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Hepatitis C virus and cumulative infections are associated with atherogenic cardiovascular events in HIV-infected subjects

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ABSTRACT

Objectives: to analyze the association between HCV coinfection and cumulative infections with the development of a cardiovascular disease in HIV-infected subjects.
Methods: HIV-infected subjects attended at Virgen del Rocio University Hospital, between January 1982 and March 2018, were considered if fulfilled the following criteria: at least two visits to the HIV clinic, clinical records with data about VZV reactivation and bacterial infections, available data on HCV coinfection status. Atherogenic cardiovascular events were registered. To analyze factors associated with the development of cardiovascular event, a logistic regression analysis was performed.
Results: 823 subjects were included in the study. During the observational period, 58/823 (7.05%) developed a cardiovascular event. Advanced age at HIV-1 diagnosis, a low T-CD4 nadir, HCV coinfection and the burden of infections were independently associated with the risk of developing a cardiovascular event, apart from lipid levels and diabetes.
Conclusions: both HCV and the burden of infections are associated with an increased risk of cardivascular event in HIV-infected patients, together with other cardiovascular risk factors. Therapeutic strategies such as HCV erradication or VZV immunization could ameliorate cardiovascular risk in these subjects.

1. Introduction

Cardiovascular disease (CVD) is currently the leading cause of death and premature disability in developed societies (Roger et al., 2012). Apart from classical cardiovascular risk factors, both acute and chronic infections have been independently associated with higher risk of developing cardiovascular events and with high levels of different atherosclerosis surrogate biomarkers (Arcari et al., 2005; Emsley et al., 2008; Kozarov et al., 2015; Warren-Gash et al., 2009), in HIV uninfected subjects.

Regarding chronic infections, CVD has emerged as a one of the main causes of morbidity and mortality among HIV-infected subjects, including those on effective combined antiretroviral therapy (cART), being considered HIV-1 itself as a major cardiovascular risk factor (Freiberg et al., 2013; Nou et al., 2016). The role of hepatitis C virus (HCV) over the cardiovascular risk has also been analyzed, but discordant results were found among different authors (Arcari et al., 2006; Oliveira et al., 2013; Wong et al., 2014). This issue can be currently overcome since high effective direct antiviral agents are now available, achieving HCV eradication on the other of 100% of subjects (Asselah et al., 2018). In addition, an increased risk of CVD with herpes zoster (VZV) reactivation, community acquired pneumonia, influenza virus

Abbrevation: CVD, cardiovascular disease; cART, combined antiretroviral therapy; HCV, hepatitis C virus; VZV, herpes zoster virus; IQR, interquartile range

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Table 1
Baseline characteristics of the global population and comparison between those subjects experiencing a CVD and those without CVD during the observation period.

	Global (N = 823)	CVD (N = 58)	No CVD (N = 765)	*P*
Age at diagnosis, years [IQR]	30.5 [24–36]	35 [28–42]	30 [24–36]	**0.002**
Male sex, n (%)	668 (81.2)	50 (86.2)	618 (80.8)	0.385
AIDS, n (%)	209 (25.4)	27 (46.6)	182 (23.8)	< **0.001**
T-CD4 nadir < 200 cell/μL, n (%)	386 (46.9)	40 (69)	346 (45.2)	**0.001**
IDU[a], n (%)	317 (38.5)	33 (56.9)	284 (37.1)	**0.005**
HIV diagnosis precART[b], n (%)	373 (45.3)	37 (63.8)	336 (43.9)	**0.004**
HCV infection[c], n (%)	297 (36.1)	32 (55.2)	265 (34.6)	**0.003**
Herpes zoster reactivation, n (%)	99 (12)	12 (20.7)	87 (11.4)	0.056
Acute bacterial infection, n (%)	137 (16.6)	15 (25.9)	122 (15.9)	0.066
Diabetes, n (%)	48 (5.8)	11 (19)	37 (4.8)	< **0.001**
Total cholesterol, mg/dl [IQR]	182 [153–209]	207 [173–230]	181 [152–207]	< **0.001**
Triglycerides, mg/dl [IQR]	139 [80–166]	202 [110–237]	134 [78–161]	< **0.001**
Cumulative infections				
None, n (%)	388 (47)	16 (27.6)	371 (48.5)	**0.002**
One, n (%)	302 (36.7)	25 (43.1)	277 (36.2)	**0.003**
≻ 2, n (%)	134 (16.3)	17 (29.3)	117 (15.3)	< **0.001**

