The Effect of Acute Infectious Illnesses on Plasma Human Immunodeficiency Virus (HIV) Type 1 Load and the Expression of Serologic Markers of Immune Activation among HIV-Infected Adults

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The Journal of Infectious Diseases 1998; 178:1642±8

Received 11 February 1998; revised 28 July 1998.
Informed consent was obtained from all study participants; human experimentation guidelines of the US Department of Health and Human Services and of the Johns Hopkins University School of Medicine were followed. The protocol and consent forms were approved by the Johns Hopkins University Joint Committee on Clinical Investigation.
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Human immunodeficiency virus (HIV) infection is characterized by persistent viral replication and progressive immune dysfunction, leading to infections by a diverse range of microorganisms. Infections with common pathogens, such as Mycobacterium tuberculosis, Mycobacterium avium-intracellulare complex, herpes simplex virus, and Pneumocystis carinii, have been associated with significant, although transient, increases in plasma HIV RNA concentration in a subset of patients [1±8]. Similarly, systemic immune challenge with antigens, such as influenza vaccine, pneumococcal vaccine, and tetanus toxoid, may stimulate HIV replication and boost plasma virus burden [9±13]. While the clinical impact of this viral activation is uncertain, several studies have observed an increased mortality rate among persons with successfully treated intercurrent infections, such as M. tuberculosis [14, 15]. Infectious pathogens may provoke cellular activation that can stimulate HIV replication within HIV target cells, primarily CD4 T lymphocytes and monocytes/macrophages [2, 16]. Efficient replication of HIV in CD4 T cells is dependent on cellular activation. The activation of naïve CD4 T cells facilitates productive infection with HIV and thereby may increase plasma viremia [12]. In addition, proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), produced by activated monocytes/macrophages, can stimulate HIV replication by increasing nuclear factor-κB (NF-κB) binding to the HIV long terminal repeat region [17].

While CD4 T cell activation and proinflammatory cytokines are capable of up-regulating HIV expression in vitro, the in vivo situation is less clear [16, 18]. Serum levels of proinflammatory cytokines may be elevated in HIV-infected persons in the absence of coinfection, and serum concentrations of soluble (s) TNF receptor (R)-II have been correlated with HIV disease progression [19, 20]. Many bacterial and parasitic infections are powerful inducers of proinflammatory cytokine release both in vitro and in vivo, and all coinfections lead to antigenic exposure that triggers T cell activation. In this manner, coinfections may promote HIV expression. However, the in vivo role of proinflammatory cytokines and cellular immune activation in the regulation of HIV replication during acute infectious illnesses has not been well-characterized.

We undertook the current study to assess the impact of the development and treatment of acute infections on plasma HIV RNA concentrations and serum levels of cytokines and soluble markers of lymphocytic and monocytic activation, including TNF-α, sTNFR-I, sTNFR-II, interleukin-2 (IL-2), sIL-2R, IL-...
6, IL-10, sCD4, and sCD8, and to characterize the relationship between these cytokines and markers of lymphocyte or monocyte activation and the changes observed in plasma HIV load.

Methods

Study population and design. Subjects were prospectively recruited and followed at the Johns Hopkins Hospital AIDS Service, which serves a heterogeneous urban population. Inpatient admissions and outpatient visits were screened for eligible subjects from August 1996 to December 1996. Patients were eligible for the study if they were diagnosed with a treatable or self-limited acute infection and if they had had no alteration in antiretroviral medications for at least 4 weeks before study entry or were not taking antiretroviral therapy. Diagnosis and treatment of the acute illness was done by the primary clinician and reviewed by study investigators. Clinical evaluations and phlebotomy were done within 48 h of initiation of treatment of the acute infection and during follow-up visits 2 and 4 weeks after study entry.

Clinical status at follow-up was categorized as “improved” or “nonimproved.” Patients were classified as improved if they demonstrated objective evidence of resolution of the acute illness, including discharge from the hospital and the normalization of abnormal clinical and laboratory parameters, such as fever, tachypnea, tachycardia, hypotension, hypoxemia, and leukocytosis. Patients were categorized as nonimproved if they remained hospitalized, did not experience normalization of abnormal clinical and laboratory parameters, or were diagnosed with a new infectious illness during the follow-up period. The clinical status of each subject was classified by investigators without knowledge of the results of the virus load and immune marker assays. Subjects were questioned, and medical charts were reviewed to assess treatment compliance and interval changes in antiretroviral medications. Patients with alterations in antiretroviral medications were discontinued from the study at the time of the change.

