A Prognostic Index for Systemic AIDS-Related Non-Hodgkin Lymphoma Treated in the Era of Highly Active Antiretroviral Therapy

Mark Bower, MA, PhD; Brian Gazzard, MD; Sundhiya Mandalia, PhD; Tom Newsom-Davis, MB BS; Christina Thirlwell, MB BS; Tony Dhillon, MB BS; Anne Marie Young, MB BS; Tom Powles, MD; Andrew Gaya, MB BS; Mark Nelson, MD; and Justin Stebbing, MA, PhD

Background: **The established International Prognostic Index for lymphomas has not included patients with systemic AIDS-related non-Hodgkin lymphoma.**

Objective: **To establish the most appropriate prognostic index for use in patients with systemic AIDS-related non-Hodgkin lymphoma.**

Design: **A prospective study involving univariate and multivariable analyses of patients with AIDS-related non-Hodgkin lymphoma whose data were used to examine standard and new criteria for survival after diagnosis.**

Setting: **The Chelsea and Westminster cohort of HIV-1–infected persons.**

Patients: **9621 HIV-positive patients, 111 in whom AIDS-related non-Hodgkin lymphoma was treated after 1996, in the era of highly active antiretroviral therapy (HAART).**

Intervention: **Cox proportional hazards regression analysis to determine the prognostic significance of multiple clinicopathologic variables.**

Results: **Survival of patients with AIDS-related non-Hodgkin lymphoma has increased in the HAART era (log-rank chi-square, 9.23; $P = 0.002$). Univariate analyses using the established International Prognostic Index factors of age, tumor stage, lactate dehydrogenase level, Eastern Cooperative Oncology Group performance status, and number of extranodal sites were confirmed to be significant variables. Regression modeling for patients in whom disease was diagnosed after 1996 revealed only 2 independent predictors of death: International Prognostic Index risk group and CD4 cell count. These predictors yielded 4 internally validated risk strata with predicted 1-year survival rates of 82%, 47%, 20%, and 15% ($P < 0.001$). Prognostic risk scores in the highest quartile yielded a likelihood ratio for death of 7.90 (hazard ratio, 1.0), whereas a prognostic score less than 1.0 yielded a likelihood ratio of 0.23 (hazard ratio, 0.15 [95% CI, 0.06 to 0.33]).**

Limitations: **The sample was small, and different HAART regimens were used.**

Conclusions: **For patients with AIDS-related non-Hodgkin lymphoma that was diagnosed in the era of HAART, application of the International Prognostic Index remains useful. The addition of CD4 cell count provides further independent prognostic information. Patients who present with AIDS-related non-Hodgkin lymphoma and a low CD4 cell count have a poor prognosis; this information can be used to guide therapeutic options.**

Ann Intern Med. 2005;143:265-273. www.annals.org
For author affiliations, see end of text.

The lymphomas are a diverse group of malignant disorders that vary in their molecular features, genetics, clinical presentation, treatment, and outcome. Major advances in our understanding of the biology of these diseases have been made, leading to new therapies and classifications. Although combination chemotherapy cures intermediate- or high-grade aggressive non-Hodgkin lymphomas in many patients, approximately 50% of patients die of the disease (1). Because Ann Arbor disease staging does not predict outcome (2, 3), the International Prognostic Index was introduced in 1993 to segregate aggressive lymphomas in terms of survival (4). From 2031 patients studied, 4 risk groups were derived on the basis of age, tumor stage, serum lactate dehydrogenase level, performance status, and number of extranodal disease sites.

As we enter the third decade of the AIDS epidemic, it is apparent that many cancers are more common in people infected with HIV. Non-Hodgkin lymphoma remains the second most common tumor in such patients (after Kaposi sarcoma), and the rate of death from systemic AIDS-related non-Hodgkin lymphoma remains high (5, 6). The median duration of survival reported with chemotherapy before the availability of highly active antiretroviral therapy (HAART) was 2 to 13 months (7). The outcome of AIDS-related non-Hodgkin lymphoma appears to have improved in the post-HAART era, and phase II studies describe median duration of survival of 15 to 34 months (8–15), an interval similar to that observed among all patients with advanced-stage, high-grade non-Hodgkin lymphoma. It is hypothesized that these improvements are associated with a change in prognostic factors. We sought to develop a new prognostic model for HIV-associated non-Hodgkin lymphoma in the era of HAART, a treatment that has been available in established market economies since 1996.

Small prognostic studies of AIDS-related non-Hodgkin lymphoma in patients who presented in the pre-HAART era suggest that application of the International Prognostic Index may be useful in HIV-infected patients (16, 17). We therefore aimed to confirm the validity of the International Prognostic Index, to identify additional prog-

See also:

Print
Editors' Notes 266
Summary for Patients I-28

Web-Only
Conversion of figures and tables into slides

Context

The International Prognostic Index (IPI) predicts survival in patients with lymphoma, but its applicability to AIDS-related lymphomas in the era of highly active antiretroviral therapy has not been evaluated. The IPI stratifies patients into risk groups on the basis of age, tumor stage, serum lactate dehydrogenase levels, performance status, and number of extranodal sites.

Contribution

Among 111 patients with AIDS-related lymphoma diagnosed since 1996, the IPI and CD4 cell count separated patients into 4 strata with 1-year survival rates of 82%, 47%, 20%, and 15%.

Implications

The IPI and CD4 cell count can help physicians predict the prognosis of patients with AIDS-related lymphoma.

–The Editors

nostic factors for patients with AIDS-related non-Hodgkin lymphoma in the era of HAART, and to devise a new prognostic model for these patients.

