REVIEW

Therapeutic Challenges of AIDS-Related Non-Hodgkin's Lymphoma in the United States and East Africa

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Non-Hodgkin's lymphoma (NHL) remains the second most common malignant complication in patients with human immunodeficiency virus (HIV) infection. As we enter the third decade of the acquired immunodeficiency syndrome (AIDS) epidemic, it is apparent that the evolution of antiretroviral therapy and the emergence of combination antiviral strategies have greatly affected the natural history of HIV infection and its neoplastic complications. For example, there may be a trend for declining incidence of AIDS-related lymphoma in the United States for the first time. However, in regions of the world where the burden of HIV infection is greatest, such as in East Africa, AIDS-related lymphoma is an increasing cause of morbidity and mortality. Treatment of lymphoma has evolved coincident with improvements in antiretroviral therapy. Infusional chemotherapy regimens may offer advantages over other regimens and schedules, but comparative trials have not been done. Clinical trial data are available on which to develop therapeutic strategies to treat this disease in East Africa where pragmatic approaches are needed. Both the differences in manifestations of HIV infection and the inherent difficulties in administering cytotoxic chemotherapy in this part of the world must be taken into consideration in planning therapeutic strategies. Improved understanding of the pathogenesis of HIV infection and lymphoma will likely yield improved therapeutic interventions as well. [J Natl Cancer Inst 2002;94:718–32]

The World Health Organization estimated that a total of 36.1 million adults and children were living with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) worldwide in 2000, over 95% of whom lived in developing countries, 25.3 million (70%) in sub-Saharan Africa *(1).* Nearly 17% of world case subjects (4.2 million) reside in East Africa, in Uganda, Kenya, and Tanzania. It goes without saying that the AIDS pandemic is evolving in different ways across the globe. Table 1 provides a demographic snapshot of the AIDS epidemic in the United States and East Africa at the beginning of 2000.

In 1990, investigators from Zaire framed seven obstacles to the optimal management of HIV infection/AIDS in Africa, which still exist today *(2).* Although an overview of each of these obstacles is beyond the scope of this review, a brief mention of the economic realities of the epidemic and discussion of some of the clinical management issues are needed. The "environment of extreme scarcity" *(2)* with which national AIDS control programs in Africa must confront the epidemic is the most important obstacle that must be overcome and reflects the greatest difference between the developed and developing world. The enormous human tragedy and economic burden of the AIDS epidemic is staggering *(3,4).* The life expectancy in the nine countries hardest hit by AIDS in Africa is projected to decrease by 16 years between 2010 and 2015 *(5).* It is estimated that the annual cost of prevention and treatment programs worldwide alone is $14 billion *(6).* As we move into the third decade of the pandemic, awareness of the global problem is surfacing in the United States *(7–12).* There is a great deal of discussion in the press, and in political and scientific communities in most of Africa as well, regarding how newer HIV treatments can be made more affordable and accessible for African patients. As world opinion regarding the feasibility of providing AIDS care in Africa is changing, it is ethically imperative to begin to devise clinical strategies that are pragmatic and suitable for implementation in this part of the world to address both HIV infection and its related opportunistic illnesses. We present here an overview of AIDS-related lymphoma and the challenge of treating this tumor that is confronting clinicians in East Africa. These clinical issues are applicable to the management of other neoplasms as well. We contend that it is both reasonable and necessary to design therapeutic trials for the treatment of AIDS-related lymphoma, i.e., non-Hodgkin's lymphoma (NHL), in this part of the world where the burden of HIV disease is greatest.

The highly active antiretroviral therapy (HAART) era dates back to 1996 with the general availability of the protease inhibitors. It is now possible, with the emergence of HAART, to achieve more sustained elevations in CD4 lymphocyte counts and effective suppression of HIV replication. Partial immune

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See "Notes" following "References."

Table 1. Comparative demographic summary of the AIDS epidemic in the United States and East Africa as of the end of 1999*

	United States	Uganda	Kenya	Tanzania
Population (millions)	276	21.2	29.5	32.8
Total HIV-infected (millions)†	.85	.82	2.1	1.3
Adult HIV prevalence rate, %	0.61	8.3	13.95	8.09
AIDS deaths/y	20 000	110 000	180 000	140 000
Median income, US $	$39 650‡	$330	$340	$210

*Data from Joint United Nations Programme on HIV/AIDS, 1999 (http://www.unaids.org, click on AIDS Epidemic Update). AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; US $ = United States dollars.

†U.S. Census Bureau, Current Population Survey, March 1998, 1999, 2000; Housing and Household Economic Statistics Division (www.uscensus.gov).

‡Estimated annual expenditure for HIV care = $18 300/patient *(157)*.

restoration is seen after suppression of HIV-1 replication, and this improvement in immune phenotype and function appears to be important in achieving both reduction in short-term opportunistic infectious complications and prolongation of overall survival *(13)*.

At the dawn of the third decade of the AIDS epidemic, it is apparent that the spectrum of neoplasia in the backdrop of underlying HIV infection and acquired immune deficiency is highly dynamic *(14)*. This is especially true for AIDS-related lymphoma. The evolution of antiretroviral therapy during this period, especially in developed portions of the world, has had a great impact on neoplastic complications of the epidemic. It is important to reconcile the natural history and therapeutic interventions reported for lymphoma in the setting of HIV immunodeficiency in the context of current antiretroviral therapy.

We have now come full circle in the management of lymphoma in HIV-infected patients. At the outset of the epidemic, dose-intense combination chemotherapy regimens were thought to be required because of the aggressive natural history of the disease *(15)*. This approach was followed by the introduction of supportive therapies (e.g., colony-stimulating factors [CSFs]) and application of dose-modification of chemotherapy because of the difficulties of patients in tolerating treatment and the inherent complications of severe underlying immunodeficiency. Presently, with the availability of improved antiretroviral therapy, prophylaxis, and supportive treatment for opportunistic infections in patients with advanced AIDS, we are returning to traditional chemotherapy approaches similar to those used in the non-HIV-infected lymphoma patient. New biologic and cellular therapies are also being developed that are based on disease pathogenesis and mechanistic principles. Given this backdrop, we present an overview of AIDS-related NHL at the start of the third decade of the pandemic. Novel investigational approaches to therapy are also presented. An emphasis on the clinicopathologic features and therapeutic challenges of this disease in the United States and in East Africa are provided as we embark on international collaborative efforts and tailor therapeutic strategies for use in developing countries.

EPIDEMIOLOGY

In the United States, the appearance of *Pneumocystis carinii* pneumonia on the West Coast and Kaposi's sarcoma (KS) on the East Coast in homosexual men in 1981 heralded the onset of the AIDS epidemic *(16,17)*. A year later, the first cases of NHL were reported *(18)*. The first cases of primary central nervous system (CNS) lymphoma were reported in New York City in 1983 *(19)*. By 1985, the Centers for Disease Control and Prevention revised the case definition for AIDS surveillance reporting to include B-cell or indeterminate phenotype NHL, because there was clear evidence of a marked increase in incidence and risk for this disease in this setting *(20)*. Near the end of the first decade of the epidemic, the burden of HIV-related lymphoma was apparent. Perhaps the most telling sign of the impact of the AIDS epidemic in the United States was the decline in overall 5-year survival rates of young men with NHL from more than 60% in 1983 through 1985 to 45% in 1986 through 1989 *(21)*.

