www.nature.com/clinicalpractice/onc

# Therapy Insight: AIDS-related malignancies—the influence of antiviral therapy on pathogenesis and management

Robert Yarchoan*, Giovanna Tosato and Richard F Little


## SUMMARY

**Patients with HIV infection are at an increased risk of a number of malignancies, including Kaposi's sarcoma (KS) and certain B-cell lymphomas. Most of these tumors are caused by oncogenic DNA viruses, including KS-associated herpesvirus and Epstein–Barr virus. HIV contributes to the development of these tumors through several mechanisms, including immunodeficiency, immunodysregulation, and the effects of HIV proteins such as Tat. The development of highly active antiretroviral therapy (HAART) has reduced the incidence of many HIV-associated tumors and has generally improved their responsiveness to therapy. However, the number of people living with AIDS is increasing, and it is possible that the number of AIDS-associated malignancies will rise and the pattern of tumors will change as more people live longer with HIV infection. The goal of KS therapy is long-term tumor control with minimal toxicity. HAART is an important component of this therapy, and some patients do not require other KS-specific therapies. By contrast, the goal of AIDS-related lymphoma therapy in most cases is the attainment of a complete response with curative intent, and the benefits of administering HAART during therapy must be weighed against possible disadvantages. The past decade has seen substantial improvements in the treatment of AIDS-related lymphoma, which is attributed partially to a shift in tumor type and more effective regimens. There is currently an interest in developing new therapies for HIV-associated malignancies, based on viral, vascular or other pathogenesis-based targets.**


**KEYWORDS AIDS, antiviral, HIV, Kaposi's sarcoma, lymphoma**

### REVIEW CRITERIA

The PubMed database was searched using Entrez for articles published up to 8 April 2005. The search criteria included "HIV malignancy", "HIV Kaposi", "HIV lymphoma", "AIDS malignancy", "AIDS Kaposi", and "AIDS lymphoma". Abstracts of retrieved relevant articles were reviewed, with an emphasis on more recent articles, and full articles obtained for those of particular relevance. This material was supplemented by information learned by the authors by attending relevant meetings and conveyed to the authors by personal communications.

### CME

This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

*R Yarchoan is Chief of the HIV and AIDS Malignancy Branch, RF Little is Senior Oncologist in the HIV and AIDS Malignancies Branch, and G Tosato is Head of the Molecular and Cell Biology Section of the Experimental Transplantation and Immunology Branch, at the Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA.*

**Correspondence**
*Bldg 10, Rm 10S255, MSC 1868, 10 Center Drive, NIH, Bethesda, MD 20892–1868, USA
yarchoan@helix.nih.gov

**Received** 2 May 2005 **Accepted** 24 June 2005
www.nature.com/clinicalpractice
doi:10.1038/ncponc0253

## INTRODUCTION

The appearance in 1981 of a cluster of cases of Kaposi's sarcoma (KS) among homosexual men in New York and other coastal cities in the US was one of the first epidemiological signs of the disease that we now call AIDS. As the epidemic unfolded, it became apparent that patients with HIV infection also had a substantially increased risk for certain types of lymphoma (Box 1).[1–4] Three tumors are now considered to be AIDS-defining in the setting of HIV infection: KS, certain aggressive B-cell non-Hodgkin's lymphomas and invasive cervical cancer.[4] In addition, individuals with HIV infection are at somewhat increased risk for several other neoplasms, including anal carcinoma, Hodgkin's lymphoma, primary hepatocellular carcinoma, certain leukemias, lung cancer, testicular seminoma and, in children, leiomyosarcoma.[2,5–7] Interestingly, the incidence of many common cancers, such as colon and breast cancer, has not been found to be increased in people with HIV infection.[7,8]

## PATHOGENESIS OF AIDS-RELATED MALIGNANCIES

Most of the tumors that are strongly associated with HIV infection are caused by oncogenic DNA viruses (Table 1).[2,9] This relationship was highlighted by the discovery, in 1994, of a new gammaherpesvirus, now called KS-associated herpesvirus (KSHV) or human herpesvirus 8.[9] This virus was shown to be the causative agent of three tumors that arise in AIDS patients: KS, primary effusion lymphoma, and multicentric Castleman's disease.[2,10] Indeed, the only AIDS-associated tumors that are not known to be strongly associated with oncogenic viruses are certain systemic B-cell lymphomas (Table 1).

Several factors contribute to the increased incidence of certain types of tumor in patients with HIV infection. Most importantly, HIV-associated

immunosuppression compromises the ability to mount an immune response against proteins encoded by the tumor viruses and potentially against cellular tumor antigens. There is evidence that immune dysregulation, and in particular increased levels of proinflammatory cytokines such as interleukin (IL)-6, might also contribute to the development of certain tumors, including B-cell lymphomas and KS.[2,3,11,12] Another mechanism by which HIV might contribute to KS is through the effects of the HIV TAT PROTEIN. This protein has been reported to enhance the response of KS SPINDLE CELLS to angiogenic factors,[13] and, more recently, to enhance the infection of endothelial cells by KSHV.[14] Not surprisingly, as discussed below, effective therapy against HIV can reduce the incidence of some of these tumors and, in the case of KS, even has antitumor activity.

