MAJOR ARTICLE

Clinical Outcomes of Elite Controllers, Viremic Controllers, and Long-Term Nonprogressors in the US Department of Defense HIV Natural History Study

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(See the editorial commentary by Hunt, on pages 1636–8.)

Durable control of human immunodeficiency virus (HIV) replication and lack of disease progression in the absence of antiretroviral therapy were studied in a military cohort of 4586 subjects. We examined groups of elite controllers (ie, subjects with plasma HIV RNA levels of <50 copies/mL; prevalence, 0.55% [95% confidence interval {CI}, 0.35%–0.80%]), viremic controllers (ie, subjects with plasma HIV RNA levels of 50–2000 copies/mL; prevalence, 3.34% [95% CI, 2.83%–3.91%]), and subjects with a lack of disease progression (ie, long-term nonprogressors [LTNPs]) through 7 years of follow-up (LTNP7s; prevalence, 3.32% [95% CI, 2.70%–4.01%]) or 10 years of follow-up (LTNP10s; prevalence, 2.04% [95% CI, 1.52%–2.68%]). For elite and viremic controllers, spontaneous virologic control was established early and was typically observed when the initial viral load measurement was obtained within 1 year of estimated seroconversion. Elite controllers had favorable time to development of AIDS ($P = .048$), a CD4 cell count of 350 cells/μL ($P = .009$), and more-stable CD4 cell trends, compared with viremic controllers. LTNPs defined by 10-year versus 7-year criteria had a longer survival time ($P = .001$), even after adjustment for differing periods of invulnerability ($P = .042$). Definitions of controllers and LTNPs describe distinct populations whose differing clinical outcomes improve with the stringency of criteria, underscoring the need for comparability between study populations.

The course of human immunodeficiency virus (HIV) infection from seroconversion to eventual progression to AIDS is dependent on both virologic and host factors. Durable control of viral replication and/or lack of disease progression occur in only a small percentage of subjects in the absence of antiretroviral therapy (ART). During the past 2 decades, a variety of definitions have been used to categorize these individuals. Early studies defined subjects with lack of disease progression that was primarily based on the stability of CD4 cell counts and the duration of symptom-free HIV infection. These subjects, known as "long-term nonprogressors" (LTNPs),

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account for ~5%–15% of individuals infected with HIV [1–5]. Published analyses of LTNPs differ in defining CD4 cell count thresholds as well as the duration of clinical and immunologic stability, with most studies ranging from 7 to 10 years or more of follow-up.

With the advent of HIV RNA testing in the mid-1990s, LTNPs were shown to have differing magnitudes of HIV RNA, although most subjects generally displayed low to intermediate plasma viral loads [5–9]. Routine availability of viral load data made it possible to show that an uncommon subset of subjects with HIV infection were able to maintain HIV RNA levels below the limit of detection of the viral load assay for long periods [10–13]. These individuals, known as "elite controllers," comprised <1% of subjects with HIV infection in 2 French multicenter cohorts [14, 15]. An additional subset of subjects with a lesser degree of virologic control, known as "viremic controllers," displayed low but detectable HIV RNA loads [16, 17].

The varying definitions and categories used in the literature may represent overlapping groups of individuals with dissimilar underlying characteristics and divergent clinical outcomes [7, 9, 18, 19]. The unique elite controller and LTNP populations achieve, through an experiment of nature, favorable outcomes that could be the best achievable goals for HIV vaccine development. The central characteristic of elite and viremic controllers is spontaneous viral control, but some of these individuals experience CD4 cell loss and progression to clinical AIDS. Likewise, some LTNPs remain clinically healthy, with preserved CD4 cell counts, but have consistently nonsuppressed viral loads. In the present study, we characterized the epidemiologic characteristics of and disease outcomes for elite and viremic controllers and LTNPs among HIV-infected military healthcare beneficiaries who were largely identified through a comprehensive population-wide HIV screening program, and we show how variation in the definition of terms results in the description of differing populations with significantly divergent clinical outcomes.

SUBJECTS, MATERIALS, AND METHODS

Study population. Subjects were identified in a clinical database of ~5000 subjects who were prospectively enrolled in the US Department of Defense HIV Natural History Study, which has followed HIV-positive individuals in the military healthcare system since 1986 [20, 21]. All subjects who were enrolled provided written informed consent and were ⩾18 years of age. Subjects are seen approximately every 6 months at participating military treatment facilities in the United States. Data are systematically collected, including demographic characteristics, laboratory data, information on medication use, and reports of clinical events with medical record confirmation. AIDS diagnoses were established using 1993 criteria [22].

Elite controllers were defined as subjects having, over ⩾12 months, ⩾3 longitudinal HIV RNA determinations below the level of detection of the assay in the absence of antiretroviral therapy (ART) for ⩾1 year before and during the period of virologic control. The limits of viral load detection improved over time, with the initial limit of <400 copies/mL followed by limits of <200 copies/mL and <50 copies/mL in assays starting in 1995 and 1998, respectively. Subjects may have HIV RNA levels of up to 1000 copies/mL as long as such episodes represent the minority of all available determinations. An HIV RNA level of >1000 copies/mL or the initiation of ART indicated the end of the elite control window.

