National Institute on Drug Abuse

RESEARCH

MONOGRAPH SERIES

Longitudinal Studies of HIV Infection in Intravenous Drug Users

109

U.S. Department of Health and Human Services • Public Health Service • National Institutes of Health

Longitudinal Studies of HIV Infection in Intravenous Drug Users: Methodological Issues in Natural History Research

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Research Monograph 109
1991

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

National Institute on Drug Abuse
5600 Fishers Lane
Rockville, MD 20857

For sale by the Superintendent of Documents, U.S. Government Printing Office
Washington, DC 20402

ACKNOWLEDGMENT

This monograph is based on the papers from a technicaI review on "Longitudinal Studies of HIV Infection in Intravenous Drug Users: Methodological Issues in Natural History Research" held on September 10, 1987. The review meeting was sponsored by the Division of Clinical Research's Clinical Medicine Branch, National Institute on Drug Abuse.

DHHS publication number (ADM) 91-1786
Printed 1991

NIDA Research Monographs are indexed in the Index Medicus. They are selectively included in the coverage of American Statistics Index, Biosciences Information Service, Chemical Abstracts, Current Contents, Psychological Abstracts, and Psychopharmacology Abstracts.

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1. Introduction

Peter I. Hartsock

The advent of AIDS, a mysterious and deadly disease about which nothing was known a little over 10 years ago, has given rise to the need for natural history studies to understand the dynamics involved in the spread of this epidemic. The term "natural history," as used in the context of this monograph, refers to the evolution or progression of the condition under scrutiny (e.g., AIDS) from its inception to termination (e.g., death or cure of the host). Since many factors, including biological (e.g., immunologic status of the host), socioeconomic, cultural, and psychological (e.g., group and individual behaviors that contribute to high risk for acquiring the condition), and medical (e.g., the administration of drugs such as AZT) have an impact on the acquisition, progression, and termination of the condition, natural history studies of AIDS must take all of these and related factors into account. Such studies have been particularly important for understanding the special relationship of drug abuse and AIDS.

Drug abuse has been recognized by the Surgeon General, the President's Commission on AIDS, the National Academy of Sciences, and the Centers for Disease Control as now being the most important factor in the spread of AIDS in the United States. Because of this, natural history studies on the relationship of drug abuse with AIDS have received a high priority from the National Institute on Drug Abuse (NIDA).

Within NIDA, the Clinical Medicine Branch has had the initial responsibility for AIDS research and the principal responsibility for AIDS natural history studies. Because of the newness of AIDS, natural history research has been fraught with a number of methodological problems. When drug abuse research is added into the picture, these problems have been multiplied. In order to focus special attention on these problems and to assist in finding solutions for them, the Clinical Medicine Branch recently

held a technical review in which grantees presented their unique perspectives on the problems involved in conducting natural history studies. These perspectives are derived from some of the very first drug abuse-related AIDS natural history studies in the world. The methodological problems observed and defined in these studies are important for determining the course of future research and for refining analytical tools in order to better understand the development of AIDS among drug abusers, their sexual partners, their children, and ultimately, the general population.

This monograph contains discussions which selected Clinical Medicine Branch grantees presented at the technical review. These papers appear in an order beginning with the most general discussions of natural history research problems and progressing to more focused consideration of specific problems.

In the first paper, Dale D. Chitwood, Mary Comerford, and Edward J. Trapido present a history of natural history studies dealing with AIDS and drug abuse. Of special importance in the development of these studies is the unprecedented interdisciplinary nature of the work being done. Researchers from areas as dissimilar as anthropology and virology have come together to pool their intellectual powers and the focuses of their disciplines.

Chitwood et al. describe the primary types and the strengths and limitations of natural history studies presently used to examine the drug abuse and AIDS relationship. Epidemiologic methods dominate these studies and comprise two basic types: descriptive and analytic. Descriptive studies are made up of three categories: case studies, correlation ecological inquiries, and cross-sectional surveys. While descriptive studies can be used in hypothesis development, they cannot be used to test hypotheses.

Analytic studies, however, can be used to test hypotheses, and Chitwood et al. describe the two most widely used forms: the cohort or longitudinal study and the case-control study. The strengths and weaknesses of analytic studies are described.

Chitwood et al. then assess the status of drug abuse and AIDS natural history research at the present time and offer directions that such work should take in the future for enhancing our knowledge of this area. Recommendations are made for the use of additional research designs and especially for the pooling of subjects from multiple site investigations.

In the next paper, Gerald Friedland discusses the development and present state of knowledge in studies of the natural history of HIV infection in the populations of (1) intravenous drug users and (2) homosexuals and bisexuals. Friedland talks about the similarities and differences between these two major populations in the HIV epidemic and the methodological problems inherent in comparing natural history research in one population with that done in another. Such problems include differences in methodologies and variations in sampling and surveillance, as well as differences in socioeconomic status between populations.

Friedland also discusses other infections and HIV-related complications that do not meet the Centers for Disease Control (CDC) AIDS surveillance definition; gives a comparison of the opportunistic infections and malignancies that do meet the CDC case definition; presents the existing data on survival once the diagnosis of AIDS has been established; and reviews selected information on cofactors that may result in acceleration of progression of HIV infection.

As Friedland discusses methodological problems in comparing the natural history of HIV infection in drug users with that of HIV infection among homosexuals, W. Wayne Wiebel explores further the methodological problems in natural history studies of HIV infection within drug abusing populations. A pivotal obstacle in this work involves sampling issues: Drug users are involved in illicit and covert activity, and this situation creates potential problems of bias. These sources of bias reflect the sampling frames used:

1. *Drug abuse treatment populations.* Only a small percentage of all drug users are in treatment and there is considerable reason to believe that those who are are not representative of those who are not. Furthermore, with heavy emphasis on methadone treatment (particularly for heroin use) in the United States, nonopiate drug users are also missed in the sampling of treatment populations. And, because heaviest emphasis has been on treatment of intravenous drug users, non-IV users too are ignored.
2. *Criminal justice populations.* Drug users involved in criminal activities to support their addictions are overrepresented.
3. *Medical service populations.* Emergency rooms: overrepresent patients (e.g., drug users) with acute conditions. Chronic care facilities: overrepresent long-term addicts with health problems associated with poor hygiene.

4. *Social network analysis populations.* These better represent not-in-treatment drug-using populations but underrepresent socially isolated addicts.

With these varying biases, according to Wiebel, agencies that support natural history studies of HIV infection in drug abusers should strive for a balance in supporting studies which utilize a range of available sampling strategies.

John K. Watters and Yu-Teh Cheng examine in further depth several issues raised by Wiebel. To begin, HIV natural history studies involving drug users whose drug problems are predominantly characterized by injection patterns other than heroin (e.g., cocaine) are often excluded from such studies. This is largely due to methadone maintenance (for heroin) being the dominant drug abuse treatment modality, this modality thus dominating the populations being sampled in natural history studies. Findings from drug users in methadone treatment may not be generalizable to those who are not. Furthermore, many IV drug users not in treatment are not oriented to entering treatment programs. Samples based primarily on clinical populations may contain substantial bias, neglecting addicts who eschew treatment and/or who use drugs other than heroin.

Convenience samples, which tap into drug users on a first-to-be-contacted, first-to-be studied basis, lack generalizability due to the reasons just cited. (See the discussion on Dorus below for more on this.) For example, when the selection of sites is based primarily on grant and contract competition, rather than on systematic review of candidate location, this has strong implications for sample construction. Sampling is nonrandom and not linked to population parameters. Furthermore, there can also be a conflict in the roles of personnel involved: interviewing and changing behavior at the same time (see Vlahov below for more on this).

Watters and Cheng cite findings from their own research to illustrate the impact of the biases they discuss and conclude that it is important to include in-treatment drug users *and* those not in treatment in natural history studies of HIV infection and associated risk factors.

Following on the conclusions of Watters and Cheng, David Vlahov and colleagues discuss selection biases from treatment populations and from outreach populations. Emphasis should be placed on consistency of findings across studies and observed differences should provide a basis for additional hypothesis formulation.

Regarding data consistency, Vlahov et al.'s ALIVE natural history study has one of the largest drug abuse HIV study populations to date and has the ability to provide systematically collected information from a population of predominantly active users outside the drug treatment and criminal justice settings.

Vlahov et al. discuss several methodological issues in natural history studies of drug abuse and HIV infection. One issue concerns the accuracy of self-reports. There are several means available for evaluating such reports:

1. corroboration, generally through urine screens, official records, and reports of family and counselors
2. corroboration of the relationship between biological parameters and reports
3. measuring the degree of "socially desirable" responding

This paper also discusses the impact of ethical constraints on studies of HIV infection in drug-using populations. For instance, information learned through required pretest conseling can have an impact on information solicited from subjects later on in studies.

According to Vlahov et al., other forms of bias in natural history studies may come from interpersonal effects between interviewers and subjects (see also Watters) and from differences in biological measures such as differences in CD 4 cell levels between study sites.

Last, selection of appropriate endpoints for longitudinal studies is regarded as a major methodologic issue and is complicated by the long incubation period for AIDS and the growing need for a wider definition of AIDS among drug users.

As well as describing present AIDS-related intervention effects among drug users, Walter Dorus and his colleagues deal with a variety of methodologic issues in natural history studies of HIV infection in this population.

One issue, alluded to by other contributions to this monograph, concerns the almost exclusive emphasis on IV drug-using populations. Related high-risk behavior with increasing non-IV use, e.g,, "sex for crack," and drug use other than intravenous use should be studied.

In addition, there is no systematic means for determining HIV seroprevalence in drug users. Prevalence is usually dependent on voluntary testing, which may underestimate the prevalence of HIV.

Self-selection of subjects for studies also presents a problem (see Watters). Persons voluntarily presenting themselves often have lower seroprevalence than those who do not, who, in turn, may underreport their high-risk behavior. Persons at highest risk for HIV may avoid testing.

Furthermore, there are problems with biological measures. ELISA-testing variability has limited the precision with which events leading to infection can be determined. False negative results also limit ELISA testing capabilities. Better precision may be possible, however, in new tests such as polymerase chain reactions.

Dorus and his colleagues state that the definition for AIDS and ARC should be evaluated.

Don C. Des Jarlais considers a number of potential cofactors in the outcomes of HIV infection in IV drug users. Part of his conclusions parallels those of Vlahov et al. and Dorus et al., in that a number of fatal illnesses do not qualify as "surveillance definition AIDS" but appear to be occurring among drug injectors exposed to HIV.

Des Jarlais also discusses cofactors for Kaposi's sarcoma; psychoactive drug use as a cofactor for progression of HIV-related immunosuppression; and gender differences as potential cofactors.

Des Jarlais states that we are now at a stage for hypothesis testing of the association of cofactors for HIV infection among drug users. He also concludes that the availability of treatments for HIV-related disease creates a need for studies of potential psychoactive drugs and their treatments.

Philip C. Cooley and his colleagues discuss the uses which mathematical modelers have for natural history data dealing with AIDS, drug abuse, and related phenomena. This is an important topic because much modeling is hypothesis- or theory-driven with only secondary or tertiary attention paid to what data are available for investigating theories. This ivory tower scenario is less than productive, especially when few or no data can be found to investigate the theories. An attribute that characterizes most NIDA Clinical Medicine Branch modeling grants is their primary emphasis on first obtaining data guided with preliminary theories and then using these data to

further develop these theories and guide data gatherers to obtain data where gaps presently exist.

Cooley et al. describe their own efforts in this process and discuss what they see are major gaps in the types of data coming from AIDS/drug abuse natural history studies, which are needed to drive accurate, empirically grounded models of the AIDS epidemic.

The papers in this monograph span a range of topics particularly concerned with methodological problems encountered in natural history studies of drug abuse-related AIDS. This span is actually a continuum, beginning, on one end, with very basic problems of obtaining valid and reliable data from populations notoriously difficult to reach, to, on the other end, problems which users of these data such as modelers encounter. The problems encountered on the data-gathering end become telescoped and magnified when data are put to analytical use.

It is advocated and hoped that those scientists dealing with opposite ends of this continuum will attempt to better understand the problems that their counterparts on other sections of the spectrum encounter. Such understanding should lead to better coordination between data gathering and data analytical efforts and points in between and thus to an increase in the quality of all efforts. The various sections of the continuum can provide valuable insights and guidance for the other sections, and it is hoped that this monograph contributes to this process in some modest fashion.

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2. Strategies for Enhancing Existing Studies of the Natural History of HIV-1 Infection Among Drug Users

Dale D. Chitwood
Mary Comerford
Edward J. Trapido

INTRODUCTION

The AIDS crisis has created an atmosphere of urgency characterized by increased funding and an expedited grant review process for the study of HIV-1 among drug users. This press for knowledge about the natural history of HIV-related disease has produced an interdisciplinary effort that is unprecedented in the study of illicit drug use. Investigators from fields as dissimilar as anthropology and virology have joined together to study HIV-1 infection and related disease among drug users, particularly parenteral users. This diversity is reflected in the disciplines of the principal investigators of the first 17 natural history studies funded by the National Institute on Drug Abuse (NIDA): two epidemiologists, three infectious disease physicians, one psychopharmacologist, three psychiatrists with drug abuse treatment backgrounds, and seven social scientists with prior experience in drug abuse research. Eight of these investigators had prior research experience specific to HIV-related disease (National Institute on Drug Abuse 1987).

This research was supported by National Institute on Drug Abuse grant nos. DA 0443 and DA 05349 and National Institute of Mental Health/National Institute on Drug Abuse Center grant no. MH42455.

Every professional who enters this arena brings the substantive knowledge and methodologic tools of his or her area of expertise to this interdisciplinary task. As a result, drug researchers with little or no previous experience with infectious disease find themselves working closely with immunologists and other colleagues who are equally unfamiliar with drug use.

Despite the wide variation in disciplines represented by these researchers, most nonlaboratory based studies of the natural history of HIV-1 infection among parenteral drug users can be classified into three groups. The earliest projects tended to be cross-sectional investigations that have documented the seroprevalencc of antibodies to HIV-1 among intravenous drug users (IVDUs) in various communities. Many of these initial studies were conducted among clients of drug treatment programs (D'Aquila et al. 1986; Levy et al. 1986; Mascola et al. 1989; Marmor et al. 1987). Among these projects arc trend studies that repeatedly collect unlinked seroprevalence data for the purpose of describing the progression of the epidemic (Brown et al. 1989).

A second tier of studies was initiated as longitudinal investigations in which cohorts of IVDUs have been screened for antibodies to HIV-1 and followed periodically (usually at 6-month intervals) to assess incidence rates (seroconversion) of antibodies to HIV-1 and/or disease progression. Some of these studies have expanded beyond estimates of prevalence to examine broader aspects of the natural history of HIV-1 such as timecourse and prognostic factors associated with disease progression from seroconversion through acute retroviral syndrome, asymptomatic periods, HIV-related disease including non-AIDS defining illnesses (Novick et al. 1986; Selwyn et al. 1989*a*; Trapido et al. 1990), AIDS, and death (Des Jarlais et al. 1988). A partial list of associated issues being addressed includes onset of needle use and other drug-related risk behaviors (e.g., sex and crack use), understanding of needle use values of IVDUs (Page et al. 1990) the infectivity of injection equipment (Chitwood et al. 1990) the effects of drugs of abuse and drugs used in drug abuse treatment on immune function (Donahoe and Falek 1988; Novick et al. 1989), and the onset of HIV-1 infection and progression to disease (Chaisson et al. 1989).

A third group of studies includes the 63 National AIDS Demonstration Research Projects funded by NIDA, which were designed primarily to implement and evaluate risk behavior reduction intervention programs among IVDUs and their sexual partners (McCoy et al. 1990; National Institute on Drug Abuse 1989). Many of these study sites arc producing data on

serostatus and have the potential to address questions about the natural history of HIV-related disease.

The urgent need to understand the natural history of HIV-related disease requires researchers who are engaged in each of these groups of studies to examine their projects to determine how they might be utilized to address questions of natural history that are not the original focus of those investigations.

The purpose of this chapter is to review basic research designs that have made contributions to the study of disease, including HIV-related disease, and to present strategies that can be initiated or expanded to enhance information that now is being produced by existing studies of IVDU and HIV/AIDS.

BASIC RESEARCH DESIGNS

Epidemiologic methods offer researchers of drug use and HIV-1 a bridge between the social sciences and medicine (Hennekens and Buring 1987). Because epidemiology investigates the etiology and natural history of disease in populations rather than individuals, methodologies have been developed to investigate large groups, and these are particularly suited to the study of the natural history of HIV-1 among IVDUs.

Epidemiologic studies may be divided into two basic groups, descriptive and analytic. Descriptive investigations provide knowledge of newly identified disease and the populations or risk groups most or least affected by the disease. The identification of a disease and/or the descriptive characteristics of persons with that disease often constitute a first step in the quest for disease etiology or for risk factors that can be altered or eliminated to prevent disease. Data from descriptive studies also are useful to public health policy planners for health care utilization and resource allocation.

Descriptive Studies

There are three general types of descriptive studies: case reports or case series, which describe the experience of an individual or group of patients with a similar diagnosis or symptoms; correlational ecological inquiries, which examine patterns of behavior and disease among populations; and cross-sectional surveys of individuals.

The early epidemiology of AIDS was first described in case reports and case series. Case reports document unusual occurrences among individuals and can represent the first clues in the identification of disease. A case series is a collection of case reports that occur within a fairly short time span. During the 8-month period from October 1980 through May 1981, five cases of Pneumocystis carinii pneumonia were reported among young, previously healthy homosexual men in Los Angeles (Centers for Disease Control 1981*a*). Several cases of Kaposi's sarcoma also were diagnosed in young homosexual men in early 1981 (Centers for Disease Control 1981*b*). Both of these case series were important because Pneumocystis carinii pneumonia previously had been seen almost exclusively in elderly cancer patients whose immune systems were suppressed, and Kaposi's sarcoma had been observed almost exclusively in elderly men and women. These descriptive studies not only were instrumental in the identification of a new disease but also in the formulation of hypotheses about risk factors for transmission even though the causative virus had not been identified. As a result of these case series, the Centers for Disease Control initiated a surveillance program to assess the magnitude of the problem and develop diagnostic criteria for what appeared to be a new disease. This program determined that homosexual men were at high risk of developing AIDS, and subsequent case reports and case series indicated that this syndrome also developed from blood-borne transmission among IVDUs and other groups. Case series methodology also has been used in the investigation of the patterns and consequences of drug use, e.g., the description by Spotts and Shontz (1980) of variations in cocaine use among nine cocaine users.

Caution must be exercised in the interpretation of findings in case series studies. While useful for hypothesis formulation, data from case reports and case series cannot be used to test for the presence of a valid statistical association because of small numbers and a lack of a comparison group.

In correlational ecological studies, measures of populations are used to describe disease in relation to population characteristics or risk behavior(s). The delineation of pattern I, pattern II, and pattern III countries is an example of the utility of this approach (Piot et al. 1988). Ecological studies of AIDS and IVDU are only now emerging, but numerous studies concerning the consequences of tobacco and other drug use exist. For example, Friedman (1967) described patterns of mortality from coronary heart disease in 1960 by correlating the death rates from coronary heart disease of 44 States with per-capita cigarette sales in those states. His early observation that mortality was highest in States with the highest cigarette sales con-

tributed to the hypothesis that cigarette smoking causes fatal coronary heart disease, which has been substantiated in subsequent analytic studies (U.S. Department of Health, Education, and Welfare 1979). McBride and McCoy (1981) reported a high correlation when they examined the association between narcotic use and crime by correlating census tract data on the prevalence of drug treatment in the population with the crime statistics for those areas.

The strength of ecological studies is that they can be done quickly and inexpensively with existing data, factors that make them useful as a first phase in investigating a possible exposure-disease relationship. The primary limitation of such studies is the inability to use these data to connect the exposure to disease in particular individuals. This misinterpretation is well known as the ecological fallacy (Goodman 1953).

A third type of descriptive investigation is the cross-sectional study in which exposure and disease status are assessed simultaneously among individuals. Cross-sectional studies look at the seroprevalence of an outcome such as HIV-1 or AIDS in a population at a particular point in time or over a specific time span such as 1 year. This research design has been the vehicle for many of the early seroprevalence surveys of HIV-1 among IVDUs (Des Jarlais et al. 1989). These data are of considerable importance to public health administrators in evaluating the health care needs of a population or catchment area.

Because cross-sectional studies assess risk behavior and disease status at the same point in time, often it is not possible to determine the extent to which the exposure preceded or followed the disease. Cross-sectional studies usually investigate prevalent rather than incident cases, and therefore the information collected is biased to some extent by the determinants of survival as well as etiology. For example, a snapshot of the seroprevalence of HIV-1 among IVDUs will identify as antibody positive not only persons who seroconverted very recently but also many others who have been seropositive for several years and have survived. Consequently, investigations that seek to use cross-sectional data on HIV-1 antibody status to address etiological questions will be unable to determine precise time order between exposure and seropositivity. This makes observations unclear and distorts the observed association between exposures and HIV-1 serostatus. While it is possible in a study of the risk factors of seroprevalent respondents to reduce the length of time since seroconversion by excluding from the study all HIV-1 antibody positive persons who have been diagnosed with AIDS (Des Jarlais et al. 1989), the length of time since exposure among the

remaining seroprevalent cases still will be considerable for an unknown number of respondents.

Analytic Studies

Analytic studies are designed to test specific hypotheses and can be divided into two major types: observational and intervention. This discussion will concern observational studies only.

The two basic types of observational analytic studies are the cohort or longitudinal study and the case-control study. Each type of study has its own strengths and limitations. The decision of which type of research design to implement depends on the specific research questions posed plus logistical factors such as time and money available to carry out the research.

Longitudinal Studies

Longitudinal studies proceed from exposure to disease by defining a group of individuals on the basis of the absence or presence of one or more exposures to a suspected risk factor for a disease (Hennekens and Buring 1987). Study participants are followed over time to observe the occurrence of that disease outcome. Most investigations of the relationship between drug use and HIV-1 infection are longitudinal studies in which IVDUs or other drug users are followed to assess diverse outcomes such as seroconversion, progression to disease. and mortality. The primary strengths and limitations of a longitudinal design are outlined in table 1.

The strengths of a longitudinal design for natural history studies among IVDUs are several. For example, drug injection is a relatively rare exposure that is most easily studied when the study population is selected for its exposure experience; several outcomes of exposure to HIV-1 that need to be investigated can be studied simultaneously; bias in the determination of exposure is minimized and incidence of seroconversion is directly measurable.

One key limitation is that longitudinal studies are more expensive to conduct than other types of studies. This is due, in part, to the potentially long duration for followup and the large number of subjects required when incident cases of HIV-1 seroconversion or a rare HIV-1 related disease such as Kaposi's sarcoma are being studied. For example, seroconversion rates among established cohorts of IVDUs appear to be low (Moss et al. 1989). Thus HIV-1 seroconversion, even in a high risk population of IVDUs, is a

relatively rare event. To obtain steady, reliable estimates of incidence, a substantial number of new cases of HIV-1 infection is required. These cases can be acquired either over a long span of time or by increasing the size of the sample. Either procedure increases the cost of the study.

Table 1. Strengths and Limitations of the Longitudinal Study Design

Strengths
Is of particular value when the exposure is rare.
Can examine multiple effects of a single exposure.
Minimizes bias in the ascertainment of exposure.
Allows direct measurement of incidence of disease in the exposed and non-exposed groups.
Limitations
Is inefficient for the evaluation of rare diseases.
Can be extremely expensive and time consuming.
Validity of the results can be seriously affected by excessive losses to followup.
Current practice, usage, or exposure to study factors may change, making findings irrelevant.