KS is a multicentric angioproliferative tumor that arises simultaneously in multiple nonmetastatic sites.[11] KS lesions appear most often on the skin, where they can be macular, nodular, or coalesce to form large plaques. Other frequent sites of involvement are the oral cavity, the gastrointestinal tract, and the lung. KS lesions involve a hyperproliferation of spindle cells, most of which are latently infected with KSHV. It has been suggested that there might be true malignant transformation in advanced cases of KS. In support of this idea, one study provided evidence that nodular KS involves a monoclonal cell population,[15] although other studies have indicated that the lesions are generally polyclonal. KS spindle cells form poorly organized vascular structures, and pooled blood and blood-breakdown products give the lesions their characteristic purplish color. Factors that

**Box 1** Principal HIV-associated non-Hodgkin's lymphomas.

- Burkitt's lymphoma
  - Classical Burkitt's lymphoma
  - Burkitt's lymphoma with plasmacytoid differentiation
  - Atypical Burkitt's lymphoma
- Diffuse large B-cell lymphoma
  - Centroblastic
  - Immunoblastic (includes most cases of primary central nervous system lymphoma)
- Primary effusion lymphoma
- Plasmablastic lymphoma of the oral cavity
- Polymorphic B-cell lymphoma

This listing is from the WHO.[3] Patients with HIV infection less frequently develop extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue or peripheral T-cell lymphoma compared with the tumors listed in this box. The 1993 Revised Classification of AIDS by the Centers for Disease Control specifies three types of lymphoma as being AIDS-defining in the setting of HIV infection: Burkitt's (or equivalent term); immunoblastic (or equivalent term); or primary of the brain.[4]

**GLOSSARY**

**TAT PROTEIN**
A *trans*-activating factor of HIV that is also an extracellular molecule, which can modulate gene expression, cell survival, growth, transformation, and angiogenesis

**SPINDLE CELLS**
Elongated cells characteristic of certain tumors

**Table 1** Viruses associated with AIDS-related malignancies.

| Malignancy | Virus |
|---|---|
| Kaposi's sarcoma | KSHV (100%) |
| Primary central nervous system lymphoma | EBV (100%) |
| Primary effusion lymphoma | KSHV (100%); EBV (~70–90%) |
| Burkitt's lymphoma | EBV (<50%) |
| Diffuse large B-cell lymphomas, centroblastic | EBV (<30%) |
| Diffuse large B-cell lymphomas, immunoblastic | EBV (>80%) |
| Plasmablastic lymphoma (oral cavity-associated) | EBV (>70%) |
| Leiomyosarcoma (in children) | EBV (~100%) |
| Hodgkin's lymphoma | EBV (70–100%) |
| Multicentric Castleman's disease | KSHV (nearly 100%) |
| Invasive cervical carcinoma | HPV (100%) |
| Anogenital cancers | HPV (100%) |
| Primary hepatocellular carcinoma | HCV and HBV |

EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; KSHV, Kaposi's sarcoma-associated herpesvirus.

**GLOSSARY**

**OPEN READING FRAME**
A long DNA sequence that is uninterrupted by a stop codon, and has the potential to encode a protein or polypeptide

**G-PROTEIN-COUPLED RECEPTOR**
Cell-surface receptors that are coupled to G proteins and have seven membrane-spanning domains, often stimulating or inhibiting the activity of downstream enzymes; G proteins consist of three subunits: the α-subunit, which contains the GTP-binding site; the β-subunit, and the γ-subunit

**VIRAL LATENT GENES**
Viral genes that are expressed during a state of infection (called the latent state), during which the virus persists in a cell but does not replicate

**NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)**
Antiretroviral drugs that are nucleoside analogs and act by inhibiting the essential and unique viral protein reverse transcriptase, which makes a DNA copy of RNA

are responsible for spindle-cell proliferation in KS lesions include KSHV-encoded mimics of human genes, such as viral IL-6 (vIL-6) and the viral macrophage inflammatory proteins (vMIP1, vMIP2 and vMIP3).[16,17] Also, OPEN READING FRAME 74 of KSHV encodes for a constitutively active G-PROTEIN-COUPLED RECEPTOR that stimulates the production of angiogenic factors, including vascular endothelial growth factor (VEGF).[18,19] Finally, there is evidence that other cellular factors, such as IL-6 or basic fibroblast growth factor, might act in an autocrine or paracrine fashion to induce KS spindle-cell proliferation.[13,20] KSHV-encoded lytic genes, including viral-encoded growth factors, can be activated by hypoxia,[21] and this relationship might account for the proclivity of KS to develop in areas of the body with a relatively poor vascular supply, such as the feet. KS spindle cells express VEGF receptor 3 (also known as Flt4), a receptor for the growth factors VEGF-C and VEGF-D, and in this regard have characteristics of lymphatic endothelial cells.[22] It is not clear whether they are derived from these cells, from endothelial precursor cells or other progenitor cells. Because of the proposed role of proangiogenic and related factors in KS pathogenesis, there is considerable interest in using antiangiogenesis approaches to treat this disease, as we discuss below.

Unlike KS, AIDS-related lymphomas (ARL) constitute a heterogeneous group of diseases (Box 1). They are generally monoclonal and are characterized by a number of common genetic abnormalities involving the *MYC* and *BCL6* oncogenes, as well as tumor suppressor genes.[3] Approximately 60% of these lymphomas are caused directly by herpesviruses.[2] Virtually all AIDS-associated primary central nervous system lymphomas (PCNSL) are associated with Epstein–Barr virus (EBV), and all primary effusion lymphomas are associated with KSHV (70–90% are also associated with EBV).[2,10] In both of these diseases, VIRAL LATENT GENES are expressed in the tumor cells and seem to have a direct role in tumor pathogenesis. In AIDS-associated Burkitt's or centroblastic diffuse large B-cell lymphomas, 30–50% of cases are associated with EBV infection, and the role of the virus in tumorigenesis is unclear. It is possible that chronic B-cell stimulation, induced in part by EBV, is an important contributory factor to the increased incidence of these tumors in AIDS, and the polyclonal or oligoclonal nature of some HIV-associated lymphoproliferations implies a multistage process of AIDS lymphomagenesis. It remains possible, however, that other factors, including an as yet undiscovered oncogenic virus, might be involved.

