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Projections of the Number of Persons Diagnosed with AIDS and the Number of Immunosuppressed HIV-Infected Persons -- United States, 1992-1994

Summary

This report presents projections of the number of persons who will initially be diagnosed with a condition included in the 1987 surveillance definition for acquired immunodeficiency syndrome (AIDS) in the United States during the period 1992-1994. The report also presents estimates and projections of the prevalence of persons infected with the human immunodeficiency virus (HIV) who have CD4+ T-lymphocyte (T-cell) counts less than 200/uL and who have not been diagnosed with a condition listed in the 1987 AIDS surveillance definition. These estimates and projections are used to predict the effect of expanding the AIDS surveillance definition to include all HIV-infected persons with a CD4+ T-cell count less than 200/uL.

Approximately 58,000 persons were diagnosed with AIDS * in the United States during 1991. During the period 1992-1994, the number of persons newly diagnosed with AIDS is expected to increase by at most a few percent annually, with approximately 60,000-70,000 persons diagnosed per year. Although AIDS diagnoses among homosexual and bisexual men ** and among injecting drug users are projected to reach a plateau during this period, the number of AIDS diagnoses among persons whose HIV infection is attributed to heterosexual transmission of HIV is likely to continue to increase through 1994. The number of living persons who have been diagnosed with AIDS is expected to increase from approximately 90,000 in January 1992 to approximately 120,000 in January 1995. There is, however, considerable uncertainty in these projections. For example, the plausible range for the number of persons initially diagnosed with AIDS in 1994 is 43,000-93,000.

CDC estimates that, as of January 1992, 115,000-170,000 U.S. residents had severe immunosuppression (a CD4+ T-cell count less than 200 cells/uL without a diagnosis of AIDS in an HIV-infected person). Only about 50,000 of these persons were receiving medical care for HIV-related conditions and were known to have a CD4+ T-cell count less than 200 cells/uL. The number of persons with severe immunosuppression is expected to increase to 130,000-205,000 by January 1995, with the actual number more likely to be in the lower half of this range than the upper half. The expanded AIDS surveillance definition, which includes severe immunosuppression, is predicted to result in an increase of approximately 75% in the number of persons reported during 1993, but an increase of less than 20%

in 1994 compared with the number of persons who would have been reported had the definition not been changed.

The projections made in this report demonstrate that the number of U.S. residents with HIV-related morbidity is unlikely to decrease, and in fact is likely to increase, over the first half of the 1990s.

INTRODUCTION

Surveillance for acquired immunodeficiency syndrome (AIDS) is the basis for monitoring severe human immunodeficiency virus (HIV)-related disease in the United States and for projecting trends in morbidity and mortality due to HIV infection. AIDS surveillance data were used in 1986 (1), in 1988 (2), and most recently in 1990 (3) to project the number of persons who will be diagnosed with conditions meeting the AIDS surveillance definition (4). This report contains similar projections for persons who will be diagnosed with AIDS during the period 1992-1994. The statistical methods are described in reference 5, Section A. ***

This report also contains projections of the number of HIV-infected persons with CD4+ T-cell counts less than 200 cells/uL who have not been diagnosed with AIDS. CDC revised the AIDS surveillance definition in 1987 to incorporate new information about serious morbidity due to HIV infection (4). Further advances in clinical knowledge have demonstrated that HIV-infected persons with less than 200 CD4+ T cells/uL are at increased risk for opportunistic infections (6). The U.S. Public Health Service has recommended prophylaxis for the prevention of Pneumocystis carinii pneumonia (PCP) among persons with this degree of immunosuppression. Estimates and projections of the number of persons with CD4+ T-cell counts less than 200 cells/uL are therefore needed for public health planning. The statistical methods used to make these estimates and projections are summarized in the Appendix and described more completely in reference 5, Section B.

This report does not contain estimates of HIV seroprevalence in the United States. The most recent U.S. Public Health Service estimate is that approximately 1,000,000 U.S. residents were infected with HIV as of late 1989, with a plausible range of 800,000-1,200,000 (3). Two of the analyses on which this report is based yield estimates (rounded to the nearest 50,000) of 850,000- 1,250,000 persons infected as of April 1990 (derived from reference 7; see also reference 5, Section A6) and 500,000-900,000 persons infected as of January 1991 (8). The differences between these estimates result from differences in statistical methodology. Both estimates are consistent with the most recent U.S. Public Health Service estimate.

In this report, "HIV infection" refers to infection with the human immunodeficiency virus, regardless of the presence of clinical manifestations. "HIV-related disease" refers to infection with the human immunodeficiency virus and the presence of clinical manifestations associated with HIV infection (9). These manifestations include some that are not life threatening, such as oral candidiasis and herpes zoster, as well as more serious diseases. AIDS is any disease or condition included in the 1987 AIDS surveillance definition (4). Unless stated otherwise, "therapy" means the use of therapy for HIV-related disease before the development of AIDS and includes both prophylactic therapy for PCP and antiretroviral therapy. "Immunosuppression" and "severe immunosuppression" are defined as a CD4+ T-lymphocyte count less than 500 and less than 200 cells/uL, respectively, in an HIV-infected person who has not been diagnosed with AIDS. "Heterosexual transmission" as a mode of HIV infection includes all adults and adolescents believed to have acquired HIV infection from heterosexual contact, with the exception of persons born in World Health Organization Pattern II countries **** for whom no other risk for HIV infection has been identified.

METHODS FOR PROJECTING THE NUMBER OF PERSONS DIAGNOSED WITH AIDS

Projections of the number of HIV-infected adults and adolescents who will be diagnosed with AIDS in each year during the period 1992-1994 were derived from back-calculation (10). Back-calculation is based on two types of data: a) the number of persons diagnosed with AIDS per month or calendar quarter, estimated from AIDS surveillance data, and b) the probability distribution of the incubation period (the time from HIV infection to diagnosis of AIDS), estimated from cohort studies. On the basis of these data, back-calculation estimates the number of persons infected with HIV during each month or calendar quarter necessary to account for the number of persons who have been diagnosed with AIDS over these same periods. The number of persons who will be diagnosed with AIDS in the future is then projected from the estimated HIV epidemic curve and the incubation period distribution.

