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Risk of Non–AIDS–Defining Events Is Lower in Antiretroviral Therapy (ART)–Naive HIV Controllers Than in Normal Progressors on Suppressive ART

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Background. We aimed to compare the non-AIDS event (nADE) risk between normal progressors using antiretroviral therapy (NP-ART) and people with human immunodeficiency virus (HIV, PWH) who naturally control HIV infection (HIV controllers), as well as the risk of nADE following ART in HIV controllers.

Methods. The primary end point was the composite of cardiovascular disease, non-AIDS malignancy, or all-cause mortality, whichever came first. The role of ART in HIV controllers was assessed as a time-varying covariate.

Results. We included 1007 ART-naive HIV controllers (60 of them were elite controllers), 1510 early-ART (<6 months after negative HIV test), and 15437 NP-ART (reference group), contributing 3813, 11 060, and 160 050 years of follow-up, respectively. HIV controllers had lower risk of the primary end point (hazard ratio [HR], 0.55; 95% confidence interval [CI]: .38–.81; $P = .0023$), all-cause mortality (adjusted HR [aHR], 0.45; 95% CI: .25–.79; $P = .0054$), and cardiovascular disease (aHR, 0.47; 95% CI: .22–.99; $P = .046$), but not non-AIDS malignancy (aHR, 0.74; 95% CI: .41–1.35; $P = .33$), compared with NP-ART. Among HIV controllers, each $\log_{10}$ lower baseline viral load further decreased the risk of a nADE (aHR, 0.54; 95% CI: .29–.99; $P = .045$). ART in HIV controllers did not reduce the risk of any nADE (aHR, 1.22; 95% CI: .66–2.29; $P = .53$).

Conclusions. HIV controllers had a lower n ADE risk than NP-ART, especially in those with low plasma viral loads. ART did not alter the nADE risk in HIV controllers. Our findings help clinicians to decide on prescribing ART in HIV controllers.

Keywords. non-AIDS–defining events; ART; HIV controllers; elite controllers; viremic controllers; clinical outcomes; cardiovascular disease; non-AIDS malignancies; mortality.

Despite antiretroviral therapy (ART), human immunodeficiency virus type 1 (HIV-1) infections continue to be accompanied by an increased risk of non-AIDS–defining events (nADEs) [1, 2]. Whether the risk of a nADE diverges between natural and ART-induced viral control is unknown [3, 4]. In contrast to normal progressors (NPs) with HIV (people with HIV [PWH]) who develop progressive immunodeficiency and have high plasma viral loads when no ART is initiated, HIV controllers spontaneously control viral replication to undetectable and low detectable plasma viral load levels and are referred to as elite controllers (ECs) or viremic controllers (VCs), respectively [5]. Depending on the definition, ECs and VCs comprise <1% and 1%–5% of PWH, respectively [6, 7]. For the most part, these individuals maintain high CD4 T-cell counts and do not experience disease progression [7]. It is hypothesized that HIV controllers exhibit increased levels of inflammation, which may augment the risk of a nADE [8–10]. The assumed risk of a nADE is a common reason to start ART in ECs and VCs, yet the evidence from controlled studies is low. The risk of HIV transmission may be an additional reason, although this risk is negligible in those with viral loads <1000 copies/mL [11]. Current guidelines recommend immediate ART for all PWH, including HIV controllers, despite acknowledging the uncertainty and scarcity of data regarding benefits and risks of ART in HIV controllers [12–15]. Additionally, a recent systematic review and a narrative review

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concluded that evidence is lacking concerning the risk of nADEs in ECs and VCs and that more data are needed [3, 4].

Here, we aimed to determine the risk of nADEs in ART-naive HIV controllers compared with NPs on suppressive ART (NP-ART). Furthermore, the impact of ART in HIV controllers on the risk of nADEs was evaluated.

METHODS

The time to first nADE was compared between 3 groups of PWH in the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort: ART-naive HIV controllers, NP-ART viral loads <50 copies/mL, and NP-ART who started ART within 6 months after a previous negative HIV test (early-ART). ATHENA has been prospectively recruiting individuals in HIV care in the Netherlands since 1998 [16].

Study Patients

Our study started on 1 January 2000. HIV controllers were defined as having 3 consecutive plasma viral load measurements <75 or 10 000 copies/mL in the absence of ART for ECs and VCs, respectively. Follow-up for HIV controllers started at the third viral load measurement and lasted until the last moment in care. Follow-up was censored when viral load exceeded 10 000 copies/mL, when ART was initiated, or on 1 May 2023, the censoring date. The NP-ART comparison group was defined as PWH who had at least 1 viral load >10 000 copies/mL in the absence of ART, subsequently initiated ART, and reached suppression of viral load. Follow-up for NP-ART started on the date of the first suppressed viral load and continued until the last moment in care or 1 May 2023, the censoring date. Early-ART were removed from the NP-ART group if they had a documented negative HIV test in the 6 months prior to HIV diagnosis.

