Influence of the Timing of Antiretroviral Therapy on the Potential for Normalization of Immune Status in Human Immunodeficiency Virus 1–Infected Individuals

Jason F. Okulicz, MD; Tuan D. Le, MD, DrPH; Brian K. Agan, MD; Jose F. Camargo, MD; Michael L. Landrum, MD; Edwina Wright, MD; Matthew J. Dolan, MD; Anuradha Ganesan, MD; Tomas M. Ferguson, MD; Davey M. Smith, MD; Douglas D. Richman, MD; Susan J. Little, MD; Robert A. Clark, MD; Weijing He, MD; Sunil K. Ahuja, MD

**Importance**

In individuals with human immunodeficiency virus 1 (HIV-1) infection who are receiving antiretroviral therapy (ART), factors that promote full immune recovery are not well characterized.

**Objective**

To investigate the influence of the timing of ART relative to HIV-1 infection on normalization of CD4+ T-cell counts, AIDS risk, and immune function.

**Design, Setting, and Participants**

Participants in the observational US Military HIV Natural History Study with documented estimated dates of seroconversion (EDS) who achieved virologic suppression with ART were evaluated. Markers indicative of immune activation, dysfunction, and responsiveness were determined. Responses to hepatitis B virus (HBV) vaccine, an indicator of in vivo immune function, were also assessed. The timing of ART was indexed to the EDS and/or entry into the cohort. The CD4+ counts in HIV-1-uninfected populations were surveyed.

**Main Outcomes and Measures**

Normalization of CD4+ counts to 900 cells/μL or higher, AIDS development, HBV vaccine response, as well as T-cell activation, dysfunction, and responsiveness.

**Results**

The median CD4+ count in HIV-1-uninfected populations was approximately 900 cells/μL. Among 1119 HIV-1–infected participants, CD4+ normalization was achieved in 38.4% vs 28.3% of those initiating ART within 12 months vs after 12 months from the EDS ($P = .001$). Incrementally higher CD4+ recovery (<500, 500-899, and ≥900 cells/μL) was associated with stepped decreases in AIDS risk and reversion of markers of immune activation, dysfunction, and responsiveness to levels approximating those found in HIV-1-uninfected persons. Participants with CD4+ counts of 500 cells/μL or higher at study entry (adjusted odds ratio [aOR], 2.00; 95% CI, 1.51-2.64; $P < .001$) or ART initiation (aOR, 4.08; 95% CI, 3.14-5.30; $P < .001$) had significantly increased CD4+ normalization rates compared with other participants. However, even among individuals with a CD4+ count of 500 cells/μL or higher at both study entry and before ART, the odds of CD4+ normalization were 80% lower in those initiating ART after 12 months from the EDS and study entry (aOR, 0.20; 95% CI, 0.07-0.53; $P = .01$). Initiation of ART within 12 months of EDS vs later was associated with a significantly lower risk of AIDS (7.8% vs 15.3%; $P = .002$), reduced T-cell activation (percent CD4+HLA-DR+ effector memory T cells, 12.0% vs 15.6%; $P = .03$), and increased responsiveness to HBV vaccine (67.9% vs 50.9%; $P = .07$).

**Conclusions and Relevance**

Deferral of ART beyond 12 months of the EDS diminishes the likelihood of restoring immunologic health in HIV-1–infected individuals.
The goal of antiretroviral therapy (ART) in patients with human immunodeficiency virus-1 (HIV-1) infection has focused primarily on achieving an undetectable plasma HIV viral load (VL), because failure to achieve this virologic landmark is associated with highly impaired immune recovery.1–3 Durable VL suppression is readily attainable with potent and well-tolerated ART, shifting attention to the goal of optimal reconstitution of a severely compromised immune system, which is the central pathogenic feature of HIV infection.4–7 However, a specific CD4+ T-cell count as a target for optimal immunologic health has not been validated, nor has an interval from infection to ART initiation that promotes this goal been established.