Projections based on back-calculation methods were made separately for the four major exposure groups of adults and adolescents: a) homosexual/bisexual men *****, b) homosexual / bisexual men who are also injecting drug users (IDUs), c) female IDUs and other male IDUs, and d) persons with HIV infection attributed to heterosexual transmission. Projections for the remaining 4%-5% of adults and adolescents, for children infected through blood products, and for groups defined by sex and by race / ethnicity were based on extrapolation models. Projections for children infected perinatally were made by estimating both the number infected during each calendar quarter and the incubation period distribution from AIDS surveillance data.

The projections in this report are derived from three analyses, provided by Ron Brookmeyer, Ph.D., Johns Hopkins University (7); Robert H. Byers, Ph.D., CDC (11); and Philip S. Rosenberg, Ph.D., Mitchell H. Gail, M.D., Ph.D., and Raymond J. Carroll, Ph.D., National Cancer Institute (8). The results are summarized as ranges. For each year (1992-1994), the lower and upper bounds for the projections are the minimum and maximum projections, respectively, including estimates of uncertainty, from the three models (see reference 5, Section A).

Projecting the Incidence of AIDS

The first type of data used in the back-calculation models was the estimated number of persons diagnosed with AIDS per calendar quarter through December 1990. These estimates included adjustments for the following three factors.

a. Estimated delays in reporting diagnoses to CDC. Reporting

delays were estimated from the difference between date of report and date of AIDS diagnosis for persons reported to AIDS surveillance through March 1991. The adjustments took into account differences in reporting delays among groups defined by mode of transmission, race/ethnicity, geographic region, and size of metropolitan statistical area of residence. It was assumed that, within each group, delays do not change over time (see reference 5, Section A1.1). For most groups, approximately 50%, 75%, and 90% of all persons with AIDS are estimated to be reported within 3 months, 1 year, and 2 years after diagnosis, respectively.

b) Persons with no identified risk for HIV infection. Some reported cases with no identified risk for HIV infection were assigned to exposure groups (12; see also reference 5, Section A1.2). The proportions assigned to specific groups were estimated from the results of interviews with persons initially reported without an identified risk. The exposure group most affected by this procedure is persons infected with HIV through heterosexual transmission.

c) Estimated completeness of reporting. Unless stated otherwise, data on the number of persons diagnosed with AIDS were also adjusted for the estimated completeness of reporting to AIDS surveillance programs. Studies have estimated that reporting was generally 85%-90% complete during

the period 1986-1989 (13,14). For consistency with previous projections (3,15), this report assumes an 85% level of completeness of reporting.

Estimating the Incubation Period Distribution

The second type of data used in the back-calculation models was the estimated incubation period distribution. Estimates of this distribution were obtained from cohorts of adults with hemophilia (16,17) and from U.S. military personnel (18). Most of these and other studies show that less than 5% of HIV-infected adults develop AIDS within 2 years of infection, and that, without therapy, approximately 20%-25% and 50% develop AIDS within 6 and 10 years after infection, respectively. Two factors affecting the incubation period distribution are a) therapy for HIV-related disease and b) the 1987 revision of the AIDS surveillance definition.

a. Therapy. Each model incorporates an estimated effect of

therapy on the incubation period. These effects were estimated from clinical trials of zidovudine (19,20) and cohort studies of homosexual/bisexual men (21,22). In some clinical trials, persons treated with zidovudine also received PCP prophylaxis. In the cohort studies, nearly all persons receiving PCP prophylaxis were receiving zidovudine. The estimated effect of therapy on the incubation period therefore includes the effect of both PCP prophylaxis and zidovudine treatment. In each model, the effect of therapy begins in 1987, and the proportion of persons being treated increases thereafter. The proportions treated with zidovudine were chosen on the basis of cohort study data (23). (See reference 5, Section A for a summary of the data on which these estimates were based and the assumptions for each model.)

b) Revision of the 1987 AIDS surveillance definition. The back-calculation procedure of Rosenberg, Gail, and Carroll explicitly models the effect of the 1987 revision of the AIDS surveillance definition, but the methods used by Brookmeyer and Byers do not. The revision allowed for presumptive diagnoses of some diseases in the previous definition and expanded the definition to include additional diseases (4). One result of the revision is that some patients probably met the AIDS case surveillance criteria earlier in their illness, thereby shortening their apparent incubation period. The revision may have had less effect on the incubation period distribution than did therapy among homosexual/bisexual men who are not IDUs (5, Section A1.3).

PROJECTIONS OF THE NUMBER OF PERSONS DIAGNOSED WITH AIDS Persons Diagnosed with AIDS, All Cases

The annual number of persons diagnosed with AIDS continues to increase in the United States (Figure 1). According to the current projections, the rate at which AIDS incidence increases will continue to slow, and incidence may reach a plateau by 1994.

CDC currently estimates that the number of persons diagnosed with AIDS in the United States increased by approximately 10% from 1989 to 1990 and from 1990 to 1991 (Table 1; as a result of reporting delays, the latter increase is greater than the 5% increase in cases reported during 1991, compared with cases reported during 1990 {24}). Based on the number of persons with AIDS who were reported through September 1992, CDC estimates that approximately 40,300, 43,700, and 49,000 persons diagnosed with AIDS during 1989, 1990, and 1991, respectively, eventually will be reported to the surveillance system and that approximately 25,000 persons diagnosed during the first half of 1992 eventually will be reported.

