National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cancer in People with HIV

Version 2.2024 — April 4, 2024

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Discussion

*Erin Reid, MD/Co-chair ‡
UC San Diego Moores Cancer Center

*Gita Suneja, MD/Co-chair §
Huntsman Cancer Institute
at the University of Utah

Borislav Alexiev, MD ≠
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Richard F. Ambinder, MD, PhD †
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Kevin Ard, MD, MPH Φ Þ
Mass General Cancer Center

Robert Baiocchi, MD, PhD †
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Thomas Campbell, MD Φ
University of Colorado Cancer Center

Evie Carchman, MD ¶
University of Wisconsin Carbone Cancer Center

Mark Dickson, MD †
Memorial Sloan Kettering Cancer Center

Gregory Eschenauer, PharmD Σ Φ
University of Michigan Rogel Cancer Center

Gaurav Goyal, MD † ‡ Þ
O'Neal Comprehensive Cancer Center at UAB

Neel K. Gupta, MD ‡
Stanford Cancer Institute

David H. Henry, MD ‡
Abramson Cancer Center
at the University of Pennsylvania

Amy Jones, MD †
UT Southwestern Simmons
Comprehensive Cancer Center

Stephen Kimani, MD, MSc † Þ
Huntsman Cancer Institute
at the University of Utah

Ann Klopp, MD, PhD §
The University of Texas
MD Anderson Cancer Center

Mark Korpics, MD §
The UChicago Medicine Comprehensive
Cancer Center

Ann S. LaCasce, MD, MMSc †
Dana-Farber/Brigham and
Women's Cancer Center

Chi Lin, MD, PhD §
Fred & Pamela Buffett Cancer Center

Toby Maurer, MD ϖ
Indiana University Melvin and Bren Simon
Comprehensive Cancer Center

Manoj P. Menon, MD, MPH †
Fred Hutchinson Cancer Center

David Morgan, MD ‡ ξ
Vanderbilt-Ingram Cancer Center

Nitya Nathwani, MD ‡
City of Hope National Medical Center

David Palm, MS ¥
AIDS Clinical Trials Group (ACTG)

Gyorgy Paragh, MD, PhD ϖ
Roswell Park Comprehensive
Cancer Center

Henry S. Park, MD, MPH §
Yale Cancer Center/Smilow Cancer Hospital

Lee Ratner, MD, PhD † Þ
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Stacey Rizza, MD Φ
Mayo Clinic Comprehensive Cancer Center

Julian Sanchez, MD ¶
Moffitt Cancer Center

John Schorge, MD Ω
St. Jude Children's Research Hospital/The
University of Tennessee Health Science Center

John Timmerman, MD †
UCLA Jonsson Comprehensive Cancer Center

Chia-Ching J. Wang, MD † ‡
UCSF Helen Diller Family
Comprehensive Cancer Center

NCCN
Deborah Freedman-Cass, PhD
Jamie Nguyen, PharmD
Ryan Schonfeld, BA

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ξ Bone marrow transplantation
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* Discussion Writing Committee Member

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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.

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

See NCCN Categories of Evidence and Consensus.

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Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 2.2024 of the NCCN Guidelines for Cancer in People with HIV from Version 1.2024 include:

HIV-B 1 of 2

- Principles of Systemic Therapy and Drug-Drug Interactions
  - DDIs
    - ◊ Bullet 5, sub-bullet 2 revised: The greatest concern for DDIs is with *ART* ~~HIV~~ regimens containing pharmacologic boosters (ie, ritonavir, cobicistat) and protease inhibitors. These drugs inhibit CYP3A4 and thus may significantly interact with agents metabolized by that pathway.

HIV-B 2 of 2

- Principles of Systemic Therapy and Drug-Drug Interactions
  - DDIs
    - ◊ Bullet 2 added: Drugs used to prevent and/or treat opportunistic infections in PWH may also interact with cancer therapies. Some examples of concern include rifamycins (via induction of hepatic metabolism), clarithromycin (via inhibition of CYP3A4), azole antifungals (via inhibition of various hepatic metabolic processes), and trimethoprim/sulfamethoxazole treatment with methotrexate (via inhibition of methotrexate renal excretion and compound of risk of bone marrow suppression). See Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/significant-drug-interactions?view=full) for more information.
  - Table and associated footnotes removed: Systemic Cancer Therapy-ART Interactions by ART Drug Class

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Updates in Version 1.2024 of the NCCN Guidelines for Cancer in People with HIV from Version 2.2023 include:

INTRO-1

- Introduction
  - Bullet 1 revised: People with human immunodeficiency virus (HIV) (PWH) and AIDS have a higher incidence of many common cancers compared with the general population. AIDS-defining cancers include aggressive non-Hodgkin lymphoma (NHL), 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*; however, the incidence of non-AIDS defining cancers has increased because of longer life expectancies due to antiretroviral therapy (ART), accelerated aging as a consequence of HIV, a higher likelihood of co-infection with oncogenic infections, and a higher prevalence of carcinogen exposure.* ~~Aging due to longer life expectancy with antiretroviral therapy (ART), co-infection with oncogenic infections, and a higher prevalence of carcinogen exposure (eg, tobacco, alcohol) have led to increased incidence of many non–AIDS-defining cancers.~~

HIV-1

- Cervical Cancer in PWH
  - Bullet 4 revised: Non-malignant causes for lymphadenopathy should be considered in PWH. ~~Biopsy of suspicious/PET-avid nodes should be more strongly considered in PWH and cervical cancer.~~ *Suspicious PET-avid lymphadenopathy should be biopsied to differentiate between nodal metastasis or infectious etiology (consult with HIV specialist). If negative for cancer, refer for an infectious disease workup.*

HIV-2

- Anal Cancer in PWH
  - Bullet 4 revised: Non-malignant causes for lymphadenopathy should be considered in PWH. Suspicious PET-avid lymphadenopathy should be biopsied *to differentiate between* ~~to rule out~~ nodal metastasis ~~of anal cancer~~ or infectious etiology (consult with HIV specialist). If negative for cancer, refer for an infectious disease workup.

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Cancer in People with HIV from Version 2.2023 include:

HIV-3 (continued)
- Non-Small Cell Lung Cancer in PWH
  - Bullet 7 revised: Non-malignant causes for lymphadenopathy should be considered in PWH. *Suspicious PET-avid lymphadenopathy should be biopsied to differentiate between nodal metastasis or infectious etiology (consult with HIV specialist). If negative for cancer, refer for an infectious disease workup.*
  - Bullet 8 revised: Workup of brain lesions in patients with NSCLC and advanced HIV-related immunosuppression should include *consideration of consultation with HIV specialist and* an evaluation to rule out infectious processes (eg, toxoplasmosis) or other malignancies such as NHL. *Consideration of relative risks based on viral load and CD4+ T-cell count may further inform these assessments.*
  - Bullet 11 revised: Evolving data suggest that immune checkpoint inhibitors (ICI) are generally safe and effective in PWH*, with the following considerations:*
  - Bullet 11, sub-bullet 1 revised: In persons with Kaposi sarcoma-associated herpesvirus (KSHV) infection, there may be increased risk of KSHV–associated inflammatory syndromes such as multicentric Castleman disease (MCD) or KSHV–associated inflammatory cytokine syndrome (KICS) *when ICIs are used*. If *the patient has a history of KSHV-associated diseases* ~~KSHV-positive~~, consider more frequent monitoring of signs and symptoms of KICS *or MCD*. (Also for bullet 9, sub-bullet 1 on HIV-4)
  - Bullet 11, sub-bullet 2 added: The use of ICIs has been linked to tuberculosis (TB) reactivation. Screening for latent TB infection can be considered before administering an ICI so that the patient can be monitored for TB symptoms and treatment of mycobacterial infection can be expedited. (Also for bullet 9, sub-bullet 2 on HIV-4)
- Footnotes (all also for HIV-4)
  - Footnote e added: Polizzotto MN, et al. Clin Infect Dis 2016;62:730-738.
  - Footnote f added: Uldrick TS, et al. JAMA Oncol 2019;5:1332-1339.
  - Footnote g added: Fujita K, et al. Open Forum Infect Dis 2020;7:ofaa067.
  - Footnote h added: Bae S, et al. J Immunother Cancer 2021;9:e002960.
  - Footnote i added: Zaemes J, et al. Eur J Cancer 2020;132:168-175.