In clinical practice, an increase in the CD4+ count to 500 cells/μL or higher while receiving ART is typically regarded as optimal immune recovery.2,8–10 However, our group previously showed that in individuals without HIV infection, the median CD4+ count is approximately 900 cells/μL. This observation raised the possibility that HIV-infected persons with CD4+ counts less than 900 cells/μL while receiving VL-suppressive ART may remain immunologically compromised. Substantiating this finding, individuals with CD4+ counts between 500 and 750 cells/μL who are receiving ART have an increased risk of AIDS compared with those having higher CD4+ counts.12

In the present study, we tested the hypothesis that normalization of CD4+ counts (>900 cells/μL), compared with attainment of lower CD4+ counts during VL-suppressive ART, is associated with (1) mitigated AIDS risk; (2) reduced T-cell activation and exhaustion, which are factors predictive of adverse clinical outcomes (death, AIDS, and non-AIDS comorbidities),12–14 and (3) enhanced T-cell responsiveness to T-cell trophic cytokines such as interleukin-7 (IL-7), a key player in T-cell homeostasis.15 We tested our hypothesis in the US Military HIV Natural History Study (NHS), a large observational cohort of individuals with HIV infection in which most participants have estimated dates of seroconversion (EDS).16–19

The results of the study in the NHS cohort affirmed our hypothesis, prompting us to identify actionable items that physicians and public health policymakers could undertake to facilitate and promote CD4+ normalization. Earlier vs later ART is traditionally defined by whether ART is initiated before or after CD4+ counts have declined below a specific threshold (eg, 500 cells/μL), rather than the duration of HIV infection before initiation of ART.2,3,20,21 However, our group’s prior analyses of the San Diego Primary HIV Infection Cohort indicated that initiating ART as soon as possible after acquiring HIV, especially within 12 months of infection, greatly promoted CD4+ normalization.

Few patients seek care during primary HIV infection. Thus, to validate as well as to extend our group’s previous finding made in a primary infection cohort to a more real-life clinical setting, we examined participants in the NHS and determined whether initiating ART after 12 months of the EDS and/or study entry was associated with 4 primary outcomes: reduced CD4+ normalization, increased AIDS risk, increased T-cell activation, and impaired in vivo functional immune responses.
In Vivo Functional Immune Responses
A positive HBV vaccine response was defined as an HBV surface antibody value of 10 IU/L or more, which is a level associated with protective immunity. The HBV vaccine response was evaluated 1 to 12 months after the last vaccine dose.

Statistical Analysis
Associations for the time to or likelihood of achieving the first CD4+ count of 900 cells/μL or higher or the first AIDS event were determined by univariate and multivariate Cox proportional hazards and logistic regression models; the rate ratios, hazard ratios, and odds ratios (ORs) with 95% CIs were estimated. These associations were determined in all participants and after categorizing participants into subsets based on ART timing and CD4+ counts at entry and pre-ART. The Kaplan-Meier plots with a log-rank test, t test, or Mann-Whitney test, Wilcoxon signed rank test, and χ2 test were used where appropriate. The incidence rate ratio per 1000 person-years for time to AIDS was also calculated. Participants with a pre-ART CD4+ count of less than 200 cells/μL were excluded when the associations for AIDS 1993 criteria were computed. Additional detailed statistical methods are outlined in the eMethods in the Supplement. Statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc).

Results

Normal CD4+ Count in HIV-Uninfected Persons
The median (interquartile range [IQR]) CD4+ counts in the HIV Neurobehavioral Research Center and National Health and Nutrition Examination Survey samples were 922 (741-1145) cells/μL and 904 (686-1126) cells/μL, respectively. The median and the mean CD4+ counts recorded in 27 studies comprising a total of 16 226 individuals was 988 (840-1036) cells/μL (Figure 2A). The fact that the median CD4+ counts in these sample sets closely approximated 900 cells/μL (Figure 2A and eTable 6 in the Supplement) provided the basis to consider this CD4+ level as a therapeutic target for HIV-infected persons receiving ART.