The results from the back-calculation models include a wide range of projected annual AIDS incidence

during the period 1992- 1994 (Table 1), but all three analyses show indications of a slowing in the rate of increase. First, although the upper bounds for these projections increase steadily, the lower bounds decrease slowly. In addition, the current upper and lower bounds for incidence during 1992 and 1993 are approximately 10,000 persons per year lower than the corresponding bounds for the projections made in 1990. Furthermore, the point estimates from the back-calculation analyses indicate that annual AIDS incidence will reach a plateau by 1994 (45,000-60,000 persons reported to AIDS surveillance {see Appendix, Table A1}, which corresponds to 50,000-70,000 persons diagnosed).

Past annual increases in the number of persons diagnosed with AIDS will result in an increasing prevalence of these persons. The number of living U.S. residents who have ever been diagnosed with AIDS is expected to increase from approximately 90,000 in January 1992 to approximately 120,000 in January 1995 (see p. 17). There will be 135,000-230,000 persons who have ever been diagnosed with AIDS alive at some time during 1994 (Table 1).

Approximately 45,000 persons with AIDS died during 1991 (Table 1). Although each lower bound for the annual number of deaths during the period 1992-1994 is also approximately 45,000, the upper bounds increase by approximately 10,000 per year. Therefore, annual mortality among persons diagnosed with AIDS will likely increase during the period 1992-1994.

Persons Diagnosed with AIDS, by Mode of Transmission

The number of persons diagnosed with AIDS continued to increase through 1991 among homosexual/bisexual men who are not IDUs, among IDUs who are not homosexual/bisexual men, and among persons infected with HIV through heterosexual transmission; the number appears to have reached a plateau, however, among homosexual/bisexual men who are IDUs (Figures 2 and 3; Table 2). From 1990 to 1991, the number of persons initially diagnosed with AIDS increased by approximately 3,200 among homosexual/bisexual men who are not IDUs, by 1,600 among IDUs who are not homosexual/bisexual men, and by 1,100 among persons infected with HIV through heterosexual transmission. The percentage increase was much greater, however, for persons infected through heterosexual transmission (28%) than for the other two groups (11%-12%). These estimates include some persons currently without an identified risk for HIV infection (see p. 4). Excluding persons without an identifiable risk, AIDS cases among persons infected through heterosexual transmission increased by 23% from 1990 to 1991.

Projections for the period 1992-1994 suggest qualitatively different trends for different risk groups (Table 2). The projections suggest that the annual number of AIDS cases among homosexual/bisexual men who are not IDUs and among IDUs who are not homosexual/bisexual men will increase relatively slowly. For both groups, the lower bounds for the projections decrease and the upper bounds increase by at most 10% per year. For each back-calculation analysis, the point estimates for both groups reach plateaus by the end of 1994, whereas the point estimates for homosexual/bisexual men who are IDUs decrease (see Appendix, Table A2).

Among all homosexual/bisexual men and among IDUs who are not homosexual/bisexual men, the upper bound of the plausible range for 1992 is at least 35% higher than the number of persons diagnosed with AIDS during 1991. Because the incidence of AIDS in these three groups has increased by less than 10% per year recently (Table 2), it is likely to be substantially below the upper bound projected for each group during the period 1992-1994. In addition, based on cases reported through September 1992, for both of these groups CDC estimates that the number of cases diagnosed during the first 6 months of 1992 was approximately half the cases diagnosed during all of 1991 (data not shown), in contrast to previous years when the number of cases diagnosed during the first 6 months predicted an increase in incidence for the year (Figure 2).

In contrast, the annual number of AIDS cases among persons with HIV infection attributed to heterosexual transmission is likely to continue increasing through 1994 (Table 2). This trend is supported by the preliminary estimate for the number of such AIDS cases diagnosed during the first half of 1992 (data not shown).

The incidence of AIDS in perinatally infected children increased substantially less rapidly after 1989 than before, and both the number of such children diagnosed with AIDS during 1990 and 1991 and the projections for 1992 and 1993 are lower than the projections for those years made in 1990 (12; Table 2). The number of these children diagnosed with AIDS is projected to increase relatively slowly (less than 10% per year) during the period 1992- 1994. These projections are lower than the previous projections because of both the change in the trend in AIDS incidence and a change in the method used to make the projections (5, Section A3.2). Data from CDC's Survey of Childbearing Women show that the annual number of children born with HIV infection has been relatively constant from 1988 to 1990 (25,26), which also suggests that AIDS incidence will increase relatively slowly among these children. However, the tabulated projections may tend to underestimate the number of perinatally HIV-infected children who will be diagnosed with AIDS during the period 1992-1994 (5, Section A3.2).

Persons Diagnosed with AIDS, by Race/Ethnicity and by Sex

AIDS incidence continues to increase among non-Hispanic whites, non-Hispanic blacks, and Hispanics, as well as among both men and women (Table 3). For all these groups, the trends in the projected number of persons diagnosed during the period 1992-1994 are qualitatively similar. For each group, the lower bounds are stable or decreasing, and the upper bounds increase by at most 15% per year (except for a larger increase in the upper bound for women from 1992 to 1993). Although annual incidence for each group increased by at most 14% in 1990 and 1991 (except among women, for whom the increases for 1990 and 1991 were 18%-20%), the upper bounds for 1992 are 30%-40% greater than the estimated numbers diagnosed during 1991. As a result, the actual numbers diagnosed are likely to be well below the upper bounds for the period 1992- 1994.

Comments

The projected AIDS incidence trends for the period 1992-1994 obtained from the three back-calculation models range from little change to steadily increasing incidence. The wide range in the projections reflects the uncertainty in knowledge about the number of persons in the United States who have been infected with HIV, when they were infected, how long it takes to be diagnosed with AIDS after HIV infection, the effect of therapy on this time interval, and the number of HIV-infected persons who receive therapy before developing AIDS. Because of this uncertainty, it is important to use the available information to determine the most plausible trend in AIDS incidence within the broad range of the projections.