In addition, if a long time span is required to accumulate cases, as in the investigation of a rare outcome for IVDUs such as Kaposi's sarcoma, results may not be obtained in a timely manner. Even if cost were not an issue, increasing the size of the sample may produce difficulties where a finite number of potential subjects exist in an area. It may be difficult in some areas of the country to locate and recruit into the study a sufficient number of IVDUs to enable the study to be completed in a relatively short time period.

Another difficulty with longitudinal studies is the adequate followup of the study participants. The maintenance of scheduled periodic followup is extremely labor intensive and expensive. This is particularly true when the study participants are drug users.

Case-Control Studies

In a case-control study, individuals with a particular condition (cases) are selected for comparison with a series of individuals in whom the condition is absent (controls). Cases and controls are then compared with respect to existing or past characteristics or exposures thought to be relevant to the development of the condition being studied. A thorough discussion of case-control design and analysis can be found in *Case-Control Studies* by John J. Schlesselman (1982).

Because of the problems involved in conducting a longitudinal study, the case-control study often is used as an alternative approach. Case-control studies have been utilized extensively in epidemiologic investigations of disease etiology and outcome. Such diverse subjects as the relationship of prenatal x-rays and childhood malignancies (MacMahon 1962) diethylstilbestrol (DES) and vaginal cancer (Herbst et al. 1971) and the role of oral contraception in the occurrence of myocardial infarction (Jick et al. 1978) have been studied using the case-control method. While seldom used in the social sciences, case-control studies are an appropriate method to investigate problems of interest to behavioral scientists and are a particularly efficient way to study issues involved in drug use including HIV-1 infection.

The major strengths and limitations of case-control studies, which in large part are the mirror image of limitations and strengths of longitudinal investigations, are summarized in table 2.

The strengths of case-control studies include efficiency of time and economy. Case-control studies usually can be completed much more quickly than longitudinal studies and cost less money to conduct. Since participants are selected on the basis of disease status, case-control investigations are well suited for the study of rare diseases. In addition, case-control studies allow the investigation of multiple potential causes of a disease or condition. This is of particular importance in the examination of HIV-1 infection among drug users. Because drug users engage in many risky behaviors, it is important to be able to determine multiple behaviors that lead to transmission and infection of the virus in this population.

It is not possible to directly measure risk using the case-control methodology, but it is possible to assess relative risk. The relative risk estimates the magnitude of an association between a characteristic and condition and indicates the likelihood of developing the condition in the

Table 2. Strengths and Limitations of the Case-Control Study Design

Strengths
Is optimal for the evaluation of rare diseases.
Can examine multiple etiologic factors for a single disease.
Is relatively quick and inexpensive.
Is particularly well-suited for the evaluation of diseases with long latency periods.
Limitations
Is inefficient for the evaluation of rare exposures.
The temporal relationship between exposure and disease may be difficult to establish.
Is prone to bias, particularly selection and recall bias.
Cannot directly compute incidence rates of disease in exposed and nonexposed groups.

group exhibiting the risk behavior compared with those not having that characteristic. Although the direct calculation of the relative risk in a case-control study is not possible relative risk can be approximated by calculating an odds ratio. The ability to express some approximation of risk is important to the success of research investigating behaviors associated with HIV-1 infection among drug users.

There are limitations to the case-control method. Generally it is not good for the evaluation of rare exposures or characteristics. If the exposure under investigation is rare, too large a sample size would be needed to efficiently utilize the methodology. Perhaps the most serious limitation of this type of study is that it is susceptible to bias, particularly selection and recall bias. The case-control study must be carefully designed and conducted so that all possible biases are minimized.

STRATEGIES FOR ENHANCING KNOWLEDGE OF HIV-1-RELATED DISEASE

Many of the initial research questions addressed by existing studies have been relatively narrow in focus—seroprevalence has been the common objective of most projects. The next step is to expand the breadth of these

natural history inquiries and to increase our knowledge of HIV-1 related disease. This can be accomplished by utilizing existing research designs, methodologies, and study populations in creative ways to address emergent research questions that were not central to the initial aims of ongoing projects.

Other Research Designs

Longitudinal research designs will continue to form the backbone of the methodology of natural history investigations. However, the demand for rapid understanding of the multiple facets of this pandemic places special responsibilities upon researchers to identify alternative research designs that will supplement longitudinal investigations with innovative studies that relatively quickly produce information on specific research questions.

In addition to the longitudinal (or cohort) study and the case-control study, a number of additional designs should be considered when questions about natural history are being addressed. These designs have different strengths and weaknesses, but arc most affected by whether:

1. the study is experimental
2. the frequency of outcome(s) to be studied is more or less than the rarity of exposure(s)
3. there is need for sequential measurements of exposure
4. there is an alternative mechanism for either the ability to detect all diseases (outcomes) in a population and/or to record relevant exposures on the entire population, without the enrollment of all members
5. the inherent costs involved in carrying out the study

Nested Case-Control Studies

The most important of these designs is the nested case-control design. A nested case-control investigation is a case-control study that is imbedded within an ongoing project. Nested case-control studies could utilize the large data base of an ongoing longitudinal study to identify cases and their controls or comparisons and enroll them in a supplementary study designed to answer specific research questions. Nested studies are particularly appealing because they enable the researcher to add new research questions to an ongoing research project for far less cost than would occur with a stand alone case-control study.

Nested case-control studies could be used for a variety of pressing issues, some of which are relevant not only for HIV/AIDS research, but also for drug use research in general. For example, knowledge of the factors related to the initiation of intravenous use, which is integral to both substantive areas of inquiry, is amenable to a nested case-control design. Questions about the initiation of IV use could be addressed by identifying cases who recently had initiated IV use from a cohort of drug users. Persons who had not progressed to drug injection would be identified from the same study population and enrolled as comparisons or controls. Similarly for questions of cessation of IV use, the nested case-control design could be used to select, from an ongoing study population of IVDUs, cases (persons who cease IV use) and compare them with controls (others who continue to inject). Information obtained in these investigations could be integrated into prevention or treatment intervention programs that seek to prevent or reduce high risk injection behavior.

While a number of studies of risk factors for HIV-1 infection among IVDUs have been reported, all of them have been based to date upon seroprevalent rather than seroincident cases. The use of prevalent cases is problematic because no one knows approximately when each prevalcnt case became seropositive for antibodies to HIV-1, and consequently it is not possible to establish with some certainty the time order of exposure behavior and seroconversion. This makes investigations of the risk factors for seroconversion imprecise and confounds the observed relationships between risk behavior and HIV-1 status. This problem would be resolved to a large extent if seroincident cases were studied.

Some ongoing longitudinal studies being undertaken by one of the authors (Chitwood) are utilizing a nested case-control design to investigate risk factors for seroconversion. Cases are identified from the larger cohort and compared with controls who also have been selected from that cohort. Nested case-control studies should be implemented to address several important questions about the natural history of HIV-1 related disease.

Additional Designs

Other less commonly used designs include case-cohort studies, followup prevalence studies, selective prevalence studies, repeated surveys, and space-time cluster studies. (See Kleinbaum et al. 1986 for a general introduction to these and related designs.) Three additional designs that deserve particular attention are discussed below.

Historical Cohort Studies

Another variation of existing methodologies is the historical cohort study. A historical cohort study is an analytic design in which the outcomes have occurred before the start of the investigation. Cohorts are established as in longitudinal studies, and exposure and outcomes are assessed from existing records. The followup period until the occurrence of disease may be wholly or partially in the past. Despite the fact that this type of study utilizes previously collected data, it is analytic or longitudinal in nature as it proceeds from cause to effect, i.e., from exposure to disease. The information collected covers a time interval extending from past to present rather than from present to future.

Historical longitudinal studies are less expensive and faster to conduct than other longitudinal studies. However, to conduct such a study the investigator must rely on records that may or may not be reliable and complete. It is often difficult to find adequate, complete records and information on a cohort of IVDUs over the required period of time. Treatment facility records offer a possible data source if they are sufficiently complete or comprehensive to document necessary exposures and outcomes. In the case of HIV-1 infection, in order to do a historical cohort study with a group of IVDUs, it is necessary to be able to document when seroconversion occurred. As more and more IVDUs in treatment programs are tested repeatedly for HIV-1 seropositivity, this may become a feasible approach in the immediate future.

Banked sera studies arc the most familiar example of the use of this type of study design for natural history studies. Several groups have reanalyzed existing sera samples to describe the prevalence of a variety of viruses such as HIV-1, HIV-2, HTLV I, and HTLV II (Saxinger et al. 1989).

Linked Record Analysis

A related approach to limiting expense and followup of a study is to use an existing system for monitoring the event or occurrence under study. For example, if AIDS or other HIV-1 related disease such as lymphomas or Kaposi's sarcoma or mortality is the outcome under study, established registries may be used to ascertain diagnosis among cohort members. If the cost of case ascertainment is already being borne by the registry, this will reduce the cost to the study. An example of this type of study is research by Selwyn ct al. (1989*b)*that examines the mortality and morbidity due to HIV-1 associated disease among clients of a methadone maintenance program in

New York City. These researchers have examined the registries of New York City and hospital records to ascertain mortality and morbidity and calculate mortality and morbidity rates for specific diseases.

Network Analysis

In addition to designs used in epidemiological studies, other disciplines also offer methodologies or unique types of studies that can add to our knowledge of the natural history of HIV-1 among IVDUs. For example, ethnographic studies can directly observe drug and needle use behavior in varied settings such as in shooting galleries. One ethnographic strategy of particular value in natural history studies is network analysis (Burt 1982). Network analysis is a tool that can aid in our understanding of HIV-1 transmission among IVDUs. Network analysis uses the networks of social relationships among IVDUs to observe and describe links among study participants that increase or decrease risk of transmitting or developing HIV-1 infection. The social relationships explored through network analysis among IVDUs are on the simplest level "drug use activated," that is, people in the network know and interact with each other for the purpose of procuring and using drugs. However, links among network participants often include other reasons for making regular contact with another person in the network, e.g., kinship, sexual postures, employment. By studying this network of social relationships, the role of both intravenous drug use and sexual behavior in the mechanisms of transmission of HIV-1 among a discrete group of people can be clarified.

Two concepts of network analysis of particular interest are the form of the network (morphology) and the reasons why people associate with each other in the network (content). For example, the morphology of a network can be dense, a situation in which everyone who participates in the network knows everyone else in the network. Or conversely, a central person in the network may have links to all the people in the network but the other people do not have links with each other. The content describes the actual interrelationships and interactions among those belonging to a specific network. Both concepts are important to the understanding of the social context of the network.

Network analysis has been used to study drug use (Hawkins and Fraser 1985; Westermeyer and Neider 1988) and the spread of AIDS (Klovdahl 1988; Laumann 1989). Because network analysis investigates relationships and behaviors in a subpopulation or network of IVDUs, it is an efficient method to study interactions and relationships that may place an IVDU at

higher risk for HIV-1 infection and to determine the social relationships and patterns involved in transmission of the virus. The type of data collected in network analysis studies is of particular interest to colleagues who are modeling the development of the AIDS epidemic.

RECOMMENDATIONS

A Proposal to Pool Subjects From Multiple Studies

Several research questions regarding rare outcomes often cannot be addressed quickly by any single research project because of the finite number of available study subjects. For rare outcomes, the nested case-control study design could be effective across study sites to accrue appropriate cases and their controls who in turn would be pooled for analysis. This approach has been used effectively for studies of rare tumors (Meinert 1986) and with clinical trials of antiviral drugs for HIV-1 such as AZT (Parks et al. 1988). Pooling of cases is of particular value when the study questions concern rare or costly to detect outcomes or relatively small demographic groups of particular research significance. Examples of subject areas for which this methodology is appropriate include risk factors for seroincidence studies of HIV-1 or queries about Kaposi's sarcoma among IVDUs. Nested case-control studies could be used to pool subjects. Study subjects who meet case criteria would be identified from various longitudinal projects and entered into a separate cooperative nested case-control study. In this manner, the number of necessary cases could be accrued in a relatively short time period.

Pooling of study subjects is not restricted to studies of rare outcomes, but is appropriate for investigations of rare exposure or risk groups as well. For instance, little is known about drug injection among Native Americans (Myers et al. 1989) and the number of Native American IV drug users enrolled within most studies of HIV-1 is relatively small. If Native American study participants from several ongoing investigations could be accrued into a separate investigation, a wide variety of research questions about HIV-1 infection and risk within this important demographic group of IVDUs could be addressed.

A model for a cooperative group multicenter investigation already exists among researchers who are conducting studies of rare outcomes, e.g., tumors (Meinert 1986). This approach should be replicated and adapted to address pressing issues about the natural history of HIV-1 infection and related disease among IVDUs.

A multisite investigation is essential when three general conditions exist. First, there should be evidence that multicenters are needed to meet the sample size requirements of the investigation. This is obvious for questions of seroincident IVDUs. No studies of seroincident IVDUs have been reported for this very reason. Second, there should be an identifiable group of investigators who are willing and able to follow specific enrollment and data collection protocols. Third, there should be an identifiable set of research centers with adequate support staff and facilities to carry out the study, whether it is epidemiologic or clinical in nature. The interdisciplinary nature of several research center teams who are now studying natural history as single site programs is clear evidence that research on all aspects of the natural history of HIV-1 related disease can be done.

The procedure is very straightforward. Each site would continue its ongoing investigations but would pool seroincident cases and other study participants or sera for studies that cannot reasonably be conducted by a single site. Funding of cooperative site investigations would not only produce findings that otherwise could not be accomplished, but would perform a dual service of strengthening the individual centers, thus enhancing their ongoing projects. Studies would be task specific and not a perpetuation of a structure that was not productive.

CONCLUSION

The urgency inherent in the AIDS epidemic has brought together into research on drug use and HIV-1 related disease a heretofore unheard of number of interdisciplinary teams of researchers. These research groups now are following large cohorts of IVDUs, other drug users, their sexual partners, and their children. Natural history studies need to expand the breadth of research questions that presently are being addressed. The use of specific research designs, e.g., nested case-control studies, to supplement ongoing single site projects will enhance the work that is in progress. However, major research questions about risk behavior and disease progression are best addressed with a study population of seroincident IVDUs. Unfortunately, single research sites have not demonstrated the ability to recruit seroincident study participants in large enough numbers to conduct these studies in a timely manner. Because of the need for information as soon as possible, it is essential that multisite cooperative groups be developed to accrue and pool sufficient seroincidcnt cases (and other similarly rare exposure groups or study populations) that are essential to the careful investigation of key research questions. This approach would provide important

information in a timely manner. Models for cooperative groups exist in medical research and should be adapted to investigate the natural history of HIV- 1 among drug users.

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3. Natural History of HIV Infection in Gay Men and Intravenous Drug Users

Gerald Friedland

This paper will address issues relating to the current state of knowledge of the natural history of HIV infection in homosexual and bisexual men and intravenous drug users. Similarities and differences between these two major populations in the HIV epidemic in the United States will be explored, including: (1) a review of the existing natural history studies in both populations, (2) a description of the infections and other HIV-related complications that do not meet the Centers for Disease Control AIDS surveillance definition (Centers for Disease Control 1987*b)* but which are of great importance in producing additional burden of HIV-induced disease, (3) a comparison of the opportunistic infections and malignancies that do meet the Centers for Disease Control AIDS case definition, (4) an exploration of the existing data on survival once the diagnosis of AIDS has been established, and (5) a review of selected information on cofactors that may result in acceleration of progression of HIV infection.

The HIV epidemic may be viewed as a series of overlapping smaller epidemics in quite disparate populations such as gay men and intravenous drug users. Although a substantial amount of information has been acquired during the past 7 years among both gay men and intravenous drug users, comparisons between these two major populations affected by the HIV epidemic are difficult. To some extent, this is the result of differences in methodologies in various studies including variations in sampling and

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Preparation of this chapter was supported by grant no. DA 04347 from the National Institute on Drug Abuse.

surveillance. Further, the assembly of some of the cohorts to study the natural history of HIV infection in these populations has started at different points in time in the epidemic, thereby limiting generalizable conclusions about natural history.

Of obvious comparative interest is the differences in sexual and drug use practice which are the major point of divergence between the two groups and which may influence natural history. Issues such as route of acquisition of infection, frequency of repetitive exposure, and change in high risk behavior are of potential importance in both infection acquisition and natural history. These must be seen, however, against a background of major differences in the two populations in geography, gender, race, ethnic background, and socioeconomic status. These demographic and socioeconomic differences likely influence the natural history of HIV disease and may be as important as, or more important than, the more obvious differences in behavior resulting in HIV acquisition. Clear socioeconomic status differences exist between drug users compared with many homosexual and bisexual men (Friedland 1989). For example, in New York City, 50 percent of intravenous drug users are on public assistance and Medicaid and have not finished high school. In contrast, among homosexual men in San Francisco, 44 percent have tax earnings over $25,000 and 55 percent have college degrees. In the Bronx, a borough of New York City, 65 percent of intravenous drug users and their families have incomes under $10,000 per year, and in 80 percent of households this income supports three or more people (Friedland et al. 1986). Over 80 percent of heterosexual intravenous drug users with AIDS in the United States are black or Hispanic, whereas over 70 percent of gay men with AIDS are white (Centers for Disease Control 1988*b)*. Health status indicators among blacks and Hispanics of low socioeconomic status indicate a higher rate of infant mortality, shorter life expectancy, and increased morbidity and mortality from injuries and infectious, cardiovascular, and malignant diseases (Centers for Disease Control 1986, 1987*a,* 1988*a;* U.S. Department of Health and Human Services, 1985). Intravenous drug users, specifically, have been known to have significantly higher age specific mortality rates than nondrug users long before the HIV epidemic (Friedland 1989). In addition to these issues of baseline health status, access to health care and quality of health care may also influence the natural history of HIV infection. Surveillance for infection and disease, early intervention, and appropriate diagnoses and treatment of HIV complications are likely to be different in the two populations as a reflection of the baseline socioeconomic differences. All of these differcnces confound pure comparisons of HIV natural history between the two

populations. Finally, biologic differences, such as those relating to age, gender, and race, likely have an influence on development of disease and survival.

There are more and larger natural history studies in homosexual and bisexual men than in intravenous drug users. However, several large cohort studies among intravenous drug users now exist, and despite the caveats noted above, it is now possible to make rough comparisons between the two populations on the basis of these studies.

NATURAL HISTORY COHORT STUDIES

HIV infection is best understood as a chronic progressive viral illness that most directly affects the immune and nervous systems. The chronicity of HIV infection and the relatively recent establishment of natural history cohorts have resulted in the development of precise information at either end of the time course of the natural history of infection. Knowledge exists about the events that occur soon after seroconversion; those events that occur after HIV infection have been established for many years. The prolonged middle period of HIV infection, which may extend from 2 to 3 years from the onset of infection to 7 to 8 years after infection has been present, has not yet been defined precisely in existing natural history studies. To define the early period of HIV infection, very large cohort studies are required that enroll substantial numbers of HIV seroconverters—initially HIV seronegative individuals who become HIV positive while under observation. Much of this early portion of HIV infection can be characterized in both gay men and intravenous drug users from several large *incident* natural history cohort studies (table 1).

There are two representative large incident natural history studies among gay men. The San Francisco men's cohort study initially enrolled men with known dates of HIV seroconversion (Lifson et al. 1989). In this study 63 of the 121 still under observation, or 52 percent, have developed AIDS at 100 months of followup. The Multicenter AIDS Cohort Study (MACS), which is being carried out in four cities in the United States, has enrolled over 200 men who have seroconverted in the study from HIV seronegative to positive (Saah et al. 1989). Twelve of these, or 5 percent, have developed AIDS at 48 months of followup. Of note, both studies indicate that among gay men the incidence of AIDS in the first 3 years from the time of HIV seroconversion is very low—4 percent and 3.2 percent, respectively. One incident natural history cohort study being performed among intravenous drug users has

Table 1. Incident natural history cohorts—Homosexual men and intravenous drug users

	No. AIDS cases/ Total (percent)	Mean followup (in months)	Follow-up rate	Case rate per year 1	2	3	4	5	6
Homosexual men									
Lifson et al. 1989 (San Francisco)	63/121 (52%)	100	45%	0	1	4	10	15	25
Munoz et al. 1989 Saah et al. 1989 (MACS/U.S.)	12/233 (5%)	48	-	0	1.6	3.2	3.7	-	-
Intravenous drug users									
Rezza et al. 1989 (Italy)	13/205 (6%)	26	69%	1.5	2.9	9.9	17.9	-	-

been published (Rezza et al. 1989). This study is being carried out at multiple sites in Italy. The study has enrolled 205 seroconverters, who have been followed for a mean of 26 months. Thirteen (6 percent) have developed AIDS, and an additional 11 (5 percent) have developed HIV-related illness. The calculated incidence rate in this population is 2.9 per 100 person/years for the development of AIDS in the first 24 months of the study.

Thus, the available studies in both gay men and intravenous drug users indicate that the vast majority of persons infected with HIV remain without disease during the first several years of HIV infection. The rate of development of AIDS showed a marked increase in the third year among drug users to 9.9 per 100 person/years. The study design, however, involves passive clinical reevaluations. Thus, those persons who are sickest may be reporting more frequently for clinical evaluations, biasing the study toward a higher complication rate. In addition, only a small number of the total cohort of 205 have been followed for more than 48 months, so calculations beyond this point

are unreliable. Enrollment of most of the cohort occurred in 1985 to 1988, and the opportunity for sufficient followup has not yet occurred. Despite these qualifications, it is reasonable to conclude that the early occurrence of the most serious complications of HIV infection is similar in both populations. For most individuals, apart from the occurrence of the acute retroviral syndrome at the time of seroconversion, there appears to be a disease-free period of several years following acquisition of HIV infection. This observation has now been supported further by a similar finding in large cohort studies among HIV positive hemophiliacs and transfusion recipients (Ward et al. 1989; Goedert 1989).

A greater number of clinical outcome measures in both gay men and intravenous drug users are available in *prevalent* natural history cohort studies (table 2). These studies enrolled patients who were either seropositive or seronegative for HIV at study initiation. The time of acquisition of infection is not known. Thus, apart from new incident seroconverters, little information is available on early HIV infection from these studies. However, because patients enrolled often have been infected with HIV for substantial periods of time, large numbers of outcome events can be documented and the later portion of HIV infection is more available for scrutiny. Four studies are available for evaluation and comparison (table 2). These include a study among gay men followed at San Francisco General Hospital (Moss et al. 1988), the Multicentcr AIDS Cohort Study (MACS) of gay men (Munoz et al. 1989), and two New York City studies of intravenous drug users, one in the Bronx (Selwyn et al. 1989*b)* and one in Manhattan (Des Jarlais et al. 1987). The large number of enrollees and reasonably good followup rates allow for comparisons between these studies. Of note, the San Francisco and Bronx studies have identical numbers of seropositive individuals at enrollment and very similar rates of development of AIDS over periods of approximately 3 years of observation. The AIDS rate in San Francisco was 17 percent among gay men and that in the Bronx was 12 percent among intravenous drug users. After 1 year of observation in these cohorts, 5 percent of the men in San Francisco developed AIDS, and 4 percent of the male and female intravenous drug users in the Bronx developed AIDS. At year 2, 11 percent and 9 percent and at year 3, 22 percent and 15 percent of individuals in the two populations developed AIDS. Although there arc possible different entry points in the course of HIV infection in these two studies that limit direct comparison, it is, nevertheless, striking that similar rates of development of AIDS and HIV-related disease appear to be occurring in these cohorts assembled in different parts of the country and among individuals with different risk behavior.

