# Followup Study of Possible HIV Seropositivity Among Abusers of Parenteral Drugs in 1971–72

W. ROBERT LANGE, MD, MPH
JOHN C. BALL, PhD
WILLIAM H. ADLER, MD
EDWARD BROWN, PA-C
ROBERT PYLE
WILLIAM HOFFMAN
ELIZABETH M. DAX, MD, PhD

The authors are with the Public Health Service. Dr. Lange, Dr. Ball, Mr. Brown, Mr. Hoffman, and Dr. Dax are with the National Institute on Drug Abuse's Addiction Research Center. Dr. Adler and Mr. Pyle are with the National Institute on Aging's Gerontology Research Center.

Tearsheet requests to W. Robert Lange, MD, NIDA, ARC, P.O. Box 5180, Baltimore, MD 21224

**Synopsis**

*Serum specimens obtained from a nationwide sample of parenteral drug abusers (PDAs) during the period 1971–72 had previously been screened for human immunodeficiency virus (HIV) antibodies. Some specimens were considered to be positive to both ELISA and Western blot (WB) analysis. These findings have been a topic of controversy, since HIV was not thought to have penetrated at-risk populations at such an early date. This study was a followup of those PDAs with apparent seropositivity to WB analysis.*

*Of 10 persons followed, only one death (in 1985) was documented, and postmortem findings were inconsistent with HIV infection. Eight of the remaining PDAs were traced and found to be alive and well in 1989. Fresh specimens were obtained from the two persons with the strongest 1971—72 WB staining and were found to be both ELISA and WB negative on retesting. Their T-cell parameters were within normal limits.*

*We concluded that the earlier WB results were most likely false positives and that definitive evidence of HIV infection in the U.S. addict population as early as 1971–72 is still lacking.*

THE CONDITION THAT BECAME KNOWN as the acquired immunodeficiency syndrome (AIDS) came to public attention in 1981 when cases of pneumocystis pneumonia and Kaposi's sarcoma were reported among male homosexuals in New York and California (*1, 2*).

The first cases of the epidemic were recognized retrospectively to 1978 (*3*). The first case of AIDS in a parenteral drug abuser (PDA) was not reported until 1980 (*4*).

Patients who met the Centers for Disease Control's surveillance definition for AIDS were reported sporadically during the pre-AIDS era (*5*). The issues of when human immunodeficiency virus (HIV) was introduced into what are now defined as at-risk populations in the United States, and how widespread its penetration was in the pre-AIDS era, are unresolved.

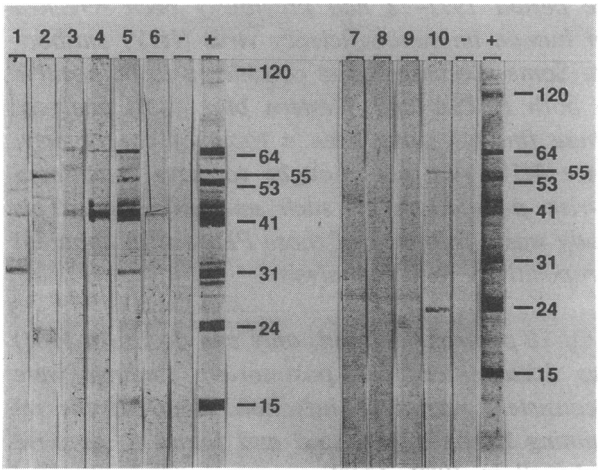
HIV antibodies were detected in banked serum specimens of PDAs from the New York City metropolitan area as early as 1979 (*6*). Whether HIV or a similar virus was present earlier is speculative. There is at least one reported case for which serologic testing of banked serum specimens substantiated that in 1968 a patient with clinical immune deficiency was infected with a virus closely related to or identical to HIV (*7*).

Investigators at the National Institute on Drug Abuse's Addiction Research Center previously reported the results of HIV-antibody testing of banked serum specimens obtained from PDAs in the period 1971–72 that had been studied in 1985 (*8*). On the basis of apparently positive Western blot (WB) data, it was suggested that PDAs may have been exposed to HIV or a related virus within the United States as early as 1971. However, another possible explanation was that the WB reactivity represented false positive or nonspecific reactions. The purpose of the investigation reported in this article was to determine which of the two alternatives is more probable.