METHODS

Patients

The Chelsea and Westminster HIV cohort is one of the largest in Europe. Clinical information on 9621 HIV-1 seropositive patients has been accumulated since 1986. All patients in whom lymphoma was diagnosed were identified prospectively; these included 215 patients with AIDS-related non-Hodgkin lymphoma, 60 with primary central nervous system lymphomas, and 26 with Hodgkin disease.

We estimated prognostic factors for AIDS-related non-Hodgkin lymphoma in the HAART era in patients receiving HAART. Patients with Hodgkin disease and primary central nervous system lymphomas were excluded. The HAART era is defined as commencing on 1 January 1996, when this treatment became routinely available at our institution and many others. One hundred eleven patients with AIDS-related non-Hodgkin lymphoma received a diagnosis after this date. Highly active antiretroviral therapy is defined as a combination of at least 3 antiretroviral agents, including a nucleoside analogue backbone combined with a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor or both classes of drug, according to generally accepted definitions (18).

All patients had histologically confirmed diagnoses of AIDS-related non-Hodgkin lymphoma, and more than 95% had aggressive B-cell disease. All patients had full staging at diagnosis, including examination of bone marrow and cerebrospinal fluid. All patients received a single dose of intrathecal chemoprophylaxis with their staging lumbar puncture. Patients with Burkitt lymphoma or bone marrow, paranasal, or paraspinal involvement received a further 5 doses of intrathecal chemotherapy. Between 1996 and 1998, the patients with AIDS-related non-Hodgkin lymphoma diagnosed in the era of HAART received chemotherapy with bleomycin, etoposide, vincristine, methotrexate, prednisolone/cyclophosphamide, and doxorubicin (18 patients) or cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisone (3 patients). A further 21 patients received chemotherapy with cisplatin, vinblastine, and bleomycin (17 patients); radiotherapy alone (3 patients); or best supportive care (1 patient). Since 1999, 59 patients have been treated with infused cyclophosphamide, doxorubicin, and etoposide chemotherapy (13, 19); 2 have received cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisone; and 8 (including 3 in whom disease was diagnosed at autopsy) received best supportive care only.

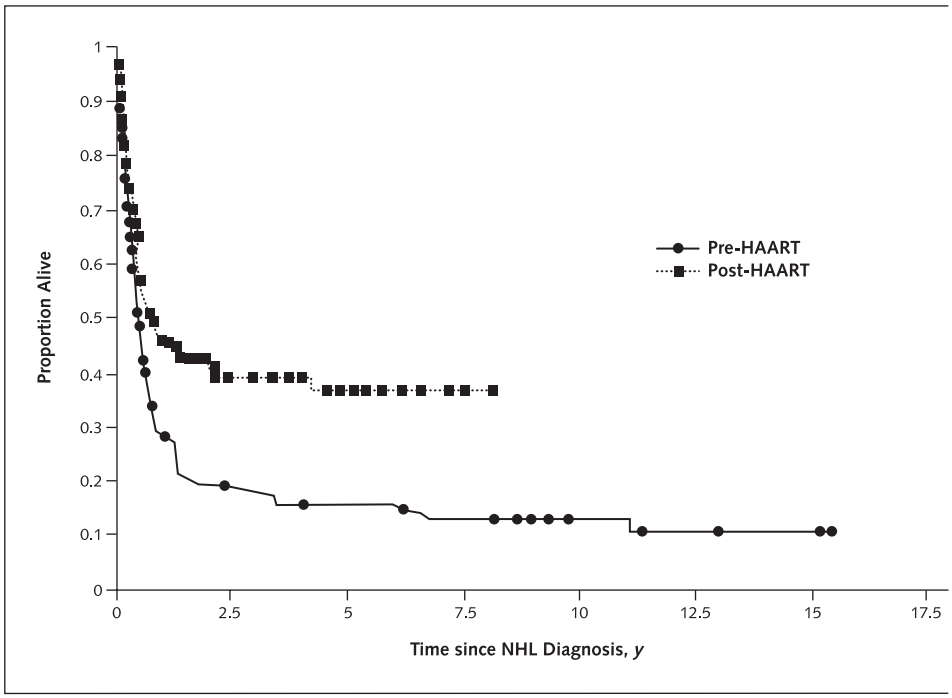
The CD4 cell subset analysis was performed by using whole blood stained with murine antihuman monoclonal antibodies to CD4 (TetraOne [Beckman Coulter, High Wycombe, United Kingdom]) on an Epics XL-MCL multiparametric flow cytometer (Beckman Coulter).

Statistical Analysis

Variables were compared between groups by using the chi-square test for nominal variables and the Mann–Whitney U test for nonparametric variables. Survival was calculated from the day of diagnosis of AIDS-related non-Hodgkin lymphoma until death or the date of last follow-up. Curves for overall duration of survival were plotted according to the method of Kaplan and Meier (20). The log-rank method was used to test for the significance of differences in survival distributions (21) and univariate Cox proportional hazards regression analysis was used to determine the prognostic significance of clinicopathologic variables at presentation with AIDS-related non-Hodgkin lymphoma. Cox multivariable modeling was used to determine independent variables predictive of survival by entering all variables that were significant in univariate analysis (at a level of $P < 0.15$). A prognostic model was then constructed from these data by dividing each β coefficient in the final multivariable models with significant predictors by the lowest β to 2 decimal places. Using these point values, a risk score was assigned to each patient by summing the values for each risk factor present. The prognostic score derived was then grouped into quartiles so that approximately equal numbers of patients were included in each of these categories. The chosen cutoff values for the prognostic risk scores were further investigated by using receiver-operating characteristic methods.

