Correlation between Human Immunodeficiency Virus Type 1 RNA Levels in the Female Genital Tract and Immune Activation Associated with Ulceration of the Cervix

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To address the hypothesis that local immune activation resulting from genital ulceration enhances human immunodeficiency virus type 1 (HIV-1) replication and shedding into the genital tract, paired plasma and cervicovaginal lavage (CVL) samples were obtained from 12 HIV-infected women before and after treatment of cervical intraepithelial lesions. Two weeks after treatment, inflammation and ulceration of the cervix were accompanied by major increases in mean concentrations of HIV-1 RNA (200-fold), tumor necrosis factor-α, interleukin 6, and soluble markers shed by activated lymphocytes and macrophages (sCD25 and sCD14, respectively) in CVL samples (P<.01 for each), but not plasma. Strong temporal and quantitative correlations were observed between concentrations of immunological markers and HIV-1 load in this compartment during a 10-week follow-up. Furthermore, in the presence of genital ulceration, HIV-1 in CVL samples was more readily captured by antibodies directed against virion-associated HLA-DR, a marker of host-cell activation, compared with virus in plasma. We suggest that local immune activation increases HIV-1 load in genital secretions, potentially increasing the risk of HIV-1 transmission.

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Immune cell activation is important in the life cycle and pathogenesis of human immunodeficiency virus (HIV) type 1 (HIV-1) infection in humans [1, 2]. Activation of mononuclear leukocytes, the principal targets of HIV infection, promotes virus entry, provirus integration into host cell DNA, and viral RNA transcription, thereby accelerating the release of mature virions [1, 2]. Thus, HIV-1 replication in the host cell is influenced not only by viral regulatory proteins but also by a complex cascade of host proinflammatory and immunoregulatory cytokines [3, 4]. Modulation of this cytokine network by other proinflammatory stimuli may therefore influence HIV-1 replication. For example, opportunistic infections [5, 6] and immunizations [7, 8] are associated with substantial increases in plasma HIV-1 RNA load and may lead to differential expression of viral quasispecies in plasma [9]. Furthermore, inflammatory stimuli within different anatomic compartments affect the biology of HIV-1 at those sites [10–12].

Little is known about the influence of immune activation on HIV-1 replication in the female genital tract. However, studies have demonstrated a clear association between sexually transmitted diseases (STDs) and increased risk of sexual transmission of HIV-1, even after adjustment for sexual behavior [13, 14]. The association with genital ulcer disease is particularly strong [15–17]. It has been hypothesized that these associations are due to loss of integrity of the genital epithelium, enhanced shedding of HIV-1 in genital secretions, and exposure of highly susceptible inflammatory cells to HIV-1 [13]. By these means, STDs, especially genital ulcer disease, may increase the risk of virus transmission by HIV-infected people and also heighten the susceptibility of HIV-negative subjects to infection.

Several studies have examined the effect of STDs on shedding of HIV-1 into the genital tract. HIV-1 detection in semen is increased in men with urethritis and gonorrhea [10, 18], and treatment of these infections lowers seminal plasma HIV-1 load.
Similarly, in women, cervical inflammation and increased vaginal discharge lead to increased detection of HIV-1 proviral DNA in the genital tract [19–21]. More specifically, Neisseria gonorrhoeae and Chlamydia trachomatis infections enhance detection of HIV-1 RNA in cervicovaginal secretions, an effect that decreases after successful treatment of the STDs [22]. Furthermore, vaginal HIV-1 RNA load is significantly increased in patients with iatrogenic ulceration of the cervix [23].

To our knowledge, the pathophysiological mechanisms by which inflammatory processes increase HIV-1 expression in the genital tract have not yet been reported. Proinflammatory cytokines are detectable in normal genital tract secretions of women who are not infected with HIV [24], but little is known regarding modulation of cytokine expression by inflammatory lesions and how changes in levels of cytokines affect local HIV-1 replication. We hypothesized that release of proinflammatory cytokines associated with ulceration in the female genital tract increases cervicovaginal HIV-1 load. In this study, we measured HIV-1 load and parameters of immune activation in paired blood and cervicovaginal lavage (CVL) samples from a group of HIV-infected women with iatrogenic ulceration and inflammation of the cervix.

