Immune activation is a hallmark of disease progression in human immunodeficiency virus (HIV) type 1 (HIV-1) and HIV type 2 (HIV-2) infection. However, the relationship between viremia and systemic immune activation is unclear. We assessed the relationship between HIV-2 plasma virus load and immune system activation in a cross-sectional study in a community cohort of HIV-1–positive, HIV-2–positive, and HIV-negative patients, in which many HIV-2–positive patients had nonprogressing infection. HLA-DR and CD38 expression on CD4+ and CD8+ T cells was measured, as were plasma β2-microglobulin levels. These markers were related to clinical (virus load and CD4+ cell count) and immunological (HIV-2–specific interferon γ secretion) correlates of delayed disease progression. A consistent positive correlation was identified between the level of HIV-2 viremia and immune activation. We propose that increasing virus load may contribute to systemic immune activation in HIV-2 infection.

Chronic human immunodeficiency virus (HIV) type 1 (HIV-1) infection is characterized by immune dysfunction accompanied by opportunistic infections and neoplastic events that eventually lead to the death of the host. Ironically, the deficiency in immune system function is accompanied by overwhelming systemic immune activation, which is manifested by elevated plasma levels of proinflammatory cytokines and increased T cell turnover, followed by a loss of T cell regenerative capacity [1, 2]. Furthermore, immune activation increases virus transcription and activates transcription from latently infected cells [3, 4]. Given that HIV infects mainly activated T cells [4, 5], this immune activation is part of a self-perpetuating cycle that allows the virus to thrive at the expense of the host.

Persistent immune activation is a feature of chronic HIV-1 infection and is the predominant determinant of survival in late-stage disease [6–9]. Despite significant differences between HIV-1 infection and HIV type 2 (HIV-2) infection, both in the rate of progression to disease and in the plasma virus load in patients matched for disease stage, immune activation occurs in the chronic phase of infection with both pathogens [10–12]. The level of immune activation is comparable between HIV-2– and HIV-1–infected patients at similar stages of disease [12, 13].

HIV-induced immune activation results from direct and indirect consequences of the infection; the relative contributions of these factors is incompletely understood. A direct effect of HIV infection on immune system activation is a reduction in activation-induced proliferation of T cells after the initiation of highly active antiretroviral therapy (HAART) [2, 14, 15] and a resumption of virus replication, followed by increased immune activation and T cell turnover, after HAART interruption [16]. However, in HIV-1–infected patients who have undetectable viremia and who are not receiving HAART, T cell activation is still observed to contribute to progressive CD4+ T cell loss [17], suggesting that virus replication is not an absolute require-
ment for systemic immune activation. This indirect effect of the virus on immune activation may be explained by microbial translocation secondary to the loss of gastrointestinal mucosal integrity [18], which is an indirect mechanism of immune activation in HIV infection. In contrast, nonpathogenic simian immunodeficiency virus infection in its natural nonhuman primate host is associated with lower immune activation despite high-level virus replication, and the infected animals are able to avoid bystander damage, AIDS [19], and virally induced CD4+ T cell depletion [20]. Therefore, the contribution of high levels of lentiviral viremia to immune activation in the natural host is unclear and varies with the virus and the host. In the present study, we investigated the relationship between HIV-2 load and systemic immune activation. The study was cross-sectional and was conducted in a large community cohort of HIV-1–positive, HIV-2–positive, and HIV-negative patients, who were drawn largely from the same ethnic group and who were living in similar environmental conditions. The cellular expression of HLA-DR and CD38 on CD4+ and CD8+ T cells was measured, as were plasma β2-microglobulin levels. The selection of these markers was based on studies that established their role as markers of immune activation in HIV-1 infection [8, 21–24]. The markers were analyzed in relation to clinical parameters (virus load, CD4+ cell count, body mass index [BMI; calculated as the weight in kilograms divided by the square of the height in meters], and Karnofsky score) and immunological parameters (HIV-2–specific interferon γ [IFN-γ] secretion) that may be relevant for the control of HIV infection.

