National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cancer in People Living with HIV

Version 1.2018 — February 27, 2018

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NCCN Guidelines Version 1.2018
Cancer in People Living with HIV

NCCN Guidelines Index
Table of Contents
Discussion

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Continue

NCCN Guidelines Panel Disclosures

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§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
Þ Internal medicine
∑ Pharmacology/Pharmacy
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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

INTRODUCTION

- **People living with HIV (PLWH) and AIDS have a higher incidence of many common cancers compared with the general population. AIDS-defining cancers include aggressive non-Hodgkin's lymphoma, Kaposi sarcoma, and invasive cervical cancer. Dramatically improved treatment of HIV over the last two decades has led to a decrease in the risk of AIDS development, an increase in immune function and survival, and a decline in AIDS-defining cancers in this population. Aging due to longer life expectancy with antiretroviral therapy (ART), co-infection with oncogenic infections, and a higher prevalence of carcinogen exposure (tobacco, alcohol) has led to increased incidence of many non-AIDS-defining cancers.**
- **PLWH who develop cancer should be co-managed with an oncologist and HIV specialist and should receive cancer treatment as per standard guidelines. Although modifications to ART may need to be made, HIV therapy should be continued during cancer therapy. Multidisciplinary decision-making, involving infectious disease and HIV specialists, is critical.**

AIDS-defining malignancies[a,b,c,d,e,f]

- **Cervical cancer** → **See Cervical Cancer in PLWH (HIV-1)**
- **Kaposi sarcoma** (**See NCCN Guidelines for AIDS-Related Kaposi Sarcoma**)
- **Aggressive non-Hodgkin's lymphomas[g]** (**See NCCN Guidelines for B-Cell Lymphomas**)

Non–AIDS-defining malignancies[a,b,c,d,e,f]

- **Anal cancer** → **See Anal Cancer in PLWH (HIV-2)**
- **Non-small cell lung cancer** → **See Non-Small Cell Lung Cancer in PLWH (HIV-3)**
- **Hodgkin lymphoma** → **See Hodgkin Lymphoma in PLWH (HIV-4)**
- **Other non-AIDS-defining malignancies** → **See NCCN Guidelines for Treatment of Cancer by Site**

[a] See Principles of HIV Management While Undergoing Cancer Therapy (HIV-A).
[b] See Principles of Systemic Therapy and Drug-Drug Interactions (HIV-B).
[c] See Principles of Radiation Therapy (HIV-C).
[d] See Principles of Surgery (HIV-D).
[e] See Principles of Supportive Care (HIV-E).
[f] See Principles of Imaging (HIV-F).
[g] Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), HHV8-positive DLBCL, NOS, primary effusion lymphoma, plasmablastic lymphoma, primary CNS lymphoma

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Cervical cancer in PLWH

- The risk of cervical cancer is elevated approximately 3- to 5-fold in PLWH.
- Persistent infection with high-risk human papillomavirus (HPV) leads to the development of cervical cancer.
- Premalignant cervical lesions are common in women living with HIV (WLWH). Treatment of these lesions are generally safe and effective regardless of HIV status. However, endocervical extension is more frequent among WLWH. Therefore, loop excision is less effective, with higher recurrence rates in WLWH than in HIV-negative patients.
- Non-malignant causes for lymphadenopathy should be considered in PLWH. Biopsy of suspicious/PET-avid nodes should be more strongly considered in WLWH and cervical cancer.
- WLWH with CIN or invasive cervical cancer should also be evaluated for field effect of HPV oncogenesis, including anal cancer or vulvar cancer.
- WLWH and cervical cancer should be referred to an HIV specialist to ensure they are on an effective ART regimen.
- WLWH should be treated for cervical cancer as per the NCCN Guidelines for Cervical Cancer, including use of concurrent chemotherapy for patients receiving definitive radiation treatment. Modifications to cancer treatment are not recommended based solely on HIV status.
- Poor performance status in WLWH and cervical cancer may be from HIV, cancer, or other causes. The reason for poor performance status should be considered when making treatment decisions. Treatment with ART may improve poor performance status related to HIV.
- Drug interactions can occur in patients with cervical cancer and HIV. Both an HIV pharmacist and an oncology pharmacist should be consulted. See Principles of Systemic Therapy and Drug-Drug Interactions (HIV-B).

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Anal dysplasia and anal cancer screening in PLWH

- PLWH are at higher risk of premalignant anal epithelial changes compared to HIV-negative patients.
- While there are no national recommendations that exist for routine screening of anal cancer, many HIV specialists do screen PLWH for dysplasia by anal cytology, high resolution anoscopy, and annual digital anal exam, though the frequency and method of surveillance vary.
- If high-grade anal squamous intraepithelial lesions (high-grade anal intraepithelial neoplasia [AIN]) are identified, then high-resolution anoscopy should be performed, if available.
- There are multiple methods by which anal dysplasia is treated: topical therapy (fluorouracil, imiquimod), excision, and ablation. These treatments are safe in PLWH and offer short-term efficacy.
- However, treatment of anal dysplasia in PLWH is associated with a higher risk of recurrence in PLWH compared to HIV-negative patients.
- In a randomized controlled trial of PLWH who engage in receptive anal intercourse, electrocautery (ablation) was found to be better than topical therapy in the treatment of anal dysplasia, even though recurrence rates were still high.

Anal carcinoma in PLWH

- PLWH have an approximately 25- to 35-fold increased likelihood of being diagnosed with anal cancer compared with HIV-negative individuals, and anal cancer accounts for approximately 10% of cancers diagnosed in PLWH.
- Anal cancer in PLWH is often associated with persistent anal HPV infection.
- HPV-related disease in PLWH is often multifocal. Therefore, WLWH diagnosed with anal cancer should have colposcopic examination by a gynecologist for presence of vulvar, vaginal or cervical disease.
- Non-malignant causes for lymphadenopathy should be considered in PLWH. Suspicious PET-avid lymphadenopathy should be biopsied to rule out nodal metastasis of anal cancer or infectious etiology (consult with infectious disease specialist). If negative for cancer, refer for an infectious disease workup.

Anal carcinoma in PLWH (continued)

- PLWH with anal cancer should be co-managed by an oncologist and HIV specialist and should be treated for anal cancer as per the NCCN Guidelines for Anal Carcinoma.
  - Modifications to cancer treatment should not be made solely on the basis of HIV status.
    - ◊ Surgical excision for appropriately selected early-stage T1 anal verge cancers is effective and safe in PLWH.
    - ◊ Although treatment response rates with chemoradiotherapy for anal cancer are high, up to 30% of patients will require abdominoperineal resection (APR) for persistent or recurrent disease. HIV status does not affect overall survival or disease-free survival in patients who require APR for recurrent or residual disease. HIV status is also not associated with worse postoperative outcomes after APR.
    - ◊ In PLWH, radiotherapy should be delivered via IMRT technique to spare as much normal tissue as possible without compromising target coverage.
- Post-treatment surveillance of PLWH should include more frequent digital rectal examinations and anoscopy than HIV-negative patients (every 3–6 months for 3 years).
- Anal cytology can be considered for the detection of anal dysplasia in survivors of anal cancer living with HIV, although its value in detection of recurrent anal cancer is limited.
- People who engage in receptive anal intercourse should discuss post-treatment pelvic physical therapy and anal dilators with an appropriate health care provider.
- Poor performance status in PLWH and anal cancer may be from HIV, cancer, or other causes. The reason for poor performance status should be considered when making treatment decisions. Treatment with ART may improve poor performance status related to HIV.
- Drug interactions can occur in patients with anal cancer and HIV. Both an HIV pharmacist and an oncology pharmacist should be consulted. See Principles of Systemic Therapy and Drug-Drug Interactions (HIV-B).

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Non-small cell lung cancer in PLWH

- The risk of lung cancer is 2 to 5 times higher in PLWH than in HIV-negative individuals, and lung cancer accounts for approximately 11% of cancers diagnosed in this population.
- Screening for lung cancer with low-dose CT should be performed in PLWH as per the NCCN Guidelines for Lung Cancer Screening. However, it should be noted that PLWH may be at increased risk for the development of lung cancer compared to the general population.
- Smoking cessation should be discussed (See NCCN Guidelines for Smoking Cessation).
- PLWH with NSCLC should be co-managed with an oncologist and HIV specialist and should be treated for NSCLC as per the NCCN Guidelines for Non-Small Cell Lung Cancer. Modifications to cancer treatment should not be made solely on the basis of HIV status.
- PLWH may be more likely to have benign lung nodules than uninfected patients. Infectious granuloma and tuberculosis are possible differential diagnoses. An infectious disease workup should be performed when indicated. Treatment for possible non-malignant diagnoses can be considered before biopsy.
- If concurrent pulmonary Kaposi sarcoma is suspected, precautions should be taken because increased bleeding may occur with biopsies.
- Lung biopsies should be cultured for bacteria, fungi, and mycobacteria acid-fast bacilli (AFB).
- Non-malignant causes for lymphadenopathy should be considered in PLWH.
- Workup of brain lesions in patients with NSCLC and advanced HIV-related immunosuppression should include an evaluation to rule out infectious processes (eg, toxoplasmosis) or other malignancies such as non-Hodgkin's lymphoma.
- Poor performance status in PLWH and NSCLC may be from HIV, cancer, or other causes. The reason for poor performance status should be considered when making treatment decisions. Treatment with ART may improve poor performance status related to HIV.
- Drug interactions can occur in patients with NSCLC and HIV. Both an HIV pharmacist and an oncology pharmacist should be consulted. See Principles of Systemic Therapy and Drug-Drug Interactions (HIV-B).

