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A Larger Spectrum of Severe HIV-1–Related Disease in Intravenous Drug Users in New York City

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Increasing mortality in intravenous (IV) drug users not reported to surveillance as acquired immunodeficiency syndrome (AIDS) has occurred in New York City coincident with the AIDS epidemic. From 1981 to 1986, narcotics-related deaths increased on average 32% per year from 492 in 1981 to 1996 in 1986. This increase included deaths from AIDS increasing from 0 to 905 and deaths from other causes, many of which were infectious diseases, increasing from 492 to 1091. Investigations of these deaths suggest a causal association with human immunodeficiency virus (HIV) infection. These deaths may represent a spectrum of HIV-related disease that has not been identified through AIDS surveillance and has resulted in a large underestimation of the impact of AIDS on IV drug users and blacks and Hispanics.

SURVEILLANCE OF ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) in the United States has depended on a surveillance case definition that defined AIDS cases as the most severe manifestations of infection with human immunodeficiency virus (HIV) type 1 (*1, 2*). This definition was initially based on the unusual occurrence of certain opportunistic infections and rare malignancies that were predictive of defects in cell-mediated immunity. These conditions were first recognized in 1981 to occur largely in homosexual men (*3–7*). This case definition has been modified as more was learned about the spectrum of severe HIV-related morbidity (*8, 9*). The AIDS surveillance systems in New York City (NYC) and elsewhere have been highly accurate in identifying diagnosed AIDS cases (*10, 11*). The information surveillance provides is important in identifying populations at highest risk for AIDS and at greatest need for prevention and health-care services and in providing data needed for projections of the future impact of AIDS.

Large increases in deaths among intravenous (IV) drug users not reported to have AIDS have occurred in NYC simultaneously with the epidemic of HIV infection. These excess deaths may represent a manifestation of severe HIV-related morbidity and resulting mortality that has not been recognized through AIDS surveillance. We describe the epidemiologic investigation of this increased mortality.

The investigation included a review of vital statistics and AIDS surveillance registry data, a medical record review of deaths among narcotic users in 1985, a histopathologic examination of lung tissue from narcotic users who died of pneumonia, and a determination of mortality in a cohort of IV drug users.

We reviewed the 7884 deaths among NYC residents that occurred between 1978 and 1986 and reported through May 1987 that had been coded as "narcotics-related." For all deaths occurring in NYC, a death certificate must be filed with the NYC Department of Health (NYCDOH). On the basis of conditions listed on the certificate, an underlying cause of death is assigned in accordance with the International Classification of Diseases, eighth and ninth revision (ICD-8 and ICD-9) (*12*). If narcotic use is listed on the certificate it is indicated with a specific code (code "9" narcotics-related). Decedents who are suspected of using illicit narcotics (almost all IV) are by law reportable to the Office of the Chief Medical Examiner (OCME), which investigates the cause of death (about half receive autopsies). After confirmation, the OCME will list narcotic use as a cause of death on the certificate. Of the 7884 narcotics-related deaths, 1803 were considered as "AIDS" (primarily ICD codes 279.1, 279.3, and 136.3). The data from the death certificates were then used to classify the 6081 "non-AIDS" deaths into the clinical categories in Table 1.

In order to determine the number of narcotics-related deaths reported as AIDS cases, all narcotics-related deaths occurring from 1982 to 1986 were matched to the NYCDOH AIDS surveillance registry (*13*)

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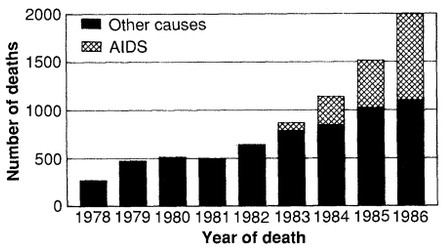

Fig. 1. Narcotics-related deaths in New York City, 1978 to 1986.

by name and birth date.

Medical records of narcotics-related deaths in 1985 in which the underlying cause of death was recorded as pneumonia, endocarditis, or tuberculosis were reviewed at six NYC hospitals, and clinical and laboratory data were collected. HIV-related conditions not meeting the AIDS surveillance case definition were defined as those with findings of oral thrush, or lymphadenopathy combined with weight loss or chronic diarrhea.