Approximately 5%–10% of HIV-infected patients are destined to develop lymphoma, and 1%–2% will develop primary CNS lymphoma *(22)*. NHL is the AIDS-defining illness in approximately 3% of HIV-infected patients. As experience with nucleoside analog (zidovudine) antiretroviral monotherapy was gained, there was some initial concern that long-term administration might increase the risk for developing lymphoma *(23–26)*. The risk of developing lymphoma steadily increases with duration of HIV infection and advancing immunosuppression. Prospects for increased survival are enhanced by HAART; however, long-term survivors of HIV infection may remain at increased risk for NHL. This would be reminiscent of the experience with patients undergoing solid organ transplantation in whom there is a lifelong increased risk of lymphoma, among other tumors, because of iatrogenic immunosuppression. In this setting, the risk ranges between 0.04% and 0.3% per annum for renal and cardiac transplant patients, respectively *(27,28)*.

Since the introduction of HAART, the incidence of opportunistic infections, KS, and primary CNS lymphoma has declined in HIV-infected patients, but a concomitant decrease in systemic lymphoma was not initially observed *(29–32)*. In one prospective European study *(33)*, 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. Only NHL increased as an AIDS-defining condition during this period; 4% of patients had lymphoma as an AIDS-defining disease in 1994 compared with 16% in 1998. By contrast, 7% of patients had KS as an AIDS-defining illness in 1994 compared with 7% in 1998. Most recently, cancer incidence data from 23 prospective cohort studies that included 47 936 HIV-infected individuals from North America, Europe, and Australia were collected and reported by the International Collaboration on HIV and Cancer *(34)*. This study *(34)* reported a decline for the first time in the incidence of NHL from 1992 through 1999, from 6.2 cases per 1000 person-years to 3.6 cases per 1000 person-years. These observations could be explained, in part, by short-term improvement in immune function attributable to HAART. The occurrence of CNS lymphoma is more closely linked to immunodeficiency than is systemic lymphoma, which may explain the disparity in declining incidence rates of CNS versus systemic disease. Notably absent from this survey were any patients from developing regions of the world. Of note, sub-Saharan Africa includes only 10% of the world's population but is home to 70% of all the world's HIV-infected people *(1,35)*. Longer follow-up periods and epidemiologic studies from other cohorts are clearly needed to further characterize the risk of lymphoma in HIV-infected individuals.

HIV-1 infection was first recognized in Uganda in 1984 and was referred to as "slim disease" *(36)*. Despite a dramatic in-

crease in the incidence of KS coincident with the AIDS epidemic in parts of Africa, a corresponding increase in the incidence of NHL over the first 15 years of the epidemic was not observed *(37–45).* It appeared that the risk of AIDS-related lymphoma in developing countries was much lower than in developed countries, although under-ascertainment and earlier death from competing mortality among other infectious diseases or AIDS-related complications could explain this observation *(46).* Data from a Ugandan case–control study of AIDS-related lymphoma between August 1994 and April 1998 have been reported *(47).* A total of 50 adult and 122 childhood cases of pathologically confirmed NHL were identified. Of these cases, 92 (31 adult and 61 childhood cases) had full phenotyping and documentation of Epstein-Barr virus (EBV) status and were considered validated. Burkitt's lymphoma and large B-cell lymphomas represented 71% of validated adult cases, and Burkitt's lymphoma comprised 92% of validated pediatric cases. EBV was present in 35% of adult cases and in 91% of pediatric cases. HIV infection was present in 34% of adult cases versus 20% of controls with other malignancies and in 4.9% of pediatric cases versus 5.0% of controls (children with benign, noninfectious surgical or orthopedic conditions). The risk of lymphoma in HIV-infected adults was approximately double that in HIV-negative adults (odds ratio [OR] = 2.2; 95% confidence interval [CI] = 0.9 to 5.1, which was not statistically significant). No increased risk of NHL was seen in HIV-infected children (OR = 0.8; 95% CI = 0.2 to 3.4). In adults the risk may be underestimated, however, because HIV prevalence is higher in patients with cancer (20%) than in the general population (approximately 8%). More recently, data from the Kampala Cancer Registry identified a statistically significantly increased incidence of AIDS-associated NHL over the latter half of the past decade in Uganda *(39).* Age-standardized incidence rates per 100 000 persons from 1960 through 1971, 1991 through 1994, and 1995 through 1997 were 3.8, 3.6, and 7.4 in males and 2.3, 2.1, and 5.7 in females, respectively *(39).* Similar reports of increased risk of NHL in other parts of Africa in HIV-infected individuals are emerging as well *(48–50).*

Clinicopathologic and tumor registry data from Kenya are limited. In one study on the histopathology of lymphoma in Kenya *(51),* evidence of EBV infection was identified in 56% of 39 cases and no analysis of HIV-1 infection was reported. In another pathology series of 146 cases of lymphoma, HIV-1 infection was confirmed in 11% of cases *(52).* Among non-HIV-related lymphomas in this study, EBV was present in 94% of pediatric Burkitt's lymphoma cases. Before the AIDS epidemic, one to two cases of adult Burkitt's lymphoma were seen annually at the national referral center, Kenyatta National Hospital, in Nairobi, Kenya *(53).* Twenty-nine adult cases of Burkitt's lymphoma were identified from among 796 total cases (all ages) of Burkitt's lymphoma between 1992 and 1996. Of the 29 cases, 66% were HIV-seropositive for antibody, corresponding to a threefold increase in the incidence of adult Burkitt's lymphoma during the period of the study; this is attributable to AIDS *(53).*

Only four cases of primary CNS lymphoma in HIV-infected patients in Africa have been reported *(54).* No cases of CNS lymphoma were identified in the recently reported Ugandan case–control study or a small HIV-1 neuropathology autopsy series from Tanzania *(47,55).* The small number of patients with CNS lymphoma is likely attributable to both limited diagnostic capability and death from other AIDS-related illnesses.

PATHOGENESIS

The pathogenesis of lymphoma in the setting of HIV infection is complex. There is likely an interaction between host factors—such as accompanying progressive immunodeficiency, which is the hallmark of untreated HIV infection—and molecular and genetic alterations, which may occur *de novo* or result from co-infection with EBV or human herpesvirus-8 (HHV-8). Progressive immune suppression, chronic antigen stimulation, and resultant B-cell proliferation—initially polyclonal and proceeding to oligoclonal and monoclonal lymphoid expansion—are important for lymphomagenesis *(56,57).* Associated immune activation and dysregulation of cytokine modulatory pathways (interleukin [IL]-6 and IL-10, in particular); altered bcl-6, p53, and c-myc proto-oncogene expression; and coexisting viral infection(s) have all been implicated in the pathogenesis of lymphoma in this setting as well *(56–63).*

HIV is not an oncogenic virus *(64).* One report, however, suggests a more direct pathogenetic role for HIV infection in oncogenesis because its genome was found incorporated into the fur gene complex on chromosome 15 in non-B-cell malignant lymphoma cells upstream of c-fes, a proto-oncogene *(65,66).* Of interest is that the HIV Tat protein is a potent growth factor for KS *(67–69).* These observations lend some support to a more direct link between HIV infection and malignant transformation.

