Effect of Glucocorticoids on Chronic Human Immunodeficiency Virus (HIV) Infection and HIV Promoter-Mediated Transcription

By Jeffrey Laurence, M. Brealyn Sellers, and Santosh K. Sikder

Corticosteroids are used in treatment of a variety of human immunodeficiency virus (HIV)-related disorders. Preliminary reports of a temporal relationship between administration of these drugs to viral carriers and development of AIDS raised the possibility that they can modify the course of HIV infection. Because glucocorticoids can alter specific gene expression in at least one immunosuppressive murine retrovirus, mammary tumor virus, we explored the ability of dexamethasone (DXM) to upregulate chronic HIV replication or to alter transcription at the HIV-1 long terminal repeat (LTR). A clone of promonocytic cells chronically infected with HIV-1 could be converted to a productive state of replication by phorbol ester or halogenated pyrimidine exposure, yet was unperturbed by DXM used over broad concentrations (10^{-4} to 10^{-8} mol/L) and time intervals (24 to 96 hours). This unresponsiveness corresponded to the lack of a positive effect of DXM on HIV associated trans-activation in both monocyctic and CD4+ T cells. These cells possessed the appropriate steroid receptors, as DXM downregulated Fcγ type-I receptors in both normal and HIV-infected promonocytic cells. In addition, DXM could block the transcriptional enhancement of an HIV-LTR-linked reporter gene by phorbol ester, while leaving basal levels of HIV-LTR-directed transcription unperturbed. These data are discussed in the context of clinical reviews of short-term steroid use in HIV-infected individuals.

HUMAN immunodeficiency virus (HIV) infection of T lymphocytes, monocytes, and possibly other cells includes a chronic or latent phase during which there is little or no viral replication. Transition to productive infection can be initiated in vitro by immunologic activation of infected cells. These signals induce cellular trans-acting factors, which in turn stimulate transcription from promoter and enhancer elements in the HIV long terminal repeat (LTR). The virus then synthesizes its own regulatory factors which further affect transcription at the LTR, leading to increased viral replication and cytopathology.

HIV mRNA accumulation is also sensitive to a variety of other stimuli. The mechanisms by which influences as disparate as cytomegalovirus (CMV) and herpes simplex virus infection, monokine and lymphokine treatment, antigenic stimulation, and phorbol ester exposure can convert a latent or chronic infection to a productive one appear to be just as varied. For example, regions in LTRs of HIV-1 and HIV-2 shared in common with consensus sequences for NF-κB, the enhancer of κ light chain Ig genes, respond to nuclear trans-acting factors activated by antigen and phorbol esters. In addition, proteins encoded by a variety of DNA viruses also augment expression from the HIV enhancer, using pathways distinct from NF-κB or the trans-acting gene product of the HIV tat gene.

In mouse mammary tumor virus (MMTV), which, like HIV, is a member of the Retroviridae family, glucocorticoids also stimulate transcription. This occurs through receptor binding to a hormone-responsive element upstream of the transcriptional start site on the MMTV LTR and may be modulated by promoter sequences outside the receptor binding sites. This phenomenon is of particular importance in AIDS, as the protein manifestations of infection with HIV encompass disorders classically treated with parenteral corticosteroids. These include mucocutaneous exanthema, lymphoid interstitial pneumonitis, demyelinating peripheral neuropathies, non-Hodgkin’s lymphomas, Hodgkin’s disease, Reiter’s syndrome, and immune thrombocytopenic purpura (ITP).

In the present study, we concentrated on HIV infection in a monocyctic cell line and its relationship to corticosteroids. We showed that dexamethasone (9α-fluoro-16α-methyl-prednisolone, DXM) was unable to rescue HIV-1 from the chronically infected promonocytic cell line U1.1, despite its ability to affect expression of its Fcγ type-I receptor (FcR-I). Neither could DXM activate the HIV tat gene in an assay for transcriptional regulation of an HIV-LTR-driven reporter gene, using either U1.1 cells or CD4+ T lymphoblasts. These results were in distinct contrast to other retroviral inducers, including the phorbol ester 13-phorbol-12-myristate acetate (PMA) and 5-iodo-2’-deoxyuridine (IUDR), which could rescue latent virus from U1.1 cells. Finally, DXM was able to block PMA-mediated enhancement of HIV-LTR-directed transcription. These data are related to putative consensus sequences for positive and negative hormone regulatory elements in HIV and MMTV; possible clinical implications are discussed.

