

2007

## AIDS-Associated Viral Oncogenesis: Overview

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Wood, Charles, "AIDS-Associated Viral Oncogenesis: Overview" (2007). *Virology Papers*. 187.  
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Published in *Cancer Treatment and Research* (Springer, 2007).  
ISBN: 978-0-387-46804-4. P. 1-19.

## AIDS-Associated Viral Oncogenesis

### 1. OVERVIEW

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It has been 25 years since the acquired immunodeficiency syndrome (AIDS) was first described and over 23 years since the human immunodeficiency virus (HIV) associated with the disease was first discovered. In spite of the tremendous progress that was made in understanding both the disease and the virus, there are still millions of people infected, died, or living with the disease. As for the year 2005 alone, the Joint United Nations Programme on HIV/AIDS (<http://www.UNAIDS.org>) estimates that there are about 40 million people living with HIV/AIDS globally, and approximately 3 million people died from AIDS in the year. Globally, it is estimated that 25 million people have died of HIV/AIDS since 1981. The impact of the epidemic is enormous, with the greatest impact in sub-Saharan Africa where about two-thirds of those living with HIV/AIDS in the world reside. A number of countries in the region have infection rates to as high as 30-40% of the population. As for South and Southeast Asia, even though the adult prevalence is lower and estimated to be less than 1%, there are still 7.4 million people living with HIV/AIDS in this region, accounting for about 18% of those living with HIV/AIDS in the world.<sup>104,114</sup> North America, Latin America, and Eastern Europe and Central Asia, each have between 1.2 and 1.8 million people living with HIV/AIDS. Although the 300,000 people living with HIV/AIDS in the Caribbean constitute a small part of the global total, they are about 1.6% of adults in the region, making the Caribbean the only region other than sub-Saharan Africa to have an adult prevalence higher than 1%.<sup>104,114</sup> Essentially, no single country can escape from the impact of HIV/AIDS.

Since the beginning of the AIDS epidemic, it was soon realized that HIV-infected individuals that are immunosuppressed are affected not only by opportunistic infections but also by other AIDS-associated diseases, including malignancies. In fact, at the onset of the AIDS epidemic in 1981, the disease was first recognized through an increase of Kaposi's sarcoma (KS) in young adult homosexual male population, which is unusual as KS is a very rare form of malignancies which are found in certain ethnic groups in the Mediterranean region and in Africa.<sup>29,57</sup> In 1992, the US Center for Disease Control and Prevention (CDC) developed the initial case definition for AIDS and included two AIDS-defining malignancies, KS and primary central nervous system lymphoma (PCNSL).<sup>2</sup> It was soon realized that patients infected by HIV are also at risk for developing both Hodgkin's and non-Hodgkin's lymphomas (NHL) when compared to normal uninfected individual, with a large number of homosexual male with AIDS developed NHL.<sup>122</sup> Subsequently, CDC has revised the definition of AIDS to include NHL in 1987<sup>1</sup> and invasive cervical cancer in 1992.<sup>3</sup> In addition to the common AIDS-defining malignancies it has been reported that AIDS and or immunosuppression may lead to an increase in other non-AIDS defining cancers, including multiple myeloma, Hodgkin's disease, leukemia, lung cancer, oral cavity cancers, and leiomyosarcoma in children.<sup>44,47</sup> These malignant tumors are generally characterized by a more aggressive behavior at diagnosis and a poorer outcome compared with the same tumors in the general population. A large-scale study by Frisch *et al.*<sup>34</sup> analyzing cancer registries from 11 sites in the US for over 300,000 HIV-infected adults showed that these individuals have a very high risk in developing AIDS-defining cancers, but in addition, non-AIDS defining cancers also showed a statistically significance increase as well. Those that showed a potential association with immunosuppression are Hodgkin's disease (HD), lung cancer, penile cancer, soft tissue malignancies, and testicular seminoma. However, most non-AIDS-defining cancers do not appear to be associated with HIV-associated immunosuppression and disease progression.<sup>36,80</sup> It is likely that other factors could be involved, including smoking and other viral coinfections.

A number of the common cancers associated with AIDS and immunosuppression were found to have infectious viral cofactors, including those classified as AIDS-defining disease, KS, NHL, and invasive cervical cancers. Kaposi's sarcoma and primary effusion non-Hodgkin's lymphomas have been linked to Kaposi's sarcoma-associated herpesvirus (KSHV) or human herpesvirus-8 (HHV-8); Hodgkin's disease and non-Hodgkin's lymphomas have been linked to EBV; and squamous cell carcinomas have been linked to human papilloma virus (HPV) (Table 1). These viral-associated AIDS-malignancies will be the major focus of this chapter.