Clinical Benefits of CD4+ Normalization
The association of CD4+ normalization with AIDS was determined in 1119 participants (Figure 1); the key characteristics of these individuals are reported in Table 1. Most participants were male (95.3%), the proportions of European Americans and African Americans were similar, and the median age at ART ini-

Table 1

<table>
<thead>
<tr>
<th>Description</th>
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<tr>
<td>Total</td>
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</tr>
<tr>
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<td>1065</td>
</tr>
<tr>
<td>Female</td>
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</tr>
<tr>
<td>Race</td>
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<td>Median</td>
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<tr>
<td>IQR</td>
<td>30-68</td>
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</tbody>
</table>

The flowchart depicts the inclusion criteria applied to the NHS participants in whom the associations of CD4+ normalization with AIDS and antiretroviral therapy (ART) timing with CD4+ normalization and AIDS were evaluated. CDC indicates Centers for Disease Control and Prevention; EDS, estimated date of seroconversion; and HIV, human immunodeficiency virus.
The median interval from ART initiation until the measurement of immunologic markers indicative of T-cell activation, dysfunction, and responsiveness was 96 (IQR, 44-126) months. The median pre-ART CD4+ and VL values in these individuals were similar to those in the larger group of 1119 study participants (eTable 1 in the Supplement and Table 1).

Immunologic Benefits of CD4+ Normalization

The median interval from ART initiation until the measurement of immune markers indicative of T-cell activation, dysfunction, and responsiveness in 124 VL-suppressed NHS participants was 96 (IQR, 44-126) months. The median pre-ART CD4+ (373 cells/µL) and VL (log10 4.57 copies/mL) values in these individuals were similar to those in the larger group of 1119 study participants (eTable 1 in the Supplement and Table 1).
Table 1. Characteristics of NHS Participants Evaluated for Associations With CD4⁺ T-Cell Count Normalization and AIDS According to Timing of ART*  

<table>
<thead>
<tr>
<th>Characteristic</th>
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<tr>
<td></td>
<td>Earlier</td>
</tr>
<tr>
<td>No. of participants, (%)</td>
<td>1119 (100.0)</td>
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<tr>
<td>Male, No. (%)</td>
<td>1066 (95.3)</td>
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<tr>
<td>Ethnicity, No. (%)</td>
<td>European American 497 (44.4)</td>
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<tr>
<td>Age at ART initiation, median (IQR), y</td>
<td>31 (29-37)</td>
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<tr>
<td>Time interval, median (IQR), mo</td>
<td>From last documented negative to first documented positive HIV-1 test 15.0 (9.9-24.2)</td>
</tr>
<tr>
<td>Study entry CD4⁺, median (IQR), cells/μL</td>
<td>456 (369-613)</td>
</tr>
<tr>
<td>Duration of VL-suppressive ART, median (IQR), y</td>
<td>4.7 (2.5-8.0)</td>
</tr>
<tr>
<td>AIDS (1987 criteria), No. (%)</td>
<td>58 (5.2)</td>
</tr>
</tbody>
</table>

Abbreviations: ART, antiretroviral therapy; EDS, estimated date of seroconversion; HIV, human immunodeficiency virus; IQR, interquartile range; NHS, US Military HIV Natural History Study; VL, viral load.

* During the 10 years of follow-up, a total of 21 195 measurements of CD4⁺ counts and 21 139 measurements of VL were analyzed. The median number of measurements of CD4⁺ counts per participant was 17 (IQR, 9-25; range, 1-127), and the median number of measurements of VL per participant was 17 (IQR, 9-26; range, 2-103). The median time between consecutive measurements of CD4⁺ counts per participant was 102 (IQR, 76-164) days and of VL per participant, 102 (IQR, 76-164) days.

** Earlier ART was defined as initiating ART within 12 months of EDS or study entry; and later ART was defined as initiating ART more than 12 months after EDS or study entry.

* P values were calculated with the use of the t test, Mann-Whitney test, or χ² test as appropriate.

* The duration of VL-suppressive ART was indexed from the date of starting ART.

