AIDS and the Central Nervous System

Implications for the Anesthesiologist

Harvey M. Shapiro, M.D.,* Igor Grant, M.D.,† Matthew B. Weinger, M.D.‡

THE nervous system is the therapeutic target organ for anesthesiologic manipulation, and is also one of the

organ systems for which the human immunodeficiency virus (HIV) has a high predilection. The central nervous system (CNS) becomes infected early after HIV enters a new host, although the precise mechanism(s) by which the virus gains entry into brain and nerve remains unknown. The spectrum of dysfunction and disease in central and peripheral nervous system (PNS) caused by HIV is quite broad. Subtle brain dysfunction can be detected in “asymptomatic” HIV-seropositive individuals using sophisticated neurophysiologic and neuropsychologic diagnostic methods. In the advanced stages of the disease, frank dementia and other central and peripheral nervous system dysfunctions are common because of direct viral effects or as a result of secondary infections and tumors associated with severe immune suppression. It is estimated that 1 in 250 United States inhabitants is HIV positive. Although the AIDS epidemic in the United States may have peaked in terms of increasing infection rates, the number of individuals with HIV infection without a diagnosis of AIDS is expected to increase by 40% by 1995. The proposed Centers for Disease Control and Prevention (CDC) expansion of AIDS surveillance to include all HIV-positive persons with laboratory evidence of severe immunosuppression measured as a reduction in T lymphocytes with CD4+ surface antigen to which HIV binds (CD4+ < 0.20 × 10⁹/l (<200/mm³)) will result in an immediate expansion in the number of persons considered to have

* Professor of Anesthesiology and Neurosurgery; Chair, Department of Anesthesiology, University of California, San Diego.
† Professor and Vice Chair of Psychiatry, University of California, San Diego; Assistant Chief of Psychiatry for Ambulatory Care, Veterans Affairs Medical Center.
‡ Associate Professor of Anesthesiology, University of California, San Diego; Staff Physician, Veterans Affairs Medical Center.

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Address reprint requests to Dr. Shapiro: Department of Anesthesiology (OB01), University of California, San Diego, La Jolla, California 92093.

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a diagnosis of AIDS by 54%. Demands on health care systems will continue to expand before this epidemic is vanquished, and anesthesiologists will be increasingly involved in the care of asymptomatic HIV positive and AIDS patients.

This paper focuses on the nervous system manifestations of HIV infection, and draws clinically relevant implications for the anesthesiologist from what is currently known about this disease. HIV can directly affect brain structure and function, create an immune-suppressed condition favoring opportunistic CNS infections, facilitate growth of CNS tumors (primarily lymphomas), and cause peripheral neuropathies. A more complete understanding of the CNS manifestations of HIV infection is emerging, and many of the findings are relevant to the practicing anesthesiologist.

HIV can infect anesthesiologists and other health care workers, who may then continue to work while seropositive, but otherwise be "asymptomatic." We close our discussion by considering the potential impact of HIV-induced mild neurocognitive impairment on health care workers, such as anesthesiologists, employed in high-stress environments, and provide some thoughts on the development of occupationally specific fitness tests for professional practice.

### HIV/AIDS-Related Nervous System Disease

#### Classification

The results of a recent attempt at classification of HIV-associated cognitive/motor complex (AIDS Dementia Complex) and other CNS complications, as well as HIV-induced peripheral nervous system (PNS) disease, are shown in tables 1 and 2. When possible, the proposed new classification system is used in our discussion, because it reflects the consensus of a task force convened to develop a nomenclature for HIV research. In some instances, reference to older or currently used clinical terminology was required. Tables 1 and 2 clearly indicate the potential for widespread CNS and PNS involvement by HIV, which can result in a highly variable clinical neurologic presentation.

#### Neopathology

**Central Nervous System.** Eighty to ninety percent of patients dying from AIDS (CDC Stage IV) have demonstrable neopathology. The CDC staging system is shown in table 3.

HIV-induced direct pathologic changes are confined largely to nonneuronal cells, including macrophages, capillary endothelium, and derivative multinucleated cells formed by fusion of macrophages and microglia. Subcortical pathology predominates in HIV-associated cognitive/motor complex, and consists of a loss of deep gray (basal ganglia) and hemispheral white matter. The subcortical changes consist of macrophage and multinucleated giant-cell infiltration, reactive gliosis, and white matter pallor (leukoencephalitis). Some evidence indicates that the destructive multinucleated giant cells, formed by fusion of mononuclear microglia, are induced by the HIV viral coat protein, gp120. However, cortical gray matter atrophic changes with neuronal loss have also been reported. The association of HIV nucleic acids with this damage indicates a direct HIV neurolytic effect. In some cases, absence of accompanying markers for direct HIV neuronal infection indicates a secondary cause of loss of cortical neuropile.

