Methods of Surveillance for HIV Infection in Primary Care Outpatients in the United States

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Synopsis

Primary care outpatients provide a good sentinel population for monitoring levels and trends of HIV infection in the United States. Because a broad cross section of the population seeks primary medical care, excess blood from specimens routinely collected for other purposes is available for anonymous, unlinked HIV testing, and all age groups and both sexes can be sampled. The CDC family of surveys includes two surveys of primary care outpatients: (a) a survey of 100,000 blood specimens per year submitted by more than 6,000 primary care physicians to a national diagnostic laboratory for complete blood count or hematocrit and (b) a survey of approximately 10,000 blood specimens per year from a network of 242 primary care physicians.

Each survey has different advantages: the laboratory-based survey has a large sample from a large population base, and the physician network survey has a well-defined patient population in which each patient's clinical condition can be determined. In the primary care physician network, a concurrent study of clinical patterns of disease in patients with recognized HIV infection provides additional information on the clinical syndromes associated with HIV infection and estimates of the occurrence of unrecognized HIV infection.

ONE OBJECTIVE OF THE CENTERS for Disease Control's (CDC) complementary family of human immunodeficiency virus (HIV) surveys and studies is to provide empirical estimates of the extent and trends over time of the HIV epidemic in the United States (*1, 2*). When results of these surveys and studies are considered together with their limitations and biases, national estimates on levels and trends of HIV infection in the United States can be made.

Three sources of empirical data from large population subgroups are used to determine national levels and trends of HIV infection in the population at large. Large populations routinely screened for HIV antibody, including applicants to the military services (*3, 4*), active duty military personnel (*5, 6*), Job Corps entrants (*7*), and blood donors (*8, 9*) are one source of data collection. The data are limited, however, because each of these groups includes only certain narrow demographic and social subgroups of the general population and because, with the exception of active duty military personnel, persons in these populations chose whether to be tested when they volunteer for the activity in question. This situation could result in self-selection bias that may reduce considerably the observed seroprevalence level (*10*).

A second data source, the National Survey of Childbearing Women (*11*), is probably the least biased population-based survey in the family of surveys; however, by definition, it includes only women who have delivered live children. The third data source, persons seeking medical care, has several important advantages: (*a*) excess blood from routinely collected specimens is available for anonymous, unlinked (blinded) HIV testing which eliminates self-selection bias (*2*), (*b*) a broad cross section of the population seeks medical care (*12*), and (*c*) all age groups and both sexes can be sampled.

Three CDC-supported surveys focus on persons seeking medical care other than in public health clinics. Two of these involve outpatients receiving primary care, and the third involves persons treated at hospitals

for reasons presumably unrelated to HIV infection or HIV risk behaviors (*13*). This article describes the two surveys of primary care outpatients.

Objectives

The principal objectives of the surveys are to estimate levels and trends of HIV infection in sentinel populations of primary care outpatients and to determine the spectrum of disease in HIV-seropositive persons identified from these sentinel populations. Data from these surveys will contribute to planning and evaluating prevention efforts in primary care settings.

Primary care outpatients are used as sentinel populations for surveillance because they are accessible for anonymous, unlinked seroprevalence studies, and their overall level of health is probably more similar to the population at large than that of persons seeking specialized medical care or requiring hospitalization. Additionally, a broad cross section of the population interacts with primary care physicians. Inherent biases of studies in medical care settings create uncertainties on how levels of HIV infection in primary care outpatients compare with those of the total population, but as long as these biases remain constant, the observed trends over time should reflect those of the population at large.

Clinical Laboratory Survey Methods

The Clinical Laboratory Survey is an anonymous, unlinked (blinded) HIV seroprevalence survey of blood remaining from specimens submitted to a national clinical diagnostic laboratory for routine clinical purposes. The laboratory's nine central laboratories and one subcontract laboratory serve annually approximately 5 million patients of 12,000 physicians in areas that include approximately 70 percent of the U.S. population. Of these physicians, more than 6,000 have submitted samples during the first 6 months of the survey, which began in February 1989.

