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MAJOR ARTICLE

Non-AIDS-Defining Events in Human Immunodeficiency Virus Controllers Versus Antiretroviral Therapy–Controlled Patients: A Cohort Collaboration From the French National Agency for Research on AIDS CO21 (CODEX) and CO06 (PRIMO) Cohorts

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Background. Low-grade chronic inflammation may persist in spontaneous human immunodeficiency virus controllers (HICs), leading to non-AIDS-defining events (nADEs).

Methods. Two hundred twenty-seven antiretroviral therapy (ART)–naive HICs (known human immunodeficiency virus type 1 [HIV-1] infection ≥5 years and at least 5 consecutive viral loads [VLs] <400 HIV RNA copies/mL) were compared with 328 patients who initiated ART ≤1 month after primary HIV infection diagnosis and had undetectable VL within 12 months following ART initiation for at least 5 years. Incidence rates of first nADEs were compared between HICs and ART-treated patients. Determinants of nADEs were assessed by using Cox regression models.

Results. All-cause nADEs incidence rates were 7.8 (95% confidence interval [CI], 5.9–9.6) and 5.2 (95% CI, 3.9–6.4) per 100 person-months among HICs and ART patients, respectively (incidence rate ratio [IRR], 1.5 [95% CI, 1.1–2.2]; adjusted IRR, 1.93 [95% CI, 1.16–3.20]). After adjustment for the cohort, demographic, and immunological characteristics, the only other factor associated with all-cause nADE occurrence was age ≥43 (vs <43) years at the beginning of viral control (IRR, 1.69 [95% CI, 1.11–2.56]). The most frequent events observed in the 2 cohorts were non-AIDS-related benign infections (54.6% and 32.9% of all nADEs, respectively, for HICs and ART patients). No differences in cardiovascular or psychiatric events were observed.

Conclusions. HICs experienced 2 times more nADEs than virologically suppressed patients on ART, mainly non-AIDS-related benign infections. Older age was associated with nADE occurrence, independent of immune or virologic parameters. These results do not argue in favor of expanding the ART indication for HICs but rather a case-by-case approach considering clinical outcomes such as nADEs besides immune activation.

Keywords. ART; controllers; HIV; non-AIDS-defining events; primary infection.

International guidelines recommend systematic and immediate initiation of antiretroviral therapy (ART) regardless of the presence or absence of symptomatology, CD4 T-cell count, or viral load (VL) level. This earliness includes many advantages such as the reduction of chronic systemic inflammation and immune activation [1, 2], which plays a major role in the occurrence of nADEs [3]. However, immunity is not fully restored for all patients [4]. Many markers of inflammation, which reflect chronic immune activation, remain higher than in the general population [5, 6]. Consequently, an excess risk of non-AIDS-defining events (nADEs) compared to the general population persists, such as malignancies; cardiovascular, liver, kidney, bone, and neuropsychiatric diseases; and a raised associated mortality, especially in patients with a CD4 count <500 cells/μL [7–9].

Human immunodeficiency virus (HIV) controllers (HICs), representing <1% of people living with HIV (PLWH), can maintain low or undetectable viremia for a sustained time in the absence of ART, due to several intricate mechanisms

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[10, 11]. The definition of HICs is based on the plasma VL through standard methods, regardless of CD4 T-cell counts, but may vary depending on the geographic area [12]. In the United States (US), HICs are divided into 2 groups based on at least 3 VLs over at least 1 year: elite controllers (HIV RNA <50 copies/mL) and viremic controllers (HIV RNA <2000 copies/mL) [13]. In France, within the French National Agency for Research on AIDS (ANRS) CODEX cohort, HICs are defined as patients naive to ART with at least 5 VLs <400 copies/mL over at least 5 years [14]. Conflicting results suggest that, compared to ART patients, HICs present either similar or higher systemic chronic inflammation [15–17] that may induce a higher risk of nADEs. Some authors reported some immunovirological benefit of ART among HICs, but this remains controversial [18–20]. Indeed, the benefit of ART on clinical outcomes in HICs has been poorly documented [21].