**Peripheral Nervous System.** Patients with asymptomatic or symptomatic HIV infection exhibit heterogeneous, often mild, PNS involvement in 15–50% of

### Table 1. Proposed Nomenclature for HIV-1-Associated Central Nervous System Disorders and Terms Currently in Use

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1-associated cognitive–motor complex</td>
<td>AIDS dementia complex</td>
</tr>
<tr>
<td>HIV-1-associated dementia complex</td>
<td>Subacute encephalitis</td>
</tr>
<tr>
<td>HIV encephalopathy</td>
<td>AIDS-related dementia</td>
</tr>
<tr>
<td>HIV-1-associated myelopathy</td>
<td>HIV encephalopathy</td>
</tr>
<tr>
<td>HIV-1-associated minor cognitive–motor disorder</td>
<td>HIV-1-associated neurocognitive disorder</td>
</tr>
<tr>
<td>HIV-1-associated neurobehavioral abnormalities</td>
<td>HIV-1-associated neurobehavioral abnormalities</td>
</tr>
</tbody>
</table>

HIV-1 = human immunodeficiency virus-1; AIDS = acquired immunodeficiency syndrome.

* Proposed nomenclature.
† Current designation, not subtype.

### Table 2. Human Immunodeficiency Virus-1-Associated Peripheral Nervous System Disorders

<table>
<thead>
<tr>
<th>Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inflammatory demyelinating polyradiculopathy (Guillain-Barré syndrome).</td>
</tr>
<tr>
<td>Predominantly sensory polyneuropathy.</td>
</tr>
<tr>
<td>Myopathy</td>
</tr>
</tbody>
</table>
Table 3. Centers for Disease Control Staging

I. Initial inoculation: asymptomatic or accompanied by influenza-like illness
II. Latent: asymptomatic, but human immunodeficiency virus antibody-positive
III. Progressive generalized lymphadenopathy
IV. Opportunistic infections or malignancies, unexplained weight loss, fever, fatigue, diarrhea, multidermal herpes zoster, oral thrush or leukoplakia, CD4+ < 200/mm³

cases. Although HIV can be isolated from nerves, pathologic changes may be multifactorial, and may also be related to leptomeningitis secondary to other microorganisms. At the time of seroconversion, acute demyelinating mono- and polyneuropathy, including distal symmetrical variants, can occur. Necrotizing vasculitis causing radiculitis has been reported. Onset of AIDS can be associated with relapsing-remitting or progressive demyelinating polyneuropathy (or mononeuropathy multiplex), as well as a predominantly sensory axonopathy, motor neuron disease similar to amyotrophic lateral sclerosis, and autonomic neuropathy. Sensory neuropathy appears to be the most common PNS manifestation of AIDS, and occurs in 10–30% of AIDS patients. The neuropathy is manifested by painful dysesthesias, especially in the feet, and is generally associated with profound immunosuppression. Antiretroviral agents and other drugs used to treat AIDS complications can, in and of themselves, cause peripheral neuropathies. These, however, are usually reversible with cessation of the drugs.

Primary and secondary muscle wasting is common in AIDS. In one autopsy series, neurogenic muscle atrophy was present in 22% of patients with AIDS. HIV-associated myopathy can present as slowly progressive proximal muscle weakness, usually with elevated creatine phosphokinase and an electromyograph consistent with myopathy.

Pediatric AIDS

Infants and children appear to develop CNS complications of HIV infection more frequently, and exhibit a different pathologic picture, than adults. The severity and likelihood of clinically evident CNS complications seems to depend, in part, on the age of onset of infection. Thus, the most serious complications arise in infants infected in utero (vertical transmission rate approximately 10%) or perinatally. Severe neurologic/developmental abnormalities occur. These correspond to brain atrophy in deep cortical structures and increased magnetic signal in white matter. Basal ganglia calcifications are frequent, but mass lesions are rare relative to their incidence in adults. Clinically, a progressive (at times fulminant) encephalitis may appear, which appears to correlate with direct HIV entry into the CNS. Secondary CNS infections are uncommon in pediatric AIDS patients.

Although the frequency of severe neurocognitive complications is high in infants, these patients may respond favorably to antiretroviral treatment. Several studies have demonstrated improvement in cognitive functioning and reduction in brain atrophy after intravenous zidovudine. School-age children (e.g., HIV-positive hemophiliacs) infrequently manifest neurocognitive disorders in the early stages of infection.

