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Hospitalization Rates and Reasons Among HIV Elite Controllers and Persons With Medically Controlled HIV Infection

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(See the editorial commentary by Karris and Haubrich on pages 1689–91.)

Background. Elite controllers spontaneously suppress human immunodeficiency virus (HIV) viremia but also demonstrate chronic inflammation that may increase risk of comorbid conditions. We compared hospitalization rates and causes among elite controllers to those of immunologically intact persons with medically controlled HIV.

Methods. For adults in care at 11 sites from 2005 to 2011, person-years with CD4 T-cell counts ≥350 cells/mm^2 were categorized as medical control, elite control, low viremia, or high viremia. All-cause and diagnostic category-specific hospitalization rates were compared between groups using negative binomial regression.

Results. We identified 149 elite controllers (0.4%) among 34 354 persons in care. Unadjusted hospitalization rates among the medical control, elite control, low-viremia, and high-viremia groups were 10.5, 23.3, 12.6, and 16.9 per 100 person-years, respectively. After adjustment for demographic and clinical factors, elite control was associated with higher rates of all-cause (adjusted incidence rate ratio, 1.77 [95% confidence interval, 1.21–2.60]), cardiovascular (3.19 [1.50–6.79]) and psychiatric (3.98 [1.54–10.28]) hospitalization than was medical control. Non–AIDS-defining infections were the most common reason for admission overall (24.1% of hospitalizations) but were rare among elite controllers (2.7%), in whom cardiovascular hospitalizations were most common (31.1%).

Conclusions. Elite controllers are hospitalized more frequently than persons with medically controlled HIV and cardiovascular hospitalizations are an important contributor.

Keywords. HIV; elite control; antiretroviral therapy; hospitalization; inflammation; psychiatric disease.

Elite controllers represent a small but important subset of persons living with human immunodeficiency virus (HIV) (PLWH) who suppress the virus and have delayed disease progression in the absence of antiretroviral therapy (ART) [1, 2]. Although prevalence of elite control is estimated at only 0.15%–1.5% of PLWH, study of these persons provides insights into HIV pathogenesis and potential mechanisms for new HIV therapies [3–6]. Despite spontaneous and durable control of HIV viremia, elite control is associated with chronic immune activation and low-grade inflammation that exceeds the level seen in persons who achieve viral suppression via ART [7–9].

Chronic inflammation among PLWH has been linked to complications such as cardiovascular disease, opportunistic infections, and neurologic disorders [10–13].

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Persistent low-grade inflammation may therefore place elite controllers at higher risk of clinical events than persons whose HIV is controlled with ART. For example, prior studies have demonstrated a high burden of coronary atherosclerosis on radiographic screening of elite controllers, but data are lacking on any association with clinical outcomes [14, 15]. The relative rarity of elite control makes it difficult to study clinical outcomes, such as disease events or hospitalizations, in this population. We used a multisite, multistate cohort of PLWH to compare hospitalization rates among elite controllers with those of immunologically intact persons with medically controlled and uncontrolled HIV.

METHODS

Site Selection and Data Collection

The HIV Research Network (HIVRN) is a consortium that includes 12 sites providing longitudinal adult HIV care in 10 US cities. Sites abstract comprehensive data from clinical records, deidentify these data, and submit them to a data coordinating center for integration into a uniform database. Eleven of the participating sites submit hospitalization data and were able to participate in chart reviews for the purpose of this study (5 Northeast, 3 West, and 3 South). Nine of these sites have academic affiliations and 2 are community-based. Inclusion in this retrospective cohort study was restricted to persons who were in active care (defined as having ≥1 outpatient primary HIV care visit, 1 CD4 T-cell count, and 1 HIV-1 RNA level during the calendar year) at these sites between 2005 and 2011. All sites contributed data for all years, except one that was not included in 2005 because of incomplete data.

The analysis was limited to persons considered immunologically intact. Person-years were excluded if they contained 2 consecutive CD4 cell counts <350 cells/mm^3 or any single count <200 cells/mm^3. If 2 consecutive measurements <350 cells/mm^3 spanned separate calendar years, both calendar years were excluded. Participants could contribute additional observation time to the analysis after consistent CD4 cell reconstitution to >350 cells/mm^3 occurred. Nadir CD4 cell count was not considered a criterion for study participation, and participants with CD4 cell reconstitution after any CD4 cell count nadir were eligible to contribute observation time during calendar years after the first year of consistent CD4 cell reconstitution to >350 cells/mm^3. All participants in this study either provided informed consent for inclusion in the HIVRN research database or had a waiver of informed consent granted by their local institutional review board. Institutional review boards at each site and at the data coordinating center at Johns Hopkins University approved the collection and use of these data for analysis and publication.

HIV Control Status

Elite control was defined by ≥3 consecutive HIV-1 RNA measurements, on separate days and spanning a period of ≥12 months, registering below the limit of detection for the assay in the absence of any ART. This definition of elite control has been used in several prior reports [3, 16, 17]. Accrual of elite control observation time began only after 1 full year of undetectable HIV-1 RNA levels to minimize misclassification due to any missing ART data. (Laboratory data before 2005 were used to establish status in 2005). During elite control, detectable HIV-1 RNA levels <1000 copies/mL were permissible as long as such episodes represented the minority of measurements during the calendar year. The calendar year during which the elite control period ends was not considered an elite control person-year. Medical records of elite controllers identified via this algorithm were manually reviewed to confirm elite control status. Individuals were excluded from the analysis if medical record review was not possible. Elite controllers were not eligible to contribute observation time to other HIV control categories.

Individuals not identified as elite controllers could contribute observation time to the following groups: medical control, low viremia, and/or high viremia. Medical control was defined by ≥3 consecutive HIV-1 RNA measurements, on separate days and spanning ≥12 months, which registered below the limit of detection for the assay, while ART was prescribed. Medical control began during the first qualifying year starting with an undetectable HIV-1 RNA level. Detectable HIV-1 RNA levels <1000 copies/mL were permissible after establishment of medical control if they represented a minority of measurements during any calendar year.