Formalin-fixed lung tissue was retrieved from the OCME on all available (84 of 115) persons aged 25 to 44 who died from narcotics-related unspecified pneumonia from 1980 through June 1983. Of the 84 decedents, 72 (86%) died in 1982 or 1983. Slides of tissue were stained by standard techniques, including those appropriate for AIDS-related pathogens, and examined microscopically.

The cumulative incidence of deaths from all causes through 1987 was determined among a cohort of 497 IV drug users who were enrolled from 1984 through 1986 in a study of risk factors for HIV infection and AIDS (*14*), which included testing for HIV-1 antibody by enzyme immunoassay (EIA) and Western blot. Persons in this cohort were matched with the NYCDOH vital statistics registry by name, date of birth, and other identifiers. The medical charts of all deaths were reviewed in order to verify the cause of death. Statistical differences in mortality in this cohort by HIV antibody status were compared.

The data from these various sources all indicated an increase in mortality among IV drug users in New York that is not captured by surveillance definition AIDS but is likely to be related to HIV infection. The annual number of narcotics-related deaths increased from 263 in 1978 to an average of 488 deaths per year from 1979 through 1981 (Fig. 1). Then from 1982 to 1986, coincident with increasing AIDS fatalities, narcotics-related deaths increased on average 32% per year from 492 in 1981 to 1996 in 1986. Narcotics-related deaths from AIDS increased from 11 in 1982 to 905 in 1986, whereas deaths from other causes increased from 633 to 1091.

The cause-specific distribution of the narcotics-related deaths in which AIDS was not recorded is shown in Table 1. Causes that account for a large proportion of the increase from 1980 to 1986 include pneumonia, endocarditis, and tuberculosis. Mortality due to various other causes showed similar increases, with the important exception of deaths classified as drug-related (generally overdose deaths) that remained essentially unchanged.

Analysis of the demographic characteristics of the 6157 narcotics-related deaths that occurred from 1982 to 1986, concurrent with the epidemic of AIDS, revealed that 15% were in whites, 53% in blacks, 25% in Hispanic, and 7% in others. Seventy-seven percent of deaths were in males, and the median age at death was 37 years.

Table 1. Causes of non-AIDS narcotics-related deaths in New York City residents, 1978 to 1986 (*33*).

Cause	Year of death								
	1978	1979	1980	1981	1982	1983	1984	1985	1986
Unspecified pneumonia	13	16	32	59	84	158	206	234	241
Liver	27	62	70	83	119	123	121	157	172
Drug-related	162	234	280	213	240	272	199	268	247
Endocarditis	7	28	29	33	44	59	88	81	113
Cardiovascular	3	16	16	8	24	22	37	45	41
Sepsis, mycoses	5	7	6	8	12	15	27	44	41
Tuberculosis	1	0	3	9	13	15	20	37	32
Gastrointestinal	2	7	3	7	9	12	26	31	36
Other respiratory	1	5	5	9	14	6	8	14	23
Neoplasms	4	0	1	4	7	7	6	9	21
Chronic renal failure	1	2	3	8	6	4	11	27	19
Intracerebral hemorrhage	2	4	2	6	4	13	13	12	15
Other central nervous system	2	2	3	5	10	10	7	10	13
Pneumococcal pneumonia	0	0	0	1	3	5	10	4	11
Injuries	9	6	8	7	7	4	8	0	11
Other genitourinary	0	0	4	6	7	17	11	7	9
Meningitis	1	1	2	1	3	5	3	9	8
All others	23	76	39	25	27	32	36	25	38
Total	263	466	506	492	633	779	837	1014	1091

Table 2. Cause of non-AIDS deaths (instances where AIDS or a condition that would meet the AIDS case definition are not listed on the death certificate or in the medical records) in 485 IV drug users enrolled in a study of risk factors for AIDS, New York City, 1984 to 1987.

Cause of death	HIV-positive (n = 230)	HIV-negative (n = 255)*
Infectious		
Pneumonia	4	0
Endocarditis	1	0
Tuberculosis	1	0
Total	6	0†
Noninfectious		
Gastrointestinal bleeding	1	1
Cancer	2	1
Homicide	2	0
Drug overdose	1	2
Drug-related	0	3
Total	6	7

*Includes ten persons with inconclusive HIV antibody results. †Fisher-Irwin exact test, infectious versus noninfectious (P = 0.034).