Specimen eligibility and selection. Eligible specimens are those submitted from noninstitutionalized patients by general internists, pediatricians, and family practitioners for complete blood count (CBC) or hematocrit, the most commonly ordered diagnostic tests. The sample size is 100,000 per year.

Routinely collected data accompanying all blood specimens received by the laboratory are logged into a computer network. A computer program sequentially selects eligible specimens until monthly predetermined age, sex, and geographic quotas are met. The annual age quotas are 0–3 years, 6,000; 4–14 years, 8,000; 15–24 years, 24,000; 25–44 years, 47,000; 45–64 years, 10,000; and 65 years and older, 5,000. The quota for each age group is divided equally between males and females. If the quantity of leftover serum or plasma is insufficient for HIV testing, additional specimens are selected until the quotas are met.

To prevent repeat testing of specimens from the same patient within a calendar year, the patient's identification number on potentially eligible specimens is compared with a file containing patient identifiers of specimens already considered for the survey. This file cannot be linked in any manner to the data file that contains HIV test results.

Information Collected in the Clinical Laboratory Surveillance System Data Set

Demographics: age, sex, postal zip code of patient, postal zip code of physician, month and year of specimen collection

Physician specialty: internist, pediatrician, family practice

Socioeconomic status: type of billing—Medicaid, private insurance, Medicare, and so forth

Diagnostic: International Classification of Diseases (ICD–9) code (usually not available)

Laboratory: all diagnostic tests ordered, complete blood count or hematocrit results, results of HIV–1 EIA and Western blot

Data processing and management. The computer assigns a unique survey number to each selected specimen and creates a data file containing the survey number, other routinely collected demographic and billing information, the names of the other diagnostic tests ordered, and the CBC or hematocrit results (see box, above). Data are limited to those routinely available; no information is specifically collected for the purposes of the survey. The HIV test results are subsequently added to the data file.

The computer also creates a candidate summary file containing the total number of eligible specimens and the number actually selected from each age, sex, and geographic quota. These data are used to determine the sampling fractions needed to estimate the HIV seroprevalence of all clinical laboratory specimens.

The blinding process. Two safeguards prevent direct linkage of HIV test results to an individual person: tubes of blood from selected specimens are relabeled with a survey number before HIV testing, and no file contains both survey numbers and personal identifiers.

To prevent indirect linkage of test results to individ-

ual persons, certain information is not collected in the data file, such as the exact date that the test was submitted to the laboratory (only month and year) or the name of the physician ordering the test. Additionally, since the HIV enzyme-immunoassays (EIA) are performed at one of the laboratories collecting specimens and the Western blot tests are done at a second laboratory, the possibility that persons labeling the blood tubes with the study numbers could gain access to HIV test results is further reduced. Finally, routinely collected data files for all submitted specimens are erased quarterly from the laboratory computer, thereby reducing the possibility of indirect linkage of these records to those in the study data base.

Survey Methods in Ambulatory Practices

The Ambulatory Sentinel Practice Network (ASPN) was established in 1978 to conduct practice-based research in primary care medicine. ASPN currently is composed of 78 practices with 242 clinicians, 90 percent of whom are family practitioners. The network has an active patient population (last physician visit within the previous 2 years) of approximately 350,000. The practices are geographically dispersed throughout the United States (69 practices) and Canada (9 practices).

HIV surveillance in ASPN has several major advantages: (*a*) the physicians are well-characterized and have both interest and experience in conducting research, (*b*) the patient population is well-defined (all patients from 64 practices are entered into an age-sex registry, and (*c*) the physicians can characterize their patients' clinical conditions. Since the patients' clinical conditions are known, the bias of including patients in the seroprevalence survey who specifically sought medical care because of HIV infection or risk factors can be assessed, and the spectrum of recognized HIV-related disease can be simultaneously determined. HIV surveillance in ASPN practices has two interrelated components: an anonymous, unlinked survey to determine the overall HIV seroprevalence in ASPN patients and a study to characterize the clinical status and spectrum of disease of patients with recognized HIV infection.