Materials and Methods

Study population. Twelve HIV-1–infected women with biopsy-confirmed squamous intraepithelial lesions of the cervix were enrolled. Six were Hispanic and 6 were black, and their mean age (± SD) was 35.5 ± 8.2 years. Before treatment of cervical dysplasia, their mean preoperative CD4+ blood lymphocyte count was 245 × 10^6 ± 171 × 10^6 cells/L. None of the women was receiving antiretroviral drugs, and none had clinical or microbiological evidence of cervicitis or genital infection. Cervical lesions included both high-grade squamous intraepithelial lesions (cervical intraepithelial neoplasia grades 2–3; n = 6) and low-grade squamous intraepithelial lesions (cervical intraepithelial neoplasia grade 1; n = 6). All patients were participants in a clinical trial that was comparing established treatments for these lesions. The treatments included the loop electrosurgical excision procedure, a procedure by which lesions are removed with a thin wire electrosurgical electrode (n = 5); cold-knife cone biopsies (n = 4); and cryosurgery, a procedure by which lesions are removed with a cryoprobe, using nitrous oxide gas as a coolant (n = 3).

Samples. Gynecological examinations were performed before treatment and at 2 and 4 weeks after treatment in all subjects. For 9 women, an additional examination was performed after a mean of 10.5 weeks (range, 8–14 weeks). Each time, the appearance of the cervix was observed, and a CVL sample was obtained by directing a stream of 10 mL of PBS at the cervix and collecting the fluid pooling in the posterior fornix. Citrated venous plasma samples were obtained at the same time. Cells within CVL samples were removed by centrifugation, and supernatants and plasma were stored at −80°C.

Measurement of HIV-1 load and markers of immune activation. Cell-free HIV-1 RNA was measured in CVL and plasma samples, as described elsewhere [25]. In brief, virus was pelleted by ultracentrifugation. RNA was then extracted with guanidinium isothiocyanate and quantified by a quantitative-competitive polymerase chain reaction (PCR) assay. The lowest quantifiable HIV-1 load was 100 HIV-1 RNA copies/mL. Plasma and CVL concentrations of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were measured by commercially available ELISAs (R&D Systems, Minneapolis). Plasma and CVL concentrations of soluble IL-2 receptor (sCD25) and soluble CD14 (sCD14)—receptors shed by activated lymphocytes and macrophages, respectively—were measured by ELISA (R&D Systems) and enzyme immunoassays (EASIA; Medgenix, Fleurus, Belgium), respectively.

Measurement of HLA-DR incorporation in the HIV-1 envelope. Incorporation of the cellular immune activation marker HLA-DR into the HIV-1 envelope was assessed with an immunomagnetic viral capture technique, as described elsewhere [26, 27]. Plasma and CVL samples with adequate HIV-1 load to permit analysis were studied. This involved the following steps.

Viral capture. HIV-1 in both plasma and CVL samples was partially purified to remove anti-HIV antibodies and other inhibitory proteins. Samples were ultracentrifuged, and the viral pellet was resuspended in PBS. Virus was then salt treated by mixing with sodium chloride (0.5 M final concentration) at 37°C for 1 h and purified by passage through Microspin S-400 HR Sephacryl columns (Pharmacia Biotech, Piscataway, NJ).

Viral capture. Sheep anti-mouse IgG magnetic beads (Dynal, Great Neck, NY) were conjugated with anti-CD44 (positive control), anti–HLA-DR, or anti–IL-6 (negative control) monoclonal antibodies (0.5 μg antibody per 1.6 × 10^8 beads) by rotation at 4°C for 1.5 h. Equal inputs of purified virions (2 × 10^4 virions) were incubated with each of the antibody-conjugated beads on a rotator at 4°C for 4 h in the presence of 5% normal human serum. Unbound virus was washed from the beads with PBS. Virus specifically captured by the beads was lysed, and the HIV-1 RNA was quantified by the Amplicor HIV-1 monitor test (Roche Diagnostic Systems, Branchburg, NJ). The relative amount of virus bound specifically to the anti-CD44 and anti–HLA-DR beads was calculated by subtracting the amount bound to the negative control beads.

Statistical analysis. Prism version 2.0 software (GraphPad Software, San Diego) was used for the analysis. HIV-1 loads and markers of immune activation were normally distributed, and parametric statistical tests were used. Analysis of changes in these variables between 2 times was made by t tests. Pearson’s correlation coefficients were calculated to assess the correlation between changes in HIV-1 RNA load and concentrations of cytokines. Statistical significance was defined as P < .05.

