

# Parturients Infected with Human Immunodeficiency Virus and Regional Anesthesia

## Clinical and Immunologic Response

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**Background:** It is estimated that 1.5 million Americans are infected with the human immunodeficiency virus (HIV-1), and the consequences of HIV infection are a leading cause of death in women aged 15-44 yr. Thus, HIV-1 disease, or acquired immunodeficiency syndrome, occurs with increasing frequency in the parturient, and there is little information concerning the risks of regional anesthesia. Fear of spreading infection to the central nervous system or adverse neurologic sequelae have led some clinicians to advise against regional anesthesia. Thus, this study was undertaken to evaluate the possible problems or risks associated with regional anesthesia in parturients infected with HIV-1 and to determine whether anesthesia affected the clinical course of the disease.

**Methods:** The clinical course and immunologic function of 30 parturients infected with HIV-1 were evaluated prospectively. Extensive medical and laboratory evaluation before

delivery and 4-6 months postpartum was undertaken. Medical problems related to HIV-1 disease and use of antiviral drugs also were monitored. The anesthetic management was dictated by the clinical situation and the patient's wishes with careful postpartum follow-up to evaluate possible neurologic changes or infection.

**Results:** Regional anesthesia was administered in 18 parturients, and 12 received small doses of opioids or no analgesia. There were no changes in the immunologic parameters studied ( $CD_4^+$  p24,  $\beta_2$  microglobulins), and HIV-1 disease remained stable in the peripartum period. There were no infections, complications, or neurologic changes in the peripartum period. Sixty-eight percent of the infants were HIV-1-negative and, in 21% of infants, the HIV-1 status was indeterminate (probably negative).

**Conclusions:** This prospective study of parturients infected with HIV-1 demonstrated that regional anesthesia can be performed without adverse sequelae. There were no neurologic or infectious complications related to the obstetric or anesthetic course. The immune function of the parturient was stable in the peripartum period. Although the number of patients studied was small, with careful medical evaluation, regional anesthesia is an acceptable choice in the parturient infected with HIV-1. (Key words: Acquired immunodeficiency syndrome. Anesthesia: obstetric. Human immunodeficiency virus.)

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Received from the Departments of Anesthesiology and Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco. Submitted for publication May 3, 1994. Accepted for publication September 14, 1994. Conducted at San Francisco General Hospital, San Francisco, California. Supported in part by the Anesthesia Research Foundation and the National Institute of Child Health and Development P01-HD24640. Presented in part at the meeting of the Society for Obstetric Anesthesia and Perinatology, Charleston, South Carolina, May 1992, and annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 17-21, 1992.

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# Centers for Disease Control and Prevention: HIV/AIDS Surveillance Report, 5. No. 3. Atlanta, Centers for Disease Control and Prevention, 1993, p 6.

AN estimated 1.5 million Americans are infected with the human immunodeficiency virus (HIV-1) and 339,250 cases (diagnosed through September 1993) of acquired immunodeficiency syndrome (AIDS).# Heterosexual transmission is increasing rapidly, and women represented 12% of the second 100,000 cases of AIDS.<sup>1</sup> More recently (July 1992-June 1993), 14.6% of newly diagnosed AIDS cases were women.# It has been reported that 75.9% of women infected with HIV-1 are between 20 and 39 yr of age, *i.e.*, childbearing age, making HIV-1 a vital concern for the increasing numbers of parturients who are infected.<sup>2</sup> Although the AIDS epidemic officially began with the report of four cases of *Pneumocystis carinii* in homosexual men in 1981,<sup>3</sup> by 1987,<sup>4</sup> AIDS was the eighth leading cause



of death in women aged 15–44 yr and the sixth leading cause of death in that age group by 1990.<sup>5</sup> Thus, the parturient infected with HIV-1 will be part of every obstetric suite in the near future, if not currently.

There is little or no information concerning choices and risks related to anesthesia in this unique group of parturients. However, it is recognized that the natural history of HIV-1 includes central nervous system infection early in the clinical course and that expression of this infection varies widely.<sup>6</sup> Some clinicians/investigators have cautioned against the use of spinal or epidural anesthesia<sup>7</sup> and others against inhalational anesthetics<sup>8</sup> in patients with HIV-1 infection. In a study of chronic epidural catheterization for pain management, Du Pen *et al.*<sup>9</sup> noted nine epidural catheter-related infections in 11 AIDS patients. This was a much higher rate of infection than that documented in cancer patients receiving the same treatment. Accordingly, the current, prospective study of HIV-1 positive parturients was undertaken to evaluate the possible problems or risks associated with regional anesthesia in this high-risk obstetric population and to determine whether the use of anesthesia affected the clinical course of the disease.