Exploratory data analysis suggested a difference in hospitalization rates above and below the HIV-1 RNA threshold of 1000 copies/mL. Therefore, low viremia was defined by all HIV-1 RNA measurements in the calendar year falling below this threshold, but not satisfying other criteria for medical control. All person-years with HIV-1 RNA measurement(s) ≥1000 copies/mL were considered high-viremia person-years. HIV control status was assessed annually and participants who were not identified as elite controllers could transition between other HIV control categories with each change in calendar year. A sensitivity analysis was performed in which participants could contribute person-time to only one HIV control status category, with data censored at the time of transition from that category.

Covariates

Age was assessed annually on 1 July. Race/ethnicity and sex were categorized based on self-report. HIV transmission risk factors were divided into mutually exclusive categories: injection drug use (IDU), men who have sex with men (MSM), heterosexual transmission, or other/unknown. Individuals who reported IDU in addition to any other risk factor were categorized as IDU. Men who reported sex with both men and women were categorized as MSM. Hepatitis B surface antigen and hepatitis C virus (HCV) antibody were used to determine hepatitis

status, and this assessment was updated annually. Outpatient HIV primary care visits were tallied annually. Insurance status, CD4 cell counts, and HIV-1 RNA measurements were updated with the first available assessment for each calendar year of observation. Participants with dual eligibility for Medicaid and Medicare were included in the Medicare category.

Outcomes

The primary outcome was all-cause hospitalization, and this was ascertained using admission and discharge dates that are reported by all HIVRN sites. We also investigated cause-specific hospitalization rates within the subgroup of 9 HIVRN sites that had *International Classification of Diseases, Ninth Revision*. (ICD-9) diagnosis code data available for each hospitalization. Hospitalizations were assigned to one of 18 diagnostic categories using a previously published algorithm [18, 19]. First, the primary diagnostic code was identified as the first-listed ICD-9 code that did not refer to HIV (042, V08, 795.71, V01.79), chronic hepatitis B virus (HBV) (070.22, 070.23, 070.32, 070.33), chronic HCV (070.44, 070.54, 070.70, 070.71), or oral candidiasis (112.0), because these represent comorbid conditions frequently recorded for billing purposes but insufficient to justify hospitalization. Second, Clinical Classifications Software (CCS) was used to assign the primary ICD-9 code into one of 18 "first-level" CCS categories [20]. Finally, we modified the CCS diagnostic categories by reassigning infections (eg, pneumonia) from organ system categories to the infection category; combining the congenital, perinatal, and unclassified categories (together representing 1% of admissions); and reassigning specific infections and malignancies into a new AIDS-defining illness category, according to Centers for Disease Control and Prevention criteria [21].

Data Analysis

All-cause and cause-specific hospitalization rates were calculated using total number of visits as the numerator and aggregate person-time as the denominator and multiplied by 100 to obtain rates per 100 person-years. Participants could contribute <1 year of observation during a calendar year owing to death or new enrollment in care. Univariable and multivariable negative binomial regression models were used to estimate incidence rate ratios (IRRs) for hospitalization rates associated with HIV control status, age, race, sex, HIV risk factor, CD4 cell count stratum, hepatitis status, number of primary HIV care visits and insurance status. Multivariable models included indicators for clinical care site to adjust for site-specific variability and for calendar year to adjust for secular trends.

All models used generalized estimating equations, clustered on person, with unstructured working correlation, robust variance estimators, and an offset for person-time. This technique adjusts the variance to account for multiple hospitalization events by a single person, including when these events occur under different exposure categories (eg, under low viremia in 1 year and medical control in a separate year) [22]. A 2-sided type I error of 5% was considered statistically significant. All analyses were performed using Stata 12.0 software (StataCorp).

RESULTS

Of 34 354 persons actively engaged in care during the study period, 23 461 satisfied the CD4 cell count criterion for inclusion in this analysis and contributed 64 290 person-years of observation. Algorithmically, 188 persons were identified as elite control candidates in the HIVRN database. Of these, 17 were excluded from the analysis because they did not have clinical records available for review and 22 were excluded because manual record review revealed they were prescribed ART. Ultimately, 149 chart-confirmed elite controllers contributed 369 person-years of observation time. The prevalence of elite control is therefore estimated to be ≥0.43% of the full population of 34 354 persons.

Among the remaining 23 273 participants, 9226 contributed 26 176 person-years of medical control, 12 044 contributed 17 313 person-years of low viremia, and 12 847 contributed 20 414 person-years of high-viremia observation time. At study entry, persons with elite control were more likely than those with medical control to be female (50.3% vs 25.7%; $P < .001$) and black (58.4% vs 40.9%; $P < .001$) (Table 1). CD4 cell counts at study entry were higher in the elite control group (median [interquartile range], 778 [580–961] cells/mm^3) than in the medical control, low-viremia, and high-viremia groups (481 [396–640], 510 [401–677], and 482 [384–634] cells/mm^3, respectively; overall $P < .001$).

There were 8456 hospitalizations among all participants. The percentage of participants ever hospitalized during time accrued in each HIV control group was 14.6% during medical control, 25.5% during elite control, 10.6% during low viremia and 15.0% during high viremia. Overall, the elite control group had the highest all-cause hospitalization rate, 23.3 hospitalizations per 100 person-years (range, 15.4–27.9), followed by the high-viremia (16.9; range, 14.1–18.8), low-viremia (12.6; range, 12.0–13.7), and medical control (10.5; range, 8.6–12.2) groups (Figure 1).