[a] Intravenous drug users.
[b] Diagnosis of HIV before 1996, when combined antiretroviral therapy was not available.
[c] HCV: positive HCV-PCR at any time during the observation period.

and even with cumulative childhood acquired infections has been recently reported (Burgner et al., 2015a,b; Kwong et al., 2018; Minassian et al., 2015; Musher D.M., 2019; Violi et al., 2017). However, the effect of HCV and/or cumulative infections over the risk of developing CVD in the context of HIV-infection has been scarcely explored (Fernández-Montero et al., 2016; Masiá et al., 2011). To explore the role of acute and chronic infections over the cardiovascular risk is relevant in order to better understanding other mechanisms involved in atherogenesis. Moreover, since effective therapy and immunization are currently available for many of these infections, CVD could be prevented through both therapeutic strategies.

Hence, the first and main objective of our study was to analyze the association between HCV coinfection with the development of a CVD in a cohort of HIV-infected subjects. Second, we aimed at analyzing whether the cumulative effect of different infections was associated with CVD in this setting.

2. Materials and methods

2.1. Patients

A retrospective observational study was designed, including 1055 patients that were attended at Virgen del Rocio University Hospital, Sevilla, between January 1982 and March 2018. The patients that fulfilled the following criteria were included in our study: at least two visits to the HIV clinic, clinical records with data about VZV reactivation and bacterial infections, available data on HCV coinfection status (HCV antibodies and qualitative HCV-PCR). These criteria were not available in 232 subjects of the 1055 patients and were excluded. Summarizing, the final study cohort was composed by 823 subjects. The Ethical Committee of the hospital approved the study and all patients signed the written informed consent.

For the purpose of this analysis, HCV infection was considered whether both HCV antibodies and qualitative HCV-PCR were positive. We considered that a patient was uninfected by HCV if the qualitative HCV-PCR was negative, independently the HCV antibodies status. Thus, we excluded patients with spontaneous HCV clearance. However, patients who had achieved sustained virological response after anti-HCV therapy were considered as HCV-infected subjects.

Apart from HCV status, in order to consider the burden of infections, VZV reactivation and acute bacterial infections (community acquired pneumonia, urinary sepsis, Fournier's gangrene) were included if documented in clinical records. Thus, this variable was considered as follows: 0) no coinfections; 1) at least one coinfection (HCV, VZV or bacterial infection); and 2) two or more coinfections. For those subjects developing a CVD, infections were considered if ocurred before the CVD. Once recurrent CVD was developed in some subjects, for the purpose of this analysis the first event was considered.

Cardiovascular events were those with an atherosclerotic origin: acute coronary syndrome, stroke, peripheral arteriopathy and mesenteric ischemia. The lipid profile determination considered in our study was the last one available in clinical records for each subject if no CVD during the observational period was developed. We considered the lipid profile determination available immediately before CVD for those patients developing a CVD.

2.2. Laboratory determinations

Absolute CD4 and CD8 T-cell counts (cells/mm3) were determined using an Epics XL-MCL flow cytometer (Beckman-Coulter, Brea, CA) according to the manufacturer's instructions. HCV-RNA (Hepatitis C virus) was determined on sera samples using an available PCR procedure kit (COBAS Amplicor, Roche Diagnosis) with a detection limit of 10 IU/mL. HCV exposure (measured by testing for the presence of anti-HCV) was detected using a HCV-specific ELISA (Siemens Healthcare Diagnosis, Malvern, Pennsylvania).