Study End Points

The primary end point was a major nADE defined as the composite of cardiovascular disease, non-AIDS malignancy, or all-cause mortality, whichever came first, as defined previously in ATHENA (Supplementary Table 1) [16].

The secondary end points were the time to other non-AIDS illnesses related to HIV or ART, which were pneumonia, severe liver disease, all-type fractures, and chronic kidney disease (ATHENA clinical definitions, Supplementary Table 1) [16].

Statistical Analyses

First, we compared the risk of a first major nADE between 3 groups: ART-naive HIV controllers, early-ART, and NP-ART. We used time-to-event methods, including Kaplan–Meier curves, log-rank tests, and the Cox proportional hazards model using the packages Survminer (version 0.4.9) and Survival (version 3.5.7) in R 4.3.1. In the Cox proportional hazards model, NP-ART was the reference group, and covariates were age at baseline, sex, and smoking status at baseline, based on Marcus et al [1]. We evaluated the proportionality of the hazards and potential nonlinear effects using the Schoenfeld and Martingale residuals, respectively, and explored the interaction between the aforementioned variables (Supplementary Table 2, Supplementary Figure 1).

We performed several sensitivity analyses for our primary end points to address potential confounding, mortality causes, and viral loads <2000 copies/mL as the VC cutoff (Supplementary Text 1).

We studied the influence of baseline viral load on nADE outcomes in HIV controllers, hypothesizing that a lower $\log_{10}$ viral load in HIV controllers was associated with a lower risk of a nADE, corrected for age and intravenous drug use, based on the forward stepwise Cox regression.

In the HIV controller group, we studied the impact of ART on time to first nADE. For this analysis, HIV controllers were not censored at ART initiation, so that the follow-up window was extended until the last moment in care or 1 May 2023, the censoring date. ART in HIV controllers was included as a dichotomous time-varying covariate in a Cox proportional hazards model, as described elsewhere [17]. In this approach, the ART-naive follow-up and on-ART follow-up were analyzed separately with the Cox model. The ART-naive follow-up included both the ART-naive follow-up window of HIV controllers who later initiated ART as well as individuals who never received ART during the follow-up window. We corrected for baseline age and CD4 T-cell count because lower CD4 T-cell counts are associated with both the risk of outcome and the chance of initiating ART in HIV controllers [18]. HIV controllers who were hepatitis B surface antigen–positive at baseline have a clear indication for ART [12, 15] and were therefore excluded. As part of the sensitivity analyses, we explored baseline viral load as an additional covariate and we compared ART-naive HIV controllers directly with on-ART HIV controllers, corrected for baseline age and CD4 T-cell count. Therefore, HIV controllers in this second sensitivity analysis exclusively contributed person-years to either the ART-naive follow-up or the on-ART follow-up.

Using the Breslow estimator, the survival probabilities were derived from the Cox model to predict survival for ART-naive HIV controllers with baseline viral loads of 50, 400, 2000, and 10 000 copies/mL, respectively. Likewise, we predicted event-free survival for an HIV controller with and without ART. Baseline covariates were set at a median age of 37.4 years, CD4 T-cell count of 750 cells/mm^3, and no intravenous drug use.

Non-AIDS Biomarkers in Plasma Before and After ART

In HIV controllers, we assessed the effect of ART on as well as the stability over time of the reported nADE biomarkers of tumor necrosis factor (TNF), interleukin (IL)-6, IL-1β, and sCD14 for ECs and VCs separately (Supplementary Text 2, Supplementary Figure 2)

RESULTS

In total, 1007 HIV controllers (60 of them were ECs), 1510 early-ART, and 15 437 NP-ART were included in the analysis