Because the performance of prognostic models may be optimistically overestimated when they are determined on the basis of a small sample, a higher apparent performance than that observed in an independent sample of patients not considered in the modeling process may result (22, 23). To formally confirm the validity of the prognostic index based on a small sample, we used the internal em-

Figure 1. **Kaplan–Meier overall survival curve for 215 patients with systemic AIDS-related non-Hodgkin lymphoma (*NHL*) diagnosed in the era before (104 patients) and after (111 patients) highly active antiretroviral therapy (*HAART*).**



All causes of death are included (log-rank chi-square, 9.23; $P = 0.002$).

pirical distribution function, placing equal probabilities on every original data value, as described elsewhere (24). Nonparametric bootstrapping was used to draw a sample by selecting independent bootstrap values (25–28). Each of these consisted of 111 data points drawn with replacement where each sample unit was replaced in the data set, such that they could be chosen subsequently in random selection. Resampled data were used to generate bootstrap estimates of the hazard ratio, based on the multivariable model presented for the HAART era. These were determined by 2000 iterations of such resampling.

RESULTS

The overall duration of survival was significantly greater for patients in whom non-Hodgkin lymphoma was diagnosed in the HAART era compared with those in whom the disease was diagnosed in the pre-HAART era (log-rank chi-square, 9.23; $P = 0.002$) (**Figure 1**). Among the 215 patients with AIDS-related non-Hodgkin lymphoma, the actuarial overall survival rate, including all causes of death, was 32% at 2 years (95% CI, 25% to 39%) and 26% at 5 years (CI, 19% to 33%).

Although patients whose disease was diagnosed in the HAART era had significantly higher CD4 cell counts at presentation (median value, 144×10^6 cells/L vs. 45×10^6 cells/L; $P < 0.001$), better Eastern Cooperative Oncology Group performance status ($P = 0.003$), and fewer previous AIDS-defining illnesses ($P < 0.001$) than did patients whose disease was diagnosed before the HAART era, the former patients were older ($P < 0.001$) and had a higher serum lactate dehydrogenase level ($P < 0.001$) (data not shown). Univariate Cox proportional hazards regression analysis identified many prognostic factors for survival after diagnosis of AIDS-related non-Hodgkin lymphoma in the HAART era, including low CD4 cell count, stage III or IV disease, B-class symptoms, lower Eastern Cooperative Oncology Group performance status, bone marrow and meningeal involvement, and more than 1 extranodal site at presentation (**Table 1**).

The originally described International Prognostic Index criteria (age, disease stage, serum lactate dehydrogenase, performance status, and extent of extranodal disease) were analyzed separately to assess their prognostic significance. All factors except age were found to be of significant prognostic value; however, only 6 patients were older than 60 years of age. These criteria were grouped to create 4 risk categories: low, low-intermediate, high-intermediate, and high. International Prognostic Index risk group was a significant prognostic factor in both patients whose disease was diagnosed in the HAART era ($P < 0.001$) and those in whom disease was diagnosed before HAART ($P = 0.011$). The International Prognostic Index was found to be significantly associated with overall survival for the whole cohort combined ($P < 0.001$).

Multivariable modeling was performed by including the International Prognostic Index scores and excluding

Table 1. **Clinicopathologic Characteristics of 111 Patients with AIDS-Related Non-Hodgkin Lymphoma Diagnosed in the Era of Highly Active Antiretroviral Therapy, and Likelihood of Death after Diagnosis, by Univariate Cox Proportional Hazards Regression**

Variable in Univariate Model	Patients Who Died (n = 62), n (%)*†	Hazard Ratio (95% CI)
Sex		
Female	6 (67)	1.01 (0.98–1.03)
Male	56 (55)	1.211 (0.52–2.81)
CD4 cell count, by interquartile range		
$<22 \times 10^6$ cells/L	15 (82)	3.75 (1.75–8.04)
23–93 $\times 10^6$ cells/L	14 (70)	2.25 (1.06–4.79)
94–231 $\times 10^6$ cells/L	20 (54)	1.43 (0.71–2.88)
$>231 \times 10^6$ cells/L	13 (36)	1
CD4 cell count		
$<100 \times 10^6$ cells/L	30 (76)	2.17 (1.31–3.59)
$\geq 100 \times 10^6$ cells/L	32 (44)	1
Previous AIDS diagnosis		
Yes	19 (64)	1.23 (0.72–2.11)
No	43 (53)	1
Stage		
I or II	7 (27)	0.30 (0.14–0.66)
III or IV	55 (65)	1
Class of symptoms		
A	8 (31)	0.35 (0.17–0.73)
B	54 (64)	1
Eastern Cooperative Oncology Group performance status		
<1	14 (25)	0.20 (0.10–0.37)
>1	48 (77)	1
Bone marrow involvement		
Yes	17 (77)	2.41 (1.36–4.26)
No	45 (51)	1
Meningeal disease at diagnosis		
Yes	14 (82)	2.26 (1.24–4.12)
No	48 (51)	1
Liver involved at presentation		
Yes	23 (64)	1.32 (0.79–2.20)
No	39 (52)	1
>1 extranodal site at presentation		
Yes	32 (68)	1.76 (1.07–2.90)
No	30 (47)	1
Increased serum lactate dehydrogenase level		
Yes	46 (64)	1.76 (0.99–3.10)
No	16 (41)	1
Burkitt lymphoma		
Yes	11 (79)	2.15 (1.11–4.16)
No	51 (53)	1
Hepatitis C diagnosed before AIDS-related lymphoma		
Not tested	38 (51)	0.82 (0.49–1.30)
Positive	2 (50)	0.77 (0.18–3.26)
Negative	22 (67)	1
Most recent hepatitis C status		
Not tested	50 (64)	2.30 (1.19–4.43)
Positive	1 (25)	0.52 (0.07–4.05)
Negative	11 (37)	1
International Prognostic Index risk group		
High	25 (96)	7.66 (3.11–18.85)
High-intermediate	18 (60)	3.42 (1.35–8.63)
Low-intermediate	13 (42)	1.90 (0.72–5.01)
Low	6 (25)	1