In our multivariable model, elite control was associated with a higher hospitalization rate than medical control (adjusted IRR [aIRR], 1.77; 95% confidence interval [CI], 1.21–2.60) (Table 2). Hospitalization rates were also elevated in the high-viremia (aIRR, 1.71; 95% CI, 1.57–1.87), and low-viremia (aIRR, 1.34; 95% CI, 1.24–1.46) groups, compared with the medical control group. Other factors independently associated with hospitalization included older age, female sex, IDU, lower CD4 cell count, HIV/HCV coinfection, HIV/chronic HBV/HCV triple infection, more outpatient visits, and Medicaid or Medicare insurance (vs

Table 1. Demographic and Clinical Characteristics at Study Entry by HIV Control Status[a]

Characteristic	Medical Control (n = 4709)	Elite Control (n = 149)	Low Viremia (n = 7998)	High Viremia (n = 10 605)
Age, y				
Median (IQR)[b]	45.4 (39.4–51.7)	46.4 (40.5–53.2)	44.2 (37.4–50.5)	40.3 (31.0–47.4)
18–34	605 (12.8)	21 (14.1)	1558 (19.5)	3690 (34.8)
35–49	2625 (55.7)	76 (51.0)	4297 (53.7)	5064 (47.8)
50–64	1360 (28.9)	49 (32.9)	1974 (24.7)	1727 (16.3)
≥65	119 (2.5)	3 (2.0)	169 (2.1)	124 (1.2)
Race/ethnicity				
White	1566 (33.3)	35 (23.5)	2403 (30.0)	2740 (25.8)
Black	1927 (40.9)	87 (58.4)	3374 (42.2)	5331 (50.3)
Hispanic	1097 (23.3)	25 (16.8)	1968 (24.6)	2241 (21.1)
Other/unknown	119 (2.5)	2 (1.3)	253 (3.2)	293 (2.8)
Sex				
Male	3498 (74.3)	74 (49.7)	5976 (74.7)	7410 (69.9)
Female	1211 (25.7)	75 (50.3)	2022 (25.3)	3195 (30.1)
HIV risk factor				
Heterosexual	1701 (36.1)	59 (39.6)	2763 (34.6)	4074 (38.4)
MSM	2081 (44.2)	39 (26.2)	3618 (45.2)	4368 (41.2)
IDU	782 (16.6)	45 (30.2)	1247 (15.6)	1714 (16.2)
Other/unknown	145 (3.1)	6 (4.0)	370 (4.6)	449 (4.2)
CD4 cell count, cells/mm^3[c]				
Median (IQR)	481 (396–640)	778 (580–961)	510 (401–677)	482 (384–634)
200–350	347 (7.4)	1 (0.7)	830 (10.4)	1650 (15.6)
351–500	2199 (46.7)	19 (12.8)	3030 (37.9)	4044 (38.1)
501–750	1411 (30.0)	45 (30.2)	2679 (33.5)	3350 (31.6)
>750	752 (16.0)	84 (56.4)	1459 (18.2)	1561 (14.7)
HIV-1 RNA, median (IQR), copies/mL[c]	Undetectable[d]	Undetectable[d]	Undetectable[d]	7640 (1124–36 702)
Hepatitis status[e]				
HIV monoinfection	2397 (50.9)	55 (36.9)	3637 (45.5)	5289 (49.9)
HIV/HBV coinfection	157 (3.3)	2 (1.3)	216 (2.7)	240 (2.3)
HIV/HCV coinfection	497 (10.6)	34 (22.8)	790 (9.9)	1055 (10.0)
HIV/HBV/HCV triple infection	55 (1.2)	2 (1.3)	105 (1.3)	150 (1.4)
Unknown	1603 (34.0)	56 (37.6)	3250 (40.6)	3871 (36.5)
Annual outpatient HIV visits				
Median (IQR)	4 (3–7)	4 (2–7)	4 (2–6)	4 (2–6)
1–2	793 (16.8)	52 (34.9)	2224 (27.8)	3694 (34.8)
3–4	1659 (35.2)	36 (24.2)	2487 (31.1)	2932 (27.6)
5–6	950 (20.2)	18 (12.1)	1498 (18.7)	1698 (16.0)
≥7	1307 (27.8)	43 (28.9)	1789 (22.4)	2281 (21.5)
Insurance[c]				
Private	638 (13.6)	18 (12.1)	1109 (13.9)	1238 (11.7)
Medicaid	1358 (28.8)	69 (46.3)	2864 (35.8)	3629 (34.2)
Medicare/dual eligible	995 (21.1)	12 (8.0)	1206 (15.1)	1078 (10.2)
Ryan White/uninsured	1497 (31.8)	46 (30.9)	2564 (32.1)	4160 (39.2)
Unknown	221 (4.7)	4 (2.7)	255 (3.2)	50 (4.7)
Year of study entry				
2005	1859 (39.5)	53 (35.6)	1501 (18.8)	2998 (28.3)
2006	1029 (21.8)	26 (17.4)	850 (10.6)	1615 (15.2)
2007	376 (8.0)	14 (9.4)	838 (10.5)	1149 (10.8)
2008	333 (7.1)	12 (8.0)	904 (11.3)	1227 (11.6)
2009	347 (7.4)	16 (10.7)	926 (11.6)	1031 (9.7)

Table 1 continued.

Characteristic	Medical Control (n = 4709)	Elite Control (n = 149)	Low Viremia (n = 7998)	High Viremia (n = 10 605)
2010	409 (8.7)	14 (9.4)	1003 (12.5)	1182 (11.2)
2011	356 (7.6)	14 (9.4)	1976 (24.7)	1403 (13.2)

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; IQR, interquartile range; MSM, men who have sex with men.

[a] Unless otherwise specified, data represent No. (%) of study participants.

[b] Age was assessed on 1 July of the year of study entry.

[c] CD4 cell counts, HIV-1 RNA levels, and insurance data used were the first available for the calendar year of study entry.