Medical records were reviewed of 21% (50/234) of all narcotics-related pneumonia deaths; 27% (22/81) of endocarditis deaths; and 43% (16/37) of tuberculosis deaths. Findings suggestive of infection with HIV were noted in 44% (22/50) of the pneumonia deaths, 32% (7/22) of the endocarditis deaths, and in 69% (11/16) of the tuberculosis deaths. Thus, for 46% of these deaths, clinical findings were consistent with HIV infection or related immunosuppression. Of the 22 decedents with pneumonia who had evidence of HIV-related disease, 7 had positive cultures for bacterial pathogens.

The microscopic findings of the lung tissue specimens from 84 decedents with pneumonia revealed pulmonary edema in 48 (57%), acute pneumonitis in 31 (37%), diffuse alveolar damage in 5 (6%), chronic interstitial pneumonia in 2 (2%), and pneumocystosis in only 7 (8%).

In the cohort of 497 IV drug users, there were 31 (6%) known deaths including 12 with AIDS as the underlying cause of death. HIV infection was significantly associated with death from infectious causes not recognized as AIDS; four of the six deaths from infectious causes were due to pneumonia (Table 2). There was no statistically significant difference in incidence of any of the noninfectious causes of deaths by HIV antibody status.

Of 6157 narcotics-related deaths reported from 1982 to 1986, 1197 (20%), had also been reported as AIDS cases to the surveillance registry. Of the AIDS cases, 1046 (87%) had AIDS coded as the underlying cause of death. The distribution by cause of

death of the remaining 13% (151/1197) is as follows: unspecified or specified pneumonia, 29; endocarditis, 5; tuberculosis, 5; chronic liver disease, 15; unspecified drug use, 44; and various other causes, 53.

Coincident with the AIDS epidemic in NYC have been large increases in deaths among IV drug users that have not been recognized as AIDS. The frequent finding of suspected HIV-related conditions associated with AIDS (*15*), and HIV-related immunosuppression (*16, 17*), among a sample of narcotics-related pneumonia, endocarditis, and tuberculosis deaths, suggest that HIV infection could be contributing to this increased mortality. Further evidence of this relation is the significant association of HIV infection with non-AIDS deaths from infectious causes among the cohort of IV drug users.

It is unlikely that these increases in non-AIDS narcotics-related deaths are explained by increases in the numbers of IV drug users in NYC. The estimated population of IV drug users is believed to have remained stable during the period of the AIDS epidemic (*14*). Nor is it likely that improved recognition and reporting of deaths in IV drug users to the medical examiner would account for an increase of this magnitude.

Bacterial infections manifested by pneumonia, sepsis, endocarditis, and tuberculosis have been associated with HIV infection (*19–22*). This is supported by evidence that HIV-induced immunosuppression affects both cellular and humoral immunity, two vital components of the host response against bacterial infections and tuberculosis (*23*). However, it is not clear whether the occurrence of bacterial infections depends on the degree of HIV-related immunosuppression. Our findings of bacterial pathogens as etiologic agents of the pneumonia and endocarditis deaths with evidence of HIV-related disease suggests that HIV-induced immunosuppression may be a predictor of a poor outcome in IV drug users with bacterial infections.

The etiologies of many of the pneumonia and other deaths are not clear from our investigation. It is possible that some of these deaths were from either undiagnosed infections that would qualify as AIDS if they had more vigorous diagnostic evaluations or from diagnosed AIDS cases that were simply not identified by the AIDS surveillance system. Many of the medical charts of the pneumonia deaths did not have enough data to determine the etiologic agent, and in some instances the patient was admitted and died before a complete diagnostic evaluation could be performed. The lung tissue specimens were selected for forensic purposes and may not have been appropriately sampled for the identification of the etiologic agent; however, the findings indicated that most (92%) of these deaths probably were not due to *Pneumocystis carinii* pneumonia, the primary respiratory manifestation of AIDS (*24*). Thus it is unlikely that these pneumonia deaths were simply misdiagnosed cases of AIDS.

