

NEOPLASTIC COMPLICATIONS OF HIV INFECTION

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| What's New – July 2007 Update |
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| <ul style="list-style-type: none">• Section V – Anal Dysplasia and Cancer |
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| KEY TO ABBREVIATED TERMS WITHIN GUIDELINES | |
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| ABVD | Adriamycin, bleomycin, vinblastine, dacarbazine |
| AMC | AIDS Malignancy Consortium |
| B-DLCL | B-cell diffuse large cell lymphoma |
| CNS | Central nervous system |
| CDE | Cyclophosphamide, doxorubicin, and etoposide |
| CHOP | Cyclophosphamide, doxorubicin, vincristine, and prednisone |
| CODOX-M/IVAC | Cyclophosphamide, doxorubicin, vincristine with high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine |
| CT | Computed tomography |
| EPOCH | Etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin |
| GI | Gastrointestinal |
| HHV-8 | Human herpesvirus-8 |
| IFN-a | Interferon-alfa |
| KSHV | Kaposi's sarcoma-associated herpesvirus |
| MRI | Magnetic resonance imaging |
| NHL | Non-Hodgkin's lymphoma |
| NNRTI | Non-nucleoside reverse transcriptase inhibitor |

I. INTRODUCTION

HIV infection has long been associated with various types of cancers, such as HIV-associated lymphomas and Kaposi's sarcoma. However, since the advent of HAART, HIV-infected individuals are living longer and are, therefore, also at risk for development of the same cancers commonly diagnosed in non-HIV-infected people.

The objective of these guidelines is to help primary care clinicians caring for HIV-infected patients to understand the presentation, evaluation, and therapeutic options available for patients with common HIV-associated and non-HIV-related malignancies. For Kaposi's sarcoma and various types of lymphoma, including systemic non-Hodgkin's lymphoma (NHL), Hodgkin's disease, and primary CNS lymphoma, the guidelines are based on the results of clinical trials,

supplemented by the practical experience of experts in the field. For anal cancer and the non-AIDS-defining cancers (i.e., cancers that are not associated with HIV infection), there are no therapeutic trials in HIV-infected adults to guide treatment; therefore, the guidelines are based on limited, primarily descriptive data in the literature. Appendix A provides an overview of treatment options for the HIV-associated malignancies described in this chapter.

II. AIDS-ASSOCIATED LYMPHOMAS

February 2007

Lymphomas have long been associated with HIV infection. A diagnosis of particular subtypes of B-cell lymphoma (Burkitt's, immunoblastic and primary CNS, or their equivalents) was one of the earliest Centers for Disease Control and Prevention (CDC) AIDS-defining illnesses and was associated with a short survival. However, the implications of developing HIV-associated lymphoma have evolved as the treatment for HIV infection has become more effective.

The lymphomas associated with HIV are heterogeneous. Each pathologic entity has its own presentation, prognosis, and treatment. Although this is true of lymphomas in general, underlying HIV infection uniquely influences each entity. Referral to centers participating in the [AIDS Malignancy Consortium \(AMC\)](#) is encouraged to facilitate research in this area. Appendix B lists the AMC sites.

A. Diagnosis

RECOMMENDATIONS:

Clinicians should perform imaging studies to evaluate for nonpalpable, pathologic adenopathy when patients present with unexplained constitutional symptoms that last for more than 2 weeks, such as weight loss, fevers, and night sweats. (I)

Clinicians should obtain biopsies of lymph nodes that are newly developed, pathologically enlarged (typically >2 cm), or progressively enlarging. (I)

Clinicians should have diagnoses confirmed by experts at a referral center or commercial laboratory whenever possible. (III)

Although the incidence of lymphoma has decreased in the era of HAART, clinicians should be vigilant for the development of lymphoma in HIV-infected patients regardless of whether or not they are receiving HAART. Incidence of cerebral lymphoma, which is typically associated with CD4 counts <50 cells/mm³, has decreased the most. However, patients are still at risk for lymphoma, particularly Burkitt's and Burkitt's-like lymphoma, which often present in patients with CD4 counts in the normal range.

In patients with poorly controlled HIV and generalized adenopathy, recognizing the development of lymphoma may be difficult. It is not feasible or warranted to continuously obtain biopsies of shotty adenopathy in HIV-infected individuals. Rather, biopsies should be obtained when lymph nodes are newly developed, pathologically enlarged (typically >2 cm), or progressive.

Lymphomatous nodes are typically non-tender. Biopsies of the liver, nodules in various organs, or the bone marrow may also lead to a diagnosis of lymphoma, particularly in patients without lymphadenopathy.

For all lymphomas, biopsies are preferable to fine-needle aspirates for a definitive diagnosis. In some situations, fine-needle aspirates may be helpful to establish that a lymphoma, rather than a carcinoma or infectious process, is present (e.g., an enlarged neck node in a smoker); however, definitive biopsy will usually be necessary to subclassify the lymphoma and may be necessary to diagnose Hodgkin's lymphoma. Although the recent World Health Organization classification of hematopoietic and lymphoid tumors has brought additional clarity to the field, hematopathology is a difficult area that is often characterized by disagreement among experts.

Staging evaluation for a patient diagnosed with systemic lymphoma typically consists of the following:

- Routine blood work: complete blood count, serum liver enzymes, serum creatinine, calcium, phosphorus, uric acid
- Serum lactate dehydrogenase
- Bone marrow aspiration and biopsy
- Contrast-enhanced MRI of the brain
- Lumbar puncture with cerebrospinal fluid analysis, cytology, and Epstein-Barr virus DNA (in selected cases where CNS disease is suspected)

Other requirements include assessment of left ventricular function prior to administration of anthracycline therapy, establishment of central venous access (Infusaport or Portacath), and assessment of immune function, determined by CD4 count.

B. Concurrent HAART and Lymphoma Therapy

RECOMMENDATIONS:

Patients currently receiving HAART should continue their ARV regimen while undergoing therapy unless there are other indications for an interruption of ARV treatment. (III) If ARV therapy is interrupted in patients receiving ARV medications with prolonged half-lives, such as NNRTIs, clinicians should consult with an HIV Specialist for guidance on how to avoid the emergence of resistance.

If possible, clinicians should avoid using zidovudine in patients receiving chemotherapy. (III)

Clinicians should individualize prophylaxis for opportunistic infections in patients receiving chemotherapy. (I) When patients present with CD4 counts in the normal range (400-1400 cells/mm³), prophylaxis should be dictated by the severity of immunosuppression anticipated from the chemotherapy regimen.

Key Point:

Although chemotherapeutic drugs may have overlapping toxicities with ARV drugs, it is common practice to continue HAART during chemotherapy. However, because experience with newer ARV medications and cancer chemotherapy is limited, the clinician should maintain vigilance for unusual or unusually severe toxicities.

The decision to continue or temporarily discontinue HAART in patients receiving ARV therapy, or to initiate HAART in ARV therapy-naïve patients, during lymphoma therapy is an ongoing area of research. Some studies have shown that combining HAART with chemotherapy is effective and tolerable¹⁻⁴; other studies have shown that temporarily discontinuing HAART to avoid toxicity is also a viable option.⁵ Because interruption of HAART may lead to advancement of disease, acute retroviral syndrome symptoms, and opportunistic infections, HAART is not usually discontinued while administering chemotherapy.

Most regimens do not cause severe chemotherapy-induced nausea and vomiting and, hence, discontinuation of HAART while receiving chemotherapy is rarely required. Alternatively, high-dose methotrexate can cause significant mucositis, and transplant-conditioning regimens can cause both mucositis and protracted nausea and vomiting. It would be reasonable to temporarily discontinue HAART under such conditions. When the decision is made to temporarily discontinue HAART in patients receiving ARV medications with prolonged half-lives, such as non-nucleoside reverse transcriptase inhibitors (NNRTIs), clinicians should consult with an HIV Specialist for guidance on how to avoid the emergence of resistance (see the section *Management of Treatment Interruption* in [Antiretroviral Therapy](#)).