## Methods

**Population.** The initial study group consisted of 1,129 addicts (949 men and 180 women) consecu-

Western blot results of selected parenteral drug abusers admitted to Lexington in the period 1971–72 whose banked serum specimens were studied in 1985




NOTE: Clinical followup was conducted in 1989. The criterion used in 1985 for a positive immunoblot was the presence of band p24 or band gp41 either alone or in combination with other bands. In followup study, Western blots with isolated p24 bands were considered to be indeterminate.

tively admitted to the National Institute of Mental Health's former Clinical Research Center at Lexington, KY, between May 15, 1971, and May 14, 1972. The demographic, drug use, and non-HIV infectious disease experience of this cohort of PDAs has been described (*9*). The subjects came from 260 metropolitan areas in 41 States. Serum specimen samples for each patient had been collected systematically and stored at a temperature of minus 70 degrees Celsius.

**Laboratory.** The WB results from the earlier study, which had employed a technique enhanced by the use of an avidin-biotin system (*10*), were reanalyzed. The Centers for Disease Control issued diagnostic criteria in 1985 recommending that a WB be considered positive if either band p24 or band gp41 was present alone or in combination with other bands (*11*). On rereading, blots with isolated p24 bands were considered to be indeterminate. One 1985 WB, with bands at both the 24 and 55 kilodalton regions, was included among the positives, since the interpretation of this pattern had previously been unclear (*12*). The 1971–72 serum specimens were not available for retesting.

The two patients with the strongest 1985 WB staining patterns (patterns 4 and 5) consented to retesting. Their serum specimens were subjected to both enzyme-linked immunosorbent assay (ELISA) and WB analysis, with current criteria for WB seropositivity considered to be the presence of gene products in the GAG, POL, and ENV regions (*13*). Selected immune function tests were conducted on the two patients, including total white cell count; differential lymphocyte subset enumeration (*14*); *in vitro* lymphocyte proliferative responses to the mitogens phytohemagglutinin, concanavalin-A, and pokeweed; and *in vitro* pokeweed-induced immunoglobulin class G (IgG) and immumoglobulin class M (IgM) synthesis (*15*). Natural killer cell activity and viral culture were not studied because of the delay between blood drawing and analysis.

**Followup.** The names of the 10 persons with potentially positive WB patterns, when the more specific 1985 criteria were used, were entered into the National Death Index (NDI) file, National Center for Health Statistics, for the years 1979—88. A supplementary mortality search was conducted through the Social Security Administration (SSA).

A status report was requested from both the local drug treatment program with which each former patient was affiliated, either before or after the Lexington admission, and from the local U.S. Attorney's office, which would have overseen the Lexington assignment under the provisions of the Narcotic Rehabilitation Act of 1966. The two sources of information were identified from the patients' Lexington medical charts. Finally, if the patient's current status still was not able to be determined, the patient, the next-of-kin, or an associate described in the medical record was asked. After current status was determined, the patient's interest in participating in a medical followup study was solicited. Informed consent was obtained and participants were reimbursed for their time and expenses.

## Results

**Mortality surveillance.** The 1985 WB patterns of the 10 persons undergoing followup are shown in the chart. NDI file data indicated only one death among the 10 patients in the period 1979–88. Supplementary SSA statistics did not confirm any additional deaths among them either for the years that NDI data were available or for the intervening years between the time of their Lexington discharge and NDI startup (1972–79).

The death occurred in June 1985, 13 years and 10 months following the Lexington admission, in a motor vehicle accident. The investigation carried out by the local medical examiner's office included a complete postmortem examination. The weight of the patient at the time of death (87.7 kilograms) was more than 30 percent higher than his weight while at Lexington (67.3 kilograms). There were no

lymphoreticular changes at autopsy, and a thorough retrospective analysis provided no evidence of either current substance abuse or HIV infection.

**Client followup.** The followup of the nine persons not identified as deceased by the mortality surveillance provided no record of subsequent death. As shown in table 1, current information was obtained on seven of them. Information was obtained on an eighth person through December 1978, 7 years and 4 months following admission to Lexington. This date corresponded to that person's discharge from a drug treatment program with a successful treatment outcome. The eighth person, and the person for whom no current assessment was available, had social security numbers. Because this information was likely to have been recorded in the NDI or SSA data, it is unlikely that they were deceased.

Of the seven Lexington addicts confirmed as livng in 1989, none was reported to be chronically ill. One subject was incarcerated, and his family reported his health to be good. One client was enrolled in a methadone maintenance program. Another was reported to be involved with illicit drugs on a sporadic basis. The others were thought to be currently drug free, except for use of alcohol and tobacco.

**Laboratory followup.** The two former patients whose 1971–72 WB results were most strongly reactive had current ELISA and WB assays that were negative. Their immune function parameters (table 2) were inconsistent with immune suppression.