The increases in other causes of narcotics-related non-AIDS deaths may represent complications of HIV-related infectious diseases or primary HIV-related disease. The deaths classified as cardiovascular and chronic renal failure may represent AIDS-associated cardiac or renal disease that have been described (*25, 26*). Other factors that may be contributing to increasing mortality among parenteral drug users are aging of the large cohort of persons who began drug injection in the late 1960s, cumulative effects of heavy alcohol use, and increasing cocaine and heroin use during the last 10 years.

Similar patterns of non-AIDS mortality have not been observed among male homosexuals in NYC (*27*). Preliminary analysis of mortality among a cohort of several thousand homosexual or bisexual men who had participated in studies in NYC of the epidemiology of hepatitis B virus or in trials of hepatitis B vaccine (*28, 29*) revealed large numbers of AIDS deaths but few deaths from other infectious diseases (*30*).

Explanations for the differential mortality between IV drug users and primarily white middle class homosexual and bisexual men include the following: first, there is a much higher likelihood of exposure to relevant pathogens among IV drug users. For example, both tuberculosis and IV drug use in NYC are primarily found among lower socioeconomic status minority groups (*31*). Second, IV drug users engage in a variety of behaviors that may serve as cofactors for the development of serious infections related to humoral immunity, such as heavy alcohol use. This was associated with nonfatal cases of pneumonia in our cohort (*32*). Finally, unlike middle class homosexual and bisexual men, IV drug users typically receive inadequate primary health care and often delay medical treatment until an illness is severe enough to prevent them from successfully seeking drugs.

The effect that these postulated HIV-related deaths would have on NYC AIDS surveillance data was estimated by comparing the observed narcotics-related deaths for 1982 to 1986 with those that would be expected independent of the AIDS epidemic and those that were reported to AIDS surveillance. If one assumes a constant number of IV drug users from 1982 to 1986 and discounts the effect of the AIDS epidemic, the average annual narcotics-related mortality for the years 1979 to 1981 (488 deaths per year) crudely represents the expected annual narcotics-related deaths for 1982 to 1986. That number would be 2440 during 1982 to 1986. Instead there was a cumulative number of 6157 narcotics-related deaths, 1197 of which were reported as AIDS cases. Subtracting the expected 2440 deaths and the 1197 deaths reported as AIDS cases from the 6157 actual deaths leaves 2520 excess deaths that we suggest are HIV-related but not yet recognized as AIDS. If these 2520 excess deaths were added to the 4998 deaths (2715 in gay or bisexual men, 1873 in IV drug users, and 410 in other risk groups) that were reported to the AIDS surveillance registry from 1982 to 1986, the AIDS case fatality rate would be 50% (2520/4998) greater overall, and 134% (2520/1873) greater among IV drug users. Because only 63% of AIDS deaths with identified IV drug use reported to surveillance through 1984 were coded as narcotics-related (*27*), the actual underestimation of the AIDS epidemic may be even greater.

Coincident with the AIDS epidemic in New York City there have been large increases in mortality from a variety of infections and other causes among IV drug users. There are supporting data for HIV infection as a causal factor in these deaths. More research is needed to better define the precise causes of these deaths in order to determine to what extent the national AIDS case definition needs to be expanded and to determine whether there are infectious diseases among IV drug users whose more precise identification and treatment may lead to improved patient survival. It is also important to learn why these deaths appear to occur more commonly among IV drug users who are largely black and Hispanic and not among largely white homosexual and bisexual men. It appears that AIDS surveillance data may have greatly underestimated HIV-related mortality in NYC; this has caused underestimation of the impact of AIDS on IV drug users and blacks and Hispanics.