HIV-A 1 of 2
- Principles of HIV Management While Undergoing Cancer Therapy
  - Bullet 1, sub-bullet 5 revised: ~~However,~~ ART interruptions should ~~generally~~ be avoided ~~unless alternate ART regimens are not available~~ because of the risk of immunologic compromise, opportunistic infection, and death. Continuation of ART might result in better tolerance of cancer treatment, higher response rates, and improved survival. *ART should not be discontinued unless in consultation with an HIV specialist.*

HIV-B 1 of 3
- Principles of Systemic Therapy and Drug-Drug Interactions
  - Section significantly revised.

HIV-B 3 of 6 through HIV-B 5 of 6
- Principles of Systemic Therapy and Drug-Drug Interactions
  - ◊ Drug Interactions with Common ART Regimens removed.

HIV-B 3 of 3
- Principles of Systemic Therapy and Drug-Drug Interactions Footnotes
  - Footnote removed: Calcium and iron-containing supplements can be administered with ART including dolutegravir (DTG) or bictegravir (BIC) if given with a meal.

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Cancer in People with HIV from Version 2.2023 include:

HIV-C
- Principles of Radiation Therapy
  - Bullet 1 revised: HIV status alone should not be a criterion for decision-making regarding radiation therapy (RT) *indications or dose*. RT should be offered as part of the cancer management approach when indicated.
  - Bullet 2 added: Dose fractionation and treatment volumes are recommended as per NCCN Clinical Practice Guidelines by disease site.
  - Bullet 5 revised: ~~Extra caution and monitoring is~~ *Additional clinical monitoring may be* required with concurrent chemoradiotherapy.
  - Bullet 6 revised: Particular attention should be paid to limit dose to the following structures using conformal techniques like IMRT*, proton therapy, brachytherapy,* or stereotactic body RT (SBRT) when deemed appropriate by the treating provider.
  - Bullet removed: ~~Older studies showed increased RT-related toxicity, particularly in patients with advanced immunosuppression. This risk may be less applicable to patients treated with contemporary ART and modern RT techniques.~~

HIV-E 1 of 2
- Principles of Supportive Care
  - Bullet 2 revised: 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 ~~and/or infectious disease~~ specialist.
  - Bullet 4 revised: PWH have 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 *infections*, ~~and~~ cytomegalovirus (CMV)*, and TB*, is appropriate; early consultation with an HIV specialist is appropriate. *See Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.*

HIV-E 2 of 2
- Principles of Supportive Care
  - Required/Strongly Recommended
    - ◊ Bullet 1, sub-bullet revised: 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 PWH. Pre-existing neutropenia and/or low CD4+ T-cell counts *(<200 cells/µL)*...
    - ◊ Bullet 4, sub-sub-bullet 1 revised: ~~Avoid~~ *Use caution when administering* trimethoprim-sulfamethoxazole (TMP/SMX) while patient is on methotrexate
    - ◊ Bullet 4, sub-sub-bullet 2 revised: G6PD deficiency screening *should be performed prior to initiation of dapsone* ~~is necessary if the patient is Black, Mediterranean, Indian, or Southeast Asian~~
    - ◊ Bullet 4, sub-bullet removed: Eg, Trimethoprim-sulfamethoxazole (TMP/SMX) 800 mg/160 mg (double-strength) 1 double-strength tablet PO three times a week OR dapsone 100 mg PO daily
- Footnotes
  - Footnote removed: Thompson MA, et al. Clin Infect Dis 2021;73:e3572-e3605.

HIV-F
- Principles of Imaging
  - Bullet 3 revised: ~~An infectious disease workup~~ *Consultation with an HIV specialist and an evaluation to rule out infectious processes (eg, toxoplasmosis) or additional malignancies* should be considered as clinically appropriate for PWH 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.

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INTRODUCTION

- **People with human immunodeficiency virus (HIV) (PWH) and AIDS have a higher incidence of many common cancers compared with the general population. AIDS-defining cancers include aggressive non-Hodgkin lymphoma (NHL), 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; however, the incidence of non-AIDS defining cancers has increased because of longer life expectancies due to antiretroviral therapy (ART), accelerated aging as a consequence of HIV, a higher likelihood of co-infection with oncogenic infections, and a higher prevalence of carcinogen exposure.**
- **Cancer in PWH should be co-managed by an oncologist, and HIV specialist, and PWH should receive cancer treatment as per standard guidelines. Although modifications to ART may be needed, HIV therapy should be continued during cancer therapy. Multidisciplinary decision-making, involving HIV specialists, is critical.**

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

- **Cervical cancer** → **Cervical Cancer in PWH (HIV-1)**
- **Kaposi sarcoma** → **See NCCN Guidelines for Kaposi Sarcoma**
- **Primary CNS lymphoma** → **See NCCN Guidelines for Central Nervous System Cancers**
- **Aggressive NHL[g]** → **See NCCN Guidelines for B-Cell Lymphomas**

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

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

[a] Principles of HIV Management While Undergoing Cancer Therapy (HIV-A).
[b] Principles of Systemic Therapy and Drug-Drug Interactions (HIV-B).
[c] Principles of Radiation Therapy (HIV-C).
[d] Principles of Surgery (HIV-D).
[e] Principles of Supportive Care (HIV-E).
[f] Principles of Imaging (HIV-F).
[g] Burkitt lymphoma; diffuse large B-cell lymphoma (DLBCL); Kaposi sarcoma associated herpesvirus (KSHV)-positive DLBCL, not otherwise specified (NOS); primary effusion lymphoma; and plasmablastic lymphoma.

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.

Cervical Cancer in PWH

- **The risk of cervical cancer is elevated approximately 3- to 5-fold in PWH.**
- **Persistent infection with high-risk human papillomavirus (HPV) leads to the development of cervical cancer.**
- **Premalignant cervical lesions are common in PWH. Treatment of these lesions is generally safe and effective regardless of HIV status. However, endocervical extension is more frequent among PWH. Therefore, loop excision is less effective, with higher recurrence rates in PWH than in patients without HIV.**
- **Non-malignant causes for lymphadenopathy should be considered in PWH. Suspicious PET-avid lymphadenopathy should be biopsied to differentiate between nodal metastasis or infectious etiology (consult with HIV specialist). If negative for cancer, refer for an infectious disease workup.**
- **PWH with cervical intraepithelial neoplasia (CIN) or invasive cervical cancer should also be evaluated for field effect of HPV oncogenesis, including anal cancer (See NCCN Guidelines for Anal Carcinoma) or vulvar cancer (See NCCN Guidelines for Vulvar Cancer (Squamous Cell Carcinoma)).**
- **PWH who have cervical cancer should be referred to an HIV specialist to ensure they are on an effective ART regimen.**
- **PWH 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 PWH 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. ART is recommended for all PWH and may improve performance status.**
- **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).**
- **For recommendations regarding HPV vaccination, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.**

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Anal Dysplasia and Anal Cancer Screening in PWH

- PWH are at higher risk of premalignant anal epithelial changes compared to patients who are HIV-negative. PWH diagnosed with vulvar, vaginal, or cervical disease should have screening for anal cancer.
- Few national recommendations for anal cancer screening in PWH exist. However, several organizations, including the HIV Medicine Association of the Infectious Diseases Society of America, International Anal Neoplasia Society, and the Association of Coloproctology of Great Britain and Ireland, recommend a routine anal Pap test in PWH who are at increased risk for anal cancer.[a] Many HIV specialists screen PWH for HPV and dysplasia by anal cytology, high-resolution anoscopy, and annual digital anal examination, although the frequency and method of surveillance vary.
- If anal squamous intraepithelial lesions (ie, high-grade squamous intraepithelial lesion [HSIL], low-grade squamous intraepithelial lesion [LSIL], atypical squamous cells of undetermined significance [ASCUS]) are identified by cytology, then high-resolution anoscopy should be performed where available.[c]
- There are multiple methods by which anal dysplasia is treated: topical therapy (ie, fluorouracil, imiquimod), excision, and ablation. These treatments are safe in PWH and are associated with a decreased risk of progression to cancer.[c]
- However, treatment of anal dysplasia in PWH is associated with a higher risk of recurrence in PWH compared to patients who are HIV-negative.
- In a randomized controlled trial of PWH who engage in receptive anal intercourse, electrocautery (ablation) was found to be better than topical therapy in the treatment of anal dysplasia, although recurrence rates were still high.[b]
- For recommendations regarding HPV vaccination, see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

Anal Cancer in PWH

- PWH have an approximately 25- to 35-fold increased likelihood of being diagnosed with anal cancer compared with individuals who are HIV-negative, and anal cancer accounts for approximately 10% of cancers diagnosed in PWH.
- Anal cancer in PWH is often associated with persistent anal HPV infection.
- HPV-related disease in PWH is often multifocal. Therefore, PWH diagnosed with anal cancer should have colposcopic examination by a gynecologist for the presence of vulvar, vaginal, or cervical disease.