**MATERIALS AND METHODS**

**Patient population.** Patients were recruited from a community cohort in Caio, Guinea-Bissau [25]. Samples were analyzed for anti-HIV antibodies, virus load, and CD4+ cell count, as described elsewhere [26]. Plasma virus load was determined by reverse-transcription polymerase chain reaction using specific long-terminal-repeat primers [27], with a detection limit of 100 copies/mL; values below this level were assigned an arbitrary value of 50 copies/mL. Clinical parameters of the patients are listed in Table 1. Samples were collected from January through April 2006 for all of the patients and again in July 2007 for a subset of 53 HIV-2–positive patients.

All participants provided written informed consent. At the time of the study, antiretroviral therapy (ART) had not yet been introduced in rural Guinea-Bissau; therefore, all participants were ART naive. Ethical approval for this study was obtained from the Gambian Government Medical Research Council Ethics Committee, from the Republic of Guinea-Bissau Ministry of Health, and from the Oxford Tropical Research Ethics Committee in the United Kingdom.

**Measurement of T cell activation marker expression.** Fresh whole blood was stabilized at a 5:1 ratio with TransFix (Cytomark) for 2–14 days and used for determination of T cell surface activation marker expression with anti–HLA-DR fluorescein isothiocyanate, CD38 phycoerythrin, CD4 peridinin-chlorophyll protein, and CD8 allophycocyanin monoclonal antibodies (BD Pharmingen). One hundred microliters of TransFix-preserved blood was incubated with the antibody cocktail for 30 min in the dark. Red blood cells were lysed using 1:10 BD FACS Lysing Solution (BD Biosciences). Cells were washed twice and fixed with a 2% paraformaldehyde–phosphate buffered saline solution. Samples were analyzed using a FACSCalibur flow cytometer (BD Biosciences), and data were analyzed using FlowJo software (Tree Star). Gating for HLA-DR and CD38+ cell populations was performed using collective quadrant gates based on HLA-DR and CD38 expression on CD4+ or CD8+ T cells of HIV-negative patients, as described by Hanson et al [13].

**Plasma soluble marker detection.** Plasma samples were obtained from centrifuged heparin-anticoagulated fresh blood samples. The samples were passed through a 0.22-μm filter and cryopreserved in liquid nitrogen until sample analysis. Plasma

---

### Table 1. Patient Clinical Parameters

<table>
<thead>
<tr>
<th>HIV status</th>
<th>Virus load, median (IQR), copies/mL</th>
<th>CD4+ cell count, percentage</th>
<th>CD4+ cell count, cells/μL</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV negative (n = 120)</td>
<td>NA</td>
<td>698 ± 278</td>
<td>42.5 ± 7.3</td>
<td>22.4 ± 3.7</td>
</tr>
<tr>
<td>HIV-1 positive (n = 14)</td>
<td>59,180 (757–873,206)</td>
<td>499 ± 243</td>
<td>23.5 ± 9.5</td>
<td>22.1 ± 4.4</td>
</tr>
<tr>
<td>HIV-2 positive (n = 107)</td>
<td>316 (50–283,542)</td>
<td>598 ± 320</td>
<td>31.3 ± 10.5</td>
<td>21.3 ± 3.2</td>
</tr>
<tr>
<td>Virus load &lt;100 (n = 39)</td>
<td>50</td>
<td>723 ± 350</td>
<td>36.1 ± 9.3</td>
<td>22.9 ± 3.7</td>
</tr>
<tr>
<td>Virus load ≥100 (n = 68)</td>
<td>15,085 (109–383,542)</td>
<td>526 ± 299</td>
<td>28.6 ± 11.6</td>
<td>20.4 ± 4.3</td>
</tr>
</tbody>
</table>

**NOTE.** Data are means ± standard deviations, unless otherwise indicated. BMI, body mass index; HIV-1, human immunodeficiency virus type 1; HIV-2, human immunodeficiency virus type 2; IQR, interquartile range; NA, not applicable.