#### AIDS-ASSOCIATED KAPOSI'S SARCOMA

KS is a very rare form of sarcoma that has become the most common neoplasm in HIV-infected individuals, since the onset of the AIDS epidemic. KS was first described by Moritz Kaposi in 1872 as an indolent tumor in elderly Mediterranean men with multifocal pig-

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Table 1. AIDS-associated malignancies with viral etiology

Malignancies	Virus
Kaposi's sarcoma	Human herpesvirus-8 (HHV-8) or Kaposi's sarcoma-associated herpesvirus (KSHV)
Non-Hodgkin's lymphomas	
Primary central nervous system lymphoma	Epstein-Barr Virus (EBV)
Primary effusion lymphoma	HHV-8
Burkitt's lymphoma	EBV
Plasmablastic lymphoma	EBV
Hodgkin's disease	EBV
Squamous cell neoplasm	HPV
Genital dysplasia	

mented sarcoma.<sup>62</sup> KS is composed of a mixture of irregular shaped, round capillaries, and slitlike endothelium-lined vascular spaces and spindle-shaped cells with infiltrating mononuclear cells. It is not clear whether KS represents a clonal neoplastic process or a polyclonal inflammatory lesion. Studies have shown that varying monoclonality, oligoclonality, and polyclonality from lesions of various patients.<sup>40</sup> The origin of KS spindle cells is also not clear; it has been suggested that KS cells represent a heterogeneous population of cells, arising from pluripotent mesenchymal precursor cells, and may be of lymphatic endothelial cell origin.<sup>28</sup>

Since AIDS was first described in the early 1980s, the annual incidence of KS in the San Francisco Bay area showed an exponential increase with the incidence rate per age group followed a bimodal distribution that peaks from 30 to 36 years of age.<sup>24</sup> KS has become the most common neoplasm in HIV-infected individuals, and has reached epidemic proportions in the developing world where HIV is widespread, such as sub-Saharan Africa. Patients in this region with AIDS-associated KS have been shown to have a high tumor burden and rapid disease course, very different from those seen in the non-AIDS-related KS. There are four different epidemiological forms of KS that showed different clinical parameters. The first is the classical or sporadic form of KS. This is associated with elderly men in the Mediterranean countries like Italy and Israel.<sup>57</sup> This form of KS is usually nonaggressive and associated with lesions in the lower extremities. It is usually not associated with HIV infection. The older the patients are, the risk for disease progression is also greater, and disseminated KS in these individuals could occur if they are immunosuppressed. The second form of KS is endemic African KS. This form of KS was found in the African continent prior to the onset of the AIDS epidemic. It is found not only in men but in women and young children as well.<sup>117</sup> This form of KS tends to be more aggressive than the classical KS and can also involve the lymph nodes. With the spread of HIV since the 1980s, the prevalence of KS in the African continent has increased substantially. A study in Uganda has shown that prior to the 1970s, KS was diagnosed in no more than 7% of the male cancer population, and none in the female.

However, by the early 1990s, it had risen to around 49% of the male cancer patients, and 18% of the female cancer patients.<sup>117</sup> and similar increases were reported in other African nations. In Zambia, in the late 1990s, KS was found to be one of the most common childhood cancers.<sup>16</sup> most likely due to HIV coinfection. The third type of KS is the Iatrogenic KS or transplant-associated KS. This normally occurs in patients after transplantation that were treated with immunosuppressive drugs, and withdrawal of therapy can lead to KS regression.<sup>53</sup> This form of KS tends to have a more rapid disease course as compared to the classical KS, but can also present as a chronic condition.<sup>53</sup> The fourth form of KS is the AIDS KS. This form of KS has been found to be associated with AIDS patients, it has increased dramatically since the onset of the AIDS epidemic and is one of the AIDS-defining illnesses.<sup>43,45</sup> This is the most aggressive form of KS and was first described in the early 1980s in the HIV-infected homosexual male population.<sup>33</sup> Unlike the classical KS, AIDS KS involves not only the lower extremities and skin, but also the upper body, the head regions, and the lymph nodes. It can also disseminate to other organs, such as the spleen, the lungs, the liver, and gastrointestinal track.<sup>53</sup>

#### Human Herpesvirus and KS

An infectious agent has long been suspected in the development of KS; herpesvirus-like particles were found in short-term KS tissue culture, and were subsequently identified as cytomegalovirus,<sup>41</sup> but the involvement of CMV in KS has not been confirmed. In 1994, a novel human herpesvirus was identified by Chang and Moore<sup>14</sup> using representational difference analyses. This virus is now known as KSHV or HHV-8 and is found to be necessary, but not sufficient for the development of all types of KS. It is clear that other cofactors, such as immunosuppression, are required for KS development. KSHV is found in all KS lesions, and is mainly located in the vascular endothelial cells and perivascular spindle-shaped cells<sup>75</sup> KSHV infection is not commonly found in low-risk population but found commonly in individuals at risk for KS.