Other concurrent viral infections in HIV-infected patients, such as EBV and possibly HHV-8, are implicated in the development of lymphoma. There are well-recognized epidemiologic links to lymphoid malignancy and/or capacity for oncogenic transformation for EBV infection *(70,71).* Both molecular and serologic epidemiologic surveys have confirmed the association between KS and HHV-8 infection *(72,73).* In addition to its role in KS, HHV-8 is associated with two lymphoproliferative disorders: primary effusion lymphoma and multicentric Castleman's disease *(74–76).* HHV-8 has also been shown to infect bone marrow dendritic cells in HIV-seronegative patients with multiple myeloma, although its role in the pathogenesis of human plasma cell dyscrasias has not been established *(77–82).* HHV-8 infection has been identified as a cause of allograft failure in a patient undergoing bone marrow transplantation *(83).* A recent study has also confirmed that $CD34^+$ hematopoietic stem cells and mesenchymal stem cells are susceptible to HHV-8 infection *in vitro,* and mesenchymal stem cells can support HHV-8 lytic replication *(84).*

EBV is equipped with the necessary genes, nuclear antigens (EBNAs), and latent membrane proteins (LMPs) that are crucial for the maintenance of viral latency and for growth transformation of the host cell. The LMP-1 gene, which is essential for transformation of infected B cells, shows increased expression of the nuclear proteins EBNA-LP and EBNA-2 in particular *(85–88).* Homologous nuclear and membrane protein genes have not been identified in other herpesviruses. In the HIV setting, infection with EBV is ubiquitous in primary CNS lymphoma and is seen in 30%–50% of patients with systemic lymphoma *(88–91).*

There is presently no direct proof that HHV-8 is oncogenic or capable of immortalizing infected B-cells either *in vitro* or in animal models. The body cavity-based lymphoma cell line, BCBL-1, however, is known to harbor the ORF73-encoded latency-associated nuclear antigen (LANA), and lytic viral replication can be induced in this cell line *(92–94).* LANA is also known to bind the p53 tumor suppressor gene and, by inhibiting

p53-mediated apoptosis, may promote the survival of HHV-8-infected cells or contribute to cellular transformation *(95).* The virus contains numerous homologous genes that stimulate cellular proliferation, e.g., v-cyclin, v-G protein-coupled receptor/v-IL-8R, v-interferon regulatory factor (vIRF), and kaposin (K12); inhibit apoptosis (vbcl-2, vFLIP [viral FLICE {Fas-associated death domain-like IL-1 beta-converting enzyme}-inhibitory protein], and vIL-6); and play a role in recruitment of inflammatory cells and angiogenesis (vIL-6, v-macrophage inflammatory protein [vMIP-1], and K1) *(96–103).* The virus is thus equipped to maintain a latent state in infected cells. The oncogenic potential of several genes, such as v-G protein-coupled receptor and K1 among others, is under investigation *(102,104).*

TREATMENT

In general, AIDS-related NHL is characterized by higher grade (40%–60%), extranodal disease (80%), advanced clinical stage (60%–70% stage III/IV), and shortened survival (median 7–8 months) when compared with lymphomas in HIV-seronegative patients *(22,105–107).* At time of clinical presentation, the median CD4 lymphocyte count is 100/μL *(108).* It was recognized early on that the clinical course of NHL was much more aggressive in HIV-infected patients than in non-HIV-infected patients *(15).* This led to the evaluation of more aggressive and dose-intense combination chemotherapy regimens for this disease at the outset of the epidemic. Early results were dismal, regimens were poorly tolerated, and there was a trend toward shortened survival *(109,110).* More traditional and dose-modified NHL combination chemotherapy regimens were then evaluated in conjunction with antiretroviral therapy *(111):* incorporation of CSFs, of which granulocyte-monocyte CSF (GM-CSF) may increase HIV replication *in vitro (112,113),* and use of various CNS prophylaxis strategies because of the proclivity of AIDS-related lymphoma to disseminate or relapse in this site *(111).* Complete responses (CRs) ranged between 20% and 60%, with median survival duration of between 4 and 7 months *(106,107,114).*

In June 1997, the AIDS Clinical Trials Group (ACTG) reported the largest randomized clinical trial in AIDS-related lymphoma, which was conducted in the pre-HAART era. The ACTG 142 study compared standard-dose (SD) m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone) with GM-CSF to a dose-modified (low-dose [LD]) m-BACOD regimen *(108).* All patients received intrathecal cytosine arabinoside for meningeal prophylaxis during the first cycle of chemotherapy. The results of this study confirm that hematologic toxicity was statistically significantly less and, overall, the dose-modified regimen was better tolerated with equivalent efficacy. CR for low dose was 41% and for standard dose it was 52% ($P = .56$), with median survival of 35 weeks for low dose and 31 weeks for standard dose ($P = .25$), respectively. A 3% CNS relapse rate was seen. Poor prognostic factors were an age greater than 35 years, history of injection drug use, stage III/IV disease, and a CD4 lymphocyte count of less than 100/μL *(108,115).* In the ACTG study, patients with no or one adverse prognostic factor had a median survival of 46 weeks; those with two factors, 44 weeks; and those with three or four factors, 18 weeks *(115),* with corresponding 3-year survival rates of 30%, 17%, and 0%, respectively.

The longest median survival reported, again in the pre-HAART era, was 18 months in a single institutional study of 46 patients *(116–118).* These patients were treated with a 96-hour continuous infusion of cyclophosphamide–doxorubicin–etoposide (CDE). The overall CR rate with this regimen was 57% *(116–118).* A confirmatory ECOG study in HIV-seropositive and HIV-seronegative patients with NHL was performed. A total of 48 patients with AIDS-related lymphoma were treated in this multi-institutional phase II study of infusional CDE. A 46% CR rate was observed, with a median survival of 8.2 months, a 1-year survival rate of 48%, and a 2-year survival rate of 35% *(119,120).* The regimen was myelotoxic, with 75% and 52% of patients experiencing grade 4 neutropenia and thrombocytopenia, respectively, and a 10% treatment-related mortality rate *(119,120).*

An oral combination chemotherapy regimen has been developed that includes lomustine (CCNU), etoposide, cyclophosphamide, and procarbazine (also pre-HAART era and single institution) *(121–123).* This regimen takes advantage of oral administration, *in vitro* synergy, and known first-line efficacy of the drugs in NHL. Two of the agents (CCNU and procarbazine) cross the blood–brain barrier. This regimen avoids the cardiotoxicity of doxorubicin-based regimens. Corticosteroids were omitted from the regimen because of additional immunosuppressive effects and possible promotion of tumor growth in patients with KS *(124–127).* The addition of granulocyte CSF (G-CSF) to the regimen decreased the frequency of hospitalization for febrile neutropenia and decreased the discontinuation of chemotherapy because of leukopenia *(123).* Thrombocytopenia was more severe. The overall objective response rate with this regimen was 66%, with a CR of 34%, a 5% CNS relapse (leptomeningeal and parenchymal) rate, and a median survival of 7.0 months *(121,123).* In addition, one third of patients survived 1 year, 13% survived 2 years, and half of all patients survived free from progression of their lymphoma.