Viremic controllers were defined similarly to elite controllers but had an HIV RNA threshold of ⩽2000 copies/mL, as described elsewhere [16, 17]. Subjects may have HIV RNA levels of >2000 copies/mL, as long as such episodes represent the minority of all available viral load determinations. Elite and viremic controllers were examined as mutually exclusive groups for comparison so that a given patient would not be a member of both populations. Periods of virologic control were confirmed with the Amplicor 1.5 multiclade assay (Roche Diagnostic Systems). Duration of virologic control was defined as the number of days from determination of the baseline HIV RNA level to determination of the last HIV RNA level meeting the aforementioned thresholds used to define elite and viremic controllers. For elite and viremic controllers, ART-naive status before the period of virologic control was defined as no previous use of any antiretroviral agents through the period of spontaneous virologic control. For all groups, the CD4 cell count at baseline and the HIV RNA level at baseline were defined as the earliest available values from the time of HIV diagnosis.

To address the variation in defining LTNPs in the literature, 2 definitions were used in the present study, depending on the duration of nonprogression. LTNPs were defined as subjects for whom all CD4 cell counts were ⩾500 cells/μL for a period of ⩾7 years (LTNP7s) or ⩾10 years (LTNP10s). These LTNP groups were defined as being exclusive of each other, for the purpose of establishing comparisons. Both LTNP groups were required to be ART naive from the time of diagnosis through the period of nonprogression. Use of ART beyond the period of nonprogression was permitted. LTNPs were also required to have no history of AIDS-defining events before or during the period of nonprogression. Reasons for termination of LTNP status included a CD4 cell count of <500 cells/μL, presence of an AIDS-defining condition, initiation of ART, death, and loss to follow-up. Controller and LTNP groups were studied against the comparatively much larger overall pool of subjects who did not meet the definitions of controllers or LTNPs.

Statistical analysis. Controller groups were compared with the remaining overall population and with each other; LTNP groups were similarly evaluated against each other and the overall population. Continuous variables were expressed as median

values and interquartile ranges (IQRs) and were compared using the Mann-Whitney *U* test. Categorical variables were evaluated using a χ^2 test or Fisher's exact test. For subjects with ⩾6 months of follow-up, time-to-event analysis was performed using Kaplan-Meier analysis, and groups were compared using a log-rank test. Prevalence rates for controllers and LTNPs were expressed using Poisson 95% CIs. Trends for CD4 cell counts from the time of the initial positive HIV test result were expressed with Loess curves for elite and viremic controller groups.

RESULTS

Characteristics at baseline. A total of 4586 subjects were enrolled in the HIV Natural History Study from 1986 through 2006. Characteristics at baseline, including age when HIV infection was documented and sex, were similar between the groups (Table 1). The median duration of follow-up for elite and viremic controllers was 7.8 years (interquartile range [IQR], 5.6–11.7 years) and 7.6 years (IQR, 4.5–11.8 years), respectively. The median duration of follow-up was 10.7 years (IQR, 8.7–16.3 years) for LTNP7s and 14.3 years (IQR, 12.2–19.2 years) for LTNP10s. A higher proportion of subjects reported themselves as being African American, compared with European American, in the viremic controller and LTNP groups ($P = .002$), but ethnic distribution did not differ significantly in the remaining groups. Median HIV RNA values at baseline were lower for each group of controllers and nonprogressors, compared with subjects classified as belonging to the "other" group (neither controllers nor LTNPs) ($P < .001$), whereas median HIV RNA levels at baseline were lower for elite versus viremic controllers ($P = .023$) and LTNP10s versus LTNP7s ($P < .001$). The CD4 cell count at baseline was greater in the elite controller ($P = .001$), viremic controller ($P < .001$), LTNP7, and LTNP10 groups ($P < .001$) than in subjects belonging to the "other" group. Similar results were obtained for the CD4 cell nadir, although LTNP10s had a higher nadir (507 cells/μL; IQR, 341–626 cells/μL) than LTNP7s (435 cells/μL; IQR, 245–540 cells/μL) ($P = .045$).

Elite and viremic controllers. There were 25 elite and 153 viremic controllers (excluding the elite controller subset). This produced in the cohort respective prevalence rates of 0.55% (95% CI, 0.35%–0.80%) and 3.34% (95% CI, 2.83%–3.91%). The combined prevalence rate for elite and viremic controllers overall was 3.88% (95% CI, 3.33%–4.49%). The median number of days of virologic control was 846 days (IQR, 534–1754 days) for elite controllers and 1085 days (IQR, 700–2031 days) for viremic controllers ($P = 0.23$). For elite controllers, 20 of the 25 subjects were defined using a viral load assay with a limit of detection of <50 copies/mL. Of the remaining 5 subjects, 3 were defined using a detection limit of 200 copies/mL and 2 with a detection limit of 400 copies/mL.

A total of 17 elite controllers (68%), 132 viremic controllers (86.3%), and 2221 noncontrollers (ie, subjects without spontaneous control of viral replication) (51.8%) had documented HIV negative and positive dates (ie, were seroconverters). To assess whether spontaneous virologic control occurred early in the course of HIV infection, the 149 controllers who were seroconverters (elite plus viremic controllers) with a median seroconversion window of 1 year (IQR, 0–2 years) were evaluated. Virologic control was established early in the course of HIV infection, at a median time of 1 year (IQR, 0–5 years) after the estimated time of seroconversion (Figure 1*A*). Even more revealing, the median time from the first viral load measurement to viral suppression was 0 years (IQR, 0–1 year)—that is, the initial measured viral load was a spontaneously suppressed viral burden for most controllers (Figure 1*B*). Of the 24 controllers who were seroconverters having a period of >2 years from the first viral load measurement to the start of viral suppression, all were subjects who were initially ineligible to be classified as controllers with spontaneous viral control, because they had received early antiretroviral therapy.