* All participants were AIDS (1987 criteria) free prior to ART initiation, and AIDS development (1987 criteria) was evaluated in these patients.
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The T-cell activation levels were lower in participants with CD4+ counts between 500 and 899 cells/μL compared with less than 500 cells/μL, but were similar between individuals with CD4+ counts between 500 and 899 cells/μL and 900 cells/μL or more (Figure 2C). Although CD4+ strata of less than 500 cells/μL, 500 to 899 cells/μL, and 900 cells/μL or more were associated with a stepwise decrement in levels of T-cell dysfunction and increments in T-cell responsiveness, these levels differed between participants with CD4+ counts between 500 to 899 cells/μL and 900 cells/μL or more (Figure 2D and E). In participants with CD4+ counts of 900 cells/μL or more, levels of T-cell activation and dysfunction remained significantly higher compared with the levels in HIV-uninfected persons (Figure 2C and D), whereas levels of T-cell responsiveness were nearly normalized (Figure 2E).

**Earlier ART and CD4+ Normalization**

The conceptual framework for the remainder of the study is depicted in Figure 3A, which shows both the CD4+ trajectory and specific time intervals from infection within which initiation of ART was associated with improved CD4+ normalization rates in a primary infection cohort: 4 or 12 months from infection for participants starting ART with CD4+ counts of less than 500 cells/μL or 500 cells/μL or more, respectively. However, the EDS, but not date of infection, was known in the NHS cohort, and the number of NHS participants accrued within 4 months of acquiring HIV infection was likely to be very low. Therefore, in the present study, we used an interval of less than or equal to 12 months and more than 12 months between EDS or study entry and ART initiation as a classifier for earlier vs later ART. Consistent with our prior work, a CD4+ count of 500 cells/μL at study entry or before ART initiation was used to classify higher vs lower CD4+ counts, because it is used as a threshold for initiation of ART in most international HIV treatment guidelines.

The median interval between the EDS and study entry was approximately 10 months; ART was initiated in 26.1% or 57.6% of the patients at 12 months or less from the EDS or study entry, respectively (Table 1). Earlier compared with later ART was associated with a significantly shorter time to VL suppression. The proportion of participants achieving CD4+ normalization was significantly greater in those starting ART earlier compared with those initiating ART later, indexed to the EDS (38.4% vs 28.3%; P = .001) or study entry (35.4% vs 24.9%; P < .001).

In univariate analyses, ART timing indexed to either the EDS or study entry, CD4+ count at study entry or pre-ART, calendar year of ART initiation, ART regimen, duration of VL-suppressive ART, and time from ART initiation to VL suppression were associated with CD4+ normalization rates (Table 2). Earlier compared with later ART indexed to the EDS or study entry and higher compared with lower CD4+ counts at entry or pre-ART were each associated with increased CD4+ normalization rates, after controlling for covariates (Table 2, models 1-4).

Participants were initially stratified into 4 sets based on the change in CD4+ counts between study entry and ART initiation referenced to a CD4+ threshold of 500 cells/μL (Figure 3B), and then into 8 subsets based on whether ART was initiated earlier vs later indexed to the EDS (Figure 3C and D) or study entry (eFigure 2 in the Supplement). In general, there was an additive effect of later ART and lower CD4+ counts at study entry and/or pre-ART on depressing CD4+ normalization rates, resulting in a hierarchical pattern of these rates (Figure 3C and D and eFigure 2 in the Supplement). First, among participants with study entry CD4+ counts of less than 500 cells/μL, earlier ART did not substantially improve CD4+ normalization rates, whereas it did so among participants with entry CD4+ counts of 500 cells/μL or more. Second, among participants with entry CD4+ counts of less than 500 cells/μL, those manifesting a spontaneous rebound to 500 cells/μL or more and having ART initiated at these higher CD4+ levels had higher CD4+ normalization rates.

To parse further the effects of progressively increasing durations of untreated infection on the likelihood of CD4+ normalization, we stratified the 4 CD4+-defined sets shown in Figure 3B into 12 subsets (subsets 1′-12′ in Figure 4). Participants were categorized according to whether they initiated ART earlier or later co-indexed to the EDS and study entry; that is, whether ART was started within 12 months of both the EDS and study entry (earlier/earlier [E/E]), after 12 months from the EDS but within 12 months of study entry (later/earlier [L/E]), and after 12 months from both the EDS and study entry (later/later [L/L]) (Figure 4).