Anal Cancer in PWH (continued)

- Non-malignant causes for lymphadenopathy should be considered in PWH. Suspicious PET-avid lymphadenopathy should be biopsied to differentiate between nodal metastasis or infectious etiology (consult with HIV specialist). If negative for cancer, refer for an infectious disease workup.
- Anal cancer in PWH should be co-managed by an oncologist and HIV specialist, and PWH should be treated for anal cancer as per the NCCN Guidelines for Anal Carcinoma.
  - Modifications to cancer treatment should not be made solely based on HIV status.
    - ◊ Surgical excision for appropriately selected early-stage T1 perianal cancers is effective and safe in PWH. 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 PWH, radiotherapy should be delivered via intensity-modulated radiation therapy (IMRT) technique to spare as much normal tissue as possible without compromising target coverage.
- Post-treatment surveillance of PWH should be as per the NCCN Guidelines for Anal Carcinoma.
- Anal cytology can be considered for the detection of anal dysplasia in survivors of anal cancer 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 PWH and anal cancer may be from HIV, cancer, or other causes. The reason for poor performance status should be considered when making treatment decisions. ART is recommended for all PWH and may improve performance status.
- 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).

[a] Thompson MA, et al. Clin Infect Dis 2021;73:e3572-e3605.
[b] Richel O, et al. Lancet Oncol 2013;14:346-353.
[c] Palefsky JM, et al. N Engl J Med 2022;386:2273-2282.

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Non-Small Cell Lung Cancer in PWH

- The risk of lung cancer is 2 to 5 times higher in PWH than in individuals who are HIV-negative, 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 PWH as per the NCCN Guidelines for Lung Cancer Screening. However, it should be noted that PWH may develop lung cancer at a younger age compared to the general population.[d] Investigations are ongoing to determine if modifications to screening guidelines for PWH are warranted.
- Smoking cessation should be discussed (See NCCN Guidelines for Smoking Cessation).
- NSCLC in PWH should be co-managed by an oncologist and HIV specialist, and PWH 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 based on HIV status.
- PWH may be more likely to have benign lung nodules than patients without HIV. 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 and stained for bacteria, fungi, and mycobacteria.
- Non-malignant causes for lymphadenopathy should be considered in PWH. Suspicious PET-avid lymphadenopathy should be biopsied to differentiate between nodal metastasis or infectious etiology (consult with HIV specialist). If negative for cancer, refer for an infectious disease workup.
- Workup of brain lesions in patients with NSCLC and advanced HIV-related immunosuppression should include consideration of consultation with HIV specialist and an evaluation to rule out infectious processes (eg, toxoplasmosis) or other malignancies such as NHL. Consideration of relative risks based on viral load and CD4+ T-cell count may further inform these assessments.
- Poor performance status in PWH and NSCLC may be from HIV, cancer, or other causes. The reason for poor performance status should be considered when making treatment decisions. ART is recommended for all PWH and may improve performance status.
- 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).
- Evolving data suggest that immune checkpoint inhibitors (ICI) are generally safe and effective in PWH, with the following considerations:
  - In persons with Kaposi sarcoma-associated herpesvirus (KSHV) infection, there may be increased risk of KSHV–associated inflammatory syndromes such as multicentric Castleman disease (MCD) or KSHV–associated inflammatory cytokine syndrome (KICS) when ICIs are used. If the patient has a history of KSHV-associated diseases, consider more frequent monitoring of signs and symptoms of KICS or MCD.[e,f]
    - ◊ Unexplained fevers should prompt workup of MCD and KICS with C-reactive protein, KSHV serum viral load, serum protein electrophoresis (SPEP), interleukin (IL)-6, and IL-10. The diagnosis of KICS requires excisional biopsy of lymphadenopathy to exclude MCD.
  - The use of ICIs has been linked to tuberculosis (TB) reactivation.[g,h,i] Screening for latent TB infection can be considered before administering an ICI so that the patient can be monitored for TB symptoms and treatment of mycobacterial infection can be expedited.

[d] Sigel K, et al. Curr HIV/AIDS Rep 2011;8:142-152.
[e] Polizzotto MN, et al. Clin Infect Dis 2016;62:730-738.
[f] Uldrick TS, et al. JAMA Oncol 2019;5:1332-1339.
[g] Fujita K, et al. Open Forum Infect Dis 2020;7:ofaa067.
[h] Bae S, et al. J Immunother Cancer 2021;9:e002960.
[i] Zaemes J, et al. Eur J Cancer 2020;132:168-175.

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Hodgkin Lymphoma in PWH

- PWH are 5 to 14 times more likely to be diagnosed with HL than individuals who are HIV-negative, and HL accounts for approximately 4% of cancer diagnosed in the PWH population.
- Compared with people without HIV, PWH more commonly present with mixed cellularity or lymphocyte-depleted histologies of HL. Ninety percent of cases of HL in PWH are Epstein-Barr virus (EBV)-associated. PWH 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 NHL in PWH, central nervous system (CNS) 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 PWH. ABVD is less toxic than Stanford V or BEACOPP and therefore may be preferred in PWH.
  - 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 an FDG-PET/CT scan showing complete response.
  - Evidence suggests that brentuximab vedotin and AVD is a safe option.[j]
  - 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 PWH, 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 PWH with severe and prolonged cytopenias.
  - If CD4+ T-cell count is <200 cells/μL, consider prophylactic antibiotics for gram-negative bacteria and *Pneumocystis jirovecii* pneumonia (PJP), in addition to appropriate opportunistic infection prophylaxis. See Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.
- FDG-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 PWH and HL may be from HIV, cancer, or other causes. The reason for poor performance status should be considered when making treatment decisions. ART is recommended for all PWH and may improve performance status.
- Adverse reactions due to drug interactions are more common with ritonavir, cobicistat, and protease inhibitors, and these antiretrovirals (ARVs) should be avoided whenever possible. Integrase strand-transfer inhibitor (ISTI)-based regimens are preferred. Drug interactions with selected non-nucleoside reverse transcriptase inhibitors (NNRTIs) are likely to result in decreased 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; very few 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. Only 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).
- Relapse/refractory HL in PWH should be managed similarly to disease in patients without HIV based on currently available evidence, and there is support for feasibility and efficacy of autologous and allogenic hematopoietic cell transplant.[k]
- Evolving data suggest that ICIs are generally safe and effective in PWH, with the following considerations:
  - In persons with KSHV infection, there may be increased risk of KSHV–associated inflammatory syndromes such as MCD or KICS when ICIs are used. If the patient has a history of KSHV-associated diseases, consider more frequent monitoring of signs and symptoms of KICS or MCD.[e,f]
    - ◊ Unexplained fevers should prompt workup of MCD and KICS with C-reactive protein, KSHV serum viral load, SPEP, IL-6, and IL-10. The diagnosis of KICS requires excisional biopsy of lymphadenopathy to exclude MCD.
  - The use of ICIs has been linked to TB reactivation.[g,h,i] Screening for latent TB infection can be considered before administering an ICI so that the patient can be monitored for TB symptoms and treatment of mycobacterial infection can be expedited.
- Caution should be used with anti-programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) therapy in patients being treated for mycobacterium given concerns for tuberculosis reactivation.

[e] Polizzotto MN, et al. Clin Infect Dis 2016;62:730-738.
[f] Uldrick TS, et al. JAMA Oncol 2019;5:1332-1339.
[g] Fujita K, et al. Open Forum Infect Dis 2020;7:ofaa067.
[h] Bae S, et al. J Immunother Cancer 2021;9:e002960.
[i] Zaemes J, et al. Eur J Cancer 2020;132:168-175.
[j] Rubinstein P, et al. Blood 2019;134:Abstract 130.
[k] Alvarnas JC, et al. Blood 2016;128:1050-1058.

