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# Non-AIDS-events in individuals with spontaneous control of HIV-1: a systematic review

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**Abstract**

**Background:** Despite antiretroviral treatment (ART), people living with HIV (PLHIV) are at increased risk for non-AIDS-defining events (nADEs), including cardiovascular events, non-AIDS malignances, hepatic disease and bacterial pneumonia.

**Setting:** This systematic review seeks to answer the question: are PLHIV who spontaneously control HIV-1 subject to an increased risk of various nADEs relative to non-controlling PLHIV on ART and people without HIV?

**Methods:** Databases were searched on June 9, 2021 with a search syntax focused on the elements 'HIV', 'spontaneous control' and 'clinical outcomes': Embase.com (includes Embase and Medline), Medline Ovid (includes PubMed), Cochrane library, Web of Science, Google Scholar. Included were studies reporting non-AIDS events in spontaneous controllers. Excluded were case reports, conference papers, editorials and reviews.

**Results:** Of 1134 identified records, 34 were assessed for full-text and 12 studies were included in the qualitative synthesis: five cohorts, two cross-sectional prevalence studies, four cross-sectional imaging studies and one case series. Four of five cohort studies showed that spontaneous controllers have a similar risk to develop nADEs compared with PLHIV on suppressive ART, specifically cardiovascular events, non-AIDS-malignancies, hepatic disease and bacterial pneumonia. Cross-sectional imaging studies showed a higher presence of subclinical cardiovascular disease in spontaneous controllers, like in PLHIV on ART, than in people without HIV.

**Conclusion:** individuals with spontaneous control of HIV-1 do not seem to be at a greater risk to develop different nADEs compared with PLHIV on suppressive ART. More data are needed, as the present conclusions are based on a limited number of studies that show a large heterogeneity among them.

**Word count: 249**

**Keywords:** HIV-1; HIV-infections/complications; antiretroviral therapy; cardiovascular diseases/complications; cancer; elite controllers



## Introduction

Worldwide, an estimated 380.000 people living with HIV (PLHIV) have spontaneous viral control in the absence of antiretroviral therapy (ART).[1] In studies, definitions for individuals with spontaneous control of HIV-1 (here termed 'spontaneous controllers') vary, and defined cohorts can differ substantially in viral load cutoff.[2] Commonly, spontaneous controllers of HIV-1 are divided into HIV controllers, viremic controllers (VCs) and elite controllers (ECs), as shown in a systematic review of HIV phenotype definitions [2]. HIV controllers (typically <400 copies/mL) and VCs (typically <2000 copies/mL) control viremia to low levels and ECs to undetectable levels.[2]

It has not been elucidated whether spontaneous controllers are at risk of various non-AIDS-defining events (nADEs), such as cardiovascular disease, non-AIDS-malignancies, hepatic and renal disease and bacterial pneumonia. Therefore, it remains a matter of debate whether and

when interventions are warranted in spontaneous controllers, including ART.[3,4] Reasons to initiate ART include prevention of transmission, anticipated loss of viral or immunological control and increased inflammation parameters which are associated with the risk of nADEs.[3] Inflammation parameters such as D-dimer, sCD14, sCD163, and high-sensitive CRP may be higher in ART-naive spontaneous controllers compared with PLHIV on suppressive ART or groups without HIV,[5-8] although at least three cohorts report no difference.[8-10] Increased levels of D-dimer and sCD14 have been directly linked to cardiovascular events, bacterial infections and non-AIDS malignancies;[11] CRP to cardiovascular events,[12,13] and sCD163 to subclinical cardiovascular disease.[14] The influence of ART initiation in spontaneous controllers on inflammation parameters remains unclear. ART induced decline in $CD8^+$ T cell activation ($CD38^+HLA\ DR^+$) in spontaneous controllers,[15,16] and increased $CD4^+$ T cell count only moderately,[17,18] or not at all.[15,16,19] Initiating ART had no significant impact on CRP, IL-6, sCD14, and D-dimer levels of spontaneous controllers.[16,19]

Knowing the prevalence of nADEs in spontaneous controllers may influence the decision to initiate targeted interventions or ART. Several studies have investigated incidence and prevalence of nADEs in spontaneous controllers compared with PLHIV using ART and/or controls without HIV, but the results were inconsistent.[20-23] Interpreting these studies is challenging, as the definitions of spontaneous controllers and control groups differ between studies. Here, we report the results of a systematic review on the occurrence of specific types of nADE among spontaneous controllers compared with PLHIV on suppressive ART and people without HIV.