## EFFECTS OF HAART ON THE INCIDENCE OF AIDS-RELATED MALIGNANCIES

Some therapeutic benefit and reduced mortality was attained with NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI) in patients with HIV infection.[23] The subsequent combination of NRTI with protease inhibitors or non-NRTI achieved almost complete suppression of HIV replication in many patients, along with a marked decrease in opportunistic infections and a substantial improvement in survival. With such highly active antiretroviral therapy (HAART), the development of resistance is substantially delayed or prevented, and patients achieve considerable reconstitution of their $CD4^+$ cell counts, although qualitative immune defects can persist.[23]

Since 1996, when HAART became the standard treatment for HIV in developed countries, there has been a marked decrease in opportunistic complications and an overall improvement in survival in HIV patients. The introduction of HAART also resulted in a decrease in the incidence of certain AIDS-related tumors, especially those associated with low $CD4^+$ counts. Studies from the US and Europe described a 50–75% decrease in the incidence of KS and an even greater decrease in the incidence of PCNSL, a tumor that develops most often in patients with less than 50 $CD4^+$ cells/mm$^3$.[3,24,25] Initially, the effects of HAART on the development of systemic ARL were unclear, but more recent studies have generally revealed an overall decrease of about 20–60%.[24,25] In one large study, the decrease in lymphomas associated with the introduction of HAART could be accounted for by a decrease in the proportion of patients with low $CD4^+$ counts.[25]

In contrast to the changes in KS and ARL, the widespread use of HAART failed to reduce the incidence of certain other tumors, such as cervical and anal carcinoma, and there is evidence that lung cancer and Hodgkin's lymphoma might be increasing in the HAART era.[8,26] The higher incidence of these tumors, which are not associated with profound immunosuppression, might be related to improved survival of HIV-infected patients

receiving HAART. Individuals who are at risk for HIV are also more likely to smoke, and many of these individuals are now living long enough to develop lung cancer.[26] Hodgkin's lymphoma is associated with subtle immunosuppression, and most cases that develop in HIV-infected patients are EBV-associated.[2] The increasing incidence of this tumor since the development of HAART might be related to HIV-infected patients living longer with partial immune dysfunction.

An important and unresolved question is what trends in HIV-associated malignancies will emerge in the future. We can identify several somewhat conflicting factors that will likely affect the incidence of these tumors. First, it is important to remember that HAART is not curative. Moreover, while the death rate from AIDS has decreased, the number of new cases of HIV infection has remained relatively constant in the developed world; in the US, for example, it is estimated that about 40,000 individuals per year are infected with HIV.[27,28] Thus, while there is a public perception that AIDS is a disease of the past, the number of individuals living with AIDS in the US has increased by more than 50% since 1996 (Figure 1).[27] We do not know what new therapies against HIV will be developed or how problematic HIV resistance will be as patients are treated for decades. It is reasonable to postulate that the cumulative hazard of an HIV-infected individual developing a malignancy might increase as their survival increases, a concept possibly foreshadowed by the increasing incidence of lung cancer and Hodgkin's lymphoma. Thus, while it is possible that the incidence of AIDS-related malignancies in the developed world will remain low, it is also quite possible that the burden of malignant complications will again increase in concert with the expanding at-risk population living longer with HIV infection. In addition, there could be a shift from AIDS-defining malignancies that occur at very low $CD4^+$ counts to other tumors that occur with more intact immune systems. There is already evidence that, since the introduction of HAART, an increasing percentage of the deaths in HIV-infected individuals are caused by cancer, especially non-AIDS-defining cancers.[29] Finally, it is worth stressing that in the developing world, and especially in Africa where there is a high prevalence of both HIV-1 and KSHV infection, HIV-related malignancies continue to occur at an extremely high frequency, and, in parts of sub-Saharan Africa, KS now surpasses all other malignancies in frequency.[30,31]

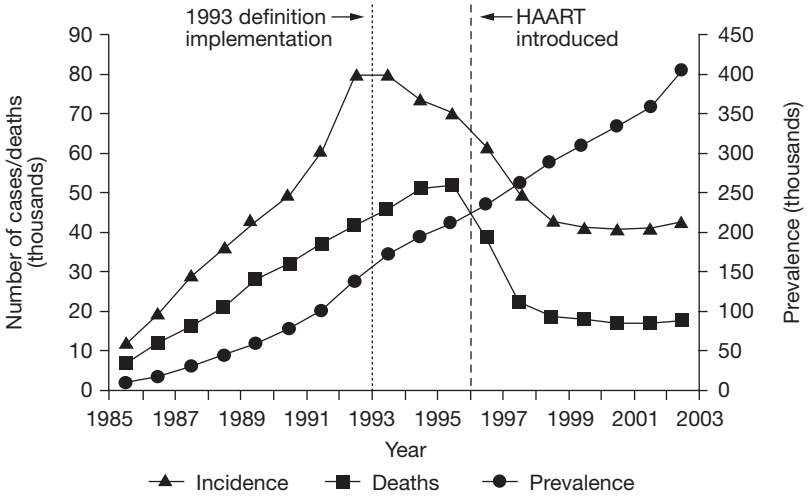


**Figure 1** Trends in the incidence of AIDS, the number of AIDS-related deaths, and the prevalence of AIDS in the US from 1985 to 2003. In 1993, the Centers for Disease Control's definition of AIDS was expanded to include patients with less than 200 $CD4^+$ cells/$mm^3$ and, as a result, there was a transient increase in the reported cases of AIDS. (Data taken from reference 27.) HAART, highly active antiretroviral therapy.

## TREATMENT OF AIDS-RELATED MALIGNANCIES

HIV-infected patients with malignancies confront the treatment team with the problem of how to deal with two complicated life-threatening disorders. Choosing the optimal therapy for such patients requires an understanding of the goals of therapy, the specific issues related to each condition, and interactions among the therapies under consideration. In many cases, non-AIDS-defining cancers can be treated according to the standards of care in the general population, although physicians should be alert for factors such as underlying immunosuppression, the potential for drug interactions, and the potential for increased toxicity that could impact on therapy. Below is a brief description of the therapy for common AIDS-defining malignancies.