HIV and Its Life Cycle

HIV is a prototypical member of the Lentivirinae subfamily of retroviruses (enveloped RNA virus with reverse transcriptase). It is distinguished from other retroviruses by its very complex viral genome complement, containing not only the three essential retroviral genes (gag, env, and pol), but at least six additional genes. The three essential genes, respectively, encode for its core nucleocapsid polypeptides, surface coat proteins, and the retrovirus characteristic reverse transcriptase and other enzymes. The six additional genes add to the relative complexity of HIV and impact on its pathogenicity and possible therapeutic approaches. Viral genome complexity increases the likelihood of transcriptional errors during viral reproduction, resulting in different viral mutant lines, some of which may be resistant to therapeutic agents. On the other hand, the complexity of the HIV genome provides an increased opportunity for errors during replication, leading to natural or therapeutically lowered pathogenicity. For example, the most clinically efficacious chemotherapeutic agents for HIV infection, the dideoxynucleosides (zidovudine and others), inhibit viral reverse transcriptase. Much antiretroviral research is based on attacking the virus at different stages of its complex life cycle, which is summarized in figure 1.
HIV is trophic to cells with the CD4⁺ surface antigen, and this antigen is mainly found on the cell surface of T lymphocytes and monocytes. The CD4⁺ antigen binds with very high affinity to the env gene mediated gp120 envelope protein of the HIV. Virion reproduction within CD4⁺ T lymphocytes ultimately kills them. These T lymphocytes are essential regulators and effectors of the immune response, and depletion of CD4⁺ T lymphocytes is considered the hallmark of progressive HIV infection. Cellular death may not occur immediately, because the virus can enter an apparent latent stage, although the often-observed slow, but progressive, decline in CD4⁺ lymphocytes indicates that latency may not be complete. Mechanisms other than direct viral killing may also lead to CD4⁺ lymphocyte depletion, including the formation, by cellular fusion, of nonviable multinucleated giant or syncytiotial cells. The CD4⁺ antigen is present on other cells (macrophages, monocytes, glia, etc.), and these cells may serve as reservoirs and migration vehicles, because HIV is not as rapidly fatal to them. It is interesting that there is also evidence for cellular penetration of HIV in neural-derived primary cells or cultured cells that do not carry the CD4⁺ surface antigen.¹⁴

Pathogenesis
Primary HIV CNS damage requires viral penetration into the brain. There is clear evidence that infection involving at least the leptomeninges occurs very early in the disease, perhaps with the first viremic episode.¹⁵ Mechanisms for nervous system infection include in-migration of systemically infected macrophages or seeding of macrophages during the initial or subsequent viremias. Although HIV is often found within CNS macrophages and microglia, direct viral penetration of neurons is very rare, and macrophage tropic HIV may be more likely to be the cause of brain infection.

Once nonneuronal CNS cells are infected, the putative mechanism(s) of neurobehavioral decay or neurodestruction may include direct toxicity, production/induction of neurotoxins, neurotransmitter blockade, interference with neurotropism, impaired substrate supply (via decreased astrocytic or capillary function), autoimmune activation, enhancement of intracellular calcium concentration, and other diverse cellular metabolic effects.¹⁶⁻²⁶

Because neurons are rarely infected, some have considered these cells to be “bystanders” (i.e., neurons sustain damage without being directly infected by HIV). The mechanisms responsible for macrophage and microglial HIV infection leading to neuronal dysfunction or demise are being investigated. Virus-derived products, such as the HIV wall protein, gp120, have been shown to induce abnormal astrocytic growth, alter capillary membranes, increase intracellular calcium to toxic levels, and block cerebral metabolism (perhaps by blocking vasoactive intestinal peptide (VIP) cortical excitatory influences on neurons).¹⁶⁻²⁶ HIV may stimulate production of immune system-generated neurodestructive compounds (e.g., cytokines, interleukin, and tumor necrosis factor).²¹⁻²⁵ A final common pathway for cytotoxicity may be the excitatory amino acid N-methyl-D-aspartate (NMDA) receptor and voltage-dependent calcium channels.²⁴⁻²⁶ The calcium channel antagonist, nimodipine, appears to block gp120-induced neurotoxicity, and gp120 is suspected to act synergistically with endogenous glutamate to increase NMDA receptor-mediated injury. Vasoactive intestinal

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peptide, a neurotransmitter and trophic factor, also antagonizes the effects of this HIV-derived protein.\(^{20}\) Additionally, \(Tat\), an HIV nucleic acid, may act as a non-specific neurotoxin by increasing membrane leakage conductance.\(^{27}\) Other HIV putative neurotoxins, direct viral derivatives as well as compounds generated by the presence of HIV in the CNS, are under investigation.

Early neurocognitive dysfunction can be quite subtle, and may even precede the onset of clinically significant immunosuppression. The diagnosis of HIV encephalitis or HIV-associated neurocognitive disorder may be complicated by opportunistic CNS infection or neoplasm. These secondary neurodestructive events are facilitated by the presence of immune suppression.

**Diagnosis and Evaluation**

Beyond establishing the serologic diagnosis of systemic HIV infection, a major challenge that remains is the early detection of physical, structural, physiologic, and biochemical correlates of CNS involvement. Asymptomatic individuals generally do not have abnormalities that are easily detectable with routine neurologic examination. Diagnosis of mild HIV-associated cognitive disorders require specialized sensitive neuropsychologic testing. Such neurosensory evaluations must be performed chronologically, and should include tests of cognitive function (attention, abstraction, language, memory, and speed of information processing), as well as perceptual motor skills (motor speed, strength, coordination, and sensory-motor integration). Structural abnormalities must be fairly large for detection by static neuroimaging techniques (MRI and CT scanning), whereas some functional neuroimaging procedures (e.g., single photon emission computerized tomography (SPECT) or positron emission tomography (PET)) may detect early prestructural metabolic defects.

