Immunologic Failure Despite Suppressive Antiretroviral Therapy Is Related to Activation and Turnover of Memory CD4 Cells

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Background. Failure to normalize CD4+ T-cell numbers despite effective antiretroviral therapy is an important problem in human immunodeficiency virus (HIV) infection.

Methods. To evaluate potential determinants of immune failure in this setting, we performed a comprehensive immunophenotypic characterization of patients with immune failure despite HIV suppression, persons who experienced CD4+ T-cell restoration with therapy, and healthy controls.

Results. Profound depletion of all CD4+ T-cell maturation subsets and depletion of naive CD8+ T cells was found in immune failure, implying failure of T-cell production/expansion. In immune failure, both CD4+ and CD8+ cells were activated but only memory CD4+ cells were cycling at increased frequency. This may be the consequence of inflammation induced by in vivo exposure to microbial products, as soluble levels of the endotoxin receptor CD14+ and interleukin 6 were elevated in immune failure. In multivariate analyses, naive T-cell depletion, phenotypic activation (CD38+ and HLA-DR expression), cycling of memory CD4+ T cells, and levels of soluble CD14 (sCD14) distinguished immune failure from immune success, even when adjusted for CD4+ T-cell nadir, age at treatment initiation, and other clinical indices.

Conclusions. Immune activation that appears related to exposure to microbial elements distinguishes immune failure from immune success in treated HIV infection.

The introduction of combination antiretroviral therapies has changed the landscape of human immunodeficiency virus (HIV) treatment. With sustained suppression of HIV replication, immune function improves and morbidity and mortality decrease dramatically [1]. Though survival has improved, it is not comparable to that of healthy uninfected subjects [2], and treated persons remain at increased risk for serious cardiovascular, malignant, and hepatic diseases [1, 3], especially among those with low CD4+ T-cell counts [3, 4]. Despite effective control of HIV replication, a substantial minority of persons receiving HIV care fail to increase CD4+ T-cell counts to “normal” levels [5, 6]. Immune failure in the setting of treatment-induced suppression of HIV replication has been studied extensively, but these studies have largely been either epidemiologic with no [5, 7, 8] or limited immunologic analyses [9], or small studies [10–17] often lacking normative data from healthy controls [11–15, 18] and/or performed among persons with either limited or unknown durations of virologic suppression [9, 11–14, 16, 17, 19–21]. To better define “immune failure” despite virologic control, we initiated a comprehensive evaluation of immune failure despite drug-induced suppression of HIV replication. As reported by us and by others in smaller studies, immune failure was associated
with increased T-cell activation [6, 9, 14, 17], here defined as coexpression of CD38+ and HLA-DR on CD4+ and CD8+ T cells, and by profound decreases in circulating naive CD4+ and CD8+ T cells [6, 16, 17]. We also show that immune failure is linked to indices of microbial translocation and inflammation, as levels of the soluble receptor for LPS (sCD14+) and levels of interleukin 6 are significantly elevated. In addition, we find that in immune failure, activation of CD4+ T cells is accompanied by increased cell cycling, especially in the memory compartment, while among CD8+ T cells that are even more frequently activated, cycling is not increased above levels seen in healthy controls or in treated patients who have “normalized” circulating CD4+ T cells. These in vivo findings are strikingly similar to the immune phenotype induced by exposure to microbial Toll-like receptor ligands in vitro [22], providing an important link between exposure to microbial elements and immune homeostasis in HIV infection.

METHODS

This work was approved by institutional review boards at University Hospitals/Case Medical Center and the Cleveland Clinic Foundation. Using cut points proposed to determine guidelines for treatment initiation, immune failure subjects had CD4+ T-cell counts <350/μL and immune success subjects had CD4+ T-cell counts >500/μL after at least 24 months of virologic control, defined by plasma HIV RNA levels below detection limits (typically 50 copies per mL). Transient viremia blips did not exclude participation if flanked by viral levels below detection limits. Controls were not matched to HIV+ subjects, but variables significantly different among the groups on univariate analysis were controlled for in subsequent multivariable analyses.

With written informed consent, blood was drawn into tubes containing ethylenediaminetetraacetic acid (EDTA). Lymphocyte phenotypes were identified using fluorochrome-labeled monoclonal antibodies (BD Biosciences and BD Pharmingen) and were enumerated by flow cytometry. Plasma was removed after centrifugation, frozen at −80°C, thawed and analyzed in batch for levels of β-dimers (Diagnostica Stago), soluble CD14 (sCD14), interleukin 6 (IL-6; R&D Systems), and bacterial lipopolysaccharide (LPS; QCL-1000, Lonza) according to manufacturers’ protocols.