## Methods

This systematic review was conducted according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses: PRISMA (Supplements, http://links.lww.com/QAI/B947).[24] Due to large variations in study design, varying definitions of spontaneous controllers, control groups and outcome parameters, study outcome could not be pooled and used for meta-analysis. The predefined protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) under ID CRD42020183598.[25]

### *Eligibility criteria*

Studies focusing on HIV controllers, viremic or elite controllers were assessed for eligibility. Randomized controlled trials, case-control studies, observational studies with or without a control group and case series were included. Excluded were case reports, conference papers, editorials and reviews.

### *Information sources, search strategy and handling of study records*

Embase.com (including Embase and Medline), Medline Ovid, Cochrane library, Web of Science and Google Scholar were searched for relevant studies published before June 9th 2021 and further eligible studies were sought through references of articles. The constructed search syntax was based on three elements, 'HIV', 'spontaneous control' and 'clinical outcomes' (Supplements, http://links.lww.com/QAI/B947). Search results were imported to Endnote library (Clarivate Analytics, Philadelphia, PA, USA). After removal of duplicates, two investigators (ALG and WAJWV) independently screened all articles on title and abstract using standardized

methods as reported before.[26-28] Articles were included for full text review if selected by either investigator. In case of doubt, articles were included for full text review. Both investigators independently assessed full texts for eligibility and extracted data. Disagreements were resolved in discussion with a third investigator (AV).

*Study outcome*

Outcome parameters were cardiovascular disease, cancers defined as non-AIDS-defining, hepatic disease, bacterial pneumonia, renal disease, non-AIDS-associated mortality and hospitalization.

*Data analysis*

Data was extracted using a standardized form which included author, year of publication, population, study design, type of outcome parameter, definition of spontaneous control of HIV-1 and of control groups, event rates of each type of nADE, and duration of follow-up. The quality of the included studies was independently assessed by two investigators (ALG and WAJWV), using to the Joanna Briggs Institute (JBI) critical appraisal tools for case series, cohort or observational studies.[29] JBI critical appraisal tools consist of a set of 8-11 questions, which must be answered by 'yes', 'no' or 'unclear', for which the total count of 'yes' indicates level of quality. Disagreements were resolved by discussion with a third investigator (AV). If not provided in the original paper, confidence intervals and unadjusted incidence rate ratios (IRRs) were calculated, using R statistical programming software version 3.6.1, packages rateratio.test and DescTools (R Foundation for Statistical Computing, Vienna, Austria, https://www.R-project.org/).

## Results

A total of 1134 records were identified after deduplication (Figure S1). After title-abstract screening, 1100 records did not fulfill the inclusion criteria. Full texts of the remaining 34 articles (3.0%) were evaluated for eligibility. Twenty-two records were excluded for the following reasons: no spontaneous controllers were included (N=8); no outcome as defined in the protocol was reported (N=7); conference abstract (N=5), speaker presentation (N=1) or a case report (N=1) (Figure S1). 12 articles were included (Table S1); five cohort[17,20-23] and two cross-sectional studies examining nADEs including cardiovascular disease, non-AIDS malignancies, hepatic disease, renal disease, bacterial pneumonia and all-type nADE,[30,31] four cross-sectional studies reporting on subclinical cardiovascular disease,[6,7,32,33] and one case series on non-AIDS malignancies.[34] HIV controller definitions in included articles were based on viral load and could be grouped into three categories: cut-off for 'HIV controllers' <400 copies/mL; for elite controllers (EC) <50, <75 or <80 copies/mL; for viremic controllers (VC) ≤2000 copies/mL (Table S2). Duration of viral control was required to be at least 1 year in six studies and at least 2 years in three studies, whereas no specific duration was mentioned in the three remaining articles (Table S2). Except for one study[32] all three categories of spontaneous controllers were ART naïve.