Clinical outcomes, especially nADEs among HICs, have been rarely evaluated. Crowell et al described a higher risk of non-AIDS-related hospitalizations among elite controllers than among patients on ART [22] in 1 study, but a similar risk among these 2 groups in another study involving a Veteran population [23]. In the Spanish cohort, Lucero et al [24] found either similar or lower risk among HICs compared to the ART group, depending on the definition of the study population, whereas Dominguez-Molina et al reported a lower risk of nADEs in HICs than ART patients [25].

We therefore assessed the rates and predictive factors of nADEs in HICs followed in the fully documented ANRS CODEX cohort in comparison to those of ART-controlled patients from the ANRS PRIMO cohort in France.

METHODS

Study Design and Population

Study populations were recruited from 2 French multicenter cohorts: ANRS CO21 CODEX [14] and ANRS CO6 PRIMO [26]. Demographic, clinical, and nADE data were collected in the same centers by the same medical staff in each cohort.

In the ANRS CODEX cohort, HICs were enrolled based on ≥5 years of known HIV infection (at least 5 last consecutive VLs <400 HIV RNA copies/mL) and controlling their HIV infection in the absence of ART (regardless of the CD4 T-cell count).

In the ANRS PRIMO cohort, patients presenting during acute or early HIV infection were enrolled. Patients who initiated ART within 1 month following diagnosis, who had a VL below the limit of detection ≤12 months following ART initiation and maintained this virological control on ART for at least 5 years, met the inclusion criteria for this study (Supplementary Figure 1).

Patient Consent Statement

In compliance with the tenets of the declaration of Helsinki and the requirements of the French Jardet law, each patient signed an informed consent form. Both the French ANRS cohorts PRIMO CO6 and CODEX CO21 have been approved by the national ethical committee (Comité de Protection des Personnes).

Outcomes

The nADEs were categorized as follows: all-cause, cardiovascular disease (CVD) (coronary artery, cerebrovascular, and peripheral arterial diseases, dilated cardiomyopathy), pulmonary (chronic obstructive pulmonary disease and community bacterial pneumonia, pulmonary embolism), hepatic (viral hepatitis), psychiatric (reported depression, psychosis, suicide attempt), bone (spontaneous nontraumatic fractures), malignancies (any system), and non-AIDS-related infections (bronchitis, upper respiratory tract infection, gastroenteritis, upper or lower urinary tract infections). Other nADEs (traumatic fracture, renal colic, hepatic colic) were considered as a category. All nADE events and the final classification were reviewed independently by 2 authors (A. C. and N. N.).

Other Covariates

We studied the following risk factors for nADEs: sociodemographic parameters (gender, age at the beginning of the observation period, ethnicity, and lifestyle [tobacco and alcohol intake]) as reported by the patient; HIV transmission risk factors (intravenous drug use, sexual transmission, blood exposure accident, or other) were also self-reported. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection status was assessed at the beginning of the observation period, as well as hypertension, diabetes mellitus, and dyslipidemia. We considered as the baseline of CD4 T cells, CD8 T cells, and CD4/CD8 ratio the closest values to the beginning of the observation period. Past medical history of nADE was considered as a potential risk factor for incident nADE.

Statistical Analysis

We used frequency and percentage to express categorical variables and median and interquartile range (IQR) to express continuous variables. We performed χ^2 and Mann-Whitney tests for comparing categorical and continuous variables across categories, respectively.

The observation period started at enrollment in the CODEX cohort to consider only incident nADEs, and 5 years after the initiation of ART in the PRIMO cohort to fulfill the same criteria (≥5 years of known HIV infection with at least 5 consecutive VLs <400 HIV RNA copies/mL).

The observation period was censored at the time of loss of virological control (2 consecutive VLs >2000 copies/mL), initiation of ART for HICs, or at the last available viremia

measurement if control was still effective. Isolated detectable VLs between 400 and 2000 copies/mL (defined as blips) were allowed during the control period for both populations.