## Materials and Methods

With approval of our institutional Committee on Human Research and patient informed consent, we prospectively evaluated the obstetric course and anesthetic management of 30 patients infected with HIV-1 as part of the Bay Area Perinatal AIDS Center research project. Patients underwent extensive medical and laboratory evaluation before delivery and at least 6 months postpartum as part of a long-term study of pregnancy and HIV-1 disease. Follow-up visits were planned at 2, 4, 6, 9, and 12 months postpartum and then every 6 months thereafter. Infection with HIV-1 was confirmed by detection of antibodies to the viral protein by the enzyme-linked immunosorbent assay (DuPont, Biotech Research Laboratories, Rockville, MD) with positive results confirmed by Western Blot assay (Wironostika Teknika, Organon, OSS, The Netherlands) immunoblot tests. The immune function was monitored by CD<sub>4</sub><sup>+</sup> (helper/inducer) T-cell lymphocyte and CD<sub>8</sub><sup>+</sup> T-cell lymphocyte counts, critical modulators of the immune system, serum p24 antigen (p24), and  $\beta_2$  microglobulin evaluations. The  $\beta_2$  microglobulin levels in serum were determined by radioimmunoassay (Pharmacia, NJ), and the HIV-1 p24 antigen was detected by enzyme-linked

immunosorbent assay. Routine blood analysis for leukocyte count and hematocrit were performed. To assess the severity or progression of the disease, patients were screened for use of antiviral drugs such as zidovudine (Azidothymidine) and chemoprophylaxis for *Pneumocystis carinii*. Disease status also was assessed by the occurrence of AIDS indicator diseases such as *P. carinii* pneumonia, Kaposi's sarcoma, *candidiasis*, cytomegalovirus disease, *Mycobacterium avium*, cervical dysplasia, cervical cancer, and/or oral hairy leukoplakia.

The anesthetic management was determined by the patient's request for elective pain relief or the necessity of surgical intervention requiring anesthesia. Decisions regarding anesthetic intervention were made in the usual clinical manner by the anesthesiologist in consultation with the obstetrician. Choices for pain relief were epidural or spinal anesthesia (regional anesthesia) or no anesthetic intervention. General anesthesia also was a choice for cesarean section. Patients with no anesthetic intervention had small amounts of opioid administered according to the obstetrician's orders or no analgesia. The newborn HIV infection rate was documented. After delivery, the patient was carefully monitored with special attention given to the immediate postpartum period and 4–6 months' follow-up for disease-related complications of any kind and their possible relationship to anesthesia. Continued extensive immunologic monitoring (CD<sub>4</sub><sup>+</sup>,  $\beta_2$  microglobulin, p24) was undertaken postpartum, as well as careful evaluation of the potential complicating infections related to AIDS. Neurologic symptoms, including unusual headaches, problems with coordination or balance, or numbing or tingling of arms, legs, or feet, were specifically surveyed (part of a follow-up questionnaire) more than 4–6 months postpartum.

Data were analyzed using the unpaired Student's *t* test when comparing the two groups, regional anesthesia group *versus* the no anesthetic intervention group. A *P* value of <0.05 was considered significant. All values are expressed as the mean  $\pm$  SD.

## Results

The study groups, regional anesthesia (N = 18) *versus* no anesthetic intervention (N = 12) were similar with respect to maternal age, weight, height, parity, and history of intravenous drug abuse (table 1). The patients were divided almost evenly with regard to parity and history of intravenous drug abuse. In the group



Table 1. Maternal Characteristics of HIV Positive Parturients

|                        | Regional Anesthesia<br>(n = 18) | No Anesthetic<br>Intervention<br>(n = 12) |
|------------------------|---------------------------------|---|
| Age (yr)               | 29.7 ± 6.1                      | 30.7 ± 5.1                                |
| Weight (kg)            | 78.5 ± 16.6                     | 76.5 ± 11.1                               |
| Height (cm)            | 164 ± 3.0                       | 158 ± 5.4                                 |
| Parity                 |                                 |   |
| Nulliparous            | 10 (55.6)                       | 6 (50)                                    |
| Parous                 | 8 (44.4)                        | 6 (50)                                    |
| Intravenous drug abuse |                                 |   |
| Yes                    | 10 (55.6)                       | 6 (50)                                    |
| No                     | 8 (44.4)                        | 6 (50)                                    |