Table 2. Prevalent natural history cohorts—Homosexual men and intravenous drug users

	No. AIDS cases/total (percent)	Mean followup in months	Follow-up rate	AIDS case rate per year (percent)	AIDS incidence
Homosexual men					
Moss et al. 1988 (San Francisco)	50/288 (17%) (19%)	36	81%	1 (5) 2 (11) 3 (22)	
Munoz et al. 1989 Saah et al. 1989 (MACS/U.S.)	304/1,628 (19%)	48	77-93%		3.8/100 person year
Intravenous drug users					
Selwyn et al. 1989*b* (Bronx)	34/288 (12%)	31	83%		4.5/100 person years
				1 (4) 2 (9) 3 (15)	
Des Jarlais et al. 1987 (Manhattan)	4/165 (3%)	9.2	83%		

An important related issue that is currently the subject of extensive study is the presence of laboratory makers that may predict outcome of HIV infection. These have been carried out largely among homosexual and bisexual

men. These studies indicate that CD4 cell count and/or percentage of CD4 cells, the presence of P24 antigen, and the level of beta 2 microglobulin predict progression to AIDS among those who are infected with HIV (Moss et al. 1988; Lang et al. 1989). The evaluation of these markers is currently being carried out among intravenous drug users, but no substantial comparative information about their utility is currently available. Use of these surrogate markers will help determine appropriate points for therapeutic and preventive medical interventions such as antiretroviral therapy or infection prophylaxis. They also may make it possible to create models of duration of HIV infection that may aid in direct comparisons of natural history cohort studies. An important caveat is the likelihood that the performance characteristics of these surrogate markers may differ in different populations. For example, HIV p24 antigen rates differ between blacks and whites at the same stage of HIV infection (Fuchs et al. 1989), and baseline B_2 microglobulin baseline values are higher among intravenous drug users than other populations (K. Davenny and G.H. Friedland, unpublished data).

SURVIVAL FROM AIDS DIAGNOSIS

The entire length of natural history of HIV infection may never be completely determined, since direct intervention with antiretroviral therapy and prevention of opportunistic infections have become standard practice. However, complete information is available about survival once the diagnosis of AIDS has been made. This represents a clearly defined point in time from which most patients are under some form of health care or observation. Because of the relatively brief survival time from the diagnosis of AIDS and the clearly defined point of death, the course of this final segment of HIV infection can be well documented.

Reported survival data in the absence of specific antiretroviral therapy arc available from several sources. These have some limitations because of the relative homogeneity of the populations studied and the discrepancies in clinical care available. The survival of AIDS patients from the time of diagnosis before specific antiretroviral therapy was available has been reported from several geographic areas, including New York City in a heterogeneous population of gay men, intravenous drug users, and others (Rothenberg et al. 1987); the Bronx, New York City, in a heterogeneous population (Friedland et al. unpublished); San Francisco among homosexual men (Bacchetti et al. 1988); New Haven in both intravenous drug users and homosexual men (Justice et al. 1989); and Barcelona in a population composed predominantly of intravenous drug users (Batalla et al. 1989). The

reported median survival of all AIDS patients in these studies was 11 months in New York City and San Francisco, 5 months in New Haven, and 12.8 months in Barcelona. In the largest series, a cohort of close to 6,000 patients with AIDS diagnosed in New York City before 1986, the cumulative likelihood of survival was 49 percent at 1 year and 15 percent at 5 years (Rothenberg et al. 1987). In a smaller but more closely followed series of over 500 AIDS patients in San Francisco who were almost all homosexual men and were followed through 1985, the estimated 1-year survival rate was 44 percent and 3-year survival rate, 11 percent (Bacchetti et al. 1988). The 1-year survival for patients presenting with Pneumocystis carinii pneumonia varied in these studies from 45 percent in New York City to 30 percent in San Francisco. Additional data indicate that survival in the Bronx population in which intravenous drug users were the major group was similar to that during a comparable time period reported from San Francisco almost exclusively in homosexual or bisexual men (Friedland et al. unpublished).

In the San Francisco study, 99 percent of patients were male homosexuals and 92 percent were white. As a result only limited survival comparisons by demography were possible. The more diverse populations in New York City and Barcelona have allowed for comparisons by risk and demography. In San Francisco among gay men, age was shown to predict survival, with older men having a significantly shorter survival than younger men. In the series from multiple institutions in Barcelona, older age was also associated with shorter survival and, interestingly, intravenous drug users had a more favorable survival than other groups. In the New York City study, excess risk was related to age and also to sex, race, and ethnic background. Women's survival was shorter than men's, and whites lived longer than blacks. These survival differences may reflect differences in availability and use of health care facilities or clinical care itself.

For example, there has been a proportionately larger increase in AIDS reporting among intravenous drug users compared with homosexual and bisexual men in the northeastern United States since the revision of the CDC case definition (Centers for Disease Control 1987*b*). This is presumably the result of more flexible and less precise diagnostic criteria allowing for the inclusion of more patients whose diagnostic evaluations were incomplete. To minimize these potential confounders, case series from single institutions where comparable clinical care is available, and a diversity of risk behavior and demography are seen, are necessary. In the series from a single institution in New Haven a diversity of risk, race, and gender were present, and some differences in survival were noted (Justice et al. 1989).

However, the numbers of patients in diagnostic and demographic categories were small and statistically significant differences were not demonstrated. In the study from the Bronx (Friedland et al. unpublished), most patients came from a single geographic area, and regardless of risk behavior were of similar socioeconomic status and received comparable clinical care from a single medical center. Here the presence of all risk behaviors, and the large number of patients with different racial and ethnic backgrounds, ages, and both male and female gender, permitted comparisons unavailable in other studies.

In most studies of survival, the initial presenting AIDS diagnosis was the most powerful predictor of survival. This is likely the result of organ system involved, degree of immunosuppression at presentation, and efficacy of available therapy. In the Bronx population, in addition to the AIDS presenting diagnosis, survival was also predicted by several demographic characteristics and risk behaviors. As in other studies, younger age and male gender emerged as predictors of a more favorable survival. In addition, within the group of patients presenting with Pneumocystis carinii pneumonia alone, different risk behaviors were associated with differing survival. Surprisingly, intravenous drug use was associated with longer survival, a result which was also found among AIDS patients in Barcelona (Batalla et al. 1989). Of note, patients who were black had the longest survival, Hispanic patients had an intermediate duration of survival, and white patients the shortest survival. The differing survival experience among these various groups may imply the presence of biologic, behavioral, or clinical care factors that might influence survival once AIDS is diagnosed. The nature of these factors remains unknown. One hypothesis explaining the longer survival in intravenous drug users is that they represent a selected *survivor* population. Intravenous drug users who develop AIDS have a mean age of 34 and thus already represent a population of survivors of long-term drug use and its complications.

Since differences in survival were most strongly associated with differences in presenting opportunistic infection, it is noteworthy that the distribution of presenting opportunistic infections appears to vary significantly between homosexual men and intravenous drug users. For example, it has been long been known that Kaposi's sarcoma, the AIDS-defining diagnosis associated with the longest survival, is most prevalent among homosexual and bisexual men and infrequent or even rare among intravenous drug users (Haverkos et al. 1985; Des Jarlais et al. 1984). An association between nitrite inhalants and Kaposi's sarcoma in HIV infected homosexual men has been made. This

or other cofactors related to a homosexual lifestyle appear important in the development of this complication of AIDS, but data are insufficient to prove the relationship or define the mechanism (Haverkos 1988). Less well known, but of similar importance, is the apparent increase among intravenous drug users in the frequency of presenting AIDS opportunistic infections that are associated with a shortened survival. For example, cryptococcal meningitis and disseminated disease and Mycobacterium avium intracellulare infection appear to be more frequent among intravenous drug users compared with gay men (G.H. Friedland, unpublished observation). The decreased frequency of Kaposi's sarcoma among intravenous drug users, which is associated with longer survival, and increased frequency of shorter survival associated fungal and bacterial infections would tend to result in shorter survival periods from the time of AIDS diagnosis in this population. This can obscure overall survival differences between populations and requires stratification by specific disease presentation. The longer pneumocystis survival among intravenous drug users compared with gay men is, therefore, particularly noteworthy.

To more fully appreciate patterns of survival, it is clear that substantially more information should be acquired related to the difference in distribution of AIDS defining illness among populations with various risk behaviors. At present, there appears to be sufficient information to state that intravenous drug users and gay men who present with the same initial AIDS defining illness may have similar survival patterns when comparable health care is available. Indeed, the length of survival among intravenous drug users in this setting may even be more favorable.

HIV-RELATED INFECTIONS AND OTHER COMPLICATIONS

As a clinical outcome, AIDS represents only a fraction of the illness associated with HIV infection. However, there are insufficient uniformly collected population-based data regarding non-AIDS HIV-related illness among both gay men and intravenous drug users. Recent observations indicate that there is a larger spectrum of severe HIV-related disease among intravenous drug users, particularly in New York City (Stoneburner et al. 1988). This spectrum of disease is not included in the Centers for Disease Control AIDS case definition and, therefore, has been underreported and is difficult to quantitate. The accumulating evidence from many quarters is convincing and seems to indicate as well that this burden of HIV-related disease is greater among intravenous drug users than homosexual men or other indi-

viduals infected with HIV. Increasing mortality in intravenous drug users not reported as AIDS occurred in New York coincidentally with the AIDS epidemic during the 5-year period from 1981 to 1986 (Stoneburner et al. 1988). Narcotics-related deaths increased an average of 32 percent per year. The increase included deaths from AIDS, but also deaths from other causes, many of which were infectious diseases. In this latter category deaths increased from 492 in 1981 to 1,092 in 1986.

Additional documentation of an increased burden of HIV-related disease in the population of intravenous drug users in the Bronx has emerged from a longitudinal study of HIV infection as well as by careful clinical observation in the Montefiore Methadone Treatment Program. The prospective population-based design of this longitudinal work has resulted in the precise documentation of the amount of excess risk of bacterial pneumonia related to HIV infection in this population (Selwyn et al. 1988). Among 144 HIV seropositive individuals without AIDS, the rate of hospitalization for bacterial pneumonia was 9.7 percent compared with a rate of 2.1 percent among 289 HIV seronegative individuals (risk ratio 4.7, 95 percent confidence limits 1.8-11.9). Controlling for active drug use did not alter this significant difference. The majority of these pneumonia episodes were with S. pneumoniae and H. influenzae. Further, pneumonia severity appeared greater among HIV seropositives. Mortality from pneumonia occurred among the HIV seropositives only, and their length of hospital stay was significantly longer than for the HIV seronegatives. Population based information is lacking about pneumonia rates in HIV positive gay men. Only one study in New York has attempted to address this issue in an epidemiologic context (Polsky et al. 1986). An apparent increased clinical occurrence of bacterial infection in gay men has been described in San Francisco as well (Krumholz et al. 1989). It appears at present that bacterial pneumonia risk is greater among HIV positive intravenous drug users. The relative rates of pneumonia in several populations are recorded on table 3. Of note is the high baseline rate of pneumonia in HIV negative intravenous drug users compared to the general population and even to gay men with AIDS (Selwyn et al. 1988; Polsky et al. 1986, Simberkoff et al. 1984; Witt et al. 1987; Schrager 1988).

Information about tuberculosis and its relationship to HIV infection and intravenous drug abuse has been acquired from several sources. The consistently downward trend in tuberculosis rates in the United States during the past 20 years ended in 1985 (Rieder et al. 1989). An excess of over 9,000 cases of tuberculosis has occurred since then. These cases are concentrated in inner city areas of high intravenous drug use and HIV infection preva-

Table 3. Incidence of bacterial pneumonia in different populations

Study	Population	Incidence per 1,000 patient years
Schrager 1988	General population	2.6
Polsky et al. 1986	Homosexual men with AIDS	17.0
Simberkoff et al. 1984	Intravenous drug users with AIDS	95.0
Witt et al. 1987	Intravenous drug users with AIDS or ARC	45.0
Selwyn et al. 1988	Intravenous drug users without AIDS	
	HIV-	27.0
	HIV+	97.0

lence. Their occurrence in time and place in parallel with the HIV epidemic strongly supports an epidemiologic association. Clinical and serologic series from inner city areas in the New York metropolitan area and other parts of the United States further support the relationship between HIV infection, drug use, and tuberculosis (Sunderam et al. 1986; Chaisson et al. 1987; Centers for Disease Control 1989). Precise calculation of the excess risk created by HIV infection requires population-based controlled studies. Such information can be derived from the longitudinal studies of HIV-related disease in the Montefiore Methadone Treatment Program (Selwyn et al. 1989*a*). Active tuberculosis developed in 8/217 HIV seropositive subjects (4 percent) and in 0/303 seronegative subjects ($p < .002$) under observation for approximately 2 years. Although the prevalence tuberculous infection as measured by PPD skin test positivity was similar for both HIV positive and HIV seronegative intravenous drug users, the risk of development of active tuberculosis was elevated only for HIV seropositive subjects, the result of reactivation of latent tuberculous infection. In this study a greater than twentyfold increase in risk of active tuberculosis resulted from HIV infection. In addition, the results supported the aggressive use of chemoprophylaxis against the development of tuberculosis in patients with HIV infection and a positive PPD test. The baseline PPD positive rate among methadone program enrollees was 20 percent to 25 percent. Although exact data are not available, the baseline PPD positive rate among middle class gay men is probably one tenth that in poor drug users of black and Hispanic back-

ground. Clinical tuberculosis will appear in populations with coinfection with M. tuberculosis and HIV. The higher baseline of M. tuberculosis infection among drug users ensures a continuing higher rate of active tuberculosis compared with gay men. Increased rates of severity of other infectious diseases traditionally associated with drug use, such as bacterial endocarditis, have also been noted (Schrager 1988).

This enhancement of risk of secondary infection is illustrated by an examination of the impact of the AIDS epidemic on morbidity and mortality in the Montefiore methadone program from 1984 to 1987 (Selwyn et al. 1989*c*). Here trends in overall and cause-specific death rates, AIDS incidence, and medical hospitalizations were followed, with outcomes identified by active surveillance and review of hospital and autopsy records. Total deaths increased from 13.3/1,000 in 1984 to 44.2/1,000 in 1987 ($p=.0001$). Whereas deaths from cirrhosis, overdose and trauma showed no significant increases, those due to AIDS (3.3 to 14.7/1,000) and bacterial pneumonia/sepsis (3.6 to 13.6/1,000) increased significantly. Further, the rates of hospitalization for these medical illnesses increased dramatically coincident with the HIV epidemic. These data indicate a profound impact of not only AIDS among intravenous drug users in treatment programs but also of the expanded spectrum of HIV-associated disease in this population. They clearly demonstrate the need for expansion of existing resources in treatment programs to meet the growing need for HIV-related care. Similar dramatic increases in this array of non-AIDS but clearly HIV-related illness among gay men has not been as clearly or precisely documented and should form the basis of further comparative studies.

COFACTORS

Cofactors that might influence the course of HIV infection have been sought in both populations. Much attention has been directed to biologic factors such as differences in the virus and differences in genetic makeup of the host. However, no clearly defined biologic cofactors have been identified. As previously noted, there appear to be differences in survival by race, age, and gender that are not currently explained. A logical area of exploration is the role of behaviorally related cofactors that may influence the progression of HIV disease. Here behavioral and disease progression comparisons between gay men and intravenous drug users may provide interesting insights.

Among those cofactors that have been postulated as influencing the natural history of HIV are those related specifically to the continuation of sexual and drug use behavior. One early study suggested that continuing high risk-sexual behavior was associated with the development of AIDS in gay men (Polk et al. 1987). However, this was likely a marker for earlier infection rather than a true cofactor. In other studies among gay men, behavioral cofactors could not be identified which predicted development of disease.

A recent study from the MACS cohort of homosexual and bisexual men examined the issue of the use of psychoactive drugs as potential cofactors in accelerating HIV progression (Kaslow et al. 1989). This study found no association with any type of psychoactive drug use and development of clinical disease or loss of CD4 cells.

Several studies have looked at the issue of continuing drug use as a cofactor for progression of HIV infection among intravenous drug users (Des Jarlais et al. 1987; Flegg et al. 1989; Schoenbaum 1989). Here, of course, the type of drug use and its extent is substantially different than among homosexual or bisexual men. Although alcohol use among intravenous drug users is frequent, the use of both heroin and cocaine is of greatest interest. The findings related to drug cofactors among intravenous drug users have been variable. In one study intravenous drug users showed more rapid loss of CD4 cells over a 9-month period of followup if they continued to use intravenous drugs (Des Jarlais et al. 1987). In this study CD4 loss was associated with frequency of drug injection and was more pronounced among heavy drug users. These results are supported to some degree by a study from Edinburgh, Scotland, in which continued intravenous drug use was also associated with greater rate of loss of CD4 cells in individuals with HIV infection (Flegg et al. 1989). In this study among 248 intravenous drug users infected in 1983 or 1984, over 50 percent continued drug use. Clinical progression was not different among those who continued to use drugs and those who did not; however, there was a greater fall in the absolute CD4 count among those who continued to inject. This progression of CD4 cell loss was not seen in a study among intravenous drug users in the Bronx (Schoenbaum et al. 1989). In this study there appeared to be no difference in the rate of fall in CD4 count among drug users who did and did not continue to inject drugs intravenously.

An additional relevant cofactor that may influence the progression to HIV infection is the occurrence of bacterial infections themselves. Several in vitro studies indicate that T-cell stimulation may result in an increase of HIV replication (Zagury et al. 1986). Since coexistent infections other than

Table 4. Natural history of HIV infection comparison between intravenous drug users and gay men

Similarities
AIDS-free time during first years of infection.
High AIDS case rate after longstanding infection.
Shorter survival time from AIDS diagnosis among older patients.
Absence or weak influence of cofactors on disease progression.
Differences
Lower socioeconomic status and less available health care among intravenous drug users.
Differing demographic composition: 70 percent gay men white; 80 percent intravenous drug users black or Hispanic; 30 percent intravenous drug users women.
Better documentation of acute rctroviral syndrome in gay men.
Increased frequency, morbidity and mortality from HIV-related bacterial infections in intravenous drug users.
Differing frequency of certain malignancies and opportunistic infection: Increased Kaposi's sarcoma and cytomcgalovirus in gay men, increased cryptococcal disease, Mycobacterium avium intracellulare infection, and tuberculosis in intravenous drug users.
Longer survival from time of AIDS diagnosis in intravenous drug users when adjusted for presenting illness.

HIV may result in macrophage stimulation, it is reasonable to assume that the frequent occurrence of complicating bacterial infection, which appears

to be more common among intravenous drug users, might itself result in more rapid acceleration in HIV-related disease. However, it has not been possible to clinically or epidemiologically confirm this hypothesis. Apart from the observation that bacterial pneumonia, oral candidiasis or tuberculosis predict the development of HIV infection (Selwyn et al. 1989*b*), their role as cofactors rather than markers for progression has not been demonstrated. Among female intravenous drug abusers, the possibility that pregnancy, which may be viewed as a state of mild immunosuppression, might result in accelerated HIV infection is the subject of active investigation. At this point there appears to be no convincing documentation that pregnancy results in more rapid acceleration of HIV-related immunosuppression.

It is disappointing that the exploration of cofactors that might influence the progression of HIV infection has yet to uncover significant findings. The duration of HIV infection itself is the strongest predictor of outcome. That cofactors altering the rate of progression exist is certain and clearly suggested by the wide difference in rates of progression to HIV infection among individuals, regardless of risk behavior, and the wide array of the different manifestations of HIV infection. However, the precise mechanisms by which biologic, behavioral, and demographic differences result in changes in the natural history of HIV infection are not known. In this, as in other ways, the similarities in HIV infection between disparate populations throughout the world remains. Careful and continuing clinical and epidemiologic observation for differences as well as similarities among different populations, particularly within existing and expanded natural history studies, is essential. In the presence of deepening biologic sophistication about HIV and its pathogenic properties, it is hoped that these observations will yield new and useful information that may be of ultimate benefit to those with and at risk for HIV infection.

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4. Sampling Issues for Natural History Studies Including Intravenous Drug Abusers

W. Wayne Wiebel

Few would take issue with the "gold standard" stature of longitudinal cohort research designs in natural history studies. No methodological alternative can rival the analytic rigor offered by prospective panel studies in delineating and characterizing factors and cofactors influencing the course of infectious disease epidemics. Likewise, in regard to sampling strategies, scientific canon dictates a clear preference to the selection of units of analysis through probability designs. As a consequence, it is not surprising to find prospective research designs and probability sampling schemes commanding considerable favor in investigations addressing the natural history of HIV infection among intravenous drug abusers (IVDAs).

Yet, as in any area of scientific inquiry, theoretical and empirical considerations alone rarely offer sufficient guidelines in determinations of the most appropriate and pragmatic means of addressing a given research problem. Compromise to scientific ideal is often required as a balance to practical constraint. In a challenging interplay of preference and feasibility, most scientists are faced with externally imposed limitations that restrict the options available to them in constructing a research design. This paper focuses on sampling issues in natural history studies of AIDS among IVDAs and suggests strategies that may improve our ability to address this key area of current public health research.

SAMPLING ISSUES

Studying the natural history of HIV infection among IVDAs is much more problematic in practice than in principle. That is, despite the clarity of

preferable design attributes, practical constraints significantly confound research potential. One such pivotal obstacle relates to our ability to identify and gain access to the universe of subjects at issue, specifically, those individuals who, as a consequence of injecting drugs intravenously, are at high risk for contracting and further spreading HIV infection.

As participants in an illicit and covert activity that has become increasingly stigmatized in our society, individuals who use drugs do not readily lend themselves to systematic identification and enumeration. This is even more likely to be the case for individuals who inject drugs. Not only do IVDAs have cause to avoid identification with their illicit activity but, by virtue of their addictive careers, they frequently live a relatively transient and impoverished existence. Thus survey techniques traditionally associated with general population studies, such as household or telephone samples, arc clearly inappropriate strategies for researching this subpopulation. Irrespective of theoretical and empirical desirability, researchers lack a viable means to accomplish representative sampling of the critical universe that defines their research problem.

If one accepts the reality of this constraint, then at the outset one must acknowledge problems of inherent bias and limited generalization of findings in studies addressing this area of inquiry. This is not, however, meant to be damning. Quite the contrary, as alluded to above, it is an almost normative condition in drug abuse research and far from uncommon in much of social science. Through an examination of the alternative sampling strategies available to researchers interested in HIV infection among IVDAs, it is hoped that potential sources of sampling bias can be more appropriately addressed and taken into account in both study design and interpretation of findings.

Faced with the necessity of compromise to scientific ideal, researchers can either redefine their focus of inquiry or adjust sampling strategy to accommodate practical constraint. In the first instance, the research problem to be addressed might be narrowed to include the natural history of HIV infection among IVDAs in treatment for substance abuse problems. Thus defined, the research population more readily lends itself to enumeration and probability sampling. In the second instance, lacking a means to representatively sample the theoretically relevant population, a nonprobability purposive, quota, or convenience strategy may be adopted.

Either of the above alternatives is legitimate, but without further justification it is not possible to establish the desirability of one approach over the

other. While the first option might seem preferable to the extent that it facilitates probability sampling, this may not be the case if the theoretical relevance of the researched population is unknown or not addressed.

Having discussed some of the more general sampling and design issues relating to natural history studies of HIV infection among IVDAs, let us proceed to a more grounded exploration of the varieties of bias that may be inherent to the more commonly utilized IVDA sampling frames.

IVDA SAMPLING FRAMES AND POTENTIAL SOURCES OF BIAS

As a consequence of events such as medical emergency, arrest, or entry into treatment for problems of drug dependence, subgroups of IVDAs become the object of official recognition and, as such, also become accessible to the researcher for purposes of sampling and subject recruitment. Most current studies rely on institutionally based sampling frames for many, if not all, of their research subjects.