The time to ART initiation, referenced from the EDS or study entry, was progressively longer in the E/E, L/E, and L/L subsets (Figure 4). The shortest interval between the EDS and study entry was in the E/E subsets (median range, 4.0-6.7 months). Among these 12 subsets, the percentage achieving CD4+ normalization was highest in the E/E, L/E, and L/L subsets in participants with CD4+ counts of 500 cells/μL or more at both study entry and pre-ART (subsets 1′ to 3′), and this was followed by the E/E subsets in participants with study entry CD4+ counts of 500 cells/μL or more but pre-ART values of less than 500 cells/μL (subset 4′) and study entry CD4+ counts of less than 500 cells/μL but pre-ART values of 500 cells/μL or more (subset 7′).

The pre-ART CD4+ counts in the E/E, L/E, and L/L subsets in participants with CD4+ counts of 500 cells/μL or more at both study entry and pre-ART were similar (approximately 600 cells/μL) (subsets 1′-3′ in Figure 4). The CD4+ count at ART initiation was an imperfect indicator of the duration of infection, as the median intervals between the EDS and ART initiation in the E/E, L/E, and L/L subsets were 6.8, 16.5, and 55.6 months, respectively (subsets 1′-3′ in Figure 4). The odds of CD4+ normalization were lower by 65% in the L/E subset (adjusted OR [aOR], 0.35; 95% CI, 0.12-1.04; P = .06) and 80% in the L/L subset (aOR, 0.20; 95% CI, 0.07-0.53; P = .001) subset compared with the E/E subset, after controlling for covariates, including 10 cells/μL differences in pre-ART CD4+ counts (subsets 2′ and 3′ vs subset 1′ in Figure 4). These data indicate that it was not the numeric CD4+ value at ART initiation per se, but rather the duration of the untreated infection that is associated with CD4+ normalization. Delaying ART from the EDS was associated with a decline in immune status, as reflected by the following percentages of reduction in CD4+ counts from entry levels: nil in E/E, 5% in L/E, and approximately 15% in L/L subsets (subsets 1′-3′ in Figure 4).
Among participants with study entry CD4+ counts of 500 cells/μL or more but pre-ART values of less than 500 cells/μL (subsets 4’-6’ in Figure 4), the odds of CD4+ normalization were lower by 72% in the L/E subset (aOR, 0.28; 95% CI, 0.09-0.87; P = .03) and 80% in the L/L subset (aOR, 0.20; 95% CI, 0.08-0.55; P < .001) compared with the E/E subset after controlling for covariates. Among participants with both entry and pre-ART CD4+ counts of less than 500 cells/μL, the proportion achieving CD4+ normalization was less than 25%, and earlier ART had minimal effects on this outcome (subsets 10’-12’ in Figure 4).

Earlier ART, AIDS, and Immune Function

Because there were few AIDS events in the present study, we aggregated all participants in the E/E, L/E, and L/L subsets, regardless of study entry or pre-ART CD4+ counts. Participants
in the aggregated L/L subsets had a significantly increased AIDS risk compared with those in the E/E subsets after adjusting for covariates including the CD4+ count at study entry and ART initiation (Figure 5A and B and eTable 8 and eTable 9 in the Supplement). Earlier vs later ART indexed to the EDS was associated with significantly lower T-cell activation during VL-suppressive ART (median percentage of CD4+ HIV-DR+ EM T cells, 12.0% vs 15.6%; P = .03) (Figure 5C). The likelihood of a positive seroresponse to the HBV vaccine was approximately 2-fold greater in therapy-naive participants who received the vaccine within 12 months of the EDS compared with later (57.1% vs 50.9%; P = .01) (Figure 5D), as well as in participants who received the vaccine after commencing VL-suppressive ART but started ART earlier compared with later (67.9% vs. 50.9%; P = .03) (Figure 5E) after adjusting for covariates including CD4+ count at the last vaccination (eTable 10 in the Supplement).

