CD4 T Cell Depletion Is Linked Directly to Immune Activation in the Pathogenesis of HIV-1 and HIV-2 but Only Indirectly to the Viral Load

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CD4 T Cell Depletion Is Linked Directly to Immune Activation in the Pathogenesis of HIV-1 and HIV-2 but Only Indirectly to the Viral Load

Ana E. Sousa, Jorge Carneiro, Martin Meier-Schellersheim, Zvi Grossman, and Rui M. M. Victorino

The causal relationships among CD4 cell depletion, HIV replication, and immune activation are not well understood. HIV-2 infection, “nature’s experiment” with inherently attenuated HIV disease, provides additional insights into this issue. We report the finding that in HIV-2 and HIV-1 patients with a comparable degree of CD4 depletion the imbalance in the relative sizes of the naive and memory T cell populations and the up-regulation of CD4 and CD8 cell activation markers (HLA-DR, CD38, CD69, Fas molecules) are similar, even though the viral load in the plasma of HIV-2-infected patients is two orders of magnitude lower than in HIV-1 patients and HIV-2 patients are known to have slower rates of CD4 T cell decline and a better clinical prognosis. Moreover, we found a similar increase in the frequency of cycling CD4 T cells (Ki67+), which was in strong correlation with the expression of activation markers. Finally, the level of T cell anergy, as assessed by the proliferative responses to CD3 stimulation and to a panel of microbial Ags, proved to be comparable in HIV-1 and HIV-2 patients with a similar degree of CD4 depletion despite large differences in viral load. Our data are consistent with a direct causal relationship between immune activation and CD4 cell depletion in HIV disease and an only indirect relation of these parameters to the virus replication rate. Invoking the concept of proximal immune activation and virus transmission, which links efficient transmission of virus to local cell activation and proliferation in response to Ags and inflammation, we propose an integrative interpretation of the data and suggest that strongly elevated immune activation induces CD4 cell depletion and not vice versa, with potential implications for the choice of treatment strategies.


Human immunodeficiency virus type 1 pathogenesis is generally seen as a relentless destruction of CD4+ T cells by the virus leading to the observed decline in CD4 cell counts over time and eventually to AIDS. The increased turnover of T cells has been viewed by some as a homeostatic response to the rapid loss of cells (1–3). An alternative assumption is that chronic, infection-induced immune activation is the force driving the progressive decline in CD4 cell numbers and other detrimental effects that result in AIDS (4–11).

In HIV-2, disease progression is slower than in HIV-1, with limited impact on the survival of the majority of infected adults (12–14), although it apparently manifests the same clinical spectrum (15, 16). Both horizontal and vertical HIV-2 transmission rates are much lower than for HIV-1 (17, 18). These epidemiological findings and the reduced frequency of successful virus isolation from the blood of HIV-2-infected patients (19) suggested very low levels of viremia, which was confirmed by recently developed methods to quantify HIV-2 RNA copies in the plasma (20–22). Interestingly, quantitative assessment of HIV-2 DNA documented proviral levels similar to those observed in HIV-1-infected individuals, which was interpreted to indicate similar target cell infectivity but a decreased rate of virus production in HIV-2 infection (23, 24).

As in HIV-1 infection, CD4 cell counts decline progressively under HIV-2, but the decline is much slower and viremia levels are lower at any stage of the disease (13, 21, 24). Studying HIV-2 infection offers the possibility to quantitatively reassess the significance of virological and immunological parameters in HIV pathogenesis in an infection with an inherently attenuated virus. We report in this work that HIV-1 and HIV-2 patients having a similar degree of CD4 depletion displayed similar levels of T cell hyperactivation and similar numbers of cycling cells in the peripheral blood despite great differences in the plasma viral load. These results and other recent reports call for reevaluation of different hypotheses about causal relationships among virus concentration, CD4 depletion, and activation and turnover of T lymphocytes.