Myelosuppression is a potential overlapping toxicity when chemotherapy and HAART are co-administered. This is particularly true for HAART regimens that include zidovudine; therefore, it is generally recommended that zidovudine be avoided if at all possible during chemotherapy. Neuropathy is also a common side effect of both vinca alkaloids and several ARV medications. Careful attention to adverse effects, reduction in the chemotherapy doses, or switching to alternative ARV medications may be necessary.

C. Specific Lymphoma Histologies

1. B-Cell Diffuse Large Cell Lymphoma (B-DLCL)

a. Treatment

RECOMMENDATIONS:

Whenever possible, HIV-infected patients should be treated with the same full-dose chemotherapy regimens that would be used in the absence of HIV infection. (III)

Clinicians should refer patients to research centers for protocol participation whenever feasible (see Appendix B). (III)

Opportunistic infections have markedly decreased in the post-HAART era. Patients often begin chemotherapy with good immune function and few or no previous opportunistic infections.

Because modified doses of chemotherapy are associated with inferior outcomes in the non-HIV-infected population, use of full-dose chemotherapy for HIV-associated lymphoma is being re-evaluated. A study conducted by the AMC has demonstrated that HIV-infected patients tolerate full-dose cyclophosphamide, doxorubicin, vincristine, and prednisone therapy (CHOP) and show a trend toward improved response rates and response duration compared with reduced-dose chemotherapy.² Alternative regimens are an active area of investigation and include the addition of rituximab to CHOP and infusion regimens, such as cyclophosphamide, doxorubicin, and etoposide (CDE); and etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone (EPOCH).^{6,7} Infusion therapies may be associated with increased morbidity, and it is not known how best to target these regimens. Although rituximab is now commonly used as part of therapeutic regimens for immunocompetent patients, its role in HIV-infected patients is not defined. There is considerable evidence that the combination of standard chemotherapy plus rituximab is more effective than standard chemotherapy alone for patients with diffuse, large B-cell lymphoma, as well as other types of CD20-positive B-cell lymphomas. There has been only one phase III trial in HIV-associated B-cell lymphoma that compared CHOP with CHOP plus rituximab, which found that the addition of rituximab to CHOP in patients with HIV-NHL may be associated with improved tumor responses⁸; however, these benefits may be offset by an increase in infectious deaths, particularly in those individuals with CD4 cell counts <50 cells/mm³. Other studies, however, have reported excellent outcomes for patients treated with CHOP or infusional chemotherapy regimens plus rituximab without a prohibitive risk of infectious death.⁹

The complete response rate for B-DLCL is reported to be from 40% to 85%, with response rates dependent not only on the treatment regimen but also on the characteristics of the treated population. Relapse rates can be as high as 50%. Factors predictive of longer disease-free survival include age <35 years, CD4 counts >100 cells/mm³, no previous opportunistic illnesses, good performance status, and stage I to III disease.¹⁰ The International Prognostic Index commonly used for diffuse large B-cell lymphoma is also prognostic of HIV-associated lymphoma; poor risk features include stage III to IV disease, elevated serum LDH, more than one extranodal site, and age >60 years.¹¹

b. CNS Prophylaxis

The risk of CNS relapse is estimated to be 30% in the non-HIV-infected patient with B-DLCL when any of the following are involved: the bone marrow, paranasal sinuses, testes, or two or more extranodal sites. The efficacy of prophylaxis is undefined. Previously, giving prophylaxis to HIV-infected patients with similar sites of involvement was recommended; however, recently it was demonstrated that the sensitivity, specificity, and positive and negative predictive values of Epstein-Barr virus (EBV) DNA detection in cerebrospinal fluid for CNS involvement by lymphoma were 90%, 100%, 100%, and 97.6%, respectively. Other factors significantly predictive of CNS involvement were EBV expression from the tumor, any extranodal disease at diagnosis other than CNS, and a non-CNS relapse.^{12,13}

c. Relapsed and Primary Refractory Disease

RECOMMENDATION:

Clinicians should consider experimental high-dose therapy and stem cell support for patients with relapsed or refractory disease who have good performance status and well-controlled HIV disease. (III) Treatment for other patients remains palliative.

The optimal therapy for relapsed and refractory disease is not established and should be individualized. Investigational chemotherapy and non-chemotherapy approaches may be applicable. In patients with uncontrolled HIV infection, including recurrent opportunistic infection and poor performance status, treatment will be primarily palliative. However, patients with limited sequelae of HIV infection are candidates for ongoing clinical trials investigating intensive therapy with curative intent.

The Parma study established high-dose therapy with stem cell support as the preferred therapy for non-HIV-associated relapsed B-DLCL.¹⁴ Investigators are now attempting high-dose therapy for HIV-infected patients and have reported impressive results in a small cohort of patients.¹⁵ This is an active area of research.

2. Primary Effusion Lymphoma

Primary effusion lymphoma is a unique, uncommon presentation of B-DLCL associated with the Kaposi's sarcoma-associated herpes virus (KSHV/HHV-8). Primary effusion lymphoma grows mainly as lymphomatous effusions without an identifiable contiguous tumor mass.¹⁶ When not exhibiting Burkitt's or Burkitt's-like morphology, it is considered a unique entity. It is typically associated with both HIV and KSHV/HHV-8 infections. Using preclinical data, a patient was successfully treated with zidovudine and interferon; however, clinical data are lacking.¹⁷

Key Point:

Specific recommendations for treatment cannot be made on the basis of clinical trials, although therapy directed at B-DLCL is reasonable.

3. Primary B-Cell CNS Lymphoma

RECOMMENDATION:

Treatment for primary B-cell CNS lymphoma is primarily palliative radiation and dexamethasone, (III) although a small, highly selected group of patients may benefit from chemotherapy.

Primary CNS lymphoma is usually associated with the presence of CD4 counts <50 cells/mm³. With the introduction of HAART and a consequent increase in CD4 counts in many patients, there has been a significant decline in incidence. CT and MRI usually demonstrate single or multiple contrast enhancing masses that may be radiographically indistinguishable from other CNS processes such as toxoplasmosis. Although both lesions will be enhancing, toxoplasma lesions are usually ring-enhancing, whereas toxoplasma encephalitis lesions are usually multiple, and CNS lymphoma lesions are usually solitary. The diagnosis can be established by brain biopsy, positive CSF cytology, or possibly the demonstration of Epstein-Barr viral DNA in the

CSF. Thallium-201 single-photon emission computed tomography (SPECT) imaging may also be helpful. Other conditions that must be considered in the differential diagnosis of an HIV-infected patient with focal brain lesions include infections, such as toxoplasmosis, or metastatic carcinoma arising from the lung or from other unknown primary sites.

Although radiotherapy results in tumor regression in most patients, median survival is only a few months. The addition of chemotherapy to radiation may prolong survival in a highly selective subgroup of patients whose medical comorbidities, including opportunistic infections, are controlled; however, most patients often have a poor prognosis due to progressive HIV disease.¹⁸ A small number of patients have been successfully treated with an antiviral therapy consisting of zidovudine, ganciclovir, and interferon.¹⁹ High-dose methotrexate with deferred radiation is also an option.

4. Burkitt's and Burkitt's-like Lymphoma

RECOMMENDATION:

There is no uniformly accepted treatment for this highly aggressive form of lymphoma. Clinicians should consider the use of regimens applicable to the non-HIV-infected population, particularly if the CD4 count is high and the associated HIV comorbidities are few. (III)

Burkitt's lymphoma and its variants can present in patients with very high CD4 counts; HIV infection is often an incidental finding in this population. These patients have an excellent prognosis from an HIV perspective, and aggressive therapy is indicated.

