AIDS COMMENTARY

Injection Drug Use and Human Immunodeficiency Virus Infection

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In this paper we discuss the epidemiology and natural history of human immunodeficiency virus (HIV) infection in users of injection drugs. Use of injection drugs plays a central role in the HIV infection/AIDS epidemic in the United States, Europe, and many parts of the developing world. The significance of this role has been underappreciated until quite recently because of a number of factors. One factor has been systematic, albeit inadvertent, underreporting of cases of HIV disease and AIDS in drug injectors as a consequence of the initially narrow surveillance case definition for AIDS. A measure of this phenomenon has been the disproportionately larger increment of new cases in this population with each successive revision of the Centers for Disease Control and Prevention's surveillance case definition for AIDS. Other reasons for the underappreciation of the magnitude and consequences of HIV infection and AIDS in injection drug users include the lack of necessary diagnostic facilities in the institutions where drug users are often treated, high mortality rates among HIV-infected drug users for whom a diagnosis of AIDS has not yet been made, the severe marginalization of this population and its lack of advocates, and the localization of the initial epidemic in this population to certain geographic areas.

Introduction

Use of injection drugs plays a central role in the HIV infection/AIDS epidemic in the United States, Europe, and many parts of the developing world. The significance of this role has been underappreciated until quite recently because of a number of factors. One of these factors has been systematic, albeit inadvertent, underreporting of cases of HIV infection and AIDS in drug injectors as a consequence of the initially narrow surveillance case definition for AIDS. A measure of this phenomenon has been the disproportionately larger increment of new cases in this population with each successive revision of the surveillance case definition for AIDS of the Centers for Disease Control and Prevention (CDC) [1–5].

The cumulative number of AIDS cases officially attributed to drug injection alone in the United States through December 993 was 87,259, ~24% of the total number of reported cases (increasing to 110,619, or 26%, when men who had sex with men who were also injection drug users were included) [6]. The proportion of AIDS cases attributed to injection drug use alone has risen annually from 17% in 1982 to 28% in 1993 [6] (figure 1). In addition, the proportion of new AIDS cases in the northeastern United States that are attributable to injection drug use has exceeded 50% since the late 1980s [4].

Injection drug users figure indirectly in an even greater proportion of the total number of AIDS cases, since this population is the major vehicle for transmitting HIV infection to heterosexual adults who do not inject drugs and to children. For instance, 66% of women with AIDS attributed to heterosexual contact were sex partners of drug injectors and 64% of children with AIDS had mothers who were drug injectors or sex partners of injectors [6]. Thus, the total proportion of AIDS cases related to drug injection in the United States exceeds 33%. Finally, injection drug use has contributed substantially to the mortality associated with the HIV infection/AIDS epidemic in the United States. In cities in the United States where drug injection is common, particularly in the Northeast, HIV disease and AIDS constitute the leading cause of death in both young men and women (age, 25–44 years) [7].

In southern Europe, particularly France, Italy, and Spain, drug injection has always been the most common vehicle of transmission in reported cases of AIDS [8–12]. More recently, information from Eastern Europe, notably Poland, indicates impressive rates of injection drug use and HIV infection [13]. Finally, in areas of production and distribution of opiates in Asia and of cocaine in Latin America, large numbers of injection drug users and high, rapidly rising rates of HIV infection have been well documented [12]. For example, Thailand, which had a very low prevalence of HIV infection through most of the 1980s, rapidly became a region with a high prevalence of this infection at the end of that decade, with the seroprevalence among drug injectors in Bangkok

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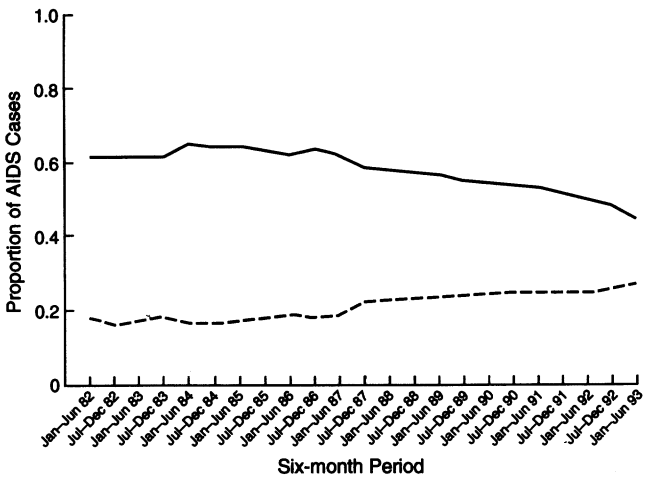

Figure 1. The changing face of the AIDS epidemic in the United States: proportion of AIDS cases in men who had sex with men (non-drug-injecting men only) and injection drug users (individuals not classified as men who had sex with men only) that were reported to the CDC, by semester of diagnosis, 1982 through mid 1993. Solid line = men who had sex with men; dashed line = injection drug users.

rising from 2% to 43% in a single year [14]. Serial surveys of seroprevalence among injection drug users and sex workers in Thailand indicate earlier HIV infection in the former group followed by increasing rates of infection among the latter group, a finding that suggests injection drug use is an initial point of entry of infection into this society [15].