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Hodgkin lymphoma in PLWH

- PLWH are 5 to 14 times more likely to be diagnosed with Hodgkin lymphoma (HL) than HIV-negative individuals, and HL accounts for approximately 4% of cancer diagnosed in the PLWH population.
- Compared with HIV-uninfected people, PLWH more commonly present with mixed cellularity or lymphocyte-depleted histologies of HL. 90% of cases of HL in PLWH are Epstein-Barr virus (EBV)-associated. PLWH often present with more advanced disease, including extranodal disease and bone marrow involvement. Bone-marrow-only presentations sometime occur. B symptoms (ie, fever, night sweats, weight loss) are also more common in this population, and should always prompt investigation of opportunistic infection. In contrast to non-Hodgkin lymphoma in PLWH, central nervous system involvement is rare with HL.
- Interpretation of diagnostic and staging imaging may be complicated by the increased incidence of non-malignant lesions that may be mistaken for cancer spread or recurrence. See Principles of Imaging (HIV-F).
- All of the standard HL regimens have been studied in PLWH. ABVD is less toxic than Stanford V or BEACOPP and therefore may be preferred in PLWH.
  - For ABVD in advanced-stage HIV-associated HL, patients who have symptoms of pulmonary compromise or fall in diffusing capacity of the lungs for carbon monoxide (DLCO) can consider dropping bleomycin after 2 cycles, particularly with a PET/CT scan showing complete response.
  - Whereas the routine use of growth factor is not recommended during ABVD treatment in the NCCN Guidelines for Hodgkin Lymphoma because of concerns with possible adverse interactions with bleomycin leading to lung toxicity, growth factors may be required in PLWH, especially if CD4+ T-cell count is low and in the setting of prolonged severe neutropenia or neutropenic fever.
  - Similarly, whereas dose reduction is not recommended for neutropenia with ABVD in the NCCN Guidelines for Hodgkin Lymphoma, dose reductions may be appropriate in PLWH with severe and prolonged cytopenias.
  - If CD4+ T-cell count is <200 cells/μL, consider prophylactic antibiotics for gram-negative bacteria and pneumocystis jiroveci pneumonia (PJP), in addition to appropriate opportunistic infection prophylaxis. Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents
  - If CD4+ T-cell count is <100 cells/μL, consider dose reduction in early cycles. See Principles of Supportive Care (HIV-E).
- PET/CT-guided therapy in HIV-associated HL is feasible; however, care should be taken to recognize potential confounding factors (ie, non-malignant causes for PET-avid regions).
- Poor performance status in PLWH and HL may be from HIV, cancer, or other causes. The reason for poor performance status should be considered when making treatment decisions. Treatment with ART may improve poor performance status related to HIV.
- Adverse reactions due to drug interactions are more common with ritonavir, cobicistat, and protease inhibitors and these antiretrovirals (ARVs) should be avoided. Drug interactions with non-nucleoside reverse transcriptase inhibitors are likely to result in decrease efficacy and should be used with caution. Zidovudine should be avoided due to myelosuppression. Didanosine and stavudine may cause additive peripheral neuropathy and should be avoided. Many HIV combination pills contain one or more of these medications. Modification of ART may need to be considered, and consultation with an HIV specialist, HIV pharmacist and oncology pharmacist is recommended. When alternate ART regimens are not available, consider holding ART until completion of course of chemotherapy. See Principles of Systemic Therapy and Drug-Drug Interactions (HIV-B).

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PRINCIPLES OF HIV MANAGEMENT WHILE UNDERGOING CANCER THERAPY

- **Linkage to HIV care from cancer providers**
  - All patients with a cancer diagnosis should be screened for HIV.[1,2]
  - All PLWH with cancer should be co-managed by an oncologist and HIV specialist.
  - HIV therapy should be initiated or continued during cancer therapy. ART interruptions should generally be avoided, due to the risk of immunologic compromise, opportunistic infection, and death.[3] Continuation of ART might result in better tolerance of cancer treatment, higher response rates, and improved survival.
  - ART may require modification by an HIV specialist in conjunction with an HIV pharmacist and an oncology pharmacist to minimize drug-drug interactions and toxicities.
  - Cancer treatment should not be delayed for HIV workup and treatment, if possible.

- **Routine HIV care in conjunction with HIV specialist during cancer therapy**
  - ART should be offered immediately (if patient not already receiving it), but may need to be adapted according to the cancer treatment plan.[4,5] See Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV.
  - To facilitate separate assessment of tolerability of ART and cancer treatment, consider initiating ART ≥7 days prior to start of cancer treatment or after cancer therapy has been initiated long enough for tolerance to be established. There may be circumstances when ART should be started immediately, regardless of the cancer therapy timing, such as with the diagnosis of progressive multifocal leukoencephalopathy (PML).
  - In patients co-infected with hepatitis B, an ART regimen that treats both HIV and hepatitis B should be initiated.
  - Laboratory testing should be scheduled for both before and after initiation of ART (See Table 3 of Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV).
  - HIV viral load and CD4+ T-cell count monitoring (See Table 4 of Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV):
    - ◊ More frequent HIV viral load testing (eg, once a month for the first 3 months and then every 3 months[6]) may be needed due to potential interactions between ART and cancer-related drugs leading to decreased effectiveness of ART.
    - ◊ Consider measuring the CD4+ T-cell count more frequently in patients receiving cancer treatments anticipated to cause lymphopenia. Decreases in CD4+ T-cell counts attributable to cancer therapy are not necessarily reflective of HIV control, which is better measured by HIV viral load. A decrease in CD4+ T-cell count will still predict increased risk for opportunistic infections. Additional risk beyond that predicted by CD4+ T-cell counts may occur due to effects of cancer-related therapy on immune function.
  - Smoking cessation should be discussed.[7,8] (See NCCN Guidelines for Smoking Cessation).

- **Primary and secondary prophylaxis for opportunistic infections during cancer treatment.**
  - Patients should receive the prophylaxis indicated by their HIV status and cancer treatment. See Principles of Supportive Care (HIV-E).

See References on HIV-A 2 of 2.

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PRINCIPLES OF HIV MANAGEMENT WHILE UNDERGOING CANCER THERAPY

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[1]Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep 2006;55(RR-14);1-17.
[2]Rizza SA, MacGowan RJ, Purcell DW, et al. HIV screening in the health care setting: status, barriers, and potential solutions. Mayo Clin Proc 2012 Sep;87(9): 915-924.
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[4]Hessol NA, Pipkin S, Schwarcz S, et al. The impact of highly active antiretroviral therapy on non-AIDS-defining cancers among adults with AIDS. Am J Epidemiol 2007;165:1143-1153.
[5]Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med 2009;360:1815-1826.
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[7]Anthonisen NR, Skeans MA, Wise RA, et al. The effects of smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med 2005;142:233-239.
[8]A clinical practice guideline for treating tobacco use and dependence: A US Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. JAMA 2000;283:3244-3254.

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PRINCIPLES OF SYSTEMIC THERAPY AND DRUG-DRUG INTERACTIONS

- **Oncology and HIV clinicians, along with both an oncology pharmacist and HIV pharmacist, if available, should review proposed cancer therapy, supportive care medications and ART for possible drug-drug interactions (DDIs) and overlapping toxicities prior to initiation.**
- **Select ARVs can be administered safely with systemic cancer therapies. With continued development of new ARVs, effective alternatives are often available to patients when the existing ART is expected to affect metabolism or transport of, or share toxicities with, systemic cancer therapies.**
- **The possibility that DDIs may enhance treatment toxicity or decrease efficacy needs to be considered. In general, CYP450 (or any enzyme or drug transporter) inhibitors increase the substrate exposure resulting in increased toxicity, while inducers decrease the exposure resulting in decreased efficacy. See Table 1: Systemic Cancer Therapy-ART Interactions by ART Drug Class. The exception to this is a prodrug (eg, irinotecan or cyclophosphamide) where the metabolite is active and the opposite effect would be observed.**
- **The greatest concern for DDIs is with HIV regimens containing pharmacologic boosters (ie, ritonavir, cobicistat) and protease inhibitors. These drugs inhibit CYP3A/4 and thus may interact with agents metabolized by that pathway. HIV regimens containing integrase inhibitors without pharmacologic boosters are favored in the setting of malignancy, due to a lower potential for DDI.**
- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs) induce CYP3A/4 and thus may cause the opposite DDI from the inhibitors.**
- **ART treatment guidelines caution against use of ritonavir- and cobicistat-boosted regimens and some NNRTIs in the context of cancer treatment (See Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV). When cancer therapy is expected to be myelosuppressive, zidovudine is contraindicated due to its likelihood to cause or exacerbate myelosuppression.**
- **Small case series favor integrase inhibitor-based ART during cancer therapy.[1,2]**
- **If a potential DDI or overlapping toxicity exists, options include (in order of preference):**
  1. **substituting a different ARV with less DDI potential;**
  2. **selecting an alternative cancer therapy regimen with less DDI potential; and**
  3. **temporarily discontinuing ART (temporary discontinuation of ART should only be undertaken in consultation with the an HIV specialist), but only if:**
     - **the above options are not advisable, cure for the malignancy is the intent, and the chemotherapy treatment course is of short duration; or**
     - **the above options are not advisable, the malignancy has a poor prognosis, and palliation is the goal.**
- **Consultation with an HIV specialist in choosing or adapting an ART regimen is essential.**

See Table 1: Systemic Cancer Therapy-ART Interactions by ART Drug Class (HIV-B 2 of 2)

[1]Casado JL, Machuca I, Bañón S, et al. Raltegravir plus two nucleoside analogues as combination antiretroviral therapy in HIV-infected patients who require cancer chemotherapy. Antivir Ther 2015;20:773-777.
[2]Torres HA, Rallapalli V, Saxena A, et al. Efficacy and safety of antiretrovirals in HIV-infected patients with cancer. Clin Microbiol Infect 2014;20:O672-679.