### Kaposi's sarcoma

The treatment goal for patients with KS is long-term palliation with minimal toxicity. Complete tumor response, even with long-term disease-free survival, does not imply that the KS has been cured. HIV is an important cofactor for the development of KS, and effective treatment of HIV can induce KS remissions. This

**GLOSSARY**

**ZIDOVUDINE**
A nucleoside reverse transcriptase inhibitor, also called azidothymidine, which is used to treat HIV infection; the first effective AIDS drug to be developed

**IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME**
Transient worsening of an AIDS-related complication caused by an immune response associated with the HAART-associated immune reconstitution

**CRYOTHERAPY**
A surgical technique that uses freezing with argon gas or liquid nitrogen to destroy or excise tissue

**PHOTODYNAMIC THERAPY**
Use of light and a photosensitizing drug, such as porfirmer sodium, to ablate abnormal tissue

**Table 2** Therapies for the treatment of patients with widespread or advanced Kaposi's sarcoma.

| Therapy | Comment |
|---|---|
| HAART | Should be used in patients with HIV-associated KS whenever possible, generally in combination with other KS-specific therapy[33–35] |
| Interferon-α | Most active in patients with relatively intact immune function; can cause flu-like symptoms and other side effects[40] |
| Liposomal anthracyclines: | |
| Doxorubicin | Often used as first-line therapy for patients requiring cytotoxic therapy[35,42,43] |
| Daunorubicin | Approved as first-line therapy for advanced KS in the US[41] |
| Paclitaxel | Responses seen in patients who have failed anthracycline therapy. Greater toxicity than liposomal anthracyclines, including neutropenia and alopecia[44,45] |

HAART, highly active antiretroviral therapy; KS, Kaposi's sarcoma.

was observed even in the initial phase I trial of ZIDOVUDINE (Retrovir®, GlaxoSmithKline, Research Triangle Park, NC),[32] and there is now substantial evidence that HAART can induce tumor responses in 20–40% or more of patients with AIDS-related KS, especially those who were previously untreated for HIV.[33–35] HAART should therefore be considered to be fundamental to the oncological therapy for HIV-associated KS, and should form part of virtually all treatment regimens (Table 2). There is some laboratory evidence to indicate that HIV protease inhibitors have direct antiangiogenic effects and might promote regression of KS by this mechanism.[36] However, two clinical trials failed to find a difference in the development of KS between patients receiving HAART regimens containing a protease inhibitor and those containing a non-NRTI,[37,38] and additional studies will be needed to assess whether the potential antiangiogenic effects of protease inhibitors have clinical significance. Finally, physicians should be aware that some patients with AIDS-related KS can experience an initial flare or progression in their KS when started on antiretroviral therapy, which could be a manifestation of IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME.

Various local therapies can be used in patients with limited mucocutaneous KS, including CRYOTHERAPY, PHOTODYNAMIC THERAPY, radiation therapy and intralesional injections with cytotoxic chemotherapy. Topical 9-*cis*-retinoic acid (Panretin® gel, Bristol-Myers Squibb, Princeton, NJ) has been approved in the US for the treatment of local KS, but can cause local pain and irritation.[39] Systemic KS therapy should be considered if HAART alone is felt to be insufficient and there is widespread disease that is not amenable to local therapy, or if there is visceral organ involvement, painful lesions, substantial edema or psychosocial withdrawal (Table 2).[40–45] Interferon-α is active in KS, especially in patients with relatively intact immune function.[40] Its use, however, is associated with a decreased white blood cell count, flu-like symptoms, and occasionally depression. Many physicians who treat KS feel that the drug of choice for patients requiring systemic therapy is generally one of the liposomal anthracyclines.[41–43] These are less toxic than the unencapsulated drugs. Even in the pre-HAART era, these drugs yielded response rates in the range of 23–52%, and response rates of up to 70–80% can be seen when they are combined with HAART.[35,41–43] Paclitaxel has been reported to have given response rates of 59–71% in the pre-HAART era,[44–45] but its use is often associated with neutropenia, alopecia and neuropathy.

Although liposomal anthracyclines frequently provide effective therapy in KS, they are palliative, and can be associated with cumulative toxicity. There is therefore an interest in developing therapy that is targeted at the disease pathogenesis. Because of the vascularity of the lesions and the involvement of VEGF and other angiogenic factors, antiangiogenic approaches are particularly attractive in KS.[46] Recent small clinical trials have shown that three such compounds—thalidomide, Col-3 and IL-12—all have activity in patients with KS.[47–49] Other antiangiogenic agents are also being assessed. Moses *et al.* found that upregulation of the c-*kit* proto-oncogene by KSHV is important in the transformation of endothelial cells,[50] and Koon *et al.* recently reported that 5 out of 10 KS patients

**Table 3** Selected recently reported trials of regimens for AIDS-related lymphoma.

| Author and reference | Regimen | Evaluable patients | Era | Median baseline $CD4^+$ cells/$mm^3$ | Complete response rate (%) | Median OS (months) |
|---|---|---|---|---|---|---|
| Kaplan *et al*. (1997)[53] | Low or standard dose m-BACOD | 175 | Pre-HAART | 100 (low)<br>107 (standard) | 41 (low)<br>52 (standard) | 8 |
| Ratner *et al*. (2001)[54] | Low or standard dose CHOP plus HAART | 53 | HAART | 119 | 30 (low)<br>48 (standard) | Not available (limited follow-up) |
| Antinori *et al*. (2001)[55] | Various chemotherapy plus HAART (retrospective) | 44 | Spans both HAART and pre-HAART | 144 | 52 (71% in long-term HAART responders) | 12 |
| Little *et al*. (2003)[56] | Dose-adjusted EPOCH | 39 | Spans both HAART and pre-HAART | 198 | 74 | Not yet reached (at 53 months, OS 60% and DFS 92%) |
| Sparano *et al*. (2004)[57] | Infusional CDE | 98 | Spans both HAART and pre-HAART | 90 pre-HAART, 227 HAART | 47 pre-HAART, 44 HAART | 7.9 |
| Kaplan *et al*. (2005)[58] | CHOP HAART with 2:1 randomization: rituximab vs no rituximab | 99 rituximab, 51 no rituximab | HAART | 133 | 58 rituximab, 47 no rituximab | 139 weeks rituximab, 110 weeks no rituximab: 14% treatment-related deaths in rituximab group, vs 2% in no rituximab group |
| Spina *et al*. (2005)[59] | Infusional CDE plus rituximab plus HAART | 74 | HAART | 132 | 70 | Not yet reached (at 23 months OS 55% and DFS 65%); high rituximab-related toxicity |

