Report of an Expert Panel on the Public Health Laboratory Role in Early Intervention and Treatment of Human Immunodeficiency Virus Infections

This report was adopted by the Executive Committee of the Association of State and Territorial Public Health Laboratory Directors in January 1990 and approved by the Association of State and Territorial Health Officers in July 1990.

The participants on the special panel and their affiliations are listed in the accompanying box.

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RECENT MODIFICATIONS IN THE CARE, management, and treatment of persons infected with the human immunodeficiency virus (HIV) have caused State and local public health laboratories to re-evaluate their traditional diagnostic and supportive roles. New guidelines call for regular monitoring of those with HIV infection by laboratory systems not characteristic of State-level public health laboratories. Immunophenotyping of lymphocytes by complex flow cytometry is the most outstanding example.

Public health virologists have become concerned about the development of viral strain resistance as zidovudine and dideoxyinosine become more commonly used. There is mounting evidence of HIV strain differences as different viral isolates are studied. Also, indicators of immune system function, such as beta-2-microglobulin and neopterin, are becoming common public health laboratory procedures.

The public health laboratory is confronted with issues such as

- investing more than $250,000 in a flow cytometry program,
- establishing retrovirology laboratories to monitor developing antiviral resistance,
- providing additional safe and appropriate laboratory facilities,
- acquiring trained staff, and
- providing polymerase chain reaction technology to diagnose HIV infection in infants born to antibody-positive mothers.

These issues and many other questions have generated a concern among directors of State public health laboratories who have sought advice and counsel from their colleagues, the Association of State and Territorial Public Health Laboratory Directors (ASTPHLD), as well as its Committee on Human Retrovirus Testing.

To address these issues, a panel of experts, endorsed by the Association of State and Territorial Health Officials (ASTHO), was convened by the ASTPHLD in Amana, IA, on December 11, 1989. A list of participants appears in the accompanying box.

While the content and direction of this report may represent a departure from current public health laboratory practice in some jurisdictions, it also represents the first opportunity for public health laboratories to call attention to their primary role in the HIV epidemic. Until now, most efforts have focused on containment or patterns to restrict spread of infection by directly linking laboratory testing with counseling. We are now entering a new age, however, with emphasis on early intervention and treatment. Counseling is a vital primary ingredient in the epidemic, but financial support for public health laboratory programs should not be directly linked to counseling. Escalating laboratory expenses for viral isolations, monitoring of immune status, and flow cytometry require new funding mechanisms. Counseling must be linked financially to screening tests and, where necessary, confirmatory tests, but beyond that level there is a great disparity—from nothing to partial—in the funding necessary for public health laboratories to provide diagnostic and disease monitoring activities.

This expert panel report is designed to encourage debate and discourse, to provide guidance to those responsible for public health laboratories, and to set future directions for addressing the complex issues of HIV epidemic control in differing jurisdictions. This is not a protocol for action.

Statement of the Problem

As recommended by the Presidential Commission on the Human Immunodeficiency Virus Epidemic (*1*), the development of an integrated program for the care of

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individuals at all stages of HIV infection is an essential component of the national response to the HIV-AIDS epidemic and should be given highest priority. The goal of this program must be early intervention to prevent transmission of HIV and to delay disease progression in infected persons. To reach these goals, such a program must be a coordinated effort consisting of medical, psychosocial, and behavioral interventions. Early intervention will significantly decrease the overall cost of care through a reduction of new infections, prolongation of productive lives, and a decrease in hospitalizations.

No single model for such a program will serve every State. Professionals from public health, private sector, university settings, and third party payors must plan, develop, and implement a program appropriate to their resources and the prevalence of HIV infection. HIV infection is a public health problem, and the State public health department should be the lead agency in assuring the coordination of all program elements. Therefore, the State public health laboratory has an important and primary role in the development, provision, and quality assurance of laboratory services for the diagnosis and management of HIV infection.

Identification of Responsibilities

The functions of a public health laboratory uniquely parallel the core functions of public health agencies (*2*), that is, assessment, policy development, and assurance and they are built on a long tradition of successful practice in public health. In assessment, the public health laboratory provides testing for surveillance and prevention of disease; in policy development, there are the direct laboratory contributions to public health as well as research on new problems; in assurance, there are major components of licensing, training, quality assurance-proficiency testing, and reference laboratory work.

In the HIV epidemic, the public health responsibility is to assure that the following coordinated services are available to all HIV-infected persons: (*a*) medical care including early intervention, (*b*) psychosocial support, and (*c*) preventive counseling. A wide range of care service systems and facilities appropriate to the needs of HIV-infected persons must be made readily available.

Laboratory services are an essential component in the detection, evaluation, treatment, and followup of the HIV-infected person. The public health laboratory director must be included in planning for the provision of laboratory services required to support HIV programs. The role of public health laboratories in the control of the HIV epidemic is to

1. Provide quality assured testing in the public and private laboratories,
2. Assure the accuracy of testing in the public and private sectors for identification and management of HIV-infected persons,

3. Develop or validate (or both) laboratory services for the diagnosis and management of HIV infections and related illnesses,
4. Train personnel to provide these services, and
5. Assure clarity and accuracy in the reporting of HIV results.

