The acute stage of human immunodeficiency virus (HIV) infection, characterized by a high level of plasma viremia and a loss of CD4+ lymphocytes, is followed by a long asymptomatic stage manifested by a slow but progressive decline in the number of CD4+ cells and low levels of detectable virus in the circulation [1–3]. It has been speculated that low-level virus expression during the clinically asymptomatic stage of disease is due in part to CD8+ cells capable of eliminating HIV-infected cells or suppressing HIV replication [3, 4]. CD8+ anti-HIV activity is mediated by both classical antigen-specific, major histocompatibility complex (MHC) class I–restricted cytotoxic T lymphocytes (CTL) and non–MHC-restricted noncytotoxic CD8+ T lymphocytes (nCTL). There is ample evidence that HIV-specific CTL appear early after infection, and their presence correlates with reduction in cell-associated and plasma viremia. This reduction in viremia may contribute to and maintain the asymptomatic stage of infection, which is characteristic of lentivirus disease pathogenesis.

Indeed, in the case of some perinatally exposed children, there is evidence for HIV-specific CTL in the absence of seroconversion and infectious virus, suggesting that these CTL can actually eliminate the virus after primary exposure [5]. Evidence for nCTL mechanisms has been demonstrated by enhanced HIV replication in CD8+–depleted peripheral blood mononuclear cells (PBMC) from HIV-positive patients and inhibition of in vitro HIV infection of CD4+ cells [4]. Anti-HIV CD8+ nCTL have been found consistently in patients with asymptomatic infections but are decreased or absent in patients with AIDS or AIDS-related complex [3, 4], supporting the contention that these CD8+ lymphocytes play a role in controlling viral replication and maintaining the clinically asymptomatic stage of infection. Although it has not been demonstrated that nCTL play a role in reducing the initial high acute-stage viremia, CD8+ anti-HIV activity is measurable relatively early in the acute disease and prior to detection of neutralizing antibodies [6].

CD8+-mediated antiviral activity has also been demonstrated in cats infected with feline immunodeficiency virus (FIV), a lentivirus that induces feline AIDS with characteristics similar to human AIDS [7, 8]. Antigen-specific CTL have been detected in the peripheral blood of cats with both acute [9] and asymptomatic [10, 11] FIV infections. In addition, anti-FIV CD8+ lymphocytes with nCTL characteristics have been observed in FIV-infected cats [12]. Similar to nCTL in HIV and simian immune deficiency virus (SIV) syndrome, these purified nCTL and their secreted factors are capable of preventing FIV infection of cultured CD4+ lymphocytes [12]. As the pathogenesis and clinical course of FIV infection closely parallel those of HIV infection, FIV infection provides a valuable model to study CD8+ lymphocytes as determinants of lentivirus expression and disease progression. In this report, we describe CD8+ anti-FIV activity in cats infected with FIV via the vaginal mucosa. The presence of CD8+ anti-FIV immunity during acute-stage infection correlated with a marked reduction, and in some cases, complete clearance of PBMC-associated virus, even in the absence of antibody response to FIV antigens.

Materials and Methods

Experimental animals and intravaginal inoculation. Nine 6-month-old female specific pathogen–free (SPF) cats (Liberty Lab-
oratories, Liberty Corners, NJ) were randomly divided into 3 groups to receive a low, medium, or high inoculum of FIV-NCSU1-infected FCD4E cells. FIV-NCSU1 was originally isolated from a naturally infected cat, and its transmission and pathogenesis has been described extensively [7, 13, 14]. Cultivation and assay of FIV in the interleukin-2-dependent feline CD4+ T lymphocyte cell line, FCD4E, has been described [7, 15]. FCD4E cells were infected with FIV-NCSU1 at an MOI of 0.1 TCID50. The cells were harvested 4 days later, washed, and counted. Cells were sedated with intravenous ketamine (20 mg/kg), and 50 µL of cell suspensions containing 10^5, 10^6, or 10^7 FCD4E cells was deposited in the anterior vagina. Inoculum discharge from the vulva was not observed. As a precaution, wide plastic Elizabethan collars were placed on the cats for 72 h to prevent them from grooming the perineal area.