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PRINCIPLES OF SYSTEMIC THERAPY AND DRUG-DRUG INTERACTIONS

Table 1: Systemic Cancer Therapy-ART Interactions by ART Drug Class

ART Drug Class	Main Mechanism(s) of Metabolism/Elimination	Effect on CYP450/Transporters	Potential for Clinically Significant Pharmacokinetic Interactions[3,4]	
			Effect of Cancer Drugs on ART	Effect of ART on Cancer Drugs
Nucleoside reverse-transcriptase inhibitors	• Renal excretion • UDP-glucuronosyltransferases • ATP-binding cassette transporters • Solute carrier transporters	No known effect or no clinically relevant effect via ATP-binding cassette transporters	Interaction unlikely or possible	Interaction unlikely or possible
Nucleotide reverse-transcriptase inhibitors	• Renal excretion • ATP-binding cassette transporters • Solute carrier transporters	Inhibitor of CYP450 enzyme and ATP-binding cassette transporters	Potential for significant interaction	Interaction possible
Non-nucleoside reverse-transcriptase inhibitors	• CYP450 enzymes • UDP-glucuronosyltransferases • ATP-binding cassette transporters	Inhibitors and inducers of CYP450 enzyme and transporters	Potential for significant interaction	Potential for significant interaction or potential critical interaction
HIV-1 protease inhibitors	• CYP450 enzymes • ATP-binding cassette transporters • UDP-glucuronosyltransferase	Inhibitors and inducers of CYP450 enzyme and ATP-binding cassette transporters and solute carrier transporters	Potential for significant interaction	Major clinically significant interaction likely or potential critical interaction
Integrase strand-transfer inhibitors	• UDP-glucuronosyltransferases • ATP-binding cassette transporters • Solute carrier transporters	Inhibitors and inducers of CYP450 enzyme and ATP-binding cassette and solute carrier transporters	Potential for significant interaction	Potential for significant interaction or potential critical interaction
Fusion inhibitors	• Catabolism	No known effect or no clinically relevant effect	Interaction unlikely or possible	Interaction unlikely or possible
Entry inhibitors (chemokine receptor antagonists)	• CYP450 enzymes • ATP-binding cassette transporters • Solute carrier transporters	No known effect or no clinically relevant effect via ATP-binding cassette transporters	Potential for significant interaction or potential critical interaction	Interaction unlikely or possible
Ritonavir- or cobicistat-boosted regimens	• CYP450 enzymes • ATP-binding cassette transporters	Inhibitors and inducers of CYP450 enzyme and ATP-binding cassette and solute carrier transporters	Potential for significant interaction	Major clinically significant interaction likely or potential critical interaction

[3]Depending on the likelihood for clinically significant pharmacokinetic interactions between cancer drugs and ART, dose adjustments, modification of therapy, and/or increased monitoring may be required (for cancer drugs, ART, or both). Drug package inserts for each individual agent should be consulted to determine the drug interaction potential and recommended dosing and monitoring instructions. Consultation with oncology and HIV clinicians, along with oncology and HIV pharmacists, if available, is strongly recommended.

[4]DDI potential/clinical relevance:

- Interaction unlikely: DDI is unlikely or there is a known minor interaction. Modification of therapy is not necessary.
- Interaction possible: DDI is possible based on drug pharmacology. No modification to therapy is necessary, but close monitoring for signs of toxicity is recommended.
- Potential for significant interaction: There is a potential for clinically significant DDI based on drug pharmacology. No modification to therapy is required, but close monitoring for signs of toxicity is recommended. If close monitoring is not feasible, then modification of therapy should be considered.
- Potential critical interaction: Clinically significant DDI is likely based on drug pharmacology or on known interaction. Drug doses should be adjusted or modification of therapy should be considered.
- Major clinically significant interaction likely: Co-administration is contraindicated, and therapy should be modified.

PRINCIPLES OF RADIATION THERAPY[1]

- **HIV status alone should not be a criterion for decision-making regarding radiation therapy (RT). RT should be offered as part of the cancer management approach when indicated.**
- **RT can be administered for cure or palliation.**
- **Older studies conducted in the pre-ART era showed increased RT-related toxicity, particularly in patients with CD4+ T-cell counts <200 cells/μL. This risk may be less applicable to patients in ART-era, particularly those with CD4+ T-cell counts >200 cells/μL.**
- **More modern data suggest RT is effective and well-tolerated for certain cancers (eg, anal cancer); in other cancers, data are insufficient to recommend a change from standard therapy (eg, lung cancer).**
- **Extra caution and monitoring is required with concurrent chemoradiotherapy.**
- **Particular attention should be paid to limit dose to the following structures using conformal techniques like intensity-modulated radiotherapy (IMRT) or stereotactic body radiotherapy (SBRT) when deemed appropriate by the treating provider:**
  - **Mucosal membranes**
  - **Skin**
  - **Bone marrow**
- **Nutritional support, pain control, and other supportive measures should be used to minimize radiotherapy interruptions.**

[1]Alongi F, Giaj-Levra N, Sciascia S, et al. Radiotherapy in patients with HIV: Current issues and review of the literature. Lancet Oncol 2018;18:e379-e393.

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PRINCIPLES OF SURGERY

- **HIV status alone should not be a criterion for decision-making regarding surgical intervention, regardless of the procedure.**
- **All surgical patients should be treated with universal precautions, and no special precautions need to be taken with PLWH.**
- **Overall health (eg, organ dysfunction, nutritional state) has been found to be a more reliable predictor of surgical outcome than CD4+ T-cell count or viral load in PLWH. The data showing that low CD4+ T-cell counts are associated with poorer prognosis have been inconsistent and viral suppression has not been conclusively shown to improve surgical outcomes.[1-5] There are no additional presurgical or postsurgical laboratory values that are needed specific to PLWH beyond the normal workup and follow-up for a surgical patient.**
- **Surgical Outcomes:**
  - **Surgery in PLWH for common malignancies (eg, prostate cancer, colon cancer) is safe and should be part of cancer management as indicated.[6,7]**
  - **Recent data demonstrate that clinical outcomes, length of stay, and complications are similar between PLWH and HIV-negative patients for most surgical procedures.[8]**
  - **A study of PLWH who required laparotomy found no increased risk of wound complications.[9]**
  - **Data from anorectal surgery for benign disease (eg, hemorrhoids, fistulas) suggest that there can be issues with delayed wound healing in PLWH, especially if the CD4+ T-cell count is <50 cells/μL.[10] However, other reports demonstrate that PLWH who undergo anorectal surgery experience normal wound healing.[11]**

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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SUPPORTIVE CARE

- The risk of infectious complications in PLWH is reduced with improved HIV control and aggressive infection prophylaxis; therefore, ART should be initiated and/or continued during cancer therapy.
- Select ARTs can be administered safely with systemic cancer therapy. With continued development of new ARVs, effective alternatives are often available to patients when the existing ARVs are expected to affect metabolism of or share toxicities with systemic cancer therapies. All ART initiation or changes should be done in consultation with an HIV specialist. See Principles of Systemic Therapy and Drug-Drug Interactions (HIV-B).
- For cancer treatment regimens that include agents associated with delayed nausea/vomiting, steroids can be used briefly as premedication for or following chemotherapy. However, general use of steroids for antiemetic therapy should be limited in PLWH because steroid use may increase the risk of opportunistic infections.
- There is an increased risk of oral mucositis, esophagitis, and colitis secondary to mucosal sensitivity and opportunistic infections. A high index of suspicion of and early testing for opportunistic infections, including fungal and cytomegalovirus (CMV), is appropriate; early consultation with an infectious disease or HIV specialist is appropriate.
- Patients desiring fertility preservation should be referred to oncofertility for a discussion of options.

Other supportive care measures:

- For most supportive care situations related to cancer treatment, PLWH should be managed as per the appropriate NCCN Guidelines for Supportive Care (available at www.NCCN.org), including:
  - NCCN Guidelines for Adult Cancer Pain
  - NCCN Guidelines for Antiemesis
  - NCCN Guidelines for Cancer-Related Fatigue
  - NCCN Guidelines for Distress Management
  - NCCN Guidelines for Palliative Care
- For general recommendations for vaccination in patients with cancer, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
  - Generally, live virus vaccines should not be administered to PLWH with CD4+ T-cell counts <200 cells/μL .
  - PLWH aged 50 years and older can receive the new recombinant zoster vaccine. Dooling K, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. MMWR Morb Mortal Wkly Rep 2018;67:103-108.

See Infectious Prophylaxis for Patients Receiving Therapy (HIV-E 2 OF 2)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF SUPPORTIVE CARE

- PLWH should receive the prophylaxis indicated by their HIV status and cancer treatment. Also see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections and Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents.
- For PLWH receiving cancer therapy where profound immunosuppression/myelosuppression is anticipated:

Required/Strongly Recommended

- Myeloid growth factor support (per NCCN Guidelines for Myeloid Growth Factors or NCCN treatment guidelines with specific recommendations)
  - Myeloid growth factor support is required in regimens that are high risk for febrile neutropenia, strongly recommended in regimens that are intermediate risk for febrile neutropenia, and should be strongly considered in regimens that are low risk for febrile neutropenia in PLWH. Pre-existing neutropenia and/or low CD4+ T-cell counts increase risk of chemotherapy-associated neutropenic fever; myeloid growth factor support is strongly recommended with these risk factors.
- Gram-negative infection prophylaxis
  - Quinolone prophylaxis or equivalent during periods of neutropenia
  - Ex. Ciprofloxacin 500–750 mg PO every 12 hours OR levofloxacin 500–750 mg PO daily
- Herpes simplex virus (HSV)/Varicella zoster virus (VZV) prophylaxis
  - Continue until completion of cancer therapy
  - Ex. Acyclovir 400–800 mg PO twice daily OR valacyclovir 500 mg PO twice daily
- Pneumocystis jiroveci pneumonia (PJP) prophylaxis* and toxoplasmosis prophylaxis[1]
  - Continue until CD4+ T-cell counts recovered to ≥200 cells/μL for ≥3 months duration post completion of cancer therapy
  - Ex. Sulfamethoxazole-trimethoprim 800 mg/160 mg (double-strength) 1 double-strength tablet PO three times a week OR dapsone 100 mg PO daily
    - ◊ Avoid TMP/SZ while patient is on methotrexate
    - ◊ G6PD deficiency screening is necessary
- Mycobacterium avium complex (MAC) prophylaxis[1]
  - Continue until CD4+ T-cell counts recovered to ≥100 cells/μL for ≥3 months duration post completion of cancer therapy
  - Ex. Azithromycin 1200 mg PO once a week
- Candida prophylaxis
  - Ex. Nystatin ± fluconazole

[1]These are specifically for prophylaxis. Refer to the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents for patients with a recent history of or current active infection.