MATERIALS AND METHODS

Cells. U1.1 cells were obtained from T. M. Folks of the National Institutes of Health (NIH). They were subcloned from U1, a clone of the human monocytic cell line U937 which had been infected with the lymphadenopathy-associated virus (LAV) strain of HIV. H9, a human CD3+, CD4+ lymphoblastoid cell line permissive for replication of HIV and partially resistant to its cytolytic effects was obtained from R. C. Gallo of the NIH. Stock samples of these cells were cultured in RPMI 1640 (Flow Laboratories, McLean, VA) plus 10% fetal bovine serum (FBS), at a concentra-

From the Laboratory for AIDS Virus Research, Department of Medicine, Division of Hematology-Oncology, Cornell University Medical College, New York.

Submitted November 14, 1988; accepted February 21, 1989.

Supported by National Institutes of Health Grant No. CA47262 and US Army Medical Research Acquisition Activity Contract No. DAMD 17-87-C-7020.

Address reprint requests to Jeffrey Laurence, MD, Cornell University Medical College, KB 122, 411 E 69 St, New York, NY 10021.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. section 1734 solely to indicate this fact.

© 1989 by Grune & Stratton, Inc.

0006-4971/89/7401-0016$3.00/0


291
tion of 5 x 10^5 cell/mL. In preliminary experiments, FBS was depleted of steroids by the charcoal-dextran method. A suspension of 0.25% Norit-A-activated charcoal powder (Sigma Chemical, St Louis) and 0.0025% dextran, molecular weight (mol wt) 500,000 daltons (Sigma), was made in 0.01 mol/L Tris-HCl, pH 8.0; 5 mL of this mixture was added to 5 mL FBS for 30 minutes at 50°C, followed by centrifugation at 2,500 rpm for ten minutes. The supernatant was collected, passed through a 0.45-μ Millipore filter, and added to RPMI 1640 to give a final concentration of 16%. Because no alteration of either PMA- or DXM-mediated effects were noted with this depleted product, all experiments reported herein used untreated FBS.

Reagents. PMA, IUdR, and DXM were purchased from Sigma. A stock solution of 100 μg/mL PMA was prepared in dimethylsulfoxide (DMSO), diluted in RPMI 1640, and used in final concentrations of 5 to 500 ng/mL. DXM was used as a stock solution of 4 mg/mL in absolute ethanol and used in final concentrations of 10^-4 to 10^-8 mol/L. IUdR was prepared as a stock solution of 50 μg/mL in 70% ethanol and diluted to give final concentrations of 10^-10 to 10^-6 mol/L. No cultures contained ethanol >0.1% by volume. These levels had no effect on cell growth or HIV replication (data not shown).

Antigen capture assay. HIV antigens were quantitated in supernatants by a monoclonal immunosorbent assay (ELISA) for viral p24 core protein. Human Ig directed against p24 epitopes (Abbott Laboratories, Chicago) contained in polyurethane beads was added to supernatants and maintained overnight at room temperature. Plates were washed with citrate-phosphate buffer and rabbit anti-HIV IgG, followed by horseradish peroxidase-labeled goat anti-rabbit antibody (Abbott) added. Color development with O-phenylenediamine as substrate, followed by 1 N H₂SO₄, was monitored. Absorbance was read at 492 nm, and data are expressed as picograms per 10^5 cells. The sensitivity of this assay is ~60 pg/mL.

DNA synthetic responses. Cells were collected and washed three times with PBS, and viability was assessed by trypan blue dye exclusion; 1 x 10^6 viable cells were resuspended in 0.2 mL medium in polyurethane flat-bottom microwell plates. Selected cultures were treated with inducing agents. All groups were assayed in triplicate. Cells were incubated for 48 hours; 18 hours before culture termination, they were pulsed with 0.1 mCi l-3H-thymidine (1.9 Ci/mmol/L, specific activity, New England Nuclear, Boston). The contents of each well were harvested and incorporation of radioactive material was measured by liquid scintillation counting.