More recent data indicate high prevalences of HIV infection among injection drug users in northern India [16], China [17], Brazil [18], Mexico [19, 20], and Argentina [21, 22]. The epidemiologic importance of HIV infection in drug injectors lies both in the extent that infection has spread in this population and in the complexity of interactions with non-drug-using populations, with the consequent potential to generate new epidemics of HIV infection while the existing ones are still growing.

Transmission

AIDS was recognized in drug injectors as early as 1981 [23], not long after its initial identification as a syndrome in homosexual men [24, 25]. The finding that the same then-unnamed condition affected drug injectors was crucial in early attempts to establish the etiology of the syndrome, as it permitted parallels to be drawn with hepatitis B. The epidemiology of viral hepatitis was already well described [26], and the potential for rapid dissemination of an infectious organism among drug injectors was evident. At the time that the first AIDS cases in the United States were being recognized, the incidence of hepatitis B in this country, which had previously been one-half or less of the case rate of hepatitis A, nearly equaled the incidence of hepatitis A [27]; its recent rapid rise is probably ascribable in large part to the sharing of drug-injecting equipment.

The early epidemiology of HIV infection in drug injectors has been well described [28–32]. The period of the early and mid 1980s was characterized by rapid dissemination of infection among drug injectors, apparently fueled by the appearance of powdered (i.e., injectable) cocaine on city streets [33] with attendant increases in injection frequency [34, 35] and in use of shared injection equipment. Sharing of needles and syringes had been previously practiced among injection drug users [36]. However, this practice became necessary in some parts of the United States and Europe in association with punitive policies and strict enforcement of laws aimed at drug users, including statutes prohibiting the purchase of syringes without a prescription and arrest policies targeting known drug users for violating laws against carrying injection equipment [37].

A tremendous amount of sharing of injection sets (a set generally includes a syringe, a needle, a "cooker" for dissolving powdered drugs [often a bottle cap], cotton for straining the injection solution, and rinse water) must have taken place in some cities during this era. It appears that HIV infection entered the drug-injecting population in New York in the mid 1970s [32] and somewhat later elsewhere. By the middle of the 1980s, the seroprevalence of HIV infection among treatment-program enrollees was >50% in Manhattan [32], 39% in the Bronx [35], 45% in Newark [38], 24.5% in Baltimore [39], and 25% in New Haven [40]. Such a rapid increase in the prevalence of infection would have required an annual incidence of ~8% among injectors. Generating an incidence of 8% from a starting prevalence of HIV infection of 1% would require that each injector share on average >1,660 injections per year (assuming the per-contact probability of transmission to be 0.5%; lower probabilities would require even more shared injections). When prevalence had reached 10%, the average number of shared injections would still have to have been >1,609 per person per year to maintain the rate at which the epidemic was increasing. Since some infection must have been occurring through sexual contact rather than by parenteral transmission, this calculation might be only approximately accurate, but it is indicative of the magnitude of the role of sharing injection equipment in the transmission of HIV infection.

What conditions could have produced this high risk of acquisition of HIV infection associated with the sharing of needles and syringes? A large population of drug injectors already existed, most of them representing a cohort of intravenous heroin users who had begun injecting during a period in the late 1960s when cheap, high-purity heroin was abundant [33]; New York City alone had an estimated 200,000 injectors [41]. Because of the social marginalization consequent to illicit drug use in the United States, most of these injectors were clustered in urban poverty zones, along with the otherwise socially and economically disadvantaged. The

period of rapid growth of methadone programs had ended; methadone treatment for opiate addiction was available for only 10%–20% of drug users [42], i.e., the ratio of treatment "slots" to injectors was no more than 1:5 and sometimes even lower than 1:10, and this rate did not increase after the mid 1970s [43]. Thus, the majority of people who used heroin continued to use it for long periods.

Onto this backdrop of heroin use in a population probably already infected with HIV in some places was grafted a critical new element in the late 1970s and early 1980s: cheap powdered cocaine [33]. Previously known as a recreational drug of the urban and suburban affluent classes, cocaine found new popularity when it was marketed as a street drug to the disadvantaged. In addition to attracting many heroin users, cheap cocaine brought with it a new cohort of first-time injectors; it is now clear that the risk of HIV infection in this cohort was extremely high [39], apparently because these new users, with their habit of injecting drugs at a high frequency, were entering social networks where the prevalence of HIV infection was high. Because the half-life of cocaine is short and the high terminates in dysphoria and a profound craving for more drug [44, 45], cocaine users inject many times per day rather than once daily, which is the pattern of heroin users [31].

