Development of Non-Hodgkin Lymphoma in a Cohort of Patients with Severe Human Immunodeficiency Virus (HIV) Infection on Long-Term Antiretroviral Therapy

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Objective: To describe the incidence of non-Hodgkin lymphoma in a group of patients with symptomatic human immunodeficiency virus (HIV) infection receiving long-term dideoxynucleoside antiretroviral therapy.

Design: We examined the records of all patients with the acquired immunodeficiency syndrome (AIDS) or severe AIDS-related complex who were entered into three long-term phase I trials of zidovudine (azidothymidine, AZT) or zidovudine-containing regimens at the National Cancer Institute between 1985 and 1987.

Setting: The Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland.

Participants: Fifty-five HIV-infected patients with AIDS or severe AIDS-related complex.

Measurements and Main Results: Eight of fifty-five patients (14.5%; 95% CI, 6.5% to 26.7%) developed a high-grade non-Hodgkin lymphoma of B-cell type, a median of 23.8 months (range, 13 to 35 months) after starting antiretroviral treatment. Using the method of Kaplan and Meier, the estimated probability of developing lymphoma by 30 months of therapy was 28.6% (CI, 13.7% to 50.3%) and by 36 months, 46.4% (CI, 19.6% to 75.5%). The patients who developed lymphoma had less than 100 T4 cells/mm³ for a median of 17.8 months (range, 7 to 35 months) and less than 50 T4 cells/mm³ for a median of 15.3 months (range, 5.5 to 35 months) before the diagnosis. All patients presented with non-Hodgkin lymphoma in extranodal sites, and two developed primary brain involvement in the setting of Toxoplasma infection.

Conclusion: Patients with symptomatic HIV infection who survive for up to 3 years on antiretroviral therapy may have a relatively high probability of developing non-Hodgkin lymphoma. Prolonged survival in the setting of profound immunosuppression with substantial T4-cell depletion is probably an important factor in the development of these lymphomas. However, a direct role of therapy itself cannot be totally discounted. As improved therapies for the treatment of HIV infection and its complications result in prolonged survival, non-Hodgkin lymphoma may become an increasingly significant problem.

In 1981, the acquired immunodeficiency syndrome (AIDS), a disorder now known to be caused by infection with human immunodeficiency virus (HIV), was first recognized as a new illness occurring in persons in certain risk groups (1-4). Soon after the recognition of AIDS as a new disease, the clustering of high-grade, non-Hodgkin B-cell lymphomas in persons in these same risk groups and infected with HIV was noted. These lymphomas frequently occurred in extranodal sites, particularly the central nervous system (5-14). In 1985, the definition of AIDS was expanded by the Centers for Disease Control (CDC) to include high-grade non-Hodgkin lymphoma as an AIDS-defining illness in certain clinical settings (15). At present, non-Hodgkin lymphoma is the AIDS-defining illness in approximately 3% of new cases of AIDS (16). The incidence of HIV-associated non-Hodgkin lymphoma continues to rise (17, 18).

The occurrence of non-Hodgkin lymphoma in other settings of immunosuppression has been recognized for years. Indeed, the interrelation between immunodeficiency and cancer has been a major focus of research for several decades. In 1973, the Immunodeficiency Cancer Registry was established to maintain a central registry of malignancies that develop in patients with genetically determined immunodeficiency diseases (19). As of 1987, nearly 500 such cases had been reported, of which 50.7% were non-Hodgkin lymphoma (20). In addition, an increased incidence of neoplasms has been documented in patients iatrogenically immunosuppressed after organ transplantation. Thirty-six percent of such neoplasms were non-Hodgkin lymphomas (21). Many of these tumors have unusual sites of presentation, including the central nervous system. Thus, it would appear that non-Hodgkin lymphoma occurs with substantially increased frequency in the setting of immunosuppression, particularly in patients with defects in T-cell function.