[d] Undetectable HIV-1 RNA refers to a level below the limit of detection for the assay used during routine clinical care, which may have been 20, 40, 48, 50, 75, 80, or 400 copies/mL.

[e] HBV and HCV status were determined by hepatitis B surface antigen and hepatitis C antibody, respectively. Hepatitis status at study entry was assessed by positive tests before entry or within 6 months after entry, or by negative test result at first testing any time after study entry.

private insurance). In the sensitivity analysis in which participants were censored at the time of transition from their first recorded HIV control category, elite control was again associated with a higher hospitalization rate than medical control in both unadjusted (IRR, 2.69; 95% CI, 1.49–4.85) and adjusted (aIRR, 2.02; 95% CI, 1.24–3.28) models.

Among the subgroup of 9 clinical care sites with available ICD-9 data, 5593 total hospitalizations were observed (Table 3). Overall, non–AIDS-defining infections were the most common reason for hospitalization, representing 24.1% of admissions. In the elite control group, however, non–AIDS-defining infections accounted for just 2.7% of admissions. Conversely, cardiovascular disease was the reason for 13.5% of admissions overall but was more common among elite controllers, accounting for 31.1% of admissions. Among elite controllers, the most common diagnoses leading to cardiovascular hospitalization were chest pain (26.1%), coronary artery disease (13.0%), and heart failure (13.0%). Pulmonary disease accounted for 4.8% of admissions overall but 21.6% of admissions in the elite control group. Among elite controllers, the most common diagnosis leading to pulmonary hospitalization was asthma/chronic obstructive pulmonary disease (87.5%). Two hospitalizations for AIDS-defining-illness occurred in the elite control group, one for Kaposi sarcoma and one for *Mycobacterium tuberculosis*.

Multivariable models were used to explore factors associated with all-cause and diagnostic category-specific hospitalization for the 5 most common diagnostic categories at sites with available ICD-9 data (Table 4). Inferences about factors associated with all-cause hospitalization were similar to those in the overall study cohort, including a similarly heightened rate among persons with elite control as compared with medical control (aIRR, 1.99; 95% CI, 1.29–3.06). The cardiovascular hospitalization rate was significantly higher among elite controllers (aIRR, 3.19; 95% CI, 1.50–6.79) than in the medical control group.

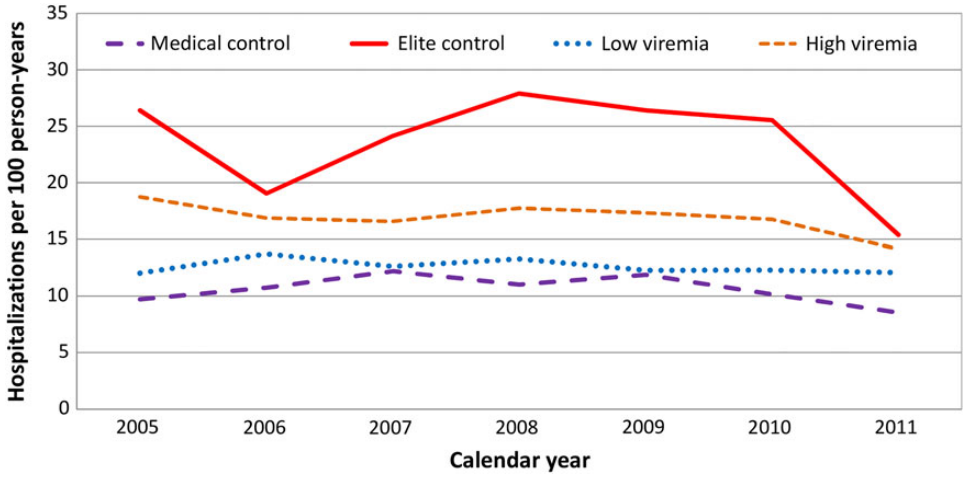

Figure 1. Unadjusted all-cause hospitalization rates by human immunodeficiency virus control status. Rates were calculated using total number of visits as the numerator and aggregate person-time as the denominator for each calendar year and standardized as hospitalizations per 100 person-years of follow-up.

Table 2. Univariable and Multivariable Analyses of Factors Associated With All-Cause Hospitalization