To serve this role there is need for adequate resources such as (*a*) financial support, (*b*) training, (*c*) reagents and standards, (*d*) protocols, (*e*) information sharing systems, and (*f*) performance evaluation. These resources should be made available at the national, State, and local levels.

Specific Laboratory Issues

To control the HIV epidemic, the following laboratory services require special attention:

1. Testing to identify HIV infection. The ASTPHLD has sponsored five consensus conferences on "Testing for Human Retroviruses" since 1986 promoting standardization of procedures and reporting of HIV screening (that is, enzyme immunoassay (EIA)) and confirmatory tests (that is, Western blot (WB) and immunofluorscence assay (IFA)). These conferences provide an effective mechanism for a continuing evaluation of program and uniform testing guidelines by public health laboratory scientists. Recognized problems are

a) The lack of FDA approval of reagents and kits as medical devices for the diagnosis of HIV infection. Currently, these materials are treated as biologics and listed by the FDA "for research purposes only." The current licensure system by the FDA Center for Biologics Evaluation and Research represents an impediment to new test development as well as an inappropriate classification and restriction on materials used in diagnosis and epidemic control.

b) The need for more comprehensive laboratory evaluation programs which consider the pre- and post-analytic phases of testing in addition to the analytic phase. Proficiency testing programs should provide a rapid assessment of laboratory performance as part of a total quality assurance program.

2. Testing to establish stage of HIV infection

a) Specific HIV antibody and antigen testing. Reagents for qualitative and quantitative measurements of HIV antibodies, antigens, and other markers for prognostic purposes should be made available. Approval of these tests as medical devices rather than biologics is strongly urged in order to make them available in a form suitable for use in early intervention programs.

b) Flow cytometry

i) Immunophenotyping of lymphocytes by flow cytometry services should include the white blood cell count, total lymphocyte count, CD3, CD4, CD8, CD19 or 20, and CD16 or 56 for diagnostic purposes and for self-consistency checks. There is need for better standardization and quality control of reagents and procedures. The proposed National Committee on Clinical Laboratory Standards H42P guideline could serve this purpose when adopted.

ii) Monoclonal antibodies for immunophenotyping of CD4 and CD8 lymphocytes are presently restricted by the FDA for research purposes only. Since early intervention and monitoring progression of infection in asymptomatic HIV-infected persons depend on the availability of CD4 and CD8 cell counts, licensure of these reagents for *in vitro* diagnostic or prognostic purposes by the FDA is urgently needed.

iii) New test development in flow cytometry, such as automated systems which require little specimen preparation, may provide more rapid and accurate analytic capabilities.

iv) Critical issues of transport time, temperature effects, and choice of anticoagulant require intensive study.

v) Since lymphocyte enumeration is a major and expensive test procedure for monitoring HIV-infected patients in this new era of early intervention, States must immediately address the availability and capacity of this procedure.

c) Virus isolation and antigen detection. The usefulness and predictive value of virus and viral component detection in clinical specimens urgently requires further investigation. Issues regarding HIV culture and antigen detection are found in the "Proceedings of the Fourth Consensus Conference on Testing for Human Retroviruses" (*3*).

d) Nonspecific markers. Controlled studies are needed to determine the usefulness and validity of monitoring HIV-infected persons with nonspecific markers such as beta 2-microglobulin. There is insuffi-

cient information to determine whether nonspecific markers can be substituted for, or are a useful adjunct to, lymphocyte subset enumeration in prognostic staging of HIV infections.

e) Opportunistic infections. Comprehensive laboratory detection capabilities for infections associated with immunodeficiency (for example, *Pneumocystis carinii* pneumonia, cytomegalovirus infections, mycotic infections, toxoplasmosis) are required. Interpretive reporting must be part of such laboratory services.

3. Testing to support control of secondary spread of disease

a) HIV culture for determining drug resistance. Very few public health laboratories have inaugurated HIV culture from clinical materials, although many routinely provide this testing in the assessment of other viral diseases. As anti-HIV compounds become more aggressively administered, it is not unreasonable to assume that changes may occur in patterns of resistance. Public health laboratories need to reassess their capabilities to support HIV isolations from clinical materials.

b) Control of other communicable infections common among HIV patients. Public health laboratories need to re-evaluate their support of tuberculosis and sexually transmitted disease clinics. Some of the laboratory assessment work currently being done in these clinics has been transferred from most State public health laboratories. New technologies in molescular epidemiology make it increasingly important to re-introduce these laboratory efforts at the State level in order to assist in the surveillance of these infections as well as HIV.

4. Additional demands for general laboratory services

a) Clinical laboratory assessments. There will be greater demands on clinical laboratories (that is, hematology, microbiology, immunology, clinical chemistry, and transfusion services) as a result of the increasing number of HIV-infected persons and their longer life span.

b) Professional interaction. A relationship should be established among ASTPHLD, AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases, Centers for Disease Control, other Federal agencies, and professional organizations for exchange of information on quality assurance, laboratory procedures, utility of tests, and emerging technologies.

c) Continuing education and methods development. Public health and clinical laboratories will be affected by developments in drug resistance testing, new markers, opportunistic infections, and new therapies. Therefore, public health laboratories, professional organizations, and appropriate Federal agencies should increase efforts to provide, or to make available, programs, presentations, and training to respond to these developments. Greater resources will be needed to meet these challenges.