Based on non-randomized studies in the non-HIV-infected population, regimens incorporating high-dose cytarabine, high-dose methotrexate, and intensive intrathecal prophylaxis, such as the CODOX-M/IVAC regimen, are thought to be superior to earlier regimens combining CHOP with high-dose methotrexate or regimens developed for treatment of acute lymphocytic leukemia.²⁰ The applicability and efficacy of this intensive regimen for HIV-infected patients was established by a retrospective analysis, which was hampered by the evolution of ARV therapy over the decades.²¹ However, a similar regimen has also been used with somewhat inferior results.²² Others have reported success using the types of infusion therapy used for B-DLCL. In all of these studies, the small sample size precludes definitive conclusions.

5. Plasmablastic Lymphoma

RECOMMENDATION:

There are no known successful treatments for plasmablastic lymphoma.

Plasmablastic lymphoma is an unusual and highly aggressive non-Hodgkin's lymphoma variant with a high proliferation rate similar to that of Burkitt's and Burkitt's-like lymphoma. It is almost exclusively observed in the setting of HIV. It typically presents with an oral cavity mass, but diffusely metastatic disease may be present. Prognosis has been uniformly poor in the largest assembled series, but treatments were not specified.²³ In the setting of limited HIV comorbidity,

aggressive therapy similar to that used to treat Burkitt's lymphoma can be justified based on the proliferative index of the lymphoma, but outcomes are not known.

6. Hodgkin's Disease

RECOMMENDATIONS:

Both ABVD chemotherapy and the more recently described Stanford V regimen are reasonable treatments for HIV-associated Hodgkin's disease. (I)

Clinicians should consider patients with relapsed or primary refractory Hodgkin's disease and well-controlled HIV for research protocols of intensive therapy with peripheral blood stem cell support. (III)

Although Hodgkin's disease is not included in the CDC definition of AIDS, strong data support an increased incidence of Hodgkin's disease in HIV-infected individuals.²⁴ These patients typically present with advanced-stage Hodgkin's disease. Standard ABVD therapy—adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine—was evaluated in the pre-HAART era and induced a response rate of 62%, but the median survival was only 1.5 years.²⁵ In the HAART era, a 91% response rate and a 2-year disease-free survival rate of 66% has been reported using the Stanford V regimen,²⁶ a 3-month program in which chemotherapy is administered weekly along with radiation to involved sites measuring >5 cm or to involved spleens. Given the advances in the treatment of the underlying HIV infection, it is difficult to compare the two regimens. There is an ongoing trial comparing ABVD and Stanford V in non-HIV-infected patients with Hodgkin's disease.

7. Indolent Lymphoma

RECOMMENDATION:

Treatment should be commensurate with the lymphoma diagnosis (I) unless precluded by HIV comorbidities (III).

Indolent lymphomas are not known to be AIDS-associated, and there are no data to support an increased incidence attributable to HIV infection. The few published data suggest that patients with indolent lymphomas show prolonged survival even without HAART.²⁷

III. KAPOSI'S SARCOMA *February 2007*

Kaposi's sarcoma (KS) was the first neoplasm described in association with HIV infection and is an AIDS-defining condition. The incidence of KS began to decline before the development of contemporary ARV drugs, but the rate of decline has accelerated since the introduction of HAART.²⁸ Nonetheless, KS continues to be diagnosed in HIV-infected patients, even among individuals with effective viral load suppression and relatively high CD4 counts.²⁹

KS is an angiogenic inflammatory neoplasm that arises from vascular endothelial cells or their circulating precursors that have been infected with human herpesvirus-8 (HHV-8), also known as the KS-associated herpesvirus (KSHV).^{30,31} Although HHV-8 infection seems to be essential for

KS to develop, not all HHV-8-infected individuals will develop the disease. The local factors that determine where KS lesions appear are not defined.

A. Diagnosis

RECOMMENDATION:

When the clinician suspects KS based on visual inspection, biopsy of at least one lesion should be obtained to confirm the diagnosis and to differentiate KS from other pigmented lesions. (III)

Although the diagnosis of KS may appear obvious, biopsy is required to confirm the diagnosis. Biopsy is particularly important for rapidly growing lesions associated with systemic symptoms (fever, chills, headache, anorexia, and malaise) to distinguish KS from bacillary angiomatosis.

1. Cutaneous KS

RECOMMENDATION:

As part of the annual skin examination, the clinician should examine the oral cavity and the entire skin surface, including the soles of the feet, scalp, external genitalia, and ears, for the presence of abnormal pigmented lesions. (I)

In the vast majority of patients, the skin is the site of initial KS presentation. An annual skin examination should be performed in all HIV-infected patients (see [Dermatologic Manifestations of HIV Infection](#)). Although lesions may occur anywhere, lesions on the soles of the feet, between the toes, behind the ears, and in the perirectal and genital areas are common but may be overlooked on cursory examination.

2. Nodal KS

Although nodal involvement is frequently present, it is usually focal and has little or no impact on prognosis or survival. Treatment decisions are generally based on the severity of KS elsewhere in the body. On rare occasions, massive, symptomatic lymph node enlargement can be caused by KS.

Key Point:

Unless lymph nodes are sufficiently enlarged or asymmetric to warrant biopsy for exclusion of lymphoma, there is no need to routinely biopsy enlarged lymph nodes in patients with biopsy-proven KS elsewhere.

3. Gastrointestinal KS

RECOMMENDATION:

In the absence of gastrointestinal symptoms, radiographic or endoscopic evaluation of the gastrointestinal tract is not recommended for routine staging of KS (III). However, when a patient with known cutaneous KS presents with unexplained gastrointestinal symptoms (particularly pain, bleeding, or signs of obstruction), the clinician should perform an endoscopic evaluation of the upper and/or lower gastrointestinal tract (I).

Gastrointestinal (GI) tract KS has been reported in approximately 40% of patients at the time of the initial KS diagnosis and in as many as 80% of patients at autopsy. GI KS may be present without cutaneous disease. Lesions may occur throughout the GI tract. In most patients, GI tract involvement is asymptomatic, and there is no evidence to suggest that asymptomatic GI KS is associated with a poor prognosis or an inferior response to treatment. Abdominal pain, signs of obstruction, and bleeding may be symptoms of GI KS. KS lesions of the GI tract are best evaluated with direct endoscopic visualization. GI lesions are often submucosal and small and are often not seen on contrast roentgenographic studies. Upper and lower GI endoscopy allows direct visualization and biopsy of the typical raised, red lesions. Although superficial biopsies may not yield diagnostic tissue, a presumptive diagnosis of GI KS can be based on the appearance of the lesions in a patient with biopsy-confirmed KS elsewhere in the body.

4. Pulmonary KS

RECOMMENDATION:

When a patient with known cutaneous KS presents with dyspnea, wheezing, and/or hemoptysis, clinicians should perform a differential diagnosis for pulmonary KS by obtaining x-rays, scans, and/or bronchoscopy to exclude infections and other neoplastic processes (e.g., lymphoma, lung cancer). (I)

Pulmonary KS may manifest as parenchymal or endobronchial lesions or pleural effusion, usually in patients with long-standing and advanced KS elsewhere. Although pulmonary KS may be asymptomatic, it more commonly presents with cough, dyspnea, wheezing, or blood-streaked sputum, occasionally accompanied by chest pain.

More than 90% of patients with pleural effusions caused by KS also have parenchymal lung lesions.³² KS-associated pleural effusions are typically serous or serosanguineous exudates with non-diagnostic cytology; pleural biopsy is generally avoided because of concerns about bleeding, pneumothorax, and the poor diagnostic yield.