* P values are for the differences between HIV-2-positive patients with a virus load of <100 copies/mL and those with a virus load of ≥100 copies/mL (2-sample unpaired t test).
levels of β2-microglobulin were quantified using an AxSYM β2-microglobulin assay (Abbott).

IFN-γ enzyme-linked immunospot assay. Peripheral blood mononuclear cells (PBMCs) from 64 HIV-2–positive patients were used in ex vivo IFN-γ enzyme-linked immunospot assays, as described elsewhere [26]. Briefly, 10^5 PBMCs were added to each well of a 96-well MultiScreen filter plate (Millipore) coated with 15 µg/mL anti–IFN-γ monoclonal antibody (1-DIK; Mabtech) and stimulated for 16 h with overlapping peptide pools spanning the HIV-2 proteome. Responses were classified as positive if they were >3 times the mean of the negative control wells and had >50 spot-forming units per 10^6 PBMCs [28].

Statistical analysis. Data analysis was performed using Stata software (version 8.0; StataCorp). Excel software (version 2003; Microsoft) and Prism software (version 4.02; GraphPad) were used for graphical presentation. Normally distributed or transformed data were analyzed using parametric tests (Pearson correlation or 2-sample unpaired Student t test). Nonnormally distributed data were analyzed using nonparametric tests (Spearman rank correlation or Wilcoxon-Mann-Whitney test). Results are presented as means with standard deviations (SDs) (parametric tests) or medians with interquartile ranges (IQRs) (nonparametric tests). Statistical test differences were considered significant if P<.05.

RESULTS

Correlation between systemic immune activation and HIV-2 load. The expression of HLA-DR and CD38 is up-regulated on T cells during activation, and their augmented expression is a strong predictor of disease progression during HIV infection [8, 21, 22, 29]. Therefore, the levels of expression of CD38, HLA-DR, and CD38/HLA-DR on CD4+ and CD8+ T cells were analyzed in relation to HIV-2 load (Table 2). A consistent positive correlation between the levels of these immune activation markers and the level of HIV-2 viremia was observed, irrespective of the markers used to define immune activation.

Low virus load in HIV-2 infection may be a surrogate marker for disease nonprogression, and low-level viremia predicts normal survival [30]. Furthermore, at a similar virus load, HIV-1– and HIV-2–infected patients experience a similar rate of CD4+ T cell decrease [31]. Therefore, we extended the analysis of the relationship between HIV-2 load and immune activation to include only those HIV-2–infected patients with a detectable virus load (≥100 copies/mL [n = 68]) and with high-level viremia (≥1000 copies/mL [n = 38]). The exclusion of patients with undetectable virus load strengthened the relationship between HIV-2 load and immune activation (denoted by r values) (Table 2).

In addition to cellular markers of activation, the plasma level of β2-microglobulin, a soluble marker indicative of systemic immune activation in HIV infection [23, 24], was examined.

In the same community cohort of HIV-2–positive patients, elevated β2-microglobulin levels are associated with a decrease in the CD4+ T cell percentage and decreased survival [11]. We observed a strong correlation between β2-microglobulin levels and HIV-2 viremia (Table 2), similar to the positive relationship between cellular immune activation and HIV-2 load. When the analysis was extended to include only HIV-2–positive patients with a detectable virus load (≥100 copies/mL [n = 68]) or with a high virus load (≥1000 copies/mL [n = 38]), the strength of the relationship between β2-microglobulin levels and HIV-2 load (r) increased (from 0.39 to 0.47 and 0.65, respectively).