Values are mean ± SD. There were no significant differences between the two groups. Values in parentheses are percentages.

who received regional anesthesia, 16 received epidural anesthesia and two received spinal anesthesia, the latter for cesarean section. No patients received general anesthesia. There were three unintended dural punctures in the epidural group (18.8%) but no postdural puncture headaches in this subgroup or the spinal anesthesia group. There were no autologous epidural blood patches, either prophylactically or postpartum. There was a 20% cesarean section rate in the study patients, two of whom received spinal anesthesia; the remaining four received epidural anesthesia.

Immunologic values and blood counts before delivery and 4–6 months postpartum are compared in tables 2 and 3. There were no significant differences between the groups, regional anesthesia and no intervention, or between predelivery and postpartum values within the two groups. The majority of patients had a CD<sub>4</sub> T-cell count greater than 200 cells/mm<sup>3</sup> both antepartum and postpartum. However, the mean CD<sub>4</sub><sup>+</sup> T-cell count was approximately half the normal (no disease) cell count in both groups. The CD<sub>4</sub><sup>+</sup> T-cell counts tended to remain stable and did not progress in most patients during the study period, and the p24 and β<sub>2</sub> microglobulin values were not significantly changed.

There were no significant differences between groups in AIDS indicator diseases, but there were four cases of *P. carinii* pneumonia in the regional anesthesia group; two cases were diagnosed antepartum and two cases postpartum (table 4). Five mothers in the regional anesthesia group and four in the no anesthesia group were given zidovudine therapy before delivery; zidovudine therapy was initiated postpartum in eight mothers in the regional anesthesia group and seven in the no intervention group, as indicated for a CD<sub>4</sub><sup>+</sup> T-

cell count of less than 500 cells/mm<sup>3</sup>. Oral hairy leukoplakia and persistent generalized lymphadenopathy were the most common indicator diseases or conditions. No cases of pulmonary mycobacterial disease or Kaposi's sarcoma were detected in the patients studied. Sixty-eight percent (n = 19) of the infants were HIV-1 negative with 21% (n = 6) having an indeterminate HIV status (probably negative) at this time, whereas 11% (n = 3) were HIV-1 positive.

Three dural punctures occurred when performing epidural anesthesia, but the epidural injections were placed successfully at another interspace without complications. Epidural catheters remained indwelling, as clinically required. There were no neurologic or infectious complications or any changes in the peripartum period or during the 4–6-month neurologic follow-up period to suggest that regional anesthesia had adverse sequelae. There were no superficial or deep infections noted at the catheter placement site. Only the visit at 4–6 months is reported here, but long-term follow-up of those patients who have continued in the study with numerous clinic visits reveals no unusual neurologic sequelae that would not be expected in the natural course of HIV-1 infection.

## Discussion

This study found no change in the disease progression or serologic markers in the parturient infected with HIV-1 that could be linked to the anesthetic management at delivery. The CD<sub>4</sub><sup>+</sup> T-cell counts, a common indicator of disease progression (*i.e.*, lower count, more advanced disease) remained relatively stable. Two other surrogate markers, the p24 antigen and β<sub>2</sub> microglobulins, were evaluated. The p24 antigen is an HIV-1 core protein, and its presence in the blood has been associated with maternal-fetal viral transmission (vertical transmission) and possibly a more rapid progression of the disease.<sup>10</sup> β<sub>2</sub> Microglobulin has been suggested as a predictor of disease progression because it indicates immune activation resulting from HIV-1 infection. Increased cord β<sub>2</sub> microglobulin also may be linked to vertical HIV-1 transmission.<sup>11</sup> We measured only maternal β<sub>2</sub> microglobulin levels in this study. Both of these surrogate markers remained stable when comparing the ante- and postpartum values. Whereas the use of p24 antigen, β<sub>2</sub> microglobulins, and CD<sub>4</sub><sup>+</sup> T-cell counts in some situations has been questioned with regard to their usefulness as indicators of disease progression, they are used frequently in many centers