We compared continuous variables using Mann–Whitney U test, Kruskal–Wallis H test, or the Jonckheere-Terpstra test as needed according to number and independence of groups compared. We fitted multiple linear regression models to control for potential confounders in comparisons of each readout; we used mixed effects models to estimate the slope of CD4+ T-cell change, controlling for potential confounders. To assess the contribution of each predictor to immunologic outcome, we fitted logistic regression models and tested for significant interaction and confounding among the predictors. All tests were 2-sided with a significance cutoff of 0.05, without formal correction for multiple comparisons.

RESULTS

Sixty immune failure patients, 20 immune success patients, and 21 healthy controls underwent detailed immunologic studies. Another 168 immune success subjects who met study criteria were identified from the Special Immunology Unit Patient Care and Research Database, and are included in all analyses except those involving immune and inflammatory markers. Characteristics of the subjects are shown in Table 1.

Immune failure patients were more likely to be male (81%) and white (60%) than immune success patients (70% and 45%, \( P = .04 \) and \( P = .01 \), respectively). They were older at the initiation of combination antiretroviral therapies (41 years vs 37 years, \( P = .011 \)). Median CD4+ T-cell count in immune failures was 258 cells/μL, 775/μL in immune successes, and 907/μL among healthy controls. CD8+ T-cell counts were higher in immune successes (820/μL) than in immune failures (620/μL, \( P = .038 \)) and healthy controls (451/μL, \( P = .004 \)). Not surprisingly, the CD4+ T-cell nadir was lower in immune failures than in immune successes (35 vs 199/μL, \( P < .001 \)).

Peak viremia tended to be higher in immune failures (227 000 vs 99 394 copies/mL), but not significantly. Median time with undetectable viremia was lower in immune failures than in the immune analysis subset of the immune success group (4.4 vs 7.5 years, \( P = .001 \)), but not different from the overall immune success group (4.6 years, \( P = .16 \)).

CD4+ T-Cell Maturation Subsets

The median numbers of each CD4+ T-cell maturation subset (naive = 54/μL, central memory = 67/μL, effector memory = 109/μL) were significantly lower in immune failures than in healthy controls (naive = 300/μL, central memory = 307/μL, effector memory = 218/μL; \( P < .001 \) for each) and immune successes (naive = 223/μL; central memory = 206/μL, effector memory = 227/μL; \( P < .001 \) for each; Figure 1). These numbers were comparable in controls and immune successes, underscoring effective numerical CD4+ T cell restoration in this group.

CD8+ T-Cell Maturation Subsets

In contrast, among CD8+ T cells, only naive cell numbers were diminished in immune failure (68/μL) compared with immune successes (157/μL, \( P < .001 \)) and healthy controls (141/μL, \( P = .001 \); Figure 2). All other CD8+ maturation subsets were increased in both patient groups compared with healthy controls, reflecting the global expansion of CD8+ memory cells characteristic of chronic HIV infection.
**T-Cell Activation**

T-cell activation is a hallmark of HIV infection, and expression of the activation marker CD38$^+$ has been linked to disease progression [23]. As naive T cells may express CD38 without activation [24], we analyzed activation as reflected by coexpression of CD38 and HLA-DR. The proportion of

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>HIV-negative controls</th>
<th>Immune failures</th>
<th>Immune analysis subset</th>
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<td>0 (0)</td>
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<td>44 (40–49)</td>
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</tr>
<tr>
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<td>48 (43–56)</td>
<td>44 (40–49)</td>
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</tr>
<tr>
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<td>35 (32–41)</td>
<td>37 (33–43)</td>
<td>7 (5–11.4)</td>
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<td>23 (12.2)</td>
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<td>1 (5)</td>
<td>23 (12.2)</td>
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<td>175 (19–301)</td>
<td>199 (82–250)</td>
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<td>Peak viremia, copies/mL</td>
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<td>258 (186–303)</td>
<td>775 (662–961)</td>
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<tr>
<td>CD8$^+$ T cells/µL</td>
<td>451 (363–732)</td>
<td>620 (450–840)</td>
<td>820 (620–1020)</td>
<td>...</td>
</tr>
</tbody>
</table>

Abbreviations: HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NA, not applicable. 

$^a$ Includes the immune analysis subset and additional subjects identified through database search.