For each cohort, the total number of first all-cause and first cause-specific nADEs was used as the numerator and the sum of each patient person-time as the denominator to calculate the incidence rate of first nADE, expressed as a number per 100 person-years of follow-up, along with its 95% confidence interval (CI). The comparison between the 2 cohorts was realized using incidence rate ratios (IRRs) and their 95% CIs, in which the PRIMO cohort was the reference. Adjusted IRRs were used to estimate associations between the cohort and the risk of nADEs, adjusted for covariates. Independent factors (year of diagnosis, gender, age, ethnicity, HBV/HCV coinfection, tobacco use, history of nADEs, baseline CD4 T-cell count) were selected from several models comprising the factor and the cohort. Known potential confounders and variables with a $P < .25$ in univariate analysis were included in multivariate Cox regression models. Kaplan Meier curves were also plotted. For all models used in this study, the proportionality of the risks has been checked. All analyses were performed using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

Patient Characteristics

Study group characteristics are described in Table 1 and Supplementary Figure 1. The 227 HICs were more likely to be female, of African ethnicity, and infected through injection drug use than the 328 ART patients. HICs were older than ART patients ($P = .005$). They were also more likely to have a history of HBV and HCV infection. Six HICs (2.6%) and 5 ART patients (1.5%) had active HBV infections (positive hepatitis B surface antigen). HICs were less likely to report smoking, although the difference was not statistically significant.

No difference in terms of baseline CD4 T-cell count or CD4/CD8 ratio was observed. The median duration of observation with viral control was significantly longer in HICs than in ART patients (5.0 [IQR, 2.8–7.1] vs 2.5 [IQR, 1.2–6.4] years). The proportion of patients who presented at least 1 blip, as well as the number of blips during the viral control, was higher in HICs than in the ART patients. However, the median value of the blips was lower in HICs than in ART-treated patients (2.8 compared to 4.5 $\log_{10}$ copies/mL; $P < .0001$).

Non-AIDS-Defining Events

During the observation period, 68 HICs and 62 ART patients experienced at least 1 nADE for a total count of 88 and 76 nADEs, respectively.

All-cause nADEs IRs were 7.8 (95% CI, 5.9–9.6) and 5.2 (95% CI, 3.9–6.4) per 100 person-months among HICs and ART patients, respectively, leading to a crude IRR for nADEs in HICs versus ART patients of 1.5 (95% CI, 1.1–2.2). The difference between the 2 groups was due to the "non-AIDS-related infections" category with a crude IRR statistically higher in HICs compared to ART patients (IRR, 2.2 [95% CI, 1.3–3.8]).

Table 1. Characteristics of the Study Population at the Beginning of the Observation Period (N = 555)

Characteristic	HIV Control Status		*P* Value
	HIC Group (n = 227)	ART Group (n = 328)	
Duration of observation, y	5.0 (2.8–7.1)	2.5 (1.2–6.4)	.0877
Year of HIV diagnosis			**<.0001**
2000 or earlier	117 (51.5)	67 (20.4)	
2001–2007	88 (38.8)	97 (29.6)	
2008–2013	22 (9.7)	164 (50.0)	
Age, y	45 (39–52)	42 (35–49)	.0055
Female	129 (56.8)	45 (13.7)	**<.0001**
Ethnicity			**<.0001**
White	134 (59.1)	298 (90.9)	
Black	87 (38.3)	24 (7.3)	
Other	6 (2.6)	6 (1.8)	
HIV risk factor			**<.0001**
Sexual	171 (75.3)	306 (93.3)	
IDU	36 (15.9)	0 (0.0)	
Blood exposure	20 (8.8)	22 (6.7)	
Tobacco use	102 (44.9)	174 (53.1)	.06
Alcohol use (n = 348)	60 (58.3)	142 (58.0)	.96
HBV or HCV status (n = 489)			**<.0001**
HIV monoinfection	103 (48.1)	208 (75.6)	
HBV antibody positive[a]	98 (45.8)	60 (21.8)	
HCV antibody positive	13 (6.1)	7 (2.6)	
Past history of nADEs	24 (10.6)	70 (25.3)	.0009
Past history of other diseases[b]	10 (4.4)	8 (2.4)	.20
Baseline[c] CD4 T-cell count (n = 520)	735 (580–942)	741 (569–948)	.69
<500 cells/μL	35 (16.6)	43 (13.9)	.40
≥500 cells/μL	176 (83.4)	266 (86.1)	
Baseline[c] CD8 T-cell count (n = 498)	643(460–926)	625 (453–872)	.61
<632 cells/μL	101 (48.6)	148 (51.0)	.59
≥632 cells/μL	107 (51.4)	142 (49.0)	
Median CD4/CD8 ratio (n = 498)	1.14 (0.80–1.60)	1.20 (0.90–1.58)	.93
CD4/CD8 ratio <1 (n = 498)	77 (44.0)	98 (56.0)	.47
Viral load			
No. of patients with ≥1 virological blip during observation period	25 (11.0)	4 (1.8)	**<.0001**
Median VL in case blip, $\log_{10}$ copies/mL	2.8 (2.6–2.9)	4.5 (4.1–4.6)	**<.0001**