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF HIV MANAGEMENT WHILE UNDERGOING CANCER THERAPY

- **Linkage to HIV care from cancer providers**
  - All patients should be offered HIV screening at least once during their lifetime. Consider HIV testing in patients with a new cancer diagnosis who have not been recently screened.[1,2]
  - Cancer in PWH should be co-managed by an oncologist and HIV specialist.
  - HIV therapy should be initiated or continued during cancer therapy.
  - ART may require modification by an HIV specialist in conjunction with an HIV pharmacist and an oncology pharmacist to minimize drug-drug interactions (DDIs) and toxicities.
  - ART interruptions should be avoided because of 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 should not be discontinued unless in consultation with an HIV specialist.
  - 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 the patient is 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 with HIV.
  - To facilitate separate assessment of tolerability of ART and cancer treatment, consider initiating ART ≥7 days prior to the 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).
    - ◊ ISTI-based regimens are preferred because they have fewer DDIs.
  - All patients with HIV should be tested for hepatitis B. Testing may be necessary prior to initiation of chemotherapy to avoid hepatic toxicity. Core antibodies should be checked in addition to surface antibodies and antigens. See Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.
  - In PWH who also have hepatitis B, an ART regimen that treats both HIV and hepatitis B should be initiated. (See Special Circumstances, HIV-E, 2 of 2).
  - Laboratory testing should be scheduled for both before and after initiation of ART (See Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents 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 with HIV):
    - ◊ If there are potential interactions between ART and cancer-related or other supportive care therapies leading to decreased effectiveness of ART, more frequent HIV viral load testing (eg, once a month for the first 3 months and then every 3 months[6]) may be needed.
    - ◊ 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 can 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).

- Patients with head and neck cancer have difficulty with oral drug administration due to feeding tubes, which could be problematic for ARVs. Consider prescribing formulations such as liquids, capsules that may be opened, tablets that may be crushed, or injectable ART. Refer to the prescribing information for individual drugs regarding feeding tube administration.
- **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).

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References on HIV-A 2 of 2

PRINCIPLES OF HIV MANAGEMENT WHILE UNDERGOING CANCER THERAPY
REFERENCES

[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;87:915-924.
[3] El-Sadr WM, Lundgren J, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. Strategies for management of Antiretroviral Therapy (SMART) Study Group. N Engl J Med 2006;355:2283-2296.
[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.
[6] Torres HA, Mulanovich V. Management of HIV infection in patients with cancer receiving chemotherapy. Clin Infect Dis 2014;59:106-114.
[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] Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, Liaisons, and Staff. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. Am J Prev Med 2008;35:158-176.

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PRINCIPLES OF SYSTEMIC THERAPY AND DRUG-DRUG INTERACTIONS

Drug-Drug Interactions (DDIs)

- **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 DDIs and overlapping toxicities prior to initiation. Coordinated care by an oncologist and HIV clinician is recommended for the duration of therapy.**
- **These Guidelines provides general guidance, but comprehensive resources for ARV drug-drug interactions should be consulted for patients with HIV and cancer. These resources include:**
  - **The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines provide comprehensive information on mechanisms of antiretroviral-associated drug interactions as well specific drug-drug interaction guidance (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/drug-interactions-overview). Of note, these guidelines do not incorporate many systemic cancer therapies. A preferred resource that does provide an interaction checker that includes cancer therapies is the University of Liverpool HIV Drug Interactions site (https://www.hiv-druginteractions.org).**
- **Select ARVs can be administered safely with systemic cancer therapies. With continued development of new ARVs, effective alternatives are almost always available to patients when the existing ART is expected to affect metabolism or transport of, or share toxicities with, systemic cancer therapies. Small case series favor integrase inhibitor-based ART during cancer therapy.[1,2] HIV regimens containing integrase inhibitors without pharmacologic boosters are favored in the setting of malignancy, due to a lower potential for DDI.**
- **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. The exception to this is a prodrug where the metabolite is active and the opposite effect would be observed.**
- **Select major considerations with ARVs include:**
  - **ARV interaction mechanisms span most metabolic pathways and transporters, including CYP enzymes, P-gp, and UGT1A1.**
  - **The greatest concern for DDIs is with ART regimens containing pharmacologic boosters (ie, ritonavir, cobicistat) and protease inhibitors. These drugs inhibit CYP3A4 and thus may significantly interact with agents metabolized by that pathway.**
  - **NNRTIs, except for rilpivirine and doravirine, induce CYP3A4 and thus may cause the opposite DDI from the inhibitors. Ritonavir is also an inducer of certain enzymes, most notably CYP2C19.**
  - **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 with HIV).**
  - **Medications and supplements with polyvalent cations (multivitamins, supplements, antacids, etc) can bind to integrase inhibitors and reduce their absorption.**
  - **Acid-reducing agents (antacids, H-2 antagonists, proton pump inhibitors, etc) can reduce the absorption of atazanavir and rilpivirine.**
  - **When cancer therapy is expected to be myelosuppressive, zidovudine is contraindicated due to its likelihood to cause or exacerbate myelosuppression.**

[1] 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.
[2] 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.

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PRINCIPLES OF SYSTEMIC THERAPY AND DRUG-DRUG INTERACTIONS

DDIs (continued)

- 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 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.
- Drugs used to prevent and/or treat opportunistic infections in PWH may also interact with cancer therapies. Some examples of concern include rifamycins (via induction of hepatic metabolism), clarithromycin (via inhibition of CYP3A4), azole antifungals (via inhibition of various hepatic metabolic processes), and trimethoprim/sulfamethoxazole treatment with methotrexate (via inhibition of methotrexate renal excretion and compound risk of bone marrow suppression). See Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/significant-drug-interactions?view=full) for more information.
- All PWH should be tested for hepatitis B by 3 tests: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc) total immunoglobulin (Ig) or IgG, and antibody to hepatitis B surface antigen. Testing is required prior to initiation of systemic therapy to avoid hepatic toxicity but anticancer therapy should not be delayed. See Hepatitis B Virus Screening and Management for Patients With Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update and Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.

Immune Checkpoint Inhibitors

- While evolving data suggest that immune checkpoint inhibitors are generally safe and effective in PWH,[3] in persons with KSHV infection, there may be increased risk of KSHV–associated inflammatory syndromes such as MCD or KICS. If the patient has a history of KSHV-associated diseases, consider more frequent monitoring of signs and symptoms of KICS or MCD.
  - Unexplained fevers should prompt workup of MCD and KICS with C-reactive protein, KSHV serum viral load, SPEP, IL-6, and IL-10. The diagnosis of KICS requires excisional biopsy of lymphadenopathy to exclude MCD.
- Caution should be used with anti-PD-1/PD-L1 therapy in patients being treated for mycobacterium given concerns for tuberculosis reactivation.

[3] Shah N, Al-Shbool G, Blackburn M, et al. Safety and efficacy of immune checkpoint inhibitors (ICIs) in cancer patients with HIV, hepatitis B, or hepatitis C viral infection. J Immunother Cancer 2019;7:353.

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PRINCIPLES OF RADIATION THERAPY[1]

- **HIV status alone should not be a criterion for decision-making regarding radiation therapy (RT) indications or dose. RT should be offered as part of the cancer management approach when indicated.**
- **Dose fractionation and treatment volumes are recommended as per NCCN Clinical Practice Guidelines by disease site.**
- **RT can be administered for cure or palliation.**
- **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).**
- **Additional clinical monitoring may be required with concurrent chemoradiotherapy.**
- **Particular attention should be paid to limit dose to the following structures using conformal techniques like IMRT, proton therapy, brachytherapy, or stereotactic body RT (SBRT) when deemed appropriate by the treating provider[2,3]:**
  - **Mucosal membranes[2,3]**
  - **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 2017;18:e379-e393.
[2] Bryant AK, Huynh-Le MP, Simpson DR, et al. Association of HIV status with outcomes of anal squamous cell carcinoma in the era of highly active antiretroviral therapy. JAMA Oncol 2018;4:120-122.
[3] Bryant AK, Mudgway R, Huynh-Le MP, et al. Effect of CD4 count on treatment toxicity and tumor recurrence in HIV positive patients with anal cancer. Intl J Rad Onc Biol Phys 2018;100:478-485.