Consider

- Antifungal prophylaxis
  - During periods of prolonged neutropenia (≥7 day)
  - Azole antifungals may interact with ART and chemotherapy. Azoles should typically be held a minimum of 24 hours prior to through 24 hours after administration of cancer therapy that is metabolized via CYP3A4.
  - Ex. Fluconazole 400 mg PO daily OR posaconazole (delayed release tablets) 300 mg PO twice daily on day 1 followed by 300 mg PO daily thereafter OR voriconazole 200 mg PO twice daily
  - In certain geographic areas: histoplasmosis, coccidioidomycosis, talaromyces marneffei

Special Circumstances

- Consultation with an infectious disease specialist is strongly recommended; in patients co-infected with HBV or HCV, consultation with a hepatologist should also be considered in the setting of advanced liver disease
  - Hepatitis B virus (HBV)
    - All patients should be on fully suppressive HIV ART
    - Ideally, the ART should include drugs that treat HBV as well as HIV
      - If not able to include drugs in ART that treats both HIV and HBV, HBV therapy will be directed by the infectious disease provider. This will likely include TDF (tenofovir disoproxil fumarate) 300 mg PO daily OR TAF (tenofovir alafenamide) 25 mg PO daily OR entecavir 0.5–1 mg PO daily
  - Hepatitis C virus (HCV)
  - CMV

Febrile Neutropenia

- Consultation with an infectious disease specialist is strongly recommended for febrile neutropenia in the context of appropriate prophylaxis. Opportunistic infections including PJP and CMV as cause of fever are more likely in PLWH receiving cancer chemotherapy; a high index of suspicion and early testing for opportunistic infections in consultation with an infectious disease or HIV specialist is appropriate.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF IMAGING

- **Interpretation of imaging for the workup, staging, and surveillance of PLWH who have cancer is complicated by the increased incidence of non-malignant lesions that may be mistaken for cancer spread or recurrence.**
  - **Lymphadenopathy seen on 18F-FDG PET/CT can be malignant or can result from opportunistic infections or HIV directly.[1]**
  - **Lung lesions may be malignant or may result from opportunistic infections, drug reactions, or immune activation.**
  - **Brain lesions may be malignant or may result from opportunistic infections, vascular complications, or hydrocephalus.**
- **Opportunistic infections and HIV-related adenopathy are more common in patients with higher viral loads and lower CD4+ T-cell counts.**
- **An infectious disease workup should be considered as clinically appropriate for PLWH whose imaging shows lymphadenopathy or lesions in the spleen, lungs, brain, bone, liver, and gastrointestinal tract, especially in the presence of a low CD4+ T-cell count and concurrent B symptoms.**
- **Lesions of uncertain etiology should be biopsied to confirm cancerous histology.**

[1]Davison J, Subramaniam R, Surasi D, et al. FDG PET/CT in patients with HIV. AJR Am J Roentgenol 2011;197:284-294.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

Table of Contents

Overview

In 2017, it is estimated that more than 1.1 million people in the United States are living with human immunodeficiency virus (HIV) infection.[1] Without treatment, HIV infection causes acquired immunodeficiency syndrome (AIDS) and AIDS-defining cancers: aggressive non-Hodgkin's lymphoma (NHL), Kaposi sarcoma, and invasive cervical cancer.[2,3] Dramatically improved treatment of HIV over the last two decades has decreased the risk of AIDS development, improved immune function and survival, and led to a decline in AIDS-defining cancers in this population.[4-6] People living with HIV (PLWH) are living longer and healthier lives; however, they are experiencing an increased risk of many non-AIDS–defining cancers.[7-12]

An estimated 7760 PLWH were diagnosed with cancer in the United States in 2010, representing an approximately 50% increase over the expected number of cancers in the general population.[13] Other studies have also noted a higher risk for developing many cancers in PLWH than in the general population, likely due to underlying immune deficiency and co-infection with viruses such as human papillomavirus (HPV), human herpesvirus 8 (HHV-8), hepatitis B virus (HBV), hepatitis C virus (HCV), and Epstein-Barr virus (EBV).[14-18] In addition, the prevalence of other cancer risk factors in the HIV population (eg, smoking, heavy alcohol consumption) likely plays a role.[19-23]

The proportions of each major cancer type among total incident cancer cases occurring in PLWH in the United States during 2010 were:[13]

- NHL 21%
- Kaposi sarcoma 12%
- Lung cancer 11%
- Anal cancer 10%
- Prostate cancer 7%
- Liver cancer 5%
- Colorectal cancer 5%
- Hodgkin lymphoma 4%
- Oral/pharyngeal cancer 4%
- Female breast cancer 2%
- Cervical cancer 1%

These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cancer in People Living with HIV provide treatment recommendations for PLWH who develop non-small cell lung cancer (NSCLC), anal cancer, Hodgkin lymphoma, and cervical cancer. In addition, the panel outlines general advice for this population regarding HIV management during cancer therapy; drug-drug interactions (DDIs) between antiretroviral treatments and cancer therapies; and workup, radiation therapy, surgical management, and supportive care in PLWH who have cancer. The panel based its recommendations on relevant data when available and on expert consensus for situations where data were not available. These guidelines are intended to assist health care providers with clinical decision-making for PLWH who have cancer. This Discussion elaborates on the guidelines and provides an overview of the literature supporting the included recommendations.

Recommendations for the management of NHL and Kaposi sarcoma in PLWH are available in the NCCN Guidelines for B-Cell Lymphomas and the NCCN Guidelines for AIDS-Related Kaposi Sarcoma, respectively (available at www.NCCN.org).

Literature Search Criteria and Guidelines Update Methodology

Prior to the development of the NCCN Guidelines for Cancer in People Living with HIV, an electronic search of the PubMed database was

performed to obtain key literature in the field published between April 11, 2007 and April 11, 2017, using the following search terms: (cancer or malignancy or carcinoma or adenocarcinoma or lymphoma or leukemia or melanoma or sarcoma or neoplasia) and (HIV or AIDS). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[24]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 771 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

Disparities in Cancer Care for PLWH

In general, PLWH who develop cancer have higher mortality compared with the general cancer population.[25-28] Reasons for this increased mortality include delayed diagnoses, advanced cancer stage, other comorbidities, and immunosuppression in PLWH.[26,29-31] However, there is also significant disparity in cancer treatment between PLWH and the general cancer population, with many PLWH not receiving any cancer treatment at all.[32,33] Results of a survey of 500 medical and radiation oncologists in the United States suggest that lack of consensus guidelines and provider education contributes to the sub-standard cancer care often offered to patients with HIV and cancer.[34] It is the hope of the NCCN panel that these guidelines can help to fill that gap in education and enable health care providers to provide optimal cancer care to PLWH.

HIV Management During Cancer Therapy

HIV Screening

One out of every 7 people in the United States who are infected with HIV are not aware of their infection status.[1] Infected individuals who are unaware of their HIV status do not receive the clinical care they need to reduce HIV-related morbidity and mortality and may unknowingly transmit HIV.[35] The Centers for Disease Control and Prevention (CDC) therefore recommends HIV screening for all patients in all health care settings unless the patient declines testing (opt-out screening).[36]

HIV testing may be particularly important in patients with cancer, because identification of HIV infection has the potential to improve clinical outcomes.[37] Results of a retrospective cohort study at MD Anderson Cancer Center revealed, however, that the rate of HIV testing in cancer clinics from 2007 to 2009 was only 19.3%.[38] Analysis of data from the 2009 Behavioral Risk Factor Surveillance System showed that only 41% of U.S. cancer survivors <65 years of age reported ever being tested for HIV.[39] Race, other demographic characteristics, and tumor type influenced the likelihood of receiving an HIV test in both studies.

The NCCN panel supports the CDC recommendation that all patients diagnosed with cancer who do not opt-out should be tested for HIV if not already known to have a documented HIV infection.

Linkage to HIV Care

The HIV Care Continuum Initiative indicates that all patients diagnosed with HIV should be referred to an HIV specialist.[40] Linkage to care and initiation of antiviral therapy has been shown to improve viral suppression.[41,42] Early initiation of ART has also been shown to improve survival in PLWH and lower incidence of AIDS-related malignancies.[43,44] Linkage to HIV care is essential for PLWH who have cancer; therefore, the oncology team should refer all PLWH who have cancer to an HIV specialist if they do not already have one. The HIV.gov website has a map that can be used to locate HIV services: https://locator.hiv.gov/.

HIV Therapy During Cancer Treatment

HIV treatment for PLWH who have cancer should be initiated and maintained by an HIV specialist, in collaboration with the oncology team. If the patient has already started ART, it should be continued during cancer treatment, although modifications may be needed. For patients who have not yet started ART, it should be initiated either ≥7 days prior to the start of cancer treatment or long enough after cancer therapy has been initiated that it is possible to distinguish between adverse effects attributable to cancer chemotherapy versus those attributable to ART.

ART interruptions during cancer treatment should generally be avoided, because they increase the risk of immunologic compromise, opportunistic infection, and death.[45] Continuation of ART may also result in better tolerance of cancer treatment, higher response rates, and improved survival.[46,47] ART can be modified as needed based on DDIs or overlapping toxicities with cancer therapy (see *Drug-Drug Interactions: Systemic Cancer Therapy and ART*, below).

Laboratory testing, HIV viral load, and CD4+ T-cell monitoring should generally be performed as per normal schedules for PLWH.[48] However, more frequent HIV viral load testing (eg, once a month for the first 3 months and then every 3 months) may be needed if systemic cancer therapy is used, especially if treatment is anticipated to cause lymphopenia.[49] In the setting of chemotherapy-associated lymphopenia, HIV viral load monitoring more accurately reflects control of HIV compared with CD4+ T-cell count. The depth of CD4+ T-cell suppression informs the risk of opportunistic infections.