Results with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy in combination with HAART (NCI-sponsored AIDS Malignancy Consortium [AMC] clinical trial No. 005) have been published *(128).* In this study, patients were sequentially treated with a modified-dose CHOP (mCHOP) (40 patients) and subsequently full-dose CHOP (23 patients) regimen with HAART (stavudine [d4T], lamivudine [3TC], and indinavir). CNS prophylaxis was recommended but not mandated by the study protocol. The median duration of therapy was 11 weeks for all patients. Grade 3 or 4 neutropenia occurred in 25% and 13% of patients on the modified-dose and standard-dose arms, respectively *(128).* Other toxicities were generally comparable between the two groups. The overall response rates were comparable: 60% with mCHOP and 57% with CHOP *(128).* The CR was higher in the full-dose CHOP group than in the modified-dose group (48% versus 30%, not statistically significant); although this was not a randomized study, there was a statistically significantly greater proportion of patients with stage IV disease treated with mCHOP (63%) than with full-dose CHOP (35%) ($P = .03$) *(128).* The median duration of response was 9 months for mCHOP and had not been reached for the full-dose group at the time of the study report *(128).*

Encouraging results have been obtained with EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) infusional chemotherapy, in which a 79% CR rate and

72% overall 2-year survival rate (median survival not attained at time of report) were observed *(129,130).* Antiretroviral therapy was temporarily suspended as part of the design of this clinical trial (discussed below). In this single institution study, 67% of patients had a CD4 lymphocyte count greater than or equal to 100/μL *(129,130).* More recently, at the Fourth International AIDS Malignancy Conference in March 2000, updated information on infusional-CDE and EPOCH regimens was reported *(130,131).* In the ECOG trial of CDE, the confirmed 42% CR rate, 17.8-month median survival time (MST), and 55% 1-year survival rate were reported for infusional-CDE in the post-HAART era versus 46% CR, 8.2 months MST, and 48% 1-year survival, respectively, in the pre-HAART era *(131).* Follow-up from the EPOCH trial did not identify an increased risk of progressive HIV infection with the temporary suspension of antiretroviral therapy during chemotherapy, and no relapses have occurred in complete responders with median follow-up of close to 3 years *(130).* Results from recent AIDS lymphoma trials in the United States are summarized in Table 2.

It is important to note that data from recent clinical trials have shown that approximately 10%–20% of patients may be cured or, more appropriately, survive free from progression of their lymphoma. In patients with no initial adverse prognostic factors, up to 30% may survive 3 years *(115).* Selected patients may be appropriate candidates for more traditional or aggressive cytotoxic therapy. As a result, salvage therapy, which has to date been very discouraging, may become increasingly important *(132).*

Impact of Chemotherapy on CD4 Lymphocyte Count and HIV Viral Load

At the outset of the epidemic, it was immediately recognized that the myelosuppressive and immunosuppressive effects of cytotoxic chemotherapy decrease CD4 lymphocyte counts in patients with AIDS-related neoplasms. HIV p24 antigenemia has been reported to increase with the concurrent administration of GM-CSF with CHOP chemotherapy *(112).* The clinical significance of this increase is unclear *(133–135).* In subsequent clinical trials with GM-CSF, increases in HIV-1 RNA levels have not been demonstrated, and some decreases in viral load have been seen *in vivo (136,137).* By contrast, with the advent of plasma HIV-1 RNA polymerase chain reaction (PCR) determination, cytotoxic chemotherapy has not adversely affected underlying viral load *(119,120,128–130,138,139).* Results from the AMC 005 trial did not show any adverse effect of either modified-dose or full-dose CHOP chemotherapy administered with concurrent HAART on HIV-1 replication; HIV-1 RNA levels actually declined over the course of therapy, and statistically significant increases in CD4 lymphocyte counts from baseline were observed *(128).* The EPOCH infusional chemotherapy regimen is also of interest, because in this study, antiretroviral therapy was suspended for the duration of chemotherapy *(129,130).* In this trial, HIV-1 RNA levels were monitored closely in eight patients on days 1 and 6 of each chemotherapy cycle and at 3 and 6 weeks after chemotherapy. Antiretroviral therapy was withheld during chemotherapy because of the potential for overlapping toxicity (pharmacokinetic interactions between HAART and cyclophosphamide in particular) and to ensure that the dosing schedule of chemotherapy would be maintained. There was no apparent increase of HIV-1 replication during chemotherapy, and there was a trend for lower RNA levels between days 1 and 6 [median day 1, 17 000 RNA copies/μL plasma versus median day 6, 8150 RNA copies/μL plasma ($P<.01$) *(138)*]. Viral load returned to baseline within 3 months, and CD4 lymphocyte count returned to baseline within 6–12 months, after chemotherapy and with the resumption of antiretroviral therapy *(129,130).* No new episodes of opportunistic infection(s) were observed during this period. Taken together, all of these results suggest that chemotherapy may not have an adverse effect on underlying HIV infection.

Table 2. Summary of results with combination chemotherapy regimens from recently reported trials in AIDS-related non-Hodgkin's lymphoma in the United States*

Regimen	Administration route	No. of patients	CR rate, %	MST	Long-term survival (%)	CSF prophylaxis	HAART era	References
m-BACOD								
SD	IV bolus	94	52	31 wk	3 y by adverse factors	Yes	Pre	*(108, 115)*
LD		98	41	35 wk	(30/17/0)†			
CDE								
Pre	96-h continuous	48		8.2 mo	1 y (48)	Yes (high grade histology;	Pre	*(131)*
Post	infusion	60		17.8 mo	1 y (55)	bone marrow involvement)	Post	
Oral regimen	By mouth	38	34	7.0 mo (31 wk)	1 y (32), 2 y (13)	No	Pre	*(121, 123)*
CHOP‡								
SD	IV bolus	23	48	9 mo§	Not available	Recommended	Post	*(128)*
LD		40	30	Not reached				
EPOCH	96-h continuous infusion	33	79	Not reached	2 y (72)	Yes	Post	*(121, 130)*

*AIDS = acquired immunodeficiency syndrome; CR = complete response; MST = median survival time; CSF = colony-stimulating factor; HAART = highly active antiretroviral therapy; m-BACOD = methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone; SD = standard dose; IV = intravenous; LD = low dose; CDE = cyclophosphamide-doxorubicin-etoposide; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

†Three-year survival rates were reported for the AIDS Clinical Trials Group trial for all patients (not by arm of study) by number of adverse prognostic factors: 0 or 1 = 30%; 2 = 17%; and 3 or 4 = 0%; see treatment section in text for details *(116).*

‡Not a randomized trial, and there was no statistically significant difference in complete response or response duration across the sequential two arms of the study; see treatment section in text for details *(129).*

§Median complete response duration reported; for entire study, median response duration was 65 weeks.