Assessment of infection. At 4 weeks after infection and at 2-week intervals thereafter, infection status of the mucosally exposed cats was determined by detection of anti-FIV antibodies using a commercial ELISA (IDEXX, Portland, ME) and confirmed by Western blot as described previously [7, 15, 16]. Seroconversion was determined with an ELISA kit specific for FIV proteins according to manufacturer's specifications (IDEXX). The presence of FIV provirus in peripheral blood leukocytes was determined by polymerase chain reaction (PCR) amplification of a 868-bp fragment of the FIV gag genome as described elsewhere [7, 13]. Plasma coculture was also used to determine viremia following previously published protocols [12].

Separation of CD8^-Mediated Anti-FIV Response

Separation of CD8^-T cells from whole blood. Whole blood was collected in EDTA by venipuncture, and PBMC were separated on a Percoll gradient [7, 12]. M450 goat anti-mouse IgG immunomagnetic beads (Dynal, Great Neck, NY) were reacted with monoclonal antibody 3.357 (specific for feline CD8^-lymphocytes [14]) using the following protocol. A total of 10^6 beads was washed twice in wash medium consisting of Hanks' balanced salt solution and 2% fetal bovine serum to remove azide. The anti-CD8^-antibody was prepared into a working dilution of 1:100 in mediated by CD8^-depleted PBMC adjusted to contain the same number of non-CD8^-cells as in the unfractinated PBMC were incubated

<table>
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<tr>
<th>Table 1. Assessment of infection for cats experimentally infected with cell-associated FIV by intravaginal inoculation.</th>
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<tr>
<td><strong>FCDE inoculum, cat no.</strong></td>
</tr>
<tr>
<td><strong>4</strong></td>
</tr>
<tr>
<td>10^5 M04</td>
</tr>
<tr>
<td>ML5</td>
</tr>
<tr>
<td>LX4</td>
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<tr>
<td>10^6 DB2</td>
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<td>DB6</td>
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<tr>
<td>10^7 BN3</td>
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NOTE. FIV antibody was determined by FIV antibody–specific ELISA using plasma samples. Provirus in peripheral blood mononuclear cells was determined by polymerase chain reaction using primers for gag sequences. FCD4E, feline CD4^-lymphocyte cell line, was infected with FIV (MOI = 0.1 TCID50) 4 days prior to intravaginal inoculation into cats (see Materials and Methods). NA, data not available.

* Plasma collected 6 weeks after infection was cultured with FCD4E cells for 21 days; supernatants were analyzed for p26 by ELISA.

for 24 h in 96-well plates in complete RPMI 1640 supplemented with 100 U/mL recombinant human interleukin-2 (Biological Resource Branch, NIH) and 10 µg/mL concanavalin A (Sigma, St. Louis). Cells were then washed, resuspended in medium, and cultured in the presence of FCD4E cells (10^5/well) for 10 or 14 days. Additionally, fractionated and unfractinated PBMC were cultured without FCD4E indicator cells at 2 x 10^5 cells/well. Levels of FIV p26 antigen in culture supernatants were determined with a commercial ELISA kit (IDEXX) following procedures specified by the manufacturer. The percent inhibition of FIV replication mediated by CD8^-cells was determined according to Jeng et al. [12], who classified a positive response as >66% inhibition.