Among both elite and viremic controllers, there were significantly fewer deaths and AIDS-defining events (Table 1), as well as a longer time to death and AIDS diagnosis, compared with findings for noncontrollers (Figure 2*A* and Figure 2*B*). When elite and viremic controllers were compared, time to AIDS ($P = .048$), but not time to death ($P = .54$), was significantly longer for the former group than for the latter. To explore whether the more stringent definition of elite controllers versus viremic controllers resulted in differing outcomes, these groups were further compared in terms of the time to development of a CD4 cell count of 350 cells/μL, which is a current threshold for consideration of antiretroviral therapy, and trends in the CD4 cell count over time. Elite controllers demonstrated a substantially more favorable time to development of a CD4 cell count threshold of 350 cells/μL than did viremic controllers ($P = .009$) (Figure 2*C*). Trends in CD4 cell counts over time demonstrated an initial increase, followed by stability, in the elite controllers, contrasting with a gradual decrease observed in the viremic controllers (Figure 2*D*).

Repetition of the aforementioned analyses restricted to the seroconverter subpopulation yielded Kaplan-Meier curves similar to those obtained with the overall population (data not shown). Time to a CD4 cell count of 350 cells/μL continues to differ significantly between elite and viremic controllers with seroconversion ($P = .04$), but the reduction in the number of subjects decreased the significance of the difference in the time to AIDS diagnosis between these groups ($P = .10$).

The proportion of elite (32.0% [8 subjects]) and viremic (18.3% [28 subjects]) controllers who have early exposure to ART before the virologic control window was not significantly different ($P = .11$). Similarly, ART use initiated after the period

Table 1. Characteristics of Subjects in the US Department of Defense HIV Natural History Study

Characteristic	Other subjects (n = 4290)	Elite controllers (n = 25)	Viremic controllers (n = 153)	LTNP10s (n = 52)	LTNP7s (n = 101)
Age at documentation of HIV-positive status, median (IQR), years	28.4 (24.1–33.7)	26.7 (24.5–32.3)	27.7 (23.0–32.7)	26.8 (23.7–31.9)	27.1 (24.2–32.6)
Sex, male	3888 (85)	20 (80)	137 (90)	49 (94)	94 (93)
Ethnicity					
European American	1903 (44)	13 (52)	49 (32)	21 (40)	31 (31)
African American	1900 (44)	11 (44)	89 (58)	28 (54)	56 (55)
Hispanic/Puerto Rican/Mexican	340 (8)	0 (0)	10 (7)	2 (4)	9 (9)
Asian/Pacific Islander	71 (2)	0 (0)	2 (1)	0 (0)	3 (3)
Native American/Alaskan	22 (1)	0 (0)	0 (0)	0 (0)	1 (1)
Other/unknown	55 (1)	1 (4)	3 (2)	1 (2)	1 (1)
ART naive before the virologic control period	NA	17 (68)	125 (82)	NA	NA
Baseline measurement					
CD4 cell count, median (IQR), cells/μL	477 (326–644)	644 (520–733)[a]	668 (526–826)[a]	907 (733–1061)[a]	810 (654–1010)[a]
CD4 cell percentage, median (IQR)	25.5 (19.0–32.0)	33.5 (26.5–41.0)[a]	34.0 (28.6–40.0)[a]	34.8 (30.0–41.3)[a]	34.0 (29.5–40.1)[a]
HIV RNA load, median (IQR), $\log_{10}$ copies/mL	4.4 (3.8–4.9)	2.6 (2.3–3.2)[a,b]	3.0 (2.6–3.6)[a]	3.5 (2.6–4.1)[a]	4.0 (3.4–4.6)[a,c]
Follow-up duration, median (IQR), years	6.2 (3.2–9.5)	7.8 (5.6–11.7)[d]	7.6 (4.5–11.8)[a]	14.3 (12.2–19.2)[a,c]	10.7 (8.7–16.3)[a]
Virologic control duration, median (IQR), days	NA	846 (534–1754)	1085 (700–2031)	NA	NA
LTNP duration, median (IQR), days	NA	NA	NA	4274 (3781–4995)[c]	2915 (2746–3231)
CD4 cell nadir, median (IQR), cells/μL	235 (59–382)	525 (448–506)[a,e]	416 (300–521)[a]	507 (341–626)[a,f]	433 (245–540)[a]
Reason LTNP period ended					
CD4 cell count of <500 cells/μL	NA	NA	NA	14	38
Developed AIDS	NA	NA	NA	4	9
Started ART	NA	NA	NA	15	18
Lost to follow-up	NA	NA	NA	19	36
Developed AIDS	2325 (54)	1 (4)[a]	25 (16)[a]	12 (23) [a]	26 (26)[a]
Hospitalized	729 (41)	7 (33)	52 (36)	21 (54)[f]	18 (33)
Death	1593 (37)	0 (0)[a]	2 (1)[a]	0 (0)[a,c]	12 (8)[a]
ART use after controller or LTNP period	NA	3 (12)	35 (23)	25 (48)	49 (49)

NOTE. Data are no. (%) of subjects, unless otherwise indicated. ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range (25th–75th percentiles); LTNPs, long-term nonprogressors; LTNP7s, 7-year LTNPs; LTNP10s, 10-year LTNPs; NA, not applicable; other subjects, neither controllers nor LTNPs.