Discussion

Our results, which affirmed our study hypotheses, have 4 broad implications for the management of care for HIV-infected patients, as well as for public policy. First, if a critical goal of HIV care is restoration of immunologic health, our data indicate that normalization of CD4+ counts may be an important therapeutic target, since attainment of this CD4+ benchmark during VL-suppressive ART was associated with maximal reductions in the AIDS risk, suppression of T-cell activation and dysfunction, and restitution of T-cell responsiveness. Second, since we found that immunologic deficits persisted, despite CD4+ normalization during VL-suppressive ART compared with HIV-uninfected persons, adjunctive therapies that specifically target these functional gaps in full immune reconstitution are needed. Potentially, these residual immunologic deficits may render HIV-infected persons susceptible to non-AIDS comorbidities.26,27

Third, the capacity for CD4+ normalization is retained if the duration of untreated infection is short and the CD4+ count at ART initiation is 500 cells/μL or more. Participants with a study entry CD4+ count of 500 cells/μL or more compared with less than 500 cells/μL had increased CD4+ normalization, but this immunologic advantage was greatly diminished if the interval between the EDS and ART initiation was more than 12 months, regardless of whether ART was subsequently initiated when CD4+ counts were still 500 cells/μL or more or deferred until the levels had declined to less than 500 cells/μL. The odds of CD4+ normalization in these latter 2 groups were 65% and 80% lower, respectively, compared with the odds in participants who initiated ART within 12 months of the EDS. Thus, the likelihood of CD4+ normalization, even among individuals with relatively preserved immune status reflected by CD4+ counts of 500 cells/μL or more at both study entry and ART initiation, was progressively lower with increasing time from the EDS.

Our group25 previously showed that the time span of 4 months since acquiring HIV infection reflects a restorative time window because during this interval CD4+ counts tend to rebound spontaneously. Initiation of ART within this restor-
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Figure 4. Likelihood of CD4+ Normalization in 1119 US Military HIV (Human Immunodeficiency Virus) Natural History Study Participants Categorized by Duration of Untreated HIV Infection Coincided by Estimated Date of Seroconversion (EDS) and Study Entry, as Well as CD4+ Counts at Study Entry and Antiretroviral Therapy (ART) Initiation

<table>
<thead>
<tr>
<th>Set 1</th>
<th>Entry CD4+ Cells/μL</th>
<th>Pre-ART CD4+ Cells/μL</th>
<th>EDS to ART/Entry to ART</th>
<th>No. of Patients</th>
<th>EDS to ART, mo</th>
<th>EDS to Entry, mo</th>
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The 4 CD4+ defined sets shown in Figure 3B were stratified into 12 subsets according to the entry and pre-ART CD4+ counts as well as timing of ART co-indexed from the EDS and study entry. Earlier/earlier (E/E), later/earlier (L/E), and later/later (L/L) indicate whether ART was initiated earlier (≤12 months) vs later (>12 months) from both the EDS and study entry. Median time from EDS to ART, entry to ART, and EDS to study entry as well as median CD4+ counts at entry and pre-ART are shown. P values are for the differences in the percent change in CD4+ counts between study entry and ART initiation and for the differences in the percent achieving CD4+ normalization among the indicated subsets. Odds ratios (ORs) were adjusted for covariates that were significant in univariate logistic regression analyses for the likelihood of achieving CD4+ normalization; the covariates were ethnicity, calendar year of therapy, ART regimen, time from ART to VL suppression, duration of viral load-suppressive ART, and each increase of 10 CD4+ T cells at ART initiation. NS indicates not significant. Limit lines represent 95% CI.

The shorter duration of untreated HIV infection greatly promoted CD4+ normalization in individuals initiating ART when their CD4+ counts were less than 500 cells/μL. Congruent with these prior observations, among NHS participants who presented with study entry CD4+ counts of less than 500 cells/μL but manifested a spontaneous rebound in CD4+ counts, the highest odds of CD4+ normalization were in participants with the shortest interval between the EDS and initiation of ART (median, 5.1 months). Thus, in participants who experienced significant immune damage, as reflected by a rapid decrease in CD4+ counts (ie, study entry CD4+ count of less than 500 cells/μL), the likelihood of CD4+ normalization was greatest when ART was initiated closer to the restorative time window.