Drug Abuse Treatment Populations

Drug abuse treatment populations represent one of the most accessible and numerous institutional resources of IVDAs. In part due to this, it is not surprising that clients in treatment are the most commonly recruited constituents of IVDA research studies. Both the number and variety in types of treatment programs from which research candidates can be enlisted are important considerations in attempting to assess potential bias. Individual programs can vary substantially in client profile. Further, categories of treatment programs including public or private, residential or outpatient, methadone maintenance or detoxification or drug free, all represent differing potentials for bias.

Several sources of bias seem likely in IVDA samples constituted from clients in treatment for problems of drug dependence. First of all, as it is estimated that this population includes only 10 to 20 percent of the total IV drug abusing population (Schuster 1988), they clearly represent only a small proportion of all individuals in this high-risk classification. Clinically conceptualized as having a chronic, progressive, and recurring disease, individuals who seek treatment for problems of drug dependence are more likely to have bottomed out and overrepresent chronic abusers approaching the end of their addictive careers. In the case of methadone treatment programs, a subset of the client population is likely to overrepresent the chronically

addicted who are not so much interested in ending their illicit use of opiates as they are interested in trying to manage habits that have gotten out of control on the streets.

In most areas of the country, the vast majority of treatment slots available to the IVDA are allocated within methadone detoxification or maintenance modalities. Consequently, clients in treatment are likely to underrepresent injectors dependent on cocaine as well as other nonopiate drugs. In most instances, treatment programs that do not address problems specific to females, including the need for child care services, are thought to underrepresent female injectors. By way of contrast, in the case of at least one State, a change in policy for publicly funded programs to fee-for-service requirements shifted the balance toward female clients as they were more likely to possess Medicaid and be able to cover their contribution with the help of public assistance (French 1987).

Additional varieties of bias are likely to correlate in degree with length of stay in treatment. Often utilized as indicators of therapeutic success, clients in treatment are less often involved in illicit drug use and criminal activities, more often employed, and otherwise leading more healthy, stabilized lifestyles. Clients who drop out of treatment, on the other hand, are more difficult to follow up and thus are more expensive to maintain in longitudinal panel designs. In addition to having a greater likelihood of being lost to followup, clinic dropouts often quickly relapse to careers of active IV drug addiction (Ball et al. 1988, Hubbard et al. 1988).

Of particular relevance to natural history studies of AIDS among IVDAs, potential sources of bias in samples based on clients who are enrolled and remain in drug treatment have significant implication for research involving various aspects of the epidemic. By virtue of their decreased drug use and more healthy, stable lifestyles, treatment client research panels are less likely to experience incident cases of HIV infection. For subjects already infected, these same attributes may moderate disease progression and the risk of acquiring infectious cofactors. The underrepresentation of cocaine-dependent IVDAs in treatment samples has further implications for understanding the course of HIV infection in this risk group. Research has already suggested that cocaine injectors may be at increased risk for HIV infection due to specific practices, such as higher frequencies of injection, associated with cocaine dependence (Chaisson et al. 1989).

Criminal Justice Agencies

Criminal justice agencies offer the researcher a second plentiful institutionally based resource for IVDAs. However, the ability to identify and gain access to such individuals for the purpose of research may be significantly more problematic than is the case with IVDAs in treatment. Specifically, the permissions required to conduct this type of research may include multiple layers of bureaucratic approval, and even when allowed, may contain numerous stipulations and restrictions that can frustrate research design implementation. Research incorporating criminal justice clients is often conducted in direct collaboration with or under primary direction of participating agencies.

Different agencies within the criminal justice system represent differing potential sources of bias in the IVDAs that fall under their authority. IVDAS who become the subject of official recognition by police, court, and criminal justice diversion agencies are most likely arrestees suspected of committing a drug-related criminal offense. Prison, parole, and probation agencies, on the other hand, deal with IVDAs who have been convicted for a criminal offense. In comparison to arrestees, individuals convicted for criminal offenses are more likely to have extensive arrest/conviction records, have committed major felony offenses, and have sufficient incriminating evidence against them to substantiate their conviction.

In general, criminal justice agencies can be expected to overrepresent IVDAs who are most actively involved in criminal behaviors as a means of supporting their addictions, least competent in their criminal activities, and more likely to have been the subject of previous arrest and/or incarceration. Injectors who have not progressed to chronic dependence, have sufficient legitimate financial resources to support their drug use, or who are otherwise are able to avoid the attention of law enforcement authorities are likely underrepresented in IVDA samples recruited through the criminal justice system.

These potential sources of bias are likely to have the following implications for natural history studies. With respect to the collection of risk factor histories, criminal justice clients may be less likely to report illicit activities that can be associated with crimes they have not been arrested for. To the extent that prospective research can be associated with the criminal justice agencies who have authority over subjects' legal status, criminal justice samples are also likely to underrepresent participation in activities (including

drug use, prostitution, and homosexual relations) that place them at risk for punitive sanctions.

Medical Service Providers

Medical service providers are the final category of commonly utilized resources for institutionally based IVDA samples. Agencies offering medical services have traditionally played a critical role in identifying and providing access to research subjects for inclusion in a broad range of epidemiologic investigations. Irrespective of risk group classification, they are both critical to and the primary resource for research relating to AIDS diagnosed cases. However, for studies addressing the natural history of HIV infection, they are a less efficient resource for identifying IVDAs who are not infected or are asymptomatic. While still an effective and capable source of IVDAs for research sampling, at any given time, medical service agencies are likely to offer access to far fewer numbers of IVDAs than either drug treatment programs or criminal justice agencies.

As in the case of other institutionally based IVDA sampling frames, potential sources of selection bias vary by category of medical service provider. For example, emergency rooms are suspect to overrepresent patients with acute conditions, hospital wards to disproportionately serve patients with chronic conditions, and private facilities of every variety to favor the insured and financially secure. In most instances, providers serving catchment areas with high rates of intravenous drug use, as well as those offering service to the indigent, will tend to be in contact with the greatest numbers of IVDAs.

Acute medical service providers, including paramedics and emergency rooms, most often come into contact with IVDAs who are either suffering adverse drug reactions and/or are the victims of physical trauma. Individuals requiring medical attention for adverse drug reactions such as an overdose are most likely to overrepresent IVDAs who are multiple drug users experiencing unanticipated drug interaction effects, novice or occasional users who have misjudged appropriate drug dosage, and the heavily intoxicated who through accident or disinhibition have exceeded toxic levels of drug consumption. IVDAs requiring medical attention for traumatic injury probably overrepresent individuals who are victims of either intentional or circumstantial violence as well as those involved in drug-related accidents.

Facilities treating chronic conditions, on the other hand, are more likely to overrepresent IVDAs who are long-time users of injected drugs, least hygienic in their drug use practices, and least attentive to maintenance of

their general health. Some of the more severe medical complications commonly associated with intravenous drug use include infectious diseases such as HIV and hepatitis, which are transmitted through the sharing of contaminated injection paraphernalia and bacterial endocarditis.

These potential sources of bias in medical service provider samples may also have implications for natural history studies. In overrepresenting trauma and adverse drug reaction cases, acute care providers are likely to offer access to potential research subjects who are in no condition to consider enrollment in a study. Once released from care, reestablishing contact and gaining the cooperation of such subject candidates may be much more problematic. By way of contrast, chronic care providers may suggest a worse-case-analysis in the relationship between HIV infection and IV drug abuse through overrepresenting long-term addicts who are least concerned about issues of hygiene in their every day lives.

In addition to these three institutionally based sources of IVDA sample recruitment, there is a fourth, community-based alternative which my own professional experience has led me to become most familiar with. This last IVDA sampling strategy and its potential sources of bias are discussed below.

Social Network

Social network samples of active IV drug abusers in community-based settings are among the least often utilized sampling frames to be adopted by researchers studying the natural history of HIV infection in this high-risk population. More often associated with qualitative rather than quantitative methodologies, ethnographic inquiry has most frequently relied upon this sampling strategy. However, multi-method research designs, including ethnographic components, have demonstrated the potential contribution of community-based IVDA samples in investigating the spread of HIV infection among this population (Wiebel 1988, Feldman and Biernacki 1988; Watters and Biernacki 1989).

While IV drug-using social networks may offer a ready means of identifying and gaining access to potential research subjects, the heterogeneous composition of different social networks implies the same differential sources of bias as were apparent within institutionally based sampling frames. In particular, membership profiles within IVDA social networks can be expected to vary based on preferred patterns of drug use, community demographics, and the shared attributes that form the basis of social bonding between

members. Unlike the externally imposed sources of recruitment bias associated with institutionally based IVDA sampling strategies, social networks of IV drug abusers in the natural setting more often establish their own definitions of group identity and the individual characteristics that are central to membership consideration. It is these criteria, however defined, which must be taken into account in assessing the inherent bias represented by any given social network sampling frame.

In our most recent work exploring AIDS intervention efficacy targeting active IV drug using social networks, an additional, research-imposed, bias is an apparent artifact of our purposive sampling strategy. That is, as a screening criterion utilized in the selection of IVDA social networks for inclusion in our sample, we purposely considered only larger networks for two reasons. The first reason is that larger networks were thought to hold the greatest potential as a focus for extended research and intervention activity. Second, as a demonstration project, we wanted to test the efficacy of this intervention model under conditions that would be of greatest relevance to public health policymakers interested in assessing the potential impact and cost effectiveness of this approach. While the composition of sampled networks intentionally included a range in the predominant variety and types of IVDAs known to be represented within a metropolitan area, our sampling strategy clearly underrepresented socially isolated IV drug abusers as well as those who limited their drug-related activities to smaller and more close-knit social networks.

These potential sources of bias suggest the following implications for natural history studies. Community-based samples of IV drug abusers, which focus on larger, high-profile social networks of IVDAs, may reflect higher rates of HIV seroconversion by virtue of the greater number of high-risk individuals subjects come into contact with as potential needle sharing and/or sex partners. Subjects recruited from social networks of active users may also experience a more rapid progression to AIDS diagnosis once infected due to their continuing drug use as well as their relative lack of attention to issues of health and hygiene.

DISCUSSION

Given current limitations that prevent us from generating true probability samples of the entire IVDA population which is of theoretical relevance, research addressing the natural history of HIV infection among this high risk population must rely on alternative sampling strategies. However such

accommodation is attained, all sampling strategies commonly employed by investigators to recruit IVDA subjects for research present inherent sources of bias. While it is impossible to know the exact source and degree of such biases, considerable advantage can be gained by taking their potential influence into account when making sampling design decisions as well as in interpreting research findings.

From the perspective of funding agencies, it may be advantageous to strive for a balance in supported studies which utilize a range in available IVDA sampling strategies. This would both help to control for the influence of biases associated with the more commonly adopted, convenience sampling frames and at the same time provide further insight into differences among these alternate sources of IVDA samples.

Though relatively underutilized in current investigations addressing natural history questions relating to HIV infection among IV drug abusers, social network samples of active users in community settings seem to hold considerable promise for inclusion in future studies. Through grounding such inquiry in the natural social context in which behaviors and other factors influencing HIV transmission and disease progression take place, it is possible that this sampling strategy might complement current research capabilities. Preliminary results from the first studies to look at HIV among active users not in treatment have demonstrated significant differences between convenience samples and those obtained by community-based outreach efforts (Watters 1987; Wiebcl et al. 1988; Raymond 1988; McCoy et al. 1989). Furthermore, our experience to date in adopting social network samples for targeting AIDS intervention activities (Wiebel 1988) suggests that this sampling strategy is an efficient means of both identifying and gaining access to active IVDAs for research purposes (Wiebel in press). Of particular relevance to longitudinal research designs, we have refined strategies to secure followup interviews with social network subjects at 6-month intervals (Johnson et al. 1989), demonstrating the potential for maintaining up to 80 percent of baseline panels at first followup. More widespread adoption of social network sampling frames may contribute to our further understanding of differences in institutionally-based and community-based IVDA samples.

While still the subject of ongoing analysis, a number of our findings to date suggest significant differences in IVDA profile for our community-based social network samples in comparison to institutionally-based research samples. In our first such comparative analysis, Lampinen found striking differences between the demographic characteristics of our community-

based IVDA research sample and those of IV drug abusers who reported to Chicago public health authority testing facilities for anonymous HIV antibody counseling and screening (Raymond 1988). Addicts sampled from active IV drug abusing social networks were four times more likely to have not completed high school, more than twice as likely to be unemployed, and almost twice as likely to report using heroin at some time in their lives. Further, significant variations in seroprevalence were found both between testing site clients and our social network subjects and among the social networks themselves. About 10 percent of IV drug abusers reporting to HIV antibody test sites were seropositive in comparison to 15.6 percent of the active injectors recruited at our southside fieldstation, 19.1 percent of the subjects from our northside fieldstation, and 29.5 percent of those from our westside fieldstation. Similar analyses comparing our social network sample profile to that of treatment programs, criminal justice agencies, and hospital facilities are currently underway.

This discussion has attempted to provoke consideration of potential sources of bias in the various sampling strategies commonly utilized to study IV drug abusers. Being far from exhaustive, it is hoped that others will offer further insight to the paucity of our current understandings. For it is only through further understanding and systematic consideration that we can hope to make more informed sampling decisions based on both theoretical and practical concerns.

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5. Toward Comprehensive Studies of HIV in Intravenous Drug Users: Issues in Treatment-Based and Street-Based Samples

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INTRODUCTION

Great emphasis has been placed on the role of intravenous drug use in the transmission of human immunodeficiency virus (HIV). Changing demographics of reported AIDS cases suggest that heterosexual intravenous drug users (IVDUs) will continue to grow as a risk group into the 21st century. This trend has stimulated unparalleled interest in IVDUs on the part of public health agencies. This interest has given rise to increased budgets for research and HIV testing programs that are directed at heterosexual IVDUs. The purpose of this research and public health intelligence is to monitor fluctuations in HIV infection rates before they surface as AIDS cases, thereby providing information to policy planners on the shape, size, and trajectory of the epidemic. Yet the published record of this surveillance effort to date has been based almost entirely on convenience samples of IVDUs enrolled in drug treatment programs (Hahn et al. 1989).

In the United States, methadone maintenance has been the dominant drug treatment modality since the early seventies (Sells et al. 1979). Conse-

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This research was supported in part by funding from the National Institute on Drug Abuse, the Centers for Disease Control, and the State of California Universitywide Task Force on AIDS.

quently, the vast majority of respondents studied in the research involving IVDUs have drug histories characterized by dependence on heroin. IVDUs whose drug profiles are predominated by injection of other drugs (e.g. amphetamine isomers or cocaine) are excluded. Several studies have found that frequent cocaine injection is associated with HIV seropositivity among methadone maintenance clients (Chaisson et al. 1989; Marmor et al. 1987; Shoenbaum et al. 1989). These findings may not generalize to populations not enrolled in methadone maintenance programs. For example, in a study of IVDUs sampled from both in-treatment and not-in-treatment settings, behavioral effects associated with HIV infection in other studies were not found to be predictive of HIV infection in multivariate analysis (Watters et al. 1989). In addition, studies of IVDUs not enrolled in treatment have found that many are not oriented to entering treatment programs (Hanson et al. 1985; Hunt et al. 1985-86; Watters and Cheng 1987). Moreover, it is estimated that only 15 percent of IVDUs in the United States are enrolled in drug treatment on any given day (Hahn et al. 1989). There is no reason to assume that the drug use profiles, patterns of risk behavior, or motivational characteristics of in-treatment and untreated IVDUs are equivalent. Indeed, one study found substantial variations in drug use preferences among IVDUS and significant differences between drug use profiles and behaviors typically associated with HIV infection (Watters et al. 1988). Consequently, samples based primarily on clinical populations may contain substantial bias. This stems from their failure to include drug users who, for whatever reasons, eschew drug treatment and those whose drug utilization profiles are dominated by drugs other than heroin.

Each of the major data sources germane to HIV infection in IVDUs is subject to its own sources of bias and suffers from methodological difficulties. These problems are not trivial and can lead to misconceptions and erroneous conclusions if data gleaned from any one source are not counterbalanced by observations from others.

The Centers for Disease Control (CDC), for example, has in place a large system of HIV surveillance for IVDUs (Jones et al., n.d.). The sampling frame consists of 41 drug treatment facilities located in 21 metropolitan areas within 19 States. Convenience samples of IVDUs are recruited on an ongoing basis from this panel of sites and plans for expansion of this effort exist. However, as useful and as important as this effort is, it may suffer from considerable bias due to the potential lack of generalizability of clinical populations of IVDUs to nonclinical populations: those who, for a variety of reasons, eschew participation in drug treatment programs. For, despite

the ubiquitous waiting list for entry into publicly funded drug treatment programs in the United States, there still remains a vast sea of IVDUs who are not oriented to treatment, who do not seek treatment, and who would not accept free treatment even if offered the next day (Watters and Cheng 1987).

In 1987 the National Institute on Drug Abuse began funding an effort that accumulates risk factor and HIV serology data from "street samples" of IVDUs in 63 cities. These studies have the potential to provide information on IVDUs who do not routinely interact with drug treatment programs and who may have differing motivational, drug preference, demographic, and HIV risk profiles from those who enter treatment programs. This innovative cluster of projects represents the first major research effort attempted in the United States that targets out-of-treatment IVDUs as research subjects. This effort has the potential to provide much useful data on the characteristics, HIV risk, and HIV exposure of IVDUs out of treatment—those who do not follow a typical pattern of opiate addiction and/or those who avoid treatment. The primary weakness of these projects is sample construction. The location of sites was determined by grant and contract competition rather than systematic review of candidate location. Sampling methods are not standardized across the 63 performance sites, and in many sites "outreach workers" are used in the dual and potentially conflicting roles of service provider and evaluator of the service provided. Since samples are nonrandom, not linked to known population parameters of IVDUs (at least to the degree that they exist), and because of the potential for bias (e.g. interviewing a client whom service providers have been counseling to use condoms and bleach; presentation of self and social desirability issues pertaining to self-report data from clients to program staff), the validity of results may be an issue.

In addition to these efforts are independent studies of HIV seroprevalcnce and IVDUs. Yet these studies, like the CDC initiatives, draw primarily on captive populations of intravenous drug users enrolled in drug treatment facilities. Hahn et al. (1989), for example, in their illuminating survey of published and unpublished seroprevalence studies circa 1987, reported findings from some 96 separate studies of IVDUs. Only three included populations sampled from noninstitutional settings. In our own studies of IVDUs we have observed differences in HIV status in association with drug treatment experience and race. Some of these findings are discussed below to help demonstrate the importance of including both in-treatment and out-of-treatment populations in surveillance efforts and natural history studies.

METHODS

Compared were three categories of treatment experience in the 5 years prior to interview: (1) no drug treatment enrollment; (2) drug treatment enrollment for a total of less than 12 months; and (3) drug treatment enrollment for a total of 12 months or more. These three groups were compared in light of demographic characteristics (age, race, and gender), HIV antibody status, and self-reports of involvement in seven risk behaviors associated with HIV infection (number of sexual partners during the past 5 years, percentage of time condoms were used during intercourse, lifetime history of syphilis and gonorrhea, frequency of drug injection during the past year, number of needle sharing partners during the past year, safe or unsafe needle hygiene, and frequency of injection of cocaine. Needle hygiene was defined as safe (not sharing, or using bleach, alcohol, peroxide, or boiling water to decontaminate needles and syringes) and unsafe (anything else).

Respondents were black and white IVDUs recruited in five semiannual cross-sections during 1987 and 1989, a period during which no significant increase in HIV infection in heterosexual injection drug users was observed in San Francisco (Chaisson et al. 1989; Watters et al. 1988). We recruited volunteers in two 21-day detoxification clinics, and in three inner city street settings using a targeted sampling method described elsewhere (Watters and Biernacki 1989). Street-recruited subjects were screened for physical evidence of past intravenous drug use.

After obtaining informed consent, respondents were interviewed by research staff. Respondents were paid $10 at intake into the study and a second $10 1 month later to attend a followup session at which time HIV test results were made available. Using standard phlebotomy protocols, 20 ml of blood was drawn at time of interview. Samples were stored at -70°C and screened for HIV antibodies using Genetic Systems Corporation (Seattle, WA) enzyme immunoassay (EIA) in duplicate. EIA positive samples were confirmed by Western blot assay using methods reported elsewhere (Consortium for Retrovirus Standardization 1988). Serology was performed at the Universitywide Task Force on AIDS-AIDS Diagnostic Laboratory at the University of California, Davis.

All nonblack/nonwhite respondents and men who admitted homosexual contact in the past 5 years were dropped from the analysis. We also dropped all observations with previous HIV tests in order to ensure that all cross-wave observations of single individuals were eliminated. Of the 1,367 cases remaining, 492 (36.0 percent) stated that they had not been enrolled in

treatment in the 5 years prior to interview, and 875 (64.0 percent) reported having been enrolled in treatment at some time over the 5 years prior to interview. Of those with previous treatment experience, 586 (42.9 percent) were enrolled in treatment at the point of interview.

The chi square statistic was used to compare treatment experience groups with demographic and risk factor data and the Mantel-Haenszel adjustment was used to control for the effect of treatment experience in analyzing risk for HIV-1 infection between black and white respondents.

RESULTS

Of the 875 respondents reporting any drug treatment in the previous years, 669 (76.5 percent) had been in drug treatment for less than 1 year, and 206 (30.8 percent) had been in drug treatment more for a year or more. Selected respondent characteristics by time in treatment are displayed in table 1. No statistically significant differences were found between the three treatment experience groups and sex, age, sexually transmitted disease (STD) history, use of condoms, or frequency of injection of cocaine. Respondents did differ in terms of some demographic and behavioral factors previous research has associated with HIV infection. These differences are outlined below.

Race

Blacks were less likely than whites to have had drug treatment in the past 5 years: Of those reporting no drug treatmenl in the past five years, 75.8 percent were black and 24.2 percent were white. Of those who had at least 1 year of drug treatment, 60.2 percent were white and 39.3 percent were black ($p < .00000$).

Sexual Activity

Ninety-five percent of those with less than 12 months of treatment in the 5 years prior to interview reported multiple sexual partners in the past 5 years compared with 78.4 percent of those reporting no treatment and 78.2 percent of those reporting 12 months or more of treatment ($p = .01074$).

Table 1. Selected respondent characteristics—heterosexual IVDUs in San Francisco

	Time in treatment past 5 years			
	None	< 1 year	≥ 1 year	*P*
Age				
<30	18.5	21.8	17.5	.09237
30-39	51.0	47.8	58.3	
>40	30.5	30.3	24.3	
Sex				
Male	68.2	68.5	60.2	.07079
Female	31.8	49.0	39.8	
Race				
White	24.2	58.4	60.2	.00000
Black	75.8	41.6	39.3	
No. of sexual partners past 5 years				
None	5.3	3.9	2.9	.01074
1	16.3	11.2	18.9	
>1	78.4	94.9	78.2	
Condom use				
Never	64.0	60.6	61.0	.34656
<50%	16.0	14.3	15.6	
>50%	20.0	25.1	23.4	
STD history				
None	46.1	49.8	47.6	.46457
Any	53.9	50.2	52.4	
Frequency of injection past year				
< 365	55.7	30.3	36.4	.00000
> 365	44.3	69.7	63.6	

Table 1. ***(Continued)*** Selected respondent characteristics—heterosexual IVDUs in San Francisco

	Time in treatment past 5 years			
	None	< 1 year	≥ 1 year	*P*
No. of needle sharing partners past year				
0	30.7	22.3	16.6	.00082
1-2	25.8	26.5	33.7	
3-5	19.2	22.5	25.4	
>5	24.3	28.6	24.4	
Needle hygiene				
Never	16.5	16.2	17.5	.00040
< Always	24.9	36.8	33.5	
Always	58.6	47.0	49.0	
Frequency of cocaine injection				
>365	13.2	10.3	14.1	.19190
>365	86.8	89.7	85.9	

Frequency of Injection

Those reporting any drug treatment were more likely than those reporting none to report more frequent injection of drugs in the past year. Among the less than 12 months group, 69.7 reported injecting at least 365 times in the year prior to interview. Among those reporting 12 months or more of drug treatment, 63.6 percent reported injecting at least 365 times in the past year. Less than half (44.3 percent) of those reporting no drug treatment reported at least 365 injections in the year prior to interview ($p < .00000$).