## Discussion

Although sporadic cases of apparent AIDS were evident prior to the start of the epidemic in 1978, we were unable to confirm earlier claims of HIV infection among PDAs in the early 1970s by clinical followup procedures. The deceased patient did not die of AIDS and did not have any evidence of lymphoid tissue depletion, the most consistent and striking autopsy finding in patients with HIV illness (*16*). There was no evidence of Kaposi's sarcoma or opportunistic infection with *pneumocystis carinii*, cytomegalovirus, or acid-fast bacilli.

The results of the ELISA and WB assays performed on the 1971–72 specimens remain an enigma. Some were interpretable as positive, although only weakly reactive. One explanation is that the results observed in 1985 were true positives, that PDAs in the early 1970s had antibodies to an HIV-like agent that was nonpathogenic, and

Table 1. Characteristics of potential HIV-positive parenteral drug abusers, 1971–72

| Subject number | Year of birth | Sex | Race | Western blot bands | Status |
|---|---|---|---|---|---|
| 1 | 1952 | Female | Black | 41, 55, 64/66 | Unknown |
| 2 | 1953 | Male | Black | 24, 41, 51/53, 55 | Alive 1989 |
| 3 | 1958 | Male | White | 41, 55, 64/66 | Alive 1989 |
| 4 | 1946 | Male | Black | 41, 55, 64/66 | Alive 1989 |
| 5 | 1943 | Male | Black | 15/17, 31, 41, 51/53, 55, 64/66 | Alive 1989 |
| 6 | 1927 | Male | Black | 41 | Died 1985 |
| 7 | 1944 | Male | Black | 24, 41 | Alive 1978, unknown 1989 |
| 8 | 1954 | Female | Black | 24, 41 | Alive 1989 |
| 9 | 1950 | Female | Black | 24, 41 | Alive 1989 |
| 10 | 1948 | Male | Black | 24, 55 | Alive 1989 |

that the WBs subsequently converted from positive to negative. Loss of HIV antibodies in asymptomatic homosexual men has been reported (*17*). It is possible that antibodies to a nonpathogenic virus would have disappeared during the 17 to 18 years between admission to Lexington and the 1989 followup. Although this potential cannot be ruled out, it is more likely that the earlier results were false positives.

The reasons for false positivity are unclear (*18*), but cross reactivity with related retroviruses may be one possibility. The HIV Western blot assay may cross-react with antibodies to HTLV-I in the p24 and p55 antigen regions (*19*), but not the gp41 region (*20*). These serum specimens were tested for the presence of HTLV-I/HTLV-II antibodies by other investigators, and a 6.3 percent seropositivity rate for the entire cohort was observed (*21*). It is not known if these 10 persons were seropositive for this related retrovirus; however, it is unlikely that this type of cross reactivity accounted for the previous results, given the distribution of the bands and the fact that reactivity was not detected during selected 1989 followup WB screening.

The earlier false positivity could be the consequence of either the state of the serum specimens or the test kit or assay employed. It has been suggested that artifactual findings may occur as a consequence of frequent thawing and refreezing of serum aliquots, and that frequent refreezing might affect the physical properties and serologic characteristics of the serum protein moieties. The available evidence would suggest that long-term storage and repeated thawing and refreezing does not affect subsequent testing for serum constituents (*22*). We recently screened 6,045 banked serum specimens for HIV antibodies from another popu-

Table 2. Immune function tests of selected parenteral drug abusers with apparent HIV seropositivity in 1971–72

| Assay | Normal values | Subject Number 4 | Subject Number 5 |
|---|---|---|---|
| Lymphocytes (N/mm$^3$) ... | 1,100–4,800 | 2,880 | 5,040 |
| B-cells ..... | 165– 720 | 480 | 950 |
| Absolute percent ..... | 15 | 17 | 14 |
| T-cells..... | 880–3,840 | 2,330 | 5,040 |
| Absolute percent .... | 80 | 81 | 80 |
| T-helper cells ..... | 440–1,920 | 1,150 | 3,110 |
| T-suppressor cells... | 260–1,150 | 1,240 | 2,970 |
| T-helper to T-suppressor ratio.. | 0.9–1.7 | 0.9 | 1.0 |
| Mitogen responses (CPM): | | | |
| Phytohemagglutinin ... | 90–120x10$^3$ | 75,316 | 103,205 |
| Concanavalin-A ..... | 70–100x10$^3$ | 22,399 | 36,786 |
| Pokeweed (PWM) ..... | 10– 50x10$^3$ | 15,863 | 15,523 |
| Background..... | 0– 2x10$^3$ | 1,616 | 1,571 |
| In vitro antibody synthesis (µg/mL): | | | |
| Background IgG..... | | 5 | 6 |
| Pokeweed stimulated IgG ..... | Positive | 583 | 308 |
| Background IgM ..... | | 7 | 4 |
| PWM stimulated IgM .. | Positive | 376 | 306 |