Opportunistic Infection Prophylaxis

The occurrence of opportunistic infections in PLWH has decreased in the ART era, mainly because effective ART reduces infection risk as CD4+ T-cell counts rise.[6,50-52] Furthermore, improvements in prophylaxis and treatment of opportunistic infections in PLWH has further reduced risk.[52,53] Still, opportunistic infections represent a major cause of morbidity and mortality in PLWH.[52,53]

The risk of bacterial, fungal, and viral infections is elevated in patients with cancer, who may experience immunosuppression resulting from cancer treatment and sometimes from the disease itself (eg, hypogammaglobulinemia in chronic lymphocytic leukemia or multiple myeloma).[54-58] In particular, chemotherapy can cause neutropenia, which is a major risk factor for the development of infections.[59] The frequency and severity of infection are inversely proportional to the neutrophil count, with the risks of severe infection and bloodstream infection greatest (approximately 10%–20%) at neutrophil counts below 100 cells/mcL.[60] Newer targeted agents are also associated with immunosuppression and increased infection risk.[61]

PLWH may be more susceptible to infectious complications following chemotherapy than their uninfected counterparts,[62] and low CD4+ T-cell counts appear to increase the risk of febrile neutropenia.[63] Furthermore, data show that certain chemotherapy regimens can cause a sustained

drop in CD4+ T-cell counts and an increased risk of opportunistic infections.[64] Other regimens, however, appear to have similar effects on myelosuppression and infectious complications in PLWH and HIV-negative patients with cancer.[65]

Overall, the NCCN panel recommends that PLWH who have cancer should receive the prophylaxis indicated by their HIV status and cancer treatment. Specific recommendations for PLWH receiving cancer therapy for which profound immunosuppression/myelosuppression is anticipated are outlined in the guidelines above (see *Principles of Supportive Care*). The U.S. Department of Health and Human Services' Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (available at www.aidsinfo.nih.gov/guidelines) and the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (available at www.NCCN.org) also contain recommendations that may be relevant to this population. If febrile neutropenia occurs in spite of prophylaxis, consultation with an infectious disease specialist is strongly recommended.

Smoking Cessation in PLWH Who Have Cancer

Smoking cessation should be offered to PLWH who smoke and have cancer (see the NCCN Guidelines for Smoking Cessation, available at www.NCCN.org). Smoking cessation after a cancer diagnosis in the general population has been linked with improved general health and well-being, reduced treatment-related complications, decreased cancer recurrence, fewer second primary tumors, and improved survival.[66-73] Data on the effects of smoking cessation specific to PLWH after a cancer diagnosis are lacking.

Recommendations for Cancer Management in PLWH

Special considerations for cancer management in PLWH and recommendations for the management of specific cancers in PLWH are discussed herein. Overall, the NCCN panel recommends that most PLWH who develop cancer should be offered the same cancer therapies as HIV-negative individuals, and modifications to cancer treatment should not be made solely on the basis of HIV status. Inclusion of PLWH in cancer clinical trials should be encouraged whenever feasible.

Cancer Workup in PLWH

Workup for PLWH who have cancer is complicated by the increased incidence of non-malignant lesions that may be mistaken for cancer spread or recurrence.[74,75] For example, HIV viremia and opportunistic infections commonly cause lymphadenopathy in PLWH, which can be seen on F-18 FDG PET/CT.[76,77] Nonmalignant causes of lymphadenopathy are more common in patients with higher viral loads and lower CD4+ T-cell counts.[78] Therefore, patients with cancer and HIV infection should have an infectious disease workup for positive lymph nodes as clinically indicated.

Similarly, an infectious disease workup is recommended as indicated for PLWH with cancer who develop splenic, brain, lung, liver, or gastrointestinal lesions, especially in the presence of a low CD4+ T-cell count and concurrent B symptoms. Opportunistic infections in the lung include mycobacterium tuberculosis (MTB), cytomegalovirus (CMV), and pneumocystis carinii pneumonia (PCP).[79] Furthermore, non-infectious, non-malignant pulmonary manifestations of HIV can be difficult to interpret on imaging studies, including drug reactions and immune activation.[79,80] Brain lesions seen in PLWH may result from opportunistic infections, such as viral encephalitis, aspergillosis,

toxoplasmosis, cryptococcosis, bacterial meningitis, tuberculosis, progressive multifocal leukoencephalopathy, and mycobacterium avium complex (MAC).[81,82] Benign, non-infectious brain lesions can also occur in PLWH (eg, vascular complications, hydrocephalus).[81,82] Bone lesions may occur with MTB infection, bacillary angiomatosis, and use of tenofovir.[83-85] Gastrointestinal lesions commonly occur during infection with CMV, candida, and cryptosporidium.[86] Liver lesions may be caused by multiple organisms including MTB, MAC, and CMV.[87] Lesions of uncertain etiology should be biopsied to confirm cancerous histology.

Drug-Drug Interactions: Systemic Cancer Therapy and ART

DDIs between anticancer therapy and antiretrovirals were first noted with the increased incidence of mucositis in PLWH who had NHL who were treated with both the protease inhibitor saquinavir and the chemotherapy regimen cyclophosphamide/doxorubicin/etoposide.[88] DDIs depend on a variety of factors, including the route of elimination and the effect on CYP450 and other drug transporter or drug-metabolizing enzymes of both of the drugs involved.[49,89] Depending on the mechanism of the interaction, DDIs can result in 1) decreased exposure and reduced efficacy of the anticancer or antiretroviral agent; or 2) increased exposure and increased toxicity of the anticancer or antiretroviral agent. In general, enzyme inhibitors increase the substrate exposure and thus increase toxicity, whereas enzyme inducers decrease the substrate exposure and reduce efficacy. The exception to this rule is for prodrugs (eg, irinotecan, cyclophosphamide) where the metabolite is the active agent. In these cases, the DDIs would be reversed (ie, enzyme inhibitors decrease efficacy; enzyme inducers increase toxicity).

The greatest concern for DDIs is with HIV regimens containing pharmacologic boosters (ie, ritonavir, cobicistat). These drugs inhibit CYP3A, increasing the exposure of protease inhibitors (eg, atazanavir, darunavir, saquinavir) and thus the effectiveness of ART.[90] These boosters may also increase exposure to and toxicity associated with any drug, including anti-cancer agents metabolized by CYP3A. In fact, preclinical studies in mice show that CYP3A inhibitors can alter exposure to erlotinib and docetaxel.[91,92] A phase I/pharmacokinetic study in 19 PLWH with cancer found that those participants receiving ritonavir-based ART experienced greater toxicity at a lower dose of sunitinib than those receiving non-ritonavir-based ART.[93] Furthermore, a retrospective analysis of PLWH treated for Hodgkin lymphoma showed that concomitant ritonavir-based HIV therapy and vinblastine can result in irreversible neurologic toxicity.[94]

Another type of ART that can cause DDIs with cancer therapy is non-nucleoside reverse transcriptase inhibitors, which induce CYP3A. These drugs may thus decrease exposure and efficacy of cancer agents metabolized by CYP3A. A preclinical mouse study showed that a CYP3A inducer decreased erlotinib exposure.[91]

HIV regimens containing integrase inhibitors without pharmacologic boosters are favored in the setting of malignancy, because of their lower potential for DDIs. Small case series have shown that integrase inhibitor-based ART is superior to other ART regimens during cancer therapy.[95,96] In one of these studies, data from 154 PLWH with cancer seen at the University of Texas MD Anderson Cancer Center between 2001 and 2012 were reviewed.[96] Non-nucleoside reverse transcriptase inhibitors and integrase strand-transfer inhibitors had comparable antiviral efficacy. The activity of these two classes was superior to the antiviral activity of protease inhibitors, but the integrase inhibitors were better tolerated during cancer therapy.

ART regimens and cancer therapies that are not involved in the same metabolic pathways can still be problematic to coadminister because of overlapping toxicities. One major concern is for neuropathy, which is associated with many cancer drugs (eg, platinum agents, taxanes, vinca alkaloids) and certain nucleoside reverse transcriptase inhibitors (eg, didanosine, stavudine).[97] Another example is neutropenia, which can be a side effect of boosted protease inhibitors and integrase inhibitors and is a common side effect of many chemotherapy regimens.[98,99] Other overlapping toxicities of cancer therapy and ART can also affect the liver, cardiovascular system, and kidneys.[49,100-102]

Despite the possibility for DDIs, select antiretrovirals can be safely coadministered with chemotherapy. Oncology and HIV clinicians, along with HIV and oncology pharmacists, if available, should review proposed cancer therapy and ART for possible DDIs and overlapping toxicity concerns prior to initiation of therapy. Consultation of the drug package inserts for further information is also recommended. Modification of ART or cancer therapy or increased monitoring may be required. With the continued development of new ART, effective alternatives are often available to patients when the currently used ART is expected to affect the metabolism of or share toxicities with systemic cancer therapies. Consultation with an HIV specialist in choosing or adapting ART regimens is essential.

If a potential DDI exists, the panel lists the following options (in order of preference):

1. Substitution of a different antiretroviral with less DDI potential
2. Selection of an alternative cancer therapy regimen with less DDI potential
3. Temporary discontinuation of ART – but only in consultation with the patient's HIV specialist and only if:
   a. The above options are not advisable, cure for the malignancy is the intent, and the chemotherapy treatment course is of short duration; or
   b. The above options are not advisable, the malignancy has a poor prognosis, and palliation is the goal.

Radiation Therapy in PLWH

Some studies conducted in the pre-ART era showed increased radiation-related toxicity in PLWH, particularly in patients with CD4+ T-cell counts <200 cells/μL.[103-105] This risk may be less applicable to PLWH in the ART era, particularly those with CD4+ T-cell counts >200 cells/μL. In fact, more modern data suggest radiation therapy for certain cancers (eg, anal cancer; see below) is effective and well-tolerated in PLWH. For other cancers, however, data on the safety and efficacy of radiation therapy specific to PLWH are limited (eg, lung cancer).[106]

The data on the use of radiation in PLWH who have anal cancer are particular strong, with >20 clinical studies published.[106] One retrospective cohort study included 175 PLWH and 1009 HIV-negative patients with anal cancer in the ART era.[107] No differences were seen in survival after chemoradiation treatment based on HIV status. In addition, a prospective study of 36 patients with anal cancer that included 14 PLWH found no differences in overall survival or in acute or late toxicities.[108]

In summary, when radiation therapy is indicated in the management of patients with cancer, HIV status alone should not be a criterion for decision-making regarding treatment. The panel recommends that particular attention be paid to limit dose to mucosal membranes, skin, and bone marrow using conformal techniques like intensity-modulated radiation therapy (IMRT) or stereotactic body radiation therapy (SBRT) for PLWH, as deemed appropriate by the treating provider. The panel

also notes that extra caution and monitoring is required with use of concurrent chemoradiation in PLWH. Furthermore, nutritional support, pain control, and other supportive measures should be used to minimize radiation therapy interruptions in this population.