KSHV belongs to the  $\gamma$ -herpesvirus family, which can further be divided into two subgroups,  $\gamma$ -1 or lymphocryptovirus and  $\gamma$ -2 or rhadinovirus. EBV is the prototype of  $\gamma$ -1 virus and the simian herpesvirus saimini is the prototype of  $\gamma$ -2 herpesvirus.<sup>96</sup> KSHV is classified as a  $\gamma$ -2 rhadinovirus and is the first human virus of this subfamily identified. Like other herpesviruses, HHV-8 is a double-stranded deoxyribonucleic acid (DNA) virus. Its genome is linear, it is about 165 kbp in length, and contains at least 87 viral genes. A feature of some DNA viruses, particularly of herpesviruses and KSHV, is the ability of these viruses to incorporate or pirate host genes into their genome: these genes can then play a role in the replication, survival, and transformation functions of the virus. KSHV was found to encode human homologous genes that regulate cell cycling like cyclin D, growth factors like interleukin 6, or genes that may prevent programmed cell death such as bcl-2. Deciphering the functions of these viral genes will lead to a better understanding of viral pathogenesis and oncogenesis.

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Unlike most other herpesviruses, KSHV infection does not seem to be widely distributed in most populations. The detection of KSHV infection relies on the presence of antibodies against either lytic and/or latent antigens and varies among the different tests that were used in different seroprevalence studies. In general, the frequency of infection appears to be low in North America, certain Asian countries, and in Northern European nations such as the UK and Germany, with most studies reporting a seroprevalence rate in normal blood donors of less than 5%.<sup>30,88,99,100</sup> In these countries the seroprevalence of KSHV in different risk groups mirrors the incidence of AIDS KS, with a seroprevalence rate of 25-50% among homosexual men. In other countries, such as Italy, Greece, and Israel, especially Southern Italy, the infection rate seems to be much higher in the general population, and is more variable, ranging between 5 and 35%. In contrast to North America and Europe, KSHV infection is widespread in the African continent. High seroprevalence rates between 40 to 50% have been found in Central, West, and South Africa.<sup>6,37,50,86</sup> Therefore, KSHV seroprevalence tracks very closely with KS, with the highest infection rate in geographic areas where classic or endemic forms of KS are more common. KS has a particularly high incidence in Central African countries like the Republic of Congo, Uganda, and Zambia; these countries also have the highest KSHV infection rates in the world.<sup>37</sup> Very little is known about KSHV infection in China even though EBV infection was found to be ubiquitous. There were only two reported studies in China; Dilnur *et al.*<sup>23</sup> found that KSHV was associated with KS in China. The study by Du *et al.*<sup>26</sup> in the outskirts of China in the Xinjiang autonomous region, where there is a high incidence of HIV-1 infection, showed that there was a high KSHV infection rate. The study found KSHV infection varied among individuals of different racial origin, it was highest in the Khalkhas population at about 48% and lowest in the Kazak and Han population at over 12%, but the specimens were screened without dilution, the reproducibility of the assay was not determined, and the prevalence among different risk groups was not studied. Thus, there is a need to perform a systematic comparison of risk groups using established assays.

### Impact of HAART on KS

Since the beginning of the AIDS epidemic in the early 1980s, AIDS KS has become one of the most common AIDS-associated malignancies with HIV-infected homosexual males at the highest risk, and those with AIDS had a 50% lifetime rate of developing KS early in the HIV epidemic.<sup>63</sup> However, the rate of AIDS KS has since steadily declined both in the US and Europe.<sup>7</sup> It has been suggested that the disease may have shifted from an early disease to a late manifestation during the HIV disease course. Since the introduction of highly active antiretroviral therapy, a further major decrease in AIDS KS was further observed.<sup>71</sup> and therapy has now made AIDS KS a relatively rare tumor in treated HIV-infected individuals.<sup>9</sup> Several studies have shown that there was a marked decrease in KS incidence since HAART was introduced, a decline of as high as 80-fold was observed. In addition, regression of KS following treatment has been reported.<sup>48,58,91,92,112</sup> Interestingly, the reduced KS risk was

only observed with HAART, but not with double or single anti-HIV drugs.<sup>59</sup> Even though the incidence of KS in the treated HIV-infected individuals in the western world has decreased dramatically, in the setting where HAART is still not widely available, such as sub-Saharan Africa, AIDS KS still remains a major problem.