NOTE: N/mm3 = number per cubic millimeter; absolute percentage = percent of total lymphocyte pool; CPM = counts per million; µg/mL = micrograms per milliliter; IgG = immunoglobulin class G; and IgM = immunoglobulin class M.

lation dating back to 1967 that had been thawed and refrozen on multiple occasions (*23*). Even though there were indeterminate WB results detected during that study, there were neither false positive readings nor artifactual bands at gp41.

The specificity of the experimental WB used in the 1985 investigation has not been clearly defined. The avidin-biotin system is an enhancing technique, with wide bioanalytical applicability (*24*). It is conceivable that, while increasing the sensitivity of the WB assay, the experimental WB may have had decreased specificity, which would have increased the likelihood of nonspecific reaction. This factor remains a distinct possibility for explaining the false positive results observed. Although it has many uses, the avidin-biotin enhancing procedure has not emerged as a technique facilitating HIV antibody testing. Limited investigation of the 1971–72 samples at the National Institutes of Health, using experimental techniques, including radioimmunoprecipitation, suggested that the original avidin-biotin enhanced assays were probably false positive.

We concluded that definitive evidence of HIV infection in the United States' addict population as early as 1972 is still lacking. The sample of Lexington addicts was of sufficient size and geographic spread that had HIV been present in PDAs in the early 1970s (except for rare, isolated occurrences), there was a strong possibility that it would have been confirmed in this investigation.

## References


1. Pneumocystis pneumonia—Los Angeles. MMWR 30: 250–252, June 5, 1981.
2. Kaposi's sarcoma and pneumocystis pneumonia among homosexual men—New York City and California. MMWR 30: 305–308, July 3, 1981.
3. Jaffe, H. W., Bregman, D. J., and Selik, R. M.: Acquired immune deficiency syndrome in the United States: the first 1,000 cases. J Infect Dis 148: 339–345 (1983).
4. Selik, R. M., Haverkos, H. W., and Curran, J. W.: Acquired immune deficiency syndrome (AIDS) trends in the United States, 1978–1982. Am J Med 76: 493–500 (1984).
5. Huminer D., Rosenfeld, J. B., and Pitlik, S. D.: AIDS in the pre-AIDS era. Rev Infect Dis 9: 1102–1108 (1987).
6. Des Jarlais, D. C., Friedman, S. R., and Hopkins, W.: Risk reduction for the acquired immunodeficiency syndrome among intravenous drug users. Ann Intern Med 103: 755–759 (1985).
7. Garry, R. F., et al.: Documentation of an AIDS virus infection in the United States in 1968. JAMA 260: 2085–2087, Oct. 14, 1988.
8. Moore, J. D., Cone, E. J., Alexander, S. S., and Jaffe, J. H.: HTLV-III seropositivity in 1971–1972 among parenteral drug abusers—a case of false positives or evidence of viral exposure? N Engl J Med 314: 1387–1388 (1986).
9. Lange, W. R., et al.: The Lexington addicts, 1971–1972: demographic characteristics, drug use patterns, and selected infectious disease experience. Int J Addict 24: 609–626 (1989).
10. Alexander, S. S., et al.: Western blot analysis of human T-cell lymphotropic virus III proteins by using an avidin-biotin system. Presentation to the American Society for Microbiology, Las Vegas, NV, March 3–7, 1985.
11. Provisional Public Health Service interagency recommendations for screening donated blood and plasma for antibody to the virus causing acquired immunodeficiency syndrome. MMWR 34: 1–5, Jan. 11, 1985.
12. Burke, D. S., et al.: Diagnosis of human immunodeficiency virus infection by immunoassay using a molecularly cloned and expressed envelope polypeptide: comparison to Western blot on 2707 consecutive serum samples. Ann Intern Med 106: 671–676 (1987).
13. Interpretation and use of the Western blot assay for serodiagnosis of human immunodeficiency virus type 1 infections. MMWR 38 (supp. 7): S1–S7, July 21, 1989.
14. Nagel, J. E., Chrest, F. J., Pyle, R. S., and Adler, W. H.: Monoclonal antibody analysis of T lymphocyte subsets in young and aged adults. Immunol Commun 12: 223–237 (1983).
15. Chrest, F. J., Nagel, J. E., Pyle, R. S., and Adler, W. H.: Human B cell function in responding and non-responding individuals. II. The role of T helper cells in promoting the PWM-induced B cell production of immunoprotein. Clin Exp Immunol 53: 465–472 (1983).
16. Welch, K., et al.: Autopsy findings in the acquired immune deficiency syndrome. JAMA 252: 1152–1159, Sept. 7, 1984.