Both the point estimates from the back-calculation analyses and the rate of growth in the number of persons diagnosed from the beginning of 1989 to the middle of 1992 suggest that the rapid increase in the annual number of persons initially diagnosed with AIDS observed during the 1980s is unlikely to continue. CDC currently estimates that approximately 58,000 persons were diagnosed with AIDS in the United States during 1991 (Table 1) and that approximately 30,000 were diagnosed during the first half of 1992. The annual number of persons diagnosed increased by about 10% during 1990 and 1991. If the number of persons diagnosed during 1992 is twice the current estimate for the first half of the year, the corresponding increase for 1992 will be less than 4%. If this trend continues, the number of persons diagnosed with AIDS will be in the middle of the projected ranges for the period 1992-1994. Although the back-calculation models use different assumptions (some that would increase and others that would decrease the projections compared with the other models {5, Section A}), all the point

estimates project at most small (less than 3%) annual increases in AIDS incidence by 1994 (Appendix, Table A1).

Projections from back-calculation models are sensitive to the incubation period distribution (8). The assumptions about therapy made in these models that affect this distribution are a) that therapy reduces the (instantaneous) risk of developing AIDS by 50%- 65% for persons with less than 200 CD4+ T cells/uL (5, Table A2); b) that treated persons do not discontinue therapy; and c) that the assumed effect of therapy continues indefinitely. The assumed effect of therapy agrees with estimates obtained from clinical trials (19,20; see also reference 5, Section A4.2) and from two cohorts of homosexual/bisexual men (Table 4); however, the other two assumptions deserve further discussion.

Because of the way the efficacy of therapy was estimated, the assumption that treated persons do not discontinue therapy might not bias the projections. The estimated therapy effects from clinical trials are based on "intent to treat" analyses in which persons randomized to active therapy who discontinue therapy temporarily or permanently are considered to be treated. Efficacy estimates from cohort studies (21, 22) consider a participant as treated during a time interval if that person received treatment at any time during that interval. Therefore, the therapy efficacy estimates used in these models may describe typical, rather than continuous, use of therapy.

Some data suggest that therapy does not remain effective indefinitely. In a clinical trial of immediate versus delayed zidovudine therapy for persons without AIDS who had 200-500 CD4+ T cells/uL, CD4+ T-cell counts seemed to decline more rapidly after 16-24 months of therapy than during the first 12 months of therapy (30). A sensitivity analysis for one back-calculation model showed that the number of persons diagnosed with AIDS may increase substantially by 1994 if therapy becomes less effective among persons treated for extended periods (8, Table III). On the other hand, the availability of new therapeutic agents may increase the number of patients for whom therapy remains efficacious and therefore decrease the number of persons diagnosed with AIDS in future years.

The projections in this report predict that 60,000 or more persons will be diagnosed with AIDS each year in the United States during the period 1992-1994. In addition, the number of persons diagnosed with AIDS who were infected with HIV through heterosexual transmission is projected to increase during the period 1992-1994, as is the number of living persons who have been diagnosed with AIDS. In 1994, there will still be many hundreds of thousands of HIV-infected persons who have not yet been diagnosed with AIDS.

METHODS FOR PROJECTING THE PREVALENCE AND INCIDENCE OF SEVERE IMMUNOSUPPRESSION

The CD4+ T-lymphocyte count is generally regarded as the best marker for the progression of HIV-related disease. As the CD4+ T-cell count declines, the risk for developing a broad spectrum of illnesses, including those meeting the AIDS-defining criteria, increases. Monitoring CD4+ T-cell counts is part of the recommended standard of care for persons with HIV infection, and CD4+ T-cell counts are used to guide clinical decisions regarding the use of antiretroviral therapy and prophylaxis against PCP. Estimates of the number of persons with CD4+ T-cell counts less than 200 cells/uL but without AIDS are therefore needed for public health planning.

This section presents estimates and projections of the prevalence and incidence of severe immunosuppression (a CD4+ T-cell level less than 200 cells/uL in the absence of an AIDS-defining condition ****** in an HIV-infected person) in the United States for the period 1992-1994. Estimates and projections are presented for two groups: a) all HIV-infected persons with severe immunosuppression (without AIDS-defining conditions) and b) persons whose severe

immunosuppression is diagnosed as part of their medical care for HIV infection. These projections are presented as ranges, which show that they are subject to substantial uncertainty. These estimates and projections are also used to predict the effect of expanding AIDS surveillance to include persons with severe immunosuppression (31).

Projecting the Prevalence and Incidence of Severe Immunosuppression

Estimates of the prevalence of severe immunosuppression were based primarily on back-calculation analyses performed by Ron Brookmeyer, Ph.D., Johns Hopkins University, and by Robert H. Byers, Ph.D., CDC (Section 2; 5, Section B). In addition to the assumptions listed on p. 4 of this report, the back-calculation estimates of the prevalence of severe immunosuppression incorporate three additional assumptions (see Appendix and reference 5, Section A5 for details):

a. The median time from the onset of severe immunosuppression

to the development of an AIDS-defining condition is 12-18 months for persons not receiving therapy. Of Brookmeyer's estimates of the prevalence of severe immunosuppression (7, Table 1), this report therefore uses those based on an 18-month median time, the shortest time he considered. In comparison, Byers used a distribution with a 13-month median time.

b) The proportion of HIV-infected persons who are diagnosed with an AIDS-defining condition before developing severe immunosuppression is 10%.

c) The proportion of severely immunosuppressed persons who die before being diagnosed with AIDS is small (less than 5%) and can be assumed to be zero for the purpose of this analysis. An alternative estimate of the prevalence of severe immunosuppression was obtained as the product of two factors:

a. the ratio of the prevalence of severe immunosuppression to

the prevalence of persons with AIDS-defining conditions (estimated from cohort studies to be approximately 1.5 {5, Section B4}) and

b) the prevalence of persons with AIDS-defining conditions (estimated from AIDS surveillance data to be approximately 90,000 in January 1992 {5, Section A5})