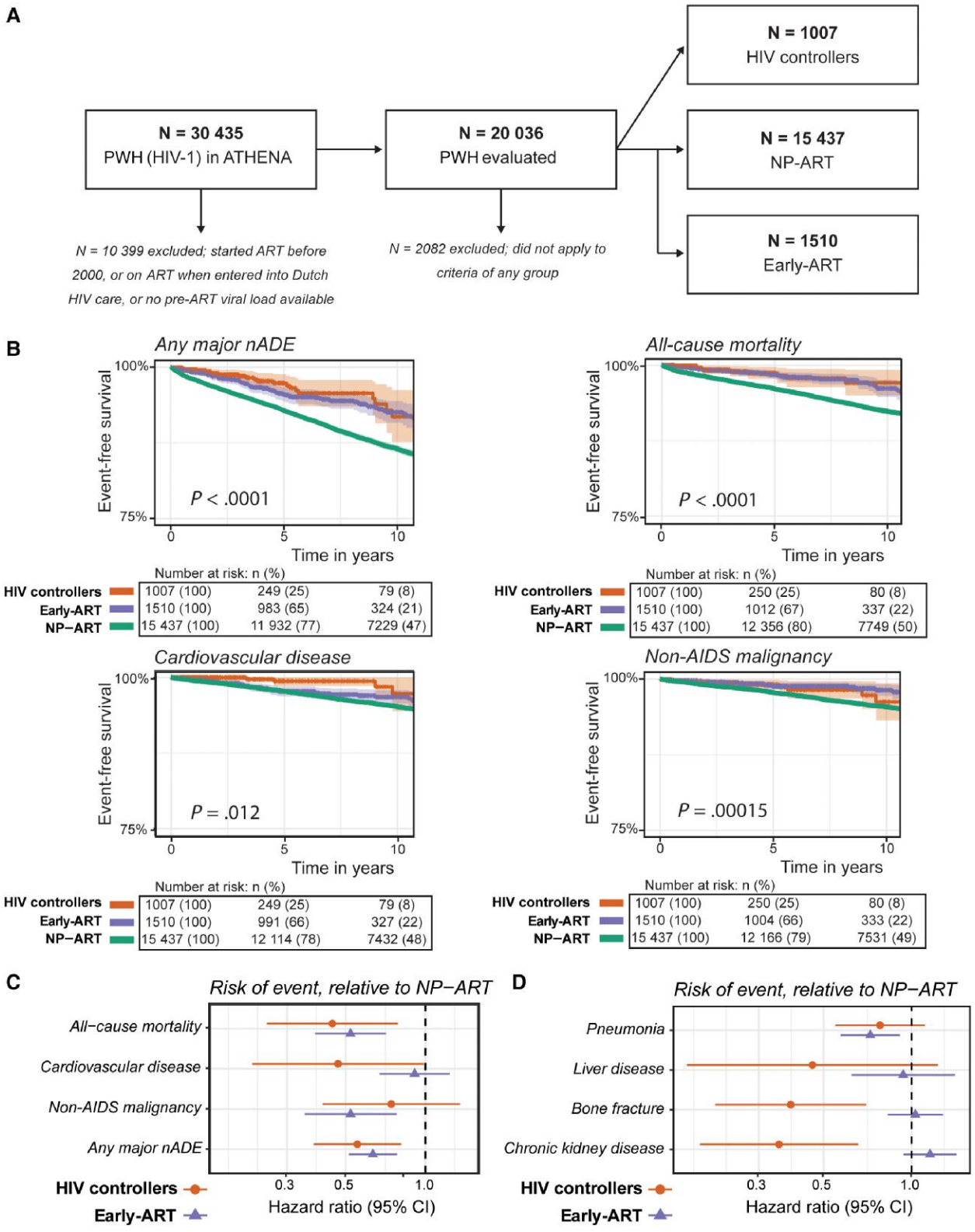

Figure 1. *A,* Study flow diagram. *B,* Kaplan–Meier curves of event-free survival among HIV controllers, NPs with HIV who initiated ART within 6 months of a negative HIV test (early-ART), and NPs on suppressive ART (NP-ART). Any major nADE refers to the first event of all-cause mortality, cardiovascular disease, or non-AIDS malignancy. *P* values were calculated with the log-rank test. *C,* Hazard ratios (HRs) of primary end points in HIV controllers and early-ART relative to NP-ART (reference) corrected for baseline age, sex, and smoking status. An HR of <1 means a shorter time to the event than for NP-ART. *D,* HRs of secondary end points corrected for baseline age, sex, and smoking status. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; nADE, non-AIDS–defining event; NP, normal progressor; PWH, people with HIV type 1.