* Percentages are derived from the full cohort of 111 patients. For example, 56 of the 62 patients who died were male, and these patients made up 55% of men with AIDS-related lymphoma diagnosed in the era of highly active antiretroviral therapy (that is, 102 of 111 patients were male).
† The mean age of the patients who died was 44.2 years, SD 10.2.

Table 2. **Multivariable Cox Proportional Hazards Regression Model Showing Significant Independent Predictors of Death after Diagnosis of AIDS-Related Non-Hodgkin Lymphoma in the Era of Highly Active Antiretroviral Therapy***

Variable	Hazard Ratio (95% CI)†	*P* Value	Hazard Ratio Bootstrap Estimate (Efron 95th-Percentile Confidence Limits)
CD4 cell count			
$<100 \times 10^6$ cells/L	2.08 (1.20–3.60)	0.009	2.39 (2.32–2.47)
$\geq 100 \times 10^6$ cells/L	1		1
International Prognostic Index risk group			
High	4.88 (1.544–15.43)	0.007	6.67 (6.02–7.33)
High-intermediate	2.74 (0.94–8.04)	0.066	3.40 (3.15–3.65)
Low-intermediate	1.73 (0.57–5.21)	>0.2	2.16 (1.20–2.32)
Low	1		1

* The model includes the International Prognostic Index risk group and excludes the list of variables from which this was derived that were significant in the univariate model. The validity of the prognostic score was calculated internally on the 111 patients in whom AIDS-related non-Hodgkin lymphoma was diagnosed in the era of highly active antiretroviral therapy; average bootstrap-estimated hazard ratios are shown, with corresponding Efron 95th-percentile confidence limits (24–27).
† Adjusted for age, sex, type B symptoms, bone marrow and meningeal disease at diagnosis, Burkitt lymphoma, and other variables in the model (see text).

the variables from which this score is derived (age, disease stage, extranodal disease, serum lactate dehydrogenase level, and performance status) to identify more variables that would add to this model. Multivariable Cox proportional hazards regression modeling for patients in whom disease was diagnosed since 1996 revealed only 2 independent predictors of death: International Prognostic Index risk group and CD4 cell count at presentation (**Table 2**). A prognostic weighting was derived for each variable, and a total prognostic risk score was calculated by addition of these weightings for both variables (**Table 3**). The highest prognostic weightings were high International Prognostic Index score (2.9), high-intermediate International Prognostic Index score (1.84), and CD4 cell count less than 100×10^6 cells/L (1.34). As with the International Prognostic Index, the prognostic risk scores were divided into quartiles: less than 1.0, 1.0 to 1.83, 1.84 to 2.90, and greater than 2.90. **Figure 2** shows Kaplan–Meier survival curves for each quartile group, and **Table 4** shows the likelihood ratio for death.

Bootstrap resampling was used to estimate the hazard ratio of the final multivariable model (24). Robust parameter estimates and standard errors were calculated from these models. Six hundred bootstrap samples were generated by using resampling with replacement, and averages of these samples are presented to demonstrate the validity of the prognostic index. The average bootstrap-estimated hazard ratios shown in **Table 2** for both CD4 cell count and the International Prognostic Index risk groups all overlap with the predicted 95% CIs calculated by using Cox proportional hazards regression based on the study sample. In addition, the Efron 95th-percentile confidence limits fall within this interval, indicating internal validity between predicted hazard ratios and bootstrap-estimated hazard ratios (25–28). Validity of predicted hazard ratios were also confirmed in a separate analysis on the patients who received a diagnosis before the era of HAART.

Table 3. **Prognostic Weightings Used To Yield the Total Prognostic Risk Score***

Variable	Weighting
CD4 cell count	
$<100 \times 10^6$ cells/L	1.34
$>100 \times 10^6$ cells/L	0
International Prognostic Index risk group	
High	2.90
High-intermediate	1.84
Low-intermediate	1
Low	0

* See Table 4 for results of application of the total prognostic risk score.