The radiographic findings of KS are varied and may include pleural effusions, nodules, or diffuse interstitial and/or alveolar infiltrates, often in a perihilar distribution. Interstitial infiltrates caused by KS may be indistinguishable from those caused by *Pneumocystis jirovecii* (pulmonary pneumocystosis) infection. Less commonly, KS presents as mediastinal and/or hilar adenopathy or an isolated pulmonary nodule. Typical CT scan findings include nodules, masses, and bronchovascular thickening, with or without pleural effusion. CT may be of particular value in monitoring the response to treatment in patients with poorly defined lesions on plain radiographs.

Bronchoscopy is the diagnostic procedure of choice to evaluate unexplained pulmonary symptoms or parenchymal radiographic findings and to distinguish KS from infectious or other neoplastic processes. Endobronchial KS can generally be visualized as red, slightly raised or flat lesions, and a presumptive diagnosis of KS is usually made on this basis. Because of bleeding concerns, confirmatory biopsies are not usually obtained. Endobronchial lesions are most commonly observed at branching points or carinas of the lower airways but are sometimes present in the trachea. When endobronchial lesions are absent, however, a diagnosis of

pulmonary KS may be more difficult because transbronchial biopsy often fails to yield diagnostic tissue. In such cases, CT-guided transthoracic biopsy may be helpful.

5. Lymphedema

Lymphedema is a common complication of KS. It may be asymmetric and most commonly occurs in the lower extremities but may also involve the periorbital tissues and external genitalia. The severity of edema may be disproportionate to the number of skin lesions. Edema usually occurs in the absence of significant regional lymph node enlargement and may be complicated by skin breakdown and infection.

B. Treatment

RECOMMENDATIONS:

Unless immediate chemotherapy is indicated, the clinician should first attempt to optimize HIV control in patients receiving no or suboptimal ARV therapy because KS may respond to this alone (I). Patients should also receive prophylaxis for and treatment of opportunistic infections (I) (for more information on infectious diseases associated with HIV infection, see [Infectious Complications Associated With HIV Infection](#)).

Clinicians should use chemotherapy consisting of either a liposomal anthracycline (liposomal doxorubicin or liposomal daunorubicin) or paclitaxel as first-line therapy for patients with the following KS manifestations (I):

- **documented pulmonary KS**
- **symptomatic visceral KS**
- **extensive, symptomatic KS-associated lymphedema**
- **extensive and symptomatic or rapidly progressive cutaneous KS**

For patients who do not require immediate chemotherapy for life-threatening or highly symptomatic KS, clinicians should use one of the following approaches (I):

- **local topical, injectable, or radiation therapy of cutaneous lesions**
- **low-dose interferon alfa**
- **participation in [clinical trials](#) of novel therapeutic agents targeting the pathogenic mechanisms involved in KS**

Optimal ARV therapy for HIV infection and prophylaxis for and treatment of opportunistic infections are important for successful KS management because KS growth is stimulated by inflammatory cytokines whose production is increased in the setting of opportunistic infections and active HIV replication. KS sometimes shows partial or complete regression after initiation of effective HAART. Therefore, optimization of ARV therapy should be a part of the management strategy for all patients presenting with KS and a detectable viral load. In the setting of a relatively low tumor burden and the absence of symptomatic lesions, a trial of ARV therapy can be considered before specific anti-KS therapy is instituted. Successful control of HIV replication does not, however, invariably lead to tumor regression; therefore, KS therapy still may be required.

In patients with widespread symptomatic KS, systemic therapy is the most reliable therapeutic approach. Although a wide variety of single chemotherapeutic agents and drug combinations have shown activity against KS, only three agents have received FDA approval for this indication: liposomal doxorubicin, liposomal daunorubicin, and paclitaxel. These drugs have acceptable toxicity profiles, are active against KS that is refractory to other agents, and are equivalent or superior in efficacy to earlier combination chemotherapy regimens.^{33,34} Problems in documenting KS regression make it difficult to state with certainty the complete and partial response rates induced by these agents; however, a large majority of patients treated with these drugs will show tumor regression and palliation of symptoms. Because advanced KS often occurs in patients with poor HIV control, it is noteworthy that the studies that documented the safety and efficacy of these agents in KS were performed in patients with very low median CD4 counts.

Both the effectiveness and toxicity of chemotherapy should be considered when selecting a systemic chemotherapy regimen for metastatic disease. For example, paclitaxel has been more extensively evaluated in patients with pulmonary involvement but is associated with alopecia and neuropathy. Liposomal anthracyclines have been more extensively evaluated in patients with cutaneous disease and is not associated with alopecia or neuropathy.

Key Point:

Advanced HIV infection itself is not a contraindication to chemotherapy for treatment of KS.

Although chemotherapy is an effective treatment for KS, it has both short- and long-term adverse effects and is probably not necessary or appropriate for the management of asymptomatic KS that is not widespread or rapidly progressive. For such patients, several other approaches may be more appropriate. When choosing a treatment modality, the systemic nature of HHV-8 infection should be considered. KS, unlike most “solid” tumors, generally does not present as a single primary tumor that spreads in a predictable pattern, but rather presents more like a hematologic malignancy, with a multifocal presentation from the outset. However, radiation therapy or locally injected or topical therapies may still be appropriate in some patients to control small numbers of lesions that present a cosmetic problem or, in the case of radiation therapy, to control localized bulky tumor masses. These approaches are unlikely to cause systemic toxicity but are also unlikely to inhibit disease progression elsewhere. Observation without treatment may be appropriate for some patients with minimal, non-progressive, asymptomatic KS, although such patients may elect to be treated with standard or investigational approaches.

Agents that may influence the mechanisms underlying the development of KS are worth considering. One such agent, recombinant interferon alfa (IFN- α), is an FDA-approved treatment for KS. IFN- α has antiviral activity against both HIV and HHV-8, synergistically inhibits HIV when combined with various ARV drugs, inhibits various cytokines and growth factors that may stimulate KS growth, inhibits endothelial cell proliferation, and is a potent inhibitor of neoplastic angiogenesis. IFN- α was initially studied and approved for KS treatment in the 1980s, before the introduction of effective ARV therapy for HIV. Under these circumstances, IFN- α was effective primarily when administered at high, toxic doses to patients with CD4 counts of >200 cells/mm³. Studies performed in the 1990s, however, showed that much lower, better-tolerated IFN- α doses (as low as 1 million IU/d) could be safely combined with ARV drugs and could induce higher

rates of KS regression, even in patients with lower CD4 counts.³⁵ Overall response rates ranging from 40% to 55% have been documented in recent trials.

The use of antiherpes drugs has also received attention.³⁶ Reduction in the incidence of KS in HIV-infected patients has been observed during treatment of cytomegalovirus retinitis with ganciclovir.³⁷ In addition, a variety of other systemically administered agents that act by different mechanisms may also inhibit the complex processes involved in KS development and progression and are under active investigation for KS treatment. Preliminary evidence for activity against KS has been reported for thalidomide, interleukin-12, 9-*cis*-retinoic acid, TNP-470 (an inhibitor of endothelial cell proliferation), and COL-3 (a matrix metalloproteinase inhibitor). Additional clinical trials are planned or are in progress with some of these agents, as well as with other matrix metalloproteinase inhibitors, inhibitors of vascular integrins, angiogenesis-promoting growth factors, and agents directed against HHV-8.