**General Screening for HIV Infection**

The ELISA (enzyme linked immunosorbant assay) and the Western Blot remain the mainstays for the initial diagnosis of AIDS infection. The former depends on antibody formation (seroconversion usually takes 6–8 weeks), and the latter detects viral protein (p24, gp41, and gp120/160) by electrophoresis. A positive diagnosis usually requires three positive tests, usually two ELISAs and one confirmatory Western Blot. Two positive ELISA tests will diagnose HIV infection with a 99.7% sensitivity with 98.5% specificity.\(^{28}\) Tests used less often are geared to detecting virus during the “window period” of initial antibody generation. The polymerase chain reaction (PCR) test uses *in vitro* techniques to replicate more than 1 million copies of HIV-1 DNA in less than 3 h from one target molecule.\(^{29,40}\) The amplified nucleotides are then easier to detect. However, the PCR test is easily contaminated by trace nucleic acids, and is relatively expensive. Polymerase chain reaction has been used in infants to detect actual viral infection in the presence of HIV antibodies transferred from mothers. Detection of other viral antigens is not helpful, because these tests are rarely positive when others are not. Viral culture techniques are accurate, and may detect virus in 30–50% or more of asymptomatic HIV+ persons. Viral culture techniques are able to detect virus in cell-free plasma in approximately 20% of asymptomatic seropositive persons, and in 50% of symptomatic patients.\(^{29}\) By way of contrast, virus can be isolated from peripheral blood mononuclear cells in virtually all seropositive individuals regardless of the stage of HIV infection.\(^{29,40}\)

**Cerebrospinal Fluid**

Among asymptomatic HIV+ individuals, a significant percentage (40–60%) have nonspecific positive cerebrospinal fluid (CSF) markers for viral infection (e.g., protein, albumin index, and various measures of CSF IgG expression), indicating early involvement of the CNS.\(^{41,42}\) Cerebrospinal fluid pleocytosis also occurs early. Over a 2-yr period, a group of neurologically normal HIV+ Air Force personnel had increased intrathecal cellular responses and IgG production, and this was independent of their CD4+ count.\(^{43}\) Polymerase chain reaction techniques can detect HIV constituents (gag, env, and pol sequences) in the CSF in over 90% of HIV+ individuals, regardless of their CDC stage. Viral culture techniques are less sensitive, and HIV is identified in CSF by this method in just over 50% of asymptomatic seropositive persons.\(^{43,44}\) Thus, most seropositive persons have HIV in the CSF.

In addition to direct culture of HIV from CSF, there are other, nondiagnostic, biochemical markers present in the CSF of HIV-infected individuals. These nonspecific changes may reflect a CNS antibody reaction, byproducts of the HIV-mediated neurodestructive process, or other secondary infectious or neoplastic destructive processes. There are currently no known specific CSF markers relating to the degree of neurocognitive impairment in early HIV-associated cogni-
tive/motor complex. The most promising candidates are β2-microglobulin, quinolinic acid, or neopterin. The putative sources for these markers are circulating activated T-lymphocytes, leakage from blood or CNS synthesis (or both), and activated macrophages.25,35,50 With onset of AIDS, the concentrations of these “early” markers, as well as others associated with greater degrees of neurodestruction, increase. Levels tend to be highest in patients with clinically obvious dementia or opportunistic brain infections. Serum neopterin and β2-microglobulin levels are also significant predictors of AIDS risk in seropositive patients; together, these parameters have a predictive value equivalent to CD4+ counts.57

Neuroimaging

Structural neuroimaging techniques, such as computed tomography (CT) and, to a lesser extent, magnetic resonance image (MRI) scanning (as used in standard clinical practice), require relatively large changes in brain anatomy, and can be expected to be relatively insensitive to early HIV CNS infection.58 Dynamic or functional neuroimaging, with positron emission tomography (PET) measurement of cerebral metabolism (CMR) or single photon emission computed tomography (SPECT) evaluation of cerebral blood flow (CBF), can demonstrate abnormalities in subcortical gray matter structures and cerebral cortex in patients with HIV-associated dementia. PET/SPECT abnormalities have been reported in HIV infection even when CT/MR are unremarkable and the patient is relatively asymptomatic. Positron emission tomography/single photon emission computed tomography may also be useful to follow progression of neurocognitive dysfunction or response to therapy.59–12 The degree of hypoperfusion of some cortical and subcortical regions parallels the development of advanced stages of dementia.41,42 Single photon emission computed tomography scanning may also detect CNS abnormalities in asymptomatic individuals.42

Neurophysiologic Evaluation

To some extent, neurophysiologic testing may be comparable to functional neuroimaging techniques and neuropsychologic testing in that they all stress neuronal network function and, thus, can detect subclinical abnormalities. In fact, a high incidence of neurophysiologic abnormalities, especially cranial nerve dysfunction, can be demonstrated in asymptomatic HIV-positive individuals. Eye movement abnormalities, neurootologic, and EEG changes have been reported. In one 2-yr study of seropositive, asymptomatic individuals, progressive electrophysiologic abnormalities (EEG and otoeureologic) were found in 67% of subjects, compared with a 10% incidence in matched controls.56 In the same study, neurologic examination, neuropsychologic testing, MR, and visual evoked potentials were not different between the two asymptomatic groups. Abnormalities in auditory evoked potential studies have also been reported for both HIV+ asymptomatic and AIDS patients. Specifically, the latency of the P300 event-related potential (e.g., increased electrical activity observed at 300 ms after the auditory stimulus) is prolonged. This electrical activity has been speculated to be generated by hippocampal neurons in response to the auditory stimulus, and may reflect memory consolidation (see below).45,46