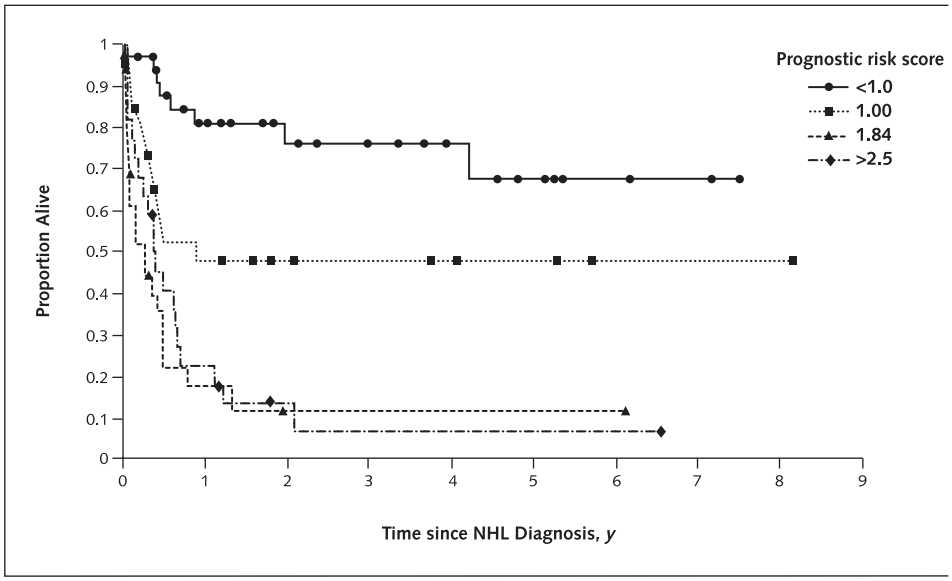
In the HAART era, a prognostic risk score greater than 2.90 yielded a likelihood ratio for death of 7.90 (hazard ratio, 1.0), whereas a prognostic risk score less than 1.0 yielded a likelihood ratio of 0.23 (hazard ratio, 0.15 [95% CI, 0.06 to 0.33]). A receiver-operating characteristic curve analysis of this model demonstrated the sensitivity and specificity of the cutoff values of the prognostic risk scores derived from Cox proportional hazards regression coefficient (**Figure 3**).

DISCUSSION

The aim of this prospective cohort study was to assess the validity of the International Prognostic Index in identifying specific risk groups with AIDS-related non-Hodgkin lymphoma in the HAART era and to propose additional prognostic markers in these patients. The International Prognostic Index (4) remains clinically useful in patients with AIDS-related non-Hodgkin lymphoma that was diagnosed during the HAART era. In addition, the CD4 cell count remains an independent significant prognostic variable ($P = 0.009$).

When all 215 patients with AIDS-related non-Hodgkin lymphoma were combined as a single cohort, we found that 3 other variables other than established International Prognostic Index risk group ($P < 0.001$ for a high International Prognostic Index score vs. other score catego-

Figure 2. **Product-limit survival plot for 111 patients with systemic AIDS-related non-Hodgkin lymphoma (*NHL*) diagnosed in the era of highly active antiretroviral therapy.**



Patients are separated into whole-cohort quartiles of prognostic risk score. All causes of death are included. $P < 0.001$ (log-rank chi-square test).

ries) were significant independent predictors of death: previous AIDS-defining illnesses ($P = 0.016$), presence of Burkitt lymphoma ($P = 0.026$), and CD4 cell count at diagnosis ($P < 0.001$). The disappearance of previous AIDS-defining illnesses and reduced incidence of Burkitt lymphoma in the era of HAART has probably resulted from improvement in the immune status of these patients as measured by the increase in CD4 cell count at presentation over these periods (1986 to 1995 vs. 1996 to the present; $P < 0.001$). Although our HAART-era data may be confounded by the different therapies used, we have previously shown no difference in the prevention of AIDS-related non-Hodgkin lymphoma (6) according to the type of HAART regimen (protease inhibitor–based or nonnucleoside reverse transcriptase inhibitor–based) used, and further analysis using this therapeutic distinction does not change our results.

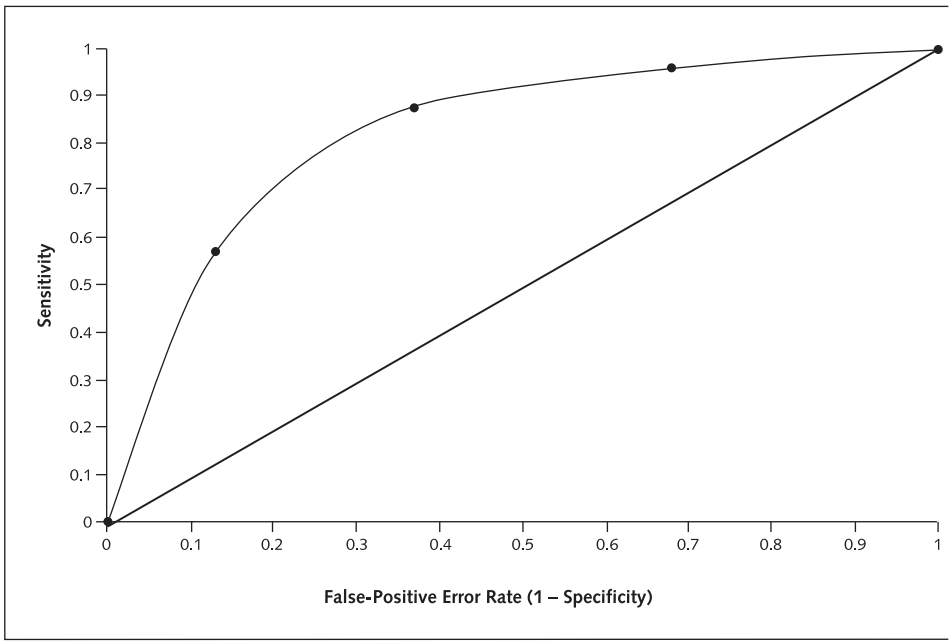
The duration of survival differed significantly in the pre- and post-HAART eras among patients with AIDS-related non-Hodgkin lymphoma ($P = 0.002$) (**Figure 1**). After the introduction of HAART, the incidence of Kaposi sarcoma decreased within a few years, but a concomitant decrease in AIDS-related non-Hodgkin lymphoma incidence was not observed over a longer period, and some studies reported no decrease at all (29, 30). In a prospective European study, the incidence of AIDS-defining illnesses decreased from 30.7 per 100 patient-years in 1994 to 2.5 per 100 patient-years in 1998 (31). Only the incidence of non-Hodgkin lymphoma increased as an AIDS-defining illnesses during this time (4% in 1994 compared with 16%