Table 1. Group Characteristics at Baseline

Characteristic	HIV Controllers	Very Early ART	NP-ART	*P* Value[a]
N	1007	1510	15 437	…
Total follow-up years	3812.9	11 059.7	160 048.2	…
Follow-up duration, median (IQR), y	2.4 (1–5)	6.8 (4.1–9.5)	10 (6.1–14.4)	<.0001
Age at baseline, median (IQR), y	36 (29–44)	37 (29–47)	41 (33–49)	<.0001
Male sex, number (%)	711 (70.6)	1441 (95.4)	12 874 (83.4)	<.0001
Smoking				
Current, number (%)	398 (39.5)	514 (34)	5353 (34.7)	<.0001
Quit, number (%)	146 (14.5)	182 (12.1)	2499 (16.2)	…
Never, number (%)	378 (37.5)	579 (38.3)	5981 (38.7)	…
Unknown, number (%)	85 (8.4)	235 (15.6)	1604 (10.4)	…
BMI, median (IQR), kg/m^2	24 (21.9–27.1)	23.1 (21.2–25.1)	23.4 (21.4–25.9)	<.0001
Unknown BMI, number (%), kg/m^2	251 (24.9)	207 (13.7)	1959 (12.7)	…
Country of birth				
The Netherlands, number (%)	512 (50.8)	1058 (70.1)	9175 (59.4)	<.0001
Sub-Saharan Africa, number (%)	97 (9.6)	174 (11.5)	1495 (9.7)	…
Caribbean/Latin America, number (%)	171 (17)	43 (2.8)	1969 (12.8)	…
Western[c], number (%)	178 (17.7)	158 (10.5)	1749 (11.3)	…
South Asia, number (%)	25 (2.5)	30 (2)	573 (3.7)	…
Other, number (%)	23 (2.3)	41 (2.7)	399 (2.6)	…
Unknown, number (%)	1 (0.1)	6 (0.4)	77 (0.5)	…
Year of HIV diagnosis, median (IQR)	2005 (2001–2008)	2015 (2011–2017)	2008 (2004–2013)	<.0001
Unknown year of HIV diagnosis, number (%)	0 (0)	0 (0)	24 (0.2)	…
Time since HIV diagnosis, median (IQR), y	1.1 (0.6–2.6)	0.5 (0.3–0.8)	1 (0.5–2.9)	<.0001
Unknown time since HIV diagnosis, number (%), y	0 (0)	0 (0)	24 (0.2)	…
Time between HIV diagnosis and ART, median (IQR), y	5.9 (3.6–8.9)[b]	0.1 (0–0.2)	0.3 (0.1–2.1)	<.0001
Unknown time between HIV diagnosis and ART, number (%)	141 (14)[b]	0 (0)	24 (0.2)	…
HIV transmission behavior				
Men who have sex with men, number (%)	531 (52.7)	1362 (90.2)	9528 (61.7)	<.0001
Heterosexual, number (%)	388 (38.5)	110 (7.3)	4513 (29.2)	…
Injection drug user, number (%)	40 (4)	1 (0.1)	197 (1.3)	…
Other, number (%)	15 (1.5)	11 (0.7)	259 (1.7)	…
Unknown, number (%)	33 (3.3)	26 (1.7)	940 (6.1)	…
CD4 T-cell count, median (IQR), cells/mm^3	640 (479.5–830)	610 (460–801)	390 (250–560)	<.0001
Unknown CD4 T-cell count, number (%), cells/mm^3	15 (1.5)	2 (0.1)	41 (0.3)	…
Viral load, median (IQR), copies/mL	1330 (342–3465)	0 (0–0)	0 (0–0)	…
D:A:D risk score, median (IQR)	0.9 (0.4–1.9)	1 (0.4–2.1)	1.3 (0.6–2.7)	<.0001
Unknown D:A:D risk score, number (%)	737 (73.2)	946 (62.6)	7875 (51)	…
SCORE2 risk score, median (IQR)	1.6 (0.6–3.3)	1.8 (0.9–3.4)	2.1 (1–3.9)	<.0001
Unknown SCORE2 risk score, number (%)	524 (52)	227 (15)	4176 (27.1)	…
Hepatitis B surface antigen–positive at baseline, number (%)	30 (3)	34 (2.3)	782 (5.1)	<.0001
Hepatitis C virus–positive at baseline, number (%)	74 (7.3)	66 (4.4)	884 (5.7)	.0074
Previous history of cardiovascular disease, number (%)	5 (0.5)	4 (0.3)	89 (0.6)	.3
Previous history of non-AIDS malignancy, number (%)	4 (0.4)	5 (0.3)	163 (1.1)	.0045

Baseline was the moment that group criteria were fulfilled. For HIV controllers, baseline was the third viral load measurement below the cutoff criterion. For normal progressors using ART and early-ART, baseline was the first ART-suppressed viral load.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; D:A:D, Data collection on Adverse effects of anti-HIV Drugs; HIV, human immunodeficiency virus; IQR, interquartile range; NP-ART normal progressor using ART; SCORE2, Systematic COronary Risk Evaluation 2.

[a]False discovery rate–adjusted *P* values were estimated with the Kruskal–Wallis test for continuous data and with the χ^2 test for categorical data.

[b]Only considering N = 446 HIV controllers who start ART during follow-up.

[c]Country in Europe or Northern-America other than the Netherlands.

(Figure 1*A*). Median age at the start of follow-up was 36, 37, and 41 years, respectively, and 71%, 95%, and 83% were male, respectively (Table 1). Follow-up was censored in 428 (43%) HIV controllers for reaching a viral load >10 000 copies/mL and in 464 (46%) HIV controllers for starting ART when viral loads were <10 000 copies/mL.

ART-Naive HIV Controllers Have Lower Risk of a nADE Than NP-ART

During follow-up, 27 (3%) ART-naive HIV controllers experienced any major nADE, a composite end point, defined as mortality, cardiovascular disease, and non-AIDS malignancies, compared with 92 (6%) early-ART and 2359 (15%) NP-ART. Event-free survival was longer in HIV controllers compared