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**Figure 1.** CD4$^+$ lymphocyte maturation subsets. Absolute numbers of circulating naive (CD45RA$^+$/CCR7$^+$), central memory (CM; CD45RA$^-$/CCR7$^+$), and effector memory (EM; CD45RA$^-$/CCR7$^-$) CD4$^+$ lymphocytes in immune successes, immune failures, and healthy controls. Lymphocytes were identified by forward and right-angle light scatter and were gated according to high-level expression of CD4. **$P < .001$ compared to Immune Success and to Controls.**
activated CD4⁺ T cells in immune failures (12%) was significantly greater ($P < .001$) than in immune successes and in healthy controls (6% for each, Figure 3A). Proportions of activated CD8⁺ T cells in immune failures (29%) were greater ($P < .001$) than in immune successes (19%) and healthy controls (14%; Figure 3B). The proportion of activated CD8⁺ T cells in immune successes was marginally higher than among healthy controls ($P = .046$).

Cell Cycling
As we [25, 26] and others [27, 28] have identified cycling and turnover of central memory CD4⁺ T cells as a possible driver of immune deficiency in chronic untreated HIV or simian immunodeficiency virus (SIV) infection, we examined the proportions of cells expressing the nuclear antigen Ki-67. While immune success patients and healthy controls had similar proportions of Ki-67⁻ CD4⁺ T cells (2.2% and 1.9%, respectively), 3.6% of CD4⁺ T cells in immune failures were Ki-67⁺, and this was greater than in both the controls and immune successes ($P < .001$, Figure 3C). Among CD8⁺ T cells, however, and despite the fact that proportionally more of these cells were activated than were CD4⁺ T cells, the frequencies of cycling cells were not different in immune failures, immune successes, and healthy controls (1.5%, 1.1%, and 1.0%, respectively).

We therefore next examined Ki-67 expression among the different CD4⁺ T cell maturation subsets (Figure 4). While proportions of cycling naive CD4⁺ T cells were comparable in all groups, proportions of cycling central memory and effector memory CD4⁺ T cells were significantly greater in immune failures (4.6 and 4.7%, respectively) than in immune successes (2.9 and 2.7%, $P < .001$) and in healthy controls (2.5% and 2.8%, $P = .001$). Proportions were comparable in immune successes and in controls.

Soluble Markers of Microbial Translocation and Inflammation
An increasing body of evidence is linking inflammation and coagulation to morbidity and mortality in chronic HIV infection [29], and work from our research collaboration has implicated translocation of microbial products from the gut as a major correlate of immune activation, coagulation, and CD4⁺ T-cell losses in chronic HIV infection [30–32]. We found that the plasma level of IL-6 in immune failures (2.5 pg/mL) was higher than in immune successes (1.53 pg/mL, $P = .003$, Figure 5), and both were higher than in controls (1.01 pg/mL, $P = .001$, $P = .018$). D-dimer levels were similar in immune failures and immune successes (427 and 401 ng/mL, respectively), and both were higher than in controls (224 ng/mL, $P = .008$, $P = .022$). Levels of LPS tended to be higher in immune failures (20.2 pg/mL) and immune successes (17.1 pg/mL) than...
in controls (13.3 pg/mL), but not significantly ($P = .16$ and 0.1). Levels of soluble CD14, the LPS coreceptor, were higher in immune failures (2453 ng/mL) than in immune successes (2056 ng/mL, $P < .001$), and both were higher than in controls (1390 ng/mL, $P < .001$).

**Coinfections and Other Illness**
Among subjects with available serologies, there were no differences in prevalence of infection with hepatitis B virus, hepatitis C virus, or cytomegalovirus in immune success and immune failure. As both malignant outcomes are more common in patients with lower CD4 T-cell counts, and treatment for malignancy might affect the magnitude of immune restoration, we found that malignancy was more frequent in immune failures (18%) than in immune successes (5.3%, $P < .01$), but in multivariable analysis (below), history of malignancy did not significantly affect the results of the study.

**Multivariable Analyses**
To exclude potential confounders, we considered the possibility that immune failure subjects could represent a subset of patients who would continue to increase CD4 T-cell counts and would have been classified as immune successes had they been enrolled into the study later during therapy. We also entertained the possibility that our results could be explained by shorter periods of virologic control or by lower nadir CD4 T-cell counts, which are linked to both higher residual inflammation/activation [12] and poor CD4 T-cell increases after highly active antiretroviral therapy (HAART) [7, 33, 34]. We found the CD4 T-cell trajectory after HAART was dramatically different in the 2 groups (Supplementary Figure 1). Mixed-effect modeling showed a significantly greater slope of CD4 T-cell gain among immune success subjects, even after controlling for nadir CD4 T-cell count, time from HAART initiation, and duration of complete virologic control.