Patients and Methods

Study population

Twenty-seven HIV-2-infected patients, 26 HIV-1-infected patients, and 25 healthy control individuals participated in this cross-sectional study. The patients currently live in Portugal and attend outpatient clinics in Lisbon. They have no known ongoing opportunistic infections or tumors. The epidemiological and clinical features of these groups were described previously (25). As shown in Fig. 1, HIV-2 viremia had a maximum of 2,754 RNA copies/ml and was <500 RNA copies/ml (detection limit) in 21 of 27 patients, as quantified using a previously described RT-PCR test (22). The geometric mean of the viral load in HIV-1 patients was 8,476 RNA copies/ml (range: 50–740,000) as quantified by RT-PCR (Ultradsensitive Test; Roche Molecular Systems, Branchburg, NJ). For the purpose of this
study, the HIV-1- and HIV-2-infected patients were classified into three groups according to the degree of CD4 depletion: >500 CD4 T cells/μl, 200–500 CD4 T cells/μl, and <200 CD4 T cells/μl. There were no statistically significant differences in the mean CD4 counts between the corresponding groups of HIV-1- and HIV-2-infected patients. The study was approved by the Ethical Board of the Faculty of Medicine of Lisbon.

**Analysis of Ki67 expression and T cell phenotype**

PBMCs were isolated from fresh heparinized blood by Ficoll-Hypaque gradient centrifugation (Life Technologies, Paisley, U.K.) immediately after venipuncture. After surface staining with anti-CD3 or anti-CD4 Tri-Color-conjugated mAbs (Caltag Laboratories, South San Francisco, CA) and anti-CD4 or anti-CD45RO-PE-conjugated mAbs (BD Biosciences, San Jose, CA), cells were permeabilized with a saponin buffer as previously described (26) and stained with the mouse anti-human Ki67 (MIB-1) FITC-labeled mAb or with isotype control (Immunotech, Marseilles, France). At least 50,000 CD3 or 20,000 CD4 lymphocytes were acquired on a FACScalibur (BD Biosciences). The frequency of Ki67+ cells was analyzed within the CD3+CD4+, CD4+CD45RO+, and CD4+CD45RO- lymphocyte gated populations using CellQuest software (BD Biosciences). Simultaneously, the proportions of CD4 and CD8 T cells expressing markers of cell activation and/or differentiation were assessed by flow cytometric phenotypic analysis (27) using the following mAbs: anti-CD27, -CD28, -CD38, -CD45RA, -CD45RO, -CD62L, -CD69, -Fas molecule (CD95), -HLA-DR (BD Biosciences).

**Lymphocyte proliferation assays**

PBMCs were cultured in complete medium as previously described (27) in triplicate for 3 days with immobilized anti-CD3 mAb in the presence or absence of soluble anti-CD28 mAb (BD PharMingen, San Diego, CA) as well as in quadruplicate for 6 days in the presence of tetanus toxoid (Connaught, Swiftwater, PA), purified protein derivative (Serum Statiensinstitut, Copenhagen, Denmark), *Candida albicans* (Greer, Lenoir, NC), the viral recombinant proteins gp105 and p26 from HIV-2 ROD and gp120 and p24 from HIV-1 IIIB (obtained from a baculovirus expression system by Dr. I. Jones, provided by the Medical Research Council, U.K., AIDS Reagent Program). Proliferation was assessed by titrated TdR (Amersham Pharmacia Biotech, Little Chalfont, U.K.) incorporation after a pulse of 1 μCi in the last 4 h of culture and counted in a gaseous scintillation beta counter (Packard Instrument, Meriden, CT); results are expressed as cpm.

**Statistical analysis**

The data are presented as arithmetic mean ± SE and were compared using an unpaired t test or Mann-Whitney test according to the type of distribution; the Pearson’s and the Spearman’s correlation coefficients were used to determine the correlation between two variables. Model I linear regression was performed to establish relationships between variables. A value of *p* < 0.05 was considered significant.