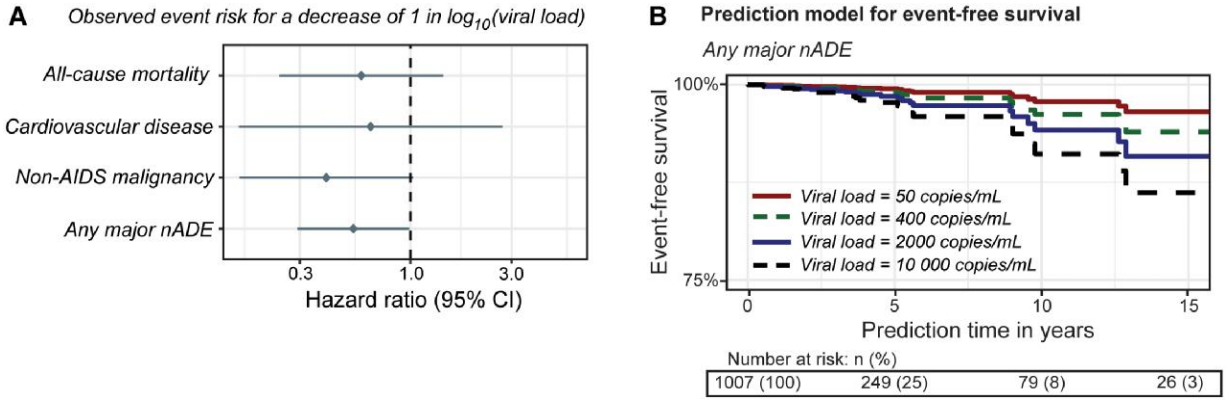

Figure 2. *A,* Hazard ratios (HRs) of primary end points among human immunodeficiency virus (HIV) controllers by $\log_{10}$ (baseline viral load) corrected for age and intravenous drug use. Any major nADE refers to the first event of all-cause mortality, cardiovascular disease, or non-AIDS malignancy. An HR of <1 means a shorter time to the event for each decrease in $\log_{10}$ (baseline viral load). *B,* Using the Breslow predictor of the Cox regression model in *A*, a prediction model for event-free survival probability was created for HIV controllers with baseline viral loads of 50, 400, 2000, and 10 000 copies/mL, respectively; all modeled with an age of 37.4 years and no history of intravenous drug use. Abbreviations: CI, confidence interval; nADE, non-AIDS–defining event.

Table 2. Baseline Factors Associated With Time-to-ART Initiation in Human Immunodeficiency Virus Controllers

Covariate	N With Available Data	Hazard Ratio	95% Confidence Interval	*P* Value	Statistical significance threshold
Age at baseline, y	977	0.99	.99–1.00	.20	…
Female sex[a]	977	1.33	1.1–1.61	.0039	*
Never smoked[a]	977	1.12	.93–1.35	.24	…
Non-Western origin[a]	976	1.21	1–1.46	.053	…
Body mass index at baseline, kg/m^2[,b]	735	0.44	.1–1.83	.26	…
Intravenous drug use[a]	977	0.86	.53–1.4	.54	…
Hepatitis C virus–positive at baseline[a]	977	0.94	.66–1.35	.73	…
Time since human immunodeficiency virus diagnosis, y[b]	977	0.89	.73–1.08	.24	…
CD4 T-cell count, cells/mm^3[,c]	963	0.92	.9–0.94	<.0001	***
Viral load at baseline, copies/mL[b]	977	1.84	1.6–2.12	<.0001	***
Time since the year 2000, y	977	1.12	1.09–1.14	<.0001	***

Hazard ratio (HR) of <1 and >1 refers to a lower and higher chance, respectively, to start antiretroviral therapy as a human immunodeficiency virus controller.

*, $P < .05$; **, $P < .001$; ***, $P < .0001$.

[a]Variable was log-transformed; in Cox model.

[b]Dichotomous variable.

[c]Variable was square-root–transformed in Cox model. HR indicates risk for increase of 1 in square root of CD4 T-cell count (1 square root increase from the median CD4 T-cell count equals 52 cells/mm^3).

with NP-ART for all-cause mortality, cardiovascular disease, and any nADE but not for non-AIDS malignancy (Figure 1*B*). The estimated hazard ratios (HRs) after correction for age, sex, and smoking were 0.45 (95% confidence interval [CI]: .25–.79; $P = .0054$), 0.47 (95% CI: .22–.99; $P = .046$), 0.55 (95% CI: .38–.81; $P = .0023$) and 0.74 (95% CI: .41–1.35; $P = .33$), respectively (Figure 1*C*, Supplementary Table 3). NPs who started ART early had a lower risk of all-cause mortality (HR, 0.52; 95% CI: .38–.71; $P < .0001$), non-AIDS malignancy (HR, 0.52; 95% CI: .35–.78; $P = .0014$), and any nADE (HR, 0.55; 95% CI: .38–.81; $P < .0001$) compared with NP-ART but a comparable risk of cardiovascular disease (HR, 0.91; 95% CI: .67–1.24; $P = .60$). Sensitivity analyses, including a Cox model corrected for age and intravenous drug use, yielded similar HRs (Supplementary Table 4, Supplementary Figure 3).