[a] $P < .01$ vs "other" group.
[b] $P < .05$, for elite vs viremic controllers.
[c] $P < .01$ for LTNP10s vs LTNP7s.
[d] $P < .05$ vs "other" group.
[e] $P < .01$, for elite vs viremic controllers.
[f] $P < .05$, for LTNP10s vs LTNP7s.

of virologic suppression was not statistically different (P = .22) between the elite controllers (3 subjects [12.0%]) and viremic controllers (35 subjects [23%]). Analyses of time to death and time to AIDS were performed for stratified subpopulations who were either receiving or not receiving ART before their control window, and they yielded curves similar to the unstratified analysis, albeit with statistical limitations resulting from divided sample size (Figure 3).

LTNPs. A total of 52 persons were LTNP10s and 101 were LTNP7s (excluding LTNP10s). For subjects with 10 and 7 years of follow-up or follow-up limited by death, the respective prevalence rates were 2.04% (95% CI, 1.52%–2.68%) and 3.32% (95% CI, 2.70%–4.01%). The prevalence rate for LTNP7s, including the LTNP10 subset, was 5.02% (95% CI, 4.26%–5.89%). A total of 41 LTNP7s (40.6%) and 15 LTNP10s (28.8%) were defined as seroconverters, compared with 2370 non-LTNPs (55.2%). The median duration of the LTNP status was 2915 days (IQR, 2746–3231 days) for LTNP7s and 4274 days (IQR, 3781–4995 days) for LTNP10s. The proportion of subjects with ART use after the LTNP window was similar for LTNP7s (49% [49 subjects]) and LTNP10s (48% [25 subjects]) (P = .96). When exclusive groups defined by 7- and 10-year criteria were contrasted, there were fewer deaths among LTNP10s than LTNP7s ($P < .001$) (Table 1), and survival time was significantly longer for LTNP10s than LTNP7s (P = .001) (Figure 4*A*).

To adjust for the period of invulnerability imbued by a definition of 7- or 10-year LTNPs, analyses were repeated for survival time with a left-censored, or initial, time beginning at the end of 7 years of follow-up (LTNP7) or 10 years of follow-up (LTNP10). This "invulnerability-adjusted" survival time remained significantly different for the LTNP10s versus the

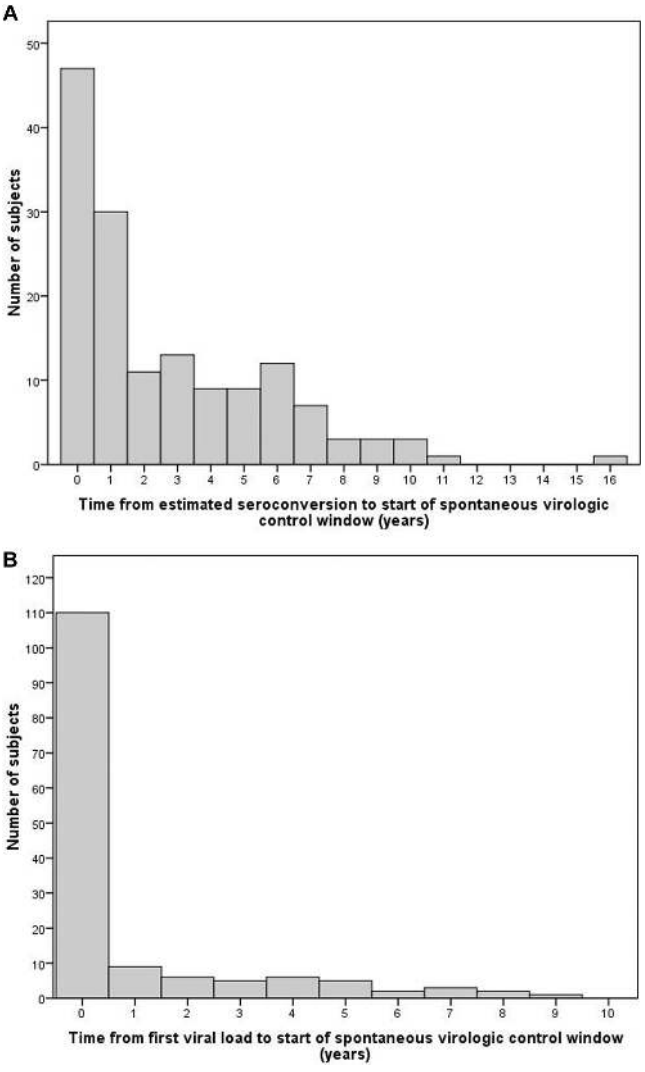

Figure 1. Histograms denoting the time from estimated seroconversion *(A)* and the time from the first viral load measurement *(B)* to the start of the spontaneous virologic control window for combined controller groups (elite controllers plus viremic controllers).

LTNP7s ($P = .042$) (Figure 4*B*). The length of follow-up beyond the invulnerability period was no different between groups ($P = .76$), with a median duration of 4.0 years (IQR, 1.9–9.8 years) and 4.3 years (IQR, 2.2–9.2 years) for LTNP7s and LTNP10s, respectively. Additional analyses were performed excluding members of the LTNP7 group with <10 years of follow up (Figure 4*C*), and differences in survival remained significant ($P = .006$). A similar trend toward improved survival was noted for LTNP10s and LTNP7s, in an invulnerability adjusted analysis of a subpopulation limited to ⩾10 years of follow-up (Figure 4*D*). Among seroconverters, time to death remained significant for LTNP7s ($P = .003$) and LTNP10s ($P = .008$) versus non-LTNPs (data not shown); other contrasts were limited by sample sizes.