Role of Antiretroviral Therapy

The cytopenias and impaired hematopoiesis in patients with AIDS-related lymphoma are attributable to advancing immune deficiency, synergistic myelotoxic effects of some antiretroviral agents (especially the nucleoside analogs) and cytotoxic chemotherapy, direct myelosuppressive effects of HIV-1, and lymphomatous bone marrow infiltration *(106,133,140–142).* Low CD4 lymphocyte counts were associated with neutropenia in the ACTG 142 trial *(108).* Emerging clinical trials data suggest that concurrent antiretroviral therapy with cytotoxic chemotherapy has bone marrow-sparing effects. It was reported that concurrent antiretroviral nucleoside analog therapy with didanosine blunted the myelosuppression of infusional-CDE chemotherapy *(117).* In the recently reported AMC 005 trial of CHOP combined with HAART, 25% of patients receiving mCHOP and 13% of patients receiving CHOP developed grade 3 or higher neutropenia, and only one patient (1.6%) in the study (receiving mCHOP) developed febrile neutropenia *(128).* There were limited numbers of patients who developed other episodes of grade 3 or 4 myelotoxicity: only four patients with anemia and three with thrombocytopenia. This myelotoxicity contrasts sharply with that reported in the ACTG 142 trial conducted in the pre-HAART era. In this study, 69% of patients receiving SD m-BACOD developed grade 4 neutropenia and 8% developed febrile neutropenia *(108).* The reduced myelotoxicity seen in the AMC 005 trial, especially in the SD CHOP cohort, suggests that the concurrent use of HAART may be important for the administration of full dosages of chemotherapy with less myelosuppression.

There is considerable interest in identifying pharmacokinetic and concomitant drug interactions of chemotherapy and HAART. In the AMC 005 study there were no significant drug–drug interactions or increases in toxicity with CHOP chemotherapy, cyclophosphamide in particular, and HAART *(128).* There is the potential for increased clinical toxicity because protease inhibitors are metabolized in the liver *via* the cytochrome P-450 pathway and also inhibit the CYP3A4 isoform. Cyclophosphamide, on the other hand, requires activation by the mixed-function oxidases in hepatic microsomes. In this trial, the plasma clearance of cyclophosphamide decreased from 70 mL/min/m^2 (historical data) to 41 mL/min/m^2 and 46 mL/min/m^2 on the mCHOP and full-dose CHOP arms, respectively *(128).* The clearance of doxorubicin and indinavir were not altered by the combination of CHOP chemotherapy and HAART. These results suggest that conventional dosages of CHOP chemotherapy and HAART are safe. The modest effects of HAART on cyclophosphamide clearance may have implications for patients receiving much higher doses of this agent, such as in the transplant setting.

HAART has had a great impact on the natural history of HIV-1 infection, with statistically significant reduction in opportunistic infection and prolonged survival *(143).* The improved survival of AIDS-related lymphoma may also be attributable to HAART. The ECOG analysis of infusional-CDE chemotherapy found that median survival (17.8 versus 8.2 months) and 1-year survival rates (55% versus 48%) of patients in the post-HAART era were superior to those in a cohort of patients treated with the identical chemotherapy regimen before the availability of HAART *(131).* Not surprisingly, patients in the HAART era also had higher median CD4 lymphocyte counts (227/μL versus 78/μL). This analysis suggests that the level of immune function and type of antiretroviral therapy may be as important as or even more important than the type of chemotherapy administered to patients with AIDS-related lymphoma in determining outcome.

The potential antitumor effect of antiretroviral therapy is of particular interest given recent observations of clinical responses in patients with KS upon the institution of HAART *(144–148).* In this situation, the antitumor effect of HAART may be a manifestation of restoration of the immune response, of the generation of cytotoxic T lymphocytes with anti-HHV-8 activity, or, possibly, of the decreased expression of HIV-1 Tat protein *(67–69,149).* With the exception of a single case report *(150),* similar responses have not been observed in patients with AIDS-related systemic lymphoma. Isolated responses to the initiation of HAART have, however, been observed in patients with AIDS-related primary CNS lymphoma *(151–156).* This phenomenon may be akin to the withdrawal of immunosuppressive therapy in patients with post-transplant EBV-related lymphoproliferative disorders, which is indicative of enhanced tumor surveillance with restoration or improvement in immune function.

Clinical Management Issues in East Africa

Several clinical management issues face physicians who manage patients with AIDS-related lymphoma in East Africa. These issues echo some of the clinical obstacles outlined by N'Galy and colleagues *(2)* and are briefly discussed below.

Antiretroviral Therapy

A recent study in the United States that examined the annual per patient expenditures for the care of HIV-infected patients and related complications since the introduction of HAART *(157)* found that the estimated annual expenditure dropped from $20 300 in 1996 to $18 300 in 1998. Although the total cost of care for adults with HIV infection has declined, expenditures for medications have increased. There are large variations in expenditures across subgroups of patients. Annual expenditures for patients with AIDS were $21 204; for those with CD4 counts of less than 50/μL, annual expenditures were $28 128. These latter two subsets are comparable to the majority of patients being treated for NHL in East Africa. The data in Table 1 show that the median annual income in Uganda and Kenya is approximately $335. There is no national public health insurance program in these countries. These economic realities clearly point out the inherent difficulties in providing new drugs and substantiate the "environment of extreme scarcity" in which clinicians must provide care to their patients in this region of the world. These difficulties do not mean that there is no access to antiretroviral therapy in these countries. Nucleoside analog therapy is available, although there is greater access to these agents in Kenya than in Uganda. HAART is not widely available. It is now possible to begin to address practical therapeutic strategies for HIV infection and related complications, including treatments for AIDS-related lymphoma, in Africa. It is prudent to avoid the myelosuppressive effects of zidovudine in patients receiving cytotoxic chemotherapy, because the other nucleoside analogs (didanosine, zalcitabine, and stavudine) are less myelotoxic.

Opportunistic Infections

The primary late complications of HIV infection in East Africa are pulmonary and extrapulmonary tuberculosis, pneumococcal pneumonia, bacteremia due to nontyphoidal salmonella, chronic diarrhea and wasting, Kaposi's sarcoma, and cryptococ-

cal meningitis *(158,159).* Tuberculosis is the most common infection in HIV-infected persons worldwide, and as the HIV epidemic continues to evolve the risk of dual infection with HIV and *Mycobacterium tuberculosis* is substantial in East Africa *(160).* Prevention guidelines for tuberculosis in HIV-infected individuals in Uganda have been established, and according to these guidelines it is prudent to offer prophylactic short-term regimens (isoniazid for 6 months or combination isoniazid and rifampin for 3 months) to PPD (purified protein derivative)-positive HIV-infected patients undergoing cytotoxic chemotherapy *(161). P. carinii* pneumonia is much less frequent among HIV-infected individuals in sub-Saharan Africa than among those in the United States *(162,163).* Thus, it may be possible to avoid the additional risk of myelosuppressive effects of *P. carinii* prophylaxis in Africa. This risk must be balanced against the potential benefit of trimethoprim–sulfamethoxazole (TMP–SMX or cotrimoxazole) prophylaxis against other infections in HIV-infected Africans. In a study from the Ivory Coast *(162),* TMP–SMX prophylaxis of HIV-positive adults coinfected with smear-positive tuberculosis statistically significantly decreased mortality, total hospital admissions, and hospital admissions for septicemia and gastroenteritis. In this trial, TMP–SMX prophylaxis was thought to work by decreasing deaths due to toxoplasmosis, salmonella, and bacterial pneumonia. Similar results have been reported from South Africa *(163).* Cotrimoxazole prophylaxis may not work as well in other parts of Africa, where there is a higher prevalence of resistance to TMP–SMX among enteric pathogens. Data from ongoing studies in Zambia, Malawi, Senegal, and other African countries will help address the usefulness of TMP–SMX prophylaxis.