Having excluded major design bias, we asked whether associations among markers of activation, microbial translocation,
and immune failure were independent of other correlates of immune failure identified in the univariate analyses shown in the figures. Logistic regression analyses showed that the number and proportion of activated (CD38\textsuperscript{+}, HLA-DR\textsuperscript{+}) CD4\textsuperscript{+} T cells (adjusted \(P = .025\) and \(.039\)), the number and proportion of activated (CD38\textsuperscript{+}, HLA-DR\textsuperscript{+}) CD8\textsuperscript{+} T cells (adjusted \(P = .027\) and \(.005\)), the proportion of total, central memory, and effector memory CD4\textsuperscript{+} T cells in cell cycle, and plasma levels of sCD14\textsubscript{+} (adjusted \(P = .011, .013, .014,\) and \(.008\)) all remained significantly associated with immune failure after adjusting for nadir CD4\textsuperscript{+} T-cell count, age at HAART initiation, race, and history of malignancy, suggesting that these differences could not be accounted for on the basis of those additional predictors.

**DISCUSSION**

In this study, we have established a phenotypic characterization of immune failure despite HAART-induced control of HIV replication. We recognize that some in this group will continue to increase CD4\textsuperscript{+} T-cell counts \([5, 35]\), yet the median time since initiation of antiretroviral therapy in immune failure patients was greater than 7 years, and analysis of the average CD4\textsuperscript{+} T-cell increases in immune failure and immune success patients demonstrates a highly significant difference in CD4\textsuperscript{+} T-cell trajectory (supplementary Figure 1), clearly indicating these patient populations are distinguishable. Thus, immune failure patients represent a population experiencing sustained periods of subclinical immune deficiency. The long-term risks of subclinical immune deficiency in this setting are not entirely known, but available data suggest that heightened morbidity and mortality is seen in persons who fail to increase their CD4\textsuperscript{+} T-cell counts while receiving effective antiretroviral therapies \([3, 4, 36]\).

This study represents the largest and most comprehensive characterization of immunophenotype, inflammation, and coagulation in persons experiencing immune failure despite long-term suppression of HIV replication. As we \([16]\) and others \([6]\) had earlier reported in smaller studies with shorter durations of post-treatment follow up, both naive and memory CD4\textsuperscript{+} T-cell populations remain diminished in immune failure patients, and here we show that this is the case in both the central memory and effector memory compartments.

We also show that immune success patients have persistent expansions of total CD8\textsuperscript{+} T-cell populations, and in both immune successes and immune failures, this comprises predominantly an expansion of more differentiated effector and terminally differentiated populations, while naive CD8\textsuperscript{+} T cells remain diminished in numbers. The determinants of persistent memory CD8\textsuperscript{+} T-cell expansion in chronic treated HIV infection are incompletely understood. Whether their persistence reflects sustained exposure to antigenic stimuli (and if so, which antigenic stimuli?) the residuum of bystander expansion in response to common gamma-chain receptor cytokines \([37]\), or persistence as a result of replicative senescence and resistance to programmed cell death remains uncertain.
In contrast to the persistent expansion of memory CD8\(^+\) T cells in both treated populations, immune failure patients but not immune success patients have profound depletion of both CD8\(^+\) and CD4\(^+\) naive T cells. This may reflect impaired thymic output seen in aging and in HIV infection [16, 38, 39], the impaired naive T-cell expansion capacity described in HIV infection [40, 41], or a compound defect that is the result of both. Both thymic failure [11, 14, 16] and naive CD4\(^+\) T-cell depletion have been linked to immune failure after application of antiretroviral therapies [11, 16, 42]. As lymphoid tissue fibrosis is associated with both diminished naive T-cell numbers and failure of immune restoration with administration of antiretroviral therapies [42, 43], it is tempting to propose that interference with maturation and homeostatic signaling in disordered lymphoid tissues may contribute to the failure of naive T-cell expansion capacity observed in vitro [40, 44, 45] and to the diminished naive T-cell numbers seen in patients with immune failure studied here.