The course of HIV infection is changing as a result of therapeutic advances. In particular, the life expectancy of patients with HIV infection is presently increasing because of improved therapies for both HIV-associated infectious complications and HIV infection itself. There is relatively little information on the incidence of lymphoma in patients with AIDS who are followed longitudinally, particularly since the advent of antiretroviral therapy.

The National Cancer Institute (NCI) has a cohort of patients who have received anti-HIV therapy for an extended period (22-25). These patients are some of the

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earliest recipients of zidovudine (azidothymidine, AZT) and zidovudine-containing regimens and, thus, may provide data on the widespread use of such therapies. We have observed the development of non-Hodgkin lymphoma in an unexpectedly high number of these patients, particularly those who were long-term survivors with decreased T4 lymphocytes. It is possible that the increased cumulative incidence of such lymphomas is an ironic by-product of prolongation of survival by effective antiretroviral therapy.

Methods

Patients

We examined the charts of 55 HIV-seropositive patients receiving long-term dideoxynucleoside antiretroviral therapy who were entered into three phase 1 studies in the Clinical Oncology Program of the NCI from 1985 to 1987. The studies included a phase 1 study of zidovudine alone (29 patients) (22, 23); a pilot study of zidovudine with simultaneously administered acyclovir (8 patients) (24); and a pilot study of zidovudine alternating with 2',3'-dideoxyctydine (18 patients) (25). These were the only studies initiated during the period in which patients receiving antiretroviral therapy were followed for more than 6 months. All patients in these three trials had either AIDS or severe AIDS-related complex, those with the latter having either an AIDS-defining illness or a profound (more than 70%) loss of CD4 lymphocytes. In general, these patients were patients with AIDS or poor-prognosis AIDS-related complex who were clinically stable at the time of entry.

Of these 55 patients, 8 developed non-Hodgkin lymphoma. The diagnosis was made before death in 7 patients and after death in 1 patient. Each patient diagnosed before death had a staging evaluation and treatment at the NCI with combination chemotherapy, radiation therapy, or a combination of these modalities. All patients in the studies were followed at the Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland. Clinical and laboratory evaluations were done every 2 to 4 weeks, and patients were admitted for evaluations and treatment when medically indicated. In all patients, lymphocyte subsets reacting to Leu 3 (CD4+, T4+), helper-inducer T cells (or to Leu 2 (CD8+, T8+), suppressor-cytotoxic T cells) were periodically analyzed by flow cytometry (22). The 1987 revised CDC criteria for AIDS were used in defining the onset of each patient’s AIDS-defining illness (26).

Immunophenotyping

The immunologic phenotype of the lymphoma cells was determined by immunostaining with monoclonal antibodies to antigens expressed on B cells, T cells, and mononuclear phagocytes (27, 28). In six cases (Patients 2, 4, 5, 6, 7, and 8), immunostaining was done on paraffin sections using the avidin-biotin-complex immunoperoxidase technique as previously described (27). Cells were stained for the B-cell-associated antigen, L26; the T-cell-associated antigen, UCHL-1; and lysozyme. In Patients 1 and 3, immunostaining was done on air-dried cytocentrifuge preparations from the lung aspirate and peritoneal fluid, respectively (27). In Patient 3, cells derived from the pleural fluid were stained with monoclonal antibodies to CD45, CD14, and CD15. In Patients 1 and 3, immunostaining was done on paraffin sections using the avidin-biotin-complex immunoperoxidase technique as previously described (27). Immunostaining was done on paraffin sections using the avidin-biotin-complex immunoperoxidase technique as previously described (27). Cells were stained for the B-cell-associated antigen, L26; the T-cell-associated antigen, UCHL-1; and lysozyme. In Patients 1 and 3, immunostaining was done on air-dried cytocentrifuge preparations from the lung aspirate and peritoneal fluid, respectively (27). In Patient 3, cells derived from the pleural fluid were stained with monoclonal antibodies to CD45, CD14, and CD15. In Patients 1 and 3, immunostaining was done on paraffin sections using the avidin-biotin-complex immunoperoxidase technique as previously described (27). Immunostaining was done on paraffin sections using the avidin-biotin-complex immunoperoxidase technique as previously described (27). Cells were stained for the B-cell-associated antigen, L26; the T-cell-associated antigen, UCHL-1; and lysozyme. In Patients 1 and 3, immunostaining was done on air-dried cytocentrifuge preparations from the lung aspirate and peritoneal fluid, respectively (27). In Patient 3, cells derived from the pleural fluid were stained with monoclonal antibodies to CD45, CD14, and CD15.