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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 patients who will have surgical treatment should be treated with standard universal precautions.**
- **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 PWH. 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 PWH beyond the normal workup and follow-up.**
- **Surgical Outcomes:**
  - **Surgery in PWH for common malignancies (eg, prostate cancer, colon cancer) is safe and should be part of cancer management as indicated.[6,7]**
  - **Data demonstrate that clinical outcomes, length of stay, and complications are similar between PWH and patients who are HIV-negative for most surgical procedures.[8,9]**
  - **A study of PWH who required laparotomy found no increased risk of wound complications.[10]**
  - **Data from anorectal surgery for benign disease (eg, hemorrhoids, fistulas) suggest that there can be issues with delayed wound healing in PWH, especially if the CD4+ T-cell count is <50 cells/μL.[11] However, other reports demonstrate that PWH who undergo anorectal surgery experience normal wound healing.[12]**

[1] Madiba TE, Muckart DJ, Thomson SR. Human immunodeficiency disease: how should it affect surgical decision making? World J Surg 2009;33:899-909.
[2] Bizer LS, Pettorino R, Ashikari A. Emergency abdominal operations in the patient with acquired immunodeficiency syndrome. J Am Coll Surg 1995;180:205-209.
[3] Yii MK, Saunder A, Scott DF. Abdominal surgery in HIV/AIDS patients: indications, operative management, pathology and outcome. Aust N Z J Surg 1995;65:320-326.
[4] Harris HW, Schecter WP. Surgical risk assessment and management in patients with HIV disease. Gastroenterol Clin North Am 1997;26:377-391.
[5] Cacala SR, Mafana E, Thomson SR, Smith A. Prevalence of HIV status and CD4 counts in a surgical cohort: their relationship to clinical outcome. Ann R Coll Surg Engl 2006;88:46-51.
[6] Izadmehr S, Leapman M, Hobbs AR, et al. Clinical characteristics and outcomes of HIV-seropositive men treated with surgery for prostate cancer. Int Urol Nephrol 2016;48:1639-1645.
[7] Silberstein JL, Parsons JK, Palazzi-Churas K, et al. Robot-assisted laparoscopic radical prostatectomy in men with human immunodeficiency virus. Prostate Cancer Prostatic Dis 2010;13:328-332.
[8] Horberg MA, Hurley LB, Klein DB, et al. Surgical outcomes in human immunodeficiency virus-infected patients in the era of highly active antiretroviral therapy. Arch Surg 2006;141:1238-1245.
[9] Chi A, Adams BE, Sesti J, et al. Outcomes following major oncologic operations for non-AIDS-defining cancers in the HIV population: A matched comparison to the general population. World J Surg 2019;43:3019-3026.
[10] Buehrer JL, Weber DJ, Meyer AA, et al. Wound infection rates after invasive procedures in HIV-1 seropositive versus HIV-1 seronegative hemophiliacs. Ann Surg 1990;211:492-498.
[11] Lord RV. Anorectal surgery in patients infected with human immunodeficiency virus: factors associated with delayed wound healing. Ann Surg 1997;226:92-99.
[12] Burke EC, Orloff SL, Freise CE, et al. Wound healing after anorectal surgery in human immunodeficiency virus-infected patients. Arch Surg 1991;126:1267-1270; discussion 1270-1271.

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PRINCIPLES OF SUPPORTIVE CARE

- **The risk of infectious complications in PWH 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).**
- **Long-term steroid use should be limited in PWH because of the risk of opportunistic infections and other complications.**
- **PWH have an increased risk of oral mucositis, esophagitis, and colitis. A high index of suspicion of and early testing for opportunistic infections, including fungal infections, cytomegalovirus (CMV), and TB, is appropriate; early consultation with an HIV specialist is appropriate. See Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.**
- **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, PWH should receive care as per the appropriate NCCN Guidelines for Supportive Care (available at www.NCCN.org), including:**
  - **NCCN Guidelines Adult Cancer Pain**
  - **NCCN Guidelines Antiemesis**
  - **NCCN Guidelines Cancer-Related Fatigue**
  - **NCCN Guidelines Distress Management**
  - **NCCN Guidelines Palliative Care**
  - **NCCN Guidelines Survivorship**
- **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 PWH with CD4+ T-cell counts <200 cells/μL.**
  - **PWH aged >50 years can receive the new recombinant zoster vaccine.[1]**

- **For recommendations regarding infectious prophylaxis in PWH receiving cancer therapy, see HIV-E (2 of 2).**

[1] 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.

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PRINCIPLES OF SUPPORTIVE CARE

- **PWH should receive the prophylaxis indicated by their HIV status and cancer treatment. CD4 thresholds for prophylaxis may be higher in patients starting an immunosuppressive regimen. Also see the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections and Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.**
- **For PWH receiving cancer therapy where profound immunosuppression/myelosuppression is anticipated:**

Required/Strongly Recommended

- **Myeloid growth factor support (per NCCN Guidelines for Hematopoietic 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 PWH. Pre-existing neutropenia and/or low CD4+ T-cell counts (<200 cells/μL) increase risk of chemotherapy-associated neutropenic fever; myeloid growth factor support is strongly recommended with these risk factors.**
- **Gram-negative infection prophylaxis**
  - **Fluoroquinolone prophylaxis or equivalent during periods of neutropenia**
  - **Eg, 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**
  - **Eg, Acyclovir 400–800 mg PO twice daily OR valacyclovir 500 mg PO twice daily**
- **PJP prophylaxis and toxoplasmosis prophylaxis[2]**
  - **Continue until CD4+ T-cell counts recovered to ≥200 cells/μL for ≥3 months duration post completion of cancer therapy**
    - ◊ **Use caution when administering trimethoprim-sulfamethoxazole (TMP/SMX) while the patient is on methotrexate**
    - ◊ **G6PD deficiency screening should be performed prior to initiation of dapsone**
- **Mycobacterium avium complex (MAC) prophylaxis[2]**
  - **PWH who have CD4+ T-cell counts <50 cells/μL and are not on ART.**
  - **Disseminated MAC disease should be ruled out before starting prophylaxis.**
  - **Eg, Azithromycin 1200 mg PO once a week**
- **Candida prophylaxis**
  - **Eg, Fluconazole and/or nystatin**

Required/Strongly Recommended (continued)

- **Antifungal prophylaxis**
  - **During periods of prolonged neutropenia (≥7 days)**
  - **Azole antifungals may interact with ART and chemotherapy. Azoles should typically be held a minimum of 24 hours prior to and through 24 hours after administration of cancer therapy that is metabolized via CYP3A4.**
  - **Eg, 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, or *Talaromyces marneffei***

Special Circumstances

- **Consultation with an HIV specialist is strongly recommended in patients with hepatitis co-infection or other opportunistic infection. 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 treat both HIV and HBV, HBV therapy will be directed by an HIV specialist.**
      - – **If the prophylaxis is not part of ART, the duration of therapy should be 1-year post-transplant, post-rituximab, or post cell-based therapy.**

Unexplained Fever or Other Infectious Episode

- **Consultation with an HIV 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 PWH receiving cancer chemotherapy; a high index of suspicion and early testing for opportunistic infections in consultation with an HIV specialist is appropriate.**

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

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PRINCIPLES OF IMAGING

- **Interpretation of imaging for the workup, staging, and surveillance of PWH 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.**
- **Consultation with an HIV specialist and an evaluation to rule out infectious processes (eg, toxoplasmosis) or additional malignancies should be considered as clinically appropriate for PWH 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 JM, Subramaniam RM, Surasi DS, et al. FDG PET/CT in patients with HIV. AJR Am J Roentgenol 2011;197:284-294.

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ABBREVIATIONS

APR	abdominoperineal resection
ART	antiretroviral therapy
ARV(s)	antiretroviral(s)
ASCUS	atypical squamous cells of undetermined significance
CIN	cervical intraepithelial neoplasia
CMV	cytomegalovirus
CNS	central nervous system
DDIs	drug-drug interactions
DHHS	Department of Health and Human Services
DLBCL	diffuse large B-cell lymphoma
DLCO	diffusing capacity of the lung for carbon monoxide
EBV	Epstein-Barr virus
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
HSV	herpes simplex virus
ICI	immune checkpoint inhibitor
Ig	immunoglobulin
IL	interleukin
IMRT	intensity-modulated radiation therapy
ISTI	integrase strand-transfer inhibitor
KICS	KSHV–associated inflammatory cytokine syndrome
KSHV	Kaposi sarcoma-associated herpesvirus
LSIL	low-grade squamous intraepithelial lesion
MAC	mycobacterium avium complex
MCD	multicentric Castleman disease
NHL	non-Hodgkin lymphoma
NSCLC	non-small cell lung cancer
NNRTIs	non-nucleoside reverse transcriptase inhibitors
NOS	not otherwise specified
PD-1	programmed cell death protein 1
PD-L1	programmed death ligand 1
PJP	pneumocystis jirovecii pneumonia
PML	progressive multifocal leukoencephalopathy
PWH	people with HIV
SBRT	stereotactic body radiation therapy
SPEP	serum protein electrophoresis
TB	tuberculosis
VZV	varicella zoster virus

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.