Table 4. **Likelihood Ratio for Death from AIDS-Related Non-Hodgkin Lymphoma in the Era of Highly Active Antiretroviral Therapy, and Sensitivity and Specificity Associated with Interquartile Range Cutoff Values**

Prognostic Risk Score	Patients Who Survived (*n* = 49), *n* (%)	Patients Who Died (*n* = 62), *n* (%)	Likelihood Ratio for Death*	Hazard Ratio (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
By quartile						
<1.00	28 (78)	8 (22)	0.23	0.15 (0.06–0.33)		
1.00–1.83	14 (52)	13 (48)	0.74	0.44 (0.22–0.88)		
1.84–2.90	5 (19)	21 (81)	3.32	1.17 (0.64–2.17)		
>2.90	2 (9)	20 (91)	7.90	1		
By interquartile range cutoff values						
<1.0	28	8			0.87 (0.76–0.94)	0.57 (0.42–0.72)
≥1.0	21	54				
≤1.83	42	21			0.66 (0.53–0.78)	0.86 (0.73–0.94)
>1.83	7	41				
≤2.90	47	42			0.32 (0.21–0.45)	0.96 (0.86–1.00)
>2.90	2	20				

* A likelihood ratio > 1 indicates greater risk for death.

Figure 3. **Receiver-operating characteristic curve showing sensitivity and false-positive error rate of mortality using the quartile cutoff values for the prognostic risk score, derived from the Cox proportional hazards regression coefficient.**



Data from 111 patients are included. The sensitivity gives the degree of certainty that patients who fall in a particular prognostic risk score group will not die. The diagonal line displays ties, and the points on the curve refer to the sensitivity and 1 − specificity (the risk for false-positive results). 1 − specificity may also be referred to as the type I error rate. This demonstrates that the cutoffs established for risk scores are predictive of mortality.

in 1998). In a meta-analysis of 23 prospective cohort studies involving 47 936 patients living in established market economies, a decrease in the incidence of non-Hodgkin lymphoma was reported from 6.2 cases per 1000 person-years in 1992 to 3.6 cases per 1000 patient-years in 1999 (29). The epidemiologic features of Kaposi sarcoma and non-Hodgkin lymphoma may differ because improvement in immune function due to HAART prevents Kaposi sarcoma during short-term therapy, but perhaps a longer duration of therapy is required to prevent non-Hodgkin lymphoma. In support of this hypothesis, we observed that increased B-cell counts protected against Kaposi sarcoma (32), and Kaposi sarcoma lesions may resolve with HAART alone (33–35); neither of these scenarios has been the case with non-Hodgkin lymphoma. These data suggest that as well as the reported decrease in incidence of non-Hodgkin lymphoma, patients also have improved survival, most likely because of better overall immune status.

The International Prognostic Index was found to be useful in 69 patients with AIDS-related non-Hodgkin lymphoma (17). Like that study, ours is limited by a small sample; however, we can propose a new prognostic scoring scheme designed for patients in whom AIDS-related non-Hodgkin lymphoma was diagnosed in the HAART era. This scoring method is based on International Prognostic Index risk group and CD4 cell count only (**Table 2**) and was internally validated by bootstrap resampling that shows tight and overlapping confidence limits around the resampled and original hazard ratios. A prognostic score less than 1.0 (the lowest quartile) yields a likelihood mortality ratio of 0.23 and a hazard ratio of 0.15 (CI, 0.06 to 0.33). These values correspond to a likelihood ratio for death of 7.90 and a corresponding hazard ratio of 1.0 (**Table 4**) among patients in the highest score quartile. In our cohort, 70 patients in whom AIDS-related non-Hodgkin lymphoma was diagnosed in the HAART era had CD4 cell counts greater than 100×10^6 cells/L at the time of diagnosis. Of these patients, 14 were in the low International Prognostic Index risk group, 21 were in the low-intermediate risk group, 20 were in the high-intermediate risk group, and 15 were in the high-risk group. The 2-year survival rates for each group were 83% (CI, 60% to 100%), 70% (CI, 49% to 90%), 42% (CI, 20% to 65%), and 7% (CI, 0% to 20%), respectively. In a historical comparison, the first 3 values do not significantly differ from the values of 88%, 74%, and 62% derived from use of the original International Prognostic Index. In contrast, however, HIV-positive patients in the high-risk group have a significantly worse 2-year overall survival rate than their HIV-negative comparators (20% vs. 7%).

Previous prognostic work has clarified that available clinical information can provide a foundation for long-term survival estimates, particularly when combined with a physician's clinical estimate (36). Use of the International Prognostic Index with CD4 cell count provides useful information for therapy and suggests that patients with a poor prognosis for AIDS-related non-Hodgkin lymphoma should be considered for additional treatment. This as-

sumes increased importance in light of the data suggesting that high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation is feasible in patients with AIDS-related non-Hodgkin lymphoma in terms of harvesting, engraftment, adverse events, and control of HIV (37). The advent of HAART has dramatically reduced morbidity and mortality due to HIV infection (38). Because HIV-infected patients are living longer, development of improved therapies for cancer and lymphoma that are based on accurate prognostic information has assumed greater clinical importance. Patients with AIDS-related non-Hodgkin lymphoma who are in a poor prognostic category should be considered for a clinical trial of newer approaches. Since the advent of HAART, being in a good prognostic quartile appropriately defines patients that can benefit from standard curative-intent therapy.