Statistical Analysis

The method of Kaplan and Meier (30) was used to estimate the probability of lymphoma developing in this group of patients as a function of time on antiretroviral therapy. Follow-up was available to the time of death or to the present in 52 of the 55 patients: 3 patients lost to follow-up were censored at the most recent point at which data were available. Twenty-nine patients who died without developing non-Hodgkin lymphoma were censored at their time of death, and 15 other patients who are alive and have not developed non-Hodgkin lymphoma were censored at the time they were last known to be alive. Confidence intervals (CIs) for the Kaplan-Meier analysis were determined using the method of Rothman (31). The 95% confidence intervals for the overall proportion of patients developing lymphoma were calculated by an exact method (32). For each of the eight patients who developed non-Hodgkin lymphoma, the time elapsed from the initial decline of their T4-cell count below 100 or 50 cells/mm^3 to the development of lymphoma was calculated. In this analysis, two consecutive T4 counts below 100 or 50 cells/mm^3 were required, and the time was calculated from the first of these determinations.

Survival of patients with non-Hodgkin lymphoma was determined from the time the diagnostic biopsy was done until the time of death. Median values, with the appropriate ranges, were then determined for each time period.

Results

Non-Hodgkin lymphoma developed in 8 of the 55 patients (14.5%; CI, 6.5% to 26.7%). As analyzed by the method of Kaplan and Meier (30), the estimated probability of developing lymphoma within 30 months of starting antiretroviral therapy is 28.6% (CI, 13.7% to 50.3%) (Figure 1). After 36 months of therapy, the estimated probability of developing lymphoma increases to 46.4% (CI, 19.6% to 75.5%); this latter number is clearly based on a very small number of patients remaining at risk for development of lymphoma. Because 15 of the original 55 patients are still alive and without non-Hodgkin lymphoma, this number may increase with time. One patient (Patient 3) developed a second distinct lymphoma 16 months after the occurrence of his first non-Hodgkin lymphoma; however, only the first occurrence of lymphoma in this patient was considered in the above calculations.

The median T4-cell count at the initiation of antiretroviral therapy for all 55 patients was 74 cells/mm^3 (range, 0 to 953 cells/mm^3). Median survival for the 55 patients overall was 22 months (data not shown).

Patients who developed lymphoma had received antiretroviral therapy for a median of 23.8 months (range, 13 to 34.5 months) before the onset of lymphoma (Table 1). The median time from the diagnosis of their AIDS-defining illness to the development of non-Hodgkin lymphoma was 22.5 months (range, 9 to 77 months). Median T4-cell counts at initiation of antiretroviral therapy in these patients and at the occurrence of non-Hodgkin lymphoma was 26 cells/mm^3 (range, 8 to 135 cells/mm^3) and 6 cells/mm^3 (range, 4 to 21 cells/mm^3), respectively (data not shown). Patients who developed non-Hodgkin lymphoma had less than 100 T4 cells/mm^3 for a median time of 17.8 months (range, 7 to 35 months). In addition, these same patients had less than 50 T4 cells/mm^3 also subjected to immunoperoxidase staining on paraffin sections.
Discussion