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NCCN Guidelines Version 2.2024
Cancer in People with HIV

Discussion

This discussion corresponds to the NCCN Guidelines for Cancer in People With HIV. Last updated: October 2, 2023

Table of Contents

NCCN Guidelines Version 2.2024
Cancer in People with HIV

Overview

More than 1.2 million people in the United States were estimated to be living with human immunodeficiency virus (HIV) infection in October 2022.[1] HIV infection causes AIDS and AIDS-defining cancers: non-Hodgkin 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 with HIV (PWH) are living longer and healthier lives; however, they are experiencing an increased risk of many non-AIDS–defining cancers.[7-13]

An estimated 7490 PWH were diagnosed with cancer in the United States in 2020.[14] Studies have noted a higher risk for developing many cancers in PWH than in the general population, likely due to underlying immune deficiency, accelerated aging, and co-infection with viruses such as human papillomavirus (HPV), Kaposi's sarcoma herpesvirus (KSHV; also called human herpesvirus 8 or HHV-8), hepatitis B virus (HBV), hepatitis C virus (HCV), and Epstein-Barr virus (EBV).[15-19] In addition, the prevalence of other cancer risk factors in the HIV population (eg, smoking) likely play a role.[20-24]

The estimated proportions of each major cancer type among total incident cancer cases occurring in PWH in the United States during 2020 were[14]:

- Prostate cancer 18%
- Lung cancer 12%
- NHL 10%
- Kaposi sarcoma 7%
- Anal cancer 7%
- Liver cancer 6%
- Oral/pharyngeal cancer 4%
- Colorectal cancer 3%
- Hodgkin lymphoma 3%
- Breast cancer 3%
- Cervical cancer 1%

Deaths due to cancer in the U.S. HIV population occurred at a rate of 484 and 314 per 100,000 person-years in 2001 to 2005 and 2011 to 2015, respectively.[25] Approximately 9.2% of deaths in PWH in the United States were attributable to non–AIDS-defining cancer and 5.0% were attributable to AIDS-defining cancers from 2001 to 2015.

These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cancer in People with HIV provide treatment recommendations for PWH 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 PWH 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 PWH who have cancer. This Discussion elaborates on the guidelines and provides an overview of the literature supporting the included recommendations.

Guidelines Update Methodology

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

Literature Search Criteria

Prior to the update of the NCCN Guidelines® for Cancer in People with HIV, an electronic search of the PubMed database was performed to obtain key literature in the field, 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 peer-reviewed biomedical literature.[26]

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 data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[27] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-fat-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms *men*, *women*, *female*, and *male* when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Disparities in Cancer Care for PWH

In general, PWH who develop cancer have a higher mortality rate compared with the general cancer population.[28-33] Reasons for this increased mortality include delayed diagnoses, advanced cancer stage, other comorbidities, and immunosuppression in PWH.[29,34-37] In fact, one study showed that PWH had fewer comorbidity-free years at 21 years of age than matched adults without HIV.[38] However, there is also significant disparity in cancer treatment between PWH and the general cancer population, with many PWH not receiving any cancer treatment.[39-43] Results of a survey of 500 medical and radiation oncologists in the United States published in 2015 suggest that lack of consensus guidelines and provider education contribute to the substandard cancer care often offered to PWH who have cancer.[44] 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 PWH.

HIV Management During Cancer Therapy

HIV Screening

In the United States, 13% of people with HIV are not aware of their HIV status.[1] PWH 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.[45] To detect HIV early, the Centers for Disease Control and Prevention (CDC) recommends regular HIV screening for everyone aged 13 to 65 years and annual testing for people with certain risk factors.[46]

HIV testing may be particularly important in patients with cancer, because identification of HIV infection has the potential to improve clinical outcomes.[47] In a multicenter prospective cohort study of more than 3000 patients diagnosed with cancer, 1.1% tested positive for HIV.[48] 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%.[49] Analysis of data from the 2009 Behavioral Risk Factor Surveillance System showed that only 41% of U.S. cancer survivors younger than 65 years of age reported ever being tested for HIV.[50] Race, other demographic characteristics, and tumor type influenced the likelihood of receiving an HIV test in both studies.

All patients should be offered HIV screening once during their lifetime. The NCCN Panel believes that HIV testing should be considered in patients with a new cancer diagnosis who have not been recently screened. Testing is particularly important in the context of suspected or confirmed Kaposi sarcoma or primary central nervous system (CNS) lymphoma, given the risk of these cancers in the United States is approximately 250- to 500-fold higher in PWH compared to those without HIV.[9,18]

Linkage to HIV Care

The HIV Care Continuum Initiative indicates that all patients diagnosed with HIV should be referred to an HIV specialist.[51] Linkage to care and initiation of antiviral therapy have been shown to improve viral suppression.[52,53] Early initiation of antiretroviral therapy (ART) has also been shown to improve survival in PWH and lower incidence of AIDS-related malignancies.[54-57] Linkage to HIV care is essential for PWH who have cancer; therefore, the oncology team should refer all PWH 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 PWH 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 or more 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.[58] Continuation of ART may also result in better tolerance of cancer treatment, higher response rates, and improved survival.[59,60] 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 in PWH with cancer as per normal schedules for PWH.[61] More frequent viral load and CD4+ T-cell testing may be needed with use of cancer or supportive therapies, which may reduce the effectiveness of ART or cause lymphopenia. A study showed that radiation and/or chemotherapy is associated with significantly reduced initial CD4+ T-cell counts compared with surgery or other treatment in PWH.[62] Other data also show that certain chemotherapy regimens can cause a sustained drop in CD4+ T-cell counts and an increased risk of opportunistic infections.[63] In the setting of radiation or chemotherapy-associated lymphopenia, HIV viral load monitoring more accurately reflects control of HIV compared with CD4+ T-cell count. Monitoring the depth of CD4+ T-cell suppression prior to and during cancer therapy is important to informing the risk of opportunistic infections.

Opportunistic Infection Prophylaxis

The occurrence of opportunistic infections in PWH has decreased in the ART era, mainly because effective ART reduces infection risk as CD4+ T-cell counts rise.[6,64-66] Furthermore, improvements in prophylaxis and treatment of opportunistic infections in PWH has further reduced risk.[66,67] Still, opportunistic infections represent a major cause of morbidity and mortality in PWH.[66,67]

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).[68-72] In particular, chemotherapy can cause neutropenia, which is a major risk factor for the development of infections.[73] 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.[74] Newer targeted agents are also associated with immunosuppression and increased infection risk.[75]

PWH may be more susceptible to infectious complications following certain chemotherapy regimens compared to individuals without HIV,[76] and low CD4+ T-cell counts appear to increase the risk of febrile neutropenia.[77] However, HIV status does not appear to differentially impact the risk of myelosuppression and infectious complications in certain cancer regimens.[78]

Overall, the NCCN Panel recommends that PWH who have cancer should receive the prophylaxis indicated by their HIV status and cancer treatment, with consideration given to the potential for increased risk of febrile neutropenia or more advanced lymphopenia in PWH, particularly with low CD4+ T-cell counts. Specific recommendations for PWH receiving cancer therapy for which profound immunosuppression/myelosuppression is anticipated are outlined in the guidelines above (see *Principles of Supportive Care* in the algorithm). The U.S. Department of Health and Human Services' Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV (available at https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new) 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 HIV specialist is strongly recommended.