Projecting the Prevalence and Incidence of Diagnosed Severe Immunosuppression The annual prevalence and incidence of HIV-related severe immunosuppression that will be diagnosed during the period 1992- 1994 were estimated from the projected annual prevalence and incidence of severe immunosuppression, the projected annual incidence of an initial diagnosis of an AIDS-defining condition, and a stochastic model. The stochastic model (see Appendix) describes whether a person with severe immunosuppression has a CD4+ T-cell count performed before being diagnosed with an AIDS-defining condition. These projections were based on the following assumptions, in addition to those listed above (also see Appendix).

a. Among persons who are diagnosed with an AIDS-defining

condition after developing severe immunosuppression:

10% do not receive health care for HIV-related disease before diagnosis of an AIDS-defining condition

the median time from the diagnosis of severe immunosuppression to a diagnosis of an AIDS-defining condition is 15 months for persons receiving medical care

the median time from the onset of severe immunosuppression to a diagnosis of an AIDS-defining condition is 12 months for persons not receiving medical care

b) Approximately 50,000 persons known to have severe immunosuppression (without AIDS-defining conditions) were receiving medical care for HIV-related disease at the start of 1992.

The prevalence in the last assumption was estimated as a product, by a procedure similar to that used to obtain an alternative estimate of severe immunosuppression (above). The first factor was 0.54, the ratio of the prevalence of persons known to have severe immunosuppression to the prevalence of persons with AIDS-defining conditions in a study of persons receiving health care for HIV infection (see Appendix). The second factor was 90,000, the prevalence of persons diagnosed with AIDS-defining conditions, because all these persons are assumed to be receiving health care after the diagnosis of their AIDS-defining condition.

Figure 4 summarizes the successive events during HIV-related disease corresponding to these assumptions and shows which events are described by the stochastic model.

The annual number of persons who will be reported under the expanded AIDS surveillance definition (31) during the period 1993- 1994 as a result of adding severe immunosuppression to the definition was then predicted from the estimates and stochastic model described above and two additional assumptions:

a. there will be 85% completeness of reporting for persons

diagnosed as severely immunosuppressed, and

b) delays in reporting CD4+ T-cell counts can be ignored. This assumption concerns the delay in reporting a CD4+ T-cell count, not the delay between the onset of severe immunosuppression and obtaining such a count, which is part of the stochastic model.

PROJECTIONS OF THE PREVALENCE AND INCIDENCE OF SEVERE IMMUNOSUPPRESSION Prevalence and Incidence of Severe Immunosuppression

The back-calculation models project that the prevalence of severe immunosuppression in the United States will increase from approximately 115,000-170,000 in January 1992 to 130,000-205,000 in January 1995 (Table 5). Both models project that the number of persons developing severe immunosuppression each year will be nearly constant during the period 1992-1994, approximately 75,000 and 60,000 each year in Brookmeyer's and Byers' models, respectively. For each model and year, the projected incidences of severe immunosuppression and of AIDS-defining conditions are similar. The estimated prevalence of severe immunosuppression in January 1992 derived from AIDS surveillance and cohort data (the "alternative estimate") is 130,000-140,000, which is consistent with the projections from the back-calculation models.

Prevalence and Incidence of Diagnosed Severe Immunosuppression

Although the percentage of persons recognized to have HIV infection who are receiving treatment increases with increasing immunosuppression and (concomitant) increased symptomatology, the models estimate that the prevalence of diagnosed severe immunosuppression is substantially lower than the prevalence of all persons with severe immunosuppression. The approximately 50,000 persons receiving health care who were known to be severely immunosuppressed in January 1992 (see p. 15) represented less than 50% of all severely immunosuppressed HIV-infected persons in the United States. This underrepresentation most likely reflects the large number of persons with undiagnosed

HIV infection. According to the estimates derived from both back-calculation models, the prevalence of diagnosed severe immunosuppression is projected to increase during the period 1992-1994, reaching 55,000- 75,000 persons by January 1995 (Table 6). In contrast, the incidence of diagnosed severe immunosuppression is projected to remain approximately constant at about 30,000-40,000 persons per year during the period 1992-1994 (5, Table B3).

Number of Persons Reported under the Expanded AIDS Surveillance Definition

Expanding the AIDS surveillance definition to include severe immunosuppression will result in a large increase in the number of persons reported during 1993 but a smaller increase during 1994 (Table 7). For example, if there are no delays in reporting severely immunosuppressed persons after the definition is expanded in January 1993, the number of persons reported during 1993 under the expanded definition is predicted to increase by 80%-100% compared with the number that would have been reported under the 1987 AIDS surveillance definition. The corresponding increase for 1994 is predicted to be approximately 10%; note that the number reported during 1994 is likely to be substantially less than the number reported during 1993. The likely effect of delays in reporting is discussed below.

Comments

The estimates of the prevalence and incidence of severe immunosuppression are based on two back-calculation models. Although these models incorporate the most recent information about the duration of severe immunosuppression and about the efficacy and use of therapy, there is substantial uncertainty in the estimates and projections. An alternative estimate based more directly on data from AIDS surveillance and cohort studies yields an estimate of the current prevalence of severe immunosuppression similar to the estimates from back-calculation, suggesting that the back-calculation projections are plausible.

The two back-calculation models give similar qualitative projections of trends in the prevalence and incidence of severe immunosuppression during the period 1992-1994 but quite different quantitative estimates (Table 5). Both models project that a) the prevalence of severe immunosuppression will increase less than 15% per year during the period 1992-1994 and b) the incidence of severe immunosuppression will be nearly constant and similar to the incidence of AIDS-defining conditions. Thus, both models project that the HIV epidemic will soon reach a plateau with respect to both the incidence of AIDS-defining conditions (Appendix, Table A1) and the prevalence and incidence of severe immunosuppression. Both back-calculation models estimate that there were greater than 100,000 persons with severe immunosuppression in the United States in early 1992.

The estimated 115,000-170,000 severely immunosuppressed persons in the United States in early 1992 are approximately 10%- 15% of the 1 million persons estimated to be infected with HIV (3). CDC previously estimated that, in early 1989, 15%-20% of HIV-infected persons in the United States had CD4+ T-cell counts less than 200 cells/uL (15, p. 10). That estimate included persons with AIDS. The current estimate of the prevalence of severe immunosuppression is therefore consistent with the previous estimate.