A number of elements needed for epidemic spread of infection were thus in place: large numbers of individuals sufficiently habituated who require injection of heroin or cocaine (or both together in a mixture called a *speedball*) one or more times per day; high prevalence of sharing of both drugs and injection paraphernalia contaminated with infected blood; injecting and sharing practices such as booting (blood is drawn up into the syringe to be sure that a vein was entered) and frontloading and backloading (drugs are divided by sequentially passing the liquid drug mixture through two syringes [46–48], thus ensuring that blood is passed from person to person); and laws that make it a crime to carry injection equipment and that ban the sale of needles or syringes without a prescription [37].

However, probably the most important factor from the epidemiologic standpoint was a new cultural phenomenon that arose out of needle sharing in East Coast cities such as New Haven, New York, Newark, Philadelphia, and Baltimore: the shooting gallery [28, 49]. A history of shooting-gallery use is one of the strongest correlates of HIV infection in drug injectors [35]. Since users could not carry drug-injecting equipment ("works") with them for fear of arrest and since use of cocaine is characterized by both urgency and high frequency of injection, the injectors needed a convenient place where they could rent and use injection equipment in relative security. Each needle and syringe set might be used by dozens of individuals in the shooting gallery before the needle was finally too dull and had to be retired. One could hardly imagine a better vehicle for dissemination of bloodborne infection—sequential, anonymous sharing of needles and syringes contaminated with infected blood. The shooting gallery also allowed effective mixing of individuals from different social groups and even geographic areas, which provided for a promiscuity of parenteral contact that sharing exclusively within social networks—apparently the previous predominant mode of drug-use practice [36]—did not provide.

Table 1. Factors associated with prevalent HIV infection in injection drug users.

Factor	Adjusted OR (per unit)*	95% CI	*P* value
Black or Hispanic	4.56	2.65–8.14	<.001
More recent year of last injection	1.24	1.13–1.35	<.001
Higher percentage of injections in shooting galleries	1.49	1.19–1.88	.002
Higher number of sex partners using intravenous drugs	1.24	1.06–1.45	.01
Lower income	1.55	1.10–2.17	.006

NOTE. Data adapted from [35].

* Associations determined by logistic regression. The following units were used for analyzed factors: black or Hispanic background, yes or no; year of last injection, calendar years from 1978 through 1985; percentage of injections in shooting galleries, 0, 25%, 50%, 75%, 100%; number of sex partners using intravenous drugs, 0 to >5; income, <$10,000, $10,000–$20,000, >$20,000.

Thus, the presence of HIV infection in this population can be understood as a subtle and complex interplay of historical developments, personal behavior, social setting, and socioeconomic status. Studies of methadone-program participants illustrated and began to quantify this interplay (table 1). In the Bronx, the prevalence of HIV infection was shown to rise in association with an increasing proportion of injections in shooting galleries, the total number of injections over time, numbers of drug-injecting sexual partners, and decrements in socioeconomic status. Odds ratios shown in table 1 each represent the impact of the given factor on the odds of being HIV-seropositive, holding constant current race and/or ethnicity as well as each of the other factors. Since the odds ratios correspond to the increase in probability of HIV seropositivity for a one-unit change in the given factor, relative to someone with the factor, an injector still shooting drugs in 1985 would have a 4.51-fold $(1.24)^7$ higher odds of seropositivity than would an individual who had stopped injecting in the reference year, 1978. Defining these phenomena has had important ramifications for prevention and policy efforts regarding HIV infection.

How HIV infection spread geographically is far less clear than how it became epidemic within a given city. In a large city like New York, drug injectors are not very mobile, except for those utilizing the fairly heavily traveled route between New York and Puerto Rico [50]. In contrast, injectors in less populous areas must often travel long distances to obtain drugs [51]. Certainly, by the late 1980s, large differ-

Table 2. Factors associated with the reduction of risk for HIV infection in injection drug users.

Education
Self-organization
Drug treatment
Harm reduction
Safer injection
Bleach and cleaning
Exchange of needles and syringes
Purchase of needles and syringes without a prescription

ences in the prevalence of HIV infection among drug injectors in various American and European cities were apparent, although they were not always easily or completely understood in terms of geography. In the United States, rates of HIV infection were highest in the Northeast, a finding that is still true today. Spatial diffusion was obviously an important factor in determining who was infected where, at least in the early stages of the epidemic [52]. For instance, D'Aquila and co-workers [40] showed that the prevalence of HIV infection in substance-abuse treatment programs in Connecticut decreased with increasing highway mileage from New York. A similar phenomenon was noted in New Jersey [38]. However, in Scotland, the cities of Edinburgh and Glasgow have had widely disparate rates of HIV infection despite close geographic proximity [12]. In that country, differences in policy toward injection drug use, most notably in the availability of sterile injection equipment, might have played an additional crucial role [53].