Controlled and uncontrolled HIV-2 replication distinguished by HLA-DR expression on CD4+ T cells. To identify the most accurate cell-surface biomarker of immune activation in HIV-2 infection, we stratified the cohort into 4 groups: HIV-negative patients, HIV-1–positive patients, HIV-2–positive patients with a virus load of <100 copies/mL, and HIV-2–positive patients with a virus load of ≥100 copies/mL. HIV-2–positive patients with a virus load of ≥100 copies/mL had CD4+ cell counts and BMIs that were statistically significantly lower than those of patients with a virus load of <100 copies/mL and that were comparable to those of HIV-1–positive patients, providing a rationale for stratifying HIV-2–positive patients on the basis of a virus load of <100 and ≥100 copies/mL (Table 1). Further support for this stratification is based on prior studies that showed that HIV-2 infection with a virus load of <100 copies/mL predicts normal survival [30] and may be a surrogate marker for long-term nonprogression. A comparison of the median level of activation of CD4+ and CD8+ T cells in the 4 groups (Figure 1) showed a consistent lack of a difference be-

Table 2. Relationship between Virus Load and Markers of Immune Activation in Human Immunodeficiency Virus Type 2 (HIV-2)–Positive Patients

<table>
<thead>
<tr>
<th>Activation marker</th>
<th>All patients (n = 107)</th>
<th>Virus load, copies/mL</th>
<th>&gt;100 copies/mL</th>
<th>&gt;1000 copies/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>HLA-DR+CD4+</td>
<td>.001</td>
<td>0.56</td>
<td>&lt;.001</td>
<td>0.52</td>
</tr>
<tr>
<td>HLA-DR+CD8+</td>
<td>.001</td>
<td>0.46</td>
<td>&lt;.001</td>
<td>0.50</td>
</tr>
<tr>
<td>CD4+</td>
<td>.005</td>
<td>0.27</td>
<td>&lt;.001</td>
<td>0.48</td>
</tr>
<tr>
<td>CD8+</td>
<td>.001</td>
<td>0.45</td>
<td>&lt;.001</td>
<td>0.67</td>
</tr>
<tr>
<td>β2-microglobulin</td>
<td>&lt;.001</td>
<td>0.39</td>
<td>&lt;.001</td>
<td>0.47</td>
</tr>
</tbody>
</table>

NOTE. The statistical analysis was performed using Spearman rank correlation. r, Spearman rank correlation coefficient.
Immune Activation in HIV-2 Infection

Figure 1. Comparison of CD4+ and CD8+ T cell surface expression levels of cellular markers of activation. Shown are results for HLA-DR (A), CD38 (B), and HLA-DR/CD38 (C) in human immunodeficiency virus (HIV)–negative patients (white bars), HIV type 2 (HIV-2)–positive patients with undetectable viremia (dotted bars), HIV-2–positive patients with virus replication (striped bars), and HIV type 1 (HIV-1)–positive patients (checkered bars). Statistical analysis was done using the Wilcoxon-Mann-Whitney test, and P values are indicated. Error bars represent interquartile ranges. NS, not significant; VL, virus load.

tween the level of activation of CD4+ and CD8+ T cells in HIV-2–positive patients with a detectable plasma virus load (n = 68) and that in HIV-1–positive individuals (n = 14), irrespective of the definition of immune activation. Of note, there was no statistically significant difference between the CD4+ cell counts in HIV-2–positive patients with detectable virus load and those in HIV-1–positive patients in the present study, despite a marked difference in the median virus load between these 2 groups.

When HIV-2–positive patients were stratified by a virus load of <100 and ≥100 copies/mL, for both CD4+ and CD8+ T cell activation there was a statistically significant difference between the 2 groups (Figure 1A and 1C). CD38 expression and CD8+ T cells followed the same trend without reaching statistical significance (Figure 1B).

The level of T cell activation in HIV-negative patients consistently and statistically significantly differed from that in HIV-2–positive patients with a virus load of ≥100 copies/mL, irrespective of the definition used to characterize T cell activation (P < .001). There was no difference between HIV-negative and HIV-2–positive patients with a virus load of <100 copies/mL in the level of T cell activation, as measured by the expression of HLA-DR on CD4+ T cells or the expression of CD38 on CD8+ T cells.