Neuropsychologic Testing

HIV-associated cognitive/motor complex is characterized initially by disturbances in learning, attentiveness, and processing of high-speed information flow. Thus, neuropsychologic testing in asymptomatic HIV-positive persons should be directed toward detecting these early-developing abnormalities. Although there is a consensus that mild neurocognitive impairment is common (up to 70% of patients) in the later stages of HIV infection (CDC Stage IV), its occurrence and significance in “asymptomatic” (CDC II and III) persons remains controversial.47–55 A major semantic problem centers on the varying definitions of “subclinical,” “asymptomatic,” “clinically significant,” and other ubiquitous terms. This problem is amplified by differing levels of occupational or environmental neurocognitive challenges, as well as differences in study populations, testing instruments, disease stage (e.g., evidence points toward higher CNS dysfunction late in the asymptomatic period), concomitant depression, and fluctuations in functional status. Another problem centers on the existence of significant variability in neuropsychologic performance among both control and asymptomatic HIV+ groups in the parameters mentioned above, as well as in verbal, language, and executive functions.55–58

Generally speaking, a cognitive disorder becomes easier to detect as the HIV disease progresses (i.e., higher CDC stage). Both for clinical management and for evaluating occupational safety, it is important to understand that dementia does not occur overnight. It is probable that, among medically asymptomatic or
mildly symptomatic HIV-positive persons (CDC II and III), 25–30% manifest subtle cognitive difficulties that should not be termed "dementia." Terms such as mild neurocognitive disorder or minor cognitive/motor disorder are preferred; the implication is that a mild deficit in two or more cognitive functions (attention, memory, speeded processing, etc.) exists, but that these mild deficits produce little impairment in ordinary social and occupational functioning. The term "dementia" (or HIV-associated dementia) should be reserved for cases of major cognitive impairment of sufficient severity to interfere markedly with day-to-day activities. For example, dementia would be incompatible with any but the most rudimentary form of work. Defined in this manner, dementia rarely occurs in CDC Stages II and III, and its annual incidence in CDC IV has been estimated at 1.4% or less.56

Recent studies employing neuropsychologic screening and computerized reaction time tests to demonstrate diminished performance of asymptomatic HIV+ subjects compared with normal controls have yielded mixed results.54,59–61 Few, if any, differences could be demonstrated on many standardized neuropsychologic test parameters. However, as reviewed by Mapou et al.60 and supported by their recent work, up to 30% of asymptomatic HIV+ individuals manifested slowed responses on reaction time tests. These results could have significant implications for the HIV+ individual whose occupation requires a rapid response to critical stimuli (e.g., anesthesiologists, surgeons, pilots, air traffic controllers, truck and bus drivers, etc.).

Anesthesia Management Issues

Systemic Disease and Overall Risk

It is beyond the scope of this presentation to discuss the ethical issues related to the costs and benefits of invasive therapeuic interventions in AIDS patients. However, physicians are increasingly faced with questions concerning the relative risks and benefits of diagnostic, palliative, and supportive surgical procedures in AIDS patients. Unfortunately, there is, currently, limited specific information concerning the overall risk of anesthesia and surgery in the HIV-positive patient. The American Society of Anesthesiologists (ASA) physical status assessment and the inherent surgical risk probably provide a measure of global risk assessment. This information, when combined with the CDC Stage of the HIV infection, the degree of immunosuppression, and the presence and severity of opportunistic infection or neoplasm, may offer the best predictor of global perioperative risk for the HIV-positive patient. However, validation of this suggestion awaits further study. The best current predictors of the magnitude of HIV-related immunosuppression, and, thus, prognosis, are the CD4+ T-lymphocyte count and the presence of opportunistic infection.2 Oral candidiasis (thrush) is the most common early opportunistic infection. Table 4 presents CD4+-based mortality data derived from a large cohort of seropositive persons.2

The physiologic consequences of severe infections (pulmonary or CNS) or advanced malignancies may seriously complicate perioperative management. Electrocardiographic and echocardiographic abnormalities have been described in a high proportion of patients with advanced AIDS, although their implications for overall risk assessment remain unclear.62

Anesthesia and Immune Suppression

A number of studies indicate that anesthesia and opiates may have a negative effect on immune function.63,64 Although this immune-suppressive effect probably is of little clinical importance in healthy individuals, its implications for the HIV-infected patient are unknown. Additionally, morphine has been shown to reactivate or stimulate HIV reproduction in in vitro cultures of human Kupffer cells or peripheral blood monocytes.64–66 Morphine may also activate HIV-1 transinfected into cultured human neuroblastoma cells.67 The authors hypothesized that opiates may activate latent CNS HIV infection. However, the in vitro effects of morphine were not reversible with naloxone. There is evidence for the presence of classic opioid receptors on peripheral blood lymphocytes and monocytes.64 It must be stressed that experimental in vitro tissue culture studies to date have required prolonged exposure (days) to the opiates. However, in vivo animal models, using a more clinically relevant time frame (<12 h),