*Cardiovascular events as nADE in spontaneous controllers*

Comparable rates of events were reported in two cohort studies comparing cardiovascular events in spontaneous controllers with PLHIV comparison groups: one study reported significantly lower rates of cardiovascular nADEs in EC and VC combined than noncontrolling PLHIV (89%

on ART) (IRR 0.42 95%CI [0.196-0.840] p=0.011);[22] and one similar to PLHIV on suppressive ART (IRR 0.60, 0.95%CI [0.15-1.69] p=0.46),[21] see Table 1A. Cardiovascular events were low: 0.212 per 100PY in EC and VC combined versus 0.501 per 100PY in noncontrollers (89% on ART) (p=0.007);[22] and 0.45 events per 100PY in EC and VC combined versus 0.76 per 100PY in PLHIV on suppressive ART (p=0.46).[21] Another cohort study reported that 31.1% (23/74) of all-cause hospitalizations among EC were due to cardiovascular events, with an cardiovascular event incidence rate ratio of 3.19 relative to PLHIV on suppressive ART (95% CI [1.250-6.79). However, neither prevalences nor rates per 100PY could be calculated for this study, since neither total PY nor group total was mentioned.[20] None of these cohort studies provided data on cerebrovascular disease.[20-22]

In the cross-sectional studies, atherosclerotic plaque prevalence was assessed in carotid arteries by B-mode ultrasound and in coronary arteries by CT angiography (CTA) (Table 1B). A higher coronary artery plaque prevalence in EC compared with controls without HIV [78% (n=7/9) vs. 42% (n=21/49) p=0.03] was reported and a similar coronary artery plaque prevalence of 60% in PLHIV on suppressive ART.[6] In another study carotid artery plaque prevalence was reported to be similar between EC, VC, PLHIV on suppressive ART and controls without HIV.[32] Of note, 0% and 5% of male and female EC, respectively, and 67.2% and 23.7% of male and female VC were ART-receiving at time of the different cardiovascular measurements. Coronary artery calcium determined by CTA was not different between spontaneous controllers and PLHIV on suppressive ART or people without HIV.[6,32] Intima-media-thickness (IMT) in the common carotid arteries varied from a greater IMT in EC than in controls without HIV (910µm vs. 720

µm; p<0.001)[7] to a comparable IMT across EC, VC, PLHIV on suppressive ART and groups without HIV (table 1B) [32].

PET-CT to determine target-to-background ratios as a measure of aortic inflammation and cardiovascular disease has been widely used and validated in PLHIV.[35,36] Aortic inflammation on PET-CT was not different between EC relative to people without HIV and PLHIV on suppressive ART controls (p>0.05).[33]

*Non-AIDS-malignancies in spontaneous controllers*

Rates of non-AIDS-malignancies were reported in two cohort studies (Table 2). In both cohorts, similar rate of non-AIDS malignancies were found between EC and VC versus PLHIV on suppressive ART (IRR 0.24 [95%CI 0.006-1.495] p=0.19);[21] and between EC and VC versus noncontrollers (89% on ART) (IRR 0.68 95%CI [0.35-1.26] p=0.20).[22] Malignancy type was not specified. A case series of 16 non-AIDS malignancies showed prevalences of 1.47% (4/272) for HIV controllers, 11.1% (4/36) for EC and 3.46% (8/231) for VC.[34] These 16 cases comprised eleven different tumor types with no apparent pattern. Another study reported that 4.0% (3/74) of all-cause hospitalizations among EC was due to non-AIDS-malignancies (prevalences and rates unavailable).[20]

*Bacterial pneumonia, hepatic and renal disease in spontaneous controllers*

Incidence rates of hepatic disease were not different for EC and VC combined, compared with noncontrollers (89% on ART) (0.500 events per 100PY vs. 0.414, p=0.466) [22] and with PLHIV on suppressive ART (0.79 events per 100PY vs. 0.76, p=1.0).[21]

Renal disease rates were either less common among EC and VC compared with noncontrollers (89% on ART) (0.004 vs. 0.225 events per 100PY, p=0.005),[22] or increased in EC and VC versus PLHIV on suppressive ART (0.91 vs. 0.19 renal events per 100PY, p=0.005).[21]
Bacterial pneumonia occurred less frequently in EC and VC than in noncontrollers (89% on ART) (0.347 events per 100PY vs. 1.04 p<0.001).[22] Likewise, in a USA cohort no differences in non-AIDS infection rates (most commonly respiratory and soft tissue infections) between controllers and PLHIV on suppressive ART control groups were observed (2.95 in EC & VC vs. 2.70 events per 100PY; p=0.73).[20,21]