Results

Intravaginal inoculation of SPF cats with cell-associated NCSU1 results in establishment of acute systemic infection. To establish a mucosal infection model for FIV, SPF cats were challenged intravaginally with FIV-infected FCD4E cells at doses of 10^5, 10^6, and 10^7 cells/animal. As shown in table 1, 7 of 9 cats seroconverted, 5 of which were positive for FIV provirus by 8 weeks after infection. A representative gel for the FIV PCR is shown in figure 1. All of the cats that seroconverted by 8 weeks after infection maintained elevated levels of anti-FIV antibodies throughout the acute infection to 16 weeks after infection, as measured by Western blot analysis (data not shown). Infectious virus was detected in plasma of 6 of 9 cats when cocultured with susceptible FCD4E cells at 6 weeks after infection (table 1). These data indicate that FIV-NCSU1 infection can be established transmucosally with relative high efficiency via the intravaginal route using infected FCD4E cells.
**CD8$$^+$$ anti-FIV activity is demonstrable during the acute stage of FIV infection.** CD8$$^+$$ cells capable of suppressing FIV replication have been described in cats infected intravenously with the NCSU1 isolate [12]. However, these studies used FIV-infected asymptomatic stage cats and did not address the question of their potential role during the acute infection or if infection initiated transmucosally would generate a similar CD8$$^+$$ anti-FIV response. To determine if CD8$$^+$$ anti-FIV activity is present during acute infection in mucosally infected cats, virus expression was measured in CD8$$^+$$-depleted and unfracti-ioned PBMC at 6 weeks after infection, when most cats had seroconverted in response to FIV and demonstrated provirus in PBMC (table 1). Unfractionated PBMC from 5 of 9 cats yielded no detectable p26 in coculture, whereas CD8$$^+$$-depleted PBMC produced high levels of p26 (figure 2).

Of interest, while FIV was not detected in intact PBMC cultured from 2 cats (LX4 and EK4) that were seronegative and provirus-negative throughout the study (table 1), high levels of p26 were produced following CD8$$^+$$ depletion. One cat (ML5) showed no evidence of FIV replication in either CD8$$^+$$-depleted or unfractionated PBMC. Both ML5 and MO4 were antibody-positive, although neither plasma virus nor provirus was detected in PBMC from MO4 (table 1). Cats showing evidence of CD8$$^+$$ antiviral activity by increased p26 expression in CD8$$^+$$-depleted PBMC cocultured with FCD4E cells also yielded high levels of p26 when CD8$$^+$$-depleted PBMC were cultured in the absence of FCD4E indicator cells (data not shown), indicating that there were ample FIV-susceptible targets in the PBMC that could be infected and replicate virus in the absence of CD8$$^+$$ cells. These results suggest that vaginally transmitted FIV induces a strong systemic CD8$$^+$$ antiviral re-

**Longitudinal analysis of cell-associated viremia and CD8$$^+$$ anti-FIV activity.** Following intravenous FIV infection, PBMC- and plasma-associated virus titers peak at 4 weeks after infection and then decline to low or undetectable levels [7, 12, 14]. Longitudinal studies of infected cats described in this study show three distinct patterns of FIV expression in PBMC that appear to be related to the presence or absence of CD8$$^+$$ anti-FIV activity. Cats EK4, LX4, and BN3 demonstrated the predicted progressive reduction in cell-associated virus when tested at 6, 12, and 16 weeks after infection (figure 3A–C). These cats all had strong CD8$$^+$$ antiviral activity at 6 weeks after infection (figure 2). In contrast, cats ML5 and ED4, with no CD8$$^+$$ anti-FIV activity at 6 weeks after infection, also had no CD8$$^+$$ anti-FIV activity at 12 and 16 weeks after infection and did not show a reduction in cell-associated virus with time after infection (figure 3d, 3e). The third pattern, represented by cat MO4, was no virus detectable, even in CD8$$^+$$-depleted cultures at any time after infection. This cat was also PCR-negative but had a strong antibody response to FIV (table 1). One other point of note is that cats LX4 and EK4 demonstrated a strong 6-week CD8$$^+$$ anti-FIV response and progressive decline in cell-associated virus in the absence of seroconversion.