The ASTPHLD National Laboratory Training Network, representing a coalition of public and private sector organizations, should assume a major role in the transfer of these technologies.

Resource Requirements

Strategies for funding of public health laboratory assessments in the early intervention and treatment era are urgently needed and must be developed at all levels of public health.

Public health laboratories have been unable to practice their commonly expected role of disease assessment throughout this HIV epidemic. Program monies have been almost exclusively linked to screening programs and, even in those instances to the contrary, the laboratory funds have been directly linked with counseling. Public health laboratory scientists fully recognize the significant importance of counseling in this epidemic, but the result has been a significant deficiency in laboratory funds necessary to monitor disease progression, viral changes, and new and innovative disease detection methodologies. In general, it appears that laboratory funds for any assessment activity are not available unless their use can be directly associated or linked to counseling.

As the need for greater interventional strategies become more apparent, the public health laboratory will be pushed to reconsider the distribution of its limited resources to accomplish new objectives. There must be renewed acceptance that public health laboratories have a primary role in this epidemic as they have had in the major epidemics of the past. This will, of course, require reassessment of the funds necessary for these essential tasks.

Significant societal savings will be achieved by a reduction in medical care, hospitalization, loss of productive life, incidence of new HIV infections, and associated opportunistic infections. The consequences of inaction and continuation of current funding strategies will be a continued escalation of all associated medical costs.

Summary

A coordinated national effort to control the HIV epidemic based on an early intervention model must be ini-

tiated. This national strategy will provide for an effective distribution, application, and utilization of limited Federal, State, and local resources.

References

1. Report of the Presidential Commission on the Human Immunodeficiency Virus Epidemic. U.S. Government Printing Office, Washington, DC, 1988.
2. Committee for the Study of the Future of Public Health, Institute of Medicine: The future of public health. National Academy of Sciences, Washington, DC, 1988.
3. Association of State and Territorial Public Health Laboratory Directors: Proceedings of the Fourth Consensus Conference on Testing for Human Retroviruses. Washington, DC, 1989.

LETTER TO THE EDITOR

FDA's Center for Biologics Evaluation and Research Comments on the Report of the Expert Panel

The Center for Biologics Evaluation and Research, Food and Drug Administration (FDA), welcomes the opportunity to comment on the article entitled "Report of an Expert Panel on the Public Health Laboratory Role in Early Intervention and Treatment of Human Immunodeficiency Virus Infections," appearing in this issue of *Public Health Reports*. The report was first released in July 1990 by the Association of State and Territorial Public Health Laboratory Directors (ASTPHLD).

The report calls for directed and expanded activities related to control of the HIV epidemic. ASTPHLD should be applauded for taking a leadership role in addressing this need, and the general finding in the report that provision of a wide spectrum of laboratory services will be critical to this effort is correct. It is necessary, however, to provide clarification of two points which were raised in the report.

First, the report criticizes the regulation of AIDS-related tests as licensed biological products rather than as medical devices, on the premise that review of these products as devices would be either less stringent with respect to required evidence of safety and efficacy or more rapid. However, the nature of the review process in this product area is not dictated by the type of application required, but rather by the need for high standards of consistency and accuracy for tests with major health significance, such as these. Also, in many cases, AIDS-related tests are used not only for clinical diagnosis, but also to screen blood donated for transfusion. The FDA recognizes the continuing public concern about the safety of the blood supply and, for this reason, also feels that it is appropriate to set high standards for approval of these tests.

Compared with laws on medical devices, laws on biologics do provide the FDA with additional tools for maintaining product standards. Among the safeguards is authority to require lot-by-lot testing and release to ensure that products meet appropriate standards.

Considering the need for extensive validation of manufacturing and clinical performance of these kits, the FDA has been expeditious in its reviews. The first kit for detection of HIV was licensed within 1 year of the discovery of HTLV-III, the virus that causes AIDS, and within 7 months of the first license application. Since that time, many additional products have been licensed in a timely fashion, including tests for HTLV-I. Apparent delays in licensing are often due to problems in manufacturing consistency, deficiencies in clinical data, or controversy over medical claims, issues which are not discussed in the public domain.

A second inaccuracy in the report is the statement that "monoclonal antibodies for immunophenotyping of CD4 and CD8 lymphocytes are presently restricted by the FDA for research purposes only." In fact, these monoclonal antibodies are marketed as medical devices subject to the medical device regulations.

The report also calls for increased cooperation among various agencies. The FDA agrees that cooperation among all institutions involved with public health is important in dealing with the AIDS epidemic. Indeed, ASTPHLD has an ongoing formal relationship with the Public Health Service through the Centers for Disease Control, which has primary responsibility for epidemic control. Additional cooperative roles are certainly possible and should be encouraged.

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