Sample collection. Pre-illness HIV RNA quantification by reverse transcriptase–polymerase chain reaction (RT-PCR) was retrospectively obtained for a subset of 18 subjects. These plasma specimens had been previously collected during periods of clinical stability. The median time from baseline specimen collection to study entry was 61 days (range, 10–192). Nine patients were taking antiretroviral therapy at the time of the pre-illness sample collection and reported no change in their antiretroviral medications before study entry. The baseline specimens were separated by centrifugation at 400 g and frozen at −70°C within 4 h of specimen collection. All other subject samples were prospectively obtained within 48 h of diagnosis and at 2- and 4-week follow-up visits. The plasma from these specimens was separated within 6 h of collection by centrifugation at 400 g and stored at −70°C until assayed. All samples were collected in Vacutainer (Becton Dickinson, Baltimore) tubes containing EDTA, and plasma specimens for each subject were assayed simultaneously during the same freeze-thaw cycle.

Laboratory assays. Plasma HIV RNA copy number was determined by RT-PCR (Amplicor HIV Monitor Kit; Roche Diagnostic Systems, Branchburg, NJ) according to the manufacturer’s specifications. Commercial ELISAs were used, following the manufacturer’s instructions, to quantitate serum levels of TNF-α, s-TNFRI, and sTNFRII (Quantikine; R&D Systems, Minneapolis); IL-6, IL-10, IL-2, and IL-2R (Endogen, Woburn, MA); and sCD4 and sCD8 (T Cell Diagnostics, Woburn, MA). CD4 lymphocyte counts were determined at the Johns Hopkins Hospital clinical laboratory by use of standard flow cytometry.

Statistical analysis. Data were analyzed by use of SAS software (version 6.11; SAS Institute, Cary, NC) and Stata software (Intercooled Stata 5.0; Stata, College Park, TX). Intra-individual paired comparisons of HIV RNA and other laboratory markers were done by the nonparametric Wilcoxon signed rank test. The nonparametric Mann-Whitney U test was used to compare these values between different groups of subjects. The generalized estimating equation regression analysis was used to analyze changes in laboratory values where there were more than two measures over time. This method adjusts for repeated intra-individual measures during longitudinal analysis [21].

Results

Study population. Thirty-two HIV-infected adults (18 females and 14 males; 27 African-American and 5 Caucasian) were enrolled in the study. The median age was 36.5 years (range, 20–56), and the initial median CD4 cell count was 91.5/μm³ (range, 1–449). Eighteen subjects had CD4 cell counts <100/μm³. Twenty-six subjects had a diagnosis of AIDS by the 1993 CDC AIDS Surveillance Case Definition. Nineteen subjects were not receiving concurrent antiretroviral therapy, and 13 patients were taking antiretroviral medications. One subject was receiving an HIV-1 protease inhibitor in combination with other antiretroviral drugs.

Subjects were diagnosed with a variety of acute infections commonly seen among HIV-infected patients, including bacterial pneumonia (10 patients), P. carinii pneumonia (5), bacteremia (4), cellulitis (3), pulmonary aspergillosis (2), febrile viral syndrome (2), herpes zoster (1), sinusitis (1), Mycobacterium kansasii pneumonia (1), disseminated M. avium–intracellulare complex (1), Toxoplasma encephalitis (1), and cryptococcal meningitis (1). Eighteen of 32 enrolled subjects had baseline HIV RNA determinations done during periods of clinical stability before study participation. Twenty-eight subjects completed at least one follow-up evaluation, and 19 subjects completed two follow-up visits. Four subjects were lost to follow-up after study entry.