We were able to evaluate only 3 cats (LX4, EK4, and ML5) at 32 weeks after infection. Cat ML5 was still seropositive and provirus-positive (table 1) and continued to show no evidence of CD8$$^+$$ anti-FIV activity (figure 4). Of interest, LX4 and EK4, which were seronegative and PCR-negative for PBMC provirus at 32 weeks after infection (table 1), also tested negative for cell-associated virus in CD8$$^+$$-depleted PBMC cocultures (figure 4). These results show that induction of a strong CD8$$^+$$ anti-FIV response early after infection correlates with a dramatic
Figure 2. CD8+ cells inhibit FIV replication in peripheral blood mononuclear cells (PBMC) during acute infection following intravaginal inoculation of cell-associated FIV NCSU1. At 6 weeks after infection, PBMC from mucosally infected cats were depleted of CD8+ cells by immunomagnetic bead isolation using monoclonal antibody 3.357 against feline CD8; 10^6 CD8+-depleted PBMC or unfractionated PBMC were cocultured with 10^5 FCD4E indicator cells and assayed for FIV gag p26 by ELISA (see Materials and Methods) after 10 days of culture. Hatched bars, FIV gag p26 production from CD8+ depleted cocultures; solid bars, unfractionated cocultures. FIV p26 values are expressed as optical densities (ODs) adjusted to negative control value of 0.2 OD (OD - 0.2 corrected OD value). Error bars indicate SE of mean of triplicate samples.

reduction in cell-associated viremia as the cats progress from acute- to asymptomatic-stage infection. Indeed, failure to detect virus in 2 cats by any conventional assay, including CD8+-depletion coculture at 8 months after infection, suggests that they may actually have cleared FIV from the circulation.

Discussion
In this study, we demonstrate that intravaginal inoculation of SPF cats with cell-associated NCSU1 FIV results in an acute systemic infection frequently accompanied by a strong CD8+ immune response capable of inhibiting viral replication in PBMC. Seven of 9 cats challenged intravaginally developed systemic FIV infection as demonstrated by the presence of antibody to FIV or the presence of provirus or plasma viremia (table 1). Two cats (LX4 and EK4) in the low- and medium-inoculum groups had no evidence of infection by any of the conventional antibody or virus detection methods (table 1). However, although no p26 was detected in cocultures of plasma or unfractionated PBMC from cats LX4 and EK4, ample p26 was detected in CD8+-depleted PBMC cocultures. Cultured PBMC from 3 seropositive cats (DB6, FE3, and BN3) also showed strong CD8+-mediated suppression of FIV replication, as demonstrated by CD8+-depletion studies (figure 2).

The presence of CD8+ anti-FIV immunity as early as 6 weeks after infection roughly correlates with the decline in plasma and cell-associated viremia observed during primary FIV infection [12]. As the current p26 ELISA kits are unable to detect FIV antigenemia even during acute-stage infection, we were unable to routinely quantitate plasma antigenemia. In the case of cell-associated viremia, cats with strong CD8+ anti-FIV function at 6 weeks after infection also showed evidence of markedly reduced cell-associated virus burden when tested at later times after infection (figure 3A–C). In contrast, cats that had no CD8+ anti-FIV activity demonstrated no reduction in cell-associated FIV with time after infection (figure 3D, E). This correlation between the presence of CD8+ anti-FIV activity and reduction in virus in the circulation suggests that these CD8+ cells may play a role in controlling the primary viremia following infection with FIV.

It has been observed that HIV-infected patients who demonstrated a strong acute-stage gp160-specific CTL response also showed a rapid reduction of plasma viremia and antigenemia [18]. In contrast, plasma viremia and antigenemia were poorly controlled in patients with low [18] or undetectable anti-HIV CTL activity [19]. These authors were unable to detect neutralizing antibodies until several weeks after viremia had decreased and concluded that HIV-specific CTL were responsible for controlling viral replication following primary HIV infection [19]. The marked reduction in cell-associated viremia in the presence of strong CD8+ anti-FIV activity and absence of antibody to FIV (cats LX4 and EK4) strongly support the HIV CTL data and provide a compelling argument for an important role of CD8+ lymphocytes in controlling the initial viremia of both HIV and FIV infections. This conclusion is consistent with observations of a parallel decline in cell-associated and plasma viremia 4–6 weeks after infection with FIV [12].