**Results**

**Naive/memory-effector distribution within the CD4 and CD8 T cells**

HIV-1 immunodeficiency is associated with a progressive decline of both CD4 and CD8 naive cells in the peripheral blood leading to an imbalance in the naive/memory-effector distribution (28). Despite the complexity of the phenotypic definition of these populations, the simultaneous expression of CD45RA and CD62L is currently thought to identify the majority of the naive lymphocytes and CD45RO is considered a memory marker. We found that, at a given degree of CD4 depletion, the proportion of CD45RA+CD62L- cells within the CD4 T cell subset does not differ significantly between the two infections (Table I). Moreover, a progressive reduction in the proportion of CD45RA+CD62L+ cells within the CD8 T cell population was also observed (Table I). As has been previously described for HIV-1 disease (28), there was a positive correlation between the declines in naive cell frequencies within the CD4 and the CD8 subsets in HIV-2 (*r* = 0.5779; *p* = 0.002) as well as in HIV-1-infected patients (*r* = 0.4601; *p* = 0.018). Importantly, the decrease in the absolute number of CD45RA+CD62L+ CD4 T cells in peripheral blood in the HIV-2 cohort was also in correlation with the progressive reduction in the number of CD45RA+CD62L+ CD8 T cells (*r* = 0.5585; *p* = 0.003).

### Table I. Imbalances of the naive/memory subsets within CD4 and CD8 T cell subsets

<table>
<thead>
<tr>
<th>Patients</th>
<th>CD4 T Cells</th>
<th>CD8 T Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD45RA+CD62L</td>
<td>CD45RO+</td>
</tr>
<tr>
<td></td>
<td>% Cells/μl</td>
<td>% Cells/μl</td>
</tr>
<tr>
<td>HIV-2+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>41.0 ± 3.5**</td>
</tr>
<tr>
<td></td>
<td>&gt;500 CD4 cells/μl</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>&gt;200–500 CD4 cells/μl</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>&lt;200 CD4 cells/μl</td>
<td>6</td>
</tr>
<tr>
<td>HIV-1+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>40.7 ± 4.2**</td>
</tr>
<tr>
<td></td>
<td>&gt;500 CD4 cells/μl</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>&gt;200–500 CD4 cells/μl</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>&lt;200 CD4 cells/μl</td>
<td>9</td>
</tr>
<tr>
<td>Controls</td>
<td>25</td>
<td>55.5 ± 2.8</td>
</tr>
</tbody>
</table>

* Significance in comparison with healthy controls: *p* < 0.05; **p < 0.01; ***p < 0.001. Significance of one phase of the HIV-2 or the HIV-1 disease in comparison with the subsequent phase: †, *p* < 0.05; ††, *p* < 0.01; †††, *p* < 0.001.

There were no significant differences between the HIV-2 cohort and the corresponding group of the HIV-1 cohort.

![Comparison of viral loads](image)
Markers of CD4 T cell activation

Having shown that, for a given level of CD4 depletion, the two infections exhibited similar imbalances of the naive/memory-effector distribution within the CD4 and CD8 T cells, we examined the expression of markers that are up-regulated upon T cell activation.

HIV-2-infected patients showed significant up-regulation of the MHC class II molecule (HLA-DR) within the CD4 T cell population similar to the one observed in the corresponding group of HIV-1 patients (Fig. 2a), with a similar inverse correlation to the peripheral blood CD4 count ($r = -0.7485$ and $p < 0.0001$ for HIV-2; $r = -0.7170$ and $p < 0.0001$ for HIV-1 disease). Moreover, the frequency of CD4 T cells expressing the marker of recent cell activation CD69 was also elevated and was not significantly different in the HIV-2 as compared with HIV-1 patients (Fig. 2a).