Intravenous Therapies

The logistic difficulties of chemotherapy administration in East Africa must be acknowledged. Most patients have reasonable peripheral intravenous access because they have had much less exposure to intravenous medications and to venipunctures than Americans have had. Intravenous access is sometimes a problem in patients with advanced KS or with severe asthenia and wasting. Short infusions or intravenous bolus chemotherapy are feasible; longer infusions are more difficult and impractical. In Africa, the availability of intravenous cytotoxic agents and the increased costs of intravenous chemotherapy are acute concerns that limit the capacity to administer chemotherapy to HIV-infected patients with lymphoma in East Africa. Examples of these costs include requirements for pharmacy preparation, the need for intravenous chemotherapy supplies, and the availability of personnel trained in the administration of intravenous chemotherapy (and in avoidance of occupational risk). Presently, treatment in East Africa is limited to those few patients who are able to pay for their chemotherapy drugs and are deemed good candidates for systemic therapy. In the majority of instances, modified-dose CHOP chemotherapy is administered. Pragmatic approaches are clearly needed, because a median survival of 15 weeks in adult patients with HIV-related Burkitt's lymphoma in Kenya is the only reported data for East Africa *(53).* We are exploring dose modification of the oral combination chemotherapy regimen in a phase II trial in Uganda and Kenya under institutional (Center for AIDS Research [CFAR]), pharmaceutical, and National Institutes of Health (NIH) sponsorship.

Other Supportive Therapies

Hematopoietic cytokine support (e.g., G-CSF, GM-CSF, and erythropoietin) is impractical in East Africa because these medications are expensive and not integrated into the supportive management of cancer patients. Similarly, there is a limited antibiotic armamentarium, although adequate agents are available to support patients through uncomplicated episodes of febrile neutropenia. Maximizing accessible caloric intake is emphasized for nutritional support. Other supplemental or total parenteral nutritional support is not routinely available. In light of limited supportive therapies, dose modification of chemotherapy is prudent to reduce myelosuppression, the attendant risks of neutropenic infectious complications, and the demands on the limited supply of blood products. Although blood banking capability exists at the major hospital centers in East Africa, there are often delays in getting suitable blood products to patients.

Treatment Recommendations for AIDS-Related NHL

In the pre-HAART era, the results of ACTG 142 implied that a dose-modified chemotherapy approach is appropriate for the majority of patients with AIDS-related lymphoma. The current status of the epidemic in East Africa is, in many respects, comparable to the pre-HAART era in the United States. In this setting, dose modification is prudent. In the HAART era, however, it will be very important to individualize therapy options because the natural history of HIV infection is changing and patients are now better able to tolerate SD cytotoxic therapy. Combination chemotherapy with CHOP in this setting is appropriate, which is consistent with the current standard of care in patients without HIV infection *(164).* Infusional chemotherapy regimens (e.g., CDE and EPOCH) appear to yield better CR rates and prospects for freedom from progression and for survival. Furthermore, the optimal therapeutic regimen remains to be established. Patients should be encouraged to participate in clinical trials addressing these issues. It is by no means standard practice to withhold antiretroviral therapy during chemotherapy, although preliminary results with this strategy using EPOCH chemotherapy are encouraging. Experience from two clinical trials *(117,128),* however, identified potential bone marrow-sparing effects of appropriate antiretroviral therapy administered concomitantly with cytotoxic chemotherapy. In the United States, all patients treated with myelotoxic chemotherapy should receive pneumocystis prophylaxis. This pathogen is less of a problem in East Africa, although benefits of antibacterial prophylaxis in Africa may have other salutary effects *(162,163).* CSF support is likely warranted in the majority of patients. The role of routine CNS prophylaxis has yet to be defined, because relapse rates are less than 5% with or without it *(108,116,117,121–123).* In a study of 62 patients treated with infusional-CDE *(165),* only seven (11%) patients had meningeal involvement at presentation or shortly after diagnosis; parenchymal CNS involvement coincided with progressive systemic lymphoma and none of the patients (of 26) in whom no CNS prophylaxis was given because of low risk developed isolated meningeal recurrence. Patients at risk for CNS dissemination, in whom CNS prophylaxis should be considered, include those with high-grade histologies, bone marrow involvement, and bulky lesions particularly of the head and neck/paranasal sinus and epidural areas that

may invade the CNS *(22,119,120,165).* Table 3 summarizes the relevant therapeutic issues in the United States and East Africa.

Primary CNS Lymphoma

Epidemiology and Pathogenesis

Since the beginning of the AIDS epidemic, primary CNS lymphoma has been regarded as an index AIDS-defining neoplasm. Whereas the incidence of this neoplasm is increasing in the general population, the incidence of primary CNS lymphoma among HIV-infected individuals is declining in the HAART era *(29,30,34,166,167).* Invariably, this tumor is encountered in patients with profound immunodeficiency (CD4 lymphocyte counts <50/μL) and it is always associated with EBV infection, which may be of considerable diagnostic importance. The diagnosis of CNS lymphoma is not made antemortem in East Africa.