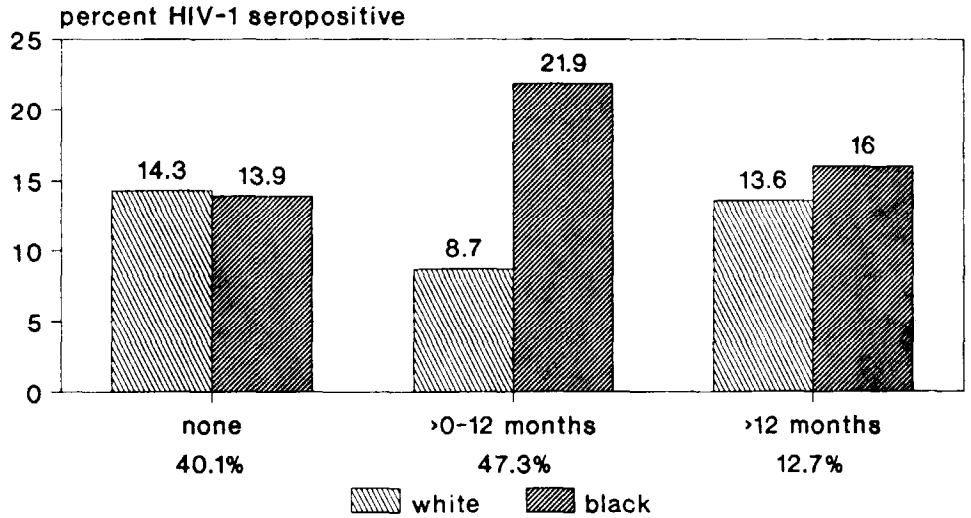
Numbers of Needle Sharing Partners

Thcre were differences in the numbers of needle sharing partners reported, with 30.7 percent of the never treated group reporting no sharing partners (not sharing) in the past year, compared with 22.3 percent of the less than 1 year group and 16.6 percent of the 12 months or more group ($p = .00082$).

Needle Hygiene

The no treatment group was more likely than the treatment groups to

Figure 1. HIV-1 seropositive heterosexual IVDUs by race, controlling for past drug treatment



N = 1,367
adj. odds ratio = 1.77
95% confidence interval = 1.29 and 2.45

report always using safe needle hygiene as defined in the methods section of this report. Fifty-nine percent of the no treatment group reported always using methods that fell into the safe category. By comparison, 47 percent of the less than 12 months and 49 percent of the 12 months or more group reported always using needle hygiene that met the safe definition. These differences were significant ($p = .00040$).

HIV-1 Serology

Several studies of HIV infection in San Francisco have found black IVDUs to be at higher risk for HIV infection than whites (Chaisson et al. 1989; Watters et al. 1988; Watters et al. 1989); consequently, we compared HIV seroprevalence rates for blacks and whites while controlling for three levels of drug treatment enrollment described in the methods section. Neither the no treatment nor the more than 12 months groups differed. But the treatment for the 12 months and less group did vary significantly with respect to HIV infection between backs and whites. In this group, 8.7 percent of the whites were seropositive compared with 21.9 percent of the blacks (adjusted odds ratio 1.77 percent; 95 percent confidence interval 1.29 and 2.45). See figure 1.

COMMENT

It was not our purpose to present an exhaustive analysis of risk factors associated with HIV. Rather we have sought to use these data to help illustrate the importance of including both drug treatment history and out-of-treatment IVDUs in studies of HIV infection and associated risk factors. Wiley and Samuel (1989) have suggested that the overall HIV and IVDU data acquisition effort as published fails to establish a "firm basis for estimating seroprevalence rates and monitoring seroconversion in the 85 percent (of IVDUs) not in treatment" and call for additional studies of this population that employ targeted samples of IVDUs in their own environments. The data presented here tend to support these assertions.

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ACKNOWLEDGMENTS

Acknowledged is the cooperation of the administration and staff of the MidCity Consortium to Combat AIDS, the Haight-Ashbury Free Medical Clinic Drug Detoxification Program, Ward 92 San Francisco General Hospital, The University of California at Davis AIDS Virus Diagnostic Laboratory, The University of California at San Francisco AIDS Tissue Bank, and the respondents who participated in this study. Peter Hartsock, Dr. P.H., served as the NIDA project officer.

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6. The ALIVE Study, A Longitudinal Study Of HIV-1 Infection in Intravenous Drug Users: Description of Methods and Characteristics of Participants

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INTRODUCTION

By 1985 the acquired immunodeficiency syndrome (AIDS) had been recognized as an epidemic of major public health importance and the primary etiologic agent, human immunodeficiency virus, type 1 (HIV-1), had been identified. At that time, major studies had started to characterize the natural history of HIV-1 infection among homosexual/bisexual men (Kaslow et al. 1987; Winklestein et al. 1987; Schechter et al. 1985), who accounted for about 75 percent of the cases of AIDS (Centers for Disease Control 1986). However, the scientific and public health importance of intravenous drug

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The research reported on in this chapter was supported by National Institute on Drug Abuse grant no. DA 04334.

users (IVDUs) in the AIDS epidemic was not widely appreciated. A limited number of seroprevalence studies and descriptive analyses of IVDUs with AIDS or AIDS-related conditions had been done (Friedland et al. 1985; Spira et al. 1984), but characterization of the impact and natural history of HIV-1 infection among IVDUs was limited. Soon thereafter, it became clear that IVDUs could represent a major source of transmission of HIV-1 infection to heterosexuals and children (Chamberland and Dondero 1987; Rogers 1987).

Because of differences in lifestyles between IVDUs and homosexual/bisexual men, it was recognized that studies among samples of IVDUs were needed to clarify the factors that might be important in parenteral, heterosexual, and perinatal transmission of HIV-1 infection. Preliminary analyses also indicated differences between these two major risk groups in the clinical features of AIDS and in the median length of survival following a diagnosis of AIDS (Rothenberg et al. 1987; Marmor et al. 1984; Des Jarlais et al. 1984). Given these findings, descriptions and comparisons of the differences in the natural history of HIV-1 infection between IVDUs and homosexual men could help clarity immunopathologic factors responsible for progression of HIV-1 infection to AIDS. To date, such comparisons have been sparse (Zolla-Pazner et al. 1987).

Thus, the ALIVE (AIDS Link to Intravenous Experiences) study was begun with the following objectives: to identify risk factors for both HIV-1 infection and for AIDS given HIV-1 infection among IVDUs; to compare data on IVDUs with data from a large natural history study of HIV-1 infection among homosexual men being conducted at the same institution (Kaslow et al. 1987); and to build a repository of biological specimens and data on IVDUs to permit future testing of hypotheses in this population. In this paper we report on the overall plan of the study, including design issues and data collection operations. The paper also describes selected characteristics of the 2,921 participants in the ALIVE study.

PROTOCOL FOR THE ALIVE STUDY: METHODS

The study protocol was specified in relation to three stages: baseline screening, return for test results, and a regular semiannual followup. The objective of baseline screening was to identify at least 640 IVDUs with antibody to HIV-1 who would consent to enrollment in a prevalent cohort for a longitudinal study of infection. The objective of followup was to monitor progression of HIV-1 infection to clinical disease in order to address the

clinical questions that, Given an IVDU is infected, what is the residual AIDS-free time and what are its determinants? During the 13-month screening stage, which lasted from February 1988 to March 1989, extensive efforts were made to attract adults who had used drugs by injection at any time during the previous 10 years. The interval of 1978-88 was considered to be the period when this population of IVDUs might have been exposed to HIV-1. When participants initially were seen at the study clinic, interviewers administered a clinical-epidemiological interview and a phlebotomist collected sera for assay of antibody to HIV-1. Participants were scheduled to return 3 to 4 weeks later to learn the results of the HIV-1 serologic test and to receive counseling. All seropositive individuals and an unselected sample of seronegative participants then were offered enrollment in a periodic, at 6-month intervals, followup study that included clinical and epidemiologic interviews, a physical examination, and blood collection for laboratory studies. The term "unselected sample" is used for the seronegatives in followup because the strategy for recruitment was not based on any a priori clinical, behavioral, or laboratory criteria. Originally, the aim was to obtain a systematic sample of seronegatives based on recruiting the next available seronegative after every fifth seropositive recruited into followup; however, on certain days, enrollment of seropositives alone taxed clinical resources so that recruitment of seronegatives had to be postponed to subsequent days when resources were adequate. Therefore, we consider the term "unselected" to be an appropriate descriptor for the sample of seronegatives achieved. Both the seropositive and seronegative participants in followup are to return at 6-month intervals for the duration of the project (4 years).

Recruitment and Enrollment

The recruitment efforts began with a series of meetings with directors and staff of agencies that served IVDUs. These agencies included Baltimore area drug abuse treatment programs, the Maryland Division of Parole and Probation, the Baltimore City Health Department's sexually transmitted disease clinics, hospital emergency rooms, and homeless shelters in the Baltimore area. During the meetings, the study was described, and agency personnel were asked to distribute printed brochures that described the study. To extend recruitment beyond these agencies, outreach efforts were developed in collaboration with the Street Outreach AIDS Prevention (SOAP) Unit of the Health Education Resource Organization (HERO), a community AIDS education group in Maryland. The SOAP unit includes 10 recovered and recovering addicts who provide AIDS education to the

inner city community through contacts on the street. These workers distributed brochures and answered questions about the ALIVE Study. Study staff also distributed brochures at local public housing projects and other public places known to be frequented by IVDUs. Finally, we anticipated that early participants in the study would encourage their friends and contacts to enroll in the ALIVE Study. Mass publicity campaigns were not planned because we feared that such efforts might mobilize adverse public attention toward the study, undermining recruitment efforts and jeopardizing the study.

To assist with recruitment and retention, an advisory board composed of persons familiar with the IVDU community was established. The board was selected by inviting directors of four large, geographically dispersed drug abuse treatment programs in Baltimore and the director of a local AIDS street outreach program to assemble a group of from 8 to 12 individuals who were willing to serve in an unpaid advisory capacity to the investigative team; the majority were to have had a history of injecting drugs. The board was to include both genders, have racial and ethnic diversity, and have a variety of backgrounds (for instance, the board was not limited to those on methadone maintenance, or fully employed, and included those with HIV-1 infection). At initial meetings, the board established procedures about meeting attendance, removal and replacement of members, and the capacity of the board. An early function of the board was to screen applicants for participant contact positions in the study so as to advise the investigators on the perceived sensitivity of applicants to the study population.

The board also reviewed and advised investigators on a variety of recruitment strategies. To facilitate recruitment and retention, a participant compensation plan was developed which included free testing and pretest/posttest counseling for HIV-1. As part of the initial consent, participants agreed to not only the baseline procedures but also the responsibility for returning to learn test results; those who might choose not to learn test results were informed prior to initial procedures that they should not enroll. The board reviewed the plan to compensate participants $10 for completion of the initial screening visit and again for returning 3 to 4 weeks later to learn the results of their test. Although the issue of remuneration of impoverished participants for visits could be considered ethically problematic, the plan was considered acceptable because all participants were informed prior to enrollment that consent was contingent upon acceptance of responsibility for returning to learn test results, that an established local precedent existed for financial compensation to this population for

participation in government-sponsored research, and more important, that investigators were committed to offering additional services, referrals, and followup within the same clinic to facilitate continuity of care. Compensation for each completed 6-month follow-up visit, which included a focused physical exam and enumeration of T-cell subsets, was $35. The services offered to participants included screening and referral of participants for HIV-related conditions, sexually transmitted diseases, other significant medical conditions, prenatal care, and treatment for drug abuse.

The board also served as advocates for the participants in several ways. For example, the board elicited information about difficulties experienced by clinic staff in referral of participants into treatment for drug abuse. Issues such as availability and eligibility of care and waiting lists were discussed by the board and presented directly to the city's commissioner of health. As participants' advocates, the board provided an additional layer of review for several proposed supplementary studies initiated by outside investigators; the board reviewed and commented on proposals from the perspectives of relevancy, interest to, and likelihood of acceptability to the population.

Finally, the board also served to increase effective communication between participants and investigators, since they were generally known and trusted throughout the local IVDU community. Participants were provided phone numbers of several board members to facilitate communication and resolution of perceived problems.

From a critical perspective, punctuality, regular attendance, and maintenance of an agenda have not been consistent for the board. The board has undergone turnover due to some members' clinical deterioration related to HIV-1, incarceration, personality conflicts between members, and flagging interest. Despite these problems, the board as a group has taken their role as advisers to investigators and advocates for participants seriously, by being vocal on issues presented to or raised by the board. Over time, the board has been consistent in upholding maintenance of commitments to strict confidentiality for participants and advocating high quality of services to this population.

Participants were informed that interview and test data would be held in strict confidence and no information on any individual would be released without that individual's written permission. A certificate of confidentiality was obtained from the Department of Health and Human Services (Public Health Science Act). To further promote a sense of confidentiality within the single clinic site, an unselected sample of 150 seroncgatives identified

from the baseline visit were enrolled into the followup component of the study along with the seropositive participants in order to prevent identification of seropositives solely because they had been enrolled in the followup clinic. The seronegatives in followup also served information goals of the study because their biological specimens were designed to be used as laboratory controls. For example, description of the rate of decline for T-helper lymphocytes in HIV-1 seropositives is complicated by variability in laboratory techniques over time; this variability can be partially offset by anchoring enumerations to period-matched specimens of seronegatives and calculating a "deficit score" (Munoz et al. 1988).

Although we recognized the value of enrolling more than 150 seronegatives into followup at the time the study was designed, a pragmatic approach was taken in limiting seronegative enrollment. Because the crude estimate for annual seroconversion would produce an insufficient number of the study endpoint (i.e., AIDS) in the 4-year time frame of data collection, and since statistical procedures had not yet been developed in 1985 to estimate onset of infection for a prevalent cohort based upon a sample of seroconverters, emphasis was placed upon devoting limited resources to establishing a prevalent cohort. Since then, multiple imputation procedures have been developed (Munoz et al. 1989). Now, all seronegatives not enrolled in followup are requested to return for serological rescreening at 6-month intervals, and seroconverters are enrolled into the followup component of the study. These seroconverters will provide the basis for analysis of risk factors for incident infection, a description of the early natural history of HIV-1 infection, and the data needed to impute onset of infection in the prevalent cohort.

Description of the Clinic

With the objective of providing an atmosphere of trust and rapport, the study clinic was located on the ground floor of a Baltimore City Health Department (BCHD) building. Although a hospital-based clinic might have been more convenient for coordinating the logistical operations of the study, IVDUs tend to perceive hospitals as hostile environments (Hansen et al. 1985). The BCHD building selected is situated in the central area of the city surrounded by public housing projects and is known to have a long history of community service and utilization by potential participants in this study. Therefore, this site was considered convenient to many potential participants. A major university hospital within walking distance can provide emergency and referral medical services.

The physical characteristics of the clinic within the BCHD building were designed to promote an atmosphere of trust and rapport. The clinic is physically separate from the rest of the building, with a separate entrance. The clinic is newly renovated, spacious, and dedicated solely to this study population. Walls of the interview and examination rooms are insulated to promote privacy of conversation. Television viewing and coffee are provided in the waiting room.

Baseline Screening

During the screening phase of the study, potential subjects were registered at the clinic only by first name and first initial of last name. A study interviewer introduced herself and escorted the potential participant to an attractively decorated, private interview room for a brief subject selection interview. The interviewer did not know the subject's name, and no identifying information was recorded on the interview form. The interview session began with an effort to engage the potential subject in the interview task and to promote trust and rapport, followed by a series of standardized questions on personal, health, and family characteristics, all intended to aid development of trust and rapport. A question on history of intravenous drug use since 1977 was nested within a short set of questions on illegal and socially disapproved behaviors. The entire series of questions on background characteristics was asked without regard to the subject's status as an IVDU in order to permit study of these characteristics among persons choosing not to participate in the study. At the close of this interview, the interviewer told the subject whether he or she qualified for enrollment but did not disclose the basis for inclusion (i.e., being age 18 or older and reporting intravenous drug use within the past 10 years). Ineligible subjects were thanked for their help and were escorted to the waiting room; these individuals remained anonymous. All other subjects were told of their eligibility; the interviewer read the disclosure statement for the study, and sought informed consent.

The informed consent procedure included pretest counseling about the HIV-1 antibody assay. The test technique, interpretation, and implications were discussed and explored with each individual prior to completing the informed consent procedure. To minimize the possibility that information on risk reduction might alter self-reports about drug use and sexual activity, counseling specifically about prevention of HIV-1 infection followed the baseline interviews, but occurred prior to participants leaving the clinic.

Consenting subjects were requested to provide personal identifying information from which contact could be established for the followup. All forms up to this point were given to a receptionist who assigned the participant a unique study number to be used on all subsequent forms and specimens. The forms with personal identifiers were stored in locked files in a separate building from the other data. In the event that participants forget their study numbers, reverse identifier cards were generated whereby a study number can be reestablished on the basis of birth date, sex, race, mother's maiden name, and the last four digits of the social security number.

During the rest of the baseline visit, a phlcbotomist drew 10 cc of blood. After venipuncture, participants returned to the interviewer who administered the baseline interview, a standardized interview schedule developed through three cycles of pretesting and revision. All elements of the baseline interview (table 1), described in detail elsewhere (Anthony et al. in press), were administered by interviewers; no parts were self-administered. These interviewers had extensive previous experience with health and behavior interviewing. All received a minimum of 2 days of additional training on the specific interview schedule, followed by supervision and quality control checks. The majority of interviews have been completed in less than 35 minutes; few exceeded 1 hour. The baseline interview elicited data on lifetime medical history, a 10-year pattern of drug use by injection, types of drugs used, sharing of needles and other injection equipment, and sexual practices. Upon completion of the baseline interview, a standardized AIDS knowledge questionnaire and an assessment of socially desirable responses were administered. Answers to the AIDS knowledge questionnaire were reviewed with each participant and serve as a focus for individualized education and counseling about HIV-1 infection. Participants were offered a small package containing bleach and condoms with instructions for their use, and the opportunity for referral to treatment for drug abuse, if desired. Finally, participants were paid and given appointments to return in 3 to 4 weeks to obtain test results.

Test Results Visit and Followup Visits

During the interval between baseline screening and the test results visit, serum specimens were assayed for antibody to HIV-1 using standardized techniques: ELISA (Genetic Systems, Seattle, Washington) and Western blot (Biotech-DuPont, Rockville, Maryland). Repeatedly reactive ELISA specimens were assayed by Western blot. A positive Western blot was defined as a band at p24 or p31 and either gp41 or gp > 110. No bands or a

Table 1. Data Collection on ALIVE study participants at entry in 1988-89

Demographics questionnaire topics

- Age
- Race, ethnicity
- Education
- Occupation
- Income
- Homelessness
- Arrest and incarceration
- Marital status
- Number of children
- Public assistance

Identifying information

Baseline questionnaire topics

Selected past medical history
- Immune disorders
- Sexually transmitted diseases
- Complications of intravenous drug use

Current medical history
- AIDS related symptoms

Transfusion (recipient and donator)

Intravenous drug use
- During 6 months prior to last use
- During 3 months after first use
- Year by year summary 1977-1988

Sexual practices
- During previous 10 years
- During previous 2 years

Scale of Socially Desirable Responses

AIDS Knowledge and Attitude Questionnaire
(modified from the National Center for Health Statistics)
10 cc blood, used for serological assays and repository storage

single p15 or p17 was defined as negative; any bands other than those meeting the criteria for positive were considered equivocal.

At the results visit, all those who were seropositive, all those with equivocal results, and an unselected sample of 150 seronegatives were recruited for the longitudinal phase of the study beginning with a brief face-to-face interview. This interview assessed health, drug use, sexual practices, and psychological status during the prior 6 months. This standardized panel interview schedule was designed to be used during the test results visit and also at subsequent visits every six months in order to assess changes in these characteristics. After completion of this interview, trained staff explained individual results of the HIV-1 antibody test to the subject and provided personal counseling. Informing and counseling subjects about their test results followed the interview because a reverse procedure was considered to be more likely to affect the quality of responses. Consent for subsequent followup components of the study was obtained after disclosure of test results, with the option to defer continuation to a later date. Seronegatives not selected for followup enrollment were counseled about their test results and scheduled to return for serologic rescreening in 6 months.

Consenting participants in the followup component of the study underwent venipuncture and a standardized physical exam conducted by a physician or physician's assistant. The exam was designed to identify stigmata of drug use, clinical features of AIDS or AIDS-related complex, and selected sexually transmitted diseases. Participants were paid and scheduled to return at 6-month intervals 10 repeat their interview, physical examination and venipuncture.

At each visit in the followup component of the study, blood was processed for complete blood count and differential, for enumeration of total (CD3+), helper (CD4+) and suppressor (CD8+) T-lymphocytes (Hoffman et al. 1980) and for storage of peripheral blood mononuclear cells, serum, and plasma. T-lymphocyte enumerations were performed by flow cytometry. At the screening and at each followup visit, blood specimens are obtained from each subject and processed. Aliquots are stored frozen in order to permit retrieval for hypothesis testing at a later date.

DATA ANALYSIS

For the data presented here, frequency distributions of study variables were generated by HIV-1 antibody status at baseline. Odds ratio, chi-square, and Fisher's exact statistics were used to guide interpretation (Fleiss 1981).

RESULTS

Of the 3,375 individuals who registered for screening at the study clinic, 378 (11.2 percent) did not qualify (age under 18 or no intravenous drug use reported in the previous 10 years). Of the 2,997 remaining, 12 were registered as non-IVDU sex partners of participants, 4 subsequently admitted to have never been an IVDU, 2 had the outcome variable (AIDS) at baseline, 18 had equivocal Western blots, and 40 were subsequently identified as having registered at least twice under different names; these 76 (2.5 percent) were excluded from baseline analyses. Of the 2,921 eligible and consenting participants, the phlebotomist observed stigmata of IV drug use on 92 percent of the participants, using only inspection of upper extremities. Although a variety of agencies had been enlisted as sources of recruitment for the study, 85.7 percent of the participants reported that they had first learned of the study by word of mouth from a friend or another participant (table 2); disproportionate referral of seropositives from STD and HIV clinics was intentional. Only 5 percent of participants reported first learning about the study as clients in drug abuse treatment; however, 51.5 percent reported at least one episode of at least 28 days in a drug treatment program at some time during the prior 10 years.

Table 2. Source of Recruitment Reported by ALIVE Study Participants, February 1988—March, 1989

	Serostatus			
	Seronegative		Seropositive	
Source	*N*	Percent	*N*	Percent
Word of mouth	1,938	87.4	564	80.2
Drug treatment program	128	5.8	35	5.0
HERO street outreach	77	3.5	45	6.4
Parole and probation	38	1.7	15	2.1
STD clinics	32	1.4	35	5.0
HIV clinics	2	0.1	8	1.1
Emergency rooms	2	0.1	1	0.2
Total	2,218	100.0	703	100.0

The youngest participant was 18 years old and the oldest 68 years, with a median of 34 years of age. As table 3 shows, the sample was predominantly black and of low socioeconomic status, as measured by legal income, education, and current employment status. A substantial proportion reported histories of arrest and incarceration, and 36 percent reported a history of homelessness at some point during the previous 10 years. Dividing the samples in half by enrollment dates, comparison of demographic characteristics were all not significant (data not shown).