Risk Reduction

By the late 1980s injection behavior had begun to change [54, 55]. Areas in which the prevalence of HIV infection among injectors stayed relatively low into that era did not attain the same high prevalence as, for example, New York and Newark. As a corollary, infection rates have stabilized even in areas with high prevalences [12]. However, these stable seroprevalence rates should not be taken to mean that new infections have ceased to occur but, rather, that HIV-infected injection drug users are dying at the same rates as other users are acquiring new infections.

The epidemiology of the transmission of HIV infection in drug users worldwide remains volatile. High-risk injection behavior appears to have been modified in developed countries—a phenomenon that is now amply documented [56, 57]—but apparently remains of great importance in the growing epidemics in Eastern Europe, Latin America, and Asia. In Europe, the United States, Canada, and Oceania, the change in behavior has likely resulted from several phenomena (table 2). Among these are increasing knowledge and concern about the risk of AIDS in injection drug users [58] and the employment of harm-reduction strategies (harm reduction is based on the view that drug use not be eliminated but that harm to both the individual drug user and society can be reduced by the employment of safer drug-use practices). Injection frequency among many groups has decreased [54, 56], and self-reported use of shooting galleries has largely disappeared [55, 57]. In addition, fewer injectors report sharing needles with strangers, and use of bleach has increased, although its value in reducing the risk of transmission of HIV infection has been questioned [59]. Finally, there has been an increase in the availability of sterile injection equipment in many cities in Europe and North America. By 1993 there were 37 needle and syringe exchanges operating in the United States, one-half of which were legal [37]. These programs had distributed >5.4 million clean injection sets to drug injectors. Needle-exchange programs, while remaining politically controversial, have received consistently positive evaluations in the United States and Europe.

A nationwide evaluation of these programs commissioned by the CDC [37] has concluded that the programs showed no evidence of increasing drug use by program clients or communities, likely decreased rates of high-risk drug-using behavior (but not high-risk sexual behavior), likely prevented substantial numbers of HIV infections, and were cost-effective. We have also concluded that the United States government should repeal the ban on the use of funds for needle-exchange services and should commit substantial funds to both needle-exchange services and research. In addition, we recommend that the laws restricting the availability of sterile syringes should be revoked and that the sale and distribution of syringes by pharmacists should be encouraged [60]. Such a policy has recently been instituted in the state of Connecticut, one of the 11 states in the United States that had previously prohibited the sale of needles and syringes without a prescription [37].

Work by Kaplan and colleagues [61, 62] has persuasively demonstrated that needle exchanges can reduce the transmission of HIV infection in an urban drug-injecting population. Needle exchange reduces the time a needle circulates on the street, thereby reducing the number of people who use that needle. In New Haven, the risk of infection in needle-exchange clients was reduced by an estimated ≥40% [63]. The 95% CI of the current seroconversion rate among needle-exchange clients in New Haven was recently estimated at 0–1.2% per year [64], a low rate supported by observations of incidences of <4% per year among other samples of injection drug users [57, 65–70]. However, whether this low incidence also characterizes the large majority of drug injectors who are not enrolled in longitudinal studies is still open to question.

Several lines of evidence do point to the current generality of the low incidence of HIV infection among injectors in the United States. First, two studies employing sampling schemes that include large numbers of drug injectors who are not currently in treatment programs [71] or not under contin-

uous follow-up [56] are among those reporting low rates of seroconversion. Second, correlates of prevalent HIV infection do not seem to differ much for users who are currently in treatment and those who are not [72], and prevalences of HIV infection at enrollment in a study of opiate users in Philadelphia were similar for users who were in (11%) and out (18%) of treatment [67], even though drug users in these two populations differ in many ways [73]. Treatment-program enrollment is not completely protective, of course: for instance, among injectors enrolled in a methadone program in the Bronx in 1985–1986, >25% reported a history of injecting drugs 100 times per month (primarily cocaine, whose use methadone is not intended to affect) [35]. However, in general, injection rates are diminished among methadone-treatment enrollees [74], and enrollment and retention in methadone programs appear to be associated with reduced risk for HIV infection [67, 75, 76]. In addition, treatment enrollment does permit injectors to be sampled and studied [77].

In an alternate approach, syringes returned to the needle exchange in New Haven were assayed for HIV by use of PCR [78], thus obviating the need to draw blood from individual drug injectors. About two-thirds of street syringes were found to be contaminated with blood containing HIV [79], at a time when <25% of treatment-program enrollees in New Haven were HIV-seropositive [80]. Ninety-two percent of syringes from a sample from a shooting gallery in New Haven were contaminated with HIV [62]. Thus, inferences about the seroprevalence and transmission rate of HIV infection must be cautiously framed, attending to the possible sample specificity of observations in this hard-to-reach population.