From The Chelsea and Westminster Hospital, London, United Kingdom.

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: Mark Bower, MA, PhD, or Justin Stebbing, MA, PhD, The Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH, United Kingdom; e-mail, m.bower@imperial.ac.uk or j.stebbing@imperial.ac.uk.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Lossos IS, Czerwinski DK, Alizadeh AA, Wechser MA, Tibshirani R, Botstein D, et al.** Prediction of survival in diffuse large-B-cell lymphoma based on the expression of six genes. N Engl J Med. 2004;350:1828-37. [PMID: 15115829]

2. **Benzel JE.** International conference on leukemia-lymphoma. Ann Arbor, Michigan, October, 1967. Del Med J. 1968;40:78-81. [PMID: 5644827]

3. **Rosenberg SA.** Validity of the Ann Arbor staging classification for the non-Hodgkin's lymphomas. Cancer Treat Rep. 1977;61:1023-7. [PMID: 902260]

4. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med. 1993;329:987-94. [PMID: 8141877]

5. **Stebbing J, Bower M.** What can oncologists learn from HIV? Lancet Oncol. 2003;4:438-45. [PMID: 12850195]

6. **Stebbing J, Gazzard B, Mandalia S, Teague A, Waterston A, Marvin V, et al.** Antiretroviral treatment regimens and immune parameters in the prevention of systemic AIDS-related non-Hodgkin's lymphoma. J Clin Oncol. 2004;22:2177-83. [PMID: 15169806]

7. **Stebbing J, Marvin V, Bower M.** The evidence-based treatment of AIDS-related non-Hodgkin's lymphoma. Cancer Treat Rev. 2004;30:249-53. [PMID: 15059648]

8. **Vaccher E, Spina M, di Gennaro G, Talamini R, Nasti G, Schioppa O, et al.** Concomitant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy plus highly active antiretroviral therapy in patients with human immunodeficiency virus-related, non-Hodgkin lymphoma. Cancer. 2001;91:155-63. [PMID: 11148572]

9. **Cortes J, Thomas D, Rios A, Koller C, O'Brien S, Jeha S, et al.** Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and highly active antiretroviral therapy for patients with acquired immunodeficiency syndrome-related Burkitt lymphoma/leukemia. Cancer. 2002;94:1492-9. [PMID: 11920506]

10. **Ratner L, Lee J, Tang S, Redden D, Hamzeh F, Herndier B, et al.** Chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma in combination with highly active antiretroviral therapy. J Clin Oncol. 2001;19:2171-8. [PMID: 11304769]

11. **Thirlwell C, Stebbing J, Nelson M, Gazzard B, Bower M.** CDE chemotherapy plus HAART for AIDS related non-Hodgkin's lymphoma [Abstract]. In: 6th International Congress on Drug Therapy in HIV Infection, 17-21 November 2002, Glasgow, United Kingdom. London: Mediscript; 2002:94.

12. **Navarro JT, Ribera JM, Oriol A, Vaquero M, Romeu J, Batlle M, et al.** Influence of highly active anti-retroviral therapy on response to treatment and survival in patients with acquired immunodeficiency syndrome-related non-Hodgkin's lymphoma treated with cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone. Br J Haematol. 2001;112:909-15. [PMID: 11298585]

13. **Sparano JA, Lee S, Chen MG, Nazeer T, Einzig A, Ambinder RF, et al.** Phase II trial of infusional cyclophosphamide, doxorubicin, and etoposide in patients with HIV-associated non-Hodgkin's lymphoma: an Eastern Cooperative Oncology Group Trial (E1494). J Clin Oncol. 2004;22:1491-500. [PMID: 15084622]

14. **Little R, Pearson D, Steinberg S, Elwood P, Yarchoan R, Wilson W.** Dose-adjusted EPOCH chemotherapy in previously untreated HIV-associated non-Hodgkin's lymphoma. Proc Am Soc Clin Oncol. 1999;18:10a.

15. **Little RF, Pittaluga S, Grant N, Steinberg SM, Kavlick MF, Mitsuya H, et al.** Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. Blood. 2003;101:4653-9. [PMID: 12609827]

16. **Navarro JT, Ribera JM, Oriol A, Vaquero M, Romeu J, Batlle M, et al.** International prognostic index is the best prognostic factor for survival in patients with AIDS-related non-Hodgkin's lymphoma treated with CHOP. A multivariate study of 46 patients. Haematologica. 1998;83:508-13. [PMID: 9676023]

17. **Rossi G, Donisi A, Casari S, Re A, Cadeo G, Carosi G.** The International Prognostic Index can be used as a guide to treatment decisions regarding patients with human immunodeficiency virus-related systemic non-Hodgkin lymphoma. Cancer. 1999;86:2391-7. [PMID: 10590382]

18. **Yeni PG, Hammer SM, Hirsch MS, Saag MS, Schechter M, Carpenter CC, et al.** Treatment for adult HIV infection: 2004 recommendations of the International AIDS Society-USA Panel. JAMA. 2004;292:251-65. [PMID: 15249575]

19. **Bower M, McCall-Peat N, Ryan N, Davies L, Young AM, Gupta S, et al.** Protease inhibitors potentiate chemotherapy-induced neutropenia. Blood. 2004;104:2943-6. [PMID: 15238428]

20. **Kaplan E, Meier P.** Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457-81.