*All-cause nADEs in spontaneous controllers*

The prevalence of all-type nADEs, was lower in controllers compared with noncontrollers (89% on ART) in one study (1.252 per 100PY in EC and VC, vs. 2.481 per 100PY respectively; p<0.001), see Table 3,[22] but this could not be confirmed in another study with $CD4^+$ T cell counts >500 cells/µL at enrollment (1.1, 1.0, and 1.5 events per 100PY for EC, VC and noncontrollers (78% on ART) respectively; p=0.25).[23]

High all-cause hospitalization rates in EC were reported in 2015, 23.3 per 100PY compared with 10.5 per 100PY in PLHIV on suppressive ART (adjusted incidence ratio 2.02; p<0.05).[20] However, in 2016, hospitalization rates in EC and VC combined were similar to PLHIV on suppressive ART (9.4 per 100PY vs. 8.8 per 100PY, respectively; adjusted incidence ratio 1.15; p>0.05).[21] An earlier study did not report a difference in hospitalization among EC (28%), VC (34%), and noncontrollers (41%; p>0.05).[17] Only one study reported all-cause mortality. In this study, ART exposure among noncontrollers was not mentioned and the mortality of these

noncontrollers was high (37.1% versus 0% in EC and 1.31% in VC; p<0.01). Time to death since diagnosis of HIV was not different between EC and VC (P=0.54).[17]

*Factors associated with nADEs in spontaneous controllers*

Active hepatitis C (HCV) co-infection was reported as an independent risk factor for nADEs in spontaneous controllers, see Table 4. However, HCV serology was not associated with cardiovascular events in the French ANRS HIV controller cohort. Another factor associated with cardiovascular events was high blood pressure (70% in those with event versus 13.9% in those without event; p=0.0001).[30] Other included studies did not analyze risk factors for nADE among spontaneous controllers separately.

*Critical appraisal of studies included*

The five cohort studies had low or average quality scores ranging from 4/11 to 7/11 (Table S3). Main methodological issues were: insufficient identification of confounders in all five studies[17,20-23], lack of correcting for those identified in three studies,[17,22,23] no mention of pre-existing nADEs,[17,20-23] and insufficient reporting of follow-up duration .[17,20,21]

Possible confounders identified in the cohort studies on non-AIDS-events were limited to age, sex, ethnicity. Age and sex were comparable between study groups (Table S1). Ethnicity was only reported for the USA cohorts, with more than half of spontaneous controllers being black (58.4 % and 54.3%) and less than a third being white (23.5% and 33.9%) and the remainder mostly Hispanic (16.8% and 6.8%). In both studies, controllers were significantly more often black than the PLHIV on suppressive ART [20,21]. Other confounders were not reported (Table

S3A). A post-hoc chart review matching EC to PLHIV in the cohort from 2015 found higher rates of smoking in EC (82% vs. 68%, p=0.001).[20]

Overall quality of the subclinical CVD studies was good, ranging from 6/8 to 8/8 on the JBI critical appraisal checklist for cross-sectional studies (Table S3B).[6,7,32,33] The two cross-sectional studies on non-AIDS events had low quality scores of 4/8 due to the lack of a control group. The case series of non-AIDS malignancies from 2016 was of good quality (Table S3C).[34]



## Discussion

This systematic review of the literature shows that there is insufficient data to argue that the rate and prevalence of cardiovascular events, non-AIDS malignancies, hepatic disease, bacterial pneumonia and all-type nADEs is increased in ART-naïve individuals with spontaneous control of HIV-1 , compared to PLHIV on suppressive ART. Although it should be noted that the number of studies is limited and their heterogeneity substantial, the best available data comes from three large cohort studies, which do not support the presumption that spontaneous controllers are at an increased risk of various types of nADEs compared with PLHIV on suppressive ART.[21-23] Additionally, subclinical cardiovascular disease in spontaneous controllers, as in ART-receiving PLHIV[37], seemed higher compared to persons without HIV.