In addition to reports of anti-HIV CTL, a number of studies have reported the existence of CD8+ lymphocytes that inhibit HIV replication by a nonlytic mechanism [20–22]. In contrast to CTL, these nCTL are not MHC-1–restricted and do not require cell-to-cell contact but may mediate their antiviral effect.
Figure 3. Longitudinal analysis of CD8<sup>+</sup> anti-FIV activity in mucosally infected cats. At 6, 12, and 16 weeks after infection, Percoll-purified peripheral blood mononuclear cells from 5 vaginally infected cats (EK4 [a], LX4 [b], BN3 [c], ED4 [d], and ML5 [e]) were depleted of CD8<sup>+</sup> cells by 3.357 anti-CD8 monoclonal antibody immunomagnetic bead sorting or left unfractionated prior to coculture with 10<sup>5</sup> FCD4E indicator cells at 1:1 ratio. Hatched bars, FIV gag p26 production from CD8<sup>+</sup>-depleted cocultures; solid bars, unfractionated cocultures. FIV p26 values are expressed as optical densities (ODs) adjusted to negative control value of 0.2 OD (OD<sub>0.2</sub> corrected OD value). Error bars indicate SE of mean of triplicate samples.

via secreted cytokines or chemokines [23]. Although it has not been demonstrated that these CD8<sup>+</sup> nCTL play a role in reducing the primary viremia in HIV infection, anti-HIV nCTL activity developed relatively early after infection and prior to detection of neutralizing antibodies [6]. How the CD8<sup>+</sup> cells, described herein, control FIV replication in cultured PBMC, and presumably in vivo, was not addressed in this study. As in HIV infection, both CD8<sup>+</sup> CTL [10, 24] and CD8<sup>+</sup> nCTL anti-FIV [12] effector cells have been described in FIV-infected cats; however, there are few data on the kinetics of their response following a primary FIV infection.

CD8<sup>+</sup> anti-FIV cells with nCTL characteristics have been detected in the peripheral blood of intravenously infected cats during acute-stage infections but were more consistently observed in cats with asymptomatic FIV infections [12]. However, as we have little information on MHC polymorphism of the cat, we can draw no conclusions as to whether the CD8<sup>+</sup> anti-FIV activity is MHC class I-resistant. It will be important
Figure 4. CD8⁺ anti-FIV activity correlates with clearance of cell-associated virus. At 32 weeks after infection, peripheral blood mononuclear cells (PBMC) depleted of CD8⁺ cells (as for figure 3) or undepleted PBMC were cocultured with 10⁵ FCD4E cells (1:1 ratio) and tested for production of FIV p26 gag by ELISA after 14 days of culture. Hatched bars, FIV gag p26 production from CD8⁺-depleted cocultures; solid bars, unfractionated cocultures. FIV p26 values are expressed as optical densities (ODs) adjusted to negative control value of 0.2 OD (OD − 0.2 = corrected OD value). Error bars indicate SE of mean of triplicate samples.

to determine if the CD8⁺ anti-FIV cells described in this study are classic CTL or nCTL effector cells. The marked reduction and, in some cases, apparent clearance of cell-associated virus and provirus from PBMC in the mucosally infected cats suggest that these effector cells are doing more than just down-regulating FIV replication and indeed may be eliminating FIV-infected cells (figure 4).

Recent observations regarding anti-HIV activity mediated by CD8⁺ cells have attributed virus reduction to the β-chemokines such as RANTES, macrophage inflammatory protein (MIP)-1α, and MIP-1β to reducing virus production by infected cells [25]. It is believed that these chemokines may be at least in part responsible for the nCTL control of HIV, although not the exclusive factor mediating this response. Studies that have addressed the role of β-chemokines in the reduction of HIV have used recombinant human RANTES, MIP-1α, and MIP-1β and have shown strong antiviral effects. However, the lack of available reagents for the study of felines has limited research on mechanisms of anti-FIV activity by CD8⁺ cells.

Despite these limitations, we tested human recombinant RANTES (Sigma, St. Louis) for its ability to inhibit FIV production from infected lymphocytes. Although our results failed to demonstrate a reduction in FIV production, we are unable to determine if these results are due to a species specificity of the β-chemokines or truly a negative result (data not shown). Studies are in progress to produce recombinant feline cytokines and chemokines that should prove immensely useful in these types of investigations.