Results

Effect of treatment of cervical dysplasia on HIV-1 load. HIV-1 RNA levels were quantifiable in pretreatment plasma samples from all 12 women; the mean HIV-1 load was 4.45 ± 0.89 log10 RNA copies/mL (range, 3.96–5.32). HIV-1 was also detectable in 9 pretreatment CVL samples and quantifiable in 7; the mean HIV-1 load was 2.22 ± 1.08 log10 RNA copies/mL (range, undetectable–3.82). Although the mean HIV-1 RNA load in plasma did not change significantly after treatment of the cervical lesions (figure 1), the mean HIV-1 load in...
CVL samples increased 200-fold (mean rise, 2.3 ± 1.0 log₁₀ HIV RNA copies/mL; \( P < .001 \)) 2 weeks after treatment. The increase in virus load in CVL samples was seen in all 12 patients and occurred at the same time that genital inflammation and ulceration were observed. The magnitude of increase was independent of the treatment modality used. At 4 weeks after treatment, mean CVL HIV-1 RNA load remained significantly elevated above the pretreatment levels but decreased to below baseline after 10 weeks (figure 1).

Effect of treatment of cervical dysplasia on concentrations of TNF-α and IL-6. We proceeded to investigate whether the cervical inflammation and ulceration were associated with changes in concentrations of the proinflammatory cytokines TNF-α and IL-6. Before treatment, TNF-α was detectable (>0.5 pg/mL) in plasma at low levels in all subjects (mean, 7.4 pg/mL; SD, 7.4) and in CVL samples of 8 women (mean = 1.7 pg/mL; SD = 1.8). Whereas mean levels of TNF-α remained unchanged in plasma following treatment (figure 2), the mean TNF-α concentration in CVL samples collected 2 weeks after treatment increased 45-fold (76.1 ± 46.1 vs. 1.7 ± 1.8 pg/mL; \( P < .01 \)). The mean TNF-α concentration in CVL samples remained elevated above pretreatment levels at 4 weeks after treatment but returned to baseline levels after 10 weeks (figure 2).

Before treatment, IL-6 was not detectable (<3.1 pg/mL) in plasma samples but was measurable in CVL samples from 7 women (mean, 19.2 pg/mL; SD, 27.9). After treatment, IL-6 remained undetectable in plasma (figure 2). However, 2 weeks after treatment, similar to the changes in TNF-α, the mean concentration of IL-6 in CVL samples increased 68-fold (1299 ± 888 pg/mL; \( P < .001 \); figure 2). The mean IL-6 level decreased between 2 and 4 weeks after treatment but returned to the baseline value after 10 weeks.

The magnitude of the changes in concentrations of both TNF-α and IL-6 in CVL samples was independent of the treatment modality used in the treatment of cervical dysplasia. This correlated with the observation that there was also no macroscopic difference in the degree of inflammation associated with the 3 methods of treatment.

Effect of treatment on macrophage and lymphocyte pools in the genital tract. To determine whether the increased concentrations of proinflammatory cytokines in the genital tract that occurred after the treatment of cervical lesions were associated with local activation of macrophage and lymphocyte cellular pools, we measured levels of sCD25 and sCD14, soluble markers shed by activated lymphocytes and macrophages, respectively. The mean pretreatment concentration of sCD25 was 1424 ± 774.1 pg/mL in plasma and 32.4 ± 11.0 pg/mL in CVL samples. sCD14 was present in mean pretreatment concentrations of 4.2 ± 1.5 ng/mL in plasma and 18.4 ± 8.8 pg/mL in CVL samples. Concentrations of neither marker increased in plasma following treatment (figure 3). However, similar to the increases in TNF-α and IL-6, mean concentrations of both sCD25 and sCD14 increased significantly in CVL samples at 2 and 4 weeks after treatment (figure 3).