#### AIDS-ASSOCIATED NON-HODGKIN'S LYMPHOMA

ARL represents a heterogeneous group of tumors that are commonly found in HIV-infected, immunosuppressed individuals. The majority of the cancers are of B-cell in origin; the development of these cancers is characterized as an AIDS-defining illness.<sup>68,74</sup> ARL in general is a late event in the HIV disease course. The risk factors for the development of ARL include low CD4 and T cell counts, high HIV viral load, and increased age.<sup>66</sup> ARL in general is classified into three groups. The first are those that can also be found in immunocompetent individuals, like Burkitt's lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL) which can further be classified into centroblastic, immunoblastic, and anaplastic subtypes. An example of DLBCL is the primary central nervous system lymphoma (PCNSL), which is a distinct extranodal presentation of DLBCL.<sup>68</sup> The second are those that are found only in HIV-infected immunosuppressed individuals. They include the primary effusion lymphoma (PEL) and plasmablastic lymphoma. The third are those that can be found also in immunosuppressed patients other than those due to HIV infection. These include post-transplant lymphoproliferative disorders. In general, the difference between ARL and NHL found in non-AIDS-associated patients is the presentation of advanced diseases, extranodal involvement, disease in soft tissues, and other locations, such as jaws and their association with viral infections, most prominently EBV and KSHV. In addition to viral coinfections, a large proportion of the ARL also have genetic abnormalities, especially among the large-cell lymphomas, Bcl-6 rearrangement occur in about 33% of the cases, c-myc rearrangement about 40%, and p53 mutations about 25% of the cases,<sup>35</sup> whether these genetic abnormalities are the causes or effect of malignant transformation is not clear.

The most commonly identified virus associated with AIDS-related lymphomas is EBV and there is a large body of published work on the oncogenic mechanisms of this agent.<sup>12, 121</sup> The second most common is KSHV, which was found to be associated with PEL associated with HIV infection.<sup>131</sup> B-lymphocytes transformed by EBV (lymphoblastoid cell lines) *in vitro* express an array of virus-encoded proteins including six EBV nuclear antigens (EBNAs) and three LMPs. EBNAs are generated from differential splicing of a transcript that arises from one of two promoters (Cp or Wp).<sup>121</sup> This form of latency is termed Latency III, and is common in immunoblastic lymphomas.<sup>12</sup> A Type II form of latency where EBNA 1, LMP-1, and LMP-2a are expressed has been identified in some EBV-associated lymphomas. In Latency I (typical of Burkitt's lymphomas) only EBNA-1 (generated from the Qp promoter) and EBV-

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encoded RNAs (EBERs) are expressed.<sup>12,121</sup> Recent studies have indicated that some heterogeneity in EBV gene expression and EBNA promoter usage exists among endemic BL.<sup>65</sup> It has been proposed that classical antigen driven B-cell proliferation may play a role in the ARL.<sup>68</sup> The hyperstimulation of B lymphocytes could be caused by HIV, EBV, and other infectious agents that may elicit the release of various growth factors and cytokines which promote the proliferation and transformation of B cells into ARC.

Among the ARL, the ones most commonly found in HIV-infected individuals are BL and DLBCL. They represent about 90% of all ARLs.<sup>8</sup> The others, such as PEL, represent less than 50% of the cases. Chemically immunosuppressed individuals, like those infected with HIV, have a much higher risk of developing lympho-proliferative disorders. The increased risk of developing ARC has been reported to range from 14-fold for low-grade lymphoma to 630-fold for high-grade immunoblastic lymphoma.<sup>21</sup> A study by Cote *et al.* has shown that the risk of HIV-infected individuals developing ARL within 3 years of being diagnosed with AIDS was 165-fold higher than those without AIDS. The same study also showed that the risk of developing BL is 261-fold higher.<sup>20</sup> In addition, it has been demonstrated that risk of AIDS patients developing PCNSL is 3,000 times higher and HD is ten times higher than HIV uninfected individuals.<sup>108</sup>