IV. CERVICAL DYSPLASIA AND CANCER *February 2007*

A. Cervical Dysplasia

Cervical dysplasia is the abnormal growth of the epithelial tissue at the squamocolumnar junction (where squamous cells on the surface of the cervix meet columnar cells in the cervical opening) of the cervix. Several classification systems are used to describe dysplasia, but they are not interchangeable. Table 1 provides a comparison of dysplasia nomenclature.

| TABLE 1 COMPARISON OF CYTOLOGICAL AND HISTOLOGICAL CLASSIFICATION OF CERVICAL DYSPLASIA | | |
|---|--|--|
| Bethesda Classification (2001) (cytology) | Cervical Intraepithelial Neoplasia (CIN) (histology) | WHO Terminology (cytology) |
| ASC-US ASC-H | Atypia | |
| LSIL | CIN I | Mild dysplasia |
| HSIL | CIN II CIN III CIS | Moderate dysplasia Severe dysplasia Carcinoma <i>in situ</i> |
| Cancer | Cancer | Cancer |

ASC-H: atypical squamous cells, HSIL cannot be excluded; ASC-US: atypical squamous cells of undetermined significance; CIS: carcinoma *in situ*; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion.

1. Screening for Cervical Dysplasia

RECOMMENDATIONS:

Clinicians should perform a gynecologic examination in HIV-infected women during the baseline evaluation. Pap tests should be performed, regardless of the woman’s sexual orientation. It should be performed during the initial physical examination, repeated at 6 months, and then repeated annually, as long as the results are normal (see Table 2).

Women with abnormal Pap tests should be referred for colposcopy and further evaluation that may include HPV DNA testing, cervical biopsy, cervical curettage, and endometrial biopsy, depending on cell type and the degree of the cytological abnormality.

| TABLE 2 ESTABLISHED CERVICAL CANCER SCREENING TIMELINE | | | |
|---|--------------------|---|--|
| Type of Cancer | Screening Strategy | Population | Frequency |
| Cervical neoplasia | Pap test | Women ≥ 18 or when sexually active, whichever occurs first | Baseline, 6 months after baseline, then annually*† |
| | Colposcopy | Any female with abnormal Pap test results | Case-by-case basis‡ |

* Annually as long as results are normal. Abnormal results should be repeated every 3 to 6 months until two successive normal Pap tests are reported.

† Patients with a history of anogenital condyloma or abnormal cervical/vulvar histology should receive an annual anal Pap test.

‡ Colposcopy should be performed for women with abnormal Pap tests. Follow-up would then vary on a case-by-case basis. Women with cervical HSIL should be referred for high-resolution anoscopy.

The purpose of cervical screening is to prevent the development of invasive cancer by identifying and treating individuals with precursor lesions that are at risk for progression to cancer. Widespread screening of all women with cervical cytology or Pap tests has led to a decline in morbidity and mortality from cervical cancer. The benefit of screening and treatment protocols for cervical abnormalities in HIV-infected women is also well-established. Although cervical cytology (Pap tests) has lower sensitivity compared to actual tissue histology, colposcopy with Pap tests has increased the effectiveness of the evaluation of women with HIV infection, particularly those women with a report of atypical squamous cells of undetermined significance (ASC-US) by delineating likely abnormal tissue for biopsy and histologic evaluation.³⁸

For recommendations for evaluation and management of cervical dysplasia, refer to the *Women’s Health Guidelines: Anogenital Neoplasia*.

B. Cervical Cancer

In the earlier years of the HIV epidemic, women presenting with invasive cervical cancer had very aggressive disease with poor response to traditional therapy and a high degree of recurrence.^{39,40} In 1993, invasive cervical cancer was added as an AIDS-defining illness to underscore the need for comprehensive gynecologic evaluation in HIV-infected women.⁴¹ Since that time, screening and treatment programs have been established for HIV-infected women and may partly explain the lack of a significantly increased incidence of invasive cervical cancer in women living with HIV. It appears that factors other than immunosuppression, such as smoking, can act as promoters of this disease.

1. Presentation

Usually patients with cervical cancer have very few symptoms and, when they do present with symptoms, more advanced disease is often found. Vaginal bleeding and post-coital bleeding are the most common symptoms. Malodorous vaginal discharge, pelvic pain, back pain, and lower abdominal pain are also common. Weight loss, leg pain, edema, and obstructive uropathy indicate advanced disease.

2. Management of Cervical Cancer

RECOMMENDATION:

Clinicians should refer HIV-infected women to a gynecologic oncologist or surgeon trained in management of cervical cancer when possible. Appropriate staging, management, and therapy for cervical cancer should be determined by a gynecologic oncologist or clinician with similar training and experience.

In general, standard therapy used to treat immunocompetent patients applies to HIV-infected women. Management and therapy should be based on the stage of disease. Treatment may include cone biopsy, total hysterectomy, radical hysterectomy, radiation therapy, chemotherapy, and combined modality therapy with radiation and chemotherapy. The increased risk for treatment failure and high recurrence rate (up to 40%) demand close follow-up.

V. ANAL DYSPLASIA AND CANCER *July 2007*

Invasive squamous cell cancers of the anal canal are associated with certain types of human papillomavirus (HPV) infection, most notably, HPV 16 and HPV 18. Although the overall incidence of anal cancer in the general population of the United States is low (approximately 0.8/100,000),⁴² its incidence varies considerably depending on the presence of risk factors such as smoking, multiple sexual partners, HPV infection, and receptive anal intercourse. HIV infection confers an additional risk for development of anal cancer.^{43,44}

Analogous to cervical tissue, the anal epithelium at the dentate line has a transformation zone between squamous and columnar epithelia; this transition zone is subject to infection with and neoplastic transformation by HPV. Precancerous lesions of the anal squamous epithelium can develop and are classified as low- or high-grade according to identical Bethesda criteria and nomenclature developed for grading cervical lesions (see Table 3).

| TABLE 3 COMPARISON OF CYTOLOGICAL AND HISTOLOGICAL CLASSIFICATION OF ANAL DYSPLASIA | | |
|---|--|--|
| Bethesda Classification (cytology) | Anal Intraepithelial Neoplasia (AIN) (histology) | WHO Terminology (cytology) |
| ASC-US ASC-H | Atypia | |
| LSIL | AIN I | Mild dysplasia |
| HSIL | AIN II AIN III CIS | Moderate dysplasia Severe dysplasia Carcinoma <i>in situ</i> |
| Cancer | Cancer | Cancer |

ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells (HSIL cannot be excluded); LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; AIN, anal intraepithelial neoplasia; CIS, carcinoma *in situ*.

A. Risk of Anal Cancer

HIV infection is an independent risk factor for anal neoplasia.^{45,46} Behaviors that have been associated with anal neoplasia include multiple sexual partners, smoking, and unprotected vaginal or anal intercourse.

1. HIV-Infected Women

The risk of anal cancer in women regardless of HIV status is highest among those who have had 10 or more sexual partners, those with a history of anal or genital warts, gonorrhea, or cervical neoplasia, and those whose sexual partners have a history of a sexually transmitted infection.⁴⁷ A history of receptive anal intercourse before 30 years of age or with multiple partners increases the risk of anal cancer.⁴⁷

Women with HIV infection are significantly more likely to have abnormal anal cytology/histology (31%) compared with HIV-uninfected women (9%).⁴⁸ Data from the United States AIDS-Cancer Registry Match calculate an increased relative risk of 134 for anal cancer among HIV-infected women younger than 30 years of age, and a relative risk of 12 for women aged 30 to 39 years compared with aged-matched non-HIV-infected women.⁴⁹ From 1973 to 1989, the incidence of anal carcinoma increased by 35% and has been increasing at a rate of 2% per year. In one report, 26% of HIV-infected women had abnormal cervical cytology, and, of those women, 44% also had abnormal anal cytology.⁵⁰ In the ongoing Study to Understand the Natural History of HIV/AIDS (SUN), the prevalence of HPV in the cervix and anus was 86% and 93%, respectively, and for HPV types that carry a high risk for malignancy, the prevalence rates were 68% and 85%, respectively.⁵¹ A history of anal sex was not predictive of an abnormal anal cytology.⁵¹ These results, although not completely independent of a history of anal intercourse, are explained by the anatomical proximity of the anus and the genital tract. HPV exposure of either anatomical site can result in tracking and infection of the other site.