Activation of the CD8 subset

HIV-2 is associated with an elevated frequency of HLA-DR$^+$ cells within the CD8 subset that increases with the progression in CD4 depletion ($r = -0.6134; p = 0.0009$) (Fig. 2b). Furthermore, the CD38 molecule is up-regulated in terms of both percentage of positive cells (Fig. 2b) and mean fluorescence intensity (data not shown). In HIV-1 infection this has been shown to be indicative of CD4 depletion and leads to adverse prognosis independent of the
viremia (29). Assessing the simultaneous expression of HLA-DR and CD38 in CD8 T cells, we found a similar expansion of this subset in both infections in the intermediate and advanced stages of CD4 depletion, although in the early stage there was a significantly lower expansion in the HIV-2 infection than in HIV-1 (Fig. 2b).

In contrast to HIV-1 infection, HIV-2 was not found to be associated with a significant increase in the proportion of CD8 T cells expressing CD69 (9.2 ± 1.3 in HIV-2-infected patients vs 6.9 ± 1.2 (NS) in healthy controls) and CD38 in HIV-1-infected subjects (p < 0.0001 and p = 0.0023, respectively). Because CD69 is only transiently expressed on T cells upon activation, this difference does not have direct bearing on the extent of overall activation in the two infections, but it does suggest differences in the pattern of CD8 activation.

**Up-regulation of the Fas molecule**

Fas (CD95) is thought to play a role in HIV-1-associated lymphocyte anergy and programmed death (30). The Fas molecule is highly expressed in the memory-effector cell population. Measuring its expression in the CD45RA−CD45RO+ subset we found major up-regulation in both HIV-1 and HIV-2 infections (Fig. 3, a and b), with a strong negative correlation to CD4 counts (r = −0.71 and p < 0.0001 for HIV-2 infection; r = −0.65 and p = 0.0003 for HIV-1 infection). For both types of infection major up-regulation of Fas was also observed within the CD45RA−CD8+ T cell subset and was found to increase with disease progression as shown in Fig. 3, c and d (correlation with the CD4 counts: r = −0.72 and p < 0.0001 for HIV-2 infection; r = −0.69 and p = 0.0001 for HIV-1 infection). Within the CD45RA−CD4 and CD8 T cell populations, both types of infections are associated with an increase in the already highly expressed Fas as compared with uninfected individuals (data not shown).

**Cell cycle status**

Because HIV-1- and HIV-2-infected individuals with similar CD4 T cell counts have different viral loads but similar degrees of CD4 and CD8 cell activation, we asked how the two infections compared in terms of T cell turnover as assessed by the expression of the nuclear factor Ki67, which is up-regulated in all cell cycle phases except G0 (31). Increased fractions of Ki67+ cells within the CD4 subset were seen in both infections (Fig. 4), with an inverse correlation to the blood numbers of CD4 T cells that was not observed in the control group (r = −0.77 in HIV-1 and r = −0.72 in HIV-2 infection, with a value of p < 0.001 in both cases). The majority of the CD4+Ki67+ T cells were found to be CD45RO+ (92 ± 0.7% and 89 ± 1.5% in HIV-1 and HIV-2 cohorts, respectively).

Fig. 4 shows a linear regression of the frequency of Ki67+ within the CD4 subset over the logarithm of the CD4 counts, which was statistically significant for both the HIV-1 and HIV-2 patients. In uninfected controls the percentage of Ki67+ cells is practically constant. The non-zero slopes observed in the infected groups (−1.9 and −1.3) were significant (p < 0.001), indicating that the turnover of CD4 T cells changes during HIV infection. The slopes obtained during HIV-1 and HIV-2 infection differ by 20% (p = 0.05), suggesting that the impact of the two viruses may differ in quantitative details while showing a similar trend as opposed to controls.

**Correlation between the frequency of cycling cells and the expression of activation markers**

The frequencies of CD4 and CD8 T cells with an activation or memory phenotype are positively correlated to the frequency of Ki67+ CD4 T cells and inversely correlated to the numbers of CD4 T cells in the blood (Table II).