Overall, the expression of HLA-DR on CD4+ T cells correlated best with virus load (Figure 1A) and showed a logical
trend in the different patient groups: a similar level of activation in HIV-negative and HIV-2–positive patients with undetectable viremia, a similar level of activation in HIV-1– and HIV-2–positive patients with a virus load of \( \geq 100 \) copies/mL, and a statistically significant difference between HIV-2–positive patients with a virus load of \(<100\) and those with \( \geq 100 \) copies/mL as well as between HIV-negative and HIV-2–positive patients with a virus load of \( \geq 100 \) copies/mL (\( P < .001 \) for both comparisons).

**Immune activation in relation to clinical parameters of disease progression.** BMI and Karnofsky score are another set of clinical parameters that predict disease progression in HIV infection [32, 33]. To test the relevance of high immune activation in patients with increasing virus load, cellular and plasma markers of immune activation were related to BMI and Karnofsky score. Among HIV-2–positive patients in the present study, BMI strongly negatively correlated with HIV-2 load (\( P = .001 \)): patients with a BMI of \(<18\) had significantly higher viremia (\( P = .002 \)) (Table 1), supporting the use of BMI as a surrogate clinical marker of disease progression. A BMI of \(<18\) is comparable to a CD4+ cell count of \(<200\) cells/\( \mu L \) in predicting 6-month mortality at baseline diagnosis of HIV infection [32]. HIV-2–positive patients with a BMI of \( \geq 18\) and a Karnofsky score of \( >80\% \) had significantly lower levels of immune activation. Remarkably, HLA-DR expression on CD4+ and CD8+ T cells (Figure 2A), as well as plasma \( \beta_2\)-microglobulin levels (Figure 2B), positively correlated with clinical parameters of disease progression (BMI, \(<18\); Karnofsky score, \(<80\%\)). This was further confirmed when the same definitions of immune activation were correlated with CD4+ T cell counts (\( P < .001 \)).

**Stability of T cell activation over time.** Many HIV-2–positive patients in the present study first received a diagnosis of HIV-2 infection in 1989 [25] and thus had been HIV-2–positive for at least 17 years at the time of the present study. To determine whether the levels of immune activation in the cross-sectional study were stable, 53 HIV-2–positive patients were recruited at an additional time point, and the surface expression levels of HLA-DR and CD38 were analyzed (Figure 3). The time between the first and second sample collection was 15–19 months, with the first time point during the dry season (January–May) and the follow-up recruitment during the wet season (July). It is important to note this variable because there are marked differences in the seasonality of coinfections in this region of Africa, with malaria and respiratory infections being more prevalent during the wet season.

Despite the seasonal differences and the \( \sim 1.5\)-year lag between the 2 data-acquisition time points, there were no statistically significant differences in the median levels of expression of the cellular markers of activation on either CD4+ or CD8+ T cells between the 2 time points. This suggests that the level of immune activation remained stable over time, as indicated by the similar median values of HLA-DR and CD38 expression on CD4+ and CD8+ T cells at both time points. This stability in immune activation over time is further supported by the consistency in the levels of systemic immune activation, as measured by HLA-DR expression on CD4+ T cells and \( \beta_2\)-microglobulin levels, across the different patient groups.
of immune activation in chronic HIV-2 infection is stable with time and does not depend on seasonal variation in endemic infections. The immune activation stability was also mirrored by stability in the mean CD4+ cell percentage ($r_s = 0.78$ and $P < .001$; $32.2\%$ [SD, 9.9\%] at $t_0$ and $30.2\%$ [SD, 10.1\%] at $t_{1.5}$) and in the median HIV-2 load ($r_s = 0.37$ and $P = .006$; 182 copies/mL [IQR, 50–1095 copies/mL] at $t_0$ and 50 copies/mL [IQR, 50–593 copies/mL] at $t_{1.5}$) between the 2 time points, similar to the results of other reports [27, 30].