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Table 4. Mortality in Human Immunodeficiency Virus–Positive Patients within Six Months after a CD4+ Determination

<table>
<thead>
<tr>
<th>CD4+ Count (per mm³)</th>
<th>Mortality (%)</th>
</tr>
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<tbody>
<tr>
<td>&lt;50</td>
<td>13.3</td>
</tr>
<tr>
<td>50–99</td>
<td>6.2</td>
</tr>
<tr>
<td>100–199</td>
<td>1.9</td>
</tr>
<tr>
<td>&gt;200</td>
<td>0.8</td>
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have also shown that opiate agonists will suppress humoral and cell-mediated immune responses.68–72 Clinical data demonstrating an adverse immunologic effect of either opiate treatment or anesthesia in general is indirect or absent. The increased susceptibility to infection seen in opiate addicts has been documented to be caused by immunologic dysfunction.73,74 Inclusion of an opiate in an epidural anesthetic technique in obstetric patients has been associated with a reactivation of herpes simplex labialis.75,76 One group suggested that general anesthesia be avoided, when a regional technique is possible, in AIDS patients because of apparent depression of cell-mediated immunity after general anesthesia.77

Nevertheless, as of yet, the clinical data do not appear to be sufficient to justify the avoidance of opiate agonists, because of immune-suppression side effects, as part of anesthetic management of HIV-infected patients. Most studies demonstrating the opiates' immunosuppressive or viral reactivation actions have required long-term use of high doses. Unless additional data are forthcoming, opiates may remain a central component of the management of pain in most patients with AIDS.

**Neurologic Considerations**

Clearly, the presence of overt AIDS dementia can compromise the ability to give operative consent, but the approach to this is no different than in other forms of dementia. There is no evidence to indicate that seropositive patients lack competence to participate in medical decision making, even when early mild neurocognitive disorder is present.

Patients with HIV-associated dementia may be expected to be more sensitive to psychoactive drugs, including the sedative effects of benzodiazepines, opiates, and neuroleptics. One possible explanation for this sensitivity may be the proposed interaction between Interleukin-1 (IL-1), a cytokine with sedative effects that is released in the body's acute phase reaction to viral or bacterial infection, and the \( \tau \)-aminobutyric acid-A (GABA-A) receptor.78 In *vitro* and *in vitro* electrophysiologic studies showed that IL-1 increased GABA-dependent chloride ion transport, thus inhibiting the CNS by a mechanism similar to that for barbiturates and benzodiazepines.79 Neuroleptic-induced extrapyramidal signs occur more frequently, and at lower doses, in HIV-infected individuals.

The presence of HIV-related CBF and CMR disturbances, as well as AIDS-related intracranial mass lesions, will affect anesthetic management. Virtually all cerebral hemodynamic abnormalities described with HIV-associated dementias are associated with regional hypoperfusion, and most likely represent reduced metabolic demand (with maintained coupling of CBF and CMR) rather than a primary cerebral ischemic event.76 Full-blown AIDS dementia is associated with cerebral atrophy, and is generally not complicated by intracranial hypertension.74 AIDS dementia tends to occur earlier in pediatric AIDS.10

Secondary AIDS-related brain disorders may be accompanied by increased ICP because of a mass effect, cerebral edema, or obstructive hydrocephalus caused by arachnoidal inflammatory reactions from opportunistic infectious agents, such as toxoplasmosis or cryptococcus.79–82 Toxoplasmosis remains the most common (3–40%) opportunistic CNS infection to cause encephalitis or focal intracerebral lesions in AIDS patients.82 These patients commonly present with headache, confusion, fever, and focal neurologic deficits. More than 90% of these patients will have cerebral edema and enhancing lesions on CT. A mass effect will be present in more than 50% of CT scans performed on patients with toxoplasmosis cerebral edema.82 Patients with advanced AIDS may actually present with a clinical picture of toxoplasmosis cerebral edema, despite the absence of antitoxoplasma antibodies. Anesthetic management principles for increased ICP should be effective in these instances.83 However, these patients usually respond to therapy with rapid clinical and radiographic resolution,82 and, thus, antibiotic treatment should probably be instituted before surgery and anesthesia.

Patients with cerebral hypoperfusion associated with opportunistic infections complicated by cerebral edema or AIDS-related secondary mass lesions probably develop intracranial hypertensive compressive ischemia, and may be expected to exhibit CBF autoregulation abnormalities. These conditions should be managed according to the anesthetic guidelines developed for intracranial hypertensive states.