CDE, cyclophosphamide, doxorubicin, and VP-16; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DFS, disease-free survival; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; HAART, highly active antiretroviral therapy; m-BACOD, moderate dose methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone; OS, overall survival.

treated with the c-*kit* inhibitor imatinib mesylate had tumor responses.[51] Finally, a recent small study showed that transplant patients with KS can respond to replacement of cyclosporine immunosuppressive therapy with sirolimus (rapamycin), an inhibitor of mTOR (mammalian target of rapamycin) with both immunosuppressive and antineoplastic activity.[52] Additional studies will be needed to assess the utility of this agent in treating patients with AIDS-related KS.

### AIDS-related non-Hodgkin's lymphoma

In patients presenting with systemic ARL, the goal of treatment is to attain a complete response and cure the tumor with acceptable toxicity. This goal needs to be balanced against the treatment of HIV and other HIV-associated complications (Table 3).[53–59]

Before the HAART era, patients with ARL frequently did not tolerate the toxicity that is associated with cytotoxic chemotherapy, and full-dose intensity did not confer a survival advantage. As a result low-dose regimens such as m-BACOD (moderate dose methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone) became the standard of care (Table 3).[53] Studies conducted in the HAART era, however, have provided substantial evidence that most patients with ARL have better outcomes—often comparable to the outcomes of those with non-HIV-related non-Hodgkin's lymphoma—with standard-dose therapy.[60] Ratner *et al*.[54] reported on a study conducted by the US AIDS Malignancies Consortium of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) administered with HAART (stavudine, lamivudine, and indinavir) in patients with ARL, the primary aims of which were to determine the toxicity of the regimens, the effect on AIDS parameters, and pharmacokinetic interactions. The first 40 patients in this study received modified CHOP therapy given in low doses, and a subsequent cohort of 25 patients received full-dose CHOP. The complete response rates were 30% on the modified CHOP arm and 48% on the full-dose CHOP arm. Overall, the full-dose CHOP was well tolerated and,

while it was not randomized, this study can be credited for providing data leading to a re-evaluation and ultimately the end of low-dose chemotherapy as the standard of care in ARL. Moreover, it provided evidence that combination chemotherapy for ARL could be safely coadministered with HAART.

Another study by the AIDS Malignancies Consortium examined the use of standard-dose CHOP plus HAART with or without rituximab, a monoclonal antibody directed at CD20.[58] Again, the study showed that full-dose CHOP could be given with HAART. There was a trend towards a higher complete response rate on the rituximab arm (58% versus 47%), but there were substantially more treatment-related infectious deaths in the rituximab arm (14% versus 2%).[58] The majority of these deaths occurred in patients with <50 $CD4^+$ cells/$mm^3$ at entry. Interestingly, there was no significant difference in the rate of grade 4 neutropenia, febrile neutropenia, or infections between the arms.

Other recent studies have explored the use of infusional regimens of CDE (cyclophosphamide, doxorubicin and etoposide) or DA-EPOCH (a dose-adjusted regimen of etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin).[56,57,59] One of these studies pooled results from three phase II trials of infusional CDE with rituximab.[59] Most patients also received HAART. The complete response rate of 70% in these pooled results was higher than the previously reported rates of 44% and 47% with infusional CDE alone,[57] but it is unclear whether this was due to the addition of rituximab. Interestingly, patients with detectable HIV viral loads at the end of treatment seemed to show an increased risk of treatment failure, raising the possibility that HAART might have a beneficial effect during antilymphoma therapy.[59] Six of the 74 patients in this trial (8%) died because of infection, and the authors suggested that adding rituximab to cytotoxic therapy in patients with ARL could increase the risk for life-threatening infection.[59] Overall, the role of rituximab in ARL is currently unclear. There appears to be a trend towards higher response rates when rituximab is added to certain cytotoxic chemotherapy regimens for ARL, but at the same time its use might be associated with a higher death rate from infection during treatment, especially in patients with very low $CD4^+$ counts.[58,59,61] Additional research will be needed to define the mechanisms by which rituximab contributes to infections in this population and the role of this agent in the treatment of ARL.

A recent phase II study conducted at the National Cancer Institute examined another infusional regimen, DA-EPOCH without rituximab.[56] In this study, 74% of patients achieved a complete remission, and at 53 months of median follow-up, the disease-free and overall survival were 92% and 60%, respectively. This compares favorably with a median survival of about 32 months recently reported with CHOP plus rituximab,[58] and also compares favorably with the overall survival of 65% and disease-free survival of 55% seen at a median of 23 months follow-up on the studies of CDE with rituximab.[59] It is possible, however, that the DA-EPOCH study benefited from patient-selection bias, as it was performed in a single referral hospital. A multi-institutional trial by the AIDS Malignancies Consortium of DA-EPOCH given concurrently or sequentially with rituximab is underway to investigate further this approach.

One argument for combining HAART and cytotoxic chemotherapy for lymphoma is the improved survival of patients with ARL in the HAART era. It is possible, however, that several other factors might contribute to this improved survival, including a greater percentage of good-prognosis tumors in patients on HAART and improved prophylaxis and control of opportunistic infections. In the DA-EPOCH trial, antiretroviral therapy was deferred until all cycles of cytotoxic chemotherapy were completed, because of concern about overlapping toxicities (leading to reduced dose intensity of the lymphoma therapy and skipped doses of antiretroviral therapy with a risk for drug resistance), unpredictable drug interactions, and the possibility that any protective effect of the HAART on $CD4^+$ counts would be lost in the face of cytotoxic chemotherapy.[56] The successful results obtained in this study indicate that HAART can be safely deferred until completion of ARL treatment.