Burkitt's Lymphoma AIDS-related BL is one of the most common ARLs found in HIV-infected individuals. Unlike other ARL, BL is unique in that presentation of the cancer can occur at relatively high CD4 T-cell count (>250 cells/mm<sup>3</sup>).<sup>90</sup> AIDS BLs share features with endemic African BL in that both over express c-myc due to reciprocal translocations that bring the transactivator under the influence of potent promoter sequences within the immunoglobulin (Ig) genes loci. Inactivating mutations and deletions of p53 are also common as in all types of BL,<sup>11</sup> but Bcl-6 rearrangements are rarely observed. A distinguishing feature between AIDS-related and endemic BL is that the former is associated with EBV far less frequently than the latter.<sup>11,72</sup> EBV has been reported to present in a subset of between 33 and 67% of these AIDS-related BL, and the type III latency expressing viral EBNAs and LMP proteins was not consistently observed. With some expressing viral antigen patterns that are similar to those seen in Hodgkin's disease.<sup>103</sup> BL often carry genetic abnormalities and chromosomal translocation, but there is no evident that EBV has been linked to these abnormalities, c-myc translocation is common in BL, with the c-myc gene transposed to the proximity of the immunoglobulin locus, and often led to the activation of c-myc expression. These tumors are incredibly aggressive with short doubling times. Flow cytometric analysis typically reveals that over 90% of the tumor cells are in S phase. Ongoing tumor lysis syndrome even in the absence of concomitant chemotherapy is often noted. AIDS-related BLs appear to carry a poor prognosis even when compared to AIDS-related DLBCL.<sup>77</sup>



### Primary Central Nervous System Lymphoma

Primary central nervous system lymphoma (PCNSL) is a distinct extranodal form of DLBCL, which is usually of the immunoblastic type. It is a rapid and fatal disease with poor prognosis, associated with HIV infection and severe immunodeficiency, usually with CD4<sup>+</sup> T cell counts of < 50 cells/mm<sup>3</sup>.<sup>85,107</sup> HIV-infected persons with PCNSL usually have tumors confined to the craniospinal axis without systemic involvement. In contrast to PCNSL in HIV negative individuals, those found in the context of HIV infection is always associated with EBV in HIV-infected patients.<sup>85</sup> Detection of EBV sequences in the CSF by polymerase chain reaction in combination with thallium spectroscopy has been shown to be a useful diagnostic tool for the disease.<sup>17</sup> Since EBV is always present in PCNSL, it is likely that this virus plays a role in cancer development. The EBV genes that are expressed include the latent gene. EBNAs and LMP-1 and -2, typical of a type III latency seen in B cells, when they are transformed by EBV *in vitro*.<sup>120</sup> These EBV genes, such as LMP-2, are known to deregulate cellular replication and may play a role in the transformation of B cells. These gene products are also good targets of cytotoxic T lymphocytes, which could account for the reduction of PCNSL in patients that were undergoing antiretroviral therapy (ART) when their cytotoxic lymphocyte response was restored. However, it has been reported that abnormalities in the T cell functions in these patients can still be observed.<sup>116</sup> Thus, other factors, including the alternation of the EBV gene expression profile could have occurred upon ART. Treatment of patients with PCNSL with conventional chemotherapy in combination with radiation therapy has not been very effective. Only a 4-month survival has been observed. However, treatment with a high dose of zidovudine and ganciclovir has been shown to lead to long-term remission,<sup>93,98</sup> again suggesting that therapy targeting EVB may be effective in controlling PCNSL.

### Plasmablastic Lymphoma

Plasmablastic lymphoma is a recently described variant form of ARL that only occurs in a low percentage of HIV-infected individuals. It was originally described by Delecluse *et al.* as a B-cell lymphoma stained by antibody specific for plasma cells, but these cells lack the classical I3-cell antigen CD20.<sup>22</sup> These cancers occur only in a small percent of HIV-infected patients and are usually associated with EEV and KSHV infection.<sup>11</sup> Patients usually develop tumors in the jaw and oral cavity and the prognosis is poor. Patients with plasmablastic lymphoma normally do not respond to conventional chemotherapy and it has been suggested that therapy targeting EBV may be beneficial.<sup>18</sup> In fact, ART and intensive chemotherapy has been shown to be encouraging as five out of six HIV-infected and treated individuals were alive with a medium follow-up of 17 months.<sup>113</sup>

### Primary Effusion Lymphoma

Primary effusion lymphoma (PEL) is a very rare subtype of NHL, predominantly associated with HIV-infected individuals. PEL was first identified as a subset of body-cavity-based lymphomas, which were subsequently called PELs.<sup>13</sup> PELs are unique as they were found to