**Lymphoproliferative responses to mitogens or Ags**

Chronic immune activation has been linked to T cell anergy in HIV-1 infection. To investigate this issue we tested the ability of the lymphocytes to proliferate in vitro in response to CD3 stimulation in the absence and presence of CD28 costimulation and in

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>HIV-1</th>
<th>HIV-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki67 (%)</td>
<td>0.65±0.05</td>
<td>−0.71±0.04</td>
<td>0.70±0.05</td>
</tr>
<tr>
<td>No. of CD4 cells</td>
<td>1.12±0.04</td>
<td>0.65±0.05</td>
<td>0.65±0.05</td>
</tr>
<tr>
<td>Fas in CD45RA−</td>
<td>0.22±0.04</td>
<td>0.45±0.05</td>
<td>0.52±0.05</td>
</tr>
<tr>
<td>Fas in CD45RO+</td>
<td>0.24±0.05</td>
<td>0.47±0.05</td>
<td>0.56±0.05</td>
</tr>
<tr>
<td>HLA DR−</td>
<td>0.06±0.03</td>
<td>0.71±0.07</td>
<td>0.66±0.08</td>
</tr>
<tr>
<td>CD69−</td>
<td>0.05±0.02</td>
<td>0.25±0.05</td>
<td>0.50±0.04</td>
</tr>
</tbody>
</table>

* Significant correlation at p < 0.01.

**FIGURE 4.** Relationship between cycling cells and depletion within the CD4 subset. Frequency of Ki67+ cells within the CD4 subset is plotted as a function of the logarithm of the total number of CD4 cells for 25 uninfected (○), 25 HIV-1-infected (○), and 24 HIV-2-infected (◊) individuals. Regression equations are as follows: controls, percentage of Ki67 = 0.6–0.5 log number of CD4 cells (p > 0.05); HIV-1, percentage of Ki67 = 5.9–1.9 log number of CD4 cells (p < 0.001) (dashed line); HIV-2, percentage of Ki67 = 4.1–1.3 log number of CD4 cells (p < 0.001) (continuous line).
FIGURE 5. Lymphocyte proliferative responses in healthy subjects and in HIV-2- and HIV-1-infected patients grouped according to a progressive degree of CD4 depletion, namely >500 CD4 cells/μl (left), 200–500 CD4 cells/μl (middle), and <200 CD4 cells/μl (right). PBMCs were cultured for 3 days with immobilized anti-CD3 mAb in the absence (a) and in the presence (b) of soluble anti-CD28 mAbs, and for 6 days in the presence of the recall Ags Candida albicans (c), purified protein derivative (d), and tetanus toxoid (e). Proliferation was assessed by tritiated TdR incorporation and results are expressed as cpm in the presence of a given stimulus minus the cpm in its absence (cpm net). Each dot represents one individual. Bars represent means.

Discussion

For the same level of CD4 T cell depletion, HIV-1- and HIV-2-infected patients exhibited similar elevations in the frequencies of activated and cycling T cells. In contrast to previous studies (32), we grouped HIV-1- and HIV-2-infected patients whose levels of CD4 depletion fell in the same range and found that with this categorization the two infections exhibit 1) a similar imbalance in the naive/memory-effector population ratios, 2) comparable up-regulation of CD4 and CD8 T cell activation markers (HLA-DR, CD38, CD69, Fas molecule), 3) a similar increase in the frequency of cycling CD4 T cells (Ki67'), which was in strong correlation with the expression of activation markers, and 4) a similar level of anergy, as assessed by the in vitro lymphoproliferative responses to CD3 stimulation in the presence or absence of CD28 costimulation and to a panel of microbial Ags. Considering that the two HIV-associated immunodeficiencies are characterized by markedly different plasma viral loads and are known to display different rates of CD4 T cell decline and to have different clinical prognosis (12–14, 24), these findings call for a reappraisal of widely held views regarding the causal relationships among chronic immune activation, T cell turnover, viremia, and the rate of CD4 decline.