**No association between immune activation and CD4+ cell counts in HIV-2–positive patients without viremia.** There is a strong negative relationship between systemic immune activation and CD4+ T cell levels in HIV-1–positive patients who control virus replication in the absence of HAART [17]. To determine whether a similar relationship could be observed in HIV-2 infection, the level of immune activation in HIV-2–positive patients with undetectable viremia ($n = 39$) was assessed. However, there was no identifiable correlation between CD4+ cell counts and the degree of systemic immune activation in HIV-2–positive patients without viremia, regardless of whether immune activation was defined by cellular or plasma markers of activation (Figure 4A and 4B).

When patients with undetectable HIV-2 viremia were grouped by CD4+ cell count (for >500 cells/µL, $n = 30$; for $\leq$500 cells/µL, $n = 9$), there was no statistically significant difference in the median levels of systemic immune activation between the 2 groups. This further emphasizes the lack of a relationship between immune activation and CD4+ cell counts in the absence of detectable HIV-2 replication.

To determine how a slight increase in virus replication affects the association between immune activation and CD4+ T cell levels, the same analysis was extended to all patients with a virus load of <1000 copies/mL ($n = 69$). The analysis revealed a weak statistically significant negative correlation between CD4+ T cell counts and immune activation, as defined by expression of HLA-DR ($P = .001; r_s = -0.38$) or HLA-DR and CD38 ($P < .001; r_s = -0.48$) on CD4+ T cells and by expression of HLA-DR ($P = .008; r_s = -0.32$) or HLA-DR and CD38 ($P = .02; r_s = -0.28$) on CD8+ T cells.
Independence of robust HIV-2–specific IFN-γ immune responses with respect to immune activation. Chronic immune activation leads to increased T cell turnover and is thought to result in exhaustion of antigen-specific T cells. Robust Gag-specific IFN-γ T cell responses characterize controlled viremia in chronic HIV-2 infection [26]. To evaluate whether T cell activation has an impact on the magnitude of antigen-specific immune responses, the magnitude of HIV-2–specific IFN-γ responses was measured in the 64 HIV-2–positive patients and analyzed in relation to global levels of immune activation.

Because HLA-DR expression on CD4+ T cells was the most specific cellular marker of activation in this cohort, this marker was used to analyze the magnitude of HIV-2 Gag–specific IFN-γ responses in relation to immune activation (Figure 5A). No statistically significant relationship between cellular immune activation and the magnitude of antigen-specific immune responses was observed. Plasma β2-microglobulin showed no association with the magnitude of HIV-2–specific immune responses (Figure 5B).

DISCUSSION

Immunodeficiency in HIV infection is accompanied by a paradoxical immune activation that results in increased cell turnover, immune system exhaustion, and AIDS. The general contribution of lentiviral replication in the chronic phase of the infection is uncertain, because there is immune activation in the absence of HIV-1 viremia [17] and a lack of immune activation in the presence of high virus load in simian immunodeficiency virus infection [19]. The present study explored the association between systemic immune activation and disease parameters in patients with chronic HIV-2 infection. A unique strength of this cross-sectional study was the large number of HIV-2–infected patients who were part of a community cohort; thus, the natural spectrum of disease progression was reflected. This contrasts with clinical HIV-2 cohort studies in which the role of immune activation in disease progression has been examined [10]. The large cohort size in the present study facilitated the identification of differences between patients who had controlled infections and those who had high virus replication.