As an immediate effect of the expanded AIDS surveillance definition, many persons with severe immunosuppression who have not developed an AIDS-indicator condition will be reported to CDC in 1993. At the end of 1992, it is likely that there will be at least 50,000 HIV-infected persons receiving health care for HIV-related disease who are known to be severely immunosuppressed and who have not developed an AIDS-indicator condition (Table 6). All these persons meet the expanded AIDS surveillance definition. Without delays in reporting, the number of persons reported during 1993 will increase by 80%-100% compared with the number that would have been reported under the 1987

surveillance definition. The actual increase will depend on how rapidly and completely health-care providers and health departments are able to report persons with severe immunosuppression. Because reporting delays are likely to occur, an expansion of the surveillance definition will probably result in an increase of approximately 75% in the number of persons reported during 1993 and an increase of 15%-20% during 1994 -- i.e., the number of persons reported in 1994 is likely to be approximately 30% less than the number reported during 1993. Note that these estimates include only the effect of adding severe immunosuppression to the surveillance definition. The three additional AIDS-indicator diseases that have also been incorporated in the definition (31) are expected to add only a few thousand cases per year beyond the effect of including severe immunosuppression.

Surveillance data suggest that less than 50% of all severely immunosuppressed persons have been diagnosed as such. Despite the many undiagnosed HIV-infected persons, including those with severe immunosuppression, these estimates show that there are now and will continue to be many persons with diagnosed HIV infection who need medical care. In January 1992 approximately 140,000 living Americans had previously been diagnosed with an AIDS-defining condition or were known to be severely immunosuppressed; this number will increase to 160,000-200,000 by January 1995 (Table 6). The number of persons known to be severely immunosuppressed who have not yet met the 1987 AIDS surveillance definition is projected to increase from approximately 50,000 in January 1992 to approximately 55,000-75,000 in January 1995. These projections do not include persons with evidence of moderate immunosuppression, i.e., CD4+ T-cell counts of 200-500 cells/uL, for whom antiretroviral therapy is indicated, or persons with undiagnosed severe immunosuppression.

These projections of the prevalence and incidence of severe immunosuppression are subject to uncertainty reflecting at least four considerations relating to the duration of and the factors that lead to the diagnosis of severe immunosuppression. First, there is substantial uncertainty about the median duration of severe immunosuppression (the median time from the onset of severe immunosuppression to the initial diagnosis of an AIDS-defining condition), among both treated and untreated severely immunosuppressed persons. Back-calculation estimates of the prevalence of severe immunosuppression increase as the median duration of severe immunosuppression increases (7, Table 1) and seem to be more sensitive to the duration of severe immunosuppression than to any other assumption made in these models. Different estimates of this duration are obtained from different cohorts of homosexual/bisexual men, and the estimates obtained from persons with hemophilia are longer than from other groups (Table 4; see also reference 32). The initial results from two cohorts suggest that the incubation period distribution among IDUs may be similar to that among homosexual/bisexual men (33,34). If the median duration of severe immunosuppression is closer to 12 months than 18 months, as some studies suggest (Table 4), the current prevalence of severe immunosuppression in the United States is likely to be in the lower half of the range shown in Tables 5 and 6.

Brookmeyer's estimates of the prevalence of severe immunosuppression are approximately 50% higher than Byers' (Table 5), most likely because Brookmeyer used a longer median duration of severe immunosuppression. Brookmeyer estimated this duration to be 42 months in untreated persons, on the basis of data from persons with hemophilia (7). This report uses his estimates of the prevalence of severe immunosuppression, corresponding to a median duration of 18 months among untreated persons, the shortest time considered in his sensitivity analysis (7, Table 1), after these estimates were adjusted on the basis of the assumptions listed on p. 14 of this report. Because Brookmeyer's projections increase as the duration of severe immunosuppression increases (7, Table 1), the estimates in this report based on his analyses are likely to represent upper bounds for the prevalence of severe immunosuppression. Byers' estimates are based on a median duration of 13 months among untreated persons, which is more similar to most of the current estimates (Table 4). The prevalence of persons with severe immunosuppression may therefore be closer to Byers' estimates than to Brookmeyer's.

Second, questions about the efficacy and use of therapy result in uncertainty about the duration of severe immunosuppression in HIV-infected persons. These estimates and projections assume that the efficacy and use of therapy will be unchanged through 1994. The median duration of severe immunosuppression will increase, however, if better therapies for severely immunosuppressed persons become available or if the use of therapy among severely immunosuppressed persons becomes more widespread. Either of these changes would increase the prevalence of severe immunosuppression. Alternatively, the same changes in the efficacy or use of therapy for HIV-infected persons with CD4+ T-cell counts greater than or equal to 200 cells/uL may decrease the incidence and prevalence of severe immunosuppression (19,22). The prospect of new or more widespread therapy therefore adds to the uncertainty of these projections and could result in prevalence levels of severe immunosuppression that are either larger or smaller than the estimates in Table 5.

Third, the projected number of persons diagnosed with severe immunosuppression is also subject to substantial uncertainty. In addition to the sources of uncertainty previously described, these projections depend on the current prevalence of diagnosed severe immunosuppression in the United States. The estimate of this prevalence in this report is based on data from one study, CDC's Adult and Adolescent Spectrum of HIV Disease (ASD) Project (29). Although this study includes diverse geographic and health-care settings and diverse groups of HIV-infected patients (by sex, race/ethnicity, and risk for HIV exposure), the sites were not chosen randomly. The patients in this study therefore may not be representative of all HIV-infected persons in health care.

The projected number of persons diagnosed as severely immunosuppressed depends on the estimated time from the diagnosis of severe immunosuppression to the diagnosis of the first AIDS-defining condition. The length of this interval is likely to be quite reliable because it is based on data from many persons (2,605 persons with CD4+ T-cell counts less than 200 cells/uL contributed to the estimate, including 754 who developed AIDS) and because the interval appears to be similar within groups defined by sex, by race, and by mode of transmission.