DISCUSSION

Durable control of HIV replication and/or lack of disease progression are difficult to achieve for the vast majority of subjects in the absence of ART. Studying these aspects could provide important information regarding pathogenesis and vaccine strategies and development of novel therapeutic agents to combat HIV. Evaluation of population extremes can reveal the effect of relatively rare but high-impact host genetic variations that might not be evident in a cohort study. Many different terms have been used to categorize individuals with delayed disease progression, spontaneous HIV viral control, or both, such as elite and viremic controllers and LTNPs. The characteristics, outcomes, and interrelationships between these nonsynonymous groups have not been previously well-described. Our study, which used a large cohort that was followed for >2 decades, found that the terms used to describe durable control of viral replication and/or lack of disease progression in the literature, such as elite and viremic controllers and LTNPs, depict distinct populations with significantly different clinical outcomes.

The Department of Defense HIV Natural History Study cohort is an ethnically balanced cohort of subjects, with the majority having well-defined HIV seroconversion windows. Analysis of the epidemiologic characteristics of controllers and LTNPs revealed no difference in either age at HIV diagnosis or sex, similar to findings from previous studies of controllers and LTNPs [18, 23, 24]. However, our study showed a significantly higher proportion of African Americans, compared with European Americans, in the viremic controller and LTNP7 groups. A previous study performed in this cohort showed that African Americans had a trend toward a slower rate of progression to AIDS and death, compared with European Americans, in the pre–highly active antiretroviral therapy era [25].

Elite and viremic controllers are defined according to the ability to spontaneously control plasma viremia. Our study showed that virologic control occurs early in the course of HIV infection in the vast majority of subjects, with a median time of 1 year after infection for seroconverters (Figure 1*A*). Further evidence of early virologic control in our study was provided by the observation that, for most subjects, the virologic control window began with the initial viral load measurement (Figure 1*B*). A study by Madec et al [13] found that spontaneous virologic control, defined by viral loads of <400–500 copies/mL, occurred at a median of 23.3 months after seroconversion. Methodologic differences between our study and the Madec study, such as the sampling interval of our population HIV screening program, estimated seroconversion windows, and ascertainment of viral load in reference to estimated seroconversion, may account for these differences. In addition, as our current research shows, differing definitions for stringency of