HIV-associated trans-activation. The ability of the tat transcription unit of HIV to enhance the expression of the chloramphenicol acetyl transferase (CAT) gene when CAT is linked to the LTR of HIV was measured as previously described,24 with the following modifications. U1.1 cells 2 x 10^6 per condition were cultured with serum-free RPMI 1640 and resuspended in 1 mL 50 μg/mL Tris (pH 7.3) containing 250 μg/mL diethylamino ethyl (DEAE)-dextran (Sigma) and 2 or 4 μg total plasmid DNA. Two plasmids, described elsewhere,25 were used either singly (HIV-LTR-CAT alone) or together (cotransfection of CAT- and tat-containing vectors). The tat plasmid pCV-1 contains a 1.8-kilobase (kb) fragment of HIV-1 cDNA encompassing the tat gene. The CAT plasmid pc15CAT contains SV40 regulatory sequences and the LTR and a portion of nef (3orf) of HIV-1. After transfection, cells were washed with serum-free RPMI 1640 and incubated in 0.5 mL culture medium for 48 hours at 37°C. Certain cultures also contained PMA and/or DXM. Cells were then harvested, washed with PBS, resuspended in 100 μL 0.25 mol/L Tris (pH 7.8), and cellular extracts prepared by three cycles of freezing (in ethanol and dry ice) and thawing at 37°C. CAT activity was determined by incubating 50 μL aliquots of cell extracts with l-3H chloride (New England Nuclear) and 2.5 mmol/L acetyl coenzyme A (P-L Biochemicals, Piscataway, NJ) at 37°C for two hours and extraction with ethyl acetate. The acetylated forms of chloramphenicol were separated from the unacetylated form by ascending thin-layer chromatography, using a chromatogram sheet (Eastman Kodak, Rochester, NY) in a chamber containing chloroform and methanol (19:1, vol/vol). The chromatogram was then autoradiographed. Areas of radioactivity were marked, cut from the sheet, and counted in scintillation fluid.

Fc receptor expression. FcR-I was analyzed by indirect immunofluorescence (IFA) using mouse IgG2a (Tago, Burlingame, CA) binding to quantitate FcR-I.26 An FITC-conjugated, affinity-purified rabbit anti-mouse IgG reagent (Tago) served as the developing antibody; 1 x 10^6 viable cells were washed twice with phosphate-buffered saline (PBS) supplemented with 1% BSA and 0.1% sodium azide. Cell pellets were incubated with 20 μL 20 μg/mL IgG2a for 30 minutes on ice. After being washed twice with PBS, the cells were incubated with 10 μL 0.1 mg/mL FITC-conjugated rabbit anti-mouse IgG antibody for 30 minutes on ice, washed three times, and analyzed by flow cytometry.

RESULTS

Induction of HIV from chronically infected cells. Certain clones of chronically infected U937 cells can be induced to produce mature virions after PMA treatment.2,3 We sought to replicate this effect and to contrast it with that of two other inducers of retrovirus replication, IUdR27 and DXM.12

U1.1 cells 1 x 10^6 per microwell were exposed to varying concentrations of PMA, and supernatants were assayed for p24 at 48 hours. Preliminary experiments indicated that maximum HIV antigen was produced within 48 to 60 hours after phorbol ester treatment. As shown in Table 1, a four- to 11-fold increase in p24 Ag occurred when PMA was added. U1.1 cells were also exposed to IUdR (10 to 100 μg/mL) for

| Table 1. Effect of Various Agents on Induction of HIV-1 From Chronically Infected U1.1 Cells |
|---------------------------------|------------------|-----------------|
| Experiment | Inducing Agent | Concentration (pg/10^6 Cells) |
| A | None | 2,920 |
| PM | PMA 5 ng/mL | 13,040 ± 1,240 |
| PM | PMA 50 ng/mL | 32,440 ± 4,920 |
| PM | PMA 500 ng/mL | 11,200 ± 600 |
| B | None | 1,672 |
| | IUdR 10 μg/mL | 6,080 |
| | IUdR 50 μg/mL | 19,840 |
| | IUdR 100 μg/mL | 30,280 |
| C | None | 1,670 |
| | DXM 10^-4 mol/L | 1,222 |
| | DXM 10^-7 mol/L | 1,819 |
| | DXM 10^-10 mol/L | 1,197 |

Cells were plated at 1 x 10^6/microwell in 0.2 mL culture medium together with the appropriate concentration of inducing agent. Supernatants were harvested 48 hours (PMA and DXM) or 96 hours (IUdR) later and tested for p24 antigen by an enzyme-linked immunosorbent assay (ELISA)-based antigen capture system. PMA data represent the mean ± SD of three separate experiments and, for IUdR and DXM, the mean ± SD of two separate experiments.
24 to 96 hours, and culture supernatant was analyzed at 24-hour intervals for p24. HIV was again upregulated in a concentration-dependent manner, with maximum expression at 96 hours (Table 1).