HIV-1 seropositivity was confirmed in 703 (24.1 percent) of the 2,921 participants. As shown in table 3, seropositivity was strongly ($p < .005$) associated with age 25-44, black race, current unemployment and a history of treatment for drug abuse; a positive association ($p < .05$) was observed by current unemployment, and a history of arrest and incarceration. Marginal associations ($p < .10$) were noted for education at or above the ninth grade and legal income under $5,000. However, gender (not accounting for sexual preference) and history of homelessness were unassociated ($p > .10$) with HIV- 1 seroprevalence.

In terms of injection history, the median duration was 12 years (range: 1-50 years), and 2,616 (89.6 percent) subjects claimed their most recent injection was during the same year as the baseline visit (this group is subsequently referred to as "current users"), with 2,252 (77.1 percent) reporting their most recent injection within 1 month prior to initial enrollment. As table 4 shows, a substantial proportion reported an injection frequency of more than once a week for the 6 months prior to last use (with 39.4 percent injecting at least daily) and more than one needle sharing partner; 922 (31.6 percent) reported using needles that were borrowed, rented, or purchased in a shooting gallery during the 6 months prior to last use. By sexual activity 245 (8.4 percent) of the males self-reported homosexual activity within the previous 10 years. For the sample as a whole, 148 (5.1 pcrccnt) reported one or no sex partner during the previous 10 years and 436 (14.9 percent) reported more than 45 partners; the median was 10. Receptive anal intercourse was reported by 157 (5.4 percent).

Of the 2,921 participants screened and interviewed at baseline, 2,632 (90.1 percent) returned to receive antibody test results. Of the 703 HIV-1 seropositives, 630 (89.6 percent) returned and consented to enrollment in the followup component of the study. Of the 630 HIV-1 scropositive and 150 HIV-1 seronegative controls at baseline, a total of 639 (81.9 percent) have returned for their first 6-month followup visit; these return rates have persisted for the 12-month followup visit. Although the study was not

Table 3. HIV-1 serostatus by demographic characteristics ALIVE Study, February 1988—March 1989

Characteristic	N	Percent HIV- 1 positive	p-value
Age in years			
18-24	216	18.1	.002
25-34	1,392	25.7	
35-44	1,098	24.9	
45+	215	15.8	
Race			
Black	2,585	26.1	.001
Nonblack	326	8.3	
Gender			
Male	2,368	23.7	.274
Female	553	25.9	
Legal income			
< $5,000	2,099	25.0	.073
> $5,000	780	21.8	
Education			
1-8	238	18.1	.080
9-12	1,379	25.5	
> 12 grade	1,303	23.6	
Current employment			
Yes	666	20.6	.016
No	2,254	25.1	
Homeless			
Ever	1,057	23.8	.384
Never	1,864	24.2	
Arrested			
Yes	2,203	25.1	.040
No	712	21.2	
Prison			
Yes	1,927	25.3	.035
No	993	21.8	
Treatment			
Yes	1,506	26.6	.001
No	1,413	21.4	

Table 4. HIV-1 serostatus by selected drug use and sexual activities during the 6 months prior to last injection—ALIVE Study, February 1988, March 1989

Variables	N	Proportion
Frequency of injection		
> 1x/day	1,153	39.4
> 1x/wk. -< 1x/day	1,006	34.5
> 1x/mo - < 1x/wk	457	15.6
< 1x/mo.	305	10.5
Number of different needle sharing partners		
1	1,367	46.9
1	637	21.8
0	879	30.1
Attendance at shooting galleries[a]		
Yes	922	31.6
	1,993	68.4
Type of drug injected		
Heroin alone	236	8.1
Cocaine alone	497	17.0
Heroin and cocaine only	1,903	65.1
Other (combinations)	285	9.8
Gender[b]		
Male-Heterosexual	2,112	72.5
Male-Homo-Bisexual	245	8.4
Female	553	19.1
Receptive anal intercourse (last 10 yrs.)		
Yes	157	5.4
No	2,764	94.6

[a]Seven participants refused to answer.
[b]Eleven missing (all males).

originally funded to follow the HIV-1 seronegatives not in followup, 1,379 of 2,068 (66.7 percent) returned at 6 months for a serological rescreen. Only minimal resources were devoted to this effort; subsequently, separate funds have been received to actively encourage returns of these participants.

DISCUSSION

These preliminary results from the ALIVE study build from a foundation of earlier work on longitudinal studies of drug users and investigations of HIV-1 infection among IVDUs, but represent just a beginning set of achievement of the study objectives. The results address several concerns about feasibility of studies in this population, namely, whether IVDUs would enroll in large numbers for a longitudinal study based in a clinic that was detached from any drug abuse treatment facility, criminal justice agency, or acute care hospital; whether it would be feasible to obtain data on sensitive behaviors; and whether subjects would return for potentially disturbing test results and 6-month repeat visits. To achieve the sample obtained, a wide variety of techniques were used. Because the recruitment goal was ambitious and the time frame for enrollment was limited, the efficacy of individual recruitment techniques was not evaluated. Given that the study population was predominantly impoverished and from the inner city, financial compensation and convenient location were probably important determinants for recruitment. However, the role of the advisory board, hiring staff sensitive to the needs of the population, assuring strict confidentiality, designing the clinic environment and study instruments to establish trust and rapport, and providing an ongoing monitor of health status with expedited referrals for additional care cannot be easily dismissed. The combination of techniques is likely to have contributed to improved recruitment, reporting of sensitive behaviors, and return visits. Relative efficacy for the different techniques requires further investigation.

Although the observed seropositivity values are comparable to those from other recent local surveys (Vlahov et al. 1989; Polk et al. 1986), the large sample size of IVDUs used to generate this data does not necessarily mean that the data are generalizable to other populations of IVDUs. Multiple reports of IVDUs suggest considerable variation between metropolitan areas for drug use practices and HIV-1 seroprevalence and transmission (Marmor et al. 1987; Chaisson et al. 1987; Lange et al. 1988; Lieb et al. 1987). Even within a single metropolitan area, considerable variation has been reported (Drucker and Vermund 1987). In Baltimore, the ALIVE cohort may be biased because of a volunteer effect; participants may have

volunteered because they considered themselves at high risk for infection. Although the cash incentive may mitigate the effect of a volunteer bias, it may have resulted in selection for lower socioeconomic status. Because high-risk behaviors among IVDUs, such as needle sharing, have been associated with economic factors (Magura et al. 1989), selection for lower socioeconomic status is not an unreasonable strategy. Nevertheless, the extent to which these data reflect characteristics of the IVDU population is unknown. The issue of representativeness and generalizability is common to studies of IVDUs because no population frame exists. Instead, investigators access IVDUs through drug abuse treatment centers (Marmor et al. 1987; Chaisson et al. 1987; Schoenbaum et al. 1986; Selwyn et al. 1987) criminal justice agencies (Vlahov et al. 1989), and ethnographic street outreach techniques (Watters and Biernacki 1989); however, each of these approaches may be subject lo selection bias. Given these limitations, emphasis should be placed upon any consistency of findings across studies, and observed differences should provide the basis for additional hypothesis formulation. Because most published reports of longitudinal studies of HIV-1 infection among IVDUs have been based upon samples obtained in drug abuse treatment centers (Selwyn et al. 1987; Des Jarlais et al. 1987), a strength of the ALIVE cohort lies in the ability to provide similar types of information from a population of predominantly active users outside the treatment and criminal justice settings.

Another methodological concern in studies of inrravenous drug users is accuracy of self-reports. Traditional approaches to evaluating self-reports have included the use of standards such as urine screens, official records, and corroboration with family and counselors. Summaries and comparisons of studies using these techniques have been reported elsewhere (Magura et al. 1987; Gibson et al. 1987). In the ALIVE study, 92 percent of participants were observed by a phlebotomist to have needle marks, using only inspection of upper extremities; a significant and positive association was noted between proportion with needle marks and frequency of injection in the 6 months prior to inspection (Anthony et al., in press). These data indicate that most ALIVE participants were intravenous drug users.

More recently, Friedman and co-workers (1988) used immune parameters associated with HIV-1 infection as a basis for comparison of self-reported data on intravenous drug use. This has prompted further exploration into hypothesized relationships between biological parameters and self-reports. For example, across previously published studies (Marmor et al. 1987; Schoenbaum et al. 1986; Chaisson et al. 1989) antibody to HIV-1 among

IVDUs has been positively associated consistently with frequency of injection, and proportion of injections that are shared with other IVDUs. Therefore, it is reasonable to suggest that subsequent studies might examine self-reports by observing whether variables such as median number of shared injections are elevated in seropositives compared to seronegatives. Similarly, because the number of CD4 cells in HIV-1 seropositives reflects in part time since onset of infection (Moss and Bacchetti 1989) subsequent studies might examine self-reports of drug use patterns over time among seropositives by stratifications of CD4 counts; seropositives with lower CD4 counts (suggesting more remote onset of infection) might be expected to exhibit high frequencies of select risky practices earlier than those with CD4 count approaching the levels of seronegative controls. These hypothesized associations were observed in the ALIVE study (Anthony et al., in press), suggesting accuracy of self-reports in these data.

Another approach to explore accuracy of self-reports is to measure the degree of socially desirable responding. This concept has been discussed elsewhere in the drug abuse research literature (Harrell 1985), and instruments lo measure socially desirable responding are available (Crown and Marlowe 1964). A more recent instrument extends earlier work by attempting to distinguish self-deception from impression management within a single instrument (Paulhus 1984). Although these instruments have been developed in populations other than intravenous drug users, we currently are testing their capacity to improve our own study of IDVUs and natural history of HIV-1 infection.

Closely related to the issue of accuracy of self-reports is the potential impact of ethical constraints on studies of HIV-1 infection in this population. These studies begin with informed consent procedures and, if serologies are to be determined, pretest counseling. Materials and explanations provided lo individuals are necessary to permit fully informed consent. However, the understanding generated by these procedures might affect responses to subsequent interview items. Therefore, a finding of nearly uniform correct responses identifying a virus as the primary etiologic agent for AIDS should not be surprising if this question follows an informed consent and pretest counseling procedure. The dilemma may extend beyond knowledge items to the actual self-report of HIV-1 risk behaviors. For example, the consent and counseling procedures may precondition the respondent to specific views about the socially desirable behaviors. To the extent that this preconditioning affects socially desirable responding or perturbs responding in other ways, subsequent self-report data on behavior may be compromised.

Given this consideration, the ordering of stages of informed consent/counseling and interviews about knowledge, attitudes, and behavior is important.

By placing informed consent/counseling into sequential stages, the following is meant. First, counseling could follow collection of knowledge, attitudes, and behavior data, while preceding the serological test. (An added benefit of the sequencing is that the knowledge questions could serve as a check to examine comprehension of pretest counseling). Second, pretest counseling can be restricted to essential information that allows informed consent for performance of the assay, but without elaboration at that lime about modes of transmission and recommended risk reduction messages. In this way, self-reported behaviors can be elicited without prior indications to suggest socially desirable responses. Notwithstanding these concerns about validity of study data, there would seem lo be an ethical consideration: counseling about high risk practices and risk reduction should be provided before the end of the initial visit.

For studies with longitudinal followup, the impact of ethical constraints on the data may be more pronounced. All participants received extensive counseling at the baseline visit, and residual effects may be seen in responses to interviews conducted in subsequent visits. Because prevention messages are likely to be reinforced al each subsequent visit, the effect may be reflected in temporal trends of self-reported risk reduction. Therefore, data from longitudinal studies in fixed cohorts which suggest risk reduction over time should be viewed with caution. More appropriately, because all study participants receive the same "intervention" of counseling at each visit, analytic strategies should emphasize internal comparisons between varying degrees of behavioral change. Moreover, if possible, the counseling and education staff should be different from the interviewing staff; these functions should be separated administratively and not linked in the minds of either staff or subjects. Otherwise, the possibility of data contaminated by counseling and education has not been kept to a minimum. In summary, ethical constraints do not invalidate longitudinal studies, but rather require investigators to carefully design and analyze appropriate comparisons.

In studies of HIV-1 infection among intravenous drug users, another methodological consideration is an effect due to interviewers. An extensive literature exists on the effect of interviewers (Sudman and Bradburn 1974; Fowler 1985). The extent to which such efforts may be operating in longitudinal studies of HIV-1 infection among intravenous drug users has not been reported. In a preliminary exploration, we focused upon three issues: (1)

analysis of the extent to which participant assignment to interviewers was a random process, (2) analysis of the extent to which reporting of sensitive behaviors varied by interviewer, and (3) the extent to which psychological mood scale responses varied by interviewer. Because the pool of applicants for interviewer positions yielded only white females at the outset of recruitment, the effect of gender and racial/ethnic matching between interviewer and respondent could not be evaluated.

In the ALIVE study, comparison of demographic characteristics of respondents by interviewer yielded no significant differences (J.C. Anthony, unpublished data). This suggests that the mechanism of participant assignment to interviewers was essentially random; a non-random distribution might have suggested that an unintentional selection process might have been operating. Evaluation of this issue is optimal early during the course of a study to permit investigators the opportunity to evaluate recruitment and interviewer assignment procedures.

Second, an analysis was performed that compared self-reported drug use behaviors, such as frequency of injection, by interviewer; no significant differences were identified (J.C. Anthony, unpublished data). This suggests that the reporting of sensitive information was relatively unaffected by interviewers.

Third, an analysis was performed which compared self-reported responses to questions about psychological mood by interviewer. Differences were noted not in the direction of responses but in the degree of responses (J.C. Anthony, unpublished data). Interestingly, responses varied between one interviewer with many years of professional interviewing experience and another interviewer with only 1 year of prior experience; the mood scale responses tended to be more extreme for the latter. Congruent with other research on psychiatric assessments (Henderson et al., 1981), this suggests that experience and, anecdotally, the degree of professional detachment of the interviewer may affect psychological mood scales.

The degree to which interviewer effects are identified presents an interesting problem for data analysis. If differences in participants' responses are identified by interviewer, then one approach might include stratification or statistical adjustment. Another approach includes collapsing response categories provided that the direction of responses are similar across interviewers. The optimal approach, however, is to carefully evaluate potential effects early during the course of a study and to provide additional training and supervision of interviewers.

Other methodologic issues are important to consider in longitudinal studies of HIV-1 infection. For example, Munoz and coworkers (1988), noting a variation of CD4 cell levels between study centers of the Multicenter AIDS Cohort Study and within a study center over time, proposed calculation of a CD4 deficit score, which involves subtracting the CD4 count of each HIV-1 seropositive from the respective time period-specific of the median of the CD4 wunt for HIV-1 seronegatives from the same laboratory. The result is a standardization of laboratory values across time and between study sites.

More recently, the selection of appropriate endpoints for longitudinal studies of HIV-1 infection among IVDUs has become a major issue. The diagnosis of AIDS as the endpoint for longitudinal studies of HIV-1 infection seems obvious, but is problematic for several reasons. First, the incubation period for AIDS is long, with a median estimated to be 7.8 years in one mathematical model (Medley et al. 1987). Therefore, a complete description of the natural history of HIV-1 infection would require extraordinarily long periods of followup. Second, the diagnosis of AIDS among IVDUs is complicated by recent reports of excess mortality due to bacterial pneumonia, endocarditis, and tuberculosis among IVDUs in New York City (Stoneburner et al. 1988). These data suggested that the current definition of AIDS might be too restrictive for this group. Third, recommendations have recently been published on chemoprophylactic measures to prevent first episode of Pneumocystis carinii pneumonia, the leading clinical presentation among cases of AIDS (Centers for Disease Control, 1989). The prevention of a major illness which has defined a large proportion of AIDS cases means that alternative endpoints, such as CD4 count below 200, may need to be considered for the purposes of establishing endpoints for longitudinal studies of HIV-1 infection.

Given these problems, the issue of appropriate endpoints requires close consideration. One strategy is to identify and apply surrogate markers for progression to AIDS. Surrogate markers possess the advantages of requiring shorter periods of followup and mitigating both the need to specify a priori types of clinical presentation and the need to redefine clinical endpoints with the advent of further advances in chemoprophylaxis for opportunistic infections. Specifically, predictors of decline in CD4 cell wunt have been discussed by Munoz and coworkers (1989) and Moss and Bacchetti (1989). Additional work in this arena is required.

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7. HIV Infection in Drug Abusers: Research Implications of Descriptive Studies

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INTRODUCTION

Increased prevalence of human immunodeficiency virus (HIV) infection in drug abusers, especially in those who share hypodermic needles, is well documented (Des Jarlais et al. 1989). However, in most geographic locations, the prevalence and incidence of HIV infection in drug abusers are so low that the usefulness of longitudinal studies is limited. Nonetheless, observations of drug abusers have led to the identification of the following topics that will be described and that will require additional research: factors related to increased risk for HIV infection in subtypes of drug abusers with regard to age, sex, race, ethnic origin, drug(s) abused, mode of drug administration, and sexual behavior; accuracy of estimates of HIV infection prevalence; methods for changing behavior to reduce the risk of acquiring or transmitting HIV infection in drug abusers; and the relationship of becoming infected with HIV, and developing HIV symptoms, to being infected with other viruses. Progress in diagnosing the presence of HIV infection by means of improved methods, as well as advances in medical intervention, will continue to influence the design of research studies on the factors that

The research reported in this chapter was supported by grant no. DA 04337 from the National Institute on Drug Abuse.

affect the incidence of HIV infection and the course of HIV illness in drug abusers.

SUBTYPES OF DRUG ABUSERS

The prevalence of HIV infection varies substantially in groups of individuals defined by racial group, type of substance abused and route of administration, and by patterns of sexual behavior.

With respect to race, black and Hispanic drug abusers are at greater risk for HIV infection than are drug abusers who are white (Chaisson et al. 1987). The reasons for the greater prevalence in these groups are not understood; whether these racial differences are the result of differences in patterns of drug use, sexual behavior, economic status, education, or other factors requires additional research.

The specific drug abused is related to the prevalence of HIV infection. Chaisson et al. (1987) studied patients in methadone treatment programs in San Francisco and found that intravenous (IV) cocaine users had a significantly higher prevalence of seropositivity to HIV antibody than did other IV drug abusers. Sixty-one percent of the patients in treatment for less than 1 year for opiate addiction had used cocaine. Of these, 26 percent began their use of cocaine, and 6 percent increased their use of cocaine, while receiving methadone treatment for their heroin addiction. These findings indicate that methadone treatment may be of limited usefulness in control of the spread of HIV infection among drug abusers. Thus, research is needed on types of interventions that can reduce cocaine abuse in patients receiving methadone treatment.

Much of the research on HIV illness in drug abusers has focused on those taking drugs intravenously. However, the seroprevalence of HIV antibody has also been determined to be higher in non-IV drug abusers than in the general population. In a study of female prostitutes (Sterk 1988) non-IV cocaine and crack users were found to have a prevalence of HIV seropositivity four times higher than that for prostitutes who used no drugs. It was presumed that an increased number of sexual encounters that occurred with the drug-using prostitutes accounted for the increased prevalence of HIV infection. Stall et al. (1986) have suggested that non-IV drug use in homosexuals is related to increases in high-risk sexual behavior, which sometimes results in transmission of HIV. Future research on HIV transmission in drug abusers should include non-IV drug abusers.

DETERMINING THE PREVALENCE OF HIV ANTIBODY

No systematic method exists for assessing the prevalence of HIV infection in drug abusers, because it is impossible to specify the population of drug abusers in a geographic area. Methods that have been employed include surveys of drug abusers in or applying for drug abuse treatment, as well as surveys of drug abusers identified by field workers in locations where drug abusers congregate. The ability to assess the prevalence of HIV infection has usually depended on voluntary consent by drug abusers to be tested. These surveys may thus provide low estimates of the prevalence of HIV infection.

We have found some differences between IV drug abusers who volunteer for HIV antibody testing and AIDS education and those who decline to participate (Schaefer et al. 1989). We evaluated 319 male veterans seeking treatment in our drug abuse program. All had used IV drugs at some time, beginning in or after 1980. Of these 319 veterans, 226 (71 percent) agreed to participate and 95 (30 percent) refused. Veterans not participating in HIV antibody testing reported significantly fewer needle-sharing partners than did participants (mean number of partners, 0.8 ± 2.4 versus 1.6 ± 3.4, $p < .01$). Nonparticipants were also older, with a mean age of 39.1 ± 6.8 years compared with 37.2 ± 6.9 years for participants ($p < .03$). The nonparticipants and participants did not differ, however, with respect to race, type of drug abused, number of sexual partners, or frequency of sexual activity.

To assess the seroprevalence of HIV antibody in nonparticipants, we carried out ELISA and Western blot testing on serum obtained for routine blood tests on 92 of the 95 IV drug-abusing patients All identifying information was removed from the tubes containing serum so that anonymity of results was assured. The percentage of nonparticipants who were HIV antibody positive (13.5 percent) was not significantly different from the percentage of participants in the voluntary testing and education program (7.2 percent).

The rate of HIV seropositivity of 7.2 percent among our volunteer patients is much lower than the approximately 20 percent reported by Wiebel and Ouellet (1989) in their study of Chicago IV drug abusers who were not in treatment. They also found that the prevalence varied from approximately 17 percent to 31 percent in different neighborhoods. In another study of anonymous testing conducted without patient consent or knowledge in other Chicago public drug abuse clinics, the rate of seropositivity ranged from 10.0 percent to 19.9 percent (Allen et al. 1988).

Because the seroprevalence of HIV antibody among the volunteer patients we studied is substantially lower than that reported in nonpatient IV drug-abusing individuals assessed in the same geographic area or than patients tested without their knowledge in a public clinic, we thought that considerable self-selection occurred in the patients presenting themselves for treatment. Our study showed that some IV drug abusers applying for treatment may refuse AIDS risk-reduction counseling and HIV antibody testing. It also indicated that the individuals who refuse to participate may underreport their high-risk behavior or engage in behaviors not ascertained in our interviews, such as using more than one drug at a time or having sexual relations with prostitutes. It is possible that patients who are at greater risk for HIV infection may resist being tested because of fear of knowing their HIV antibody status, or because of denial that they are engaging in risky behavior. Voluntary antibody testing and education programs may miss some IV drug abusers at highest risk for HIV infection.

These differences between patients volunteering for testing and those not volunteering or not in treatment need to be replicated. If these findings persist, it will be important to identity what keeps these groups with high seroprevalence from entering treatment and what kind of programming can reduce risk in these nonpatient drug abusers. In view of the self-selection of patients participating in such research, techniques effective in intervention for groups may not be applicable to other groups of patients.

BEHAVIORAI, CHANGE THAT REDUCES RISK OF INFECTION

Rituals and shared beliefs regarding drug use may develop in peer groups of drug abusers. Such rituals may involve high-risk behavior, such as needle sharing (Ginzburg et al. 1986). Counseling provided to a single individual or to only a few of the members of such a group might have limited impact on such group-sanctioned behaviors. Counseling of friendship groups, or of social networks, may provide more effective intervention (Wiebel 1988). Risk-reduction educational counseling or psychotherapy conducted in peer groups may be superior to individual counseling. An important strategy might be to identify networks or friendship groups of drug abusers, particularly of relatively new drug abusers, with the goal of using peer influence to modify the risky behavior of the network members. Early intervention, before group norms or rituals become too firmly established, is likely to be most effective.