Characteristic	Incidence Rate Ratio (95% CI)	
	Unadjusted	Adjusted[a]
HIV control status		
Medical control	1.0 (Reference)	1.0 (Reference)
Elite control	**2.08 (1.34–3.23)**	**1.77 (1.21–2.60)**
Low viremia	**1.18 (1.98–1.29)**	**1.34 (1.24–1.46)**
High viremia	**1.56 (1.43–1.69)**	**1.71 (1.57–1.87)**
Age, y[b]		
18–34	1.0 (Reference)	1.0 (Reference)
35–49	**1.22 (1.09–1.36)**	1.02 (.91–1.14)
50–64	**1.72 (1.53–1.93)**	**1.26 (1.12–1.42)**
≥65	**2.85 (2.35–3.45)**	**2.00 (1.64–2.44)**
Race		
White	1.0 (Reference)	1.0 (Reference)
Black	**1.31 (1.19–1.44)**	1.00 (.90–1.12)
Hispanic	0.95 (.84–1.07)	**0.80 (.71–.91)**
Other/unknown	**0.68 (.48–.94)**	**0.69 (.50–.95)**
Sex		
Male	1.0 (Reference)	1.0 (Reference)
Female	**1.54 (1.42–1.68)**	**1.31 (1.18–1.45)**
HIV risk factor[c]		
Heterosexual	1.0 (Reference)	1.0 (Reference)
MSM	**0.66 (.60–.72)**	**0.88 (.78–.99)**
IDU	**1.60 (1.44–1.78)**	**1.19 (1.06–1.33)**
Other/unknown	**1.47 (1.20–1.82)**	**1.34 (1.08–1.66)**
CD4 cell count, cells/mm^3[d]		
>750	1.0 (Reference)	1.0 (Reference)
501–750	**1.17 (1.07–1.28)**	**1.16 (1.06–1.27)**
≤500	**1.39 (1.26–1.52)**	**1.33 (1.21–1.46)**
Hepatitis status[e]		
HIV monoinfection	1.0 (Reference)	1.0 (Reference)
HIV/HBV coinfection	1.07 (.83–1.38)	1.12 (.87–1.45)
HIV/HCV coinfection	**2.08 (1.86–2.32)**	**1.35 (1.20–1.52)**
HIV/HBV/HCV triple infection	**1.47 (1.03–2.09)**	**1.55 (1.09–2.18)**
Unknown	**1.15 (1.05–1.26)**	1.05 (.95–1.15)
Annual outpatient HIV visits		
1–2	1.0 (Reference)	1.0 (Reference)
3–4	0.96 (.88–1.06)	0.98 (.89–1.08)
5–6	**1.28 (1.16–1.42)**	**1.27 (1.15–1.42)**
≥7	**2.53 (2.30–2.78)**	**2.40 (2.15–2.67)**
Insurance[d]		
Private	1.0 (Reference)	1.0 (Reference)
Medicaid	**2.39 (2.10–2.71)**	**1.89 (1.65–2.16)**
Medicare/dual eligible	**2.40 (2.09–2.75)**	**1.95 (1.69–2.25)**
Ryan White/uninsured	1.08 (.94–1.23)	1.10 (.95–1.27)
Unknown	0.97 (.78–1.20)	1.05 (.83–1.34)
Calendar year		
2005	1.0 (Reference)	1.0 (Reference)
2006	1.00 (.89–1.12)	1.01 (.90–1.14)
2007	1.02 (.91–1.15)	1.05 (.93–1.18)
2008	1.00 (.89–1.12)	1.05 (.94–1.18)
2009	0.97 (.87–1.09)	1.04 (.92–1.16)
2010	**0.89 (.90–1.00)**	0.99 (.88–1.11)
2011	**0.77 (.69–.87)**	**0.89 (.79–1.00)**

Table 2 continued.

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men.

[a] The multivariable model included all listed variables and also an indicator variable for clinical care site. Results in **bold** are statistically significant ($P \leq .05$).

[b] Age was assessed on July 1 of each calendar year.

[c] HIV risk factors were considered mutually exclusive; subjects who reported IDU in addition to any other risk factor were categorized as IDU, men who reported sex with men and women were categorized as MSM.

[d] CD4 cell counts and insurance data used in this analysis were the first available measurements for each calendar year.

[e] HBV and HCV status were determined by hepatitis B surface antigen and hepatitis C antibody, respectively, as measured before 1 July of each calendar year. Negative test results were carried backward to the time of study entry, and positive test results were carried forward for all subsequent years.

Psychiatric hospitalization rates were higher in the elite control (aIRR, 3.98; 95% CI, 1.54–10.28), low-viremia (aIRR, 1.65; 95% CI, 1.15–2.37); and high-viremia (3.14; 2.35–4.2) groups than in the medical control group. Compared with medical control, elite control was associated with a trend toward a lower non–AIDS-defining infection hospitalization rate (aIRR, 0.32; 95% CI, .08–1.30), whereas higher rates were seen in the low-viremia (aIRR, 1.57; 95% CI, 1.31–1.88) and high-viremia (aIRR, 2.48; 95% CI, 2.10–2.93) groups.

The elite control group included a single participant with 21 hospitalizations during the study period. A sensitivity analysis was performed excluding this person. In this analysis, the all-cause hospitalization rate in the elite control group was attenuated, but remained significantly greater than in the medical control reference group (aIRR 1.56; 95% CI, 1.09–2.24). Many of this person's admissions were related to asthma/chronic obstructive pulmonary disease, and in the sensitivity analysis pulmonary admissions accounted for just 3.8% of admissions in the elite control group, similar to the overall study population (4.5%). Cardiovascular disease remained the most common reason for admission among elite controllers (30.2%).

DISCUSSION

This study identified an increased rate of hospitalization among persons with elite control of HIV as compared with medical control. Furthermore, elite control was associated with a higher rate of cardiovascular hospitalization, which was the most common type of hospitalization among elite controllers. Non–

Table 3. Hospitalizations by Diagnostic Category at 9 Sites With ICD-9 Data

Diagnostic Category[a]	Hospitalizations, No. (%)				
	Overall (n = 5593)	Medical Control (n = 1999)	Elite Control (n = 74)	Low Viremia (n = 1341)	High Viremia (n = 2179)
Non–AIDS-defining infection	1347 (24.1)	394 (19.7)	2 (2.7)	318 (23.7)	633 (29.0)
Cardiovascular	756 (13.5)	335 (16.8)	23 (31.1)	167 (12.4)	231 (10.6)
Gastrointestinal/liver	521 (9.3)	243 (12.2)	5 (6.8)	107 (8.0)	166 (7.6)
Psychiatric	444 (7.9)	114 (5.7)	7 (9.5)	92 (6.9)	231 (10.6)
Endocrine	346 (6.2)	136 (6.8)	3 (4.0)	98 (7.3)	109 (5.0)
Injury/poisoning	302 (5.4)	123 (6.2)	2 (2.7)	80 (6.0)	97 (4.4)
Renal	298 (5.3)	129 (6.4)	3 (4.0)	62 (4.6)	104 (4.8)
Pulmonary	267 (4.8)	84 (4.2)	16 (21.6)	66 (4.9)	101 (4.6)
Non–AIDS-defining cancer	247 (4.4)	104 (5.2)	3 (4.0)	74 (5.5)	66 (3.0)
Orthopedic	205 (3.7)	85 (4.2)	0 (0)	41 (3.1)	79 (3.6)
Neurologic	194 (3.5)	66 (3.3)	0 (0)	63 (4.7)	65 (3.0)
Symptom based	154 (2.8)	50 (2.5)	2 (2.7)	35 (2.6)	67 (3.1)
Hematologic	143 (2.6)	41 (2.0)	4 (5.4)	41 (3.1)	57 (2.6)
AIDS-defining illness	125 (2.2)	38 (1.9)	2 (2.7)	22 (1.6)	63 (2.9)
Obstetric/gynecologic	106 (1.9)	18 (0.9)	0 (0)	34 (2.5)	54 (2.5)
Congenital/perinatal/ unclassified	57 (1.0)	19 (1.0)	1 (1.4)	18 (1.4)	19 (0.9)
Missing	46 (0.8)	13 (0.6)	0 (0)	14 (1.0)	19 (0.9)
Dermatologic	35 (0.6)	7 (0.4)	1 (1.4)	9 (0.7)	18 (0.8)