Nevertheless, it is clear that at least some regimens for ARL, such as CHOP and infusional CDE, can be administered with HAART,[54,59] and there is evidence that some of the theoretical concerns regarding HAART coadministration during ARL therapy do not pose a substantial problem in practice. The concern that dose intensity might be compromised has not been substantiated and, in at least one study, higher dose intensities were achieved when HAART was

given.[55] Also, the ability to maintain undetectable HIV viral loads in most studies indicates that antiretroviral adherence is not compromised. Informal comparison of the National Cancer Institute's DA-EPOCH trial with studies in which HAART is given with chemotherapy suggest that $CD4^+$ cell counts might return to the prelymphoma therapy baseline faster when HAART is coadministered.[54,56,59] No prospective trials have specifically addressed whether HAART should be administered during antilymphoma therapy, however. In the absence of such guidance, physicians will have to carefully assess the available evidence as it applies to any given patient. When patients are already receiving HAART, some physicians with experience in this area will continue this treatment during lymphoma therapy; they will avoid starting HAART and antineoplastic therapy at the same time, however.

There are few data that address specifically the role of HAART in the treatment of PCNSL, but the available evidence supports its initiation as soon as possible.[62] Before the introduction of HAART, whole-brain radiation therapy was the standard treatment for patients with PCNSL, and, even with this treatment, median survival was generally 2–4 months, owing to recurrent lymphoma or other complications of AIDS.[63] Although radiotherapy remains the standard of care for HIV-associated PCNSL, there is an interest in exploring chemotherapy-based approaches with HAART, as a means of reducing the risk of late radiation-induced neurotoxicity.

## VIRAL TARGETS IN HIV-ASSOCIATED MALIGNANCIES

There is currently an interest in developing vaccines for human papillomaviruses and other oncogenic viruses that cause AIDS-associated malignancies, and this approach has the potential to reduce greatly the incidence of tumors caused by these viruses.[64] There is also an interest in exploiting viral targets for therapy. Putting this latter approach into practice, however, is proving to be difficult.

In the case of KS, there is evidence that administration of antiherpes drugs can prevent tumor development. The best evidence came from a randomized trial of ganciclovir (Cytovene®, Hoffman-La Roche, Nutley, NJ) in patients with AIDS-associated cytomegalovirus retinitis.[65] There are also several case reports to indicate that occasional patients with KS can respond to antiherpes therapy. However, in a small trial of CIDOFOVIR (Vistide®, Gilead Sciences, Inc., Foster City, CA) conducted by our group in the National Cancer Institute, no KS responses were observed.[66] An alternative approach in KS is to activate KSHV lytic replication, which in turn induces cellular apoptosis. The AIDS Malignancies Consortium has initiated a trial of valproic acid[67] to begin to explore this approach (R Ambinder, personal communication).

Similarly, there is an interest in using antiherpes drugs to target lymphomas or other tumors caused by EBV or KSHV. Both of these viruses have kinases that can activate certain drugs—such as zidovudine or ganciclovir—to toxic forms,[68,69] and several investigators are studying the feasibility of combining viral activation and antiherpes approaches.[70,71] Case reports have described the activity of such agents in AIDS-related PCNSL or multicentric Castleman's disease,[72,73] but some animal experiments have indicated that it might be difficult to achieve toxic levels of the antiherpes drugs in tumor cells,[71] and additional research is needed to assess such approaches in various herpesvirus-associated tumors.

## CONCLUSION

The development of effective antiretroviral therapy has profoundly changed the epidemiology of AIDS-related complications, including AIDS malignancies. In settings where HAART is available, the incidence of some AIDS malignancies has decreased substantially, although cancer-related mortality has surpassed mortality from infectious complications as the leading cause of death in HIV-infected individuals.[29] Since HAART was introduced, the number of people living with AIDS in the US has increased (Figure 1), and these individuals are at risk for developing a wide range of malignancies in the future. Additional research will be needed to develop strategies to reduce the risk of malignant complications in patients with chronic HIV infection and to treat them optimally when their condition develops.

**GLOSSARY**

**CIDOFOVIR**
An antiviral medication used for the treatment of cytomegalovirus infection

**References**

1 Levine AM *et al.* (1985) Retrovirus and malignant lymphoma in homosexual men. *JAMA* **254:** 1921–1925
2 Boshoff C and Weiss R (2002) AIDS-related malignancies. *Nat Rev Cancer* **2:** 373-382
3 Jaffe E *et al.* (2001) *Pathology and genetics of tumours of haematopoietic and lymphoid tissues*. Lyon: IARC Press