The occurrence of non-Hodgkin lymphoma in the setting of HIV infection is well established, and high-grade non-Hodgkin lymphomas account for approximately 3% of the initial AIDS-defining illnesses in reported adult and adolescent cases of AIDS (5-14, 16, 26). However, little has been reported on the temporal development of non-Hodgkin lymphoma in cohorts of patients with AIDS or severe AIDS-related complex, particularly since the development of effective antiretroviral therapy. We selected three of these protocols for analysis because they represent the first three studies by our group in which patients were followed for long periods of time on antiretroviral therapy. Included in this cohort are the first patients to have ever received zidovudine (22). However, we have also observed the development of lymphoma in HIV-infected patients on other antiretroviral protocols. In particular, one patient developed stage IE primary small-noncleaved-cell lymphoma of the liver while receiving dideoxyadenosine in a phase I trial (33), whereas a second patient initially entered in a study of recombinant soluble CD4 developed stage IVB large-cell immunoblastic lymphoma. A third patient initially entered in the phase I study of 2’,3’-dideoxyxycytidine subsequently developed stage IVB Hodgkin disease.

The patients we describe were followed for up to 38 months while receiving continuous antiretroviral therapy with zidovudine or zidovudine-containing regimens. It is possible that because of the screening process (for example, patients had to be free of active opportunistic infections), the study patients are not representative of patients with AIDS or AIDS-related complex in the general population. Nevertheless, the estimated probability of lymphoma developing in 46.4% of patients by 36 months after starting antiretroviral therapy is a striking finding, although the CI of 19.6% to 75.5% reflects the variability of the estimate at 36 months. Further evaluations of larger populations will be needed to define more accurately the probability of patients with severe HIV infection on antiretroviral therapy developing a non-Hodgkin lymphoma. Our data indicate that non-Hodgkin lymphoma may well become a limiting factor in the survival of patients with HIV infection as improved antiretroviral therapies are developed. It will be important to learn how to prevent this complication. For example, earlier intervention with antiretroviral therapy may delay the decline of the T4-cell count below 100/mm³ (34, 35), and this may result in a lower incidence of lymphoma. This possibility requires further study.

Because lymphomas can be difficult to diagnose in patients with HIV infection, non-Hodgkin lymphoma in such patients may be underreported. For example, two cases of lymphoma in this study occurred in patients (Patients 5 and 7) being treated for cerebral toxoplasmosis who developed new or enlarging brain lesions. Also, in none of the eight cases had the diagnosis been established by biopsy of a lymph node. Patients with lymphoma in the setting of AIDS pose substantial therapeutic challenges. Despite the interventions used, the overall survival in the patients after the development of
lymphoma was poor (Table 1). One patient developed a
dramatic flare of his Kaposi sarcoma when administered
a steroid-containing chemotherapeutic regimen for the
lymphoma, which is consistent with previous reports
(36-38). Improved therapeutic strategies for these con-
tions are needed, and this will be an important area for
future research.

Although the mechanism underlying the development
of AIDS-related non-Hodgkin lymphoma is not known,
many interrelated factors have been postulated to be
involved. It has been found that patients with AIDS or
AIDS-related complex have a polyclonal B-cell prolifer-
ative lymph node expansion (39-41). Several factors
may contribute to this process. Polyclonal B-cell activ-
cation can be a direct response to HIV infection, either
through mitogenic or antigenic stimulation (42-44).
Patients with HIV infection have increased numbers
of circulating Epstein-Barr-virus-infected cells, which may
in part be due to these patients' profound defect in
T-cell immunity (44, 45). However, direct involvement
of Epstein-Barr virus in tumor has not been docu-
mented in most patients with HIV-associated lymph-
oma, and this issue bears further study. Whatever the
mechanism, polyclonal B-cell proliferation may provide
a milieu for the development of transforming events.
Although these transforming events have not yet been
delineated, there is evidence that in many cases of
AIDS-related Burkitt lymphoma, a c-myc oncogene re-
arrangement similar to that seen in endemic spor-
adic Burkitt lymphoma occurs (41, 46, 47). Unregu-
lated oncogenic expression could then become the
proximal cause of the transformed state in patients.
Alternately, it is possible that the replication of an as
yet unidentified oncogenic virus may be enhanced in
patients infected with HIV.