Diagnostic Evaluation

The diagnosis of AIDS-related primary CNS lymphoma is challenging because of its protean manifestations. The lack of focal findings and the broad differential diagnosis in HIV-infected patients who present with nonspecific neurologic findings often contributes to a delayed or missed diagnosis *(166–168).* In one series of AIDS patients with primary CNS lymphoma, an antemortem diagnosis was established in only half *(168).* In the majority of patients, single and multiple contrast-enhancing lesions may be seen on computerized tomography (CT) and magnetic resonance imaging (MRI) scans of the head *(166).* In AIDS-related CNS lymphoma, lesions are usually hypodense in the absence of contrast and involve the basal ganglia, cerebellum, brain stem, and cerebral hemispheres. Ring enhancement may be demonstrated in up to 40% of patients; however, up to 10% of patients may show no contrast enhancement at all *(166).* MRI is more sensitive than CT at identifying primary CNS lymphoma. Because radiographic findings in CNS lymphoma are variable, other modalities are needed to complement the diagnostic evaluation of patients. The differential diagnosis of a space-occupying CNS mass lesion in an HIV-infected patient is broad and includes toxoplasmosis, which may be on the decline as a result of HAART and widespread use of TMP–SMX prophylaxis. Progressive multifocal leukoencephalopathy, fungal and bacterial abscess, tuberculosis, gummatous lesions, infarct, and glioma can also present as focal lesions. Because ring enhancement is often a nonspecific accompanying radiographic sign, biopsy has been recommended to establish a diagnosis. Tissue can be obtained and studied by a variety of methods: by stereotactic brain biopsy, by lumbar puncture for CSF cytology [between 20% and 25% of AIDS patients have positive cytology *(166)*], from the orbit for aqueous tumor cytology, and from cerebrospinal fluid for EBV DNA analysis. A careful ophthalmologic and slit-lamp examination may prove helpful to establish vitreal involvement. Initial studies *(169,170)* suggest that the presence of EBV DNA in cerebrospinal fluid, as detected by PCR, has a specificity of 100% and a sensitivity of 80%–98.5% for CNS lymphoma in AIDS. Thallium single-photon emission computed tomography (SPECT) scanning has demonstrable diagnostic utility as well *(171).* Thallium uptake is high in rapidly dividing malignant cells and has been used to differentiate between neoplastic and infectious brain lesions in HIV-infected patients. In a series of 61 patients, investigators reported that 95.2% of AIDS-related CNS lymphoma cases have positive SPECT scans *(172).* In another, smaller study *(173),* thallium–brain SPECT scanning had a sensitivity of 100% and a specificity of 90%. The combination of SPECT scanning and PCR assay to detect EBV in cerebrospinal fluid may further improve diagnostic accuracy. In a study of 31 consecutive HIV-infected patients with focal brain lesions, SPECT scans were negative in 16 of 18 patients with non-neoplastic lesions and positive in only one patient with primary CNS lymphoma *(174).* EBV DNA was not detected in the cerebrospinal fluid of any patient with a non-neoplastic etiology; however, two of 13 patients with primary CNS lymphoma did not have detectable EBV DNA in the cerebrospinal fluid. A positive SPECT scan was 92% sensitive with a 94% negative predictive value in patients with primary CNS lymphoma. Increased uptake on SPECT scanning and/or a positive cerebrospinal fluid EBV PCR was 100% sensitive with a 100% negative predictive value for the diagnosis of primary CNS lymphoma in this study. The detection of EBV DNA in cerebrospinal fluid and the use of thallium–brain SPECT scanning may prove to be valuable in establishing a diagnosis of primary CNS lymphoma and may complement or replace current diagnostic methods. Which approach is preferable depends on the available expertise at any treatment center.

It is often appropriate to embark on a course of empiric treatment for toxoplasmosis in patients with serum antibodies to *Toxoplasmosis gondii* who are clinically stable. In this instance, anti-toxoplasma therapy has been administered for 7–14 days and head CT/MRI is repeated to document substantial improvement of CNS mass lesions consistent with a diagnosis of toxoplasmosis. If there is no response, it is appropriate to proceed to

Table 3. Clinical issues in the treatment of AIDS-related non-Hodgkin's lymphoma in the United States and East Africa*

	United States	East Africa
Dose of chemotherapy	Standard dose (100% dose)	Dose modification (50% dose)
Intravenous chemotherapy	Standard	Definite limitations; costly, not widespread access
Opportunistic infection prophylaxis	Pneumocystis pneumonia, toxoplasmosis	Tuberculosis, pneumococcal disease, nontyphoidal salmonella infection, toxoplasmosis
Supportive care		
Antiretrovirals	HAART	No HAART; avoid zidovudine with chemotherapy
CSFs	Available (e.g., erythropoietin, G-CSF, and GM-CSF)	No CSFs
Febrile neutropenia	Monotherapy (imipenem or ceftazidime) or extended spectrum penicillin + aminoglycoside ± vancomycin (full-range antibiotic support)	Penicillin + gentamicin ± metronidazole ± third-generation cephalosporin (e.g., ceftriaxone and others per availability)
Blood banking	Full support	Often limited

*AIDS = acquired immunodeficiency syndrome; HAART = highly active antiretroviral therapy; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-monocyte colony-stimulating factor.

biopsy. It is important to recognize that concurrent administration of corticosteroids for cerebral edema or mass effect may mask a diagnosis of CNS lymphoma, with resolution of mass lesions. For this reason, CNS lymphoma has been aptly termed the "ghost tumor," and patients need to be carefully monitored for signs and symptoms of relapse in this situation *(166).* For patients in whom a CNS mass lesion is the initial AIDS-defining event and/or those with clinically significant intracranial disease (e.g., mass effect) it is generally advisable to proceed directly to biopsy to offer diagnosis-specific therapy *(166).*

Therapeutic Approach

Median survival for AIDS-related primary CNS lymphoma ranges from 2 to 3 months *(166–168).* Survival is likely to be better in patients without prior AIDS-defining opportunistic infections and with good performance status (Karnofsky Performance Status [KPS]>70%) *(166,167,175).* This aspect of the natural history of the disease is important to consider in clinical decision making, because up to 20% of patients may survive 1 year following a course of radiotherapy *(167,175).* For patients suspected of having CNS lymphoma with profound immunosuppression, advanced AIDS, and poor clinical status, establishing a diagnosis and/or offering therapy may be moot, because survival is poor (1–2 months) *(22,166).* The clinical status of a patient must be viewed in the context of prior antiretroviral therapy, and prospects for improved outcomes are likely enhanced in patients who are HAART naive *(152).* It is appropriate to aggressively manage such patients.

Radiotherapy has been the primary treatment modality for CNS lymphoma. Combined chemotherapy and radiation therapy appears to improve median survival (approximately 3 years) in HIV-seronegative individuals and is now preferred over radiotherapy alone for such patients *(167).* This combined modality therapy must be regarded as an investigational approach in HIV-infected persons in whom trials are currently underway to define the feasibility, toxicity, and efficacy. There may be a role for initiation of HAART in this setting, because isolated responses have been observed in patients with CNS lymphoma *(152,155,156).* The AMC is currently investigating induction antiviral therapy for CNS lymphoma with zidovudine, ganciclovir, and IL-2 in a pilot study (AMC 019). The rationale for this approach builds on the consistent detection of EBV in CNS tumor tissue, the prospect for cytoreduction of post-transplant lymphoproliferative B-cell tumors in selected patients receiving antiviral therapy (with combination zidovudine and ganciclovir), the ability of IL-2 to enhance the immune response and increase the number of circulating immune effector cells, and encouraging preliminary experience with this combination *(176).* In the absence of a clinical trial, definitive radiation therapy and consideration of concurrent chemotherapy in selected patients for one cycle is an appropriate treatment plan. Corticosteroids should be tapered as rapidly as possible.

Primary CNS lymphoma is rare in East Africa, and the diagnosis is seldom made for reasons that have already been discussed. Resources are limited for both diagnostic and therapeutic intervention for these patients. In some instances, the administration of corticosteroids may provide meaningful palliation of symptoms for patients with pathologically confirmed primary CNS lymphoma or for those with a high index of clinical suspicion. Comfort and end-of-life care are appropriate for most patients. Table 4 summarizes the salient biologic and clinical features of AIDS-related lymphoma and compares these features with those of lymphoma seen in the post-transplant and HIV-1-uninfected patients.