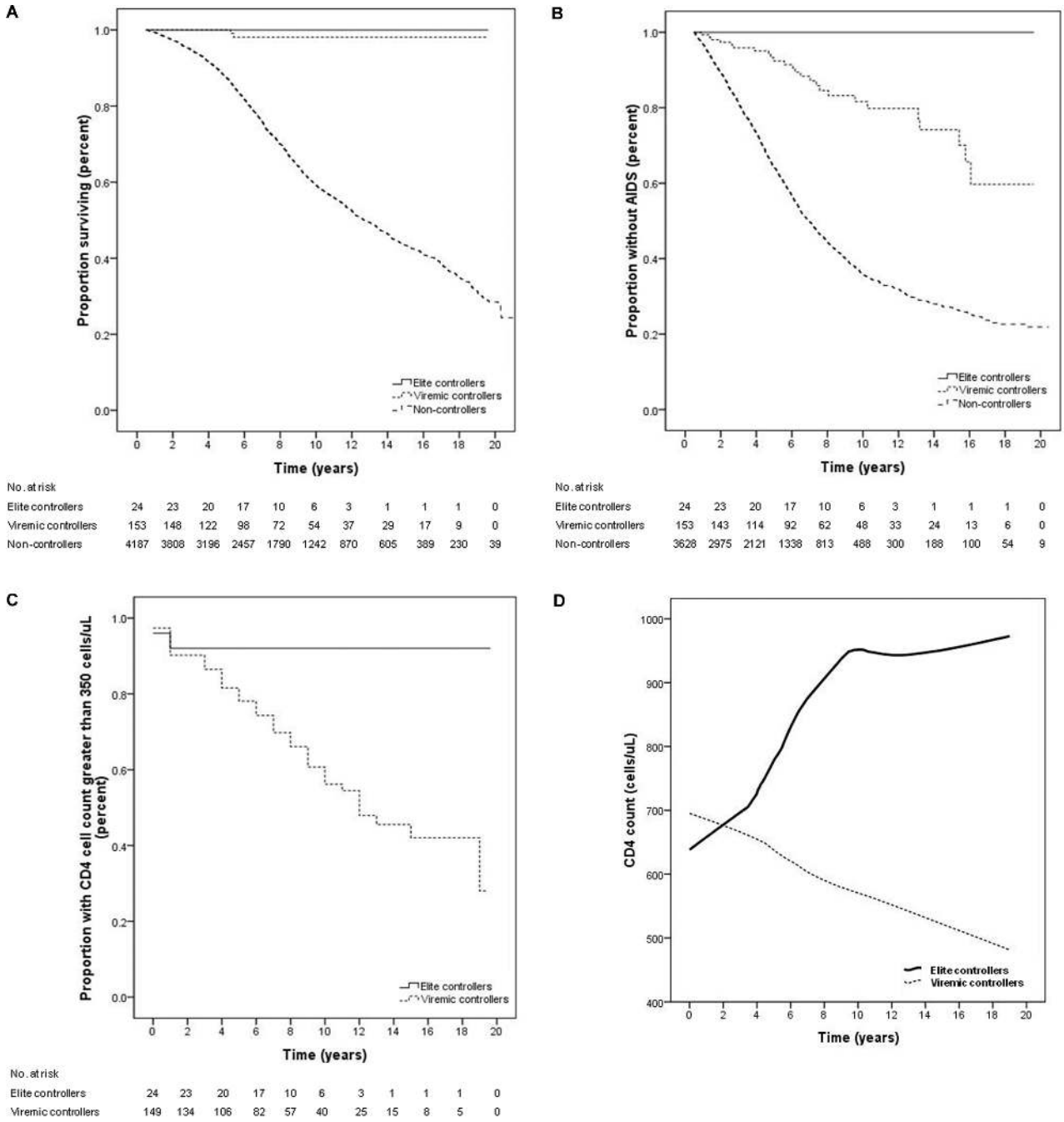

Figure 2. Kaplan-Meier plot demonstrating the survival time for elite controllers, viremic controllers, and noncontrollers *(A).* Survival time was significantly longer for both elite ($P = .001$) and viremic ($P < .001$) controllers than for noncontrollers. The elite and viremic controllers had similar survival times ($P = .54$). *B,* Kaplan-Meier curve for time to AIDS diagnosis for elite controllers, viremic controllers, and noncontrollers. Elite and viremic controllers similarly had a significantly longer time to AIDS diagnosis than did noncontrollers ($P < .001$, for both). Among controllers, a longer time to AIDS progression was observed for elite versus viremic controllers ($P = .048$). *C,* Kaplan-Meier plot demonstrating a longer time to development of a CD4 cell count of <350 cells/μL for elite, compared with viremic, controllers ($P = .009$). *D,* Loess curves showing a stable CD4 cell count trend over time in elite controllers versus the CD4 cell count decreases noted in viremic controllers.