The FIV mucosal infection model described herein may prove to be relevant to better understanding the mechanism(s) leading to clearance of HIV in some perinatally infected children. HIV-specific CTL were demonstrated in a 13-month-old child born to an HIV-positive mother, whereas there was no evidence of any of the standard markers for infection, including infectious virus, proviral DNA, RNA, or antibody [25]. The presence of HIV-specific CTL in the peripheral blood of as many as 25% of presumed uninfected children born to HIV-infected mothers has also been reported [27]. All HIV-specific CTL-positive children were seronegative at the time of the study and were virus-negative by PCR for provirus and in vitro coculture of PBMC. Cell-mediated immune responses to HIV antigens by PBMC from seronegative homosexual men with recent exposure to HIV suggests a similar CTL protective response to sexually transmitted virus [28]. These patients were also coculture-negative and HIV PCR-negative. Whether the patients in these studies were never infected or transiently infected and cleared the virus is not known. However, a transient viremia and provirus in the PBMC of a child who subsequently cleared the virus in the absence of seroconversion suggests that some individuals are capable of clearing the infection [5]. In agreement with this observation, 6 children born to HIV-infected mothers were virus-positive early in life and negative thereafter, a response consistent with clearance of infection [29]. As with the other studies, these children were seronegative for HIV.

Our data on mucosally transmitted FIV also support the argument that some lentivirus-exposed subjects may experience only a transient infection due to a strong cell-mediated immune response. Cats that developed an early CD8⁺ anti-FIV response demonstrated a marked reduction in cell-associated viremia in later assays, whereas cats that did not generate CD8⁺ anti-FIV activity failed to demonstrate a reduction in viremia. Indeed, in 2 of the CD8⁺ anti-FIV responsive cats (LX4 and EK4), we were unable to detect PBMC-associated virus by any of these standard virus detection techniques, including CD8⁺-depletion coculture at 16 and 32 weeks after infection, suggesting that these cats had cleared the virus from their circulation, at least well into the early asymptomatic stage (32 weeks) of infection.
Antibody response did not correlate with virus clearance, as LX4 and EK4 never seroconverted. These observations offer a compelling argument for the importance of these CD8\(^+\) cells in control and perhaps elimination of virus following a primary FIV infection.

While there are strong correlates between CD8\(^+\) responses and virus levels, the reduction in viremia during acute-stage infection may not be the exclusive property of the CD8\(^+\) effector cells, as natural killer and lymphokine activated killer cells have also been demonstrated to be cytotoxic for HIV- and FIV-infected cells [30, 31]. It will be important to further characterize the cell-mediated immune response(s), including the CD8\(^+\) antigen effector cells, and to determine their mechanism of activation and tissue distribution.

In summary, we have demonstrated that cell-associated FIV is efficiently transmitted via the vaginal mucosa. Moreover, the virus and immune response patterns of transmucosally FIV-infected cats are remarkably similar to those of humans with perinatally and sexually transmitted HIV infection, in that potent CD8\(^+\) anti-FIV effector cells are induced with or without seroconversion, and their presence correlates with clearance of FIV from the blood. These results suggest that FIV vaginal infection will not only be a powerful tool for the study of virologic and mucosal characteristics of transmucosal lentivirus infection but will also provide an excellent animal model by which to better understand the immunologic mechanisms that determine why some HIV exposed children and adults have only transient infections. Indeed, if it can be demonstrated that some cats have completely eliminated virus from the circulation, even in the absence of seroconversion, specific questions can be addressed regarding determinants of resistance to lentivirus infection. A better understanding of the mechanism of CD8\(^+\)-mediated clearance of the primary HIV and FIV infection may have important implications for a more rational approach to vaccine development and immune-based therapies.

Acknowledgments

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21. Koup R, Safrit J, Cao Y, et al. Temporal association of cellular immune response did not correlate with virus clearance, as LX4 and EK4 never seroconverted. These observations offer a compelling argument for the importance of these CD8\(^+\) cells in control and perhaps elimination of virus following a primary FIV infection.

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References