Specimen eligibility and selection. As of December 1, 1989, 51 ASPN practices had agreed to participate in the HIV seroprevalence survey. Patients, ages 15 to 49 years, who have blood drawn for clinical purposes, are eligible for the survey. Sampling occurs during a 3-month period each year in each participating practice. Patients younger than 15 years are excluded, since the sample size for this age group would be too small to make precise seroprevalence estimates. Patients older than 49 years are excluded to allow participating physicians to focus their efforts on age groups expected to be at the highest risk for HIV exposure. To ensure that a patient only has one specimen included in each survey period, blood specimens are excluded if the patient had blood drawn earlier in the sampling period. The annual sample size is approximately 10,000 specimens.

Data processing and management. When a blood specimen is ordered for an eligible patient, the physician completes a survey information card which contains demographic, HIV risk factor, and clinical information (see box page 161). HIV risk factor information is the physician's *perception of risk* because patients cannot be questioned about risk behaviors specifically for the purposes of this anonymous, unlinked survey. Blood in excess of that required for the ordered tests is then sent to ASPN headquarters for HIV testing. Study information cards are sent to ASPN headquarters separately for computer entry. The HIV antibody testing is conducted at a central laboratory, and the results are linked to demographic and other survey information.

The blinding process. After the routine clinical testing is complete, the leftover blood specimens are relabeled with a survey number and the patient identifiers are removed. The survey information card, also labeled with the study number, has no patient identifier. No data file contains both patient identifiers and study numbers.

To prevent indirect linkage of study information to a person, survey results are reported only by geographic region. Practice-specific data are not released to participating physicians. Furthermore, only the quarter year of the patient's visit and the patient's age by 5-year intervals are collected. To further ensure anonymity, 2 percent of the selected specimens and their corresponding data cards are randomly discarded before HIV testing.

Spectrum of disease study. The primary objectives of this survey component are to enumerate and characterize clinically persons with recognized HIV infection in ASPN primary care practices. These data help to evaluate the national AIDS surveillance case definition and the CDC HIV classification system in identifying persons with severe HIV-related morbidity and in staging or categorizing the range of manifestations of HIV infection (*14, 15*). The data also provide ASPN physicians with information about the illness and needs of their patients with HIV and help to clarify the role of primary care physicians in providing their care.

Patients with HIV infection are systematically identified and longitudinally followed for 5 years.

Throughout the study period, participating physicians record demographic data, mode of HIV exposure, and pertinent clinical and laboratory data on a standard data collection form for all living patients known to have HIV infection. At 12-month intervals, clinicians complete followup questionnaires to update clinical and laboratory information on enrolled patients. Only the physician is able to link the followup information with the individual patient; ASPN headquarters collects no patient identifiers. The followup component will be undertaken within the context of a surveillance initiative, and accordingly, the project uses clinical information recorded during the provision of routine medical care, rather than information obtained from a preset battery of clinical and laboratory tests.

The proportion of ASPN patients who have diagnosed HIV infection is calculated using the ASPN age-sex registry. This proportion is compared with the HIV prevalence rates determined by the concurrent anonymous, unlinked seroprevalence surveys in these practices to estimate the proportion of ASPN patients with HIV infection who are recognized by their physicians as being infected. Disease progression during the study period will also be evaluated.

HIV Testing and Serum Bank

Blood specimens are tested for HIV antibodies by an EIA licensed by the Food and Drug Administration (FDA) and according to the manufacturer's recommendations. Serums repeatedly reactive by EIA are tested with a Western blot assay licensed by the FDA or an assay shown to be equivalent to a licensed Western blot assay. The presence or absence of each virus-specific band is recorded and reported to CDC. Laboratories performing the tests are required to participate in the laboratory quality assurance program provided by CDC (*16*). All leftover serum or plasma specimens are stored for future study.