2.3. Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences software (SPSS 23.0, Inc, Chicago, USA). All continues variables were expressed as median (interquartile range, IQR), and categorical ones as number of cases (percentage). Differences between groups were analyzed with the Mann-Whitney *U* test for continuous variables, while the chi-square test was used for categorical ones. To analyze the independent factors associated with the development of the first CVD, a bivariate logistic regression analysis was performed and variables with p values < 0.1 in the bivariate analysis were included in a multivariate logistic regression analysis. All differences with $p < 0.05$ were considered statistically significant.

3. Results

Baseline characteristics of the global population and comparison between subjects developing or not a CVD are shown in Table 1. During the observational period, 58 subjects experienced a cardiovascular event (58/823, 7.05%). The most frequent CVD was the acute coronary syndrome, developed by 38 subjects. Median age when subjects

developed CVD was 47 years (IQR: 41–53). Additionally, 14 patients developed recurrent cardiovascular events (14/58, 24.14%), all of them but one expressed as acute coronary syndrome. From 58 patients that experienced a CVD, 21 of them died after developing the cardiovascular event (21/58, 36.21%). Causes of death among these patients were CVD (17/21, 80.95%), cancer (2/21, 9.52%), acute bacterial infection (1/21, 4.76%) and end-stage liver disease (1/21, 4.76%).

Interestingly, 50/58 (86.2%) of these subjects experienced a CVD despite an effective cART, since HIV viral load was persistently undetectable before developing the CVD. Furthermore, other traditional CVD risk factors were scarcely represented in these subjects, since hypercholesterolemia (cholesterol levels > 200 mg/dl) was present in 31/58 patients (53.4%) and only 11/58 subjects (19%) had diabetes mellitus. Taking altogether, 24/58 subjects (41.38%) experienced a CVD with a median age of 47 years (IQR 41–53), despite an effective cART, without diabetes and with normal lipid levels. Among these 24 "low-risk" subjects, 5 (5/24, 20.8%) developed recurrent CVD and 8 (8/24, 33.3%) died after the development of CVD.

When variables potentially associated with the development of a CVD were analyzed, advanced age at HIV-1 diagnosis, a low T-CD4 nadir and HCV coinfection were independently associated with the risk of developing a CVD, apart from other traditional strong predictors of CVD such as lipid levels (total cholesterol and tryglicerides) and diabetes (Tables 2 and 3). Since VZV reactivation and acute bacterial infections nearly reached statistical significance, our aim was to analyze if the cumulative effect of different infections herein considered, acute and chronic, could play a role regarding an increased risk for developing CVD. As shown in Tables 4 and 5, the burden of infections analyzed in the present study was an independent risk factor for CVD in this setting, as well as other well-known risk factors.

4. Discussion

Our manuscript shows that both HCV coinfection and the cumulative effect of different infections increase the risk of developing a CVD in HIV-infected subjects, together with traditional predictor factors of CVD.

Although atherosclerosis is traditionally considered a consequence of lifestyle in developed countries, recent paleogenetic studies have shown that atherosclerosis was present at least 5000 years ago in humans from ancient cultures and in different geographic areas with different lifestyle, diet and genetic backgrounds, reflecting that atherosclerosis development and subsequent CVD is influenced by other conditions together with traditional CVD risk factors (Thompson et al., 2013; Zink et al., 2014). Furthermore, it has been recently reported that if only traditional risk factors are considered, CVD risk prediction may be underestimated mainly in HIV-infected subjects (Long et al., 2018;

Table 2
Factors associated with the development of a CVD. Bivariate regression logistic analysis.