The appearance of peripheral nervous system abnormalities, such as polyneuropathy and myopathy with associated active muscle wasting, should alert the anesthesiologist to the possibility of succinylcholine-induced hyperkalemia, although, to our knowledge, this has not been reported in AIDS patients. Patients with painful peripheral neuropathies may present to anesthesiologists for pain management. Diagnostic cerebrospinal fluid sampling has resulted in postdural puncture headaches in seropositive patients, and these
individuals may undergo epidural blood patching. As previously discussed, HIV infection of the CNS occurs very early in the course of the disease, and there is no evidence that lumbar puncture facilitates CNS disease by introducing virus from blood into the CSF. Also, one study found no increase in neuropsychologic abnormalities in seropositive individuals receiving an epidural blood patch to control severe postlumbar puncture headache.\textsuperscript{84}

\textbf{Ethical and Social Issues}

It is beyond the scope of this presentation to discuss in detail the ethical and social dilemmas stemming from HIV infection in patients and physicians. However, these concerns revolve around three key issues: (1) the desirability of the anesthesiologist knowing the HIV status of all of his or her patients, (2) the desirability of the patient (and coworkers) knowing the HIV status of their anesthesiologist, and (3) the concerns of society about the cognitive performance of the HIV-infected or otherwise-impared anesthesiologist. This last issue will be dealt with in the next section.

Although the HIV-positive patient who presents for surgery may raise special anesthetic considerations, optimal patient evaluation and management should only be significantly affected in advanced stages of the disease, when the diagnosis should be readily apparent to the anesthesiologist. Therefore, if \textit{Universal Precautions are practiced}, the need to provide optimal patient management will not require that the anesthesiologist know every patient's HIV status.

As reviewed by Glantz \textit{et al.},\textsuperscript{85} the argument for routine testing of health care workers for HIV seropositivity is untenable on both scientific and ethical grounds. The scientific data to date indicates that the risk of a health care worker, using proper Universal Precautions, transmitting HIV to a patient is extremely remote. Thus, the exclusion from practice of HIV+ physicians would unreasonably deprive them of personal freedom and the opportunity to earn a living. At the same time, this would represent poor public policy, because the screening program would divert resources from other, more effective, strategies for fighting the HIV epidemic, and would also remove from the work force highly trained contributing individuals.\textsuperscript{86}

\textbf{The HIV Asymptomatic Anesthesiologist and Neuropsychologic Impairment}

Current approaches to physicians who are HIV positive, and who otherwise appear to be unaffected by the virus, lean toward the permissive side with regard to continuing their practice. This is consistent with the aims of the Americans with Disabilities Act of 1990.\textsuperscript{§} The focus is on preventing transmission of HIV infection from health care workers to patients, and, as long as an HIV-positive physician presents no infectious risk to the patient, he or she is permitted to continue to practice. Emphasis has, thus, been placed on the seropositive practitioner's ability to abide by Universal Precautions for infectious materials.

However, as has been discussed above, apparently asymptomatic HIV-positive patients can manifest subclinical degrees of neurocognitive impairment. Thus, another consideration for HIV seropositive physicians may be the influence of mild neurocognitive impairment on clinical judgment and skills. This may be of particular significance in clinical situations when voluminous data collection, prioritization of complex tasks, rapid decision making, and fine motor skills are required to assure patient safety. In critical clinical situations, even minor degrees of mental or physical dysfunction could impair the provider's ability to respond optimally to the emergency. Physiologic or psychologic stress can augment the deleterious effects of mild cognitive impairment.\textsuperscript{87} Anesthesiologists, surgeons, and critical care and other acute care physicians most frequently find themselves working under these clinical conditions.

Anesthesia delivery involves complex monitoring tasks that require sustained vigilance, and this type of task is thought to be particularly susceptible to degradation by human factors affecting job performance.\textsuperscript{87} It is recognized that much of the morbidity and mortality in anesthesia is caused by human error. The operating room environment can be characterized as a high-technology, high-workload, high-risk environment requiring rapid complex integration, decision making, and action. This may be an inappropriate occupational environment for anesthesiologists with impaired cognitive or psychomotor function, regardless of the etiology. The solo practice nature of anesthesia precludes backup, and increases the potential danger of neurocognitive functional degradation.

The anesthesia work environment is often compared with the cockpit of an airplane with regard to
task characteristics, workload, performance requirements, and types of work stress. The interest in developing anesthesia simulators, like those used in the aviation industry, is consistent with this analogy.\textsuperscript{86,89} Along this line, it is informative to examine the approach of the airline industry to the HIV-positive pilot.

Consistent with the FAA’s approach to pilots with other causes of mental and physical impairment, the Aerospace Medical Association recently took the position that “the HIV-infected pilot places the flying public at increased and unnecessary risk, and therefore supports testing of pilots for infection for the HIV virus. Individuals confirmed to be so infected should be found medically disqualified for flying duties.”\textsuperscript{90} Aside from potential legal problems associated with this position, it moves in a direction opposite to positions espoused by professional medical associations with regard to preserving the rights of asymptomatic HIV+ practitioners to work without limitation.\textsuperscript{1} The Federal Aviation Administration supports a guideline that permits asymptomatic seropositive pilots to fly as long as they are taking no medications.\# In light of data indicating the ability of zidovudine (AZT) to prevent the onset of AIDS in HIV+ patients, the FAA approach seems overly restrictive, and places the affected pilot in an untenable position (\textit{i.e.}, lose one’s livelihood or increase the risk of losing one’s life).\textsuperscript{91-95}