Finally, the projections for diagnosed severe immunosuppression are based on current patterns of testing for both HIV antibody and CD4+ T-cells and of access to health care. If either type of testing becomes more common or if access to health care improves, more HIV-infected persons with severe immunosuppression will be identified before they are diagnosed with an AIDS-defining condition. These circumstances would tend to make the projections of the number of persons diagnosed with severe immunosuppression too low.

The projections in this report indicate that the annual number of persons developing severe immunosuppression, as well as the annual number diagnosed with AIDS-defining conditions, has nearly reached a plateau for the United States as a whole. Nonetheless, the prevalence of those with severe immunosuppression or AIDS-defining conditions is and will remain high, probably totaling at least 200,000 persons alive on each date through the end of 1994. In addition, it is likely that the incidence and prevalence of persons with severe immunosuppression and persons with AIDS-defining conditions will continue to increase in some subgroups defined by geography, sex, race/ethnicity, or mode of HIV transmission, such as persons infected through heterosexual transmission.

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APPENDIX

This appendix contains additional information about acquired immunodeficiency syndrome (AIDS) case projections and about the methods used to estimate the prevalence of severe immunosuppression (a CD4+ T-lymphocyte {T-cell} count less than 200 cells/uL in a person infected with the human immunodeficiency virus {HIV} who has not been diagnosed with AIDS). More detailed information is provided in (A1).

AIDS Case Projections

Tables A1 and A2 contain CDC's estimates of the number of AIDS cases diagnosed in the United States during 1991 and 1992 that ultimately will be reported through AIDS surveillance, based on cases reported through September 1992. These tables also contain the corresponding point estimates for each year, 1991-1994, from the three back-calculation analyses used in this report. These point estimates correspond to particular assumptions (different for each model) about the incubation period distribution, the effect of therapy on this distribution, and the numbers of persons infected during the period 1990-1994 (A1, Section A2). These analyses also made corresponding estimates that include sources of uncertainty (A1, Tables A4-A8).

Estimates of the Prevalence and Incidence of Severe Immunosuppression and of Diagnosed Severe Immunosuppression

Back-calculation estimates of the prevalence of severe immunosuppression at the start of each year during 1992-1995 were adjusted according to the assumptions listed on p. 14 of this report. Projections of the annual incidence of severe immunosuppression during 1992-1994 were derived from these prevalence projections and the corresponding projections of the annual number of persons first diagnosed with AIDS-defining conditions. The annual prevalence and incidence of severe immunosuppression among persons whose condition was diagnosed in the process of receiving health care for HIV-related disease were then estimated from a stochastic model that incorporates information about the natural history of HIV-related disease obtained from cohort and surveillance studies.

This section contains additional information about the models used to obtain the estimates and projections, discussed in this report, and about the parameter estimates used in those models. For further information, see (A1, Section B). In this discussion, "therapy" means use of antiretroviral therapy or therapy to prevent the development of Pneumocystis carinii pneumonia by persons who have not been diagnosed with AIDS-defining conditions.

Estimating the Prevalence of Severe Immunosuppression

The results presented on pp. 16-18 of this report are based on the back-calculation analyses performed by Ron Brookmeyer (Johns Hopkins University) and Robert Byers (CDC), who used incubation period distributions with two and six stages, respectively. In each model, the final stage was defined by a CD4+ T-cell count less than 200 cells/uL. These analyses assumed that all HIV-infected persons

develop severe immunosuppression before being diagnosed with AIDS-defining conditions and that no HIV-infected persons die before developing AIDS-defining conditions. Estimates of the prevalence of severe immunosuppression obtained from these models should therefore be reduced by the proportion of persons who develop AIDS-defining conditions before severe immunosuppression and increased by the proportion of severely immunosuppressed persons who die before being diagnosed with AIDS-defining conditions. Back-calculation results must also be adjusted for incomplete reporting of persons diagnosed with AIDS-defining conditions.

It was assumed that these proportions have not changed over time. If P* is the prevalence of severe immunosuppression estimated from back-calculation and P is the prevalence adjusted for these factors, then P=((1-a)/(1-d)(1-r))P* where a is the proportion of persons who have a CD4+ T-cell count greater than or equal to 200 cells/uL when they are diagnosed with AIDS-defining conditions, d is the proportion of persons with severe immunosuppression who die before being diagnosed with AIDS-defining conditions, and r is the proportion of persons diagnosed with AIDS-defining conditions who are not reported to surveillance. The results on pp. 16-18 of this report are based on estimates that r = 0.15 and that a = 0.10 and d = 0.00. As a result, P = 1.06P.* Brookmeyer adjusted his estimates of the prevalence of severe immunosuppression (A3, Table

1. for 90% completeness of reporting, so that P* corresponds to 90% of his estimates. Our estimate of P is therefore obtained by multiplying his published estimates by 0.953 = 0.9 x 0.9/0.85.

Projecting the Number of Persons who Develop Severe Immunosuppression

To determine the incidence of severe immunosuppression, let Pt be the prevalence of severe immunosuppression at the start of year t. Let It and At be the incidence of severe immunosuppression and of persons with an AIDS-defining condition during year t, respectively (estimated from back-calculation). Then, aside from deaths in severely immunosuppressed persons (before they are diagnosed with an AIDS-defining condition), Pt+1 = Pt + It - (1- a)At where a=0.10. The incidence of severe immunosuppression is obtained by solving this equation for It.