Smoking Cessation in PWH Who Have Cancer

A study found that in the United States, 42% of PWH use tobacco.[79] Help with smoking cessation should be offered to PWH 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.[80-87] Data on the effects of smoking cessation specific to PWH after a cancer diagnosis are lacking. The Infectious Disease Society of America recommends implementing an Ask-Advise-Connect framework to initiate smoking cessation, prescribe pharmacotherapy (preferably varenicline) and provide direct connection to behavioral therapy to increase the likelihood of successful cessation in PWH.[79] The National Cancer Institute has begun an initiative to advance research into smoking cessation treatment for PWH.[88]

Recommendations for Cancer Management in PWH

Special considerations for cancer management in PWH and recommendations for the management of specific cancers in PWH are discussed herein. Overall, the NCCN Panel recommends that most PWH who develop cancer should be offered the same cancer therapies as those without HIV. Modifications to cancer treatment should not be made solely based on HIV status. Evidence suggests that immunotherapies are generally safe and effective in PWH, although, in persons with KSHV infection, there may be increased risk of KSHV–associated inflammatory syndromes such as multicentric Castleman disease or KSHV–associated inflammatory cytokine syndrome (KICS).[89-100] Inclusion of PWH in cancer clinical trials should be encouraged whenever feasible.

Cancer Workup in PWH

Workup for PWH who have cancer is complicated by the increased incidence of non-malignant lesions that may be mistaken for cancer spread or recurrence.[101,102] For example, HIV viremia and opportunistic infections commonly cause lymphadenopathy in PWH, which can be seen on F-18 FDG PET/CT.[103,104] Nonmalignant causes of lymphadenopathy are more common in patients with higher viral loads and lower CD4+ T-cell counts.[105] Therefore, PWH who have cancer should have an infectious disease workup for lymphadenopathy as clinically indicated.

Similarly, an infectious disease workup is recommended as indicated for PWH 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).[106] Furthermore, non-infectious, non-malignant pulmonary manifestations of HIV can be difficult to interpret on imaging studies, including drug reactions and immune activation.[106,107] Brain lesions seen in PWH may result from opportunistic infections, such as viral encephalitis, aspergillosis, toxoplasmosis, cryptococcosis, bacterial meningitis, tuberculosis, and progressive multifocal leukoencephalopathy.[108-110] Benign, non-infectious brain lesions can also occur in PWH (eg, vascular complications, hydrocephalus).[108,109] Bone lesions may occur with MTB infection, bacillary angiomatosis, and use of tenofovir.[111-113] Gastrointestinal lesions commonly occur during infection with CMV, candida, and cryptosporidium.[114] Liver lesions may be caused by multiple organisms including MTB, mycobacterium avium complex (MAC), and CMV.[115] Lesions of uncertain etiology should be biopsied to confirm cancerous histology.

DDIs: Systemic Cancer Therapy and ART

DDIs between anticancer therapy and antiretrovirals (ARVs) were first noted with the increased incidence of mucositis in PWH who had NHL who were treated with both the protease inhibitor saquinavir and the

chemotherapy regimen cyclophosphamide/doxorubicin/etoposide.[116] 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.[117,118] 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, 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 strongly inhibit CYP3A, increasing the exposure of protease inhibitors (eg, atazanavir, darunavir, saquinavir) and thus the effectiveness of ART.[119] 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.[120,121] A recent phase I pharmacokinetic study found that exposure of erlotinib 75 mg combined with ritonavir is similar to erlotinib 150 mg.[122] A phase I pharmacokinetic study in 19 PWH 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.[123] Furthermore, a retrospective analysis of PWH treated for Hodgkin lymphoma showed that concomitant ritonavir-based HIV therapy and vinblastine can result in irreversible neurologic toxicity.[124-126]

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.[120]

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.[127,128] In one of these studies, data from 154 PWH with cancer seen at the University of Texas MD Anderson Cancer Center between 2001 and 2012 were reviewed.[128] Non-nucleoside reverse transcriptase inhibitors and integrase strand-transfer inhibitors (ISTI) 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, brentuximab, proteasome inhibitors) and certain nucleoside reverse transcriptase inhibitors (eg, didanosine, stavudine).[129] 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.[130,131] Other overlapping toxicities of cancer therapy and ART can affect the liver, cardiovascular system, and kidneys.[118,132-134]

Despite the possibility for DDIs and overlapping toxicities, ARVs can be safely coadministered with chemotherapy. In general, ISTI-based regimens are preferred because they have fewer DDIs. 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, and co-management by oncology and HIV clinicians is recommended for the duration of therapy.

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 PWH

Older studies showed increased radiation-related toxicity in PWH, particularly in patients with advanced immunosuppression.[135-137] This risk may be less applicable to PWH treated with contemporary ART and modern RT techniques.[138] In fact, more modern data suggest that radiation therapy for certain cancers (eg, anal cancer; see below) is effective and well-tolerated in PWH. For other cancers, however, data on the safety and efficacy of radiation therapy specific to PWH are limited (eg, lung cancer).[139]

The data on the use of radiation in PWH who have anal cancer are particularly strong, with greater than 20 clinical studies published.[139] One retrospective cohort study included 175 PWH and 1009 people without HIV who had anal cancer in the ART era.[140] 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 PWH found no differences in overall survival or in acute or late toxicities.[141]

In summary, when radiation therapy is indicated in the care 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 PWH, as deemed appropriate by the treating provider. The panel also notes that extra caution and monitoring is required with use of concurrent chemoradiation in PWH. Furthermore, nutritional support, pain control, and other supportive measures should be used to minimize radiation therapy interruptions in this population.

Cancer Surgery in PWH

Older data from anorectal surgery for benign disease (eg, hemorrhoids, fistulas) indicate that PWH can experience delayed wound healing, especially if the CD4+ T-cell count is less than 50/µL.[142] Other reports, however, demonstrate that PWH who undergo anorectal surgery have uncomplicated wound healing.[143] Furthermore, a study of PWH who required invasive procedures found that wound infection rates were not

associated with HIV status.[144] In addition, studies evaluating surgical outcomes in PWH demonstrate that clinical outcomes, length of stay, and complications are similar between PWH and patients without HIV for most surgical procedures.[145,146]

Studies have also shown that surgery for common malignancies (eg, anal cancer, prostate cancer, colorectal cancer) in PWH is safe and effective.[147-152] In particular, ample data suggest that surgical management in PWH with early-stage anal cancer or recurrent anal cancer is safe and effective.[147-149] 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.[148] However, postoperative hemorrhage occurred more frequently in the PWH 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 PWH and 125 patients without HIV who had hepatocellular carcinoma.[153] HIV status did not affect overall survival or cancer recurrence rates.

PWH should be treated with standard universal precautions, and no additional pre- or postoperative laboratory testing is needed specific to PWH beyond the normal workup and follow-up for a patient undergoing surgery. 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 PWH. 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.[154-158]

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 PWH

Patients with advanced HIV often suffer from fatigue, weight loss, pain, anorexia, and anxiety.[159] ART may cause side effects including nausea/vomiting, diarrhea, constipation, cough, dyspnea, insomnia, and depression.[159] Cancer and its treatment can also cause all of these symptoms and PWH report greater cancer treatment toxicity.[160] Managing these symptoms can be critical, because studies show that treatment side effects may decrease completion of cancer treatment in PWH and compromise cancer outcomes.[160-162]

For most supportive care situations related to cancer treatment, PWH should be cared for 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
- NCCN Guidelines for Survivorship

In addition, recommendations for fertility preservation can be found in the NCCN Guidelines for Adolescent and Young Adult (AYA) 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 PWH who have cancer. For instance, long-term steroid use should be limited in PWH because of the risk of opportunistic infections and other complications.

In addition, the risk of infections in PWH is increased during cancer treatment.[68-72,75] Opportunistic infection prophylaxis thus plays a critical role in the supportive care of PWH who have cancer (see *Opportunistic Infection Prophylaxis*, above).

Recommendations for Specific Cancers in PWH

NHL in PWH

NHL is an AIDS-defining cancer, and the risk of NHL is elevated 7- to 23-fold in PWH, with the risk being even higher for certain subtypes such as primary CNS lymphoma.[8,9,17,18] The development of NHL in PWH is associated with recent immunosuppression and prolonged HIV viremia.[163] In the ART era, the incidence of NHL has declined.[11,18] One study showed that the increased risk of NHL in PWH compared with the general population declined from 28-fold in 1996 to 1999 to 8-fold in 2009 to 2012.[18] In 2010, NHL accounted for about 21% of cancers diagnosed in PWH.[164]

For recommendations regarding the management of NHL in PWH, see the NCCN Guidelines for B-Cell Lymphomas (available at www.NCCN.org), the NCCN Harmonized Guidelines for Sub-Saharan Africa for B-Cell Lymphomas (available at www.NCCN.org/harmonized), and, for other lower-resource regions, the NCCN Framework for Resource Stratification of NCCN Guidelines for B-Cell Lymphomas (available at www.NCCN.org/framework).