Correlation between changes in immune markers and HIV-1 load in CVL. After treatment, the change in mean concentrations of cytokines (TNF-α and IL-6), soluble cellular activation markers (sCD14 and sCD25), and HIV-1 RNA load occurred contemporaneously in genital secretions, whereas the concentrations in plasma remained unchanged (figures 1 and 2). At 2 weeks after treatment, the increases in concentrations of TNF-α, IL-6, and sCD25 in CVL samples were strongly correlated with the increase in HIV-1 loads in lavages at that time (table 1). Also, changes in mean concentrations of immune markers and of HIV-1 RNA in lavages were strongly correlated during the total follow-up period (table 2), indicating a strong temporal association.

**Table 1.** Correlations between changes from pretreatment concentrations of immune markers (U/mL) and human immunodeficiency virus type 1 RNA load (log₁₀ HIV RNA copies/mL) in cervicovaginal lavage samples 2 weeks after treatment.

<table>
<thead>
<tr>
<th>Immune marker</th>
<th>Pearson’s correlation coefficient, ( r )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>0.62</td>
<td>0.05</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.69</td>
<td>0.01</td>
</tr>
<tr>
<td>sCD25</td>
<td>0.68</td>
<td>0.01</td>
</tr>
<tr>
<td>sCD14</td>
<td>0.44</td>
<td>0.15</td>
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**Figure 1.** Changes in mean (± SE) human immunodeficiency virus type 1 (HIV-1) RNA loads (log₁₀ RNA copies/mL) in plasma and cervicovaginal lavage (CVL) samples following treatment of cervical dysplasia in 12 HIV-infected women. Results are expressed as change from mean pretreatment values. Mean HIV-1 RNA load in plasma did not change significantly at 2 and 4 weeks after treatment, compared with the pretreatment level. In contrast, a mean increase of 2.3 log₁₀ HIV-1 RNA copies/mL (\( P < .001 \)) in CVL samples was observed at 2 weeks after treatment, and this increase was 1.4 log₁₀ above the mean pretreatment level at 4 weeks (\( P = .01 \)).
Figure 2. Changes in mean (± SE) concentrations of tumor necrosis factor-α (TNF-α; top) and interleukin-6 (IL-6; bottom) in plasma and cervicovaginal lavage (CVL) samples following treatment of cervical dysplasia in 12 human immunodeficiency virus-infected women. Results are expressed as change from mean pretreatment levels. Mean TNF-α and IL-6 concentrations remained unchanged in plasma. However, mean concentrations of both cytokines increased markedly in CVL samples 2 weeks after treatment (for TNF-α; for IL-6) and were still elevated at 4 weeks, compared with pretreatment levels (P = .09 for TNF-α; P = .15 for IL-6).

creations was derived from locally activated cells, we assessed incorporation of HLA-DR in the HIV-1 envelope. HIV-1 acquires host cell–surface proteins as it buds from host cells [28] and in this way acquires an envelope phenotype that reflects that of the host cell [29]. We used an immunomagnetic capture technique to analyze virus in paired plasma and CVL samples from 3 women 2 weeks after treatment. The mean ratio of HIV-1 captured from plasma and CVL was 1.0 : 1.1 when we used antibodies to CD44 (a cell-surface antigen constitutively expressed by host cells). In marked contrast, when we used antibodies to HLA-DR, the mean ratio of HIV-1 captured from plasma and CVL samples was 1.0 : 7.6 (figure 4).

We previously found that ~20% of HIV-1 stock virus derived in vitro from either highly activated (by use of phytohemagglutinin) peripheral blood lymphocytes or highly activated macrophages can be captured with antibodies directed against HLA-DR (authors’ unpublished data). The mean proportion of virus captured from CVL samples was similar to this (19.0% ± 8.0%), compared with only 2.5% ± 1.0% of virus in plasma. Analysis of these data suggests that the increase in virus load in genital secretions was derived from highly activated cells localized in the genital tract.

Discussion

In this study, we found that concentrations of the proinflammatory cytokines TNF-α and IL-6 increased in the genital secretions of women who developed inflammation and ulceration of the cervix following treatment of local dysplasia. Elevated levels of soluble markers of macrophage and lymphocyte activation accompanied the cytokine response, and these increases in indicators of immune activation correlated strongly with increases in HIV-1 load in genital secretions. This study suggests that immune activation may represent an important pathophysiological mechanism whereby genital ulcers result in enhanced HIV-1 replication in the genital tract and potentially increase the risk of sexual transmission of HIV-1.