	Univariate		
	OR	IC 95%	*p*
Age at diagnosis, years	1.04	[1.01–1.06]	**0.002**
Male sex	1.49	[0.69–3.2]	0.31
AIDS	2.79	[1.62–4.8]	< **0.001**
T-CD4 nadir < 200 cell/μL	2.69	[1.52–4.8]	**0.001**
IDU[a]	2.24	[1.3–3.84]	**0.003**
HIV diagnosis precART[b]	2.25	[1.29–3.92]	**0.004**
HCV infection[c]	2.32	[1.36–3.98]	**0.002**
Herpes zoster reactivation	2.03	[1.04–3.99]	**0.039**
Acute bacterial infection	1.84	[0.99–3.41]	0.054
Diabetes	4.61	[2.21–9.6]	< **0.001**
Total cholesterol, mg/dl	1.01	[1.005–1.016]	< **0.001**
Triglycerides, mg/dl	1.005	[1.003–1.007]	< **0.001**

[a] Intravenous drug users.
[b] Diagnosis of HIV before 1996, when combined antiretroviral therapy was not available.
[c] HCV: positive HCV-PCR at any time during the observation period.

Table 3
Factors associated with the development of a CVD. Multivariate regression logistic analysis.

	Multivariate		
	OR	IC 95%	*p*
Age at diagnosis, years	1.08	[1.04–1.11]	< **0.001**
AIDS	1.65	[0.89–3.06]	0.11
T-CD4 nadir < 200 cell/μL	2.18	[1.13–4.2]	**0.02**
IDU[a]	1.23	[0.46–3.25]	0.68
HIV diagnosis precART[b]	2.14	[0.99–4.58]	0.05
HCV infection[c]	2.84	[1.1–7.4]	**0.031**
Herpes zoster reactivation, n (%)	1.82	[0.88–3.8]	0.11
Acute bacterial infections, n (%)	1.22	[0.61–2.42]	0.57
Diabetes	3.01	[1.32–6.86]	**0.009**
Total cholesterol, mg/dl	1.011	[1.005–1.02]	< **0.001**
Triglycerides, mg/dl	1.003	[1.001–1.005]	**0.022**

[a] Intravenous drug users.
[b] Diagnosis of HIV before 1996, when combined antiretroviral therapy was not available.
[c] HCV: positive HCV-PCR at any time during the observation period.

Table 4
Factors associated with the development of a CVD, considering the burden of infection. Univariate regression logistic analysis.

	Unadjusted model		
	OR	IC 95%	*p*
Age at diagnosis, years	1.04	[1.01–1.06]	**0.002**
AIDS	2.79	[1.62–4.8]	< **0.001**
T-CD4 nadir < 200 cell/μL	2.69	[1.52–4.8]	**0.001**
IDU[a]	2.24	[1.3–3.84]	**0.003**
HIV diagnosis precART[b]	2.25	[1.29–3.92]	**0.004**
Diabetes	4.61	[2.21–9.6]	< **0.001**
Total cholesterol, mg/dl	1.01	[1.005–1.016]	< **0.001**
Triglycerides, mg/dl	1.005	[1.003–1.007]	< **0.001**
Cumulative infections			
0 (Ref)	1	NA	**0.003**
1	2.09	[1.1–3.99]	**0.025**
➢ 2	3.37	[1.65–6.88]	**0.001**

[a] Intravenous drug users.
[b] Diagnosis of HIV before 1996, when combined antiretroviral therapy was not available.

Table 5
Factors associated with the development of a CVD, considering the burden of infection. Multivariate regression logistic analysis.

	Adjusted model		
	OR	IC 95%	*p*
Age at diagnosis, years	1.07	[1.03–1.01]	< **0.001**
AIDS	1.75	[0.95–3.24]	0.074
T-CD4 nadir < 200 cell/μL	2.01	[1.04–3.85]	**0.037**
IDU[a]	1.67	[0.72–3.87]	0.24
HIV diagnosis precART[b]	2.35	[1.12–4.94]	**0.025**
Diabetes	2.95	[1.31–6.68]	**0.009**
Total cholesterol, mg/dl	1.01	[1.004–1.016]	**0.001**
Triglycerides, mg/dl	1.003	[1.001–1.005]	**0.021**
Cumulative infections			
0 (Ref)	1	NA	
1	2.05	[0.95–4.42]	0.067
➢ 2	3.63	[1.48–8.9]	**0.005**

[a] Intravenous drug users.
[b] Diagnosis of HIV before 1996, when combined antiretroviral therapy was not available.