Although the cellular events involved in the patho-
genesis of AIDS-related non-Hodgkin lymphoma have
not been elucidated, immunosuppression probably plays
a substantial role (48). The development of high-grade,
B-cell lymphomas (particularly at extranodal sites) in
patients with other forms of immunodeficiency, either
primary (for example, the Wiskott-Aldrich syndrome
and ataxia telangiectasia) or that resulting from immu-
nosuppressive therapy, has been well documented (19-
21, 49-54). Prolongation of survival in patients with pri-
mary immunodeficiency has been felt to increase the
cumulative risk for the development of a non-Hodgkin
lymphoma. In patients with the Wiskott-Aldrich syn-
drome, for example, the overall risk for developing a
malignancy has been calculated to be 126 times that of
the general population, with a cumulative risk of 2% per
year for the first 25 years of life. Most of these mali-
gnancies are lymphoreticular in origin (74.5%), and high-
grade, B-cell lymphomas, frequently occurring in extra-
nodal sites (particularly the central nervous system),
predominate (51, 53). Thus, with enhanced control of
infection and other therapeutic advances, the cumula-
tive probability of such patients developing a non-
Hodgkin lymphoma has increased along with life ex-
pectancy.

Recent evidence suggests that as a result of clinical
advances in the therapy for HIV infection (22, 55-57),
patients with this disease are experiencing an improve-
ment in survival. For example, the median survival of
patients diagnosed with AIDS reported to the San Fran-
cisco Department of Public Health has increased from
10.8 months for those diagnosed in 1985 to 15.6 months
for those diagnosed in 1987 (58). This improvement has
been particularly striking for those who present with
Pneumocystis carinii pneumonia as their AIDS-defining
illness; in these patients, the median survival during the
same period has increased from 10.5 to 17.9 months
(58). Although earlier diagnosis and improved methods
of treatment and prophylaxis of P. carinii pneumonia

**Table 1. Clinical Information on Patients with Human Immunodeficiency Virus (HIV) Who Developed Non-Hodgkin Lymphoma**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis at Time of Entry</th>
<th>Anti-HIV Regimen</th>
<th>Time on Anti-HIV Therapy before Lymphoma</th>
<th>Time from Diagnosis of AIDS to Lymphoma</th>
<th>Time with a T4-Cell Count of Less Than 100/mm³ before Lymphoma</th>
<th>Survival Time from Diagnosis of Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AIDS (Pneumocystis carinii pneumonia)</td>
<td>zidovudine</td>
<td>20.5</td>
<td>24</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>AIDS (the wasting syndrome)</td>
<td>zidovudine</td>
<td>13</td>
<td>13</td>
<td>12</td>
<td>4.4</td>
</tr>
<tr>
<td>3*</td>
<td>AIDS (Kaposi sarcoma)</td>
<td>zidovudine</td>
<td>28</td>
<td>32</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>AIDS (Kaposi sarcoma)</td>
<td>zidovudine and acyclovir†</td>
<td>16.5</td>
<td>21</td>
<td>16.5</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>AIDS-related complex</td>
<td>zidovudine and dideoxycytidine‡</td>
<td>16.5</td>
<td>9</td>
<td>16.5</td>
<td>3.2</td>
</tr>
<tr>
<td>6</td>
<td>AIDS-related complex</td>
<td>zidovudine and acyclovir†</td>
<td>27</td>
<td>10</td>
<td>21</td>
<td>1.5</td>
</tr>
<tr>
<td>7</td>
<td>AIDS (P. carinii pneumonia)</td>
<td>zidovudine and dideoxycytidine‡</td>
<td>30</td>
<td>35</td>
<td>27</td>
<td>2.5</td>
</tr>
<tr>
<td>8</td>
<td>AIDS (Kaposi sarcoma)</td>
<td>zidovudine and acyclovir†</td>
<td>34.5</td>
<td>77</td>
<td>35</td>
<td>Diagnosed at autopsy</td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
<td></td>
<td>23.8</td>
<td>22.5</td>
<td>17.8</td>
<td>2.5</td>
</tr>
</tbody>
</table>