We used frequency and percentage to express categorical variables and median and interquartile range to express continuous variables. Values in bold are considered statistically significant.

Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIC, human immunodeficiency virus controller; HIV, human immunodeficiency virus; IDU, intravenous drug use; nADE, non-AIDS-defining event; VL, viral load.

[a]HBV coinfection: 6 (2.6%) and 5 (1.5%) were active infections in HICs and ART patients, respectively.

[b]Other diseases: hypertension, dyslipidemia, and diabetes mellitus diagnosed before the beginning of the observation period.

[c]Baseline means within a window period of −12 and +12 months around the beginning of the observation period.

Regarding other cause-specific nADEs, no statistical difference was observed between the 2 groups for cardiovascular (IRR, 0.9 [95% CI, .2–3.6]), pulmonary (IRR, 1.1 [95% CI, .3–4.3]), hepatic (IRR, 0.4 [95% CI, .1–1.7]), psychiatric (IRR, 1.6 [95% CI, .6–4.4]), malignancies (IRR, 0.6 [95% CI, .2–2.0]), or bone (IRR, 0.8 [95% CI, .1–10.6]) categories (Table 2).

The most common total count cause-specific events for HICs and ART patients were non-AIDS-related infections (54.6% and 32.9%, respectively, $P = .0012$), followed by psychiatric (13.6% and 13.2%, respectively, $P = .42$), malignancies (5.7% and 13.2%, respectively, $P = .55$), pulmonary (6.9% and 8.0%, respectively, $P = .76$), and cardiovascular events (4.5% and 7.9%, respectively, $P = .95$) (Figure 1), without any significant differences between the 2 cohorts. Non-AIDS-related infections were located in the bronchi, and the ear-nose-throat (ENT), digestive, and urinary systems. All reported infections were nonsevere and did not lead to hospitalizations (Supplementary Table 1). The 15 malignancies (5 in HICs, 10 in ART patients) affected all organs: digestive (large and small bowels, liver, rectum, pancreas), genital (breast), respiratory (lung), and ENT (tonsil, larynx). No renal failure was collected among HICs whereas 2 cases of renal failure were declared in the ART group.

We observed 2 (0.9%) and 4 (1.2%) non-AIDS-related deaths among the HIC group and ART group, respectively ($P = .70$); causes of death were: pulmonary adenocarcinoma and alcoholic cirrhosis for HICs, and rectal carcinoma and pancreatic

Table 2. All-Cause and Cause-Specific Incidence Rates of First Non-AIDS-Defining Events, by HIV Control Status