Cancer Surgery in PLWH

Older data from anorectal surgery for benign disease (eg, hemorrhoids, fistulas) indicate that PLWH can experience delayed wound healing, especially if the CD4+ T-cell count is <50/µL.[109] Other reports, however, demonstrate that PLWH who undergo anorectal surgery have uncomplicated wound healing.[110] Furthermore, a study of PLWH who required invasive procedures found that wound infection rates were not associated with HIV status.[111] More recent data demonstrate that clinical outcomes, length of stay, and complications are similar between PLWH and HIV-negative patients for most surgical procedures.[112]

Recent studies have also shown that surgery for common malignancies (eg, anal cancer, prostate cancer, colorectal cancer) in PLWH are safe and effective.[113-118] In particular, ample data suggest that surgical management in PLWH with early-stage anal cancer or recurrent anal cancer is safe and effective.[113-115] For example, a retrospective review of 1725 U.S. patients with anal cancer (18% HIV-positive) who received an abdominoperineal resection (APR) saw no differences in mortality, length of hospital stay, or hospitalization costs based on HIV status.[114] However, postoperative hemorrhage occurred more frequently in the HIV-infected group (5.1% vs. 1.5%; $P = .05$). Liver transplantation for hepatocellular carcinoma in the setting of HIV infection also appears to be feasible. A multicenter study in Italy compared the outcomes of liver transplantation in 30 PLWH and 125 HIV-negative patients with hepatocellular carcinoma.[119] HIV status did not affect overall survival or cancer recurrence rates.

PLWH do not have special needs with respect to surgical precautions or pre- or postoperative laboratory testing. Overall health (eg, organ dysfunction, nutritional state) has been found to be a more reliable predictor of surgical outcome than CD4+ T-cell counts or HIV viral loads in PLWH. Data showing that low CD4+ T-cell counts are associated with poorer prognosis have been inconsistent, and viral suppression has not been conclusively shown to improve surgical outcomes.[120-124]

Overall, the panel recommends that HIV status alone should not be a criterion for decision-making regarding surgical interventions in patients with cancer, regardless of the procedure being considered.

Supportive Care During Cancer Therapy in PLWH

Patients with AIDS often suffer from fatigue, weight loss, pain, anorexia, and anxiety.[125] ART may cause side effects including nausea/vomiting, diarrhea, constipation, cough, dyspnea, insomnia, and depression.[125] Cancer and its treatment can also cause all of these symptoms.

For most supportive care situations related to cancer treatment, PLWH should be managed as per the appropriate NCCN Guidelines for Supportive Care (available at www.NCCN.org), including:

- NCCN Guidelines for Adult Cancer Pain
- NCCN Guidelines for Palliative Care
- NCCN Guidelines for Antiemesis
- NCCN Guidelines for Cancer-Related Fatigue
- NCCN Guidelines for Distress Management

In addition, recommendations for fertility preservation can be found in the NCCN Guidelines for Adolescent and Young Adult Oncology, and vaccination recommendations can be found in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (both available at www.NCCN.org).

The panel notes some special considerations for PLWH who have cancer. For instance, general use of steroids for antiemesis should be limited in PLWH because steroids may increase the risk for opportunistic infections. However, when cancer treatment involves regimens that include agents associated with delayed nausea/vomiting, steroids can be used briefly following chemotherapy in PLWH.

In addition, the risk of infections in PLWH is increased during cancer treatment.[54-58,61] Opportunistic infection prophylaxis thus plays a critical role in the supportive care of PLWH who have cancer (see *Opportunistic Infection Prophylaxis*, above).

Recommendations for Specific Cancers in PLWH

NHL in PLWH

NHL is an AIDS-defining cancer, and the risk of NHL is elevated 7- to 23-fold in PLWH, with the risk being even higher for certain subtypes such as primary CNS lymphoma.[8,9,16,17] In the ART era, the incidence of NHL has declined.[11,17] One study showed that the increased risk of NHL in PLWH compared with the general population declined from 28-fold in 1996 to 1999 to 8-fold in 2009 to 2012.[17] In 2010, NHL accounted for about 21% of cancers diagnosed in PLWH.[13]

For recommendations regarding the management of NHL in PLWH, see the NCCN Guidelines for B-Cell Lymphomas (available at www.NCCN.org).

Kaposi Sarcoma in PLWH

AIDS-related Kaposi sarcoma is also an AIDS-defining cancer. The risk for Kaposi sarcoma in the setting of HIV has been as high as 3640-fold increased over the general population,[8-10,16,126] but this risk has declined in the ART era.[8,11,17,127] Still, estimates indicate that the risk of Kaposi sarcoma in PLWH between the years 2009 and 2012 was elevated approximately 257-fold compared with the general U.S. population,[17] and, in 2010, Kaposi sarcoma accounted for approximately 12% of cancers diagnosed in PLWH.[13]

Recommendations for the management of Kaposi sarcoma in PLWH are presented in the NCCN Guidelines for AIDS-Related Kaposi Sarcoma (available at www.NCCN.org).

Lung Cancer in PLWH

Lung cancer is the most common non-AIDS–defining cancer in PLWH.[9,12] In the year 2010, lung cancer accounted for approximately 11% of cancers diagnosed in PLWH.[13] The risk of lung cancer is about 2 to 5 times higher in PLWH than in HIV-negative individuals.[9,10,17,128] Some data suggest that the incidence of lung cancer in PLWH has been declining since the beginning of the ART era,[8,17] but other studies demonstrate an increase.[12]

Smoking is a well-known risk factor for lung cancer, and smoking prevalence is higher in PLWH than in HIV-negative individuals.[19,22,129] Thus, smoking likely contributes to the increased risk of lung cancer in PLWH. However, immunosuppression also likely plays a role.[3,130,131] Overall, PLWH who smoke and are on ART are 6 to 13 times more likely to die of lung cancer than of AIDS-related causes.[132]

Screening for Lung Cancer in PLWH

Because of the increased risk for the development of lung cancer in PLWH, lung cancer screening has the potential to play an important role in early detection in this population. In the National Lung Screening Trial (NLST), annual low-dose helical chest CT screening in high-risk smokers was associated with a reduction in lung cancer-specific mortality.[133,134] However, data informing the potential role of lung cancer screening in PLWH are limited.[135-137] One study assessed annual CT-

based lung cancer screening (up to 4 scans) in 224 PLWH who were current and former smokers with a ≥20 pack-year history.[135] Screening between 2006 and 2013 identified 1 case of lung cancer in 678 patient-years. Another study assessed a single CT scan to screen for lung cancer in 442 HIV-infected smokers with a ≥20 pack-year history and a CD4+ T-cell nadir count of <350 cells/µl.[136] Lung cancer was diagnosed by the CT scan in 9 patients (2.0%; 95% CI, 0.9–3.8). Longer follow-up of these trials should be informative.

At this time, the panel recommends that screening for lung cancer should be performed in PLWH based on the same criteria used in the general population (see the NCCN Guidelines for Lung Cancer Screening, available at www.NCCN.org).

Workup for Lung Cancer in PLWH

The NCCN panel recommends that all patients with NSCLC should be tested for HIV if not already known to have a documented HIV infection. PLWH should be referred to an HIV specialist if they do not already have HIV care established (see *HIV Management During Cancer Therapy*, above).

Patients with NSCLC and HIV may be more likely to have benign lung nodules (see *Cancer Workup in PLWH*, above). Infectious granuloma or tuberculosis are possible differential diagnoses. An infectious disease workup should be performed for lesions in the lung, and treatment for other possible diagnoses (and potential complications) should be considered before biopsy. For example, if pulmonary Kaposi sarcoma is suspected, biopsies should be performed with bleeding risk in mind. Lung biopsies should be cultured for bacteria, fungi, and mycobacteria acid-fast bacilli (AFB).

Non-malignant causes for lymphadenopathy should be considered in PLWH who have lung cancer. Similarly, workup of brain lesions in patients with NSCLC and advanced HIV-related immunosuppression should include an infectious disease evaluation to rule out infectious processes (eg, toxoplasmosis) and other malignancies such as NHL (also see *Cancer Workup in PLWH*, above).[81,82] Treatment for possible non-malignant diagnoses can be considered before biopsy.

Additional workup for NSCLC in PLWH should be performed as described in the NCCN Guidelines for Non-Small Cell Lung Cancer (available at www.NCCN.org).

Management of Lung Cancer in PLWH

Some studies have shown that outcomes of PLWH and lung cancer are similar to those of HIV-negative patients with lung cancer.[138,139] Other studies, however, have found disparities in receipt of cancer treatment and/or survival.[140,141] For example, a registry-based analysis found that PLWH diagnosed with lung cancer between 1995 and 2009 were less likely to receive cancer treatment and had higher lung cancer-specific mortality.[141] The effect of HIV on lung cancer-specific mortality was partially reduced in those who received cancer treatment. Furthermore, a single-center, retrospective cohort study that compared outcomes following resection in 22 PLWH who have lung cancer with outcomes following resection in 2430 patients with lung cancer and unknown HIV status from 1985 to 2009 showed that the PLWH group had more postoperative pulmonary and infectious complications ($P = .001$ and $P < .001$, respectively), faster disease progression ($P = .061$), and shorter survival ($P = .001$).[142]

Overall, the NCCN panel recommends that PLWH should be treated for NSCLC as per the NCCN Guidelines for Non-Small Cell Lung Cancer (available online at www.NCCN.org). In those guidelines, performance

status is taken into consideration when making treatment decisions in patients with NSCLC. In patients with HIV and NSCLC, poor performance status may result from HIV, lung cancer, or other causes. The panel recommends that the reason for poor performance status should be considered when making treatment decisions. For example, if poor performance status is the result of cancer-related symptoms that may be reversed with cancer therapy, treatment initiation should be strongly considered. Similarly, treatment with ART may improve poor performance status related to HIV. As in other cancers, modifications to cancer therapy should not be made solely on the basis of HIV status.