These experiments were repeated with DXM. U1.1 cells were treated with physiologic (10^{-7} to 10^{-8} mol/L) and supraphysiologic (10^{-4} to 10^{-5} mol/L) levels of DXM for 24 to 96 hours. Viral expression was not upregulated (Table 1), nor were levels of HIV-1 altered in a subclone of U1.1 selected for high-level constitutive production of virus (data not shown).

**Effect of inducing agents on U1.1 growth characteristics.** As previously shown, proliferation of U1.1 was inhibited after treatment with >5 ng/mL PMA (Table 2), while viability remained unaltered (≥95%). IUdR had a similar effect (data not shown). In contrast, over a wide dosage range, DXM had little effect on cell replication (Table 2).

**Effect of inducing agents on FcR-I expression.** PMA augments FcR expression in U937 as well as peripheral monocytes, whereas DXM downregulates these receptors.

The effect of these agents on HIV-infected cells of the monocyte lineage is unknown. FcR-I was measured after a 48-hour exposure of cells to PMA or DXM, the optimum period as determined in preliminary kinetic experiments. A concentration-dependent PMA-mediated upregulation was noted by the IgG2a binding method in both uninfected U937 cells and chronically infected U1.1 clones. PMA 5 ng/mL increased FcR-I from 55% to 82% in U937 cells, and from 45% to 77% in U1.1 cells. In contrast, 10^{-8} mol/L DXM decreased FcR-I expression from 55% to 36% in U937, and from 45% to 30% in U1.1. Demonstration of some steroid-mediated effect in these cells was important since although monocytes and U937 cells have glucocorticoid receptors, HIV infection may have altered these molecules.

**Relationship of PMA and DXM effects to tat-mediated trans-activation.** Cellular responses to phorbol esters mimic responses to growth factors, hormones, and immunologic activation. Because DXM can also modulate MMTV expression through its LTR, we used a transient cotransfection assay to study possible activation or repression of HIV-LTR-mediated gene expression with PMA or DXM added. As shown in Fig 1, conversion of radiolabeled chloramphenicol to its acetylated forms was markedly enhanced when the HIV-LTR-CAT, and tat plasmids were cotransfected into PMA-stimulated U1.1 cells. In contrast, DXM had no effect at concentration ranges (10^{-7} and 10^{-6} mol/L) capable of affecting FcR-I expression in these clones, and at concentrations as high as 10^{-5} mol/L (data not shown). These experiments and results were replicated in a cell of different lineage, the CD4+ T-lymphoblastoid cell line H9 (data not shown).

Because DXM has negative regulatory effects on gene expression in some systems, its ability to alter PMA-mediated enhancement HIV-LTR-CAT was investigated. As shown in Fig 2, 10^{-5} DXM blocked the PMA-driven upregulation of CAT by 92.6%, while again having no significant effect on tat itself (2.7% decrease in baseline activity).

**Review of prednisone administration in clinical HIV infection.** One hundred eleven homosexual males with ITP, >90% HIV-seropositive, were followed by four groups of investigators. Depending on the study, 0% to 24% (mean 8 of 65 or 12.3%) developed AIDS when treated with prednisone or prednisolone followed by splenectomy, whereas 0% to 17% (mean 4 of 41 or 9.8%) developed AIDS if left untreated, a statistically insignificant difference (Table 3). The period of follow-up and mean time to development of clinical AIDS were similar for both treated and untreated individuals. Moreover, in studies that recorded the absolute CD4+ T-cell count, arguably the most significant prognostic indicator in HIV infection, there was no difference in baseline values between the untreated and prednisone groups.

**DISCUSSION**

Control of the rate of transcription is one of the primary strategies for selective expression of genetic information. It can arise from specific interactions between a regulatory protein and DNA sequences proximal or distal to the locus whose expression is modulated. In MMTV, hormone-receptor complexes regulate the transcription of particular genes positively (eg, the rate of transcription of MMTV DNA is stimulated by glucocorticoids through a mechanism that rapidly and selectively increases utilization of a transcription initiation site within the MMTV-LTR). We concentrated on chronic HIV-1 infection in a monocytoid cell, U1.1, and its relationship to potential inducers. We showed that, in contrast to strong induction of viral replication by PMA and IUdR, DXM had no effect. In addition, although transcriptional enhancement could be demonstrated for PMA, DXM had no positive effect on HIV-LTR-driven trans-activation in either promonocytic (U1.1) or CD4+ T-lymphoblastoid (H9) cell lines.