Patients who have HIV-2 infection with elevated viremia are at risk for CD4+ T cell depletion and AIDS-defining events [31]. For each logarithmic increase in virus load in HIV-2–infected patients, the rate of CD4+ T cell decrease is similar to that in HIV-1–positive patients [31]. Thus, the level of HIV-2 viremia strongly influences the progression to immunodeficiency. However, it is clear that not all HIV-2–positive patients respond to the infection in the same way. The present study demonstrates that immune activation in HIV-2–infected patients with a detectable virus load (≥100 copies/mL) is similar to that in HIV-1–infected patients, whereas patients with undetectable viremia have levels of immune activation that differ strongly from those of HIV-2–infected patients with high virus loads and that are indistinguishable from those of HIV-negative patients. The present study also demonstrates that the very strong relationship between virus load and immune activation is even further augmented in patients with high-level viremia. Furthermore, there is lack of a relationship between immune
activation and CD4+ T cell levels in patients with undetectable viremia and the appearance of this association in patients with even low-level virus replication (<1000 copies/mL). These findings support the hypothesis that HIV-2 viremia could contribute directly to global immune activation.

The level of expression of major histocompatibility complex (MHC) class II antigen (HLA-DR) on CD4+ T cells was the most accurate marker of cellular immune activation in relation to virus load in this cohort of patients with chronic HIV-2 infection. An association between increased HLA-DR expression on T cells and disease progression has been reported previously for HIV-2 [10, 12] and HIV-1 [22] infections. Thus, HLA-DR expression on CD4+ T cells could potentially be used to discriminate between HIV-2–positive patients with high and low virus loads in a setting where access to virus load assays is limited.

Gag-specific IFN-γ immune responses are strongly related to virus control in HIV-1 [34] and HIV-2 [26] infection, and there is a positive correlation between HIV-2 Gag–specific CD4+ T cells and CD4+ T cell activation [35]. It is possible that the ability of HIV-2 to activate T cells is due to the presentation of a greater amount of HIV-2 antigens [36]. However, in the HIV-2–positive patients included in the present study, no association was detected between the magnitude of the HIV-2–specific immune response and T cell activation. These data suggest that, in this community cohort, high antigen-specific IFN-γ secretion in low-level viremia [26] is not due to nonspecific T cell activation. They also suggest that the increased T cell turnover that accompanies high immune activation does not affect the frequency of HIV-2–specific T cells. IFN-γ, however, is not the only effector cytokine secreted by antigen-specific memory T cells. It is thus possible that other effector functions of multifunctional HIV-2–specific T cells [37] are affected by systemic immune exhaustion. The absence of a relationship between systemic immune activation and antigen-specific T cells also suggests that cellular immune responses do not have a significant contribution to overall immune activation in HIV-2 infection. During high-level viremia, it is possible that, rather than acting as antigens for antigen-specific T cells, HIV-2 proteins act nonspecifically to stimulate the innate immune system.

Systemic immune activation influences the function of antigen-specific T cells [1]. Continuous cell activation due to exposure to high virus levels in chronic infection leads to altered CD8+ T cell function and differentiation state, biasing these cells away from an effective cytolytic response and toward the production of deleterious inflammatory cytokines [38, 39]. The low immune activation in HIV-2–positive patients with low virus replication may prevent this shift in T cell function and phenotype in chronic infection. Despite the lack of association between immune activation and HIV-2–specific IFN-γ secretion, immune activation may influence the phenotype and function of HIV-2–specific lymphocytes. Analysis of antigen-specific CD8+ T cells with MHC class I tetramers would help to determine how systemic immune activation affects these parameters in HIV-2 infection.

In summary, we propose that HIV-2 replication is directly related to immune activation during the chronic phase of infection. Because antigen is the positive regulator of the immune system [40], antigen persistence at high levels can result in immunopathology. Therefore, in patients with detectable viremia and progressive disease, lowering the rate of HIV-2 replication by means of HAART, thereby reducing antigen levels, is likely to be an important intervention to prevent excessive turnover, differentiation, and functional exhaustion of T cells. Chronic HIV infection is characterized by immunodeficiency that is preceded by dramatic CD4+ T cell depletion. In HIV-2 infection, low virus replication results in lower immune activation, and as a consequence T cell turnover may be reduced. This would account for the maintenance of T cell function and the prevention of progression to immunodeficiency, a hallmark of HIV-2 infection.

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