As for all PLWH who smoke, smoking cessation should be offered to PLWH with lung cancer as indicated (see the NCCN Guidelines for Smoking Cessation, available at www.NCCN.org and see *Smoking Cessation in PLWH Who Have Cancer*, above).

Drug-drug interactions can occur in patients with NSCLC and HIV. When possible, an HIV pharmacist and an oncology pharmacist should be consulted. Also see *Principles of Drug-Drug Interactions* in the algorithm and *Drug-Drug Interactions: Systemic Cancer Therapy and ART*, above.

Anal Cancer in PLWH

Anal cancer in PLWH is often associated with persistent anal HPV infection, which is likely due to immune suppression.[143] Studies have shown that PLWH have an approximately 15- to 35-fold increased likelihood of being diagnosed with anal cancer compared with the general population.[15-17,144] Analysis of the French Hospital Database on HIV also showed a highly elevated risk of anal cancer in PLWH, including in those who were on ART and whose CD4+ T-cell counts were high.[145] In this analysis, the standardized incidence ratios between PLWH and HIV-negative men who have sex with men (MSM) was 109.8 (95% CI, 84.6–140.3). Overall, anal cancer accounts for approximately 10% of cancers diagnosed in PLWH,[13] and the current risk of anal cancer in PLWH is elevated approximately 15- to 19-fold over the general U.S. population.[17,144]

Some evidence suggests that ART may be associated with a decrease in the incidence of high-grade anal intraepithelial neoplasia (AIN) and its progression to anal cancer.[146,147] However, the incidence of anal cancer in PLWH has not decreased much, if at all, over time.[10,17,144,145]

Screening for and Management of Precancerous Anal Lesions in PLWH

PLWH are at higher risk of anal squamous epithelial neoplasia (AIN) compared to HIV-negative patients.[148] High-grade AIN can be a precursor to anal cancer,[149-152] and treatment of high-grade AIN may prevent the development of anal cancer.[153] Therefore, many clinicians routinely screen PLWH for anal dysplasia, even though randomized controlled trials showing that such screening programs are efficacious at reducing anal cancer incidence and mortality are lacking.[154-161] Screening methods include anal cytology, high resolution anoscopy, and annual digital anal exam.

Multiple methods are used to treat anal dysplasia, including topical therapy (fluorouracil, imiquimod), excision, and ablation.[159,162-164] These treatments are safe in PLWH and offer short-term efficacy.[165-167] However, treatment of anal dysplasia in PLWH is associated with a higher risk of recurrence compared to HIV-negative patients.[154,165] In a randomized controlled trial of HIV-positive MSM, electrocautery (ablation) was found to be better than topical therapy in the treatment of anal dysplasia, even though recurrence rates were still high.[168] The subgroup with perianal AIN appeared to respond better to imiquimod than those with intra-anal AIN.

The large, ongoing, randomized phase III ANCHOR trial is comparing topical or ablative treatment with active monitoring in PLWH with high-grade AIN. The primary outcome measure is time to development of anal cancer, and the study is estimated to be completed in the year 2022 (clinicaltrials.gov NCT02135419).

Workup for Anal Cancer in PLWH

The NCCN panel recommends that all patients with anal cancer should be tested for HIV if not already known to have a documented HIV infection. Viral load and CD4+ T-cell counts should be determined in PLWH who have anal cancer. Low CD4+ T-cell counts prior to anal cancer treatment have been shown to be associated with an increased risk for acute hematologic toxicity.[169,170] PLWH with anal cancer should be referred to an HIV specialist if HIV care has not yet been established (see *HIV Management During Cancer Therapy*, above).

Additional workup for anal cancer in PLWH should be performed as described in the NCCN Guidelines for Anal Carcinoma (available at www.NCCN.org). HPV-related disease in PLWH is often multifocal. Therefore, women living with HIV (WLWH) diagnosed with anal cancer should have colposcopic examination by a gynecologist to evaluate for the presence of vulvar, vaginal, or cervical disease.

Management of Anal Cancer in PLWH

Most evidence regarding outcomes in PLWH with anal cancer comes from retrospective comparisons, a few of which found worse outcomes in PLWH.[171,172] Most studies, however, have found outcomes to be similar in PLWH and HIV-negative patients.[107,108,113,114,170,173-175] For example, in a retrospective cohort study of 1184 veterans diagnosed with squamous cell carcinoma of the anus between 1998 and 2004 (15% of whom tested positive for HIV), no differences with respect to receipt of treatment or 2-year survival rates were observed for PLWH compared with HIV-negative patients.[107] Furthermore, a population-based study of almost 2 million patients with cancer, 6459 of whom were infected with HIV, found no increase in cancer-specific mortality for anal cancer in PLWH.[26] Recent phase II studies in anal cancer have included PLWH.[176,177] Although the numbers of PLWH in these trials have been small, the efficacy and safety results appear similar regardless of HIV status.

Based on these data, the NCCN panel recommends that PLWH should be treated for anal cancer as per the NCCN Guidelines for Anal Carcinoma (available online at www.NCCN.org), and that modifications to cancer treatment should not be made solely on the basis of HIV status. Additional considerations for PLWH who have anal cancer are outlined in these guidelines, above, and include normal tissue-sparing radiation techniques, such as IMRT. In addition, non-malignant causes for lymphadenopathy should be considered in PLWH, with referral for an infectious disease workup if suspicious/PET-avid nodes are seen (also see *Cancer Workup in PLWH*, above). Poor performance status in PLWH and anal cancer may be from HIV, cancer, or other causes. The reason for poor performance status should be considered when making treatment decisions. Treatment with ART may improve poor performance status related to HIV.

The phase II AIDS Malignancy Consortium 045 (AMC045) trial evaluated the safety and efficacy of cetuximab with cisplatin/5-FU and radiation in PLWH with anal squamous cell carcinoma. Preliminary results from this trial and a similar trial in immunocompetent patients (ECOG 3205), reported in 2012, were encouraging with acceptable toxicity and 2-year progression-free survival (PFS) rates of 92% (95% CI, 81%–100%) and 80% (95% CI, 61%–90%) in the immunocompetent and PLWH populations, respectively.[178] Longer-term results from E3205 and AMC045 were published in 2017. In a post hoc analysis of E3205,

the 3-year locoregional failure rate was 21% (95% CI, 7%–26%).[179] The toxicities associated with the regimen in ECOG 3205 (immunocompetent patients) were substantial, with grade-4 toxicity occurring in 32% of the study population and 3 treatment-associated deaths (5%). In AMC045 (PLWH), the 3-year locoregional failure rate was 20% (95% CI, 10%–37%) by Kaplan-Meier estimate.[180] Grade 4 toxicity and treatment-associated rates were similar to that seen in E3205, at 26% and 4%, respectively. The addition of cetuximab to standard chemoradiation is therefore not recommended in PLWH or HIV-negative patients with anal cancer at this time.

Surveillance and Survivorship in PLWH Treated for Anal Cancer
Surveillance following treatment of anal cancer in PLWH should be performed as described in the NCCN Guidelines for Anal Carcinoma (available at www.NCCN.org), except with more frequent anoscopy for PLWH (every 3–6 months for 3 years). A small retrospective study of 93 patients with anal cancer found that recurrence rates were not affected by HIV status.[175] However, a nationwide retrospective cohort study of 142 HIV-positive veterans with stage I-III anal cancer found that those with lower post-treatment CD4+ T-cell counts had an increased risk for cancer recurrence.[169]

Regular anal cytology can also be considered for the detection of anal dysplasia in survivors of anal cancer living with HIV, although data informing its value in detection of recurrent anal cancer are lacking. If high-grade AIN is identified, then high-resolution anoscopy should be performed if available.

PLWH diagnosed with anal cancer should be counseled on infertility risks and referred for fertility counseling as appropriate. PLWH who engage in receptive anal intercourse should discuss post-treatment pelvic physical therapy and anal dilators with an appropriate health care provider.

Hodgkin Lymphoma in PLWH
PLWH are 5 to 14 times more likely to be diagnosed with Hodgkin lymphoma than uninfected individuals.[9,10,16,17] The incidence of Hodgkin lymphoma in PLWH increased through 2002,[8,9] but studies that assessed the trends of incidence from 1996 through 2010 or 2012 found it to be decreasing.[11,17] Evidence regarding the role of immunosuppression in the development of lymphoma are conflicting.[3,16,181,182]

Hodgkin lymphoma is classified into nodular-lymphocyte-predominant Hodgkin lymphoma and classical Hodgkin lymphoma. Only classical Hodgkin lymphoma has been linked to HIV infection. Classical Hodgkin lymphoma is further subclassified as nodular sclerosis, lymphocyte-rich, mixed cellularity, and lymphocyte-depleted.[183] PLWH who develop Hodgkin lymphoma typically present with mixed cellularity or, less commonly, nodular sclerosis or lymphocyte-depleted histologies of classical disease.[184-188]

In contrast to patients without HIV, nearly 90% of cases of Hodgkin lymphoma in PLWH are EBV-associated.[183,189] PLWH often present with more advanced disease, including extranodal disease and bone marrow involvement.[184,185,189,190] Bone-marrow-only presentations sometimes occur,[191] whereas central nervous system involvement is rare.[192] PLWH with Hodgkin lymphoma have also been shown to present with more aggressive disease and worse performance status. However, they have similar response rates and short-term survival as their HIV-negative counterparts when they receive standard cancer treatment.[185,193,194]

Workup for Hodgkin Lymphoma in PLWH

Approximately 4% of 22,355 patients with Hodgkin lymphoma in the SEER database from 2000 to 2010 were infected with HIV at the time of diagnosis.[195] The NCCN panel recommends that all patients with Hodgkin lymphoma be tested for HIV if not already known to have a documented HIV infection. PLWH should be referred to an HIV specialist (see *HIV Management During Cancer Therapy*, above). Use of effective ART has been associated with increased cancer-specific survival and overall survival in PLWH with Hodgkin lymphoma.[46,196]

Diagnosis and staging workup for Hodgkin lymphoma in PLWH should be performed as described in the NCCN Guidelines for Hodgkin Lymphoma (available at www.NCCN.org). However, it should be noted that both opportunistic infection and HIV itself can lead to FDG-avid lymphadenopathy and organ lesions (see *Cancer Workup in PLWH*, above). Non-malignant causes for lymphadenopathy and organ lesions should be considered, with referral for an infectious disease evaluation as indicated.