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Infection and Replication of HIV-1 in Purified Progenitor Cells of Normal Human Bone Marrow

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Myeloid progenitor cells were highly purified from normal human bone marrow by positive immunoselection with high-affinity monoclonal antibodies linked to magnetic beads and were successfully infected in vitro with the human immunodeficiency virus type 1 (HIV-1). From 99 to 100 percent pure bone marrow cells expressing the CD34 phenotypic marker were obtained. These cells were devoid of mature myeloid or T cell surface and intracellular markers as analyzed by immunohistochemical staining and flow cytometry. HIV-1 particles were detected by supernatant reverse transcriptase activity and transmission electron microscopy 40 to 60 days after infection. Viral particles were predominantly observed assembling and accumulating from within intracellular membranes, while phenotypically the cells were observed to have differentiated into CD4$^+$ monocytes. These studies have important implications in understanding the pathogenesis of HIV-1 as well as the possible cause of certain of the observed hematologic abnormalities in HIV-1 infection. They also indicate that the bone marrow may serve as a potentially important reservoir of HIV-1 in the body.

A SPECTRUM OF HEMATOLOGIC ABnormalities have been described in patients with the acquired immunodeficiency syndrome (AIDS) and human immunodeficiency virus type 1 (HIV-1)–related disorders. These have included peripheral blood cytopenias of all cell types (*1*) as well as bone marrow abnormalities such as myelodysplasia (*2–4*). Indirect evidence of infection of bone marrow cells has been reported and proposed as a potential explanation for these abnormalities. Busch *et al.* (*5*) detected the presence of HIV-1 mRNA in myelocytes and monomyelocytes from bone marrow of patients with AIDS using in situ hybridization, suggesting that myeloid precursors might be infected. Donahue *et al.* (*6*) reported that immune mediated mechanisms might be responsible for the ineffective hematopoiesis seen in patients with AIDS and AIDS-related complex (ARC). They found that antibodies to the envelope glycoprotein (gp120) of HIV-1 could suppress granulocyte-macrophage colony stimulating factor–dependent colony formation by low density, nonadherent bone marrow cells from HIV-1–infected individuals but not from normal controls. They postulated that antibody to gp120 recognized this virus-encoded protein expressed on the surface of HIV-1–infected progenitor cells, but not on normal cells, and directly or indirectly blocked their growth. In the absence of antibody to gp120, the proliferative potential of the cells was not grossly altered, indicating that HIV-1 may not be directly cytotoxic to the myeloid precursors. This raises the possibility that the bone marrow may serve as a reservoir for HIV-1 in the body.

The ability to study directly the hypothesis that HIV-1 can infect myeloid progenitor cells has been hampered by the difficulty of obtaining these cells in highly purified suspensions devoid of contaminating cells known to be susceptible targets of HIV-1, such as CD4 lymphocytes (*7*) and mature monocytes (*8*). In the present study we examined virtually pure preparations of normal human bone marrow cells expressing the CD34 antigen, which were obtained with a novel positive immunoselection procedure. This small subset of bone marrow cells (0.5 to 2%) is highly enriched in hematopoietic progenitors of all lineages (*9*,

Table 1. Phenotypic profile of fractionated bone marrow cells. Red cells were lysed in buffered ammonium chloride solution. A fraction of Fc receptor bearing cells was magnetically depleted by adherence to preformed human and mouse immune complexes coupled to BioMag beads (Advanced Magnetics). Positive immunoselection was performed with K6.1 (IgG2a) antibody crosslinked onto Dynabeads M-450 (Dynal), and cells were recovered by cleaving the antibody-bead linkage. Antibodies were purchased from Becton Dickinson or Coulter. These were either directly conjugated with fluorescein or phycoerythrin, or if they were of the IgG1 or IgM isotypes were detected with conjugated isotype-specific secondary antibodies (Fisher Biotech). Negative controls were matched for isotype, mode of conjugation, and source. Cells were analyzed on an Ortho Cytofluorograf. Cells that showed less than 1% positivity were considered not detectable (ND). Some additional phenotypic properties of the CD34$^+$ cells have been reported (*11*, *20*).

Monoclonal antibody	Percent positive
Myeloid	
CD34 (MY10)	99
CD13 (MY7)	75
CD33 (MY4)	50
CD11b (M01, CR3)	ND
CD14 (M02, Leu-M3)	ND
T lymphocyte	
CD3 (T3, Leu-4)	ND
CD4 (T4, Leu-3)	ND
CD5 (Leu-1)	ND
CD8 (T8, Leu-2)	ND
Null lymphocyte	
CD16 (Leu-11a)	ND
Class II MHC	
Dr	85–90

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