4 Centers for Disease Control (1992) 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep* **41:** 1–19
5 Goedert JJ *et al.* (1998) Spectrum of AIDS-associated malignant disorders. *Lancet* **351:** 1833–1839
6 Gallagher B *et al.* (2001) Cancer incidence in New York State acquired immunodeficiency syndrome patients. *Am J Epidemiol* **154:** 544–556
7 Frisch M *et al.* (2001) Association of cancer with AIDS-related immunosuppression in adults. *JAMA* **285:** 1736–1745
8 Herida M *et al.* (2003) Incidence of non-AIDS-defining cancers before and during the highly active antiretroviral therapy era in a cohort of human immunodeficiency virus-infected patients. *J Clin Oncol* **21:** 3447–3453
9 Chang Y *et al.* (1994) Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* **266:** 1865–1869
10 Cesarman E *et al.* (1995) Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. *N Engl J Med* **332:** 1186–1191
11 Antman K and Chang Y (2000) Kaposi's sarcoma. *New Engl J Med* **342:** 1027–1038
12 Aoki Y *et al.* (2000) Viral and cellular cytokines in AIDS related malignant lymphomatous effusions. *Blood* **96:** 1599–1601
13 Ensoli B *et al.* (1994) Synergy between basic fibroblast growth factor and HIV-1 Tat protein in induction of Kaposi's sarcoma. *Nature* **371:** 674–680
14 Aoki Y and Tosato G (2004) HIV-1 Tat enhances Kaposi sarcoma-associated herpesvirus (KSHV) infectivity. *Blood* **104:** 810–814
15 Rabkin CS *et al.* (1997) Monoclonal origin of multicentric Kaposi's sarcoma lesions. *N Engl J Med* **336:** 988–993
16 Moore PS *et al.* (1996) Molecular mimicry of human cytokine and cytokine response pathway genes by KSHV. *Science* **274:** 1739–1744
17 Boshoff C *et al.* (1997) Angiogenic and HIV-inhibitory functions of KSHV-encoded chemokines. *Science* **278:** 290–294
18 Bais C *et al.* (1998) G-protein-coupled receptor of Kaposi's sarcoma-associated herpesvirus is a viral oncogene and angiogenesis activator. *Nature* **391:** 86–89
19 Masood R *et al.* (1997) Vascular endothelial growth factor/vascular permeability factor is an autocrine growth factor for AIDS-Kaposi sarcoma. *Proc Natl Acad Sci U S A* **94:** 979–984
20 Miles SA *et al.* (1990) AIDS Kaposi sarcoma-derived cells produce and respond to interleukin 6. *Proc Natl Acad Sci U S A* **87:** 4068–4072
21 Haque M *et al.* (2003) Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) contains hypoxia response elements: relevance to lytic induction by hypoxia. *J Virol* **77:** 6761–6768
22 Folpe AL *et al.* (2000) Vascular endothelial growth factor receptor-3 (VEGFR-3): a marker of vascular tumors with presumed lymphatic differentiation, including Kaposi's sarcoma, kaposiform and Dabska-type hemangioendotheliomas, and a subset of angiosarcomas. *Mod Pathol* **13:** 180–185
23 Flexner C (1998) HIV-protease inhibitors. *New Engl J Med* **338:** 1281–1292
24 International Collaboration on HIV and Cancer (2000) Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. *J Natl Cancer Inst* **92:** 1823–1830
25 Besson C *et al.* (2001) Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy. *Blood* **98:** 2339–2344
26 Clifford GM *et al.* (2005) Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst* **97:** 425–432
27 Centers for Disease Control and Prevention: Cases of HIV infection and AIDS in the United States, 2003 [www.cdc.gov/hiv/stats.htm] (accessed 30 June 2005)
28 Jaffe H (2004) Public health. Whatever happened to the U.S. AIDS epidemic? *Science* **305:** 1243–1244
29 Bonnet F *et al.* (2004) Malignancy-related causes of death in human immunodeficiency virus-infected patients in the era of highly active antiretroviral therapy. *Cancer* **101:** 317–324
30 Mbulaiteye SM *et al.* (2003) Epidemiology of AIDS-related malignancies an international perspective. *Hematol Oncol Clin North Am* **17:** 673–696
31 Wabinga HR *et al.* (2000) Trends in cancer incidence in Kyadondo County, Uganda, 1960–1997. *Br J Cancer* **82:** 1585–1592
32 Yarchoan R and Broder S (1987) Preliminary results on the use of dideoxynucleosides in the therapy of AIDS. In *Vaccines 87: Modern Approaches to New Vaccines: Prevention of AIDS and other Viral, Bacterial, and Parasitic Diseases*, 214–224 (Eds Chanock RM *et al.*) Cold Spring Harbor: Cold Spring Harbor Laboratory Press
33 Dupont C *et al.* (2000) Long-term efficacy on Kaposi's sarcoma of highly active antiretroviral therapy in a cohort of HIV-positive patients. CISIH 92. Centre d'information et de soins de l'immunodeficience humaine. *AIDS* **14:** 987–993
34 Noy A *et al. (*2005) Angiogenesis inhibitor IM862 is ineffective against AIDS-Kaposi's sarcoma in a phase III trial, but demonstrates sustained, potent effect of highly active antiretroviral therapy: from the AIDS Malignancy Consortium and IM862 Study Team. *J Clin Oncol* **23:** 990–998
35 Martin-Carbonero L *et al.* (2004) Pegylated liposomal doxorubicin plus highly active antiretroviral therapy versus highly active antiretroviral therapy alone in HIV patients with Kaposi's sarcoma. *AIDS* **18:** 1737–1740
36 Sgadari C *et al.* (2002) HIV protease inhibitors are potent anti-angiogenic molecules and promote regression of Kaposi sarcoma. *Nat Med* **8:** 225–232
37 Portsmouth S *et al.* (2003) A comparison of regimens based on non-nucleoside reverse transcriptase inhibitors or protease inhibitors in preventing Kaposi's sarcoma. *AIDS* **17:** F17–F22
38 Nasti G *et al.* (2003) AIDS-related Kaposi's Sarcoma: evaluation of potential new prognostic factors and assessment of the AIDS Clinical Trial Group Staging System in the Haart Era—the Italian Cooperative Group on AIDS and Tumors and the Italian Cohort of Patients Naive From Antiretrovirals. *J Clin Oncol* **21:** 2876–2882
39 Walmsley S *et al.* (1999) Treatment of AIDS-related cutaneous Kaposi's sarcoma with topical alitretinoin (9-cis-retinoic acid) gel. Panretin Gel North American Study Group. *J Acquir Immune Defic Syndr* **22:** 235–246
40 Krown SE *et al.* (1983) Preliminary observations on the effect of recombinant leukocyte A interferon in homosexual men with Kaposi's sarcoma. *N Engl J Med* **308:** 1071–1076
41 Gill PS *et al.* (1996) Randomized phase III trial of liposomal daunorubicin versus doxorubicin, bleomycin, and vincristine in AIDS-related Kaposi's sarcoma. *J Clin Oncol* **14:** 2353–2364
42 Stewart S *et al.* (1998) Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma. *J Clin Oncol* **16:** 683–691

