds ratio.

DISCUSSION

Very few studies with a longitudinal design have to date evaluated the role of coinfections in cIMT. We found a relationship of the coinfection with both sexually transmitted herpesviruses HHV-8 and HSV-2, and among them especially with HHV-8, and faster progression of cIMT in virologically suppressed PLWH after adjustment for HIV-related and cardiovascular-related factors, which suggests a potential contributing role to the pathogenesis of atherosclerosis. This effect could be, at least partially, mediated through systemic inflammation, as shown by the higher levels of hsCRP associated with HHV-8 infection and by the mitigation of the effect of the virus on cIMT progression when hsCRP was incorporated into the analysis. The study also showed a strong association of the Framingham risk score with cIMT progression. Framingham risk score was also independently associated with either new developing plaques or cardiovascular events during the study.

Inflammation is considered a central factor in the pathogenesis of atherosclerosis [4, 17]. Infectious agents have been implicated in atherogenesis, both through direct infection of the vessel wall cells, where they cause a local inflammatory response, and through systemic inflammatory reaction mediated by inflammatory cells and cytokines, which could exacerbate the atherogenic processes occurring in the vessel wall [18]. Infection with co-pathogens has also been included among factors contributing to persistent inflammation and immune activation in chronically treated HIV infection and, accordingly, has been implicated in the pathogenesis of non-AIDS events (NAEs), including cardiovascular disease [19]. Although the *Herpesviridiae* family represents the most widely explored infectious agents contributing to cardiovascular disease within this population, limited information is available to date about their role in the progression of atherosclerosis.

Table 3. Univariate General Linear Mixed Model Showing Factors Associated With Progression of Carotid Intima-Media Thickness at the Bulb

Variable	Coefficient	*P* Value
CD4 cell count, cell/μL	0.0000163	.850
CD8 cell count, cell/μL	0.0000193	.639
Carotid plaque (cIMT >1.5 mm)	0.3361776	<.001
Lipodystrophy	0.0782997	.224
Hepatitis C coinfection	–0.0045131	.963
Dyslipidemia	0.1743712	.001
Lipid-lowering therapy	0.1677437	.004
Hypertension	0.1130260	.052
Antihypertensive therapy	0.1531224	.016
Smoking	–0.0279689	.616
Previous smokers	–0.0130822	.863
Alcohol	–0.0679639	.449
Framingham risk score, %	0.0131646	.000
hsCRP, mg/mL	0.0086430	.001
HHV-8 seropositivity	0.1526580	.009
HSV-2 seropositivity	0.1103244	.049
VZV seropositivity	–0.0342831	.832
CMV seropositivity	0.0388794	.658
PI-including regimen	0.0521954	.366
INSTI-including regimen	0.0234031	.717

Abbreviations: cIMT, carotid intima-media thickness; CMV, cytomegalovirus; HHV-8, human herpesvirus 8; hsCRP, highly sensitive C-reactive protein; HSV-2, herpes simplex type 2; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; VZV, varicella zoster virus.

When we longitudinally assessed factors associated with the rate of progression of subclinical atherosclerosis through the cIMT, we found an association of the simultaneous coinfection of HHV-8/HSV-2 with cIMT progression. However, when the independent role of each virus was assessed, we found that only HHV-8 retained a close to significant relationship with the progression of cIMT, and the association of HSV-2 found in univariate analysis vanished. HSV-2 is a sexually transmitted herpesvirus that causes genital herpes. It was associated with subclinical coronary atherosclerosis, measured through coronary artery calcium by computed tomography scan, in a cross-sectional study in PLWH [7]. HHV-8 is also a prevalent sexually transmitted gamma herpesvirus among MSM, especially in those infected with HIV, in whom prevalence twice as high as that in HIV-negative people has been described [20, 21]. Its pro-atherogenic properties in studies in vitro at the vessel wall, and the finding of higher frequency of macroscopic atheromatous lesions in patients with Kaposi's sarcoma in a postmortem report, support the hypothesis of the role of the virus in atherogenesis [12], but to date no clinical studies have associated HHV-8 infection with atherosclerotic disease. Our findings support the role of herpesviruses, as well as the hypothesis of the infectious burden in the pathogenesis of atherosclerosis previously reported [7, 22]. The study analyzed only cIMT progression and factors contributing to a more rapid progression rather than the net effect of HHV-8 and HHV-2 on the evolution of the cIMT. As a consequence, our results might support the involvement of the viruses in the progression of cIMT but do not implicate that the pathogens alone are associated with atherosclerosis progression in all the infected PLWH.

Interestingly, participants coinfected with HHV-8 showed higher levels of inflammation measured with hsCRP. Higher levels of hsCRP were likewise associated with faster cIMT progression in our study. This finding might point to systemic inflammation as one of the underlying pathogenic mechanisms participating in atherosclerosis progression in PLWH coinfected with HHV-8, in addition to the potential viral local effects described on endothelial vascular cells. Such systemic action would explain the attenuation of HHV-8 on cIMT progression when both variables coexisted in the same model. It might have also contributed to explaining the higher levels of baseline cIMT in participants coinfected with HHV-8, a factor that could also be associated with higher cIMT progression. Both, inflammation and HHV-8 might have contributed to explaining the progression of the cIMT at the carotid bulb, a region where atherosclerosis has previously been described to preferentially progress in PLWH [15]. The carotid bifurcation is a location with low endothelial shear stress, and it has been hypothesized that this could increase vascular susceptibility to the effects of chronic inflammation. Accordingly, and similar to our findings, the cIMT progression at the bulb has been associated with higher hsCRP levels in PLWH [15, 23] and in non-HIV-infected people [24].