These findings are in clear contrast to at least one murine retroviral system. However, unlike MMTV, many murine retroviruses do not have a steroid-inducible promoter. Thus, examination of the nucleotide sequences of HIV-1 LTRs for potential hormone-responsive regions was important. For glucocorticoids, the areas required for receptor binding also act as hormone-responsive elements in vivo. These nucleo-

---

**Table 2. Effect of Inducing Agents on Proliferation of U1.1 Cells**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Inducing Agent</th>
<th>Concentration</th>
<th>cpm ± SD</th>
<th>Inhibition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A None</td>
<td>—</td>
<td>8,808 ± 430</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>PMA 5 ng/mL</td>
<td>9,534 ± 775</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMA 50 ng/mL</td>
<td>5,766 ± 260</td>
<td>34.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMA 500 ng/mL</td>
<td>4,412 ± 657</td>
<td>49.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B None</td>
<td>9,636 ± 608</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXM 10^{-8} mol/L</td>
<td>10,702 ± 1,598</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXM 10^{-6} mol/L</td>
<td>8,331 ± 332</td>
<td>13.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXM 10^{-7} mol/L</td>
<td>10,019 ± 1,523</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXM 10^{-6} mol/L</td>
<td>10,332 ± 963</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DXM 10^{-5} mol/L</td>
<td>9,016 ± 737</td>
<td>6.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

U1.1 cells were plated as described in the footnote to Table 1, and DNA synthetic responses were measured at 24 hours by determination of ³H thymidine incorporation; cpm represent the mean ± SD of triplicate wells.
These observations should lead to further exploration of the way in which steroid hormones may affect HIV transcription. Their relevance to the therapeutic use of steroids is less clear. These data do complement our review of clinical studies with short-term steroid use in HIV infection, lending support to the concept that although DXM may increase retroviral replication and disease in mice, no conclusive information shows that it does so in humans.

Anecdotal evidence for a temporal relationship between administration of steroids to HIV-seropositive individuals and subsequent development of AIDS has been reported, but establishment of a definitive link between steroid use and AIDS in these case reports is impossible. In this group, the cutaneous disorders for which steroids were used may be harbinger of AIDS, and steroid treatment may simply have been coincidental in its development. Data concerning ITP (Table 3) provide more compelling evidence for the lack of adverse reactions. In addition, the actuarial incidence of development of AIDS among thrombocytopenic HIV-seropositive homosexual men in New York City, 36.5% in 37...
GLUCOCORTICOIDS AND CHRONIC HIV INFECTION

Table 3. Relationship Between Glucocorticoid Administration and Subsequent Development of AIDS in Homosexual Men With ITP

<table>
<thead>
<tr>
<th>Clinical Parameters and Outcomes</th>
<th>Walsh et al²⁵</th>
<th>Abrams et al²⁶</th>
<th>Goldswig et al²⁷</th>
<th>Oksenhendler et al²⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>33</td>
<td>35</td>
<td>25</td>
<td>18</td>
</tr>
<tr>
<td>HIV seropositive (%)</td>
<td>93</td>
<td>100</td>
<td>NR²⁹</td>
<td>100</td>
</tr>
<tr>
<td>Mean platelet count (per μL)</td>
<td>50,000</td>
<td>21,000</td>
<td>47,000</td>
<td>14,000</td>
</tr>
<tr>
<td>Follow-up, mo, mean (range)</td>
<td>20 (2-44)</td>
<td>20 (1-36)</td>
<td>14 (1-38)</td>
<td>15 (6-41)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>15 (45.5)</td>
<td>7 (20.0)</td>
<td>13 (52.0)</td>
<td>6 (33.3)</td>
</tr>
<tr>
<td>No. (%) developing AIDS</td>
<td>2 (13.3)</td>
<td>0 (0.0)</td>
<td>1 (7.7)</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Prednisone or prednisone plus splenectomy</td>
<td>17 (51.5)</td>
<td>24 (68.6)</td>
<td>12 (48.0)</td>
<td>12 (66.7)</td>
</tr>
<tr>
<td>No. (%) developing AIDS</td>
<td>4 (23.5)</td>
<td>3 (12.5)</td>
<td>1 (8.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Mean time to development of AIDS (mo)</td>
<td>16.7</td>
<td>28.0</td>
<td>9.5</td>
<td>15.0</td>
</tr>
</tbody>
</table>