With regard to non-AIDS illnesses related to HIV or ART, the risks of pneumonia and severe liver disease were comparable between HIV controllers and NP-ART (HR, 0.78; 95% CI: .55–1.11; $P = .17$ and HR, 0.46; 95% CI: .17–1.23; $P = .12$, respectively), whereas the risks of bone fractures and chronic kidney disease were lower in HIV controllers than in NP-ART (HR, 0.39; 95% CI: .21–.70; $P = .0017$ and HR, 0.35; 95% CI: .19–.66; $P = .0010$, respectively; Figure 1*D*, Supplementary Table 5). Severe liver disease had a background of viral hepatitis in 100% (4 of 4), 56% (14 of 25), and 64% (256 of 403) of HIV controllers, early-ART, and NP-ART, respectively (Supplementary Table 6). After restricting the HIV controller group to only those with viral loads <2000 copies/mL, the risks of all-cause mortality and any major nADE, including pneumonia, bone fractures, and severe liver disease, were all significantly lower than in NP-ART (Supplementary Table 7).

Lower Baseline Viral Load in ART-Naive HIV Controllers Is Protective Against a nADE

As a subgroup analysis, we determined whether HIV controllers with lower baseline viral load have a lower risk of a nADE. We calculated the HR of a decrease of 1 $\log_{10}$ viral load at baseline, corrected for baseline age and intravenous drug use (Figure 2*A*,

Supplementary Table 8). Each lower $\log_{10}$ baseline viral load decreased the risk of any major nADE (HR, 0.54; 95% CI: .29–.99; $P = .045$) but was not statistically significant for all-cause mortality (HR, 0.58; 95% CI: .24–1.43; $P = .24$), cardiovascular disease (HR, 0.65; 95% CI: .15–2.72; $P = .55$), or non-AIDS malignancy (HR, 0.40; 95% CI: 0.156–1.03; $P = .058$). Using the Breslow predictor of the Cox proportional hazards model, we modeled the nADE-free survival probability of specific baseline viral load values (50, 400, 2000, and 10 000 copies/mL) in HIV controllers (Figure 2*B*) and lower baseline viral loads in HIV controllers were associated with trends toward decreases in nADE risk.

ART in HIV Controllers Does Not Alter the Rate of nADEs

We analyzed the impact of ART on nADEs in 963 HIV controllers who were hepatitis B virus–seronegative and had an available CD4 T-cell count at the start of follow-up. Of these, 446 initiated ART when the viral load was still <10 000 copies/mL and contributed 4514 years of follow-up with a median follow-up duration on ART of 9.1 years (interquartile range, 6.3–13.1). All starting regimens were oral multidrug ART (Supplementary Table 9). Factors associated with earlier ART are listed in Table 2.

Sixty-two (7%) nADEs occurred in HIV controllers during on-ART follow-up. Corrected for age and CD4 T-cell count, no difference was found in the HR for the effect of ART on all-cause mortality (HR, 2.03; 95% CI: .89–4.60; $P = .092$), cardiovascular disease (HR, 0.86; 95% CI: .27–2.80; $P = .81$), non-AIDS malignancy (HR, 1.21; 95% CI: .45–3.25; $P = .70$), and any nADE (HR, 1.22; 95% CI: .66–2.29; $P = .53$; Figure 3*A*, Supplementary Table 10). Sensitivity analyses yielded similar results (Supplementary Figure 4). Using the Breslow predictor of the Cox model, we predicted event-free survival for ART-naive HIV controllers and HIV controllers on ART, which was similar (Figure 3*B*).

ART in ECs and VCs Does Not Alter the Rate of Non-AIDS Biomarkers

Additionally, we evaluated the effect of time and ART on the well-established nADE, and there were no significant differences, except for a decrease of TNF after ART in VCs (Supplementary Figure 5, Supplementary Table 11).

DISCUSSION

In our nationwide ATHENA cohort of 20 036 PWH and 174 921 follow-up years, we observed a lower risk of nADEs in ART-naive HIV controllers than in NP-ART. Within the HIV controller group, a lower baseline viral load was associated with a lower risk of a nADE. Prescribing ART in HIV controllers with stable low viral loads did not alter the risk of a nADE. In sensitivity analyses, we addressed potential confounding effects with consistent results.