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contain KSHV DNA and are most frequently found in men and in AIDS patients. This type of lymphoma is distinguished from others as having a distinctive morphology, bridging large cell immunoblastic lymphoma and anaplastic large cell lymphoma. PELs often present as lymphomatous effusions in the pleural, peritoneal, and/or pericardial cavity. These cells are usually CD20 negative, often express CD45 marker but lack 13-cell-associated antigens. PELs have 13 cell origins with clonal immunoglobulin gene rearrangements. Gene expression profiling of PEL by Klein *et al.*<sup>67</sup> showed that PEL displayed a common gene expression profile that is distinct from ARL and NHL in HIV uninfected individuals. The profile also showed elements seen in EBV transformed lymphoblastoid cell lines, AIDS immunoblastic lymphoma, as well as multiple myeloma. Further confirming the notion that PEL is distinct and yet a subtype of NHL. Most PELs are coinfecting with EBV and KSHV and lack *c-myc* gene rearrangements. PELs are extremely rare tumors, and estimated to be about 0.13% of all AIDS-related malignancies in AIDS patients in the US.<sup>80</sup> Thus, KSHV-associated lymphomas represent a rare, distinct pathobiologic category which often, but not always, associates with an effusion in AIDS patients. The role of KSHV in the development of these lymphomas is not clear since this type of malignancies is still rare even in the populations with high KSHV seroprevalence rate. However, KSHV has always been found in these lymphomas, suggesting that this virus is necessary, but other factors must be needed for the development of PELs. These factors could be EBV infection and/or immunosuppression. Recently, solid tumor variants with plasmablastic features have been reported and these tumors tend to be rapidly fatal although recent data suggest that some PEL lines are quite sensitive to inhibition of NF- $\kappa$ B,<sup>64</sup> suggesting that inhibitors of NF- $\kappa$ B potentially can be developed as therapy for patients with PEL.

### ARL in the Era of Highly Active Antiretroviral Therapy

Since the introduction of HAART in the 1990s, the spectrum of ARL in the context of HIV infection has been substantially influenced. The epidemiology of ARL has been changed and the outcome of these tumors has been impacted. Prior to HAART, the prognosis of ARL was poor because the tumors tended to be more aggressive; there was an increase in hematological toxicity, and further complications occurred due to a high rate of opportunistic infection in the patients.<sup>61,106</sup> Risks for development of ARL increased as the HIV disease progressed and CD4<sup>+</sup> T cells declined. With HAART, the prognosis of ARL has improved. There was a better tolerance to chemotherapy, a higher rate of complete remission, and the death rate has been reduced.<sup>8,39</sup> However, HAART appears to have differential effects on different subtypes of ARL. A recently completed study performed by the NCI sponsored AIDS malignancy consortium (AMC) demonstrated the feasibility of concomitant chemotherapy with HAART.<sup>94</sup> Probably the best reported results for chemotherapy in AIDS NHL were from Dr. Little's group at the National Cancer Institute. Using the EPOCH regimen, the group achieved remission in 22 of 24 patients with a progression free survival of 23 months. These patients had favorable prognostic factors (median CD4<sup>+</sup> lymphocyte count of 233 mm<sup>3</sup>/ml.<sup>119</sup>

Enhanced toxicity of rituximab and CHOP chemotherapy was recently noted in a large multicenter trial conducted by the AMC.<sup>60</sup> The addition of rituximab to standard-dose CHOP as compared to CHOP alone led to increased infectious complications and deaths attributable to sepsis. It is possible that delayed recovery of humoral immunity could contribute to this increased risk of life-threatening bacterial infections in HIV-infected patients. There have been several reports on the feasibility and efficacy of high-dose chemotherapy and autologous stem cell transplant for ARL.<sup>69,95</sup> It is reasonable to assume that patients with well-controlled HIV and good performance status should be considered candidates for this therapy. Newer approaches that may benefit patients with ARL include EBV specific cytotoxic T cells and agents that activate the lytic program of gamma herpesviruses, thereby sensitizing the tumors to antivirals.<sup>70,97</sup>

The effects of HAART on PCNSL are more dramatic than other systemic ARL. The standard treatment of PCNSL is whole brain irradiation, but the median survival time is still just 2.5 months or less. With the addition of HAART to radiotherapy, several studies have shown an improvement in survival.<sup>56,85</sup> In the meta analysis of 11 studies, it was estimated that the decline of PCNSL in the HAART era has declined by 58%. In addition, it was shown that HAART therapy alone has led to a regression of PCNSL.<sup>81</sup> It is possible that with HAART, the restoration of cytotoxic T cells against latently expressed EBV antigens may have played a role in the reduction in the incidence of PCNSL, further confirming the role of EBV in the development of this malignancy.

In contrary to PCNSL, the effects of HAART on systemic ARL seem to be less dramatic.<sup>9,46</sup> A number of studies, including a EuroSIDA study on 8,599 HIV-infected individuals, showed that all types of lymphomas were reduced after the widespread use of HAART in the late 1990s, and demonstrated that there was a decline in systemic lymphomas ranging from twofold to sevenfold since HAART.<sup>8,66,84</sup> However, these studies also showed that the incidence of Burkitt's lymphomas appeared to be largely unaffected. In spite of the reduction of ARL in the HAART era, the risk of developing ARL in HAART-treated HIV-infected individuals is still about 20-fold higher than in uninfected individuals.<sup>19</sup> Whether this is due to the emergence of drug resistant viruses and immunosuppression, or due to prolonged mild immunosuppression and partial immune reconstitution, thus leading to an increase in developing cancers, is unknown. These risk factors remain to be elucidated.