*Not reported.
†Received IV gammaglobulin.

months, does not differ from the incidence in a nonthrombocytopenic cohort.⁴⁷ One confounding variable in the ITP survey was use of splenectomy in conjunction with prednisone. Splenectomy itself was hypothesized to compromise the immune system in HIV-infected individuals further.⁴⁸ However, this has not been a problem in two prospective evaluations of splenectomy alone in treatment of HIV-seropositive ITP patients.²³,⁴²

The potential of an indirect steroid effect through rescue of latent viral intermediates other than HIV in vivo also exists. This hypothesis is based on three sets of experimental evidence. First, steroids activate in vivo DNA viruses which frequently infect HIV-seropositive individuals. Clinical herpes simplex virus type 1,²¹ CMV,⁴³ and hepatitis B virus⁴⁴ infections can be induced by glucocorticoids. Second, these viruses can activate transcription of HIV through its LTR in vitro.³⁴ Third, such interrelationships have been implicated in augmentation of HIV-related pathology in vitro⁷ and in vivo.⁴⁵

Because PMA-mediated effects use some of the regulatory sequences shared by these DNA viruses,¹⁰¹¹ we also evaluated the effect of DXM on PMA enhancement of transcription. U1.1 cells were exposed to both DXM and PMA immediately after cotransfection with HIV-LTR-CAT and tat. DXM completely abrogated the PMA-mediated enhancement of HIV-LTR–associated CAT activity (Fig 2). This paralleled the ability of DXM to downregulate FcR-I expression. Experiments to map potential DXM-negative regulatory elements, recognized in other systems,⁴⁶ are underway. The MMTV promoter lacks such a negative element,⁴⁴ and one lymphokine upregulated in HIV infection, interleukin-1β (IL-1β),² has recently been described to be augmented by PMA in U937 and downregulated by DXM.⁴⁸

Finally, the varied effects, inhibitory and stimulatory, which steroids have on all aspects of immunity could also accentuate the immune deficiency characteristic of HIV infection, apart from any direct effect on HIV and its replication. Glucocorticoids perturb T-lymphocyte function,⁴⁹ B-cell maturation,⁵⁰ and myelomonocytic differentiation.⁵¹ The precise mechanisms of immune suppression in vivo are poorly understood, but probably involve lymphocyte depletion,⁵² a specific depression of CD4⁺ helper/inducer T cells,⁵² and alterations in IL-2 production and IL-2 receptor expression and binding.⁵³ Until more is known about interactions of corticosteroids with HIV-infected cells in vivo, examination of alternate therapeutic strategies in HIV-related disease would be prudent. Indeed, splenectomy or intravenous γ-globulin may be equivalent to or more efficacious than steroids in HIV-linked ITP.⁵⁴,⁵⁵ Alternatively, under certain circumstances, the benefits of short-term steroid use may outweigh these theoretic risks (eg, there may be a role for brief administration of methylprednisolone to AIDS patients with respiratory failure due to Pneumocystis carinii pneumonia⁵⁶).

Definitive assessment of the contribution of corticosteroids to development of progressive immune suppression in HIV infection obviously is still incomplete. Our data and clinical review indicate that steroid-mediated rescue of chronic HIV does not occur in vitro and that deleterious clinical effects of short-term steroid use are unlikely.

REFERENCES


8. Laurence J, Sikder SK, Jhaveri S, Salomon JE: Phorbol ester-mediated rescue of HIV from a chronically infected promonocyte clone: Blockade by protein kinase C inhibitors and independence from 


13. Cato AGB, Skroch P, Weinman J, Butkeraitis P, Ponta H: DNA sequences outside the receptor-binding sites differentially modulate the responsiveness of the mouse mammary tumour virus promoter to various steroid hormones. EMBO J 7:1403, 1988


Effect of glucocorticoids on chronic human immunodeficiency virus (HIV) infection and HIV promoter-mediated transcription

J Laurence, MB Sellers and SK Sikder