	HIC Group			ART Group			
nADEs Category	No.	PM	IR (95% CI)	No.	PM	IR (95% CI)	IRR (95% CI)
All-cause	68	876.0	7.8 (5.9–9.6)	62	1202.3	5.2 (3.9–6.4)	**1.5 (1.1–2.2)**
Cardiovascular	4	1080.2	0.4 (.0–.7)	6	1386.1	0.4 (.1–.8)	0.9 (.2–3.6)
Pulmonary	5	1073.0	0.5 (.1–.9)	6	1409.6	0.4 (.1–.8)	1.1 (.3–4.3)
Hepatic	3	1090.2	0.3 (.0–.6)	9	1400.8	0.6 (.2–1.1)	0.4 (.1–1.7)
Psychiatric	11	1047.1	1.1 (.4–1.7)	9	1395.7	0.6 (.2–1.1)	1.6 (.6–4.4)
Malignancies	5	1088.4	0.5 (.1–.4)	10	1386.2	0.7 (.3–1.2)	0.6 (.2–2.0)
Bone	2	1086.0	0.2 (.0–.2)	2	1414.5	0.1 (.0–.3)	0.8 (.1–10.6)
Non-AIDS-related infections	40	974.1	4.1 (2.8–5.4)	25	1326.8	1.9 (1.2–2.6)	**2.2 (1.3–3.7)**
Other nADEs[a]	8	1077.2	0.7 (.2–1.3)	8	1382.6	0.6 (.2–1.0)	1.3 (.4–3.9)

Values in bold are considered statistically significant.

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIC, human immunodeficiency virus controller; HIV, human immunodeficiency virus; IR, incidence rate (per 100 person-months); IRR, incidence rate ratio; nADE, non-AIDS-defining event; PM, person-months.

[a]Other nADEs: traumatic fracture, renal colic, hepatic colic.

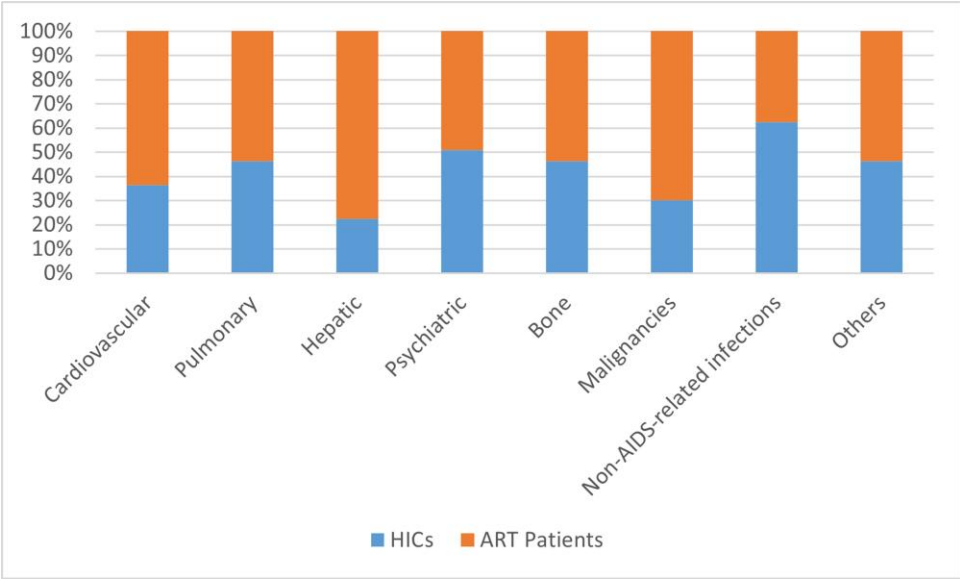

Figure 1. Distribution of specific-cause non-AIDS-defining events among all non-AIDS-defining events, in human immunodeficiency virus controller (HIC) and antiretroviral therapy (ART) patient groups.

adenocarcinoma, hepatocarcinoma, and cardiac failure for ART patients.

Besides nADEs, 2 (0.9%) cases of tuberculosis among HICs and 2 cases of tuberculosis and 1 case of Kaposi sarcoma (0.9%) among ART-treated patients were identified as AIDS events.