Plasma HIV RNA concentration during acute infection. Characteristics of the 18 patients with HIV RNA levels determined before, during, and after an acute infection are shown in table 1. The median pre-illness HIV RNA concentration was 108,442 copies/mL determined before study entry (median, 61 days; range, 10–191). During acute infection, the median plasma HIV load increase above pre-illness levels was 428,896 copies/mL (intraquartile range, 122,868–663,414), representing a median 7.8-fold (intraquartile range, 2.2–31.5) change (P = .001). Ten of 18 patients experienced a >4-fold increase in
plasma HIV RNA concentration. Subjects receiving concurrent antiretroviral therapy (n = 9) had a median plasma virus load increase of 495,386 copies/mL, while those not receiving antiretroviral medication (n = 9) exhibited a smaller median increase of 210,880 copies/mL; however, this difference was not statistically significant (P = .14). At the first follow-up visit (median, 15 days; range, 13–41), the median plasma HIV RNA concentration was 285,893 copies/mL, and the median decrease from HIV RNA levels at acute illness was 1.5-fold (intraquartile range, 1.1–2.2) increase above levels at the time of diagnosis (figure 1). Four of these 5 subjects had increases in plasma virus load. However, even among subjects with clinical improvement, convalescent HIV RNA levels tended to be higher than pre-illness levels, although this difference did not attain statistical significance (P = .08). Four patients exhibited a >4-fold reduction in plasma HIV RNA.

**Impact of clinical status on plasma HIV RNA levels during convalescence.** At the time of acute illness, 32 subjects had a median plasma HIV load of 429,393 copies/mL. Of these patients, 28 were evaluated at a 2-week follow-up visit (median, 15 days after entry; range, 10–48). Twenty subjects had clinical improvement, while 8 remained ill or experienced a secondary infection. Patients with clinical improvement had a median decrease in plasma HIV RNA level of 103,862 copies/mL (intraquartile range, –133,366 to –2906), representing a 1.5-fold (intraquartile range, 1.0–3.2) reduction from the time of acute illness (P = .01). Fifteen of these 20 subjects had decreases in plasma virus load. The 8 subjects without clinical improvement had a median decrease in plasma HIV load of 10,862 copies/mL (intraquartile range, –27,194 to 82,636), representing no significant change from levels during acute illness (P = .57).

At the second follow-up evaluation (median, 30 days after entry; range, 25–92), 14 of 19 subjects had evidence of clinical improvement, while 5 had persistent illness or had developed a secondary infection. For patients with clinical improvement, the median decrease in plasma virus load from acute illness was 196,024 copies/mL (intraquartile range, –296,402 to –44,353), representing a 2.3-fold (intraquartile range, 1.4–2.8) reduction in plasma HIV RNA (P = .025). Eleven of the 14 subjects with clinical improvement demonstrated decreases in HIV RNA. In contrast, the 5 subjects without clinical improvement experienced continued elevation in plasma viremia, with a median increase in plasma HIV RNA of 54,156 copies/mL (intraquartile range, 20,773–221,223), reflecting a 1.5-fold (intraquartile range, 1.1–2.2) increase above levels at the time of diagnosis (figure 1). Four of these 5 subjects had increases in plasma virus load. However, even among subjects with clinical improvement, convalescent HIV RNA levels tended to be higher than pre-illness levels, although this difference did not attain statistical significance (P = .09 at 2 weeks and P = .28 at 4 weeks).

**Cytokines and soluble immune activation markers during acute infection.** TNF-α, sTNFR-I, and sTNFR-II levels are shown in table 2. Levels of these markers were not significantly different between baseline assessment and acute illness or between acute illness and the 4-week evaluation were lower than at the time of acute illness among subjects with clinical improvement (P = .05); no significant change was noted for subjects without clinical recovery. Stratification by patients’ clinical status at 4 weeks revealed a trend toward significant differences in the change in TNF-α (P = .026) and sTNFR-II (P = .043) levels from those during acute illness. Clinical improvement was associated with decreasing levels of TNF-α and sTNFR-II; conversely, increasing levels were seen among subjects with persistent illness.
Levels of IL-6, IL-10, IL-2, sIL-2R, sCD4, and sCD8 are shown in Table 3. Median levels of these markers did not vary significantly over the course of the infectious illness, and stratification by CD4 T cell count at baseline and clinical status at the time of follow-up revealed no significant effect on levels of these markers (data not shown).

**Correlates of virus load change.** The change in plasma HIV RNA level over the course of illness was analyzed by use of the generalized estimating equation regression model. Change in plasma HIV RNA levels correlated significantly with simultaneous changes in levels of sTNFR-I (P = .001), sTNFR-II (P = .005), and sIL-2R (P = .002). Change in HIV RNA level was not associated with change in plasma levels of TNF-α, IL-2, IL-6, IL-10, or sCD4 or sCD8 T cell markers.