HIV infection is not the only possible cause of subtle impairment of cognitive and psychomotor performance. A wide variety of physical (\textit{e.g.}, cerebrovascular events, endocrine/metabolic disorders, tumors, etc.) and mental (\textit{e.g.}, bipolar affective disorder, Alzheimer’s disease, etc.) illnesses can affect cognitive function and the ability to perform one’s job. In addition, substance abuse, a well recognized occupational hazard of anesthesiologists,\textsuperscript{94} impairs job performance. For example, alcohol, at blood levels as low as 0.02\%(well below that considered legally drunk), has been shown to degrade both cognitive and psychomotor skills.\textsuperscript{95} Furthermore, performance can be impaired for up to 14 h after alcohol ingestion (“hangover effect”).\textsuperscript{96,97} Other, more common behaviors may occasionally affect anesthesiologists’ ability to perform their job. For example, sleep deprivation and circadian rhythm disturbances can dramatically impair the performance of cognitive tasks,\textsuperscript{98} particularly during novel complex stressful clinical situations.\textsuperscript{87}

From our review, it is evident that asymptomatic HIV seropositivity, as an isolated finding, cannot be considered a certain marker of neuropsychologic impairment. Furthermore, some authorities have argued that, even if minor cognitive changes are demonstrated in an asymptomatic HIV carrier, such changes are of little clinical significance. However, the difference between clinically significant and occupationally significant neuropsychologic impairment may be highly variable, and may depend on the unique performance demands of the occupation.

Thus, an approach based on objective criteria for neuropsychologic impairment seems warranted when issues of public and patient safety are involved. The first step would be to determine, using valid and reliable testing approaches, whether a neurocognitive disorder, in fact, exists. One approach may be the neuropsychologic battery recommended by the National Institute of Mental Health.\textsuperscript{99} However, as of yet, there are insufficient data to clearly link performance on neuropsychologic tests and actual occupational performance.

An alternative approach would be to employ more occupationally relevant tests to screen for the presence of significant neurocognitive impairment in anesthesiologists (not only from HIV infection, but also as a result of other illnesses, alcohol or substance abuse, sleep deprivation, aging, etc.). Development of such tests would require evaluation of the actual anesthesia work environment to determine the key component cognitive and psychomotor skills required for acceptable job performance.\textsuperscript{100-102} Although potentially less expensive and more readily available than objective real-time evaluation of either actual job performance or performance in full-task anesthesia simulators,\textsuperscript{88,89,102} such derivative test methodologies would require careful validation. The few full-task anesthesia simulators already in existence may be quite useful in developing derivative neurocognitive testing protocols.

The use of occupationally relevant performance assessment to determine “fitness for duty” in individuals diagnosed with a medical condition is gaining increasing acceptance in military and commercial aviation.\textsuperscript{61} For example, COGSCREEN, an 11-test, 45-min computerized battery designed for the FAA, was developed

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\textsuperscript{1} ASA House of Delegates, Committee on Occupational Health of Operating Room Personnel, 1992 Session.

\# Engelberg AL, Dooge TC: Review of part 67 of the federal air regulations and the medical certification of civilian airmen. Submitted to the Federal Aviation Administration under contract #DTRA01-83-C-20066 by the American Medical Association. Vol 1, 1986.
to test cognitive, psychomotor, and perceptual abilities thought to be important to piloting aircraft." An updated version of COGSCREEN is currently being used to study the relationship in pilots between medical diagnoses (including HIV infection), test performance, and performance in full-motion flight simulators. A number of other performance assessment screening tests are being developed and evaluated.

Any anesthesiology "fitness-for-duty" test, however configured, may need to be administered to all anesthesiologists at risk for cognitive impairment, not just those who have been unfortunate enough to have been specifically identified, for example, because their HIV seropositivity has become public knowledge. There is legal precedent indicating that policies that punish those who are unfortunate enough to have been identified as HIV positive without requiring screening of all possible infected individuals is discriminatory. Additionally, any policy that would discourage potentially affected physicians from seeking diagnosis and treatment would be detrimental to both the individual and society. These issues have been discussed in detail by Glantz et al.

This review has considered the primary and secondary nervous system complications of HIV infection within the context of the practice of anesthesia. Workplace problems that may complicate HIV's mild neurocognitive disorder have also been discussed. It is possible for HIV-infected persons to develop subtle, but occupationally significant, neuropsychologic impairment that could be otherwise clinically silent. An extraordinarily high level of neurocognitive demands are placed on anesthesiologists by the nature of their work. Our specialty should seriously consider applying the combined skills of anesthesiologists, psychiatrists, psychologists, and individuals skilled in ergonomics, bioengineering, and occupational design to the development of objective neuropsychologic testing criteria for potentially impaired practitioners, including those infected with HIV. These measures of performance, while potentially infringing on privacy rights, would provide protection to that majority of seropositive phy-


† District 27 Community School Board v. Board of Education of the City of New York, 502 N.Y.S. 2d 325 (Sup Ct, Queens Co. 1986).**

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