Reports have varied on the percentage of drug-abusing patients willing to participate in HIV antibody testing and educational programs. Weddington and Brown (1988) reported that 100 of 101 cocaine-abusing patients who kept their initial appointments and met criteria for a clinical research program agreed to participate in HIV antibody testing when it was offered at the time of admission. They concluded that voluntary HIV antibody testing in drug abuse treatment clinics is feasible and does not deter persons from entering treatment for drug abuse.

We have observed great variability in the percentage of patients participating in HIV antibody testing and risk reduction education programs at different methadone treatment clinics. Unlike the patients described by Weddington and Brown (1988), the patients were applying for treatment without knowledge that they would be asked to participate in research programs. In one private methadone treatment program in Chicago at which one author is a medical director, less than 5 percent of patients agreed to participate in HIV antibody testing and risk reduction education, but at our nearby Veterans Affairs methadone clinic, approximately 70 percent participated. Patients at both clinics, however, have shown substantial interest in AIDS education programs. Counselors at both clinics are trained in risk reduction education, and most have received National Institute on Drug Abuse (NIDA) training. The most notable difference between these two programs is that the low participation private program relies on the regular program counseling staff to involve patients, whereas the high participation VA program has staff members whose only responsibility is to recruit patients into the antibody testing and risk reduction education program. This observation suggests that drug abuse counselors may not be ideally suited for HIV risk-reduction education. Research is needed for identification of the most effective organization of staff for involving patents in drug abuse treatment in risk-reduction programs or to determine if patient differences contributed to the findings.

Inclusion of drug abusers' sexual partners in antibody testing and education programs may benefit those individuals who are at high risk of infection. These sexual partners may also provide a source of support for behavior change in drug abusers. We have encountered resistance, however, to the involvement of spouses and other sexual partners in our risk-reduction program. Of 259 heterosexual patients who reported having a current sexual partner, 30 (12 percent) agreed to have these partners participate in the program. Most of the patients would not allow us to contact their sexual partners. The most frequent reason given for not permitting the partner to

participate was the fear that the partner would terminate the relationship upon discovering that the patient used drugs or used drugs intravenously. In other instances, the patient was fearful that the sexual partner would incorrectly believe that the patient was infected with HIV. In discussions on sexual behaviors, it has become obvious that many patients rarely discuss the subject of potential HIV infection with their partners. Often patients also have not discussed details of their drug use with their sexual partners.

Patients are fearful, sometimes with justification, that involvement of their sexual partner would compromise the relationship. We have found for those patients who have participated with sexual partners in risk-reduction programs that the experience is useful to both partners. A need exists to develop methods for engaging both the substance-abusing patient and his or her sexual partners in a way that is acceptable and does not disrupt relationships. Interventions involving both may be more effective than interventions directed only at the substance-abusing patient.

Risk reduction related to IV drug use is not necessarily correlated with risk reduction in other kinds of behavior (Huang et al. 1989). Successful HIV risk-reduction treatment for IV drug users may not decrease the risk for HIV from other modes of drug use. Previously, the risk associated with non-IV drug use has not been appreciated. Non-IV drug use could result in an increase in impulsive behavior, including risky sexual behavior engaged in as an exchange for the acquisition of drugs. Alternatively, a reduction in risk associated with drug use could lead subjects to consider that they were now safe from HIV infection. This is illustrated by the example of the recovering alcoholic who feels less fearful about speeding because he knows that he cannot be arrested for drunken driving. Similarly, the non-IV cocaine user may have an unfounded sense of security regarding the risk of acquiring HIV infection, although the frequency of his or her sexual high-risk behavior has not diminished.

There may be no correlation between risk reduction related to IV drug use behavior and risk reduction related to sexual behavior. Patients who participated in our HIV antibody testing and risk reduction education program appeared to reduce their needle sharing more than they reduced their high-risk sexual behavior. Methods need to be developed that will make it easier for drug abusers to generalize risk-reduction behaviors that they have acquired to areas of behavior other than drug use. Systematic research is needed that will enable us to understand demographic, drug-use, psychiatric, and treatment-related factors that contribute to risk reduction, or to a lack of risk reduction.

THE EFFECT OF OTHER VIRUSES ON HIV INFECTION

Infection with HIV is only one of several viral infections transmitted by IV drug use. These other infections may influence the natural history of HIV infection or may cause additional symptoms.

One coexisting retroviral infection that we have evaluated is the human T-lymphotropic virus, type I (HTLV-I). This virus has been recognized as the etiologic agent in human T-cell leukemia-lymphoma and in chronic progressive myelopathy. In a 1987 study, this virus was shown to be present in 17.3 percent of IV drug users in Brooklyn, 2.9 percent in Baltimore, and 12.9 percent in Detroit. The prevalence of HIV infection among IV drug users in Venice and Amsterdam was 33 percent and 28 percent, respectively, and the prevalence of simultaneous HTLV-I infection was 4.3 percent and 1.3 percent (Lentino et al. 1989).

We have prospectively evaluated more than 150 IV drug abusers in our Veterans Affairs treatment program in Chicago. The prevalence of antibody to HIV and HTLV-I was 6.7 percent and 8.7 percent, respectively. Significantly lower absolute numbers of CD_4 helper T-lymphocytes were noted among the HIV-infected patients than in patients who were seronegative for HIV, or in those who showed serologic evidence of HTLV-I infection. In our sample, with the exception of one patient, patients did not have antibodies to both HTLV-I and HIV. However, race was associated with HTLV-I infection; 12 of 14 subjects who were seropositive for HTLV-I were black.

In cities on the east coast, HIV is much more prevalent than HTLV-I; in contrast, we found a similar prevalence of the two infections. The reason for this difference is not clear. Drug use behavior among IV drug abusers in Chicago may have different patterns, or abusers may differ in other behaviors that account for difference in prevalence of the infections. HTLV-I infection may be higher in areas with large numbers of black drug abusers because the infection is more prevalent among blacks than among whites in the United States.

The clinical importance of HTLV-I infection is not known because the incubation period is extremely long and the disease-to-infection ratio is low, thought to be in the range of 1 to 200. It is also possible that our findings reflect cross-reactivity of antibodies. Newer techniques, such as the polymerase chain reaction (Murakawa et al. 1988), need to be utilized for confirmation of the findings to date.

Other common chronic viral infections, such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), and herpes simplex virus (HSV), have been associated with immunologic abnormalities and could promote HIV infection or the development of AIDS. In our patients who were tested for HIV antibody, the prevalence of CMV, HSV, and EBV infection, as measured serologically, was 86 percent, 86 percent, and 100 percent, respectively (Pachucki et al. 1989). Patients with active EBV infection had a lower percentage of CD_4 cells and a lower CD_4/CD_8 than all other patients. Patients with active EBV infection also infected with CMV had higher CD_8 and lower CD_4 than all other patients. In contrast, patients with active EBV and no antibody to CMV had a lower percentage of CD_8 compared with all patients and compared with patients with active EBV and antibody to CMV. The combination of active EBV and HSV infection produced a lower percentage of CD, cells compared to other combinations of viral infections. Patients without serologic evidence for CMV alone or in combination with active EBV had lower CD_8 and a higher CD_4/CD_8 as compared with all other patients. These patients had no clinical evidence of infection to EBV or CMV. These latent infections may be important in the pathogenesis of HIV infection, because the HIV virus requires activated lymphocytes in order to establish infection in the host; antecedent or coexisting infections may contribute to HIV infection and to replication of the HIV virus in lymphocytes (Haverkos 1987). These findings will require long-term followup of these patients with immunologic studies, viral serology, and testing for the HIV virus.

Other sexually transmitted diseases (STDs), including syphilis, gonorrhea, and genital ulcer disease, may also represent risk factors for HIV infection. When these diseases are present before exposure to HIV, they may act as facilitators of infection (Handsfield et al. 1987). In other instances, these STDs may act as cofactors to the progression of HIV infection and to the development of AIDS. Studies are needed for confirmation of the relationship of these STDs, especially genital ulcer disease, to the transmission of HIV and to the progression of HIV illness.

PROGRESS IN MEDICAL TREATMENT: DIAGNOSIS AND TRFATMENT OF IIIV INFECTION

Descriptive studies have focused on determination of the prevalence of HIV infection as determined by ELISA tests, with Western blot confirmation of positive results, and on determination of the development of AIDS in seropositive drug abusers. When the first descriptive studies were planned, it was thought that the seroconversion rates would be of sufficient magni-

tude that differences in these rates could be assessed in samples with different ethnic or demographic characteristics. Happily, the seroconversions that we and others have observed are too infrequent to enable us to pursue this type of study. This low rate probably is, at least in part, a function of the education that most participants in studies are receiving, which results in reduced needle sharing. Those not in treatment have also probably benefited by the counseling or instruction that occurs as a part of participation in research. At least in some locations, the prevalence of HIV seropositivity has not increased, contrary to predictions made a few years ago.

The recent advances in detecting HIV infection will allow a more accurate description of the natural history of this infection. Based on evidence from transfusion data for which the time of infection is known, seropositivity, as determined by ELISA testing, does not occur until several weeks to 3 months after infection. For some individuals, seroconversion may not occur for years. This ELISA testing variability has limited the precision with which the events that lead to infection can be determined. That portion of the illness, varying in length in different individuals, which took place before serologic evidence of the disease was apparent, has limited our understanding of the development of the illness in infected individuals. The possibility of false negative results also has limited the specificity of counseling that could be given to patients receiving test results, because there was always the possibility that high-risk patients had an undetected infection. Tests for the presence of viral nucleic acid by polymerase chain reaction promise to increase the precision with which the presence of infection can be detected. By use of polymerase chain reaction, HIV DNA has been detected in some high-risk individuals 36 months prior to antibody seroconversion, and in seronegative partners of seropositive individuals (Loche and Mach 1988). These techniques should be utilized in future research, because very early identification of infected individuals could enable physicians to identify medical and psychiatric abnormalities associated with the infection. Such identification could also be of help in measures for control of the spread of infection to sexual partners or to fetuses.

The utility of the present definitions of ARC and AIDS in future research on HIV infection in drug abusers must be evaluated. Until recently, AIDS was thought of as an essentially untreatable, rapidly fatal condition; now it is understood that AIDS is the end stage of a chronic progressive illness, the complications of which can be treated, and which can be controlled medically with increasing success. Prophylactic treatment with pentamidine for prevention of Pncumocystis carinii pneumonia, for example, holds the

promise of extending the life expectancy and increasing the quality of life of patients. Zidovudine may be more effective in controlling viral growth in patients early in the course of the illness, before AIDS develops and perhaps even before any clinical symptoms develop, than when it is administered later in the illness.

These advances in the concept of HIV illness as a chronic, progressive disease and in the treatment of the illness and its major complications have a major implication for future research. An increased urgency to identify patients who are infected exists, because effective treatment early in the course of the disease is now available. Monitoring of seropositive patients without active medical intervention is no longer acceptable. Studies of the natural history must now incorporate the need for aggressive medical intervention. Studies must be designed in which the most promising techniques for engaging drug abusers in treatment are compared.

CONCLUSION

Research on HIV infection in drug abusers has shown that substantial differences in prevalence exist in different subgroups of drug abusers. Cocaine, whether used intravenously or by other routes, has emerged as the drug of abuse that carries the highest risk for acquisition of HIV infection. Some drug abusers are able to change their behavior and to participate in education, counseling, and HIV antibody testing programs designed to reduce the risk of infection. Recent advances have resulted in the possibility of early identification of all infected individuals. Early identification is critical because treatment that slows the progression of the illness in its early stages is now available. In future studies, emphasis should be placed on techniques for identifying drug abusers drawn from populations larger than those obtained from treatment programs. They should incorporate intervention methods whose efficacy is assessed, and they should be flexible enough to accommodate the rapid advances occurring in medical treatment.

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8. Potential Cofactors in the Outcomes of HIV Infection in Intravenous Drug Users

Don C. Des Jarlais

The term "cofactor" has been used to describe a variety of possible effects on HIV infection. There are potential cofactors that might affect the biological transmission of HIV, such as the presence of genital ulcer disease. Transmission cofactors could occur in either the infected person serving as the source or in the person who becomes infected. The term "cofactor" has also been used for conditions that may influence the course of HIV infection once the infection has been established. These infection outcome cofactors might influence the rate at which infection progresses to clinical disease and/or the specific clinical manifestations of the HIV-related diseases that occur. Discussion of possible infection outcome cofactors has included genetic differences, other concomitant viral infections, general immunologic stimulation, and a panoply of behaviors that might affect the immune system.

There is very great variation in the "latency" period between initial infection with the human immunodeficiency virus (HIV) and the development of clinical AIDS. Estimates of the range of the latency period run from a minimum of less than a year to a maximum of over a decade. There is also great variation in the specific clinical manifestations of AIDS, with over 20 different "opportunistic" infections as well as several malignancies, "wasting syndrome," and AIDS dementia currently included in the surveillance definition of AIDS (Centers for Disease Control, 1987). This variation in the latency period and in the clinical manifestations suggests that there may be several cofactors that influence the outcomes of HIV infection. Despite the great variance that could be explained by infection outcome cofactors,

research to date has not identified any single factor that appears to have a strong direct effect on the outcomes of HIV infection.

Intravenous (IV) drug users should be an excellent group for studying potential infection outcome cofactors, as they engage in a wide variety of behaviors that may expose them to potential cofactors. In this paper, I will review current research on potential cofactors in outcomes of HIV infection in intravenous drug users. Much of the data reviewed will be from New York City, in part because the relatively large number of cases of AIDS among IV drug users in New York has provided more statistical power in conducting research on outcomes of HIV infection. I will conclude with suggested directions for future research in the area.

POTENTIAL COFACTORS FOR KAPOSI'S SARCOMA

The differential rates of Kaposi's sarcoma (KS) among the various AIDS risk groups is an excellent example of where a cofactor appears to be operating, but research efforts have not yet been able to identify the cofactor with certainty. From the beginning of the AIDS epidemic, KS has been a much more frequent manifestation of HIV infection among homosexual/bisexual men than among intravenous drug users. (Homosexual/bisexual men who also inject drugs have KS rates intermediate between homosexual/bisexual men who do not inject illicit drugs and heterosexual drug injectors.) This relative ordering of the frequency of KS among the persons exposed through male-to-male sexual activity compared with sharing of drug injection equipment has remained even as the percentage of cases with KS has declined dramatically in all groups over the course of the AIDS epidemic (Des Jarlais et al. 1987*b*).

Haverkos and colleagues (1985) have argued for the use of volatile nitrites as the cofactor responsible for KS as the clinical manifestation of HIV disease. Nitrites do affect immune functioning so that there is an inherent plausibility that their use might interact with HIV to increase the development of KS. Although precise data are not available, it is likely that the use of nitrites among groups at risk for AIDS probably does match the epidemiology of HIV-related KS, both over time and across risk groups. Homosexual/bisexual men probably had high rates of nitrite use early in the HIV/AIDS epidemic, and they have undoubtedly decreased their use over the course of the epidemic. Data on trends in nitrite use among IV drug users are not readily available, but our ethnographic studies in New York suggest that nitrite use among IV drug users was both lower than that

among homosexual men early in the epidemic and has also declined over the course of the AIDS epidemic (W. Hopkins, personal communication, 1987).

Drew has argued for cytomegalovirus (CMV) as the cofactor responsible for KS (Drew et al. 1985). Again, there is a reasonable fit with the epidemiologic data, as homosexual/bisexual men are more likely to have been exposed to CMV than IV drug users are (Marmor et al. 1985).

An alternative to the nitrite and CMV hypothesis is that there is some other viral cofactor, such as human herpes simplex virus type 6, that is transmitted through sexual activity and is responsible for the development of KS in persons also exposed to HIV. Nitrite use and CMV exposure may be associated with high rates of sexual activity, and thus might serve as markers for exposure to this other factor.

Kaposi's sarcoma provides a cogent example of where a cofactor appears to be operating in HIV infection. There are several candidates for this cofactor, but so far, researchers have not been able to find ways of determining which of the candidates is the actual cofactor for KS.

POTENTIAL COFACTORS FOR "NON-AIDS" MANIFESTATIONS OF HIV INFECTION

One of the most dramatic differences in response to HIV infection between IV drug users and homosexual/bisexual men in the United States has been in the number of "non-AIDS" deaths among IV drug users. Studies in New York indicate epidemic level increases in deaths from bacterial pneumonias, tuberculosis, endocarditis, and other infections among IV drug users coincident with the HIV epidemic (Des Jarlais et al. 1988). These fatal illnesses do not qualify as surveillance definition AIDS, but appear to be occurring among drug injectors exposed to HIV. Reviews of medical records show frequent indications of HIV infection among IV drug users dying from these non-AIDS diseases, for example, as in the presence of oral candidiasis. In a prospective cohort study, all deaths from these non-AIDS infectious diseases occurred among IV drug users who had been exposed to HIV and had significant HIV-related immunosuppression (Stoneburner et al. 1988). Another cohort study has shown HIV infection strongly associated with nonfatal cases of bacterial pneumonia among IV drug users (Selwyn et al. 1988). In New York, the total number of HIV seropositive IV drug users who have died from infections that are not currently classified as AIDS is probably greater than the number who have died from officially classified AIDS.

Studies of homosexual/bisexual men with HIV infection have not shown the same mortality from non-AIDS infections as has occurred in IV drug users. There are several possible mechanisms that might explain this large difference in fatal non-AIDS infections between IV drug users and homosexual/bisexual men. First, socioeconomic factors may lead IV drug users to be exposed to a wider variety of pathogens than are homosexual/bisexual men. Tuberculosis would be a good example. Second, the much larger amounts of psychoactive drug use typically found among IV drug users may be playing a role. Third, there may be genetic/ethnic group differences. Fourth, there may be general lifestyle differences such as nutritional status that affect immune functioning and interact with HIV. Finally, the quality of health care typically received by IV drug users is clearly less than that typically received by homosexual/bisexual men in research studies. It is possible that, with good health care, more IV drug users might avoid these HIV-related "non-AIDS" fatal illnesses long enough to develop surveillance definition AIDS.

No studies comparing seropositive IV drug users to seropositive homosexual men have yet found a basis for selecting among these hypotheses.

PSYCHOACTIVE DRUG USE AS A COFACTOR FOR PROGRESSION OF HIV-RELATED IMMUNOSUPPRESSION

Psychoactive drugs other than nitrites have been considered as potential cofactors for the development of AIDS. Most psychoactive drugs have at least in vitro effects on some aspect of immune function, so that the cofactor hypotheses are certainly plausible.

There have been two published longitudinal studies that examined psychoactive drug use as cofactors for progression of HIV-related immunosuppression. Kaslow and colleagues recently reported on psychoactive drug use in the MACS cohort of homosexual/bisexual men (Kaslow et al. 1989). We had previously reported on psychoactive drug use in a cohort of IV drug users (Des Jarlais et al. 1987*a*). Both studies looked for effects on CD4 cell loss as a measure of HIV-related immunosuppression. The Kaslow et al. study examined potential effects of psychoactive drug use on the development of clinical AIDS. Both studies reported no effects associated with the use of alcohol, marijuana, nitrites, stimulants, sedatives, noninjected cocaine, and noninjected opiates (including methadone in the IV drug user study).

The only difference in the findings of the two studies was with respect to illicit drug injection. In the study of IV drug users, there was an association between continued injection of illicit drugs and an increased rate of CD4 cell loss. This was not specific to the drug injected—the effect was similar for injections of heroin alone, cocaine alone, and heroin and cocaine injected together. Compared to the background rate of CD4 cell loss over time, the effect of continued drug injection was moderate in size. It was observed only among subjects injecting at high frequencies. The MACS study did not find an effect of drug injection, but the number of injectors in the study was "small," and it is not clear if any of the subjects was injecting at a high frequency.

There have been at least two other reports of increased HIV-related immunosuppression associated with continued drug injection. Selwyn and colleagues (1987) found the frequency of "nonsterile" injections at intake into the study was associated with the development of AIDS in a cohort of IV drug users. (The relationship was not significant after controlling for AIDS-related symptoms at intake, however.) Flegg and colleagues recently reported increased CD4 cell loss associated with continued injection in a cohort of IV drug users in Scotland. This has been the only study of continued injection as a cofactor that used subjects with similar times since initial HIV exposure (Flegg et al. 1989).

There are several possible mechanisms through which continued drug injection could lead to increased HIV immunosuppression other than a pharmacologic effect of the drug being injected. Most, if not all, injections of illicit drugs are nonsterile, and the resulting immunologic stimulation may increase HIV replication. This has been demonstrated in vitro, resulting in increased rate of CD4 cell death (Zagury et al. 1986). Continued drug injection may also lead to reexposure to HIV, including exposure to more virulent strains of the virus. Finally, continued injection may lead to exposure to some other pathogen that serves as a cofactor to increase HIV-related immunosuppression. Of these possible mechanisms, there is in vitro support only for immunologic stimulation, so that this should probably be considered the most likely method through which continued injection could lead to increased HIV-related immunosuppression.

Despite the fact that many psychoactive drugs have been proposed as cofactors for HIV disease, there is currently no in vivo evidence that any psychoactive drug has a pharmacologic effect on the rate of progression of HIV infection. There is some in vivo evidence for a method of drug administra-

tion, nonsterile injections, as a cofactor, but, as noted above, even this appears to be a moderate effect.

GENDER DIFFERENCES AS POTENTIAL COFACTORS

Because the vast majority of AIDS cases in the United States and Europe have occurred in males, there has been little study of potential sex differences in response to HIV. There are a few hints of potentially important sex differences. Based on data from persons entering drug abuse treatment and samples recruited from street settings in New York City, between 25 percent and 30 percent of the IV drug users in the city are females (Des Jarlais and Friedman, 1988). The rate of HIV exposure among female drug injectors in New York is equal to or higher than the rate among male drug injectors (Marmor et al. 1987). Yet females represent only 22 percent of the cases of AIDS among heterosexual IV drug users in the city (New York City Department of Health, 1989). One study that examined rates of HIV immunosuppression in male versus female IV drug users did find a nonsignificant trend toward a lesser rate of CD4 cell loss among the females (Des Jarlais et al. 1987*a*).

Conversely, female IV drug users have a shorter time from diagnosis of AIDS to death than do male IV drug users in New York (Rothenberg et al. 1987). It is possible that the differences in time of diagnosis to death are the result of female IV drug users waiting until they are "sicker" before seeking treatment for AIDS, although there is no evidence for this or an immediately obvious reason why it should occur.

There are anecdotal reports of increased gynecological problems in females exposed to HIV, but to date there has not been sufficient research on this topic to draw even tentative conclusions about possible cofactors.

Sex differences have been observed in response to other viruses such as hepatitis B, and it is possible that they are also occurring in response to HIV. The question of possible gender-linked cofactors should be addressed as more research studies examine HIV-related disease in females.

FUTURE DIRECTIONS

In searching for cofactors for outcomes of HIV infection, we are clearly at a stage where hypothesis testing is appropriate. The lack of a suitable animal model for HIV infection makes such hypothesis testing quite difficult. Another difficulty from a purely research perspective is the growing number

of treatments available for HIV infection, including prophylactic treatment for some opportunistic infections. At a minimum, the use of such treatments will add complexity to studies attempting to find cofactors for the outcomes of HIV infection.