Varying incidence and prevalence between the five cohort studies of several nADEs in spontaneous controllers may be explained by control group characteristics. The observation by Dominguez-Molina et al. of significantly lower nADEs in EC and VC combined may be a reflection of the control group which includes 11% individuals not on ART,[22] as higher viremia

in PLHIV is associated with nADEs.[38,39] Similarly, the more favorable survival time in EC and VC compared with noncontrollers found by Okulicz et al. could be, at least in part, due to an unknown percentage of untreated PLHIV in the control group.[17] Variations in event rates may further be explained by variation in biological sex (ranging from 49.7% to 90%), ethnicity, and age, since cohorts derived from the USA Natural History Study were substantially younger than the other cohorts.[21,40] Finally, three cohorts reported hospitalization rates,[10,21,40] which may not fully reflect the nADE rates reported by others.[22,23] Whereas the cohort studies compared types of nADE in spontaneous controllers exclusively to noncontrollers or PLHIV on suppressive ART, cross-sectional studies on subclinical cardiovascular disease compared spontaneous controllers also to people without HIV. Both coronary plaque prevalence on CTA and carotid IMT were higher among EC compared with people without HIV, but comparable to PLHIV on suppressive ART.[6,7] A large study could not reproduce these results, probably because nearly half of the spontaneous controllers did not apply to the HIV controller definition anymore at the time of measurement, due to the time elapsed since enrollment.[32]

The 2015 paper by Crowell et al. stands out as the only one with higher observed rates of cardiovascular event-related and all-cause hospitalizations among EC, relative to PLHIV on suppressive ART.[20] Absolute event rates per 100PY in EC from the USA were surprisingly high; more than twice the rate found in another USA HIV controller cohort[21] and at least twenty times the rate of events found in two Spanish cohorts.[22,23] At least four factors may explain why Crowell et al. observed that many events among EC. First, the follow-up duration was limited with 149 EC contributing to 369PY of follow-up. Moreover, person-years with low $CD4^+$ T cell counts were excluded from the analysis (below 200 cells/$mm^3$ or on two consecutive years below <350 cells/$mm^3$). As lower $CD4^+$ T cell counts are a risk factor nADEs[41] and average $CD4^+$ T

cell counts are substantially higher in spontaneous controllers than PLHIV on suppressive ART,[40,42] this may have relatively decreased the observed hospitalization rates of PLHIV on suppressive ART. Moreover, smoking was more common among EC and data on other cardiovascular risk factors were unavailable.[20] Finally, events in PLHIV on suppressive ART were potentially underreported, as they could also contribute person years, and therefore events, to viremic groups when viremia occurred during follow-up. Taken together, these factors may explain why only the study by Crowell et al. from 2015 found higher rates of nADEs in EC compared with PLWH on suppressive ART, contrary to the other studies.

We did not identify studies comparing nADEs between ART-treated and ART-naïve spontaneous controllers. Currently, ART is often initiated in spontaneous controllers, especially in VC who have detectable viral loads or in those with decreasing $CD4^+$ T cell counts.[17] Other reasons to initiate ART in spontaneous controllers are anticipated loss of virological or immunological control; preventing HIV transmission for viremic controllers; limiting inflammation; a high-cardiovascular risk profile; and patient preference.[3,43] It has been suggested to monitor $CD4^+$ T cell count patterns, including $CD4^+$:$CD8^+$ ratio, and viral load measurements to anticipate loss of spontaneous control.[3,44] However, ART in spontaneous controllers does not reduce inflammatory biomarkers such as sCD14, IL-6, D-dimer, and hsCRP.[16,19] Indeed, the data in our review shows that, overall, spontaneous controllers seem to have the same risk of cardiovascular disease, non-AIDS malignancies, hepatic disease, bacterial pneumonia as PLHIV on suppressive ART. This should be clearly stated in HIV treatment guidelines, which currently advice treatment in all PLHIV (WHO, BHIVA, EACS, DHHS, IAS),[45-49] even though two guidelines briefly mention the uncertainty regarding the benefit of ART regarding spontaneous controllers (DDHS, IAS).[48,49] The impact of ART initiation in spontaneous controllers on these

nADEs is unknown and ART may not reduce nADE rates to those in people without HIV.[16,19] Rather, proactive personalized cardiovascular risk management in spontaneous controllers is essential,[21] taking into account general nADE-associated risk factors for all PLHIV, such as higher age and intravenous drug use.[20-23,30,31] Likewise, appropriate immunizations and monitoring of hepatic disease should be advised, according to guidelines for noncontrolling PLHIV on ART.[48,49] Hepatitis C infection seems to be a risk factor for cardiovascular events and all-type nADEs in spontaneous controllers,[22,31] whereas successfully treated or cleared HCV was not associated with cardiovascular events.[30]