According to one paradigm, the demand for CD4 T cell production in response to rapid virus-mediated destruction is the direct cause of increased turnover (1–3). Progressive depletion of CD4^+ T cells is accordingly seen as a failure of production to keep up with the rate of loss. This hypothesis has been challenged on several grounds. In particular, the increase in the average T cell turnover rate appears to be due to recurrent Ag- and inflammation-driven expansion and subsequent contraction of a fraction of the clonal repertoire, as was suggested by an analysis of in vivo DNA labeling results (6, 33, 34) and by correlations between immune activation, viral load, and CD4 counts during highly active antiretroviral treatment (HAART) (35, 36). Recent observations indicate that CD4 depletion during the chronic phase of HIV/SIV infection is more directly related to the overall activation and turnover of T cells than to the turnover of infected CD4^+ cells and free virus (37–39). These observations contradict a basic tenet of the destruction-demand hypothesis (1–3), which links overall T cell turnover to the turnover of infected cells and attributes depletion to the latter. Levels of immune activation, CD4^+ T cell depletion, and viremia in untreated HIV-1-infected patients have been compared with those measured in HAART-failing patients who maintain increasing CD4 cell counts. For any level of viremia, CD4^+ cell turnover rates were higher in patients with wild-type virus than in patients with drug-resistant virus (37). Yet the turnover rates of infected CD4^+ T cells in treated and untreated patients are probably not significantly different, because treatment of both with effective HAART regimens result in similar decay rates of plasma HIV-RNA (40). Furthermore, the natural hosts of SIV, sooty

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3 Abbreviation used in this paper: HAART, highly active antiretroviral treatment.
mangabeys and African green monkeys, show no significant increase in immune activation and turnover (38, 39). Despite high-level virus replication and rapid death of infected cells (M. B. Feinberg, personal communication), they do not develop progressive depletion of CD4 T cells.

The quantitatively similar association between CD4 depletion and immune activation in HIV-1 and HIV-2 infections we report in this work supports the hypothesis that immune activation drives depletion (11). This hypothesis is further supported by the observation of reduced CD4 T cell counts and increased CD8 counts, accompanied by elevated immune activation, in HIV-negative humans chronically infected with helminths and other parasites (41). It is very unlikely that the similar rates of CD4+ T cell turnover, found in HIV-1 and HIV-2 patients with comparable levels of CD4 depletion, are associated with similar turnover rates of infected cells despite the large difference in viremia levels. The lower per-cell production of HIV-2 can account for the lower viremia levels. But to account for similar infection rates (23, 24), HIV-2 should be inherently much more infectious than HIV-1, and there is no evidence for this (16). Although similar proviral levels were found in HIV-1- and HIV-2-infected individuals (23, 24), a large proportion of the provirus-containing cells in the blood of HIV-2-infected individuals may be latently infected rather than virus-producing cells—a cumulative measure of the infection rather than a measure of ongoing replication.

The reasons for the generalized immune activation and the mechanisms whereby it may affect the homeostatic regulation of T lymphocytes are not well understood (11). Bursts of T cell proliferation continuously occur, stimulated by proinflammatory factors and Ags (6). Bursts may also occur in futile response to “homeostatic” signals in lymphoid sites irreversibly depleted of CD4 T cells (42). Immune activation maintains targets for viral replication and, coupled to virus-mediated attrition, may drive the progression of HIV disease by destabilizing or progressively changing the homeostatic steady states of resting cell populations, naive and memory (4–11). Possible mechanisms include reduced production and increased differentiation of naive T cells and net loss in the number of resting memory T cells—especially CD4+ cells—during immune activation cycles. It is also conceivable that products of activation, such as proinflammatory factors, affect the migration patterns, viability, and response characteristics of the resting lymphocytes (4, 27). The effect of immune activation on total T cell numbers is complex. While the numbers of resting T cells decline, the number of activated cells increases. CD8+ T cells are known to expand more extensively than CD4+ T cells during immune responses, and this might account for the overall increase in CD8 T cell counts during the less-advanced stages of progression, while CD4 counts progressively decline.