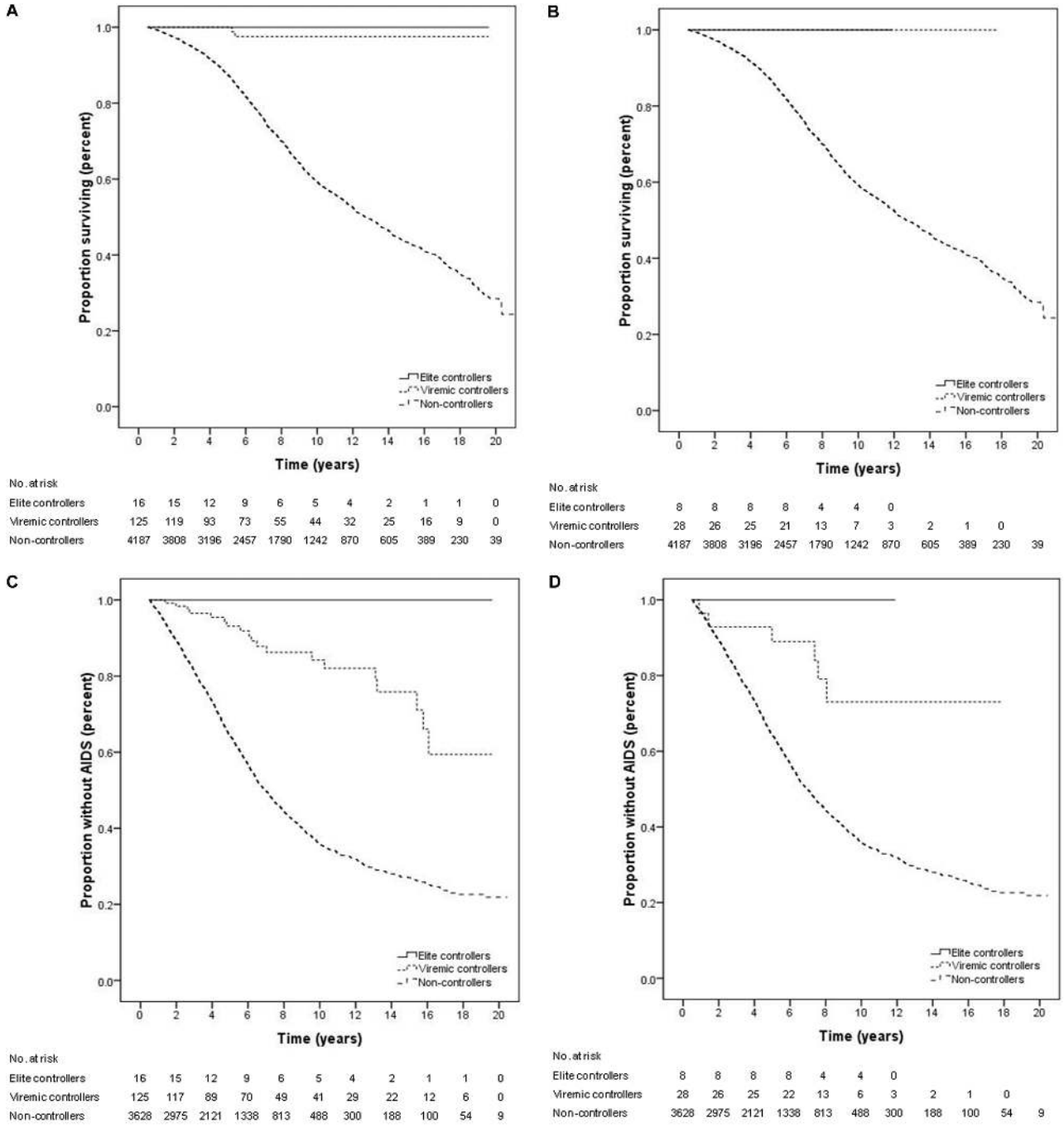

Figure 3. Kaplan-Meier plot demonstrating time to death for elite and viremic controllers who were antiretroviral therapy (ART) naive *(A)* or who received ART *(B)* for a period before the window of spontaneous virologic control. For ART-naive subjects *(A),* both elite ($P = .008$) and viremic ($P < .001$) controllers had a longer time to death than did noncontrollers. For subjects receiving ART before the window of spontaneous virologic suppression *(B),* time to death was significantly longer for viremic controllers ($P < .001$) than for noncontrollers, whereas a similar trend was observed for elite controllers ($P = .07$) versus noncontrollers. Kaplan-Meier curves for time to diagnosis of AIDS for ART-naive *(C)* and ART-experienced *(D)* controllers before the window of spontaneous virologic control. *C,* ART-naive elite ($P = .001$) and viremic ($P < .001$) controllers had a significantly longer time to diagnosis of AIDS than did noncontrollers. *D,* Similarly, elite ($P = .009$) and viremic ($P = .001$) controllers who received ART before the window of spontaneous virologic control had a longer time to the development of AIDS than did noncontrollers. Contrasts between elite and viremic controllers regarding survival and AIDS end points, with and without presuppressive therapy, were similar to findings from the unstratified analysis but had too few events for statistical comparison.

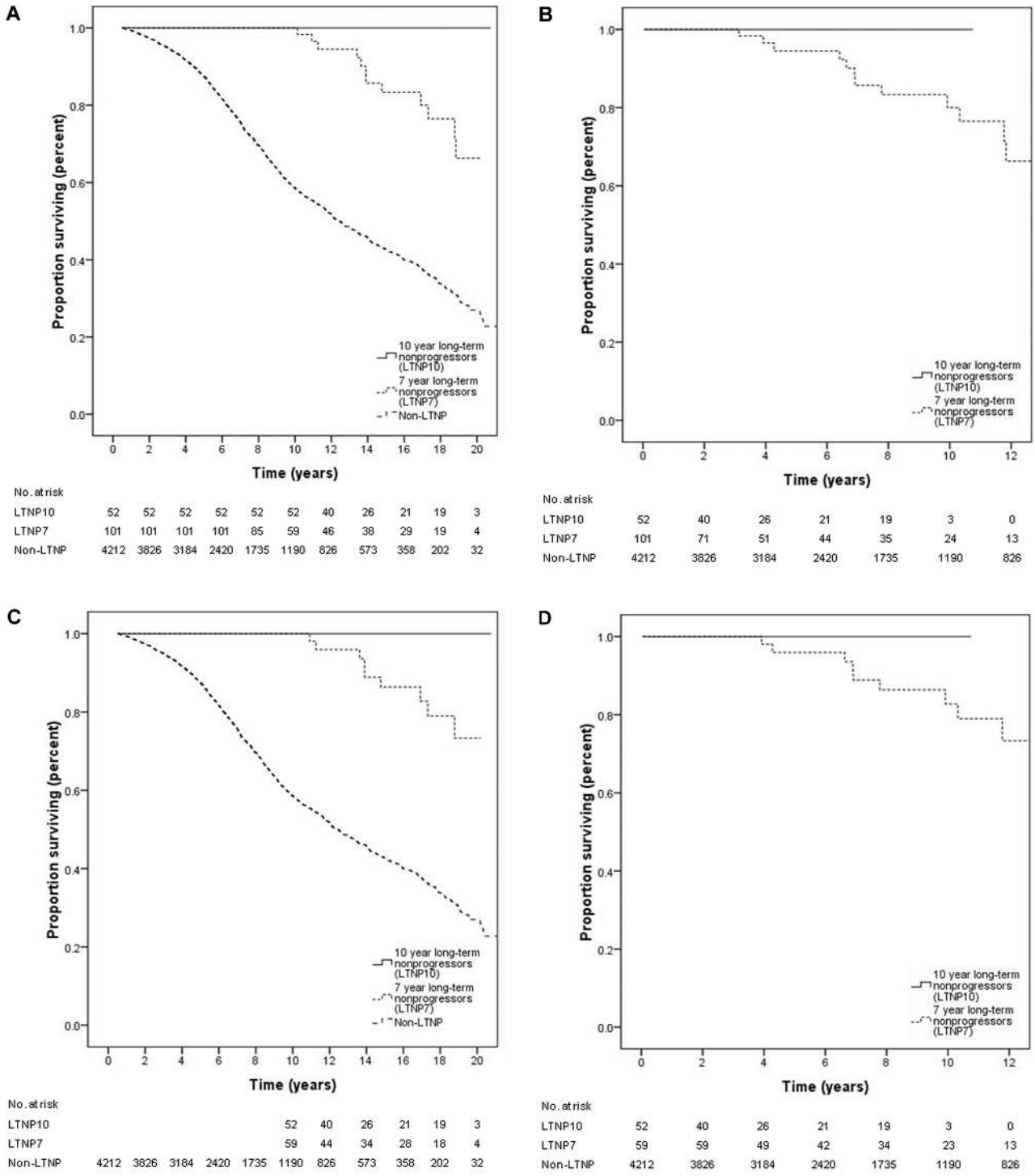

Figure 4. Kaplan-Meier analysis of time to death for 7- and 10-year long-term nonprogressors (LTNP7s and LTNP10s, respectively) and non-LTNPs *(A).* Time to death was significantly longer for LTNP10s (no events) than for LTNP7s ($P = .001$) and for both LTNP7s and LTNP10s than for non-LTNPs ($P < .001$). *B,* Kaplan-Meier curves for LTNP groups, adjusted for the duration of invulnerability to death, with time zero equaling year 7 for LTNP7s and year 10 for LTNP10s. Even after adjustment for the definition-associated period of invulnerability, survival time remained significantly longer for LTNP10s than for LTNP7s ($P = .042$). *C,* Kaplan-Meier plot of time to death for a subgroup of LTNP7s with ⩾10 years of follow-up, LTNP10s, and non-LTNPs. Time to death remained significant for LTNP7s versus LTNP10s ($P = .006$). *D,* Kaplan-Meier curves for the LTNP7 subgroup with at least 10 years of follow-up and for LTNP10s, additionally adjusted for the duration of invulnerability to death, show a trend toward longer survival for LTNP10s than for LTNP7s ($P = .07$).

viral control can be associated with variation in clinical outcomes. Our findings support the idea that the establishment of spontaneous virologic control is determined early in the course of HIV infection and that the achievement of spontaneous virologic control during the later, chronic phase of infection is less common.