We previously reported that increases in HIV-1 load in female genital tract secretions occur following treatment of cervical lesions [23]. In our initial study, assessment of blood contamination of CVL samples and genotypic comparison of HIV-1 quasispecies in blood and CVL samples demonstrated that the increases in HIV-1 load were attributable to enhanced local HIV-1 production in the genital tract rather than blood contamination or plasma transudation [23]. In the patients included in this study, a 200-fold (2.3 log10) increase in genital tract HIV-1 RNA concentrations occurred 2 weeks after treatment, and HIV-1 load remained significantly elevated above pretreatment levels even after 4 weeks (figure 1). These data suggest that cervical ulceration and inflammation are potent and sustained stimuli that enhance local HIV-1 replication.

The host inflammatory response is orchestrated by a complex cascade of proinflammatory and immunoregulatory cytokines. However, TNF-α and IL-6 play important roles in the host response to infection and tissue injury [30, 31] and are also key modulators of HIV-1 replication [3, 4]. TNF-α increases HIV-1 load, and IL-6 increases the expression of co-stimulatory molecules on activated lymphocytes, thereby enhancing HIV-1 replication.

Table 2. Correlations between changes in mean human immunodeficiency virus type 1 load (log10 HIV RNA copies/mL) and mean concentrations of immune markers (U/mL) in cervicovaginal lavage samples from pretreatment levels through follow-up.

<table>
<thead>
<tr>
<th>Immune marker</th>
<th>Pearson’s correlation coefficient, r</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>.96</td>
<td>04</td>
</tr>
<tr>
<td>IL-6</td>
<td>.97</td>
<td>03</td>
</tr>
<tr>
<td>sCD25</td>
<td>.99</td>
<td>01</td>
</tr>
<tr>
<td>sCD14</td>
<td>.92</td>
<td>08</td>
</tr>
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NOTE. TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; sCD25, soluble marker shed by activated lymphocytes; sCD14, soluble marker shed by activated macrophages.

We previously found that ~20% of HIV-1 stock virus derived in vitro from either highly activated (by use of phytohemagglutinin) peripheral blood lymphocytes or highly activated macrophages can be captured with antibodies directed against HLA-DR (authors’ unpublished data). The mean proportion of virus captured from CVL samples was similar to this (19.0% ± 8.0%), compared with only 2.5% ± 1.0% of virus in plasma. Analysis of these data suggests that the increase in virus load in genital secretions was derived from highly activated cells localized in the genital tract.
Figure 3. Changes in mean concentrations of soluble markers shed by activated lymphocytes (sCD25) and macrophages (sCD14) in plasma and cervicovaginal lavage (CVL) samples following treatment of cervical lesions. Results are expressed as fold change from mean pretreatment values. Two weeks after treatment, mean sCD25 concentrations had increased 7.2-fold in CVL samples ($P < .001$) and were still elevated at 4 weeks ($P = .06$). Similarly, mean concentrations of sCD14 in CVL samples had increased 4.8-fold at 2 weeks ($P < .001$) and were mildly elevated at 4 weeks ($P = .09$). Plasma concentrations of sCD25 and sCD14 did not change significantly during follow-up.

1 proviral transcription, whereas IL-6 acts synergistically with TNF-α to enhance HIV-1 replication at transcriptional and posttranscriptional levels [3]. Furthermore, even in the absence of inflammation, HIV-1 replication in the human cervix occurs in immunologically activated cells, as indicated by coexpression of TNF-α [32]. In this study, marked and sustained increases in concentrations of both TNF-α and IL-6 in the genital tract correlated with similar local increases in HIV-1 RNA concentration (figures 1 and 2; table 1). The anatomic compartmentalization of both the immune and virus load changes was striking. Cytokines released in inflammatory tissue surrounding cervical ulcers are likely to have diffused into genital tract secretions and the bloodstream. However, we suggest that the much smaller dilutional volume of the genital secretions resulted in higher cytokine concentrations, thereby leading to compartmentalized increases in HIV-1 load in the genital tract.