17. Farzadegan, H., et al.: Loss of human immunodeficiency virus type 1 (HIV-1) antibodies with evidence of viral infection in asymptomatic homosexual men. A report from the Multicenter AIDS Cohort Study. Ann Intern Med 108: 785–790 (1988).
18. Dock, N. L., et al.: Evaluation of atypical human immunodeficiency virus immunoblot reactivity in blood donors. Transfusion 28: 412–418 (1988).
19. Groopman, J. E., et al.: Serological characterization of HTLV-III infection in AIDS and related disorders. J Infect Dis 153: 736–742 (1986).
20. E. I. DuPont and Co.: Human immunodeficiency virus (HIV) Biotech/DuPont HIV western blot kit. Package insert. Wilmington, DE, 1988, 22 pp.
21. Saxinger, C., et al.: Retrospective study of HTLV 1/HTLV 2-related antibody reactivity in U.S. drug abusers. Presented at 4th International Conference on AIDS, Stockholm, June 12–16, 1988.
22. DiMagno, E. P., et al.: Effect of long-term freezer storage, thawing, and refreezing on selected constituents of serum. Mayo Clin Proc 64: 1226–1234 (1989).
23. Lange, W. R., et al.: Are missionaries at risk for AIDS? Evaluation for HIV antibodies in 3,207 protestant missionaries. South Med J 82: 1075–1078 (1989).
24. Wilchek, M., and Bayer, E. A.: The avidin-biotin complex in bioanalytical applications. Anal Biochem 171: 1–32 (1988).

# Comparison of Examination Fees and Availability of Routine Vision Care by Optometrists and Ophthalmologists

MORDACHAI SOROKA, PhD

Dr. Soroka is with the Center for Vision Care Policy, State College of Optometry, State University of New York, 100 East 24th Street, New York, NY 10010. Tearsheet requests to Dr. Soroka.

**Synopsis**

*A national telephone survey of eye care practitioners shows that the average fee for routine eye examinations was less among optometrists than ophthalmologists. The average wait for the earliest appointment was 5 days for optometrists and 20 days for ophthalmologists. Weekend and evening appointments were also more obtainable among optometrists. The study did not determine what tests were included in the routine examination of each practitioner.*

*Optometrists are licensed to use diagnostic drugs in all 50 States and prescribe therapeutic drugs for the treatment of ocular diseases in 25 States. Legislation that would update State laws permitting doctors of optometry to prescribe and use pharmaceutical agents for the treatment of eye diseases has been introduced in many of the remaining States. Supporters of bills permitting therapeutic pharmaceutical optometry contend that these changes would ensure the availability of quality eye care at significant savings, since optometric fees are generally lower than opthalmological fees. In addition, it has been argued that optometrists are equitably distributed geographically and are more likely to have weekend and evening office hours, thus enabling increased patient access to eye care. When considering cost-effectiveness and accessibility, this study may provide information to those States considering changes in the scope of optometric licensure.*

MOST EYE CARE EXAMINATIONS in this country are provided by optometrists and ophthalmologists. Optometrists (doctors of optometry, [ODs]) provide complete eye examinations including tests for ocular disease and refractions for eyeglasses. Optometrists are licensed to use diagnostic drugs in all 50 States and prescribe therapeutic drugs for the treatment of ocular disease in 25 States. They are trained to diagnose eye diseases and detect ocular manifestations of other systemic diseases.

Ophthalmologists (MDs) are physician specialists who perform eye surgery, treat ocular disease, and provide general eye examinations including refractions. The services of optometrists and ophthalmologists overlap in the provision of general eye examinations and tests to diagnose disease. The overwhelming number of eye care visits are for these services.

In 1988, there were 26,100 active optometrists (*1*) and 15,581 active ophthalmologists in the United States (*2a*), with 10.6 optometrists per 100,000 population as compared with 6.3 ophthalmologists (table 1). The ratio of both optometrists and ophthalmologists varies considerably among States. Ophthalmologists tend to be concentrated in the Northeast and Midwest, while optometrists have above-the-average ratios in all census regions of the country except the South (*3a*).