Despite having only low-level viremia, some viremic controllers eventually experienced progression to AIDS and death, albeit over a significantly longer period, compared with noncontrollers. Although the virologic thresholds of serum HIV RNA for elite and viremic controllers differ by less than one-half log, the ability of elite controllers to further suppress viral replication below the limit of detection is associated with a significant additional reduction in the risk of AIDS and prolongation of the time when the CD4 cell count is >350 cells/μL, compared with viremic controllers (Figure 2*B* and Figure 2*C*). The prevalence of elite controllers was observed to be similar to previous findings [14, 15]. Only 1 AIDS event (pulmonary tuberculosis presenting along with HIV infection) occurred in the elite controller group, compared with 25 AIDS events occurring in the viremic controller group. That subject maintained elite controller status from the first viral load measurement obtained after seroconversion through >15 years of follow-up with no subsequent AIDS-associated illness.

A study by Hunt et al [19] showed diminishing CD4 cell counts and diagnosis of AIDS in several elite controllers over time. Although we also observed decreases in CD4 cell counts in the minority of elite controllers, longitudinal trends in CD4 cell counts showed contrasting results between controller populations, with elite controllers experiencing an initial increase in CD4 cells, followed by prolonged stability versus viremic controllers who demonstrated a trend of gradual decrease in CD4 cells over time (Figure 2*D*).

Analyses were performed to examine the influence of ART for controllers before the window of spontaneous virologic suppression. Kaplan-Meier curves for subsets of ART-experienced and ART-naive subjects were similar to findings of unstratified analyses (Figure 3). Although receipt of ART after the spontaneous virologic control window was somewhat more common for viremic controllers (35 subjects [23%]) than for elite controllers (3 subjects [12%]) in this observational cohort, the latter group maintained favorable CD4 cell counts and had a longer time to reach a CD4 cell count of 350 cells/μL or an AIDS diagnosis.

The contrast between elite and viremic controllers regarding increased control of viremia, stability of CD4 cell counts, and improvement in clinical outcome is reminiscent of ART studies in which virologic control with HIV RNA levels $\leqslant$50 copies/mL was superior to low-level viremia in improving outcomes [26, 27]. Thus, whether in the setting of natural viral suppression or response to ART, increased viral suppression leads to a better clinical end point. Further study is needed to hone definitions and to understand and predict the factors that lead to HIV progression in controllers, although recent studies suggest that variation in human immune response genes plays an important role in clinical outcome independent of viral load [28, 29].

Comparison of LTNP7s and LTNP10s (Figure 4*B*), even after their respective "invulnerable periods," shows a dramatically different survival outcome for groups defined by these 2 criteria. Although the first deaths in the LTNP7 group were observed after 10 years of follow-up, no deaths were observed in the LTNP10 group after 20 years of follow-up. This difference in mortality was unlikely to be attributable to ART use, because a similar proportion of subjects received ART after the LTNP period ended. At a minimum, these findings raise the possibility that mechanistic or pathogenic differences contribute to sorting between these categories.

The observation that approximately one-half of the LTNP7s and LTNP10s eventually lose enough CD4 cells to qualify for an AIDS diagnosis implies that a significant proportion of LTNPs will eventually have disease progression with prolonged follow-up. These results are in agreement with previous studies showing that LTNP is more often than not an impermanent state, with most subjects eventually experiencing progression with increasing HIV RNA levels and decreasing CD4 cell counts [5–9]. The LTNP designation is an epidemiologic description that likely involves genetic heterogeneity, with different genetic variants leading to this favorable outcome in different individuals. Selecting for subjects with longer asymptomatic follow-up of $\geqslant$10 years may better differentiate "true" LTNPs who never have disease progression from those undergoing delayed progression of HIV disease. As reported elsewhere [7, 18, 30], this finding demonstrates the importance of defining the length of nonprogression for LTNP studies.

The plasma HIV RNA level has been shown to be a strong independent predictor of disease progression [31, 32]. By definition, controllers had low median baseline HIV RNA levels, but LTNP10s were also found to have relatively low median HIV RNA levels of ~3000 copies/mL at baseline (Table 1). Of the population of LTNPs (LTNP7s or LTNP10s), 35 (22.9%) also met criteria for classification as elite or viremic controllers. It is also notable that viral replication–independent mechanisms influencing clinical outcome were also evident, with 1 LTNP10, for example, having a baseline HIV RNA level of >152,000 copies/mL. Interestingly, both overlapping and nonoverlapping segments of these population extremes are defined by virologic control and long-term immunologic stability.

These results underscore the finding that spontaneous virologic and immunologic control lead to longer AIDS-free intervals as well as improved survival, and that gradations in virologic and immunologic control are associated with increas-

ingly favorable clinical outcomes. Further investigation to elicit the mechanisms responsible for durable control of viral replication and/or lack of disease progression may offer insight for the future development of HIV vaccines and novel treatment strategies.

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