To our knowledge, little is known about local cytokine production associated with genital ulcers. In vitro, lactobacilli (constituents of the normal vaginal flora) and Gardnerella vaginalis have been shown to enhance HIV-1 expression in mononuclear cells by a mechanism involving nuclear factor kB and the HIV long-terminal repeat promoter [33, 34]. This may be the result of TNF-α signal transduction [34]. However, limited in vivo studies have not demonstrated significant changes in genital tract proinflammatory cytokine levels in women with uncomplicated vaginitis or gonococcal cervicitis [35, 36]. In view of the considerable inflammation that accompanies genital tract ulcers, it is likely that such lesions are potent sources of pro-inflammatory mediators. The inflammation may result from both the presence of pathogenic organisms and the normal bacterial flora of the genital tract. Exposure of ulcers to bacterial products may serve to enhance proinflammatory cytokine release [34], increase the susceptibility of mononuclear cells to HIV infection [37], and induce HIV-1 replication by a TNF-dependent pathway [34]. By these means, immune cell activation may be an important pathophysiological mechanism whereby genital ulcer disease increases sexual transmission of HIV-1.

Dendritic cells, macrophages, and possibly lymphocytes have been identified as targets for either HIV-1 or simian immunodeficiency virus infection in the genital tract [32, 38, 39]. However, it is not known which of these cellular pools represents important reservoirs of infection in the genital tracts of women with established HIV-1 infection. sCD14 and sCD25 are cell activation markers shed by macrophages and lymphocytes, respectively, during inflammatory processes [40, 41]. The local increases of both receptors, taken in parallel with the changes in HIV-1 RNA load and cytokines in the genital tract, indicate that both cellular pools were involved in the inflammatory process (figure 3). However, no inference can be drawn from these data regarding the actual cellular origin of increased HIV-1 production, and this question remains to be addressed in future studies. Cellular origin of HIV-1 in the genital tract is an important issue, because origin might influence cellular tropism and transmissibility of virus shed into genital secretions [42].

To investigate the activation status of cells supporting HIV-1 replication, we previously used an immunomagnetic viral cap-
ture technique to detect host cell–surface antigens incorporated into the virion envelope [26]. We used monoclonal antibodies linked to magnetic beads to target HLA-DR, a well-established marker of cellular immune activation, and the constitutively expressed surface molecule CD44 in the virion envelope. The greater ability to capture HIV-1 from CVL rather than from plasma by use of antibodies directed against HLA-DR incorporated in the virion envelope further suggested that the increase in CVL HIV-1 load was derived from locally activated cells in the genital tract. It is of additional importance that HLA-DR in the HIV-1 envelope is functional and enhances viral infectivity by promoting cellular entry [43, 44]. Thus, inflammation within the genital tract may lead to the production of HIV-1 with enhanced infectivity and, potentially, increased transmissibility.

The immunological changes associated with genital ulcers of iatrogenic and infectious etiology may not be identical, and further studies are needed to examine this issue. Ulcers of infectious etiology are likely to have a proinflammatory stimulus, provided by the presence of the causative pathogenic organism, in addition to vaginal commensal bacteria. It has been demonstrated that following uncomplicated surgical procedures that do not result in prolonged inflammation, the resolution of the proinflammatory cytokine response occurs in a few days [45]. It is thus likely that our finding of markedly increased levels of proinflammatory mediators 2 and 4 weeks after treatment of cervical dysplasia was not primarily the result of the initial surgical trauma but rather the result of ulceration and inflammation of the genital mucosa exposed to bacterial contamination in the genital tract.

This study provides evidence for a possible pathophysiological mechanism that would help to explain the epidemiologic findings of a strong association between genital ulceration and increased risk of heterosexual HIV-1 transmission. Sexual partners of HIV-infected people with genital ulceration may be exposed to genital secretions containing very high HIV-1 load, high concentrations of proinflammatory cytokines that could promote HIV infection, and virus of increased infectivity attributable to the presence of HLA-DR in the viral envelope. Furthermore, cytokine release in genital ulcers in people uninfected with HIV may render cells within the ulcers more susceptible to HIV-1 infection and promote systemic spread of HIV-1 infection beyond the genital tract. Thus, as a consequence of immune activation, it is possible that genital ulcers enhance transmission, acquisition, and progression of HIV infection. Future studies could extend these observations by determining the effect of genital ulceration on production of other local inflammatory mediators that might also affect HIV-1 replication and transmission. In addition, the impact of genital ulceration on infectivity of genital secretions, the relative importance of cell-associated and cell-free HIV-1, and the effect of antiretroviral treatment are further important issues that remain to be addressed.

References