* Patient 1 developed a stage IE small-nodular-cell lymphoma, B-cell type, of the brain 16 months after occurrence of his first non-Hodgkin lymphoma.
† Simultaneous zidovudine and acyclovir.
‡ Alternating weekly zidovudine and 2',3'-dideoxycytidine.
§ The median survival of patients presenting with primary visceral disease (Patients 1, 2, and 3) was 7 months (range, 0.4 to 18 months), whereas
that of the patients presenting with primary central nervous system disease (Patients 4, 5, 6, and 7) was 1.8 months (range, 0.6 to 3.2 months).
Table 2. Pathologic Findings in the Eight Patients with Human Immunodeficiency Virus (HIV)-Associated Non-Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cell Type</th>
<th>Immunologic Phenotype*</th>
<th>Stage at Diagnosis</th>
<th>Site of Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Large-cell immunoblastic</td>
<td>B cell</td>
<td>IE</td>
<td>Lung</td>
</tr>
<tr>
<td>2</td>
<td>Large-cell immunoblastic</td>
<td>B cell</td>
<td>IV</td>
<td>Esophagus, liver, spleen</td>
</tr>
<tr>
<td>3†</td>
<td>Large-cell immunoblastic</td>
<td>Null cell</td>
<td>IV</td>
<td>Ascitic fluid; pleural effusion</td>
</tr>
<tr>
<td>4</td>
<td>Small-nonecleaved</td>
<td>B cell</td>
<td>IE</td>
<td>Brain</td>
</tr>
<tr>
<td>5</td>
<td>Small-nonecleaved</td>
<td>B cell</td>
<td>IE</td>
<td>Brain</td>
</tr>
<tr>
<td>6</td>
<td>Large-cell immunoblastic</td>
<td>B cell</td>
<td>IE</td>
<td>Brain</td>
</tr>
<tr>
<td>7</td>
<td>Small-nonecleaved</td>
<td>B cell</td>
<td>IE</td>
<td>Brain</td>
</tr>
<tr>
<td>8</td>
<td>Small-nonecleaved</td>
<td>B cell</td>
<td>IE</td>
<td>Leptomeninges</td>
</tr>
</tbody>
</table>

* B cell = B-cell markers present; null cell = negative for B-, T-, and histiocytic markers.
† Patient 3 developed a stage IE, small-nonecleaved-cell lymphoma. B-cell type, of the brain 16 months after his initial occurrence of non-Hodgkin lymphoma.

may have contributed to this phenomenon (59-63), there is evidence that the use of zidovudine has resulted in prolonged survival over and above any effect of prophylaxis for *P. carinii* pneumonia (56. 58, 64). The median survival of 22 months (CI, 33.5% to 62.4%) in this study population lends further support to this impression. Therefore, patients with profound immunodeficiency are living longer, theoretically allowing more time for the development of non-Hodgkin lymphoma or other malignancies.