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Table 2. Laboratory Analysis of Immune Function Parameters: Predelivery and Six Months Postdelivery

|  | Regional Anesthesia     |                          | No Anesthetic Intervention |                           |
|--|-------------------------|--------------------------|----------------------------|---------------------------|
|  | Predelivery<br>(n = 18) | Postdelivery<br>(n = 18) | Predelivery<br>(n = 12)    | Postdelivery<br>(n = 10)† |
| Red blood cells ( $\times 10^{12}/l$ ) | 3.80 $\pm$ 0.43         | 4.27 $\pm$ 0.69          | 3.75 $\pm$ 0.44            | 4.14 $\pm$ 0.51           |
| White blood cells ( $\times 10^9/l$ )  | 7.60 $\pm$ 2.40         | 5.34 $\pm$ 1.69          | 7.41 $\pm$ 2.01            | 4.93 $\pm$ 1.83           |
| Hemoglobin (g/dl)                      | 11.7 $\pm$ 1.3          | 12.6 $\pm$ 1.5           | 11.1 $\pm$ 1.3             | 12.0 $\pm$ 1.3            |
| Hematocrit (%)                         | 34.5 $\pm$ 3.6          | 37.8 $\pm$ 4.3           | 32.9 $\pm$ 3.0             | 35.4 $\pm$ 3.2            |
| CD4 (cells/mm <sup>3</sup> )*          | 495 $\pm$ 357           | 491 $\pm$ 360            | 452 $\pm$ 327              | 470 $\pm$ 237             |
| CD8 (cells/mm <sup>3</sup> )**         | 837 $\pm$ 379           | 979 $\pm$ 359            | 848 $\pm$ 374              | 993 $\pm$ 479             |
| CD4:CD8 ratio                          | 0.61 $\pm$ 0.31         | 0.50 $\pm$ 0.29          | 0.54 $\pm$ 0.45            | 0.65 $\pm$ 0.38           |

Values are mean  $\pm$  SD. There were no significant differences.

\* CD 4 = T-helper lymphocytes; \*\*CD8 = T-suppressor lymphocytes.

† Laboratory values are unavailable for two patients.

as clinical and/or research tools and, in this study, provide further evidence of the clinical stability of these patients in the peripartum period.

We found no neurologic or infectious problems in the immediate postpartum period or at the 4–6-month follow-up visits. This latter finding is in agreement with the related report of no sequelae related to performance of epidural blood patches in nonobstetric patients who are HIV-1-positive<sup>12</sup> and initial findings similar to ours.<sup>13,14</sup> However, in a study of patients in whom epidural catheters were placed for chronic pain management, Du Pen *et al.*<sup>9</sup> found nine infections (six at the catheter-exit site, two deep-track infections, and one epidural infection) in patients with AIDS. These infections cleared after antibiotic therapy. Although the difference in findings may lie solely in the use of prolonged catheterization *versus* acute use of regional anesthesia, it may be that most of our obstetric AIDS patients were in the early stages of the disease ( $CD_4^+$  T-cell count  $> 200$  cells/mm<sup>3</sup>). Indeed, one limitation of our study is that the majority of our patients had  $CD_4^+$  T-cell counts greater than 200 cells/mm<sup>3</sup> (largely Centers for Disease Control class A<sub>2</sub> or B<sub>2</sub>) and, thus, were relatively healthy. Therefore, our findings might not apply to patients with further advanced HIV-1 disease.

This is the first prospective study of the clinical and immunologic function of the HIV-1 positive parturient to include relevant evaluation of the effects of anes-

thetic management on the disease and to evaluate maternal outcome. Because individuals infected with HIV-1 have depressed immune function, there is obvious concern that anesthesia and surgery may further impair the patient's immune status with an increased risk of infection, extension of HIV-1 disease, or poor wound healing. There is a critical lack of information regarding the effects of anesthesia in these patients, and that which exists is often only contradictory medical opinions.<sup>7,8,14</sup>

However, there are data documenting isolated, transient immunologic consequences secondary to anesthesia and surgery in patients with normal immune systems, but this is rarely correlated with adverse clinical outcome.<sup>15</sup> Markovic *et al.*<sup>16</sup> demonstrated that halothane and isoflurane induced "anesthetized natural killer (NK cells) system," which could lead to changes in clinical management as we better understand the mechanisms involved.<sup>17</sup> However, we did not measure  $CD_4^+$  T-cells or other surrogate markers frequently enough (repeated acute measurements within the days before and immediately after the anesthetic intervention) to see such transient effects. Despite this, our data indicate no real change over time in the function of the parturient's immune system or the disease process that were related to anesthesia in the parturient infected with HIV-1.