**Differences between bacterial and P. carinii pneumonia.** Patients with P. carinii pneumonia demonstrated a trend toward lower CD4 cell counts and higher plasma HIV RNA levels than those parameters in subjects with bacterial pneumonia, although these differences were not significant. At pre-illness measurements, subjects with P. carinii pneumonia had higher levels of TNFRI (P = .03) and IL-2R (P = .03), although data were available for only 7 patients (P. carinii pneumonia, 3; bacterial pneumonia, 4). At the time of acute illness, patients with P. carinii pneumonia tended to have higher levels of TNF-α, sTNFR-I, sTNFR-II, IL-10, IL-2, sIL-2R, and IL-6 than did those with bacterial pneumonia (table 4).

**Discussion**

The data demonstrate that common acute infectious illnesses may be associated with significant increases in HIV replication. During acute illness, 10 of 18 subjects with pre-illness specimens had a >4-fold increase in plasma HIV load, indicating an increase above that attributable to temporal or assay-related variability [22]. Among subjects experiencing clinical recovery, such HIV load increases were generally transient, and most subjects had a return of plasma HIV RNA levels toward baseline levels within 2–4 weeks of treatment. However, the plasma HIV load did not return to pre-illness levels in all subjects, despite the clinical resolution of their illness.

These data are consistent with prior studies of plasma HIV RNA levels during acute infectious illnesses. Bush et al. [5] retrospectively evaluated plasma virus load changes among 13 subjects with bacterial pneumonia. All subjects had increases in plasma viremia, which returned toward baseline levels after a median of 2.4 months of follow-up. Similarly, Bush et al. [3] examined plasma virus load and neopterin levels during episodes of P. carinii pneumonia. Nine of 10 subjects had reversible increases in plasma virus burden, while levels of neopterin, a marker of monocyte or lymphocyte activation, were stable. Cooper et al. [7] reported a 1-log decrease in plasma HIV RNA levels among 4 of 5 children treated for disseminated M. avium-intracellulare complex infection. Mole et al. [1] found transient increases in plasma virus load and intracellular HIV gag mRNA concentration among persons with herpes simplex virus outbreaks.

In contrast to these studies, the prospective component of our study allowed for the careful assessment of the presence and duration of virus load elevation in subjects with clinical resolution of illness, as well as the impact of ongoing clinical infection on plasma HIV load. In subjects with clinical recovery,

### Table 2. Baseline and change in tumor necrosis factor-α (TNF-α) and soluble TNF receptor (sTNFR)-I and -II levels during illness.

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 12)</th>
<th>Change, baseline to acute (n = 12)</th>
<th>Acute (n = 32)</th>
<th>Clinical status</th>
<th>Change, acute to week 2 (n = 27)</th>
<th>Change, acute to week 4 (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α (pg/mL)</td>
<td>9.32 (6.12–17.65)</td>
<td>0.69 (−5.81 to 1.5)</td>
<td>8.84 (6.61–17.60)</td>
<td>I</td>
<td>−0.02 (−2.54 to 2.42)</td>
<td>−1.52 (−2.85 to 0.32)</td>
</tr>
<tr>
<td>sTNFR-I (pg/mL)</td>
<td>1123 (712.3–3218)</td>
<td>−23.75 (−965.5 to 138.3)</td>
<td>1038.5 (759.65–2133.5)</td>
<td>I</td>
<td>20.0 (−106.7 to 307.3)</td>
<td>−260.90 (−752.3 to 23.0)</td>
</tr>
<tr>
<td>sTNFR-II (pg/mL)</td>
<td>6734.5 (4364.5–11,186.5)</td>
<td>149.5 (−1620 to 744.5)</td>
<td>6337.5 (3956.5–8306.5)</td>
<td>I</td>
<td>−46.0 (−900 to 1914)</td>
<td>−345.9 (−1318 to 0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NI</td>
<td>194.00 (−492 to 1055)</td>
<td>929.00 (151–994)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are median (interquartile range).

* Clinical status category: I = improved, NI = non-improved.

* Week 2: I = 20 subjects, NI = 7 subjects.

* Week 4: I = 13 subjects, NI = 5 subjects.

* P <.05 for change in TNF-α levels and P <.05 for change in sTNFR-II levels for improved vs. nonimproved subjects by Mann-Whitney test.
plasma virus load returned toward baseline levels over a 4-week period. However, patients experiencing progressive or recurrent illness demonstrated persistent elevation of plasma HIV RNA levels, and some experienced further increases in plasma virus burden.