#### HUMAN PAPILOMA VIRUS-ASSOCIATED NEOPLASMS

Genital cancers have been a world-wide public health problem, especially in the context of HIV infection and immunosuppression. They are common malignancies found in AIDS patients. HIV infection has been shown to substantially enhance the development of cervical cancer and cervical cancer precursor lesions.<sup>10,78</sup> It is also the most common female malignancy in many developing countries.<sup>118</sup>

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Genital cancers and cervical intraepithelial neoplasia (CIN) have been strongly implicated in association with HPV infection. The first report demonstrating the association of HPV and cervical cancer was published by Zur Hausen *et al.*,<sup>123</sup> showing that cervical cancer in the female genital tract has HPV-associated lesions. HPV infection of genital can either lead to asymptomatic infection or a wide range of genital lesions, ranging from genital warts to mild dysplasia to invasive carcinomas. Genital lesions are often referred to as cervical intraepithelial abnormalities or CIN, which is graded from I to III depending on the degree of epithelium abnormality. CIN I encompasses mild dysplasia or low-grade squamous intraepithelial lesions (SIL). CIN II represents high-grade SIL with moderate dysplasia, while severe dysplasia is referred to as CIN III.<sup>79</sup>

In 1993, the CDC has included invasive cervical cancer as one of the AIDS-defining illnesses. HIV infection has become an important risk factor for HPV infection and the development of genital cancers. HIV and HPV infections have a number of common features; both are sexually transmitted diseases (STD), and there is a high prevalence of HPV infection among HIV seropositive women, especially those that are immunosuppressed with low CD4<sup>+</sup> T cell counts.<sup>5,111</sup>

Up to 20% of the HIV and HPV coinfecting individuals developed HPV-associated premalignant lesions of the uterine cervix within 3 years of HIV infection.<sup>31</sup> The progression of an untreated HPV-induced dysplasia could then lead to cervical cancer. A number of studies have shown that HIV positive women have 2-3 times more HPV DNA in cervicovaginal washings and 15 times more in anal swabs as compared to HIV negative individuals.<sup>15,54,111</sup> HIV-infected women were also shown to be much more likely to develop cervical intraepithelial abnormalities. The prevalence and severity of genital tract infection in these women are also more pronounced.<sup>27,83</sup> The rates of invasive cervical carcinoma are 15-18 times higher in women with AIDS compared to the general population.<sup>32,102</sup> Men fare no better – the incidence of anal cancer in men with history of anal intercourse is at 35 per 100,000 individuals, a number equivalent to that of cervical carcinoma before the advent of Pap-smear screening.<sup>89,110</sup> The mechanism by which HIV increases the risk of HPV infection and cervical dysplasia is likely due to immunodeficiency, resulting in the inability of the immune response to control HPV infection. Indeed, cervical dysplasia increased progressively as the patients immune function declined, as determined by CD4<sup>+</sup> T cell counts.<sup>52</sup> A large, long-term prospective cohort studying of over 1,800 HIV positive and over 500 HIV negative women was carried out to determine how HIV RNA levels and CD4<sup>+</sup> T cell counts are associated with the natural history of HPV infection.<sup>109</sup> The results demonstrated that in HIV-infected women, the HIV plasma viral load in combination with CD4<sup>+</sup> T cell counts has a strong correlation with the detection of HPV infection and reactivation. However, there was only a moderate correlation between HIV coinfection and HPV persistent infection. This partially explains why cervical cancer rates are not even higher than what was observed in HIV+ infected women.