Abbreviation: ICD-9, *International Classification of Diseases, Ninth Revision*.

[a] Diagnostic categories are listed in order of frequency in the overall study population. Results are given for the 9 sites with available hospitalization diagnostic data.

AIDS-defining infections, though a common reason for admission in the overall study population, were relatively rare among elite controllers. Finally, female sex was associated with elite control.

To date, data on hospitalizations among elite controllers are scarce. Two previous studies reporting no increased hospitalization risk for elite controllers both included only 25 elite controllers and examined hospitalization as a secondary outcome [3, 23].

We are unaware of previous studies specifically evaluating cardiovascular hospitalizations among elite controllers. Prior studies have shown an increased prevalence of atherosclerotic plaques among elite controllers compared with HIV-negative controls but not compared with PLWH treated with ART [14, 15]. In addition, elite controllers have been shown to have elevated levels of activated CD8 T cells, D-dimer, soluble tissue factor, and interferon γ–induced protein 10 levels compared with both HIV-seronegative persons and persons with medically controlled HIV infection [7–9]. The cause of immune activation in elite controllers is unclear, but the presence of replication-competent virus [24], persistent low-level viremia [25], ongoing low-level viral replication [26–28], and the vigorous immune response that controls this viral replication [29] may be important factors. These pathophysiologic factors could contribute to higher hospitalization rates for cardiovascular disease among elite controllers.

If immune system activation is a contributor to the excess rate of cardiovascular and other hospitalizations among elite controllers, then ART and/or anti-inflammatory medicines, such as statins or aspirin, may be beneficial for this group. Prior studies have demonstrated that ART can decrease T-cell activation [28, 30–32] and/or increase CD4 cell counts [33, 34] among elite controllers. In our cohort, only 10 participants known to be elite controllers were ever exposed to ART, so we could not effectively evaluate differences in hospitalization. Prospectively assessing the effect of ART and/or anti-inflammatory medicines on hospitalization rates among elite controllers and understanding the potential role of chronic inflammation would inform the clinical care of elite controllers and may inform research on interventions that aim to induce an elite control state, such as some candidate HIV vaccines.

Non–AIDS-defining infections accounted for relatively few hospitalizations among elite controllers in our study (2.7%), despite being the most common reason for admission overall (24.1%). Elite control is characterized by a variety of unique immunologic parameters, including differences in class I antigen presenting molecules and CD8 T-cell populations that may also plausibly affect susceptibility to other infectious diseases [29]. Future studies should evaluate immunologic response to bacterial and other pathogens among elite controllers to clarify any protective mechanisms that

Table 4. Multivariable Analyses of Factors Associated With Cause-Specific Hospitalization at 9 Sites With ICD-9 Data[a]