2. HIV-Infected Men

Prior to the onset of the AIDS epidemic, the risk of anal cancer was estimated to be as high as 35/100,000 among men with a history of receptive anal intercourse.⁵² The risk in HIV-infected men who have sex with men (MSM) is between 70/100,000 and 144/100,000,^{53,54} and this risk does not appear to decrease with effective immune reconstitution as a result of HAART.⁵⁵⁻⁵⁹

Among men who do not engage in receptive anal intercourse, the risk of anal cancer is associated with 10 or more sexual partners and a history of anal warts, syphilis, or hepatitis.⁴⁷ In MSM, receptive anal intercourse is the most common risk factor and compounds the risks noted above.

B. Screening and Diagnosis

RECOMMENDATIONS:

At baseline and as part of the annual physical examination for all HIV-infected adults, regardless of age, clinicians should:

- **Inquire about anal symptoms, such as itching, bleeding, diarrhea, or pain**
- **Perform a visual inspection of the perianal region**
- **Perform a digital rectal examination (III)**

Clinicians should refer women with cervical HSIL and any patient with abnormal anal physical findings, such as warts, hypopigmented or hyperpigmented plaques/lesions, lesions that bleed, or any other lesions of uncertain etiology, for high-resolution anoscopy and/or examination with biopsy of abnormal tissue.

Clinicians should obtain anal cytology at baseline and annually in the following HIV-infected populations⁶⁰⁻⁷⁴:

- **Men who have sex with men**
- **Any patient with a history of anogenital condylomas**
- **Women with abnormal cervical and/or vulvar histology**

Delayed diagnosis of anal cancer is common. MSM, the group with the highest risk of anal cancer, often have benign conditions such as fissures or infections that may mask the diagnosis. Rectal bleeding, which is the most common presenting symptom of anal cancer, is often attributed to hemorrhoids. Only 30% of patients have pain or the sensation of an anal mass. As with cervical carcinoma, the precancerous stages of anal intraepithelial neoplasia are generally asymptomatic until there is invasion beyond the epithelial basement membrane, concurrent with tumor enlargement. Patients may complain of thickening and irritation of perianal skin, itching, bleeding, tenesmus, pain with defecation, constipation, change in stool caliber, or receptive anal dyspareunia. Upon visual inspection, clinicians should examine for abnormal anal physical findings, such as warts, hypopigmented or hyperpigmented plaques/lesions, or lesions that bleed.

1. Digital Rectal Examination

The standard screening test for all anal cancers is an annual digital rectal examination, which permits the clinician to feel for masses that may be missed by cytology or even by direct

visualization during standard or high-resolution anoscopy (HRA). All HIV-infected adults should have an annual digital rectal examination.

Key Point:

If the digital rectal examination is performed in conjunction with anal cytology and/or HRA, the cytology must be obtained first, *before* lubrication is introduced into the anal canal.

2. Anal Cytologic Screening

Rationale

The risk of anal cancer in the MSM population (between 70/100,000 and 144/100,000) is double the rate that prompted the recommendations for universal cervical screening of women.^{53,54} Universal cervical Pap screening for adult females was recommended in the United States in the 1960s before either the pathophysiology or oncogenesis of HPV was elucidated. There has never been a randomized control trial for standard cervical Pap screening, nor would it be ethical to conduct such a study today. The efficacy of Pap screening in preventing cervical malignancies rests exclusively on decades of epidemiological data for validation. Given that 1) it is unlikely that a 10-year clinical trial demonstrating the efficacy of obtaining anal cytology in any HIV-infected population will ever be performed and 2) HPV-initiated carcinomas are clearly preventable malignancies, this committee recommends obtaining routine anal cytology in populations that are clearly at risk.

Anal Pap testing using a Dacron swab is a well-validated technique with comparable sensitivity and specificity to cervical cytology.⁷⁵ Pap test screening of the cervix has led not only to a markedly decreased incidence of invasive cervical cancer but also to an understanding of how precursor lesions of the cervical epithelium can progress to invasive disease.⁷⁶ As with cervical cancer screening, cytologic screening of the anal canal is expected to reduce the incidence of invasive anal cancer and allow the detection of precancerous dysplastic lesions or treatable early invasive disease. Pap tests of the anal canal are simple to perform, clinically effective, and cost-effective to reduce the incidence of invasive disease in high-risk individuals.^{77,78}

Technique

There is no preparation necessary before obtaining anal cytology. If the digital rectal examination is performed in conjunction with anal cytology and/or HRA, the cytology must be obtained first, *before* lubrication is introduced into the anal canal. Patients should not have received an enema or engaged in receptive anal sex within 24 hours before sampling because these activities can adversely affect specimen quality.

The standard technique used in obtaining anal cytology is as follows: a Dacron swab (a cotton swab will not yield accurate results) is moistened with sterile or non-sterile water. The anus is spread with the index and thumb of the non-dominant hand so that the anoderm pouts out. The swab is then gently inserted into the anal canal as far as it will go, until it hits the wall of the rectum. If the swab does not go in easily, the angle of insertion should be adjusted. The presence of external hemorrhoids may cause resistance; in this case, different insertion points should be tried until the anal canal is easily accessed. The swab must be inserted above the squamocolumnar transition zone, which is approximately 2 cm (1 inch) from the anal verge.

The swab is then slowly moved in and out without completely withdrawing it, while *rotating* it in a spiral motion and applying mild pressure to the anal wall. After several rotations, the swab should be withdrawn and immediately immersed in methanol-based preservative-transport solution. Feces or traces of blood on the swab will not affect the result. The swab should be agitated in the solution for 60 seconds to transfer cells from the swab to the medium.

Slides made by the thin-layer liquid-based cytology process display a thin, uniform layer of cells at a controlled density. Red blood cells and mucus are removed while the background pattern and the cell clusters are preserved. The use of this process results in increased detection of abnormal cytology. The absence of columnar cells in the sample does not affect the validity. The sensitivity, specificity, and predictive value do not hinge on the presence or absence of these columnar cells; cytological specimens should not be rejected solely on this basis.^{79,80} If only anucleated squamous cells are present on the sample, the swab was not inserted far enough into the anal canal, and the specimen is inaccurate or non-diagnostic.

An instructional video on performing anal Pap smears is available on CD-ROM and can be purchased by calling the Johns Hopkins Local Performance site at 888-333-2855, or www.aids-ed.org/doc/pama_anal-pap-video.doc

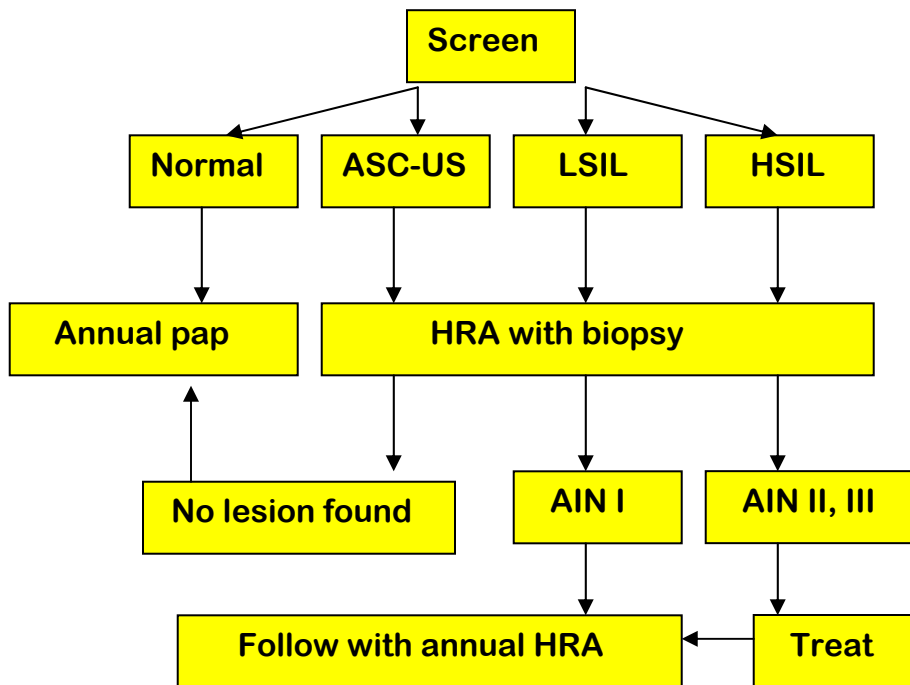
Follow-up

RECOMMENDATION:

Clinicians should refer patients with abnormal anal cytology for high-resolution anoscopy and possible biopsy.