Triant et al., 2018), concordant with data presented herein in which CVD is developed in HIV-infected subjects with low cardiovascular risk attending to traditional risk factors.

Although HIV-1 infection is a well-known CVD risk factor (Freiberg et al., 2013; Nou et al., 2016), our results suggest that HCV has a cumulative effect in HIV-infected subjects, increasing the risk of developing CVD. The role of HCV as a CVD risk factor has been discussed and discordant data have been reported (Arcari et al., 2006; Oliveira et al., 2013; Wong et al., 2014). However, in the context of HIV infection, HCV-coinfection seems to have major importance regarding the risk of CVD as we show in our work and recently described by other groups (Fernádez-Montero et al., 2016). Additionally, a low T-CD4 nadir showed to be an independent predictor of CVD in HIV-1 infected subjects. Our results clearly suggest that CVD could be ameliorated in HIV-1 infected subjects through two strategies: 1) starting cART as soon as possible, in order to avoid HIV-1 progression and low T-CD4 nadir; 2) treatment of HCV-coinfection with direct antiviral drugs, in order to reduce chronic systemic inflammation secondary to HCV replication.

Regarding VZV reactivation, recent data have shown an association with the risk of developing a cardiovascular event among HIV-1 uninfected individuals (Mnassian et al., 2015). According to our results, VZV reactivation itself showed no independent association with the risk of CVD in HIV-1 infected subjects. However, the cumulative effect of different acute bacterial infections, VZV reactivation and HCV infection increased the cardiovascular risk in the context of HIV-1 infection.

As mentioned above, HIV-1 itself is a cardiovascular risk factor, but an optimal immunovirological response to cART is not enough to prevent CVD, since it has been shown that low grade systemic inflammation and endothelial dysfunction biomarkers remain at high levels after successful cART (Beltrán et al., 2014; Méndez-Lagares et al., 2013). Hence, apart from an effective cART and control of classical predictor factors of CVD risk, immunization for different infections (VZV, pneumococco) and high effective-well tolerated therapy for chronic HCV infection must be considered. The potential role of these strategies for preventing CVD in HIV-1 infected subjects should be addressed in further studies.

Underlying mechanisms through which CVD is increased in HIV-1 infected patients may be similar to those observed in chronic HCV infection and cumulative infections, such as immune hyperactivation and low-grade systemic inflammation driving to endothelial dysfunction (Nou et al., 2016; Peters et al., 2014). In this setting, we have shown that HIV-1 infected subjects with the toll-like receptor 4 Asp299Gly polymorphism cause high levels of proinflammatory cytokines (Tarancón-Díez et al., 2018), reflecting the role of innate immunity in the development of CVD (Fuster, 2018). Therefore, different bacteria in the atheroma plaque of patients with both asymptomatic atherosclerosis and after acute coronary syndrome have been found (Pessi et al., 2013; Rosenfeld et al., 2011). Moreover, an association between infectious diseases and the further development of ischemic events has been described in the last decade (Burgner et al., 2015; Qanitha et al., 2016; Smeeth et al., 2004).

Our study has several limitations, such as the retrospective design. Additionally, pre-cART era was also considered when mortality was mainly due to AIDS-related conditions and CVD was scarcely represented. Another limitation is the burden of infections considered for the present study. It could be discussed if other acute and chronic infections should have been included, but we have considered those consistently documented in clinical records and in which an association with CVD has been previously reported in different clinical setting apart from HIV-1 infection. Finally, the use of statins has not been considered, since prescription of this drug rely on the family doctor and was not strictly controlled.

4.1. Conclusions

Results presented herein show that CVD in the context of HIV infection is influenced by other factors apart from traditional CVD risk factors, acquiring a relevant role both HCV coinfection and the burden of infections. According to these results, potential strategies to minimize CVD risk in these subjects could be treating HCV coinfection in all subjects independently the liver fibrosis stage, starting cART as soon as possible and immunization for those infections in which effective vaccine are available.

Declarations of interest

None.

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