The persistent up-regulation of viral replication among patients nonresponsive to treatment suggests that chronic or recurrent infectious illnesses may contribute to sustained, high levels of viremia and may, thereby, accelerate HIV disease progression. While the clinical significance of the plasma virus load increases observed in our study is not known, several studies suggest that concurrent infections are associated with HIV disease progression. Whalen et al. [15] demonstrated that active *M. tuberculosis* infection was associated with decreased survival among HIV-infected patients, after controlling for CD4 cell count, antiretroviral therapy, and previous opportunistic infection. Similarly, Chaisson et al. [14] reported that despite its successful treatment, the development of an opportunistic infection was an independent risk factor for death among an urban patient cohort. Alcabes et al. [23] found that pyogenic bacterial infections were associated with an accelerated rate of CD4 cell decline. Thus, immune activation–driven HIV replication may, in part, explain the aggressive course of HIV infection in some persons and may provide a likely mechanism for the postulated more rapid course of immunologic decline among HIV-infected persons in sub-Saharan Africa, where coinfections are common and often continuous [24].

While we have demonstrated the virologic impact of acute infectious illnesses among our study population, these findings may not be generalizable to other populations, such as persons with preserved immune function or those receiving highly effective antiretroviral therapy. Mole et al. [1] found that the increase in plasma HIV RNA was greater among herpes simplex virus–infected subjects not taking concurrent antiretroviral agents, suggesting that antiretroviral therapy may prevent HIV up-regulation during periods of immune activation. Al-Harthi et al. [25] demonstrated the ability of an HIV-1 protease inhibitor (ritonavir) to block TNF-α, IL-6, and IL-1β–induced HIV replication in vitro. While we found a trend toward smaller increases in virus load during acute infectious illness among subjects taking antiretroviral therapy, our study is limited by the small number of subjects receiving effective antiretroviral therapy and by the relatively high proportion of subjects with advanced HIV disease. Further investigations of the impact of acute intercurrent infections among HIV-infected persons with preserved CD4 T cell counts and effective pharmacologic virus suppression are warranted.

Our study extends the findings of previous investigations by providing evidence of mechanisms that may be responsible for infection-related changes in viral replication. We found that changes in plasma HIV RNA concentration correlate with simultaneous changes in serum sTNFR-I, sTNFR-II, and sIL-2R levels. The former two likely represent an integration of previous TNF-α release, although they may also be induced by

### Table 3. Levels of activation markers before, during, and after illness.

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 12)</th>
<th>Acute (n = 32)</th>
<th>2-week follow-up (n = 28)</th>
<th>4-week follow-up (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2, pg/mL</td>
<td>44.76 (40.45–57.14)</td>
<td>57.35 (45.68–72.51)</td>
<td>60.20 (50.80–70.67)</td>
<td>68.27 (48.41–81.61)</td>
</tr>
<tr>
<td>IL-2R, pg/mL</td>
<td>976.72 (658.69–1746.09)</td>
<td>1155.95 (641.73–1736.47)</td>
<td>999.54 (669.38–1386.66)</td>
<td>1060.85 (714.80–1250.33)</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>1.53 (0.55–3.76)</td>
<td>4.61 (0.61–16.50)</td>
<td>2.39 (0.49–8.69)</td>
<td>1.02 (0.6–6.15)</td>
</tr>
<tr>
<td>IL-10, pg/mL</td>
<td>6.32 (0.40–30.34)</td>
<td>6.89 (0.43–47.9)</td>
<td>6.88 (0.44–46.16)</td>
<td>22.42 (0.56–50.65)</td>
</tr>
<tr>
<td>sCD4, U/mL</td>
<td>17.27 (13.02–22.92)</td>
<td>16.21 (13.28–23.93)</td>
<td>16.52 (13.05–22.01)</td>
<td>17.96 (13.90–22.06)</td>
</tr>
<tr>
<td>sCD8, U/mL</td>
<td>300.73 (197.45–422.61)</td>
<td>247.64 (145.71–321.10)</td>
<td>193.62 (108.76–272.34)</td>
<td>314.36 (193.62–314.37)</td>
</tr>
</tbody>
</table>

NOTE. Data are median (intraquartile range). IL, interleukin; R, receptor; s, soluble.