Patients in our series had AIDS for a median period of 22.5 months (range, 9 to 77 months) and had less than 50 T4 lymphocytes/mm$^3$ for a median of 15.3 months (range, 5.5 to 35 months) before the development of lymphoma. Before the development of antiretroviral therapy, it would have been relatively unusual to have such prolonged survival after the development of AIDS or profound T4-cell depletion. Lymphomas may develop in HIV-infected patients at any point in the course of their illness (7, 9-14). However, although the numbers are small, the findings here suggest that patients who survive for long periods with profound immunodeficiency manifested by less than 50 T4 cells/mm$^3$ may have a particularly high likelihood of developing high-grade lymphomas. Indeed, assuming a 10-year incubation period from the initial infection with HIV to the development of AIDS (65) and that non-Hodgkin lymphoma represents 3% of AIDS-defining illnesses, then the yearly incidence of the development of non-Hodgkin lymphoma in early stages of HIV infection is approximately 0.3%. If we were to assume that the development of non-Hodgkin lymphoma is constant over the period of follow-up, then the estimated incidence of non-Hodgkin lymphoma in our cohort of patients with AIDS and severe AIDS-related complex is nearly 9% per year of follow-up. This wide disparity again indicates that non-Hodgkin lymphoma is much more likely to develop in the setting of severe immunodeficiency and thus may be considered an "opportunistic" tumor.

Finally, one must wonder if zidovudine or other antiretroviral drugs directly contribute to the development of lymphoma in these patients. Zidovudine can act as a mutagen, and vaginal malignancies have been reported to develop with increased frequency in mice and rats receiving lifelong high-dose zidovudine (66, 67). Further research is needed to determine if the same effects occur in humans. The lymphomas in our patients are of the same type as those that typically develop in the setting of HIV infection (Table 2), suggesting that zidovudine therapy was less likely to be a direct cause of these tumors. There is no question that zidovudine is associated with improved rates of morbidity and mortality in persons with HIV infection. Nevertheless, the direct oncogenic potential of zidovudine and related drugs cannot be discounted. This serves as an incentive to find the lowest effective doses for such agents. It will be important to sort out the relative contribution of immunosuppression, prolonged survival, a possible effect of antiretroviral therapy, and perhaps other unrecognized factors in the development of lymphomas to learn how to minimize the occurrence of this condition.

The AIDS epidemic is already changing the demographics of lymphoma in the United States, and such effects are likely to be amplified in the near future. In 1989, there were 34,598 cases of AIDS in adults and adolescents reported to the CDC; in 948 (3%) cases, patients initially presented with high-grade non-Hodgkin lymphoma as their AIDS-defining illness (16). The number of cases of AIDS is expected to rise over the next decade. As stated previously, there was a 14.5% incidence of non-Hodgkin lymphoma in our cohort of patients with AIDS or severe AIDS-related complex on long-term antiretroviral therapy. If this sample is roughly representative and one presumes that none of the remaining 15 patients who are alive without non-Hodgkin lymphoma will develop this malignancy, then of the population initially diagnosed with AIDS in 1989, nearly 4,900 (CI, 2,187 to 8,985) of those patients with an AIDS-defining illness other than lymphoma may be estimated to develop an "opportunistic" non-Hodgkin lymphoma at some time during their illness. Although this sample selected for phase I studies may not be representative and many other factors may influence this extrapolation, the results do suggest that the incidence of non-Hodgkin lymphoma in the setting of AIDS is likely to significantly increase with time.

In the last 17 years, the Surveillance, Epidemiology, and End Results (SEER) Program data base of the NCI has shown a steady increase in the incidence of non-Hodgkin lymphoma. From 1973 to 1987 (the last year in which final figures are available), the incidence of non-
Hodgkin lymphoma increased by more than 50% (68). The factors contributing to this rise are not known. The rise was observed before the epidemic of HIV infection, and available information indicates that lymphomas associated with AIDS account for only a very small percentage of this increase. For example, in 1990, there will be an estimated 36,000 cases of non-Hodgkin lymphoma, and approximately 18,000 non-Hodgkin lymphoma-related deaths. Most of these estimated cases will be outside the setting of HIV infection. The addition of an increasing number of cases of AIDS-related non-Hodgkin lymphoma to the HIV-independent group will represent a new burden and pose crucial challenges to physicians and the health care delivery system of the United States. For this reason, it is important that we learn more about the prevention and optimal treatment of this formidable complication of HIV infection.

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