It is likely that the injecting population in many communities is close to being saturated with HIV infection, while in others many injectors are still susceptible to infection. Among those injectors who have not been well studied, a great concern is with young or new-onset injectors. A study in Baltimore showed that the prevalence of HIV infection was highest among people who had started injecting most recently [39], a finding that probably represents the riskiness of acculturation to cocaine use in an area where the prevalence of HIV infection is high. In addition, since needle sharing appears to be inversely related to income [35], as is expected in an environment of relative scarcity, younger (and probably poorer) injectors might be most likely to have to share needles and syringes and hence incur the risk of HIV infection.

Although a great deal has been learned about the risk of using injection drugs and about risk reduction, sexual transmission of HIV infection among injection drug users is very poorly understood. Sexual intercourse already appeared to be an important route of transmission among drug injectors by the late 1980s [35, 81, 82]. In a recent analysis of drug-injecting women, those with a history of often trading sex for money or drugs had a threefold higher odds of HIV seropositivity, even when injection-related variables were held constant [83]. Sexual transmission of HIV infection among drug injectors and their non-drug-using partners is likely to be much more difficult to reduce than parenteral spread. Understanding the dynamics of the spread of HIV infection among drug injectors and particularly making projections for the future will be limited if the interrelation of sharing injection equipment and drugs with sexual contacts is not taken into account. Models attempting to do this have been proposed [84] but thus far suffer from a paucity of reliable data on sex-partner choice and change in this population. Since use of injection drugs and heterosexual transmission of HIV infection are so tightly entwined in this society, the need to study such behavior in this population is obvious.

Natural History

In general, HIV infection seems to progress similarly in all adults regardless of the supposed mode of transmission (except for transfusion recipients [85]), i.e., drug injection does *not* appear to confer a different natural history in terms of the rate of progression of HIV disease. However, several distinct characteristics of the natural history of HIV disease in drug injectors are noteworthy.

Incubation period. The distribution of incubation periods for AIDS appears to be essentially identical among drug injectors and men who had sex with men [86, 87], with clinical AIDS (1987 case definition of the CDC [1]) developing in about one-quarter of infected individuals in either group within 7 years of seroconversion [87–92] and in 50% within ~10 years [87, 90–94] (see [95] for review). When the CD4 cell count is held constant, there is no difference in the incidence of clinical AIDS or in the time to diagnosis of AIDS among HIV-infected drug injectors and other groups [96, 97]. Thus, the distribution of rates at which the pathogenesis of HIV infection progresses appears to be the same for drug injectors and other groups.

A caveat regarding such comparisons should be mentioned: these comparisons have been made by use of data from early in the epidemic, as nowhere in the United States or in Europe is the epidemic of HIV infection even 20 years old. In a city where the epidemic is 10 or 12 years old (e.g., New York in the late 1980s or Baltimore or Chicago in 1990 [32, 98]), one-half of the individuals infected in the earliest wave of transmission of HIV infection have not yet been observed to have AIDS, and many infections will have occurred more recently and be less advanced. Further, because HIV seroconversions are so rarely observed, it has been necessary to use prevalent cohorts [99, 100]—individuals who were already HIV-positive at first observation—to study the progression of HIV infection.

As a result, statistical models have been required to overcome potential biases inherent in the study of immature epi-

demics [93, 101] and in the use of prevalent cohorts [99] when they compare the progression of HIV infection across groups. Such models have often employed the CD4 cell count as a marker of time since infection. This procedure has been questioned on theoretical grounds [102, 103], but it appears to be useful in terms of estimating parameters in practice [104–106]. However, if the relation of time since infection (or seroconversion) to CD4 cell count differs between drug injectors and other groups, the similarity of progression rates could be in question. Therefore, it is important that the rates of decline in CD4 cell count have themselves been measured. Two studies, using different statistical models of the nonlinear course of decreased CD4 cell counts in HIV-infected drug injectors prior to the onset of AIDS and antiretroviral therapy, estimated almost identical rates of decline in CD4 cell count: 22 and 23 cells/mm^3 per 6 months, respectively [107, 108]. These rates were lower than those reported in some studies of men who had sex with men [109–111]. Such differences are difficult to explain, given the similarity in incubation period. Most likely, they arise because of differences in the maturity of the epidemic in different samples, since the rate of decreased CD4 cell count changes over the course of infection [107]. In one direct comparison of rates of decreased CD4 cell counts in drug injectors and in men who had sex with men, Galai et al. [97] found no overall difference.