ART-naive HIV controllers in our cohort had improved event-free survival compared with NP-ART for all-cause mortality, cardiovascular disease, and any major nADE. Additionally, the risks of non-AIDS malignancy, pneumonia, and severe liver disease were comparable between the groups, whereas the risk of all-type fractures and chronic kidney disease was significantly lower in the ART-naive HIV controllers than in NP-ART. In 3 multicenter cohorts, lower, higher, or similar rates of nADEs in HIV controllers were reported [19–21]. In contrast to our study, these cohort studies could insufficiently correct for confounders [3, 12, 15], which may explain the different risk of a nADE in HIV controllers. Most importantly, 2 cohorts did not evaluate smoking behavior [20, 21] and, in the cohort that reported higher rates of nADEs, a post hoc chart review revealed that smoking was substantially more common in ECs [19]. Another difference between our study and the previously reported 3 cohort studies is the definition of a nADE that in other cohorts included a wide variety of illnesses but not mortality. One cohort defined nADE as cardiovascular disease, malignancies, hepatic diseases, metabolic disorders, bacterial pneumonia, renal disease, and osteonecrosis [21]. The 2 other cohorts reported all-cause hospitalizations from 18 categories based on modified *International Classification of Diseases, Ninth Revision, Clinical Modification*, diagnosis codes [19, 20]. Summarizing these into a single outcome obfuscated the interpretation [19–21]. For example, the study that found similar rates of all-cause hospitalization rates observed trends toward lower rates for cardiovascular disease (0.45 vs 0.76 per 100 person-years) and non-AIDS malignancies (0.11 vs 0.47 per 100 person-years) in HIV controllers compared with NP-ART. In our cohort, we restricted the primary end points to the major nADEs that are the most relevant to PWH, specifically mortality, cardiovascular disease, and non-AIDS malignancies, thus applying more precise definitions. We aimed to mitigate potential confounding bias through several sensitivity analyses, yielding consistent results. An additional distinction of our cohort is that we obtained a larger sample size, used time-to-event methods, and restricted the analysis to first events rather than incidence rates.

In contrast to other studies of VCs that typically used viral loads <2000 copies/mL as the cutoff [5], we applied a cutoff of <10 000 copies/mL to increase statistical power and to study the outcomes for various viral load thresholds. Indeed, our findings illustrate the relationship between viral control and nADE, which also implicates the potential benefit from ART. On a population level, individuals with spontaneous or ART-mediated viral suppression during acute HIV have a lower risk of a nADE compared with NP-ART. This correlation holds true within the HIV controller group, as a lower baseline viral load was associated with a lower nADE risk. Contrary to NPs, for whom ART is known to reduce the risk of a nADE [22], we did not observe a reduction of this risk following ART in the HIV controller group. Similarly, ART did not affect the clinical outcomes observed in the Strategic Timing of Antiretroviral