Another relevant finding from our study was the strong association of the Framingham risk score with cIMT progression in PLWH, which remained significant throughout all analyses. Our results support the central role that traditional cardiovascular risk factors play in the pathogenesis of atherosclerosis in the HIV population. This reinforces the importance of prioritizing strict control of cardiovascular risk factors among the measures necessary to decrease the incidence of cardiovascular disease in PLWH.

The study has some limitations. First, it focused on cIMT progression, and therefore results cannot be extrapolated to all HHV-8-coinfected individuals. Second, most covariates, excluding CD4 cell counts and HIV-RNA levels, were only measured at baseline, and changes might have occurred throughout the study period. We could not rule out new HHV-8 coinfections during follow-up in those who were initially seronegative. However, according to previous epidemiological studies, the risk of seroconversion would have been very low (1.4 per 1000 susceptible persons) [25] and unlikely to impact the results. The population included in the study represents a pool of participants from a high-income country, and then the generalizability of results could be uncertain in low-income countries like sub-Saharan Africa. Finally, although a strong association between cIMT and CVD events has been established, the association between individual cIMT progression and future CVD events remains unproven [26, 27]. The strengths are the

Table 4. Multivariate-Adjusted General Linear Mixed Model Showing Factors Associated With Progression of Carotid Intima-Media Thickness at the Bulb

Model	Variable	Coefficient	(95% CI)	*P* Value
A	Time, y	0.0338	(–0.0089 to 0.0765)	.118
	Framinghamrisk score, %	0.0090	(–0.0003 to 0.0183)	.057
	CD4 cell count, cell/mm^3	0.0014	(–0.0077 to 0.0106)	.758
	Age, y	0.0045	(–0.0003 to 0.0094)	.066
	HHV-8 seropositivity	0.1252	(–0.0048 to 0.2551)	.059
	HSV-2 seropositivity	–0.0270	(–0.1626 to 0.1086)	.693
	VZV seropositivity	–0.0942	(–0.4309 to 0.2424)	.579
	CMV seropositivity	–0.0352	(–0.2369 to 0.1664)	.729
	Hepatitis C coinfection	0.0376	(–0.2061 to 0.2813)	.760
	PI-including regimen	0.0290	(–0.0907 to 0.1487)	.632
	INSTI-including regimen	0.0003	(–0.1329 to 0.1336)	.996
B	Time, y	0.0359	(–0.0063 to 0.0782)	.094
	Framinghamrisk score, %	0.0080	(–0.0011 to 0.0170)	.084
	CD4 cell count, cell/mm^3	0.0010	(–0.0080 to 0.0100)	.825
	Age, y	0.0044	(–0.0003 to 0.0091)	.068
	hsCRP, mg/mL	0.0063	(0.0007 to 0.0119)	.027
	HHV-8 seropositivity	0.0869	(–0.0437 to 0.2176)	.189
	HSV-2 seropositivity	–0.0340	(–0.1660 to 0.0890)	.611
	VZV seropositivity	–0.0719	(–0.4014 to 0.2575)	.666
	CMV seropositivity	–0.0140	(–0.2120 to 0.1840)	.889
	Hepatitis C coinfection	0.040	(–0.1970 to 0.2784)	.735
	PI-including regimen	0.0218	(–0.0950 to 0.1385)	.712
	INSTI-including regimen	0.0041	(–0.1256 to 0.1338)	.950
C	Time, y	0.0297	(–0.0122 to 0.0720)	.166
	Framinghamrisk score, %	0.0097	(0.0007 to 0.0187)	.035
	CD4 cell count, cell/mm^3	0.0010	(–0.0080 to 0.0100)	.826
	Age, y	0.0048	(0.0001 to 0.0096)	.046
	HHV-8 seropositivity	–0.1156	(–0.3616 to 0.1304)	.354
	HSV-2 seropositivity	–0.1151	(–0.2680 to 0.0379)	.139
	HSV-2 + HHV-8 seropositivity	0.3230	(0.0330 to 0.6076)	.027
	VZV seropositivity	–0.0552	(–0.3851 to 0.2747)	.741
	CMV seropositivity	–0.0436	(–0.2408 to 0.1535)	.661
	Hepatitis C coinfection	–0.0034	(–0.2429 to 0.2362)	.978
	PI-including regimen	0.0122	(–0.1049 to 0.1294)	.836
	INSTI-including regimen	0.0395	(–0.0940 to 0.1729)	.559

Time denotes number of years between cIMT measures.

Abbreviations: cIMT, carotid intima-media thickness; CMV, cytomegalovirus; HHV-8, human herpesvirus 8; hsCRP, highly sensitive C-reactive protein; HSV-2, herpes simplex type 2; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; VZV, varicella zoster virus.

longitudinal nature of the study, which allows a more accurate assessment of the role of an infectious agent in the course of atherosclerosis than that offered by cross-sectional studies, and the consistency of the results obtained, as shown by the strong association of the Framingham risk score with cIMT progression.

In conclusion, among virologically suppressed PLWH, HHV-8 and HHV-8-induced systemic inflammation could contribute to faster progression of cIMT, and this potential effect would be more evident when coinfection with HSV-2 occurs. Our results also confirm that traditional cardiovascular risk factors have a prominent role in the pathogenesis of atherosclerosis within this population, and preventive actions should maximize efforts to achieve their optimal control.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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