Our study is the first systematic analysis of studies evaluating nADEs in spontaneous controllers, and also separately analyzes different types of nADEs. Previous non-systematic analyses attributed differences between studies to varying definitions of spontaneous controllers. Our review shows that the control group definitions also strongly impact the results. The strength of our systematic review is that the search strategy and study design are reproducible and evidence-informed,[50,51] and the predefined protocol was published on PROSPERO. Furthermore, structured critical appraisal with the JBI checklists has been used widely, also in the field of HIV.[52-54] A limitation is the heterogeneity between studies, which prevented a quantitative meta-analysis. Cross-cohort alignment of both HIV controller definitions, control groups, and outcome measures is needed to facilitate a meta-analysis of HIV controller cohorts to determine the impact of ART and nADE-type-specific interventions in this population. Another limitation is that for some studies, individuals were mostly male.[6,7,17,21,33] More spontaneous controller cohorts are needed, as the available studies originated from a limited number of study populations with overlap between cohorts. No studies were conducted in Asia, Africa, Eastern Europe or Latin America. Additionally, since no study focuses on elderly populations, continued

follow-up may prove valuable to evaluate cerebrovascular disease and malignancies. Our qualitative synthesis describes the variety across studies, and shows that spontaneous controllers are most likely not at an increased risk of any type of nADE compared with PLHIV on suppressive ART.

## Conclusion

In this systematic review, ART-naïve individuals with spontaneous control of HIV-1 did not seem to have a greater risk of various types of nADEs compared with noncontrolling PLHIV on suppressive ART. Similar to ART-receiving PLHIV, the risk of subclinical cardiovascular disease seems to be higher for ART-naïve spontaneous controllers than for persons without HIV. Compliance with existing prevention and management guidelines for nADEs is therefore strongly recommended, while the impact of ART on nADEs in spontaneous controllers is unknown.

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**Table 1 - Cardiovascular disease among individuals with spontaneous control of HIV-1**

**A CARDIOVASCULAR NON-AIDS DEFINING EVENTS**

| Study | HIV controllers | EC | VC | EC/VC combined | PLWH on suppressive ART | Noncontrollers | HIV-uninfected |
|---|---|---|---|---|---|---|---|
| **France**[30]<br>N=269 HIV controllers | cardiovascular nADE prevalence 4% (10/269) | - | - | - | - | - | - |
| **United States**[21]<br>N=33 EC & 188 VC (882 PY)<br>N=870 on ART (4217 PY) | - | - | - | 0.45 per 100PY (95%CI 0.12-1.15) | 0.76 per 100PY (95%CI 0.52-1.07) p=0.46 | - | - |
| **Spain**[22]<br>N=138 EC & 182 VC (5191.5 PY)<br>n=632 'noncontrollers', 89% on ART (7981.6 PY) | - | - | - | 0.212 per 100PY (95%CI 0.110-0.379) | - | 0.501 per 100PY (95%CI 0.358-0.682) p=0.007 | - |

**B CROSS SECTIONAL CARDIOVASCULAR IMAGING STUDIES**

| CTA coronary artery plaque (prevalence) | HIV controllers | EC | VC | EC/VC combined | PLWH on suppressive ART | Noncontrollers | HIV-uninfected |
|---|---|---|---|---|---|---|---|
| **United States**[6]<br>N=10 EC<br>N =103 on ART<br>N =49 without HIV | - | 78% (7/9) | - | - | 60% (62/103) p=0.28 | - | 42% (21/49) p=0.03 |
| **United States**[32]; *MACS*<br>N=11 EC & 67 VC<br>N =483 on ART<br>N =499 without HIV | - | "similar to HIV-uninfected" (data not available) | - | - | - | - | - |
| **CT (conventional or CTA) coronary artery calcium prevalence** | **HIV controllers** | **EC** | **VC** | **EC/VC combined** | **PLWH on suppressive ART** | **Noncontrollers** | **HIV-uninfected** |
| **United States**[6]<br>N=10 EC<br>N =103 on ART<br>N =49 without HIV | - | 70% (7/10) | - | - | 41% (42/103) p=0.11 | - | 34% (17/49) p=0.11 |
| **United States**[32]; *MACS*<br>N=11 EC & 67 VC<br>N =483 on ART<br>N =499 without HIV | - | - | - | only available for EC/VC/LTNP combined (11.2%) | 35.9% | - | 38.6% |