Anal cytology has a high sensitivity (95%) for detection of dysplasia (ASIL) but a low specificity (50%) for predicting the severity of the abnormality in subsequent biopsy. Even patients with cytologic diagnoses of ASC-US and LSIL have a significant risk (46% to 56%) of being diagnosed with HSIL (AIN 2, 3) at biopsy.^{81,82} Although the appropriate follow-up for abnormal anal cytology remains an active area of investigation, Figure 1 provides a straightforward evaluative approach.

Figure 1: Anal Screening Evaluation



ASC-US, atypical squamous cells of undetermined significance
 LSIL, low-grade squamous intraepithelial lesions
 HSIL, high-grade squamous intraepithelial lesions
 AIN, anal intraepithelial neoplasia

Algorithm adapted with permission from Chin-Hong PV, Palefsky JM. Natural history and clinical management of anal human papillomavirus disease in men and women infected with human immunodeficiency virus. *Clin Infect Dis* 2002;35:1127-1134. University of Chicago Press, Copyright © 2002.

3. High-Resolution Anoscopy (HRA)

HRA applies the techniques of standard cervical colposcopy to the examination of the anal mucosa and is the preferred method for visualization of the anal canal in otherwise asymptomatic individuals.^{83,84} A swab, wrapped and soaked in 3% acetic acid (as opposed to 5% in colposcopy) is passed through the anoscope; the anoscope is then removed, leaving the acetic acid-soaked gauze to oppose the epithelial tissue for at least 2 minutes. The gauze is removed, the anoscope is then reinserted, and a standard colposcope is used to visualize the perianal skin, anal canal, and distal rectal tissue.⁸⁵ The dilute acetic acid highlights the mucosal abnormalities; the colposcopic magnification allows visualization and discernment of the abnormal aceto-white mucosal lesions.

The squamocolumnar junction, including inflamed and dysplastic tissue, will appear dull and white. Vascular punctuation and mosaicism are indicative of dysplasia, and biopsy should be obtained. Some clinicians find that the addition of the iodine-based Lugol's further delineates healthy from dysplastic tissue. Lugol's is absorbed only by healthy epithelial tissue, and it appears a deep mahogany color; the dysplastic tissue does not concentrate the solution and appears a weak, mustard-yellow color. Squamous metaplasia, a normal finding, can also fail to absorb the Lugol's solution. The combination of acetic acid and Lugol's solution with the HRA magnification permits the identification of the subtle mucosal abnormalities that are virtually undetectable with conventional anoscopy alone.

Because obtaining routine anal cytology is a new standard of care, clinicians may face challenges identifying providers to whom they can refer patients for follow-up HRA. Currently, few primary care clinicians have expertise in HRA, although the techniques and tools have become a standard part of many obstetrical, gynecological, colorectal, surgical, and gastrointestinal clinics, practices, and training programs. The American Society for Colposcopy and Cervical Pathology offers an annual High Resolution Anoscopy Workshop in conjunction with a colposcopy postgraduate course (www.asccp.org/meetings.shtml). Alternatively, gynecologists or other providers, such as nurse practitioners and physician assistants, who often perform cervical colposcopy, can easily learn the techniques necessary to perform the procedure in the anus. Clinicians experienced in HRA can also train other interested clinicians outside of a formal course.

In communities where there are no clinicians available to perform HRA, patients with abnormal anal cytology should be referred to a surgeon for evaluation.

C. Treatment of Anal High-Grade Squamous Intraepithelial Lesions

RECOMMENDATION:

Patients should receive post-treatment serial monitoring with annual HRA.

In the cervix, HSIL is often treated by excision of the transformation zone (LEEP, conization), but this cannot be done in the anal canal.⁸⁶ Therefore, traditional treatment of anal HSIL (AIN II, III) disease is surgical excision by a qualified colorectal surgeon. Infrared coagulation, originally developed to treat hemorrhoidal tissue, has been effectively used.^{85,87} Local ablative techniques are well tolerated, have minimal morbidity, and can be performed in an office setting by non-surgeons.⁸⁵ *In situ* lesions also can be treated with local ablative therapy. Regardless of the modality used, local recurrences are to be expected. Successive treatments can lead to decreased recurrence rates. Post-treatment serial monitoring with annual HRA is recommended. Preventing the development of cancer is underscored by the substantial morbidity that even successful treatment can cause, primarily due to the radiation.

D. Treatment of Anal Cancer

RECOMMENDATIONS:

Primary care clinicians should refer HIV-infected patients with anal cancer to an oncologist for treatment.

For patients with untreated invasive anal cancer without evidence of distant metastases and CD4 counts >200 cells/mm³, combined modality therapy with concurrent radiation and combination chemotherapy should generally be administered. *In situ* carcinoma is not treated with radiotherapy or chemotherapy.

Combined modality therapy (CMT) should also be considered in patients with untreated invasive anal cancer who are more severely immunosuppressed; however, abdominal perineal resection is an alternative treatment in such patients.

1. Tumors of the Anal Canal

Patients found to have invasive squamous lesions of the anal canal require staging prior to treatment. Examination under anesthesia generally provides a good assessment of the size of the primary tumor. Mobile lesions of ≤ 2 cm (T1) can be cured in approximately 80% of cases, whereas tumors ≥ 5 cm (T3) are cured in $<50\%$ of cases.^{88,90} Detection of minimally invasive lesions is rare but may become more common with cytologic screening and HRA. Pelvic computed tomography, positron emission tomography, or magnetic resonance imaging is used to assess local extension and nodal involvement. Tumors of the anal canal drain to inguinal and femoral lymph nodes. When inguinal lymph nodes are enlarged on physical examination, the cure rate decreases to 20%; however, these patients are generally still treated with curative intent. Newly diagnosed patients should also be evaluated for lung and liver metastases. Patients with distant metastases are not considered curable. Overexpression of p53 in anal cancer has been associated with poorer local control, disease-free survival, and overall survival.

2. Minimally Invasive Anal Cancer

The best treatment for minimally invasive anal cancer is not defined, and it is not known whether local excision or systemic therapy results in the best outcome. Solitary lesions on the perianal skin are often treated with wide excision; combined modality therapy is often recommended for multifocal disease. In the vast majority of patients with anal cancer, however, macroscopic disease is present, and CMT with chemotherapy (5-fluorouracil in combination with either mitomycin-C or cisplatin) and radiation is preferred. CMT cures approximately 70% of patients; however, a number of acute and chronic complications are associated with this approach and may be more severe in some subsets of HIV-infected patients.

3. Invasive Anal Cancer

The best therapy for invasive anal cancer in HIV-infected patients is not defined. Published studies are retrospective and reflect experience prior to HAART. The local toxicity of CMT has been poorly tolerated in patients with CD4 counts ≤ 200 cells/mm³ who were treated with standard doses. The tolerance of CMT in patients with higher CD4 counts seems to be acceptable and should be the approach in patients with well-controlled HIV infection. There is current interest in studying radioprotective agents to ameliorate local mucosal toxicity, particularly in patients with low CD4 counts. Abdominal perineal resection may be appropriate in some patients with advanced HIV infection who are unlikely to tolerate intensive chemoradiation therapy.