Associated Factors

In a multivariate model (Table 3) including HIV control status, year of diagnosis, age, gender, ethnicity, tobacco use, history of nADEs, HBV/HCV status, and baseline CD4 T-cell counts, the risk of all-cause nADEs was significantly different in HICs compared to ART patients (aIRR, 1.93 [95% CI, 1.16–3.20]). Age ≥43 (vs <43) years was significantly associated with a higher risk of all-cause nADEs among HICs in both unadjusted (IRR, 1.76 [95% CI, 1.22–2.54]) and adjusted (aIRR, 1.69 [95% CI, 1.11–2.56]) models. None of the other studied factors was associated with the occurrence of nADEs.

The association of non-AIDS-related infections and different covariates was also assessed by using Cox regression models after adjustment for the HIV control status, demographic, and immunological characteristics (Supplementary Table 2). The adjusted IRR (aIRR) for non-AIDS-related infections in HICs versus ART patients was 2.85 (95% CI, 1.40–5.80). For age and CD4 T-cell count, the aIRRs were 1.27 (95% CI, .72–2.24) and 1.12 (95% CI, .52–2.40), respectively. None of the other studied factors were associated with the occurrence of non-AIDS-related infections. No factor other than age was associated with noninfectious nADEs (Supplementary Table 3).

DISCUSSION

Our study shows that (1) HICs experienced 2 times more all-cause nADEs than ART-treated patients from the PRIMO cohort, (2) non-AIDS-related infections represented the most common type of nADE, and (3) age was the only independent factor associated with all-cause nADE occurrence, whereas immunovirological parameters were not significantly associated with nADE occurrence.

The main nADEs in our study were non-AIDS-related infections, followed by psychiatric events, malignancies, and pulmonary and cardiovascular events. These findings are in line with previous reports on the overall risk of nADEs in PLWH [27, 28]. More specifically in HICs, Crowell et al showed that non-AIDS-related infections were the most common nADEs followed by cardiovascular, gastrointestinal/liver, and psychiatric events in a US Veteran cohort [23]. Dominguez-Molina et al [25] reported that hepatic diseases, bacterial pneumonia, and cancer were the main events, and Lucero et al [24] reported similar findings (surgery procedures followed by infections, non-AIDS-defining malignancies, and CVD) in HICs. Of note, only benign infections were observed in our study, without any need for hospitalization (Supplementary Table 1). In contrast, the frequency of cancer was lower in our study compared with the Spanish studies.

Factors such as the duration of viral control and CD4 T-cell counts/CD4:CD8 ratio are associated with the risk of HIV disease progression among PLWH [4]. Thus, differences in the definition of viral control might influence the risk of reported nADEs in controllers. In the present study, HICs were defined based on 5 years of spontaneous viral control and were ART naive, in line with the CODEX cohort criteria, which is a stricter definition than some other cohorts of HICs [13]. All HICs remained ART naive and maintained viral control across the follow-up period (ie, no viral progression or loss of HIC definition) [29, 30]. In their study on 140 controllers (64 elite controllers, 76 viremic controllers) compared to 434 patients on ART, Lucero et al [24] observed non-AIDS-defining events at a similar rate between controllers and noncontrollers. However, when a stricter redefinition of elite controllers was used (all VLs below detectable level), no nADEs were observed. In our study, we could not estimate the association between blips and nADEs because of the limited number of blips.

Immunological parameters might influence the risk of clinical events. In their first study showing a higher rate of hospitalizations related to nADEs in HICs than ART-controlled patients, Crowell et al excluded patients whose CD4 T-cell counts were <200 cells/μL [22]. In another study, without any selection on the CD4 T-cell count, the authors described a similar risk in controllers and ART-controlled patients [23]. Dominguez-Molina et al reported a lower risk of nADEs among controllers compared to ART patients in all CD4 T-cell count strata [25]. In our study, neither CD4 T-cell counts nor CD4/CD8 ratio was associated with the risk of nADEs.