| B-mode US CCA median IMT (µm) | HIV controllers | EC | VC | EC/VC combined | PLWH on suppressive ART | Noncontrollers | HIV-uninfected |
|---|---|---|---|---|---|---|---|
| **United States**[7]<br>N =33 EC<br>N =180 on ART<br>N =93 without HIV | - | 910 | - | - | IMT unavailable p=0.49 | - | 720 p<0.001 |
| **United States**[32]; *MACS*<br>N=11 EC & 67 VC<br>N =483 on ART<br>N =499 without HIV | - | 704 (674-775) | 759 (674-889) | - | 717 (659-810) | - | 739 (IQR 676-831) non-significant |
| **United States**[32]; *WIHS*<br>N=19 EC & 38 VC<br>N =657 on ART<br>N =493 without HIV | - | 736 (682-787) | 715 (686-753) | - | 710 (646-778) | - | 702 (IQR 642-769) non-significant |
| **B-mode US CCA plaque prevalence** | **HIV controllers** | **EC** | **VC** | **EC/VC combined** | **PLWH on suppressive ART** | **Noncontrollers** | **HIV-uninfected** |
| **United States**[32]; *MACS*<br>N=11 EC & 67 VC<br>N =483 on ART<br>N =499 without HIV | - | 27.3% (3/11) | 29.9% (20/67) | - | 26.9% (130/439) | - | 29.3% (146/499) non-significant |
| **United States**[32]; *WIHS*<br>N=19 EC & 38 VC<br>N =657 on ART<br>N =493 without HIV | - | 5.3% (1/19) | 2.6% (1/38) | - | 8.9% (46/516) | - | 6.5% (32/496) non-significant |
| **Aortic inflammation on PET-CT (target to background ratio)** | **HIV controllers** | **EC** | **VC** | **EC/VC together** | **ART-suppressed** | **noncontrollers** | **HIV-uninfected** |
| **United States**[33]<br>N= 7 EC<br>N= 34 on ART<br>N= 29 without HIV | - | "similar to HIV-uninfected and ART-suppressed" (data in Figure S1*) | - | - | - | - | - |

HIV controllers were defined as viral load cut-off of <400 copies/mL; EC as undetectable (cut-off <50, <75 or <80 copies/mL); VC as detectable viremia ≤2000 copies/mL. In some studies, analyses were done with EC and VC combined. PLWH on suppressive ART had the same viral load cutoffs as elite controllers. Noncontrollers were those not applying to controller definitions with varying ART-exposure. ART, antiretroviral treatment; CTA, CT angiography; CCA, common carotid artery; IMT, intima-media thickness; MACS, Multicenter AIDS Cohort Study; PET-CT, positron-emission tomography and computed tomography; PY, person years of follow-up; LTNP, long term non-progressor; WHIS, Women's Interagency HIV Study.

*Figure S1 of original paper[33]

**Table 2 - Non-AIDS malignancies among individuals with spontaneous control of HIV-1**

| | HIV controllers | EC | VC | EC/VC combined | PLWH on suppressive ART | Noncontrollers | HIV-uninfected |
|---|---|---|---|---|---|---|---|
| **France**[34] *ANRS*<br>N=272 HIV controllers | prevalence 1.47% (4/272) | - | - | - | - | - | - |
| **United States**[34]; *NHS*<br>N=36 EC & 231 VC | - | prevalence 11.1% (4/36) | prevalence 3.46% (8/231) | - | - | - | - |
| **United States**[21]<br>N=33 EC & 188 VC (882 PY)<br>N=870 on ART (4217 PY) | - | - | - | 0.11 per 100PY (95%CI 0.002-0.63) | 0.47 per 100PY (95%CI 0.29-0.73) p=0.19 | - | - |
| **Spain**[22]<br>N=138 EC & 182 VC (5191.5 PY)<br>n=632 'noncontrollers', 89% on ART (7981.6 PY) | - | - | - | 0.308 per 100PY (95%CI 0.176-0.501) | - | 0.451 per 100PY (95%CI 0.316-0.624) p=0.20 | - |

HIV controllers were defined as viral load cut-off of <400 copies/mL; EC as undetectable (cut-off <50, <75 or <80 copies/mL); VC as detectable viremia ≤2000 copies/mL. In some studies, analyses were done with EC and VC combined. PLWH on suppressive ART had the same viral load cutoffs as elite controllers. Noncontrollers were those not applying to controller definitions with varying ART-exposure.