Characteristic	Adjusted Incidence Rate Ratio (95% CI)[a]					
	All-Cause	Non–AIDS-Defining Infection	Cardiovascular	Gastrointestinal/Liver	Psychiatric	Endocrine
HIV control status						
Medical control	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Elite control	**1.99 (1.29–3.06)**	0.32 (.08–1.30)	**3.19 (1.50–6.79)**	1.32 (.52–3.33)	**3.98 (1.54–10.28)**	1.14 (.32–4.06)
Low viremia	**1.39 (1.26–1.54)**	**1.57 (1.31–1.88)**	1.11 (.87–1.42)	0.91 (.68–1.23)	**1.65 (1.15–2.37)**	**1.54 (1.14–2.08)**
High viremia	**1.79 (1.61–1.99)**	**2.48 (2.10–2.93)**	1.18 (.92–1.51)	1.15 (.85–1.54)	**3.14 (2.35–4.21)**	**1.42 (1.00–1.99)**
Age, y[b]						
18–34	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
35–49	1.10 (.94–1.28)	1.09 (.87–1.36)	**2.20 (1.25–3.88)**	1.23 (.81–1.87)	1.07 (.64–1.78)	**1.72 (1.00–2.94)**
50–64	**1.36 (1.15–1.59)**	1.18 (.92–1.51)	**3.63 (2.05–6.44)**	1.26 (.79–2.02)	0.72 (.42–1.26)	**2.33 (1.38–3.93)**
≥65	**2.24 (1.77–2.83)**	**1.44 (1.00–2.07)**	**7.86 (4.06–15.20)**	**2.25 (1.25–4.08)**	0.94 (.35–2.49)	**3.95 (2.02–7.72)**
Race						
White	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Black	1.05 (.92–1.20)	0.85 (.69–1.04)	1.25 (.92–1.69)	0.94 (.68–1.30)	1.17 (.80–1.71)	1.39 (.96–2.03)
Hispanic	**0.84 (.72–.97)**	**0.71 (.56–.88)**	1.04 (.75–1.43)	0.97 (.70–1.35)	0.79 (.48–1.30)	1.10 (.66–1.86)
Other/unknown	0.75 (.52–1.09)	**0.53 (.29–.96)**	1.08 (.48–2.46)	0.50 (.17–1.42)	0.80 (.33–1.97)	0.51 (.16–1.67)
Sex						
Male	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Female	**1.23 (1.09–1.39)**	1.19 (.99–1.42)	0.98 (.76–1.26)	1.09 (.80–1.48)	0.93 (.66–1.33)	1.30 (.91–1.86)
HIV risk factor[c]						
Heterosexual	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
MSM	**0.83 (.72–.96)**	1.08 (.88–1.33)	**0.62 (.46–.85)**	0.92 (.64–1.30)	0.96 (.63–1.46)	0.73 (.46–1.14)
IDU	**1.23 (1.06–1.42)**	**1.56 (1.26–1.92)**	**0.71 (.51–.97)**	**1.47 (1.03–2.10)**	**2.15 (1.44–3.33)**	1.21 (.77–1.89)
Other/unknown	1.21 (.96–1.53)	1.23 (.87–1.74)	0.74 (.46–1.20)	1.20 (.71–2.04)	1.58 (.61–4.08)	1.79 (.93–3.48)
CD4 cell count, cells/mm^3[d]						
>750	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
501–750	1.11 (.99–1.23)	1.08 (.90–1.28)	0.89 (.70–1.13)	1.11 (.83–1.50)	1.32 (.95–1.84)	1.18 (.82–1.71)
≤500	**1.28 (1.15–1.43)**	**1.28 (1.08–1.52)**	1.00 (.78–1.30)	1.17 (.86–1.58)	1.16 (.82–1.63)	1.18 (.83–1.69)
Hepatitis status[e]						
HIV monoinfection	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
HIV/HBV coinfection	1.07 (.78–1.46)	1.21 (.87–1.69)	0.72 (.32–1.63)	1.03 (.54–1.99)	0.87 (.38–1.98)	0.94 (.34–2.58)
HIV/HCV coinfection	**1.36 (1.17–1.57)**	**1.33 (1.07–1.66)**	**1.53 (1.11–2.10)**	1.33 (.94–1.90)	1.29 (.85–1.96)	1.40 (.90–2.16)
HIV/HBV/HCV triple infection	1.40 (.95–2.08)	1.18 (.78–1.80)	**2.41 (1.17–4.96)**	1.51 (.80–2.86)	0.25 (.04–1.74)	0.80 (.32–2.01)
Unknown	1.06 (.94–1.20)	0.94 (.78–1.13)	1.27 (.98–1.65)	1.13 (.84–1.52)	**1.48 (1.02–2.17)**	0.73 (.48–1.09)
Annual outpatient HIV visits						
1–2	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
3–4	0.93 (.82–1.06)	0.81 (.65–1.01)	0.87 (.58–1.30)	1.04 (.73–1.48)	0.77 (.54–1.09)	1.06 (.70–1.60)
5–6	**1.30 (1.13–1.48)**	**1.27 (1.01–1.59)**	1.24 (.83–1.84)	**1.52 (1.03–2.24)**	0.97 (.65–1.44)	**1.96 (1.24–3.11)**
≥7	**2.68 (2.34–3.07)**	**2.64 (2.11–3.31)**	**3.04 (2.02–4.57)**	**3.88 (2.76–5.46)**	**2.01 (1.43–2.82)**	**3.53 (2.32–5.36)**
Insurance[d]						
Private	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Medicaid	**1.72 (1.47–2.02)**	**1.91 (1.47–2.47)**	**2.15 (1.42–3.27)**	1.21 (.82–1.78)	**2.47 (1.55–3.93)**	1.57 (.91–2.72)
Medicare/dual eligible	**1.81 (1.53–2.15)**	**2.08 (1.59–2.72)**	**2.08 (1.38–3.13)**	1.29 (.86–1.92)	**2.78 (1.72–4.48)**	**2.45 (1.47–4.08)**
Ryan White/uninsured	1.08 (.91–1.28)	1.26 (.96–1.67)	1.44 (.94–2.21)	0.70 (.45–1.09)	**1.94 (1.21–3.10)**	1.14 (.65–2.02)
Unknown	0.99 (.75–1.30)	1.05 (.64–1.72)	**1.98 (1.07–3.67)**	0.56 (.22–1.45)	1.51 (.66–3.48)	0.43 (.08–2.26)
Calendar year						
2005	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
2006	0.95 (.81–1.10)	0.85 (.66–1.10)	1.43 (.97–2.12)	0.94 (.58–1.52)	**0.49 (.32–0.76)**	1.33 (.75–2.38)
2007	1.10 (.95–1.27)	1.01 (.78–1.31)	1.41 (.97–2.04)	1.06 (.67–1.69)	0.68 (.43–1.08)	**1.68 (1.02–2.74)**
2008	1.04 (.90–1.20)	0.94 (.74–1.20)	1.26 (.87–1.84)	1.18 (.75–1.86)	0.74 (.49–1.12)	1.42 (.83–2.44)

Table 4 continued.

Characteristic	Adjusted Incidence Rate Ratio (95% CI)[a]					
	All-Cause	Non–AIDS-Defining Infection	Cardiovascular	Gastrointestinal/Liver	Psychiatric	Endocrine
2009	1.04 (.90–1.19)	0.92 (.72–1.16)	1.13 (.78–1.65)	1.49 (.97–2.28)	**0.42 (.28–.64)**	**1.82 (1.02–3.23)**
2010	1.01 (.88–1.16)	0.88 (.69–1.13)	1.33 (.92–1.93)	1.42 (.93–2.15)	0.74 (.51–1.10)	1.47 (.87–2.47)
2011	0.96 (.84–1.11)	0.99 (.78–1.26)	0.88 (.60–1.27)	1.30 (.85–1.99)	**0.42 (.26–.67)**	1.55 (.92–2.62)

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICD-9, *International Classification of Diseases, Ninth Revision*; IDU, injection drug use; MSM, men who have sex with men.