Fourth, a shorter duration of untreated HIV infection was associated with improved immunologic and clinical outcomes. A unique aspect of our study was evaluation of the immunologic sequelae of untreated HIV infection in vivo by using the seroresponse to HBV vaccine as an indicator of immune responses that has been independently associated with the risk of AIDS and death.23 The seroresponse to HBV vaccine was approximately 2-fold greater in untreated participants receiving the vaccine within 12 months of the EDS, as well as in participants who received the vaccine after initiating VL-suppressive ART, provided the interval from the EDS to ART initiation was less than 12 months. These data indicate that the integrity of functional immune responses is substantially compromised if the duration of untreated HIV infection is greater than 12 months. Antiretroviral therapy within 12 months of the EDS also associated with reduced T-cell activation. These beneficial immunologic effects of earlier ART, along with those reported by others,11,28-33 may together account for our finding that participants who initiated ART within 12 months of the EDS had the lowest risk of developing AIDS. This is consistent with the results of a recent clinical trial.34 An added advantage of earlier ART would be reductions in HIV transmission, especially since we observed that earlier compared with later ART was associated with a more rapid suppression of VL, which is a key determinant of transmission rates.30

Limitations of the present study include the predominance of young men in our cohort; therefore, the findings may not be generalizable to HIV-infected women or older adults. The participants were predominantly infected with HIV-1 subtype B; therefore, our results may not be applicable to populations with other HIV-1 subtypes. Treatment decisions were not randomized. In addition, we could not evaluate the long-term toxicity of ART or the beneficial effects of early ART on non-AIDS events.
There are significant immunologic and clinical advantages of achieving CD4+ normalization (≥900 cells/μL). Congruent with our prior work in a primary infection cohort, we demonstrated in the present study that there is a narrow time window after acquiring HIV infection within which commencement of ART favors CD4+ normalization. Achieving CD4+ normalization is an imminently feasible therapeutic goal, provided ART is started within 12 months of the EDS at higher CD4+ counts (≥500 cells/μL). The importance of a public health strategy that includes frequent HIV testing in persons at risk and prompt initiation of ART after diagnosis is underscored by 2 findings: the rate of unwitnessed CD4+ count decline that occurs in the interval between HIV acquisition and diagnosis.

A and B, Kaplan-Meier plots depict progression to AIDS in participants who were classified to the E/E, L/E, and L/L time-indexed subsets shown in Figure 4. Incidence rate ratios (IRRs) and hazard ratios (HRs) were adjusted for the calendar year of ART, higher vs lower CD4+ counts at study entry and pre-ART, ART regimen, interval from ART initiation to viral load (VL) suppression, and duration of VL-suppressive ART. Data in panel A were derived from 1119 US Military HIV Natural History Study (NHS) participants; data in panel B were derived from 956 NHS participants because individuals with pre-ART CD4+ counts of less than 200 cells/μL (n = 163) were excluded from these analyses. C, Association of the duration between estimated date of seroconversion (EDS) and ART initiation with the percentage of CD4+HLA-DR+ effect memory (EM) T cells in participants receiving VL-suppressive ART. The box-and-whisker plots depict the median (horizontal line in box), upper and lower quartiles (ends of box), and extremes (symbols outside of box). The symbols inside the boxes indicate the mean. D, The proportion of the responders (filled box) vs nonresponders (open box) to hepatitis B virus (HBV) vaccine in HIV-infected patients who received the vaccine while they were therapy naive within or after 12 months of the EDS. E, The proportion of the responders (filled box) vs nonresponders (open box) to HBV vaccine in HIV-infected patients who received the vaccine while receiving VL-suppressive ART; patients were stratified according to whether VL-suppressive ART was initiated within or after 12 months of the EDS. Anti-HBs indicates HBV surface antibody.

**Conclusions**

There are significant immunologic and clinical advantages of achieving CD4+ normalization (≥900 cells/μL). Congruent with our prior work in a primary infection cohort, we demonstrated in the present study that there is a narrow time window after acquiring HIV infection within which commencement of ART favors CD4+ normalization. Achieving CD4+ normalization is an imminently feasible therapeutic goal, provided ART is started within 12 months of the EDS at higher CD4+ counts (≥500 cells/μL). The importance of a public health strategy that includes frequent HIV testing in persons at risk and prompt initiation of ART after diagnosis is underscored by 2 findings: the rate of unwitnessed CD4+ count decline that occurs in the interval between HIV acquisition and diagnosis.
sition and diagnosis cannot be predicted, and the duration of the infection cannot be predicted by the CD4+ count. This strategy may offer the best chance for rapidly terminating the progressive immune damage (eg, lymphoid tissue fibrosis) that constrains optimal immune reconstitution with ART.