How can substantially lower viral loads in HIV-2 infection be associated with levels of immune activation similar to those documented in HIV-1 infection? What is the basis for the slower rate of progression of HIV-2 infection compared with HIV-1?

The “proximal activation and transmission” model (43, 44) offers potential explanations. When “latently” infected memory cells are involved in activation bursts, they spark local bursts of infection. The local nature of virus replication (“proximal activation and transmission”) is supported by in situ analyses of HIV and TCR molecular sequences (45–47). Infection bursts end in the death of most activated cells, including virus-producing CD4+ T cells, but newly generated memory cells that contain provirus survive and spark new infection bursts (11). The production of free virus during each prolonged burst involves several rounds of infection. Because of this amplification, the amount of virus produced per burst should be very sensitive to the efficacy of transmission (43, 44). Because HIV-1 and HIV-2 showed a similar destructive impact when tested in a human lymphoid tissue culture model (48), it is likely that certain host factors limit HIV-2 replication rate in vivo, perhaps by acting on target cells (49–51). We have reported marked immunosuppressive effects of the HIV-2 envelope protein (52), which may reduce the probability of virus transmission among T cells responding to virus Ags or to other pathogens. Even a modest reduction of this probability may have a drastic effect on the virus produced in local infection bursts because of the amplification factor. In contrast, the contribution of each burst to systemic activation, related to HIV-mediated enhancement of APC-lymphocyte interactions, is likely to be relatively insensitive to the amount of free virus produced in such a burst. In that case, the systemic level of activation would reflect mainly the frequency of bursts initiated by infected memory cells rather than the amount of free virus produced in each burst. In contrast, the viremia level is proportional to the product of these two parameters.

HIV-1- and HIV-2-infected individuals would thus manifest comparable levels of immune activation and CD4 depletion when they have accumulated comparable numbers of infected memory cells leading to comparable frequencies of infection bursts, but viremia levels in HIV-2 infection would remain much lower because of the inefficient replication of HIV-2 within expanding populations of activated CD4+ T cells. This interpretation can explain our findings and is also consistent with the finding of roughly similar amounts of proviral DNA in peripheral blood mononuclear cells from people infected with either HIV-2 or HIV-1, despite the large difference in RNA amounts (23, 24). Inefficient replication of HIV-2 would likely be associated with a slower accumulation of infected memory cells and therefore with slower progression of HIV-2 infection compared with HIV-1 (12, 14, 20).

Despite the overall similarity, we have noted certain quantitative differences between HIV-1 and HIV-2 infection in the patterns of immune activation for similar levels of CD4 depletion. Notably, there were more CD8 T cells expressing CD69 in HIV-1-infected patients than in HIV-2-infected patients and slight differences in the linear regression lines of the frequency of Ki67+ CD4 T cells over the CD4 counts (see Results). These differences may be related to the large difference in the amount of viral Ag. One should bear in mind that different activation markers are likely associated with different immune activation events that contribute to “chronic immune activation,” and that some of these events are bound to be more closely associated with CD4 depletion than others.

In summary, our findings support a close linkage between immune activation and CD4 cell depletion in HIV infection and only an indirect relationship of these parameters to the virus rate of replication. Although the destruction-replacement hypothesis has been forcibly advocated, a strong case can be made for alternative, immune activation-centered hypotheses. Further comparative studies of the different host/virus systems would allow a more definitive delineation of cause and effect in HIV disease progression, with implications for the choice of treatment strategies.

Acknowledgments


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