[a] The multivariable models used to calculate adjusted incidence rate ratios included all listed variables and also an indicator variable for clinical care site. Results in **bold** are statistically significant ($P \leq .05$).

[b] Age was assessed on July 1 of each calendar year.

[c] HIV risk factors were considered mutually exclusive; subjects who reported IDU in addition to any other risk factor were categorized as IDU, men who reported sex with men and women were categorized as MSM.

[d] CD4 cell counts and insurance data used in these analyses were the first available measurements for each calendar year.

[e] HBV and HCV status were determined by hepatitis B surface antigen and hepatitis C antibody, respectively, as measured before 1 July of each calendar year. Negative test results were carried backward to the time of study entry, and positive test results were carried forward for all subsequent years.

contribute to the low rate of non–AIDS-defining infections in this population.

We are uncertain why elite controllers were hospitalized more frequently for psychiatric conditions. This association may warrant investigation in other cohorts.

Elite controllers in our study were more likely to be female than were persons in other HIV control categories. This is consistent with trends seen in several other studies of elite controllers, though in most studies the sex difference was not statistically significant [3, 7, 17, 35–38]. This is also consistent with prior observations that women tend to have lower HIV-1 RNA levels than men, particularly within the first year after seroconversion [39]. Few prior studies contained both an appropriate comparison group of non–elite controllers and sufficient power to detect a sex difference in the prevalence of elite control. If a sex difference is confirmed in additional studies, that may provide clues to the immunologic mechanisms underlying elite control.

Our study also provides an updated estimate of the prevalence of elite control among PLWH. Our estimate of 0.43% is within the range suggested by other studies [3–5]. It is likely that this number slightly underestimates the true prevalence, given that some potential elite controllers were excluded from the analysis because manual review of medical records was not possible.

A major strength of our study is its large sample of elite controllers. Among published cohorts, only the International HIV Controller Consortium reports a larger sample of elite controllers [17]. A limitation of our study is the potential for selection bias owing to our data being limited to persons actively engaged in HIV care. Because of no perceived need for ART, elite controllers might be less likely than other PLWH to be engaged in care, so that elite controllers with additional serious medical conditions are preferentially captured in our cohort. This could contribute to an increased hospitalization rate compared with the rate for members of the cohort whose only serious medical condition may be HIV infection. However, our study captured 93% of the elite controllers (14 of 15) otherwise known to local investigators at 2 clinical care sites with unrelated ongoing studies of elite controllers, suggesting both good sensitivity of our study definition for elite control and minimal impact of selection bias.

Duration of HIV infection may influence hospitalization rates, but this information was not available for participants in this cohort. Hospitalizations occurring outside each participant's HIV care institution may not have been completely captured, though we would not expect this to have a differential impact by HIV control status. This study was limited to person-years with high CD4 cell counts to provide meaningful comparators to the primary group of interest, elite controllers, who by nature of their disease process tend to have preserved CD4 cell counts. The medical control population does not necessarily reflect the full spectrum of patients seen routinely in HIV clinics, which may, at any given time, include a subset with low CD4 cell counts.

Another limitation is our lack of data on smoking, which are not routinely collected in this cohort but represent an important risk factor for all-cause and cardiovascular hospitalization. In general, smoking rates among PLWH are high, with 46%–67% categorized as current smokers by recent estimates [40–44]. We conducted a focused chart review to investigate smoking within our study population. All elite controllers were randomly matched with up to 4 persons with medical control, based on clinical care site, sex, race, and age in 5-year

bands. Records of the 149 elite controllers and of 581 matched persons with medical control were then searched to determine ever versus never smoking status. Data were available for 134 elite controllers and 555 persons with medical control. We found that 110 of 134 elite controllers (82%) and 377 of 555 (68%) with medical control had ever smoked ($P = .001$). Smoking was thus common in both groups, and though the higher rate among elite controllers may have contributed to more hospitalizations, it is unlikely to explain the near doubling in adjusted all-cause hospitalization rate or the tripling in cardiovascular hospitalization rate associated with elite versus medical control.

This study demonstrates that elite control of HIV is associated with higher hospitalization rate than is medical control of HIV with ART. Cardiovascular disease seems to be a major driver of this association. Compared with other HIV-infected patients, elite controllers had relatively few admissions due to non–AIDS-defining infections. These findings could reflect clinical manifestations of ongoing immune activation in elite controllers. Further investigations are needed to evaluate the mechanisms underlying these associations and to clarify the potential benefit of ART and/or anti-inflammatory agents in the management of elite controllers.

Notes

HIVRN Participating Sites. Alameda County Medical Center, Oakland, California (H. E.); Children's Hospital of Philadelphia, Pennsylvania (R. M. R.); Trillium Health, Rochester, New York (R. B. C.); Drexel University, Philadelphia (Jeffrey Jacobson, MD; S. L. A.); Fenway Health, Boston, Massachusetts (Stephen Boswell, MD); Johns Hopkins University, Baltimore, Maryland (K. A. G.; R. D. M.; Allison Agwu, MD); Montefiore Medical Group, Bronx, New York (R. B.); Montefiore Medical Center, Bronx (L. H. H.); Oregon Health and Science University, Portland (P. T. K.); Parkland Health and Hospital System, Dallas, Texas (A. E. N.; Muhammad Akbar, MD); St Jude's Children's Hospital and University of Tennessee, Memphis (Aditya Gaur, MD); St Luke's Roosevelt Hospital Center, New York, New York (V. S., Stephen Arpadi, MD); Tampa General Health Care, Florida (C. S.); and University of California, San Diego (W. C. M.);

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Data Coordinating Center. Johns Hopkins University (R. D. M.; Jeanne Keruly, CRNP; K. A. G., MD; Cindy Voss, MA; Nikki Balding, MS).

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