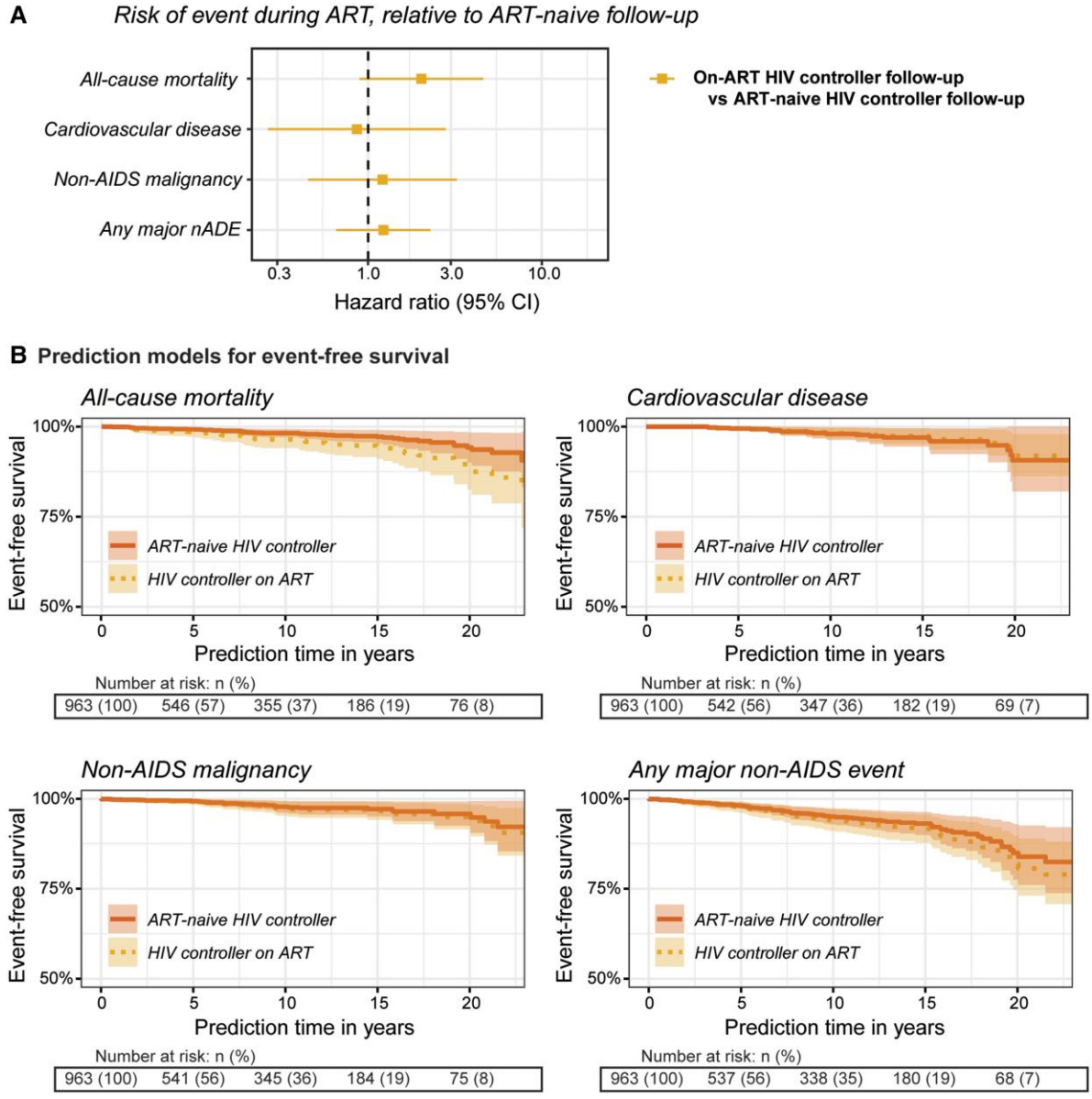

Figure 3. *A,* Hazard ratios (HRs) of first nADE in HIV controllers during ART-naive follow-up and on-ART follow-up, as assessed using the multivariate Cox models and corrected for age and baseline CD4 T-cell counts. An HR of <1 indicates lower risk during on-ART follow-up. "Any major non-AIDS event" refers to the first event of all-cause mortality, cardiovascular disease, or non-AIDS malignancy. *B,* Predicted event-free survival probabilities for an HIV controller with a median age of 37.4 years and baseline CD4 T-cell count of 750 cells/mm^3 on ART vs ART-naive. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; nADE, non-AIDS–defining event.

Treatment (START) study subgroup analysis of PWH with baseline viral loads <3000 copies/mL (HR, 1.1; 95% CI: .77–1.56) [23]. On a more individual level, a subset of HIV controllers may benefit more from ART, specifically those with substantial residual viremia of between 2000 and 10 000 copies/mL. Not only do our data show that these individuals have a slightly increased risk of any major nADE compared with ECs, but they also have to start ART more often due to increasing viral loads [24]. Furthermore, the risk of HIV transmission may be a reason to start ART in this group.

Current treatment guidelines still recommend lifelong ART for HIV controllers, referring to the risk of a nADE, potential immunological benefit, and HIV transmission [12, 13, 15]. On a population level, preventing HIV transmission is a clear benefit of ART, especially for viremic controllers. However, our findings reinforce that the individual benefit of ART for HIV controllers is strongly dependent on contextual factors. For all HIV controllers, therefore, we recommend shared decision-making that touches on the often temporal nature of HIV control, the potential toxicities

and immunological benefit of ART, the HIV transmission risk in the case of residual viremia >1000 copies/mL, and, importantly, personal preferences, as has been argued elsewhere [4]. Our data indicate that starting ART solely for concerns of nADEs, especially in HIV controllers with low viral loads, may not be required. Although we observed a trend toward fewer nADEs in HIV controllers with lower viral loads, our statistical power was insufficient to define a precise viral load cutoff for which the risk of a nADE and the benefit of ART become similar to the risk and benefit in NPs. Others have advocated for watchful waiting as long as viral loads are <1000 copies/mL and CD4 T-cell counts and CD4/CD8 ratios are stable [4, 18]. Such an individualized approach, rather than a strong recommendation to prescribe lifelong ART per se, may benefit HIV controllers.

Limitations of this study include its observational nature, which always leaves the possibility of unidentified residual confounding or channeling bias. Despite our large sample size, the absolute number of events was relatively low, which rendered stratification by sex, ethnicity, or EC status unfeasible. Evaluation of ischemic stroke was also not feasible because of the limited number of elderly ART-naive HIV controllers. Substantial biological variation in biomarker expression resulted in high standard errors, and their interpretation should be approached with caution. A large proportion of HIV controllers (N = 428; 43%) was censored for losing viral control, reiterating the importance of being able to predict this phenomenon. Nonetheless, our study is the largest on non-AIDS events in HIV controllers and uses clear definitions and a thorough exploration of potential confounding effects.

CONCLUSIONS

Current guidelines recommend starting ART in PWH irrespective of CD4 T-cell counts both for an individual benefit to reduce the risk of a nADE and for a population benefit as prevention. Here, we show that ART-naive HIV controllers have a lower risk of a nADE than PWH who need suppressive ART to control viremia. This effect is most evident in ECs, and initiation of ART in HIV controllers did not alter the nADE risk. Our findings help clinicians to decide on prescribing ART in HIV controllers, especially ECs, when concerns for nADEs play a prominent role.

Supplementary Data

Supplementary materials are available at *Clinical 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. A. L. G., A. v d V., and A. V. designed the study. A. V. and C. R. supervised the study. A. L. G., P. M. A., and F. W. analyzed the data. A. L. G. wrote the first draft. T. O., W. A. J. W. V., M. J. T. B., L. E. v E., N. V., J. v L., and A. v d V. contributed to data interpretation. All authors reviewed the manuscript.

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