Crowell et al highlighted CVD as the main contributors of nADEs in elite controllers selected from routine consultation in the US [22], and some studies point to a cardiovascular risk in this population [31, 32]. In this study as well as in our previous work, we did not confirm this risk in the French cohort [33]. Our findings are rather similar to other cohorts of controllers [24, 25]. The difference in the prevalence of cardiovascular risk factors such as tobacco use, hypertension, diabetes mellitus, and obesity in each country might explain this difference. Several studies have established the link between immune activation/inflammation and a higher risk of clinical events among PLWH, especially the risk of CVD [8, 34, 35]. In our previous studies, we showed that some HICs had detectable immune activation and inflammatory biomarkers [15, 36], whereas HICs with virological control during the entire observation period had very low levels of inflammation [14]. However, we could not test the role of immune activation for nADEs occurrence in our study because data on immune activation were available in only a subset of patients in the 2 cohorts analyzed.

Table 3. Factors Associated With Occurrence of a First All-Cause Non-AIDS-Defining Event

Characteristics	HR (95% CI) Univariate	*P* Value	HR (95% CI) Multivariate	*P* Value
HIV control status		**.02**		**.01**
ART	**1**		1	
HIC	**1.53 (1.07–2.18)**		**1.93 (1.16–3.20)**	
Year of diagnosis		.68		.21
2000 or earlier	1		1	
2001–2007	1.08 (.73–1.59)		1.46 (.91–2.35)	
2008–2013	1.28 (.73–2.24)		1.62 (.84–3.12)	
Age, y		**.03**		**.01**
<43	**1**		**1**	
≥43	**1.76 (1.22–2.54)**		**1.69 (1.11–2.56)**	
Gender		.29		.99
Male	1		1	
Female	0.81 (.54–1.20)		0.99 (.61–1.62)	
Ethnicity		.07		.51
White	1		1	
Black	0.55 (.34–.91)		0.70 (.36–1.33)	
Other	0.99 (.32–3.16)		0.75 (.18–3.06)	
HIV risk factor		.23		.78
Sexual	1		1	
IDU	1.66 (.93–2.96)		0.95 (.42–2.13)	
Blood exposure	1.11 (.59–2.07)		1.26 (.64–2.45)	
Viral hepatitis status		.61		.84
HIV monoinfection	1		1	
HBV antibody positive	1.14 (.76–1.69)		1.15 (.72–1.83)	
HCV antibody positive	1.47 (.63–3.44)		1.17 (.44–3.07)	
Tobacco use		.45		.37
No	1		1	
Yes	1.14 (.81–1.61)		1.22 (.79–1.87)	
Alcohol use		.90		
No	1		…	
Yes	0.97 (.59–1.61)		…	
Past history of nADEs		.34		.46
No	1		1	
Yes	1.25 (.79–1.98)		1.23 (.71–2.12)	
Past history of other diseases		.94		
No	1		…	
Yes	1.04 (.38–2.82)		…	
CD4 T-cell count		.58		.82
<500 cells/μL	1.15 (.70–1.87)		1.07 (.62–1.84)	
≥500 cells/μL	1		1	
CD8 T-cell count		.99		
<632 cells/μL	1		…	
≥632 cells/μL	1.0 (.69–1.45)		…	
CD4/CD8 ratio				
<1	1.0 (.67–1.47)	.97	…	
≥1	1		…	

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIC, human immunodeficiency virus controller; HIV, human immunodeficiency virus; HR, hazard ratio; IDU, intravenous drug use; nADE, non-AIDS-defining event.

Crowell et al reported a higher risk of comorbidities and hospitalizations for "psychiatric" reasons in HIV controllers [22]. However, this study was retrospective and data collection was based on *International Classification of Diseases, Ninth Revision* coding without specificity. The authors underlined in the discussion that they were "uncertain why elite controllers were hospitalized" with this code. In our study, we did not find such an elevated risk, but this risk is under investigation.

In our study, the occurrence of the first nADE was not statistically associated with HIV/HCV coinfections, although this association has already been described [22, 24, 25]. In these studies in controllers from Spain and the US, the prevalence

of HIV/HCV coinfection was higher than in the French cohorts (47.9% in the Dominguez-Molina et al cohort, 22.8% in the Crowell et al cohort, and only 4.0% in our study). This observation deserves to be better investigated on a larger sample, especially by differentiating between active hepatitis at the time of the event and cured infection.