The availability of treatments for HIV-related disease also creates a need for studies of potential interactions between psychoactive drug use and the treatments. For example, preliminary findings from Brettle and his group suggest that methadone use changes the pharmacokinetics of AZT, leading to a longer time for clearance of AZT (Brettle et al. 1989). Again, there is the potential for great complexity; such interactions may occur both in terms of pharmacokinetics and in terms of immune function. The need for such studies is becoming urgent, however. Such treatments are now showing significant effects in increasing quality of and prolonging time of life for persons exposed to HIV. There will be more than enough difficulties in providing good clinical care to IV drug users exposed to HIV without having unknown interactions with psychoactive drugs as an additional source of problems.

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9. How Can Results of Longitudinal Studies Help Mathematicians Model the HIV Epidemic Among Intravenous Drug Abusers and the General Population?

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INTRODUCTION

This paper describes a simple model of the AIDS epidemic that has been developed to explore some fundamental relationships among factors that characterize that epidemic. These factors include: (1) needle sharing and sexual contacts with individuals within and among risk groups; (2) the rate of progression from infection with HIV to diagnosis of AIDS; (3) the nature of viral transmission, including infectivity of the virus; and (4) the survival rates of persons with AIDS. These factors are imperfectly understood by the sci-

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Preparation of this chapter was supported by grant no. DA 05152 from the National Institute on Drug Abuse.

entific community, and until their influence on the epidemic can be evaluated, no reliable projections of the spread of HIV can be developed.

In this model we estimate risk-group specific contact rates that are consistent with AIDS incidence. Our estimates of AIDS incidence are based on cases reported to the Centers for Disease Control (CDC) adjusted for certain biases.

The Methods section of this chapter describes the model. The Longitudinal Studies section identifies the natural history studies that influenced model implementation. The Critique identifies points in the model at which either a lack of data or a lack of knowledge about the natural history of the disease leads to logical inconsistencies and parametric imprecision. The Discussion provides a summary of future efforts.

METHODS

Model Logic

Figure 1 is a schematic diagram depicting the process under investigation. Non-CDC AIDS cases are HIV-infected individuals who contract and eventually die from complications due to HIV-related illnesses, but whose diagnoses do not meet the CDC AIDS surveillance definition. Unreported CDC AIDS cases are cases whose diagnoses satisfy the definition of AIDS as formulated by the CDC.

Figure 2 is a diagram depicting the Research Triangle Institute (RTI) model used to represent the process shown in figure 1. This figure identifies major subpopulation categories tracked by the model and illustrates the progression through these subpopulations for a given risk group. The subpopulations are:

- The susceptible population—The population whose behavior places them at risk for HIV infection but who have not yet become infected with HIV—$S_j(t)$ is the size of this population at time t for risk group j.

Figure 1. Population progression (general case)

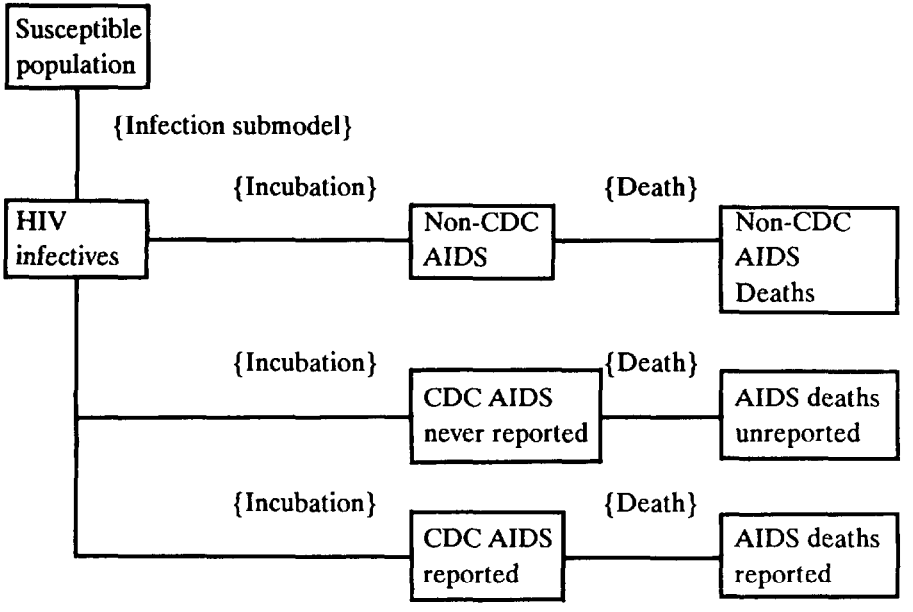
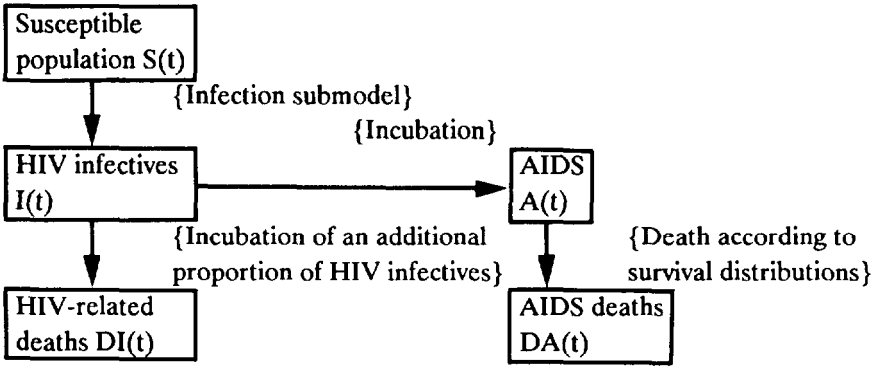


Figure 2. Population progression for a given risk group as characterized by model



- The infected population—Those infected with HIV, but not yet displaying clinical manifestations of the AIDS disease. $I_j(t)$ is the size of this population at time t for risk group j.

- The AIDS population—That segment of the population that has been diagnosed with CDC-defined AIDS. $A_j(t)$ is the size of this population at time t for risk group j.

- The AIDS death population—That segment of the population that has died as a consequence of CDC-defined AIDS. $DA_j(t)$ is the size of this population at time t for risk group j.

- The non-AIDS HIV-related death (NAHD) population—That segment of the infected population that has died of HIV-related complications not meeting the CDC AIDS definition. $DI_i(t)$ is the size of this population at time t for risk group j.

At the start of the simulated epidemic, the susceptible population is distributed among eight distinct risk groups (see table 1). The distribution of susceptibles by risk groups at the beginning of the epidemic is assumed to be the same as the distribution of AIDS cases by risk group reported to the CDC through March 1989.

We assume one infected person in each risk group at the start of the epidemic, T_o. The model estimates risk-group-specific infection rates that reproduce (within a specified level of accuracy) the AIDS incidence data adjusted for (1) reporting delays; (2) change in case definition; and (3) underreporting (Hamill et al. 1989). Infection rates are estimated within each time interval. These infection rates can be expressed as a function of the probability that a contact is safe (i.e., the probability that a contact involves

Table 1. Risk group definitions

1. Homosexual males who do not use IV drugs (HM)
2. Homosexual males who also use IV drugs (HMI)
3. Bisexual males who do not use IV drugs (BM)
4. Bisexual males who also use IV drugs (BMI)
5. Other males who do not use IV drugs (OM)
6. Other males who use IV drugs (OMI)
7. Females who do not use IV drugs (FM)
8. Females who use IV drugs (FMI)

needle cleaning and/or protected intercourse), the number of contacts, and probability of infection per contact. Changes in IV drug use and/or sexual behavior are reflected in changes in the infection rates. Using the infection rate estimates, the model then estimates HIV incidence (i.e., the number of new infections in each interval) according to the infection submodel defined below. New infectives are incubated to AIDS diagnosis; the number that develop AIDS during each time interval is recorded.

Evidence suggests that survival from time of diagnosis differs by type of AIDS diagnosis (Rothenberg et al. 1987). Accordingly, AIDS cases in the model are assigned an initial diagnosis (Kaposi's sarcoma, Pneumocystis carinii pneumonia, other); assignment is based on risk-group membership with simulated distribution of cases among diagnosis types reflecting distribution of observed cases among diagnosis types. A diagnosis-specific survival function is then applied to estimate the number of persons with AIDS dying during specific time intervals.

In summary, the model estimates infection rates by comparing the resulting estimated AIDS incidence with observed, adjusted AIDS incidence. Estimates of HIV incidence, HIV deaths, and AIDS deaths are also produced.

Mathematical Description

Equations (1) to (5) (corresponding to the five states identified in figure 2) describe the model dynamics of the i^{th} risk group. They are presented as differential equations but are implemented as difference equations.

1. Susceptibles

$$\frac{\partial S_i(t)}{\partial t} = \delta_i S_i(T_o) - [\mu_i + \lambda_i(t)]\, S_i(t) \qquad (1)$$

The susceptible population in the i^{th} risk group increases according to the recruitment rate, δ_i, (always applied to the initial populatio $[S_i(T_o)]$), and decreases according to the attrition rate, μ_i, and to the rate of HIV infection, $\lambda_i(t)$.

2. Infectives

$$\frac{\partial I_i(t)}{\partial t} = \lambda_i(t)\, S_i(t) - [\lambda_i(t) + B_i(t) + \mu_i]\, I_i(t) \qquad (2)$$

The infected population increases according to the rate of HIV infection, $\lambda_i(t)$, and decreases according to the rates of progression to AIDS $[\lambda_i(t)]$, to non-AIDS HIV deaths $[B_i(t)]$, and non-HIV related deaths $[\mu_i]$.

The rate of progression to AIDS, $\lambda_i(t)$, is defined as:

$$\lambda_i(t) = \rho_i \int_{T_o}^{t} \lambda_i(s)\, S_i(s)\, f_i(t|s)\, ds\, I_i(t)$$

where

$\lambda_i(s)\, S_i(s)$ = the number of new infections in risk group i at time s

p_i = the proportion of HIV infectives in the i^{th} risk group that progress to AIDS rather than non-AIDS HIV-related death

and

$f_i(t|s)$ = the density function for progression to AIDS at time t given infection at time s for risk group i.

The rate of progression to non-AIDS HIV-related death (NAHD) is:

$$B_i(t) = (1 - \rho_i) \int_{T_0}^{t} \lambda_i(s)\, S_i(s)\, g_i(t|s)\, ds\, I_i(t)$$

where

$g_i(t|s)$ = the probability distribution for progression to NAHD at time t given infection at time s for risk group i.

3. Persons with AIDS

$$\frac{\partial A_i(t)}{\partial t} = \gamma_i(t)\, I_i(t) - \Lambda_i(t)\, A_i(t) \qquad (3)$$

The AIDS population increases according to the rate of progression to AIDS, $\gamma_i(t)$, and decreases according to the death rate, $\Lambda_i(t)$. The death rate depends on the distribution of initial diagnoses. Let M_{ik} be the probability of being diagnosed with the k^{th} AIDS type and $d_k(t|s)$ be the density function of death at time t given diagnosis at s for the k^{th} AIDS type. With this notation, the death rate is defined as:

$$\Lambda_i(t) = \sum_k M_{ik} \int_{T_0}^{t} \gamma_i(s)\, I_i(s)\, d_k(t|s)\, ds\, A_i(t)$$

where

$\gamma_i(s)\, I_i(s)$ is the number of new persons with AIDS in risk group i at time s.

4. AIDS Deaths

$$\frac{\partial DA_i(t)}{\partial t} = \Lambda_i(t)\, A_i(t) \qquad (4)$$

5. Non-AIDS HIV Deaths

$$\frac{\partial DI_i(t)}{\partial t} = B_i(t)\, I_i(t) \qquad (5)$$

AIDS deaths and non-AIDS HIV deaths depend on their respective death rates $\Lambda_i(t)$ and $B_i(t)$.

6. New Infections (Homogeneous Mixing)

If $C_i(t)$ is the average number of contacts per partner (sexual or needle sharing) for a susceptible in the i^{th} risk group, $P_i(t)$ is the rate of partner acquisition for the i^{th} group, and

$$\alpha_i(t) = C_i(t)\, P_i(t)$$

then $\alpha_i(t)$ represents the rate of contacts for an individual in the i^{th} group.

The proportion of total contacts that occur with members of the j^{th} risk group is $\beta_j(t)$. Under the homogeneous mixing assumption, $\beta_j(t)$ depends on the ratio of the size of the j^{th} group to the total, i.e.,

$$\beta_j(t) = \frac{N_j(t)}{\sum_k N_k(t)}$$

where

$$N_j(t) = S_j(t) + I_j(t) + A_j(t).$$

The product $\alpha_i(t)\,\beta_j(t)$ represents the rate of contacts with members of the j^{th} risk group for an individual in the i^{th} group.

Under the assumption of homogeneous mixing, the probability that a given contact is with an infected member of the j^{th} group is:

$$q_j(t) = \frac{I_j(t) + A_j(t)}{N_j(t)}$$

Define H_{ij} as the probability that a given contact between a susceptible in the i^{th} group and an infective in the j^{th} group produces an HIV infection. Table 2 identifies the composition of the $H = \{H_{ij}\}$ matrix; each element represents infectivity in terms of the mode of transmission between the corresponding pairs of risk groups as defined in table 1.

Thus the rate of new infections per susceptible at time t is:

$$\lambda_i(t) = \alpha_i(t) \sum_j \beta_j(t)\, q_j(t)\, H_{ij}$$

LONGITUDINAL STUDIES

This section contains a review of the studies that have provided information used in model implementation. Specifically, these studies are the sources of parameter values and assumption justifications.

Table 2. Transmitter to recipient infectivity probability matrix (H_{ij})

			TRANSMITTERS							
			HM 1	HMI 2	BM 3	BMI 4	OM 5	OMI 6	FM 7	FMI 8
	HM	1	h_1	h_1	h_1	h_1	0	0	0	0
R	HMI	2	h_1	h_5	h_1	h_5	0	h_2	0	h_2
E										
C	BM	3	h_1	h_1	h_1	h_1	0	0	h_3	h_3
I										
P	BMI	4	h_1	h_5	h_1	h_5	0	h_2	h_3	h_6
I										
E	OM	5	0	0	0	0	0	0	h_3	h_3
N										
T	OMI	6	0	h_2	0	h_2	0	h_2	h_3	h_6
S										
	FM	7	0	0	h_4	h_4	h_4	h_4	0	0
	FMI	8	0	h_2	h_4	h_7	h_4	h_7	0	h_2

where

h_1 = male to male sexual infectivity

h_2 = shared needle infectivity

h_3 = female to male sexual infectivity

h_4 = male to female sexual infectivity

h_5= average of male to male sexual infectivity and shared needle infectivity

h_6 = average of female to male sexual infectivity and shared needle infectivity

h_7 = average of male to female sexual infectivity and shared needle infectivity

Published Results

1. ***Survival with AIDS***

Rothenberg and colleagues (1987) reviewed the survival histories of 5,833 persons with AIDS. Their results indicated that type of AIDS manifestation is a major influence on survival time.

2. ***Type of AIDS***

The distribution of cases by type of AIDS manifestation (initial diagnosis) was estimated from the CDC AIDS surveillance data analyzed by risk group.

3. ***Risk Group Distribution***

The distribution of HIV infecteds by risk group was assumed equal to the distribution of AIDS by risk group, estimated from the CDC AIDS surveillance.

4. ***The Size of the AIDS At-Risk Population***

Data based on a national sample were used to obtain an estimate of the number of U.S. citizens practicing behavior that placed them at risk for AIDS (Wells et al. 1989).

5. ***Incubation Function***

The distribution of time from infection to diagnosis with AIDS was based on the results of Bacchetti and Moss (1989).

6. ***Infectivity Probabilities***

The probability of infection given high risk was based on a number of studies, including:

male-to-male sexual contact (Peterman et al. 1988)
female-to-male sexual contact (Wiley 1987)

male-to-female sexual contact (Wiley 1989)
shared needle contact (D.C. Des Jarlais, personal communication, 1989).

7. *The Number of Non-AIDS HIV Deaths*

The distribution of non-AIDS HIV deaths was based on the initial study of Stoneburner, Des Jarlais, et al. (1988) subsequently refined by Des Jarlais (1989).

8. *Persons With AIDS*

The estimated number of persons with AIDS was based on CDC's AIDS surveillance data with adjustment for underreporting and late reporting. The extent of these biases was examined in two studies (U.S. General Accounting Office 1989; Hamill et al. 1989).

Studies Not Yet Published

1. *NIAID Clinical Trials*

The National Institute on Allergy and Infectious Diseases is sponsoring a study to examine the efficacy of a number of different antiviral drugs proposed for the treatment of AIDS. Preliminary results indicate that AZT dramatically slows the rate of progression to AIDS in persons with T4 counts below 500. As results of this study become more available, an incubation function for treated individuals may be characterized and incorporated into the model.

2. *The Dannenburg Study*

The objective of this study is to assess cause-specific mortality among civilian applicants excluded from military service due to the presence of HIV. A case-control study is being performed with cases defined as applicants to the military service infected with HIV and controls defined as applicants excluded from service for non-HIV medical conditions. It is anticipated that this study could identify the number of AIDS cases not reported to CDC and the non-AIDS HIV death rates in cases not fulfilling the CDC definition. This would provide better accuracy in AIDS incidence estimates.

3. *NIDA Outreach Program*

The National AIDS Demonstration Research (NADR) program offers a wide range of interventions intended to reduce or eliminate high-risk behaviors involving needle sharing, polydrug abuse, and unsafe sexual activities. These comprehensive, individualized programs involve a structured pattern of research interventions involving education, individual counseling, skills development, HIV testing, and small group professional and peer-led support counseling. The NADR programs all offer referrals to community resources as well.

Located in 29 cities with large intravenous drug user (IVDU) populations, the NADR programs are structured around community outreach. In each of the NADR target populations, in areas of known drug trafficking and drug abuse, trained indigenous outreach workers contact individuals on the streets, in criminal justice facilities, in shelters, in emergency rooms, and in other institutional settings. Once a contact has been made, the subject is screened for program eligibility. To be eligible, a subject must be (1) an active IV drug user who has not had treatment in the past 30 days, (2) the sexual partner (during the past 6 months) of an active drug abuser, or (3) a prostitute.

Once accepted into the program, the participant is administered an AIDS Initial Assessment questionnaire. The AIDS Follow-up Assessment questionnaire is administered 6 months later. At both times the individual is offered the opportunity to have an HIV blood screening. Data from the AIDS Initial Assessment questionnaire, the AIDS Follow-up Assessment questionnaire, and HIV blood screenings are linked using a unique, anonymous identifier and stored in a central data base that is being developed under an ongoing NIDA contract.

CRITIQUE

Model Characteristics

The RTI model adopts an objective approach for portraying transmission between risk group pairs. Transmission is based solely on the sizes of groups,

seroprevalence of transmitters, and the model of transmission between groups. A single parameter is estimated for each risk group within each year. This parameter (contact rate) is interpreted as the average number of total contacts per year. The set of parameters for all risk groups is estimated by the RTI model so as to minimize the difference between the AIDS incidence series produced by the model and CDC's AIDS incidence data, adjusted for reporting biases.

One potential limitation of the model is that the homogeneous random mixing model for representing contacts between risk groups may be overly simplistic. The true nature of behavior affecting contacts is probably more complex. Before a more realistic representation can be incorporated into the model, for example, one based on partnership formation, further information is needed regarding the following parameters within risk groups (Dietz 1989; Anderson and May 1988):

- the average of needle sharing contacts per partner
- the average number of partners per susceptible
- the distribution (degree and extent) of behaviors that determine infectivity per episode
- the determinants of those behaviors

Kaplan (1989) describes some alternative models that use these data.

In the RTI model, contact rates that explain AIDS incidence for a given incubation function are estimated. By comparison, in the backward calculation model (Gail and Brookmeyer 1988), HIV AIDS incidence data are used to "back calculate" HIV incidence, which, with an assumed incubation function, are used to estimate future AIDS incidence. The accuracy of results from both models greatly depends on the accuracy of the AIDS data. However, significant differences exist between the two approaches. For example, back-calculation models estimate incidence of only those HIV infecteds who eventually develop AIDS: These models ignore the population

of infecteds who die from competing risks before ever progressing to AIDS. The RTI model, on the other hand, has the ability to estimate all infecteds by use of the attrition rate and NAHD death rate. With either of these rates set to a positive number, non-AIDS infecteds dying from other risks and infecteds dying from HIV-related illnesses can be estimated.

Natural History Concerns

A number of prominent issues are imperfectly understood and as a result may be incorrectly represented in current models. This section enumerates these major concerns.

1. *Transmission Infectivity*

How does infectivity vary during the course of the infection? Is infectivity related to antigen production? What effect do antivirals have on infectivity? In the RTI model infectivity is assumed to be constant, and antiviral activity is ignored.

2. *Behavior*

Do individuals continue to practice high-risk behavior during the AIDS stage of the infection? What proportion of needle sharing contacts involve clean needles? What proportion of sexual contacts involve condoms? What is the distribution of partnership associated with needle sharing and sexual behaviors? What is the distribution of contacts per partner by risk group (i.e., by mode of transmission)?

3. *Disease Incubation*

The RTI model uses an incubation function that is based on the published results of Bacchetti and Moss (1989). The Bacchetti and Moss function is based on 10 years of natural history, but the disease can incubate much longer than 10 years. What does the tail of the distribution look like? Does it have a constant or increasing hazard property? What population segments does the Bacchetti and Moss incubation function represent? It is based on a cohort of homosexual men that live in San Francisco—sexually active men

with a high incidence of antiviral use (e.g., AZT). Does the Bacchetti and Moss function accurately portray disease progression in the early stages of the epidemic? The IVDU population segment? The nontreated component of the HIV infected population?

Representation of progression to AIDS in IVDUs is a significant issue since the proportion of AIDS cases associated with IVDUs is increasing and smaller proportions of IVDUs are being treated with antivirals. We hope to test the hypothesis that IVDUs progress to AIDS faster than non-IVDUs by using the RTI model to estimate contact rates for New York and San Francisco for the Bacchetti and Moss incubation function, which is based on three cohorts of gay men. (We will be finding out if the progression rates differ between the two groups.) We would expect to see more violations of internal validity checks in the model for New York (which has a much higher proportion of IVDUs) than for San Francisco.

A related incubation issue is associated with HIV infecteds with opportunistic infections that do not fit the CDC definition of AIDS. Many of these infecteds, particularly IVDUs, die before meeting the CDC case definition. We refer to them as non-AIDS HIV deaths (NAHDs). What is the NAHD incubation function? If CDC AIDS is the endpoint used by the Bacchetti and Moss procedures, what is the appropriate endpoint in the NAHD situation? What are the determinants of the NAHD rate? How have changes in the AIDS definition affected the NAHD rate?

DISCUSSION

The epidemiology of AIDS is changing rapidly. This is evidenced by a number of factors that include

- changing distribution of AIDS cases by risk group over time
- the influence of antivirals on disease progression
- the number of HIV infectives who are being treated with antivirals

- behavior changes in risky behavior participants including the utilization of bleach and condoms

Because of the long latency period of AIDS, it is important to understand as much as possible about the natural history of the disease as rapidly as possible. We may never be able to characterize the early stages of the disease because (1) our knowledge of disease traits in those stages is not sufficiently supported by well-designed natural history studies, and (2) the characteristics of the disease during those stages no longer exist. This is best illustrated by the incubation function studies. As discussed above, there has been a high rate of rate of antiviral use in the cohort studies that are the basis for the assessment of the rate of progression to AIDS. As a result, the rate of progression data reported by Bacchetti and Moss may not be appropriate for portraying rates of progression in the early stages of AIDS. We are investigating other methods that may be used to assess progression to disease during those stages.

In summary, modelers depend on natural history studies to foster a clearer understanding of the changes in disease characteristics. Without this understanding of past characteristics, confidence in the future projections of the epidemic is undermined.

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Printed 1991