ARTICLE INFORMATION

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Author Affiliations: Infectious Disease Clinical Research Program, Uniformed Services University of Health Sciences, Bethesda, Maryland (Okulicz, Agan, Landrum, Ganesan, Ferguson); Infectious Disease Service, San Antonio Military Medical Center, Fort Sam Houston, Texas (Okulicz); Veterans Affairs Research Center for AIDS and HIV-1 Infection, South Texas Veterans Health Care System, San Antonio (Le, Camargo, Clark, He, Ahuja); Veterans Affairs Center for Personalized Medicine, South Texas Veterans Health Care System, San Antonio (Le, Camargo, Clark, He, Ahuja); Department of Medicine, The University of Texas Health Science Center, San Antonio (Le, Camargo, Clark, He, Ahuja); currently with Division of Transplant Infectious Diseases, Department of Medicine, University of Toronto, Toronto Health Network, Toronto, Ontario, Canada (Camargo); The Henry M. Jackson Foundation for the Advancement of Military Medicine Inc, Bethesda, Maryland (Agan); Infectious Disease Service, Brooke Army Medical Center, Fort Sam Houston, Texas (Landrum); currently with Bellin Health, Green Bay, Wisconsin (Landrum); Department of Infectious Diseases, Alford Hospital, Melbourne, Victoria, Australia (Wright); The Burnet Institute, Melbourne, Victoria, Australia (Wright); Department of Infectious Diseases, Monash University, Melbourne, Victoria, Australia (Wright); The Henry M. Jackson Foundation for the Advancement of Military Medicine Inc, Lackland Air Force Base, Texas (Dolan); Infectious Disease Service, Walter Reed National Military Medical Center, Bethesda, Maryland (Ganesan); Infectious Disease Service, Tripler Army Medical Center, Honolulu, Hawaii (Ferguson); Department of Medicine, University of California, San Diego (Smith, Richman, Little); Veterans Affairs San Diego Healthcare System, San Diego, California (Smith, Richman); Department of Pathology, University of California, San Diego (Richman); Department of Microbiology and Immunology, The University of Texas Health Science Center, San Antonio (Ahuja).

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Study concept and design: Okulicz, Le, He, Ahuja.

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Invited Commentary

Defining Success With Antiretroviral Therapy

Timothy W. Schacker, MD

Two critically important issues in human immunodeficiency virus (HIV) therapeutics are when to start antiretroviral therapy and how well these medications restore immunity. In this issue of JAMA Internal Medicine, Okulicz et al describe a prospective cohort study of 1119 US military service persons with known seroconversion dates who were monitored for several years. Because the dates of seroconversion were known for these individuals and their immunologic status was well characterized, the data from this valuable cohort enable us to better answer these fundamental questions about HIV treatment.

The primary outcome measures for this study were normalization of peripheral blood CD4+ T cells, which the researchers defined as 900 cells/μL or higher (based on an analysis of 27 studies of 16 226 HIV-negative persons), development of an AIDS diagnosis, response to hepatitis B vaccine, and normalization of measures of T-cell activation. Okulicz et al found that initiation of antiretroviral therapy within 12 months of the estimated date of seroconversion was associated with a higher likelihood of achieving a CD4+ T-cell count of 900 cells/μL or more, fewer cases of AIDS, and better responses to vaccination. However, even among patients starting therapy this early in their infection, only 38.4% achieved a CD4+ T-cell count of 900 cells/μL or more, and in individuals waiting until after 12 months of the infection to start therapy, only 28.3% achieved a normal CD4+ T-cell count. A higher level of CD4+ T-cell recovery was associated with decreases in the frequency of an AIDS diagnosis, normalization of markers of immune activation, and better response to hepatitis B vaccination.