Interpretation of Findings

Each of these surveys will provide estimates of levels and trends of HIV infection in large groups of primary care outpatients unbiased by self-selection. Several other considerations, such as how well practices of the surveyed physicians represent all primary care practices and to what degree the sampled patients represent all patients in those practices, must be taken into account if these results are generalized to all primary care outpatients. Some factors causing possible misrepresentation by the sampled practices, such as their geographic distribution, can be partially controlled for in the analysis, but other factors, such as the fact that ASPN includes only physicians interested in research, are difficult to assess. The representativeness of the sampled patients to all patients is also difficult to assess since it is not known if patients who have blood drawn are more or less likely to have risk factors for HIV than patients who do not have blood drawn. Nevertheless, if these biases remain constant, seroprevalence trends over time in these sampled populations should reflect those of all primary care outpatients.

Information Collected in the Ambulatory Sentinel Practice Network HIV Survey Data Set

Demographics: age (5-year intervals), sex, race and ethnicity, region of country, quarter year of specimen collection

HIV risk category: physician's perception of risk

Diagnostic: HIV test ordered this visit, previously known HIV-related infection, previously diagnosed AIDS

Laboratory results: HIV–1 EIA and Western blot results

Considerable caution must be exercised when generalizing the results of epidemiologic studies in medical care settings to the general population. Even if observed seroprevalence levels in these surveys reflected all primary care outpatients, they may not reflect those in the population at large because of the uncertainty of whether HIV-infected persons are more or less likely to seek primary medical care than those not infected with HIV. One bias that will result in an overestimate of the true HIV prevalence in the population at large is that persons may *specifically* seek medical care for reasons directly or indirectly related to HIV. Although attempts can be made to eliminate these persons from the final analysis—based, for example, on whether tests such as HIV serology or lymphocyte subtyping were ordered—this bias probably cannot be completely eliminated. Alternatively, many persons at increased risk, particularly intravenous drug users, may be less likely to seek primary medical care in a private clinical practice setting, causing the primary outpatient studies to underestimate the true seroprevalence in the general population. Because the severities of these biases are difficult to assess, extrapolating observed levels of infection to the population at large must be considered in the context of the findings from the other national seroprevalence surveys (*2*, *17*). However, if these biases remain constant, the observed secular HIV prevalence trends in the primary care outpatient surveys should reflect those of the population at large.

Data from the primary care surveys can also be used to target, plan, and evaluate HIV prevention and treatment efforts in the primary care setting. The ability of

prophylactic therapies to prevent or slow HIV related morbidity emphasizes the need for primary care physicians to identify and follow asymptomatically HIV-infected persons (*18*). Data from the ASPN studies can indicate what percentages of the HIV-infected patients were correctly identified as having high-risk behavior for HIV (and who should be screened for HIV antibodies), what percentage of HIV-infected patients have already been identified as HIV positive, and what percentage of those already identified have been evaluated for prophylactic therapy and subsequently treated. Some caution is necessary in generalizing these results to all primary care practitioners since active participation in an HIV study will likely increase physicians' awareness about HIV infection and make them more likely to identify and screen their patients at risk.

Conclusion

These two primary care outpatient surveys should determine levels and trends of HIV infection in a broad segment of the general population unbiased by self-selection. Importantly, all age groups and both sexes can be sampled. HIV seroprevalence levels in primary care outpatients sampled in these surveys should be cautiously extrapolated to all primary care outpatients or to the population at large only within the context of other sources of national surveillance data. Nevertheless, if the biases inherent in sampling from a population seeking medical care remain constant, secular seroprevalence trends should reflect those of the general population. Because of effective therapies for preventing or deterring severe HIV-related disease, primary care physicians will increasingly need to detect and follow HIV-infected persons (*19*). Data from these surveys will help target and evaluate these efforts in the primary care setting.

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