The effects of HAART on HIV and the immune status of HIV-infected individuals are well established, but their effects on the course of HPV-related cervical lesions in HIV-infected women are still not well established. HAART has not been shown to affect HPV detection and its effects on the natural history of cervical intraepithelial neoplasia are unclear.<sup>87</sup> There were a number of studies examining the effects of HAART on the course of cervical lesions.<sup>4,51</sup> A study by the Women's Interagency HIV Study (WIHS) group has reported an association of the regression of cervical lesions with HAART<sup>82</sup> whereas others cannot.<sup>76</sup> In addition, a multicenter study of HAART on the regression of cervical lesions in over 700 women followed for over 5 years also did not show any correlation.<sup>101</sup> However, these studies primarily focused on evaluating the effects of HAART on prevalent cervical lesions and the date of onset of those lesions is not known, thus it is not surprising that the outcome of these studies was controversial. To address these concerns, a study by Ahdieh-Grant *et al.*<sup>4</sup> determined whether HAART alters the natural history of CIN among HIV-infected women that were regularly followed every 6 months for 7 years. This study provided evidence that HAART has a modest benefit for HIV-infected women that were at risk for cervical neoplasia, with women receiving HAART will survive longer and have better control over cervical HPV infection and low-grade squamous intraepithelial lesions. However, HAART does not seem to lead to a complete reconstitution of the immune system for it to control HPV, the rates of regression among HIV-infected women receiving HAART remained lower than HIV-infected women that were never on HAART or among HIV-uninfected women. Thus, there is a need to actively seek and treat CIN in HIV-infected women, including those that are responding to HAART.

#### HODGKIN'S DISEASE

Hodgkin's disease (HD) or Hodgkin's lymphoma has not been classified as an AIDS-defining illness but HIV-related HD is also increasing in the context of HIV infection, and is clearly related to the immunosuppression in the infected patients.<sup>42,47</sup> Almost all HIV-related HD are EBV positive. The clinical presentations of HD in HIV-infected individuals are unique as compared to uninfected individuals, patients are more likely to have more advanced disease stage, extranodal involvement, and often involve bone marrow.<sup>25, 105, 115</sup>

Prior to the HAART era, the treatment outcome for HIV HD is poor, with a medium survival rate between 1 and 2 years. A clinical trial on treatment using doxorubicin, bleomycin, vinblastine, and dacarbazine on AIDS patients showed severe hematologic toxicity and a poor survival rate of only 1.5 years.<sup>73</sup> More recently the outcome of treatment in combination with HAART appears to be improving, patients treated with HAART and responded to the treatment within 2 years of the development of HD have improved survival rates compared to those that are not responders.<sup>38,55</sup> The use of HAART in combination with chemotherapy has substantially improved both the response rate and the survival time. In a trial on using

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HAART and a combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP), 9 out of 12 treated patients have complete remission after a medium follow-up of 49 months.<sup>49</sup> These studies suggest that HAART in combination with conventional chemotherapy will be beneficial for patients with HD, whether the effect is due to the restoration of the immune response in HIV-infected individuals or due to the effects of EBV remained to be determined.

## CONCLUSION

AIDS malignancies have been recognized as a major complication of the HIV disease course, and the high mortality rate in AIDS patients is in part due to this complication. A number of factors have been implicated to be playing a role in the increase incidence of malignancies in AIDS patients. These factors include immunosuppression and a deficient immune surveillance by T cells in eliminating the transformed cells; viral cofactors such as EBV and KSHV have also been associated with malignant transformation of the infected cells. The prognosis of ARL in HIV-infected individuals was extremely poor prior to the HAART era, but the advent of HAART, there was a dramatic improvement in the prognosis of ARL in these patients. The survival rate has improved, especially for those ARL that were found to be associated with herpesviruses such as EBV and KSHV. There were a substantial decrease in the number of cases of KS and NHL, in association with HAART, and the decrease in incidence appear to be independent of CD4 counts, substantiating the notion that coinfecting viruses may be playing a role in the disease. Most newly diagnosed cases of KS are patients that are either drug naive or have virological failure upon treatment. In spite of the improvement in prognosis, HAART alone is inadequate for the majority of the antiviral naive patients. A combination of HAART and conventional chemotherapy appears to be most effective. Moreover, the positive effects of HAART on some ARL and KS are not consistently observed for HPV-associated malignancies, including cervical and anal cancers.

Given the prolonged survival rate of HIV-infected individuals with HAART, it is likely that ARL will continue to pose a challenge in the AIDS epidemic. HAART treatment, even though appears to be effective, still only leads to partial immune reconstitution. Prolonged immunosuppression is likely to lead to a resurgence of AIDS-associated cancers. In addition, HAART is still not widely available in parts of the world where AIDS has the greatest impact, such as the African continent. It is expected that AIDS-associated cancers will continue to pose a major challenge in the population for quite a while. Thus, more understanding on the role of oncogenic viral cofactor in the disease will be of great significance. ARL represents an intersection of virology, immunology, and tumor biology. A better understanding of the disease, the immune response, will provide useful information for the development of novel therapy and provide insights into cancer biology beyond the AIDS epidemic.

## ACKNOWLEDGMENTS

This publication was made possible, in part by support from the following NIH grants: PHS award CA76958, NCRR COBRE grant RR15635, and INBRE grant P20 RR016469. The author also wishes to acknowledge Ms. Dianna Wright for help with the preparation of this chapter.

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