ANRS, 'Association Nationale de Réadaptation Sociale' National Association of Social Rehabilitation; ART, antiretroviral treatment; PY, person years of follow-up; NHS, (US military) natural history study.

**Table 3 – All-type non-AIDS defining events, hospitalizations and survival among individuals with spontaneous control of HIV-1**

| Any non-AIDS defining event | HIV controllers | EC | VC | EC/VC combined | PLWH on suppressive ART | Noncontrollers | HIV-uninfected |
|---|---|---|---|---|---|---|---|
| **Spain**[22] N=138 EC & 182 VC (5191.5 PY) N=632 noncontrollers, 89% on ART (7981.6 PY) | - | - | - | 1.252 per 100PY (95%CI 0.974-1.586) | - | 2.481 per 100PY (95%CI 2.153-2.845) p<0.0001 | - |
| **Spain**[23] N=64 EC & 76 VC N=434 'noncontrollers', 78% on ART (6062 PY for entire cohort) | - | 1.1 per 100PY (95%CI 0.6-1.9) | 1.0 per 100PY (95%CI 0.5-1.8) | - | - | 1.5 per 100PY (95%CI 1.2-1.9) p=0.25 | - |
| **United States**[31] N=55 HIV controllers | History of nADE 35% (19/55) | - | - | - | - | - | - |
| **All-cause hospitalizations** | **HIV controllers** | **EC** | **VC** | **EC/VC combined** | **PLWH on suppressive ART** | **Noncontrollers** | **HIV-uninfected** |
| **United States**[17] N=25 EC & 153 VC N=4290 noncontrollers, % on ART unknown (PY unknown) | - | history of hospitalization 28.0% (7/25) | history of hospitalization 34.0% (52/153) | - | - | history of hospitalization 41.0% (729/1778) | - |
| **United States**[20] N=149 EC (369 PY) N=9226 on ART (26176 PY) | - | 23.3 per 100PY (95%CI 19.1-28.0) | - | - | 10.5 per 100PY (95%CI 1.3-15.6) adjusted p<0.05 | - | - |
| **United States**[21] N=33 EC & 188 VC (882 PY) N=870 on ART (4217 PY) | - | - | - | 9.4 per 100PY (95%CI 7.6-11.5) | 8.8 per 100PY (95%CI 8.0-9.7) adjusted p>0.05 | - | - |

HIV controllers were defined as viral load cut-off of <400 copies/mL; EC as undetectable (cut-off <50, <75 or <80 copies/mL); VC as detectable viremia ≤2000 copies/mL. In some studies, analyses were done with EC and VC combined. PLWH on suppressive ART had the same viral load cutoffs as elite controllers. Noncontrollers were those not applying to controller definitions with varying ART-exposure.

ART, antiretroviral treatment; PY, person years of follow-up.

**Table 4 – Hepatitis C co-infection as risk factor for non-AIDS defining events in individuals with spontaneous control of HIV-1**

| Study | Definition | Outcome | Factor | Association |
|---|---|---|---|---|
| **France**[30] N=269 HIV controllers | HIV controllers | Risk of CVD | HCV seropositivity (IgG+) | 30% (3/10) HCV IgG seropositive in those with CVD event, 21.1% (52/247) in those without CVD event p=0.45 |
| **Spain**[22] N=138 EC & 182 VC (5191.5 PY) vs. n=632 'noncontrollers' (7981.6 PY) | EC/VC combined | Risk of any nADE | HCV co-infection (PCR+) | OR 3.361 (1.495-7.556) p=0.002 |
| **United States**[31]; N=55 HIV controllers | HIV controllers | Risk of "complications" | HCV co-infection (PCR+) | aHR 4.78 (95%CI 1.50-15.28) p=0.01 |

HIV controllers were defined as viral load cut-off of <400 copies/mL; EC as undetectable (cut-off <50, <75 or <80 copies/mL); VC as detectable viremia ≤2000 copies/mL. PLWH on suppressive ART had the same viral load cutoffs as elite controllers. Noncontrollers were those not applying to controller definitions with varying ART-exposure.

ART, antiretroviral treatment; HCV, hepatitis C virus; nADE, non-AIDS defining events; PY, person years of follow-up.