Cofactors of progression. Examination of rates of decline in CD4 cell counts, incidence of AIDS-defining diagnoses, or remaining time free of AIDS can be used to evaluate predictors of more rapid progression of HIV infection. In injection drug users, CD4 cell count and percent, immune activation markers, clinical symptoms, viral phenotype, and certain infections have all been described to predict progression of HIV disease [112–117]. However, immune activation markers such as β_2-microglobulin and neopterin appear to be less consistently predictive of disease progression in injection drug users than they are in other populations with HIV disease [118, 119]. This may be, in part, a function of the effect of active drug use on these markers, independent of HIV infection [120, 121]. In addition, some of the above predictors will prove to be simply markers for longer time since infection [100], but others might be cofactors—independent determinants of the rate of progression to clinical HIV disease. A method for evaluating whether an observed predictor of clinical progression might be a cofactor or not is to assess prospectively its effect on the rate of decline of CD4 cell counts [109]. With the use of these procedures, it appears that pyogenic bacterial infection not only is itself an outcome of HIV-associated disease but also accelerates progression of HIV disease in drug injectors: bacterial infections, which confer a more than twofold increase in the risk of clinical AIDS [114], produce a persistent acceleration of the rate at which the CD4 cell count declines prior to the diagnosis of AIDS [108], even after the current CD4 cell count is held constant.

Other cofactors for the progression of HIV disease for which there is good evidence in general are age and infecting dose [85, 86, 122, 123]. As a result of the presence of substantial numbers of women in longitudinal cohorts of injection drug users, studies of injection drug users have been able to demonstrate that rates of progression to AIDS are the same among men and women [96, 112, 114], although AIDS in women appears to progress to death more rapidly [124], perhaps the result of differential access to medical care. However, there is no question that older age in drug injectors is also related to faster progression to AIDS [86, 124]. Curiously, several studies have demonstrated a survival advantage for injection drug users compared with men who have sex with men after AIDS has been diagnosed [124, 125], although other investigators found lower survival rates among drug users [126, 127].

The issue of the role of infecting dose or repeated exposure to HIV after initial infection remains open. An initial single large parenteral inoculum, as is the case in transfusion-associated disease, appears to result in more rapid progression of disease [85]. However, whether multiple infected inocula, as might be the case in injection drug users, accelerate the progression of HIV disease has not been resolved. Several studies have concluded that continued drug injection is predictive of more rapid progression [128–130], potentially representing a dose effect on the rate of progression, since more injections could be inoculating more virus or more virulent virus. However, other investigators found no effect [114, 131] (see [132] for review).

In preliminary analyses of data from a cohort of HIV-infected injectors in the Bronx, subjects who injected drugs (mostly cocaine) at extremely high frequencies over a long period seemed to be at higher risk of developing AIDS (E. E. Schoenbaum, unpublished data), while HIV infection did not progress more rapidly in cohort members who used crack at similarly high frequencies. This finding, if substantiated, could suggest any of a number of "cofactor" phenomena: there might be a dose effect on the progression of HIV disease, under the assumption that more injections mean more shared injections and hence more HIV-contaminated inoculation; there could be a direct effect of the drugs themselves on enhancing replication of HIV [133, 134]; there could be an immune-related effect of injection of foreign substances (i.e., not the drug itself but filler materials) that interact with HIV; or users who inject at high frequencies might constitute a special group with some other characteristics—nutritional deficiency, greater propensity for bacterial infection, or less access to and adherence with therapies that slow HIV disease —that tend to accelerate their HIV disease. None of these possibilities can as yet be ruled out. Whether the above cofactors or any other putative cofactor can influence the spe-

Table 3. Expanded spectrum of HIV-related disease in injection drug users.

Pyogenic bacterial infections
Pneumonia
Streptococcus pneumoniae
Haemophilus influenzae
Bacterial endocarditis
Staphylococcus aureus
Streptococci
Enteric gram-negative bacilli
Tuberculosis
Reactivation
Primary infection
Sexually transmitted diseases
Syphilis
Human papillomavirus infection
Hepatitis A, B, C, and D (delta virus)
Human T cell lymphotrophic virus type II infection
Renal disease
Cancer
Lung and oropharynx, larynx
Cervix

NOTE. Data adapted from [139].

cific outcome of HIV disease in drug injectors has not been studied.