21. **Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al.** Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer. 1977;35:1-39. [PMID: 831755]

22. **Harrell FE Jr, Lee KL, Califf RM, Pryor DB, Rosati RA.** Regression modelling strategies for improved prognostic prediction. Stat Med. 1984;3:143-52. [PMID: 6463451]

23. **Steyerberg EW, Eijkemans MJ, Harrell FE Jr, Habbema JD.** Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. Med Decis Making. 2001;21:45-56. [PMID: 11206946]

24. **Steyerberg EW, Harrell FE Jr, Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD.** Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol. 2001;54:774-81. [PMID: 11470385]

25. **Efron B, Gong G.** A leisurely look at the bootstrap, the jack-knife, and cross-validation. The American Statistician. 1983;37:36-48.

26. **Efron B, Tibshirani R.** Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. Statistical Science. 1986;1:54-75.

27. **Efron B, Tibshirani R.** An Introduction to the Bootstrap. Number 57 in Monographs on Statistics and Applied Probability New York: Chapman and Hall; 1993.

28. **Efron B, Halloran E, Holmes S.** Bootstrap confidence levels for phylogenetic trees. Proc Natl Acad Sci U S A. 1996;93:13429-34. [PMID: 8917608]

29. **International Collaboration on HIV and Cancer.** Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. J Natl Cancer Inst. 2000;92:1823-30. [PMID: 11078759]
30. **Matthews GV, Bower M, Mandalia S, Powles T, Nelson MR, Gazzard BG.** Changes in acquired immunodeficiency syndrome-related lymphoma since the introduction of highly active antiretroviral therapy. Blood. 2000;96:2730-4. [PMID: 11023505]
31. **Mocroft A, Katlama C, Johnson AM, Pradier C, Antunes F, Mulcahy F, et al.** AIDS across Europe, 1994-98: the EuroSIDA study. Lancet. 2000;356:291-6. [PMID: 11071184]
32. **Stebbing J, Gazzard B, Newsom-Davis T, Nelson M, Patterson S, Gotch F, et al.** Nadir B cell counts are significantly correlated with the risk of Kaposi's sarcoma. Int J Cancer. 2004;108:473-4. [PMID: 14648716]
33. **Jacobson LP, Yamashita TE, Detels R, Margolick JB, Chmiel JS, Kingsley LA, et al.** Impact of potent antiretroviral therapy on the incidence of Kaposi's sarcoma and non-Hodgkin's lymphomas among HIV-1-infected individuals. Multicenter AIDS Cohort Study. J Acquir Immune Defic Syndr. 1999;21(Suppl 1):S34-41. [PMID: 10430217]
34. **Stebbing J, Portsmouth S, Gazzard B.** How does HAART lead to the resolution of Kaposi's sarcoma? J Antimicrob Chemother. 2003;51:1095-8. [PMID: 12668573]
35. **Murdaca G, Campelli A, Setti M, Indiveri F, Puppo F.** Complete remission of AIDS/Kaposi's sarcoma after treatment with a combination of two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor [Letter]. AIDS. 2002;16:304-5. [PMID: 11807324]
36. **Knaus WA, Harrell FE Jr, Lynn J, Goldman L, Phillips RS, Connors AF Jr, et al.** The SUPPORT prognostic model. Objective estimates of survival for seriously ill hospitalized adults. Study to understand prognoses and preferences for outcomes and risks of treatments. Ann Intern Med. 1995;122:191-203. [PMID: 7810938]
37. **Gabarre J, Marcelin AG, Azar N, Choquet S, Levy V, Levy Y, et al.** High-dose therapy plus autologous hematopoietic stem cell transplantation for human immunodeficiency virus (HIV)-related lymphoma: results and impact on HIV disease. Haematologica. 2004;89:1100-8. [PMID: 15377471]
38. **Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al.** Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med. 1998;338:853-60. [PMID: 9516219]

Current Author Addresses: Drs. Bower, Gazzard, Mandalia, and Nelson: The Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH, United Kingdom.
Drs. Newsom-Davis, Dhillon, Young, and Powles: Charing Cross and Hammersmith Hospitals NHS Trust, London W6 8RF, United Kingdom.
Dr. Thirlwell: Cancer Research UK, Lincoln's Inn Fields, London WC2A 3PX, United Kingdom.
Dr. Gaya: Northwick Park Hospital, Watford Road, London HA1 3UJ, United Kingdom.
Dr. Stebbing: St. Bartholomew's Hospital, Bodley Scott Chemotherapy Unit, East Wing, West Smithfield, London EC1A 7BE, United Kingdom.

Author Contributions: Conception and design: M. Bower, B. Gazzard, S. Mandalia, M. Nelson, J. Stebbing.
Analysis and interpretation of the data: M. Bower, B. Gazzard, T. Newsom-Davis, C. Thirwell, T. Dhillon, J. Stebbing.
Drafting of the article: M. Bower, A. Gaya, J. Stebbing.
Critical revision of the article for important intellectual content: M. Bower, A.M. Young, T. Powles, A. Gaya, J. Stebbing.
Final approval of the article: M. Bower, B. Gazzard, C. Thirwell, T. Dhillon, A.M. Young, A. Gaya, J. Stebbing.
Provision of study materials or patients: M. Bower, A.M. Young, J. Stebbing.
Statistical expertise: M. Bower, S. Mandalia, J. Stebbing.
Obtaining of funding: M. Bower, B. Gazzard, J. Stebbing.
Administrative, technical, or logistic support: M. Bower, B. Gazzard, A.M. Young, J. Stebbing.
Collection and assembly of data: M. Bower, B. Gazzard, T. Dhillon, A.M. Young, J. Stebbing.