Management of Hodgkin Lymphoma in PLWH

Cancer mortality can be similar between PLWH and HIV-negative patients with Hodgkin lymphoma.[26,28,185] However, disparities in treatment received results in increased mortality in PLWH whose cancer is not treated.[32,33,197] In a population-based study of 2090 PLWH, unadjusted 5-year overall survival was decreased in PLWH (66% vs. 80% for HIV-negative patients), whereas the difference disappeared in those who received chemotherapy.[197] One large database study, however, found that overall survival was decreased in PLWH who have Hodgkin lymphoma (HR, 1.47; 95% CI, 1.25–1.74), even though the population was matched by treatment characteristics.[198] Cancer-specific survival was not assessed in this study.

Treatment with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) has been shown to be safe and effective in PLWH who have Hodgkin lymphoma, with oncologic outcomes similar to HIV-negative patients.[185,187,190,194] Good results have also been seen with Stanford V (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone).[199] BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) is also active but associated with more toxicity and treatment-related mortality than Stanford V and ABVD.[200,201]

When using these regimens, ART with overlapping toxicities or direct interactions with chemotherapy should be avoided (see *Drug-Drug Interactions: Systemic Cancer Therapy and ART*, above). Drug-drug interactions are common in patients with Hodgkin lymphoma and HIV. For example, a clinically significant interaction between vinblastine and antivirals ritonavir and lopinavir has been associated with neurotoxicity.[202] Similarly, vinblastine and ritonavir may be associated with hematologic toxicity.[202] When possible, an HIV pharmacist and an oncology pharmacist should be consulted regarding chemotherapy in PLWH who have Hodgkin lymphoma. Also see Principles of Drug-Drug Interactions in these guidelines and *Drug-Drug Interactions: Systemic Cancer Therapy and ART*, above.

Autologous stem cell transplantation also appears to be safe and effective in PLWH who have recurrent/relapsed Hodgkin lymphoma. The AIDS Malignancy Consortium study 020 found that dose-reduced high-dose busulfan, cyclophosphamide, and autologous stem cell transplantation were effective and well tolerated in a selected group of PLWH with Hodgkin lymphoma.[203] In addition, a retrospective matched cohort analysis showed that relapse, overall survival, and PFS were similar between PLWH and HIV-negative patients with Hodgkin lymphoma who received autologous stem cell transplantation.[186] A

retrospective, multicenter, registry-based study in Europe also found autologous stem cell transplantation to be a beneficial option in this population.[204] Most recently, autologous transplant was established as a standard of care for PLWH who have Hodgkin lymphoma in a study run jointly by the AMC and Blood and Marrow Transplant Clinical Trials Network that included 15 patients with Hodgkin lymphoma and 25 patients with diffuse large B-cell lymphoma.[205]

Limited experience with PET/CT-guided therapy, based on interim or final post-treatment restaging in HIV-associated Hodgkin lymphoma, indicates that it is feasible, despite potential confounding factors (ie, non-malignant causes for PET-avid regions).[206,207]

Based on these data, the NCCN panel recommends that PLWH should be treated for Hodgkin lymphoma as per the NCCN Guidelines for Hodgkin Lymphoma (available online at www.NCCN.org), and that modifications to cancer treatment should not be made solely on the basis of HIV status. Poor performance status in PLWH who have Hodgkin lymphoma may be from HIV, cancer, or other causes. The reason for poor performance status should be considered when making treatment decisions. Treatment with ART may improve poor performance status related to HIV. ABVD is less toxic than Stanford V or BEACOPP and therefore may be preferred in patients with HIV. Extrapolating from randomized data in the general Hodgkin lymphoma population, bleomycin can be discontinued after 2 cycles in PLWH who have advanced-stage Hodgkin lymphoma and a PET/CT scan showing response.[208] It is also reasonable to discontinue bleomycin in patients who have symptoms of pulmonary compromise or fall in diffusing capacity of the lungs (DLCO). Whereas the routine use of growth factors is not recommended during ABVD treatment because of concerns about possible adverse interactions/lung toxicity with bleomycin in the NCCN Guidelines for Hodgkin Lymphoma (available at www.NCCN.org), growth factors may be required in PLWH especially if CD4+ T-cell counts are low and in the setting of prolonged severe neutropenia or neutropenic fever. Similarly, whereas dose reduction is not recommended for neutropenia with ABVD in the NCCN Guidelines for Hodgkin Lymphoma (available at www.NCCN.org), dose reductions may be appropriate in PLWH. Prophylactic antibiotics and dose reduction in early cycles can be considered in patients with low CD4+ T-cell counts.

B symptoms, which include fever, drenching night sweats, and/or weight loss of >10% body weight, are common in PLWH who have Hodgkin lymphoma.[209] B symptoms may also indicate a concurrent opportunistic infection if CD4 counts are low.

Cervical Cancer in PLWH

Persistent infection with high-risk HPV, the etiologic agent of cervical cancer, is more likely in women living with HIV (WLWH) than HIV-negative women,[210-212] and the incidence of cervical cancer in WLWH is about 3 to 5 times higher than that in HIV-negative women.[8,9,16,213,214] Some evidence suggests that ART lowers the risk of persistent HPV infection and the prevalence of cervical intraepithelial neoplasia (CIN), precursors of cervical cancer.[215-218] However, evidence that the incidence of cervical cancer in WLWH has decreased significantly in the modern ART era is lacking.[8,10,12,17,127,219] In the year 2010, cervical cancer accounted for about 1% of cancers diagnosed in the HIV population.[13] This number is likely so low only because the U.S. HIV population is mostly male. Cervical cancer is a major health problem in developing countries struggling with high HIV and HPV prevalence.

Management of Precancerous Cervical Lesions in PLWH

Treatment options for CIN include cryotherapy, loop electrosurgical excision procedure, and cold knife conization.[220] These options are

generally safe and effective for WLWH.[221-226] However, endocervical extension is more frequent among WLWH.[227] Therefore, loop excision is less effective and recurrence rates are higher in WLWH than in HIV-negative patients.[227-230]

Workup for Cervical Cancer in PLWH

The NCCN panel recommends all patients with cervical cancer be tested for HIV if not already known to have a documented HIV infection. As in all cancers, PLWH should be referred to an HIV specialist (see *HIV Management During Cancer Therapy*, above).

Additional workup for cervical cancer in WLWH should be performed as described in the NCCN Guidelines for Cervical Cancer (available at www.NCCN.org). In addition, WLWH with CIN or invasive cervical cancer should also be evaluated for field effects of HPV oncogenesis, namely anal and vulvar cancer.

Management of Cervical Cancer in PLWH

A systematic review published in 2015 identified only 8 studies (3 prospective and 5 retrospective) addressing the management of cervical cancer in PLWH.[231] Hematopoietic grade 1 and 2 toxicity rates were higher in PLWH than in HIV-negative patients. Grade 3 and 4 events that differed by HIV status were anemia (4% in WLWH vs. 2%) and gastrointestinal reactions (5% in WLWH vs. 2%). This systematic review also found that WLWH who started ART early were more likely to complete cancer treatment. Additional data following the 2015 systematic review also suggest that WLWH who have cervical cancer are more likely to experience hematologic toxicity and less likely to complete a full course of chemotherapy than HIV-negative patients.[232]

A prospective cohort study of 348 patients with cervical cancer in Botswana compared outcomes between the 66% who were infected with HIV and those who were not.[31] The WLWH had median CD4+ T-cell count of 397 cells/μL (interquartile range, 264–555). Following an adjusted analysis, HIV infection was significantly associated with an increased risk of death among all women (HR, 1.95; 95% CI, 1.20–3.17) and among the subset of those who received guideline-concordant curative therapy (HR, 2.63; 95% CI, 1.05–6.55). These results suggest that HIV infection has an adverse effect on cervical cancer survival. That this effect was greater for women with a lower CD4+ T-cell count (P = .036) suggests that immune suppression plays a significant role. Of note, the study was conducted in a resource-limited environment, and survival of both PLWH and HIV-negative patients with cervical cancer was lower than would be expected in the United States.

Based on these limited data, the NCCN panel recommends that WLWH be treated for cervical cancer as per the NCCN Guidelines for Cervical Cancer (available online at www.NCCN.org), and that modifications to cancer treatment should not be made solely on the basis of HIV status. The NCCN panel also notes that non-malignant causes for lymphadenopathy should be considered in PLWH who have cervical cancer, with referral for an infectious disease workup if suspicious/PET-avid nodes are seen (also see *Cancer Workup in PLWH*, above). Poor performance status in WLWH who have cervical cancer may be from HIV, cancer, or other causes. The reason for poor performance status should be considered when making treatment decisions. Treatment with ART may improve poor performance status related to HIV.

Summary

Cancer treatment is generally as safe and effective for PLWH as it is for patients who are HIV-negative, and the NCCN panel recommends that most PLWH who develop cancer should be offered the same cancer therapies as HIV-negative individuals. Modifications to cancer treatment

should not be made solely on the basis of HIV status. However, PLWH who have cancer require special considerations, including the possible need to modify ART or cancer therapy based on the potential for DDIs, the need for an infectious disease workup for possible non-malignant imaging findings, and the need for more intensive monitoring for toxicities. Furthermore, performance status is taken into consideration when making treatment decisions in patients with cancer. In patients with HIV and cancer, poor performance status may result from HIV, cancer, or other causes. The panel recommends that the reason for poor performance status should be considered when making treatment decisions and notes that treatment with ART may improve poor performance status related to HIV. The panel strongly recommends that an HIV specialist be involved in comanagement of PLWH during cancer treatment.

Unfortunately, data on the treatment of PLWH who have cancer are relatively limited. Increased accrual of this population to clinical trials should be a goal of the oncology community. Based on recommendations from the ASCO and Friends of Cancer Research HIV Working Group, PLWH should not be excluded from most cancer clinical trials if they meet specified criteria.[233] Clinicians who work with PLWH who have cancer should encourage participation in clinical trials (see www.clinicaltrials.gov).

As more evidence becomes available, the panel will update these guidelines accordingly.

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