43 Northfelt DW *et al.* (1998) Pegylated-liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine in the treatment of AIDS-related Kaposi's sarcoma: results of a randomized phase III clinical trial. *J Clin Oncol* **16:** 2445–2451
44 Welles L *et al.* (1998) Phase II trial with dose titration of paclitaxel for the therapy of human immunodeficiency virus-associated Kaposi's sarcoma. *J Clin Oncol* **16:** 1112–1121
45 Gill PS *et al.* (1999) Paclitaxel is safe and effective in the treatment of advanced AIDS- related Kaposi's sarcoma. *J Clin Oncol* **17:** 1876–1883
46 Yarchoan R (1999) Therapy for Kaposi's sarcoma: recent advances and experimental approaches. *J Acquir Immune Defic Syndr* **21 (Suppl 1):** S66–S73
47 Cianfrocca M *et al.* (2002) Matrix metalloproteinase inhibitor COL-3 in the treatment of AIDS-related Kaposi's sarcoma: a phase I AIDS malignancy consortium study. *J Clin Oncol* **20:** 153–159
48 Little RF *et al.* (2000) Activity of thalidomide in AIDS-related Kaposi's sarcoma. *J Clin Oncol* **18:** 2593–2602
49 Pluda JM *et al*. (1999) Preliminary results of a pilot study of the administration of interleukin-12 to patients (pts) with AIDS-associated Kaposi's sarcoma (KS) [abstract]. *J Human Virol* **2:** a200
50 Moses AV *et al.* (2002) Kaposi's sarcoma-associated herpesvirus-induced upregulation of the c-*kit* proto-oncogene, as identified by gene expression profiling, is essential for the transformation of endothelial cells. *J Virol* **76:** 8383–8399
51 Koon HB *et al.* (2005) Imatinib-induced regression of AIDS-related Kaposi's sarcoma. *J Clin Oncol* **23:** 982–989
52 Stallone G *et al.* (2005) Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* **352:** 1317–1323
53 Kaplan LD *et al.* (1997) Low-dose compared with standard-dose m-BACOD chemotherapy for non-Hodgkin's lymphoma associated with human immunodeficiency virus infection. National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group. *N Engl J Med* **336:** 1641–1648
54 Ratner L *et al.* (2001) Chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma in combination with highly active antiretroviral therapy. *J Clin Oncol* **19:** 2171–2178
55 Antinori A *et al.* (2001) Better response to chemotherapy and prolonged survival in AIDS-related lymphomas responding to highly active antiretroviral therapy. *AIDS* **15:** 1483–1491
56 Little RF *et al.* (2003) Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. *Blood* **101:** 4653–4659
57 Sparano JA *et al.* (2004) 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* **22:** 1491–1500
58 Kaplan LD *et al.* (2005) Rituximab does not improve clinical outcome in a randomized phase III trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin's lymphoma: AIDS-malignancies consortium trial 010. *Blood* [doi: 15914552]
59 Spina M *et al.* (2005) Rituximab plus infusional cyclophosphamide, doxorubicin, and etoposide in HIV-associated non-Hodgkin lymphoma: pooled results from 3 phase 2 trials. *Blood* **105:** 1891–1897
60 Thirlwell C *et al.* (2003) Acquired immunodeficiency syndrome-related lymphoma in the era of highly active antiretroviral therapy. *Clin Lymphoma* **4:** 86–92
61 Straus DJ (2005) HIV-associated lymphoma: promising new results, but with toxicity. *Blood* **105:** 1842
62 Newell ME *et al.* (2004) Human immunodeficiency virus-related primary central nervous system lymphoma: factors influencing survival in 111 patients. *Cancer* **100:** 2627–2636
63 Donahue BR *et al.* (1995) Additional experience with empiric radiotherapy for presumed human immunodeficiency virus-associated primary central nervous system lymphoma. *Cancer* **76:** 328–332
64 Schiller JT and Lowy DR (2001) Papillomavirus-like particle vaccines. *J Natl Cancer Inst Monogr* **58:** 50–54
65 Martin DF *et al.* (1999) Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. Roche Ganciclovir Study Group. *N Engl J Med* **340:** 1063–1070
66 Little RF *et al.* (2003) A pilot study of cidofovir in patients with Kaposi's sarcoma. *J Infect Dis* **187:** 149–153
67 Shaw RN *et al.* (2000) Valproic acid induces human herpesvirus 8 lytic gene expression in BCBL-1 cells. *AIDS* **14:** 899–902
68 Gustafson EA *et al.* (2000) Human herpesvirus 8 open reading frame 21 is a thymidine and thymidylate kinase of narrow substrate specificity that efficiently phosphorylates zidovudine but not ganciclovir. *J Virol* **74:** 684–692
69 Cannon JS *et al.* (1999) Human herpesvirus 8-encoded thymidine kinase and phosphotransferase homologues confer sensitivity to ganciclovir. *J Virol* **73:** 4786–4793
70 Feng WH *et al.* (2004) Lytic induction therapy for Epstein-Barr virus-positive B-cell lymphomas. *J Virol* **78:** 1893–1902
71 Staudt MR *et al.* (2004) The tumor microenvironment controls primary effusion lymphoma growth *in vivo*. *Cancer Res* **64:** 4790–4799
72 Raez L *et al.* (1999) Treatment of AIDS-related primary central nervous system lymphoma with zidovudine, ganciclovir, and interleukin 2. *AIDS Res Hum Retroviruses* **15:** 713–719
73 Casper C *et al.* (2004) Remission of HHV-8 and HIV-associated multicentric Castleman disease with ganciclovir treatment. *Blood* **103:** 1632–1634

**Competing interests**
The authors declared competing interests; go to the article online for details.