Finally, the age at the beginning of the viral control period was statistically significant for the all-cause category. This result is similar to the findings from previous studies [24, 25, 37] as well as in the general population outside HIV infection, where the risk of clinical events increases with aging. ART-treated patients were included during PHI and treated very early (within 1 month) with undetectable VL, thus conferring a low immune activation and inflammation level in the long term. This could have led to a very low risk for nADEs. Previously published studies from the PRIMO cohort and other groups focusing on primary infection have shown the persistence of significantly increased levels of some inflammatory biomarkers evidencing the persistence of chronic inflammation [2, 6, 38]. We were not able to investigate the role of inflammaging in the 2 cohorts and decipher the role of immune exhaustion in the occurrence of clinical events. Other clinical parameters could also explain such a difference. The body mass index and a more detailed lipid profile as well as the Framingham score would have also been relevant considerations in the critical importance of metabolic dysfunction in nADE occurrence [39].

A major strength of our study is the number of spontaneous HIV controllers included, either 2 or 3 times the number of equivalent published studies. The long duration of the control required to be included in the CODEX cohort is also a major factor relative to other publications [22, 23]. The 5-year time frame considered in the definition of spontaneous controllers without ART ensures prolonged viral control in these patients compared to other studies with a less strict definition.

Our study has some limitations. Our 2 groups have differences in terms of HBV/HCV coinfection, gender distribution, and different risk factor distribution (in particular intravenous drug exposure). These differences have already been described in the cohorts of HIV controllers, as compared with other PLWH. To limit the role of such differences in the interpretation of our study's findings, we first tried to match the subjects between the 2 cohorts, but we were unable to make a consistent match. We thus opted for an adjustment for all clinically relevant confounding variables. Another point is that our study compares strictly defined HIV controllers versus early-treated patients from the PRIMO cohort. These patients treated early are clearly less exposed to nADEs than patients treated in the chronic phase of the infection. However, the fact that HICs have a similar risk of noninfectious events than early ART-treated patients in our cohorts is reassuring.

This study raises the question of the potential benefit of ART in HIV controllers. This is a matter of debate, as international recommendations claim for an early introduction of ART in PLWH. HICs might start therapy for 2 main reasons: mainly a decline in the CD4 levels (independently of viral control loss) or viral control loss [29, 40]. We had already shown that clinical events leading to CD4 decline were scarcely reported [29] and mainly consisted of nonsevere infections, as reported in our current study. However, studies analyzing the effect of ART in HICs have mainly shown an effect on the HIV VL and immune activation parameters, but data on CD4 T-cell counts or CD4:CD8 ratio normalization remain controversial [20, 40]. Furthermore, the impact of ART on reducing the risk of nADEs beyond improvement in inflammatory biomarkers has not been firmly proven. Recently, the Strategic Timing of Antiretroviral Treatment (START) study study enrolled participants with low viremia to start ART immediately. Patients experienced higher CD4 counts, a greater proportion of suppressed viremia, and decreases in D-dimer levels, but there were no differences in serious clinical outcomes [41].

In conclusion, we report that in a large cohort of strictly defined untreated HIV controllers, the risk of nADEs is mainly linked with that of non-AIDS-defining infections. Age is a major factor involved in the risk of events, but the role of residual inflammation is still to be investigated. Studies aimed at measuring the effect of ART in HICs might consider clinical outcomes besides immune activation through a case-to-case approach.

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.

Notes

Author contributions. F. B., N. N., C. G., and C. M. designed the study. A. E. and A. S. assured patient enrollment and provided for data collection. A. C., C. G., A. E., and F. B. defined the clinical categories and classified pathologies. A. M. performed the statistical analysis. A. M., F. B., and N. N. wrote the manuscript. L. M., C. G., and O. L. reviewed the manuscript.

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