Estimating the Prevalence and Incidence of Diagnosed Severe Immunosuppression

The annual prevalence and incidence of diagnosed severe immunosuppression during the period 1992-1994 were projected from the projected prevalences of severe immunosuppression (Table 5), the projected annual incidences of severe immunosuppression and of persons with an AIDS-defining condition (Table 5), and a stochastic model for the process (Figure 4). The stochastic model is based on the assumptions listed on pp. 14-15 of this report and on the following four assumptions:

a. The time from the development of severe immunosuppression

to the initial diagnosis of an AIDS-defining condition has an exponential distribution. The parameter for this distribution depends on whether a person with severe immunosuppression is receiving medical care for HIV-related disease before being diagnosed with an AIDS-defining condition, and, if receiving medical care, whether severe immunosuppression has been diagnosed.

b) Among persons receiving medical care for HIV-related disease before being diagnosed with an AIDS-defining condition, the time from the onset of severe immunosuppression to its diagnosis also has an exponential distribution.

c) Among persons receiving medical care for HIV-related disease before being diagnosed with an AIDS-defining condition, the development of such a condition and the diagnosis of severe immunosuppression are independent stochastic processes.

d) Within each calendar year during the period 1992-1994, the incidence of severe immunosuppression does not vary from month to month.

The parameters for the exponential distributions were chosen on the basis of available data and by requiring that projections from the stochastic model of the incidence of AIDS-defining conditions fit back-calculation projections. It was assumed that the median time from the onset of severe immunosuppression to the initial AIDS-defining condition is 12 months for persons not receiving medical care for HIV-related disease, consistent with the estimates in Table 4 for persons not receiving therapy. Based on data from CDC's Adult and Adolescent Spectrum of HIV Disease (ASD) Project, it was assumed that the median time from the diagnosis of severe immunosuppression to that of the initial AIDS-defining condition is 15 months. The competing risks model implies that the hazard for the diagnosis of severe immunosuppression is proportional to the hazard for being diagnosed with an AIDS-defining condition before a diagnosis of severe immunosuppression among persons receiving health care for HIV-related disease. On the basis of data from the ASD Project, it was assumed that the constant of proportionality is 1.5-2.5. Finally, the hazard for being diagnosed with an AIDS-defining condition before being diagnosed with severe immunosuppression among persons receiving health care for HIV-related disease was chosen to minimize the sum of squares of the annual incidence of AIDS-defining conditions projected by the stochastic model during the period 1992-1994 minus the corresponding incidence projected by the back-calculation model.

Estimating Model Parameters

Most parameters estimated for persons receiving health care for HIV-related disease were chosen based on data from CDC's ASD Project. This is a surveillance study in which collaborating health departments monitor illnesses among HIV-infected persons receiving care at selected sites in nine metropolitan areas in seven states (A4). In this report, we used data on the 12,562 persons included in this project from January 1990 through February 1992. Data used to choose four important parameters are summarized below. For additional information, see (A1, Section B).

Mortality before AIDS-defining conditions develop. In the ASD Project, the Kaplan-Meier procedure estimates that approximately 1% of persons who are diagnosed as severely immunosuppressed die within 12 months after this diagnosis and before being diagnosed with AIDS-defining conditions. If the median time from the onset of severe immunosuppression to a diagnosis of AIDS-defining conditions is less than 24 months, as suggested by available data (Table 4), a competing risks model predicts that the proportion of severely immunosuppressed persons who die before being diagnosed with AIDS-defining conditions is less than 3%.

Proportion of HIV-infected persons diagnosed with AIDS-defining conditions before severe immunosuppression develops. A method similar to the Kaplan-Meier procedure, replacing follow-up time by minimum observed CD4+ T-cell count (A5), estimates that 6.6% of HIV-infected persons in the ASD Project will be diagnosed with AIDS-defining conditions when they have a CD4+ T-cell count of greater than or equal to 200 cells/uL. This estimate is likely to be less than the corresponding proportion among all HIV-infected persons in the United States. Therapy delays the development of AIDS-defining conditions in persons with CD4+ T-cell counts of 200- 499 cells/uL (A6-A8). In the ASD Project, 75% of persons with CD4+ T-cell counts in this range received therapy before being diagnosed with AIDS (CDC, unpublished data); this is likely to be a much higher proportion than for all HIV-infected persons in the United States (see 9). The model assumes that 10% of HIV-infected persons are diagnosed with their initial AIDS-defining condition before the onset of severe immunosuppression.

Ratio of the prevalence of severe immunosuppression to the prevalence of persons with AIDS-defining

conditions. Of the 12,562 ASD participants included in this analysis, 1,853 persons were alive with severe immunosuppression and 3,417 were alive with AIDS-defining conditions at the end of their baseline data-abstraction period. This yields a prevalence ratio of 0.54.

Proportion of HIV-infected persons who are not receiving medical care for HIV-related disease before being diagnosed with AIDS-defining conditions. This proportion was estimated by comparing two estimates of the proportion of persons diagnosed with AIDS-defining conditions who die during the month of the diagnosis of their initial AIDS-defining condition. This proportion is approximately 5%-6% in the ASD Project and 10%-13% for cases reported to AIDS surveillance (the actual proportion depending on the HIV transmission group examined). The excess in AIDS surveillance would include some (but not all) of those persons who are not receiving medical care for HIV-related disease before being diagnosed with AIDS-defining conditions. It was assumed therefore that 10% of persons diagnosed with AIDS-defining conditions do not receive health care for HIV-related disease before the diagnosis of their first such condition.

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- In this document, the term AIDS refers to conditions meeting the 1987 surveillance definition for AIDS. ** This category includes men who have sex with men who do not identify themselves as homosexual or bisexual. *** Copies of the technical report (5) containing additional information about the analyses on which this report is based can be obtained from the CDC National AIDS Clearinghouse, P.O. Box 6003, Rockville, MD 20849-6003; telephone 800-458-5231. **** These are countries in sub-Saharan Africa and in the Caribbean where a) most reported cases occur as a result of heterosexual transmission, b) the male-to-female ratio of cases is approximately 1:1, and c) injecting drug use and homosexual transmission occur at low levels. ***** This category includes men who have sex with men but who do not identify themselves as homosexual or bisexual. ****** AIDS-defining conditions are those listed in the 1987 surveillance definition for AIDS (4).

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