Finally, as with other populations with HIV disease, existing evidence indicates that the rate of progression of HIV disease can be slowed among injection drug users by medical interventions. Although fewer data are available for injection drug users than for other populations, observational studies have shown the benefit of antiretroviral therapies as well as prophylaxes for opportunistic infections [114, 135]. Analyses of subgroups in clinical trials indicated similar responses to zidovudine therapy in drug injectors and others, but these findings are limited by the small number of injection drug users who were enrolled [136]. Ultimately, newly developed therapies must be tested in people living with HIV disease who are willing and not likely to drop out of clinical trials. For ethical, scientific, and practical reasons, trials must be widely inclusive. Only limited information exists on the efficacy and toxicity of most newly developed agents in the populations who form the future majority of persons with HIV disease, including drug users. Concerns that heterogeneity among study participants may confound interpretation of results are likely unwarranted, and there is little justification for restricting trials to narrowly defined populations. Furthermore, disease issues specific to drug injectors require their participation in trials: these issues include specific pharmacokinetic and pharmacodynamic differences in drug disposition and drug interactions. For example, preliminary information indicates that methadone can alter the pharmacokinetics of the disposition of zidovudine, resulting in significantly increased exposure to the drug [137]. Similarly, substances of abuse, including opiates, cocaine, and alcohol, might alter the efficacy of other therapies.

However, the enrollment and retention of injection drug users in clinical trials can be difficult, so that conducting the studies necessary to assess potential interactions of drugs with therapies for HIV infection or to evaluate specific prophylactic interventions is challenging. Active drug users are not now considered to be suitable candidates for long-term trials, but former drug users or those with relatively controlled drug use have been able to participate successfully when trials are conducted with sensitivity and attention to their special needs [138]. Making existing therapies available to injection drug users is clearly possible both in drug-treatment programs and in more conventional clinical settings, but the special characteristics of this population need to be appreciated (see [139] for review of this issue).

HIV-associated diseases. The spectrum of outcomes for HIV-infected drug injectors is clearly distinct from that for other groups (table 3). HIV infection appears to exacerbate injection-related conditions, primarily bacterial endocarditis and pneumonia [140]. Although the incidence of both of these diseases is high among drug injectors independent of HIV infection [141–144], HIV infection confers an increase in risk for each disease, as well as increased mortality [114, 145–147] (see [148] for review). In addition, the relation of declining CD4 cell count to increased incidence of these bacterial infections among HIV-positive drug injectors for whom AIDS has not yet been diagnosed appears to have almost exactly the same pattern as, albeit slightly weaker than, the relation of declining CD4 cell count to the incidence of clinically defined AIDS [113]: relative risks for those with 201–500, 151–200, and <150 CD4 cells/mm^3 were 1.6, 1.6, and 3.6, respectively, for pyogenic bacterial infections prior to AIDS and 3.3, 3.2, and 15.7, respectively, for the diagnosis of AIDS itself. These results suggest that pyogenic bacterial infection in drug users with HIV infection is equivalent to the more universally appreciated HIV-associated opportunistic infections cited in the 1987 case definition for AIDS of the CDC [1].

In a longitudinal study of methadone-program enrollees infected with HIV in the Bronx, excess mortality attributable to bacterial infections *before* the criteria for a diagnosis of AIDS were met was estimated at 1.6% per year [114]. This excess burden of disease and associated mortality among drug injectors that was not accounted for by diagnosed cases of AIDS was first identified in New York City in the middle 1980s [149, 150]. The increased incidence of bacterial pneumonia among drug injectors infected with HIV has been recognized by the inclusion of recurrent (more than once within 12 months) bacterial pneumonia in the newest case definition for AIDS of the CDC [2], although other pyogenic bacterial infections or single episodes of pneumonia, also clearly

related to HIV infection [113, 114, 146], are not yet part of the case definition.

Because the majority of habitual drug injectors in American cities where HIV infection is most prevalent are poor and live in densely populated neighborhoods where access to services can be difficult [28], they have higher rates of diseases associated with poverty and crowding—most notably tuberculosis, which was identified as prevalent among drug users even before the AIDS epidemic began [151]. It is now clear that HIV infection increases manyfold the probability of activation of latent *Mycobacterium tuberculosis* infection in drug injectors [152–155]. In addition, new tuberculous infection is more likely to progress to active disease in the presence of HIV infection [156, 157]. Initially it was assumed that reactivation of existing tuberculous infection accounted for most of the newly diagnosed cases of tuberculosis; however, results of recent studies in New York and San Francisco suggest that as many as 40% of new cases of active tuberculosis in areas where the epidemic of HIV infection is extremely mature (i.e., where many individuals have been infected with HIV for a long enough time to have advanced immune suppression) might represent recently transmitted and rapidly progressive primary *M. tuberculosis* infection [158, 159]. These findings await corroboration but indicate that vigilance for new tuberculous infection in drug injectors in American cities—who can be assumed to represent a population affected by a mature epidemic of HIV infection even when individual data on status of antibody to HIV are unavailable —must be continual and vigorous and must be coupled with adequate tuberculosis prophylaxis.