Future Directions

Investigational approaches are warranted for AIDS-related lymphoma because the majority of patients present with advanced AIDS and poor prognostic factors, and less than one third have no adverse prognostic factors and reasonable prospects for long-term survival. There is considerable interest in the use of the anti-CD20 monoclonal antibody (rituximab) in patients without HIV infection given recent observations of enhanced cytoreduction and statistically significant duration of freedom from progression and of survival in the salvage treatment of low-grade follicular lymphoma *(177–180).* These tumors overexpress CD20, providing a mechanistic rationale for this type of therapy. Preliminary experience with this agent added to standard CHOP combination chemotherapy for patients with intermediate-grade or high-grade lymphoma is encouraging, and there are currently several ongoing trials of this regimen *(181–183).* In post-transplant lymphoproliferative disorders, the use of rituximab is promising, with 54% complete and 15% partial response rates seen in 26 evaluable patients *(184,185).* These results may have implications for AIDS patients, and presently AMC is in the midst of a randomized trial of CHOP with and without rituximab in patients with intermediate-grade and high-grade lymphomas as characterized by CD20 expression (AMC 010).

Given the prospects of statistically significantly improved antiretroviral therapy and immune reconstitution in the HAART era, it is appropriate to address the role of myeloablative therapy with stem cell support, or adoptive immunotherapy approaches with mini-conditioning, nonmyeloablative preparative regimens in bone marrow transplantation. Bone marrow transplantation has a clear role in the management of lymphoma in patients without HIV infection *(186–189).* Of pivotal importance is the finding that hematopoietic stem cells are resistant to HIV-1 infection both *in vitro* and *in vivo* despite cell-surface chemokine receptor expression *(190).* This observation provides a rationale for considering stem cells as therapeutic tools to deliver anti-HIV constructs for possible immune cell and bone marrow reconstitution. The use of specific cell-based therapies in the setting of EBV-related post-transplant lymphoproliferative disease with the adoptive transfer of lymphocytes has also shown early promise *(191–193).* Presently, AMC is launching a pilot safety and feasibility trial of autologous peripheral stem cell transplantation for patients with relapsed AIDS-related lymphoma (AMC 020). A protocol exploring delayed donor leukocyte infusion in patients receiving allogenic peripheral blood stem cells following a mini-conditioning (nonmyeloablative) regimen for refractory AIDS-related lymphoma is also being developed (AMC 028).

Finally, AMC has launched a limited phase I trial of combination bryostatin 1 and vincristine (AMC 029). This trial builds on initial observations of demonstrable clinical efficacy and lack of myelotoxicity in patients with refractory B-cell neoplasms in phase I and phase II studies *(194–197).* The rationale for this regimen are the antitumor and immunomodulatory effects of bryostatin 1 and vincristine in preclinical models presumably *via* inhibition of protein kinase C expression *(198–201).* Bryostatin

Table 4. Salient biologic and clinical features of AIDS-related non-Hodgkin's lymphoma (NHL), post-transplant lymphoproliferative disorders (PTLD), and *de novo* (HIV-seronegative/indeterminate) NHL*

	AIDS-related NHL	PTLD	*de novo* NHL
Incidence	Decreasing; likely lifelong risk	Lifelong risk following transplant	Increasing
Pathology			
Tumor grade	Low, <5% Intermediate, 75% High, 25%	Plasmacytic hyperplasia Monomorphic Polymorphic (immunoblastic lymphoma and multiple myeloma)	Low, 40%–50% Intermediate, 40% High, 10%–20%
Tumor clonality	Usually monoclonal	Monoclonal or polyclonal	Monoclonal
Molecular markers	bcl-6	c-myc	Low, bcl-2 Intermediate, bcl-6 High (BL), c-myc
Associated viruses			
EBV	CNS, 100%; systemic, 30%–50%	100%	Endemic BL, 100%; sporadic BL, 30%
HHV-8	PEL, 100%; PEL-EBV, 90%; KS link to IBS	—	—
Extranodal disease			
At presentation	+++	++ (GI tract common)	+
Bone marrow	25%	Seen with extensive disease	Low, 80%–100% Intermediate/high, 20%–25%
CNS disease	<5%	Seen with extensive disease	<10%–20% (especially high-grade histology and bone marrow involvement)
Treatment	Systemic chemotherapy; role of immune reconstitution; role of CD20 MoAb; radiation for PCL	Immunosuppression withdrawal; local regimen, surgery; antivirals; interferon; role of CD20 MoAb; systemic chemotherapy	Systemic chemotherapy ± radiotherapy; CD20 MoAb (addition to CHOP under study); bone marrow transplant
Median survival	Systemic, 7–8 mo (30% long term with no adverse factors); primary CNS, 2–3 mo; East African BL, 3–4 mo	30% Long term	Low, 7 y Intermediate, 1.5–2 y High, 1 y

*Percentages given in the table are approximations, because the status of many findings is still under investigation. In many instances, the confirmatory studies are ongoing or are needed. AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; BL = Burkitt's lymphoma; EBV = Epstein-Barr virus; CNS = central nervous system; HHV-8 = human herpesvirus-8; PEL = primary effusion lymphoma; KS = Kaposi's sarcoma; – = not applicable; +++ = highly common; ++ = common; + = less common; IBS = immunoblastic lymphoma; GI = gastrointestinal; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone; CD20 MoAb = monoclonal antibody against CD20 (rituximab); PCL = primary CNS lymphoma.

has been reported to enhance the efficiency of IL-2 to prime cytotoxic T cells *in vivo,* to increase the expression of IL-2 receptors on T cells, to promote development of CTLs from resting naive T cells, and to increase IL-6 and TNFα levels after short infusions *(199,200).* These effects on IL-2 and IL-2 receptor expression would be of particular interest in the HIV setting because chronic administration of IL-2 is known to increase CD4 lymphocyte counts *(202).*

Conclusions

AIDS-related lymphoma remains a major cause of morbidity and mortality among HIV-infected patients in the United States, and the burden of this disease is clearly gaining in sub-Saharan Africa as we embark on the third decade of the AIDS epidemic *(203).* With the emergence of HAART, prospects for prolonged survival of patients with HIV infection are enhanced. Chemotherapy has continued to evolve coincident with improvements in the underlying management of HIV infection. Infusion-based chemotherapy regimens appear to be more active and yield improved survival compared with bolus-administered regimens. Comparative trials, however, have not been done. The impact of HAART in the context of treating lymphoma in this setting remains to be assessed. It is possible that treatment of HIV infection may be as important as selection of the chemotherapy regimen for patients with AIDS-related lymphoma. Available clinical trial data should be used to develop therapeutic strategies to manage AIDS-related lymphoma in regions of the world where the burden of HIV disease is greatest, such as in East Africa. Dose modification of chemotherapy and development of pragmatic therapeutic approaches, such as oral chemotherapy, are needed. The manifestations of HIV disease in East Africa are different from those in the United States and have important implications for the diagnosis and treatment of lymphoma in this part of the world. Equally important is to determine the incidence of the lymphoma in East Africa, because the majority of large collaborative epidemiologic studies have not included cohorts of patients from this region and may therefore have underestimated the burden of lymphoma in this region. An improved understanding of lymphomagenesis should lead to improved therapeutic strategies.

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