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 5)</th>
<th>Acute (n = 10)</th>
<th>2-week follow-up (n = 5)</th>
<th>4-week follow-up (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cell count/mm³</td>
<td>62 (11–64)</td>
<td>195 (28–335)</td>
<td></td>
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</tr>
<tr>
<td>HIV RNA, copies/mL</td>
<td>603.470 (418.051–1457.455)</td>
<td>492.131 (281.059–504.550)</td>
<td></td>
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</tr>
<tr>
<td>TNF-α, pg/mL</td>
<td>10.06 (6.07–13.69)</td>
<td>8.57 (6.88–9.06)</td>
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</tr>
<tr>
<td>sTNFR-I, pg/mL</td>
<td>2102 (1512–2165)</td>
<td>854.5 (505.2–1260)</td>
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</tr>
<tr>
<td>sTNFR-II, pg/mL</td>
<td>8694 (6389–11,079)</td>
<td>4361 (3793–5541)</td>
<td></td>
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<tr>
<td>IL-2, pg/mL</td>
<td>74.43 (72.72–90.93)</td>
<td>49.85 (39.53–56.17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sIL-2R, pg/mL</td>
<td>1320.88 (1128.3–1467.7)</td>
<td>641.73 (413.34–899.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>28.75 (5.2–29.92)</td>
<td>0.27 (0–4.01)</td>
<td></td>
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</tr>
<tr>
<td>IL-10, pg/mL</td>
<td>45.19 (36.80–58.1)</td>
<td>4.10 (0–32.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCD4, U/mL</td>
<td>17.62 (15.06–18.92)</td>
<td>14.02 (12.81–16.37)</td>
<td></td>
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</tr>
<tr>
<td>sCD8, U/mL</td>
<td>159.0 (143.3–315.4)</td>
<td>261.4 (163.9–315.1)</td>
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</tr>
</tbody>
</table>

NOTE. Data are median (intraquartile range). TNF, tumor necrosis factor; s, soluble; R, receptor; IL, interleukin.

* Mann-Whitney test.
other cytokines, such as IL-6 and IL-2, whereas sIL-2R levels can correlate with both macrophage and lymphocyte activation.

However, the data do not exclude the possibility that other cytokines influence HIV replication during acute infectious illnesses. Cytokines typically have short serum half-lives; consequently, the measured serum concentrations of these markers may not correlate temporally with their immunologic or virologic effect. In addition, different infectious processes may stimulate distinct immune response patterns, depending on their chronicity. We found that patients with P. carinii pneumonia, a subacute process, had higher levels of proinflammatory cytokines than did those with acute bacterial pneumonia at the time of diagnosis. Thus, while not definitive, the data suggest that host immune activation, particularly TNF-α and its soluble receptors, may be important in the in vivo regulation of HIV expression during acute infectious illness.

TNF-α has been shown to stimulate HIV expression in peripheral blood mononuclear cells and can stimulate HIV replication in vitro by activation of the cellular transcription factor NF-κB [17, 26]. TNF-α interacts with responding cells via two membrane-bound receptors, TNFR-I (55 kDa) and TNFR-II (75 kDa), which are expressed on multiple cell types [27–29]. The extracellular domains of these receptor molecules are released after binding by TNF-α and are easily measured in plasma, whereas TNF-α is rapidly cleared from circulation and may be difficult to quantitate in clinical specimens. Consequently, serum levels of sTNFRs may more accurately reflect in vivo activity of TNF-α [30–32].

Serum levels of sTNFR-II may be elevated among HIV-infected persons, and levels correlate with HIV disease stage and disease progression [18, 19, 33–35]. Bilello et al. [35] found that serum sTNFR-II strongly correlated with HIV RNA copy number among stable HIV-infected persons. Godfried et al. [20] demonstrated that serum sTNFR-II levels were predictive of subsequent progression to AIDS. Recently, Stein et al. [19] found that sTNFR-II levels predicted the rapid progression of HIV disease and death and may increase the predictive value of HIV RNA determinations among participants in the Multicenter AIDS Cohort Study. Finally, levels of sTNFR-II appear to decline in response to antiretroviral therapy, suggesting a relationship between immune activation, HIV replication, and antiviral efficacy [36, 37].

In conclusion, our data suggest a link between in vivo immune activation and the regulation of HIV expression during acute infectious illnesses. Further studies are needed to define the role of individual cytokines and to determine the clinical and virologic significance of infection-related HIV expression, particularly among patients receiving highly effective antiretroviral therapy. Nonetheless, our findings underscore the importance of the prevention and prompt treatment of intercurrent infections among HIV-infected persons and emphasize the caution needed in the clinical interpretation of plasma virus load measurements during periods of acute infection.

References