As was shown earlier [9, 13, 14, 17, 19, 20], immune failure in treated HIV infection is associated with immune activation, here reflected in coexpression of CD38 and HLA-DR on both CD4\(^+\) and CD8\(^+\) T cells. What then, is driving T-cell activation in the setting of virologic suppression? Conceivably, immune failure patients could have higher levels of viral replication, though still below the limits of detection by the commercial assays used in this study. We did not collect sufficient volumes of plasma to perform these assays, thus this hypothesis remains untested in this data set.

On the other hand, our data indicate that systemic translocation of microbial products may distinguish immune failure from immune success in the setting of antiretroviral therapies. Phenotypic indices of T-cell activation (specifically CD38\(^+\)) and plasma IL-6 levels are predictive of disease progression [29, 46], and expression of both can be induced by microbial products in vitro [22, 31]. Not surprisingly, plasma levels of IL-6 are higher in immune failure than in immune success patients, and in both populations, levels are higher than in healthy controls. LPS levels tended to be higher in both patient populations than among controls, although these differences did not achieve statistical significance. And soluble levels of the LPS coreceptor (sCD14) in immune failures were higher than levels in immune success patients, and in both populations, these levels were higher than among healthy controls. Microbial products may contribute to immune activation in vivo, as both indices were significantly correlated with plasma levels of IL-6 and both CD4\(^+\) and CD8\(^+\) T-cell expression of CD38 and HLA-DR (not shown). Interestingly, in this study, we did not find a significant correlation between plasma levels of LPS and sCD14 as we

Figure 5. Soluble markers of microbial translocation, inflammation, and coagulation. Plasma levels of IL-6 were higher in immune failure patients than in immune success patients, and the levels in both patient groups were higher than in controls. d-Dimer levels were comparable in both patient groups but higher than among controls. Levels of bacterial lipopolysaccharide (LPS), though nominally higher in immune failure patients than in immune success patients and controls, were not significantly elevated, while levels of the soluble LPS receptor CD14\(^+\) were higher in immune failure patients than in immune success patients and were higher in each patient group than in controls.
had previously [30, 31]. In this study and in a recent analysis of the Strategies for Management of Antiretroviral Therapy (SMART) study [47], sCD14 appears to be a better correlate of immune failure vs immune success groups

<table>
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Abbreviations: CM, central memory; EM, effector memory; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IL-6, interleukin 6; LPS, lipopolysaccharide.
work that gender determines the magnitude of cellular restoration, Gandhi et al. [20] also found better immune recovery in HAART-treated women. This should be explored further. It is not surprising that age is linked to immune failure because both thymic function and T-cell responsiveness to homeostatic cytokines [49] diminish with age.

Perhaps the most important, if not most obvious, predictor of immune failure is CD4⁺ T-cell nadir. While a low nadir does not universally predict immune failure (half of our immune success patients began antiretroviral therapies with CD4⁺ T-cell nadirs less than 200/μL), initiating HAART at higher CD4⁺ T-cell numbers is virtually guaranteed to sustain and will typically increase CD4⁺ T-cell counts. It should also be noted that initiating antiretroviral therapies at higher CD4⁺ T-cell counts also predicts a better in vivo immune response (as determined by immunization responses), even in subjects with “normal” circulating CD4⁺ T-cell counts [50]. Immune function assays and measures of inflammation and coagulation may help to provide more discriminating readouts of immune restoration that predict clinical outcome than do circulating CD4⁺ T-cell counts alone. Our data support the importance of early recognition of HIV infection so that infected persons can be offered HAART before irreversible immune deficiency develops.

Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online (http://www.oxfordjournals.org/our_journals/jid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Perhaps the most important, if not most obvious, predictor of immune failure is CD4⁺ T-cell nadir. While a low nadir does not universally predict immune failure (half of our immune success patients began antiretroviral therapies with CD4⁺ T-cell nadirs less than 200/μL), initiating HAART at higher CD4⁺ T-cell numbers is virtually guaranteed to sustain and will typically increase CD4⁺ T-cell counts. It should also be noted that initiating antiretroviral therapies at higher CD4⁺ T-cell counts also predicts a better in vivo immune response (as determined by immunization responses), even in subjects with “normal” circulating CD4⁺ T-cell counts [50]. Immune function assays and measures of inflammation and coagulation may help to provide more discriminating readouts of immune restoration that predict clinical outcome than do circulating CD4⁺ T-cell counts alone. Our data support the importance of early recognition of HIV infection so that infected persons can be offered HAART before irreversible immune deficiency develops.

Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online (http://www.oxfordjournals.org/our_journals/jid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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