Among other HIV-associated diseases special to injection drug users are sexually transmitted diseases, notably syphilis and human papillomavirus infection; hepatitis A, B, C, and D; human T cell lymphotrophic virus type II infection; and rapidly progressive renal failure (which is similar to heroin-induced nephropathy clinically and pathologically, but the rapid tempo of its progression is distinct). The etiology of rapidly progressive renal failure due to HIV disease remains undefined [160, 161], and its incidence and prevalence remain unknown. Renal failure due to HIV infection invariably requires dialysis as a life-prolonging measure. How this affects the progression of HIV disease remains to be studied. Finally, preliminary data suggest that injection drug users with HIV infection might be at increased risk for non-AIDS-defining solid tumors of the lung, oropharynx, and pharynx [162, 163]. These findings are in sharp contrast to the well-known infrequency of Kaposi's sarcoma, which is described in 2%–3% of HIV-infected injection drug users compared with 20%–43% of men who have sex with men [164, 165].

The order in which these and other HIV-related diseases in drug injectors occur varies greatly between individuals. Constitutional symptoms in drug injectors can result either from HIV infection or from injection itself [166]. However, the occurrence of a second type of constitutional symptom in a drug injector who has previously had episodes of only one kind of symptom is closely linked with progression of HIV disease [114, 115]. At low CD4 cell counts (e.g., <200/mm^3), constitutional symptoms occur equally commonly in HIV-infected drug injectors and in men who had sex with men, as does oral candidiasis in individuals with any CD4 cell count [166]. However, a second constitutional symptom often occurs in drug injectors before immune suppression is profound (median CD4 cell count, 397/mm^3) [114], whereas oral candidiasis is typically diagnosed when immune deficit is more advanced (median CD4 cell count, 324/mm^3) [114]; its prevalence exceeds 20% only when the CD4 cell count falls below 200/mm^3 [166]. Pyogenic bacterial infections and active tuberculosis appear to occur in individuals with similarly depressed CD4 cell counts (median CD4 cell count, 317/mm^3 [114], which is similar to that associated with oral thrush).

The extent of immune deficit at the time of diagnosis of AIDS in drug injectors depends on the defining diagnosis. *Pneumocystis carinii* pneumonia was the AIDS-defining illness in ~40%–50% of drug injectors in the United States in the late 1980s and early 1990s [87, 167], but the distribution of diagnoses of other AIDS-defining illnesses can vary widely. Indeed, in terms of extent, the AIDS-defining illnesses that injection drug users present with are similar to those that other populations present with, but the proportional distribution of these illnesses is different. For example, compared with men who have sex with men, injection drug users have proportionately more cryptococcal disease, *P. carinii* pneumonia, wasting syndrome, and tuberculosis and significantly less cytomegalovirus disease, non-Hodgkin's lymphoma, and Kaposi's sarcoma [165].

Inclusion of the criterion of the CD4 cell count of 200/mm^3 in the case definition for AIDS of the CDC [2] dramatically increased the numbers of HIV-infected injectors with AIDS, as the great majority of injectors with this CD4 cell count remain free of clinically defined AIDS [113]. Indeed, the risk of clinically defined AIDS (1987 case definition [1]) in HIV-infected drug injectors in one study did not increase when subjects' CD4 cell counts of 201–500/mm^3 dropped to 151–200/mm^3 but rose fivefold when the CD4 cell count fell to <150/mm^3 [113]. This finding suggests that the recent expansion of the case definition for AIDS will reduce the specificity of surveillance data for tracking serious HIV disease, at least in this population. As prophylaxis for and treatment of specific opportunistic infections become more widely used in the drug-injecting population, it is likely that differences in the local incidence of particular AIDS-defining conditions will increasingly determine the natural history of HIV infection in this group, as has already been documented for American men in the Multicenter AIDS Cohort Study [168].

Conclusion

Considerable knowledge of the epidemiology of HIV disease in drug users has been accrued over the past decade, including improved documentation of infection and disease, understanding of routes and risks of transmission of HIV infection, potential modes of intervention (notably provision of sterile injection equipment), and the effectiveness of such interventions as needle-exchange programs. Similarly, the natural history of HIV infection in drug injectors has been shown to be similar in its essentials to that in nonusers of drugs, albeit with many unique details, particularly with respect to the spectrum and timing of onset of outcomes of HIV-related disease. Pharmacotherapies for HIV-associated infection appear to be as effective in drug users as they have been shown to be in other persons.

However, a number of areas of uncertainty remain: additional study is needed on sexual activity and its interrelation with drug use in order to better understand the dynamics of epidemics of HIV infection; more information is needed on how to present and target harm-reduction activities ancillary to needle exchanges such as education regarding safe injection practices and generally improved primary care; pharmacological interactions between abuse substances and HIV infection–related medications must be studied further; the question of the effect of continued drug injection on the natural history of HIV infection remains to be resolved; and whether treatment for drug use can have benefits in terms of improved health status in HIV-infected persons deserves serious study. Possibly the most important advance in the area of treatment of HIV-infected drug injectors would be finding ways to improve access of this largely marginalized population to currently available clinical interventions that are known to be beneficial.

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