The results of the current study support the growing evidence that pregnancy has no obvious effect on the progression of HIV-1 disease in generally asymptomatic parturients.<sup>18–20</sup> The risk of vertical HIV-1 transmission appears to be the chief concern associated with pregnancy. Our newborn HIV-1 infection rate of approxi-

\*\* Gershon RY, Williams DM, Berry AJ, Lindsay MK, Watkins C: The effect of anesthesia on the infected parturient (abstract). *ANESTHESIOLOGY* 77:A1037, 1992.



Table 3. Laboratory Analysis of Immune Function in HIV Infected Parturients\*

|  | Regional Anesthesia     |                          | No Anesthetic Intervention |                          |
|--|-------------------------|--------------------------|----------------------------|--------------------------|
|  | Predelivery<br>(n = 17) | Postdelivery<br>(n = 17) | Predelivery<br>(n = 11)    | Postdelivery<br>(n = 10) |
| CD4 <sup>+</sup> T-lymphocyte (cells/mm <sup>3</sup> ) |                         |                          |                            |                          |
| <200   | 0                       | 1                        | 1                          | 1                        |
| 200–500  | 11                      | 12                       | 5                          | 5                        |
| >500   | 6                       | 4                        | 5                          | 4                        |
| p24 antigen†   | (n = 14)                | (n = 16)                 | (n = 10)                   | (n = 7)                  |
| Positive   | 3                       | 6                        | 3                          | 1                        |
| Negative   | 11                      | 10                       | 7                          | 6                        |
| β2—Microglobulin levels (μg/l)                         | (n = 14)                |                          | (n = 14)                   |                          |
|  | 2.67 ± 0.95             | 3.16 ± 0.92              | 2.41 ± 0.62                | 2.62 ± 0.47              |

Values are mean ± SD.

\* Laboratory values were not available for all patients at each time period.

† p24 is measured as antigen positive or negative.

mately 11% is in marked contrast to early studies reporting rates as high as 73%,<sup>15</sup> and our reported lower rate may be decreased further by maternal zidovudine therapy.<sup>21</sup>

Of particular concern in the patient infected with HIV-1 is the extensive neurologic complications that may appear early in the disease and progress with time.<sup>6,15</sup> HIV-1 infects the central nervous system early in the course of the disease, and isolation of the virus from cerebrospinal fluid specimens of seropositive patients with and without neurologic symptoms has been

reported.<sup>22,23</sup> A recent report would suggest that failure to obtain positive cerebrospinal fluid cultures from patients who are HIV-1-seropositive probably results from sampling error, not absence of the virus from the cerebrospinal fluid.<sup>24</sup> Thus, it is our view that the anesthesiologist performing regional anesthesia need not fear contamination of the cerebrospinal fluid with HIV-1, for it is present very early in the disease.

This prospective study of parturients infected with HIV-1 (n = 18) is too small to declare that regional anesthesia is "safe" in this patient population. Further, the relatively stable HIV-1 infections in our patients may not be representative of a larger group of parturients. However, in the patients studied, there were no neurologic or infectious complications related to the anesthetic or obstetric course. In the immediate postpartum period, the immune function measurements remained essentially unchanged, as did the severity of the disease. Thus, we believe these data, though limited, support the use of regional anesthesia in the parturient infected with HIV-1 after careful clinical evaluation and review of routine data.

The authors thank Sara Tarbox, for her administrative support, and Winifred von Ehrenburg, for her editorial assistance.

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Table 4. Medical Problems and Drug Therapy

|  | Predelivery | Postdelivery |
|--|-------------|--------------|
| Regional anesthesia (n = 18)                             |             |              |
| Asymptomatic infection                                   | 8           | 7            |
| Endocarditis   | 1           | 0            |
| Oral hairy leukoplakia                                   | 2           | 3            |
| Persistent generalized lymphadenopathy (lymphadenopathy) | 4           | 8            |
| Pneumocystis pneumonia                                   | 2           | 2            |
| Zidovudine use   | 5           | 8            |
| No anesthetic intervention (n = 12)                      |             |              |
| Asymptomatic infection                                   | 5           | 4            |
| Endocarditis   | 1           | 0            |
| Oral hairy, leukoplakia                                  | 4           | 4            |
| Persistent generalized lymphadenopathy (lymphadenopathy) | 3           | 4            |
| Pneumocystis pneumonia                                   | 0           | 0            |
| Zidovudine use   | 4           | 7            |



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