4. Residual or Recurrent Anal Cancer

The options for patients with residual or recurrent anal cancer are limited. In two large trials of CMT in non-HIV-infected patients, distant metastases developed in 10% and 17% of patients.^{91,92} The liver is the most common site of distant metastases, and no curative therapy is available. Locally recurrent or persistent anal disease after CMT, without distant metastasis, can be managed with abdominal perineal resection; this results in long-term control in approximately 50% of patients.^{93,94} Alternatively, patients who have not received cisplatin as part of their initial chemotherapy regimen may be treated with this drug. An additional radiation boost may be possible in patients who have received relatively low doses of radiation as part of initial therapy. The applicability of these salvage treatments to HIV-infected patients is unknown.

VI. NON-AIDS-DEFINING CANCERS

February 2007

RECOMMENDATIONS:

Clinicians should promote risk-reduction behaviors, such as smoking cessation, and should adhere to standard, age-appropriate screening recommendations, such as mammography and colonoscopy, that apply to the non-HIV-infected population. (I)

Although there are no specific guidelines for the treatment of incident, non-AIDS-defining cancers in HIV-infected patients and treatment needs to be individualized, clinicians should not a priori treat such patients with less aggressive therapy than would be used in similarly staged patients without HIV infection. (III)

Key Point:

Clinicians should be vigilant for the development of cancers that are not specifically associated with HIV infection but that are common in the general population, such as lung cancer, breast cancer, colorectal cancer, prostate cancer.

HIV-infected patients are also at risk for development of the same cancers commonly diagnosed in non-HIV-infected people. As improvements in HIV treatment extend the lives of HIV-infected patients, incident cancers that are common in the general population, which increase in frequency with age, are likely to arise. In an analysis of cancers in more than 300,000 adults with HIV/AIDS, 4422 non-AIDS-defining cancers were found in linked population-based AIDS and cancer registry data from 11 geographically diverse areas in the United States.⁹⁵ The overall relative risk of developing a non-AIDS-defining cancer was 2.7 (95% confidence interval, 2.7-2.8).

Several individual cancers, including Hodgkin's disease, lung cancer, penile cancer, soft-tissue malignancies, lip cancer, and testicular seminoma, met the prospective criteria established in this study for a potential association with immunosuppression. An earlier, smaller study also suggested increased rates of multiple myeloma and brain cancer.⁹⁶ An analysis of cancer death rates among HIV-infected persons from 1990 to 1995 showed a significant increase in the relative risk of dying with non-AIDS-defining cancers (i.e., cancers other than Kaposi's sarcoma or non-Hodgkin's lymphoma).⁹⁷ Significantly increased age- and race-standardized relative risks for death with cancer were observed for several individual cancers, including head and neck,

rectal, and lung cancers in men and women; malignant melanoma, multiple myeloma, liver, and testes cancers in men; and larynx, urinary bladder, cervical and non-cervical uterine cancers in women. None of the studies were controlled for potential confounding factors (e.g., tobacco, alcohol, or illicit drug use, or exposure to sexually transmitted pathogens, such as human papillomavirus), which may be more common among HIV-infected persons than in the general population.

Little information is available concerning the presentation, clinical course, and treatment of common cancers that are non-AIDS-defining. There is a widespread perception that incident cancers in HIV-infected patients behave more aggressively than similar cancers in the non-HIV-infected general population, are less likely to respond to treatment, and are more likely to be complicated by serious treatment-related toxicities. This has led, in some cases, to the recommendation of less aggressive therapy for HIV-infected individuals than would be considered standard. However, it should be taken into consideration that most of the published data on treatment patterns and outcomes are from small series or individual case reports that may be more likely to select for patients in whom the clinical presentation of cancer was atypical or the outcome was poor. In addition, the overwhelming majority of data were published in the pre-HAART era. As with the lymphomas, these perceptions about therapy may need to be reexamined now that many patients have well-controlled HIV infection, fewer opportunistic infections, and are more immunocompetent.

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APPENDIX A

| Appendix A Treatment Options for HIV-Associated Malignancies | |
|---|--|
| Type of Cancer | Treatment Options |
| B-cell diffuse large cell lymphoma | <p><i>Initial Treatment:</i></p> <ul style="list-style-type: none"> • CHOP, or • Infusional chemotherapy regimens (infusional CDE, EPOCH), or • Consider concurrent administration of chemotherapy plus rituximab (anti-CD20 monoclonal antibody) in selected patients if CD4 count is at least 50 cells/mm³ <p><i>Relapsed or Refractory:</i></p> <ul style="list-style-type: none"> • Individualize based on HIV status, or • Investigational therapy (e.g., intensive chemotherapy with peripheral blood stem cell support) |
| Primary effusion lymphoma | Optimal therapy not defined; ZDV + IFN alfa active in single case report |
| Primary central nervous system lymphoma | <ul style="list-style-type: none"> • Palliative RT + dexamethasone +/- chemotherapy • ZDV + IFN alfa + GCV active in small series • High-dose MTX with deferred brain irradiation |
| Burkitt's or Burkitt's-like lymphoma | <ul style="list-style-type: none"> • Aggressive multi-agent regimens (CODOX-M/IVAC, Hyper-CVAD with MTX and ARA-C), or • Infusional regimens (CDE, EPOCH) plus concurrent rituximab |
| Plasmablastic lymphoma | Optimal therapy not defined; consider regimens used for Burkitt's lymphoma |
| Hodgkin's disease | <p><i>Initial treatment:</i></p> <ul style="list-style-type: none"> • ABVD or • Stanford V <p><i>Relapsed or refractory:</i></p> <p>Investigational therapy (e.g., intensive chemotherapy with peripheral blood stem cell support)</p> |
| Kaposi's sarcoma | <p><i>All stages:</i></p> <p>Optimize or initiate ARV therapy</p> <p><i>Limited, asymptomatic, or minimally symptomatic:</i></p> <ul style="list-style-type: none"> • Observation only, or • Investigational agents (e.g., angiogenesis inhibitors), or • Interferon alfa, or • Local therapy (e.g., radiation, topical or injectable agents) |

| | |
|-----------------|---|
| | <p><i>Widespread or symptomatic:</i></p> <ul style="list-style-type: none"> • Systemic chemotherapy (liposomal anthracyclines or paclitaxel), or • Investigational therapy (second-line) |
| Cervical cancer | <ul style="list-style-type: none"> • Cone biopsy • Total hysterectomy • Radical hysterectomy • Radiation therapy • Chemotherapy • Combined modality therapy (chemoradiation) |
| Anal cancer | <p><i>Initial Treatment:</i></p> <ul style="list-style-type: none"> • Combined modality therapy (chemoradiation) • Local excision (for selected patients with early stage disease) <p><i>Relapsed or refractory:</i></p> <ul style="list-style-type: none"> • Abdominal perineal resection in selected cases |

ARA-C, arabinosyl cytosine; GCV, ganciclovir; Hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; MTX, methotrexate; RT, radiation therapy; ZDV, zidovudine.

APPENDIX B

AIDS MALIGNANCY CONSORTIUM SITES

New York State AIDS Malignancy Consortium Sites

<http://pub.emmes.com/study/amc/public/index.htm>

Albert Einstein Comprehensive Cancer Center, Bronx

1300 Morris Park Avenue

Bronx, NY 10461

Phone: 718-430-2302

Study Coordinator:

Una Hopkins, CFNP

Phone: 718-405-8522

Email: uhopkins@montefiore.org

Memorial Sloan-Kettering Cancer Center, New York

1275 York Avenue

New York, NY 10021

Phone: 212-639-2000

Study Coordinator:

Christy Giordano

Phone: 646-227-2174

Email: giordanc@mskcc.org