Kaposi Sarcoma in PWH

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,[8-10,17,165] but this risk has declined in the ART era.[8,11,18,166,167] Still, estimates indicate that the risk of Kaposi sarcoma in PWH between the years 2009 and 2012 was elevated approximately 498-fold compared with the general U.S. population.[18] In 2010, Kaposi sarcoma accounted for approximately 12% of cancers diagnosed in PWH, with an estimated 765 to 910 cases diagnosed per year in the United States.[164,168]

Recommendations for the management of Kaposi sarcoma in PWH are presented in the NCCN Guidelines for Kaposi Sarcoma (available at www.NCCN.org). For recommendations for patients in sub-Saharan Africa, please see the NCCN Harmonized Guidelines for Sub-Saharan Africa for Kaposi Sarcoma (available at www.NCCN.org/harmonized).

Lung Cancer in PWH

Lung cancer is the most common non-AIDS–defining cancer in PWH.[9,12] In the year 2010, lung cancer accounted for approximately 11% of cancers diagnosed in PWH.[164] The risk of lung cancer is about 2 to 5 times higher in PWH than in those without HIV.[9,10,18,169] Some data suggest that the incidence of lung cancer in PWH has been declining since the beginning of the ART era,[8,18] but other studies demonstrate an increase.[12] Mortality is also increased in people with lung cancer who also have HIV, compared to those without HIV.[170-172]

Smoking is a well-known risk factor for lung cancer, and smoking prevalence is higher in PWH than in those without HIV.[20,23,173] Thus, smoking likely contributes to the increased risk of lung cancer in PWH. However, immunosuppression also likely plays a role.[3,174,175] Overall, PWH who smoke and are on ART are 6 to 13 times more likely to die of lung cancer than of AIDS-related causes.[176]

Recommendations for the management of lung cancer can be found in the NCCN Guidelines for Non-Small Cell Lung Cancer (available at www.NCCN.org), the NCCN Harmonized Guidelines for Sub-Saharan Africa for Non-Small Cell Lung Cancer (available at www.NCCN.org/harmonized), and the NCCN Framework for Resource

Stratification of NCCN Guidelines for Non-Small Cell Lung Cancer (available at www.NCCN.org/framework).

Screening for Lung Cancer in PWH

Because of the increased risk for the development of lung cancer in PWH, 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.[177,178] However, data informing the potential role of lung cancer screening in PWH are limited.[179-181] One study assessed annual CT-based lung cancer screening (up to 4 scans) in 224 PWH who were current and former smokers with a greater than or equal to 20 pack-year history.[179] 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 PWH who smoke with a ≥20 pack-year history and a CD4+ T-cell nadir count of less than 350 cells/µl.[180] Lung cancer was diagnosed by 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 PWH 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 PWH

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

PWH may be more likely to have alternative causes of lung nodules (see *Cancer Workup in PWH*, above). Infectious granuloma or tuberculosis are possible differential diagnoses as is Kaposi sarcoma or lymphoma. Consideration of alternative causes of lung lesions may warrant an infectious disease workup. The differential diagnosis should be considered before biopsy to inform studies to be performed on biopsy (ie, cultured for bacteria, fungi, and mycobacteria acid-fast bacilli [AFB] when relevant) and consideration of biopsy risks. For example, if pulmonary Kaposi sarcoma is strongly suspected, the risk of bleeding complications needs to be considered.

Non-malignant causes for lymphadenopathy and organ lesions should be considered, with referral for an infectious disease evaluation as indicated. 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 PWH*, above).[108,109] Treatment for possible non-malignant diagnoses can be considered before biopsy.

Additional workup for NSCLC in PWH 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 PWH

Some studies have shown that patients with lung cancer show similar outcomes regardless of their HIV status.[182,183] Other studies, however, have found disparities in receipt of cancer treatment and/or survival.[184,185] For example, a registry-based analysis found that PWH diagnosed with lung cancer between 1995 and 2009 were less likely to receive cancer treatment and had higher lung cancer-specific mortality.[185] The effect of HIV on lung cancer-specific mortality was partially reduced in those who received cancer treatment. A phase II

trial evaluated carboplatin plus pemetrexed (CaP) in patients with non-squamous non-small cell lung cancer (NS-NSCLC) and HIV.[186] Half the patients achieved a disease control rate (DCR) ≥30%, which can be compared to 57% found in the general population with NS-NSCLC.[187] Overall survival was shorter at 7.6 months compared to 13.4 months in the general population with NS-NSCLC.[188] Furthermore, a single-center, retrospective cohort study that compared outcomes following resection in 22 PWH 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 PWH group had more postoperative pulmonary and infectious complications ($P = .001$ and $P < .001$, respectively), faster disease progression ($P = .061$), and shorter survival ($P = .001$).[189] In contrast, another study found that PWH who had lung cancer resections between 2000 and 2016 experienced similar short-term complications as patients without HIV.[190]

Overall, the NCCN Panel recommends that PWH 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 PWH who have NSCLC, poor performance status may result from HIV, lung cancer, or other causes. ART is recommended for all PWH and may improve performance status. The panel recommends that the reason for poor performance status should be considered when making treatment decisions. If poor performance status is the result of cancer-related symptoms that may be reversed with cancer therapy, treatment initiation should be strongly considered. As in other cancers, modifications to cancer therapy should not be made solely on the basis of HIV status.

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

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

Anal Cancer in PWH

Anal cancer in PWH is often associated with persistent anal HPV infection, which is likely due to immune suppression.[191] A meta-analysis of anal cancer burden across major groups known to be at elevated risk showed that anal cancer risk is highest among men who have sex with men (MSM) living with HIV, with incidence rates up to 85 times higher than in the general population (85 cases per 100,000 person-years vs. 1–2 per 100,000, respectively).[192] Analysis of the French Hospital Database on HIV also showed a highly elevated risk of anal cancer in PWH, including in those who were on ART and whose CD4+ T-cell counts were high.[193] In this analysis, the standardized incidence ratio (SIR) between MSM living with HIV compared to the general population was 109.8 (95% CI, 84.6–140.3) in the years 2005 to 2008. Between other men with HIV and the general population, it was 49.2 (95% CI, 33.2–70.3). For women with HIV, the corresponding SIR was 13.1 (95% CI, 6.8–22.8) compared to the general population. Overall, anal cancer accounts for approximately 10% of cancers diagnosed in PWH,[164] and the current risk of anal cancer in PWH is elevated approximately 15- to 19-fold over the general U.S. population.[16-18,194]

Anal cancer is preceded by precursor lesions called anal intraepithelial neoplasia (AIN), which can be further subdivided into high-grade AIN (or HSIL) and low-grade AIN (or LSIL).[195] Some evidence suggests that ART may be associated with a decrease in the incidence of high-grade

AIN and its progression to anal cancer.[196-198] However, the incidence of anal cancer in PWH has not decreased much, if at all, over time.[10,18,193,194]

Recommendations for the management of anal cancer are presented in the NCCN Guidelines for Anal Carcinoma (available at www.NCCN.org) and the NCCN Harmonized Guidelines for Sub-Saharan Africa for Anal Carcinoma (available at www.NCCN.org/harmonized).

Screening for and Management of Precancerous Anal Lesions in PWH

PWH are at higher risk of AIN compared to those without HIV.[199] High-grade AIN can be a precursor to anal cancer,[200-203] and treatment of high-grade AIN may prevent the development of anal cancer.[204] Therefore, many clinicians routinely screen PWH for HPV and anal dysplasia, even though randomized controlled trials showing that such screening programs are efficacious at reducing anal cancer incidence and mortality are limited.[205-212] In addition, the panel recommends that PWH diagnosed with vulvar, vaginal, or cervical disease should have screening for anal cancer. Screening methods include anal cytology, high-resolution anoscopy, and annual digital rectal exam (DRE). Some data suggest that screening protocols that include cytology and HPV testing are most effective.[213]

Multiple methods are used to treat anal dysplasia, including topical therapy (ie, fluorouracil, imiquimod), excision, and ablation.[210,214-216] These treatments are safe in PWH and are associated with a decreased risk of progression to cancer.[217-220] However, treatment of anal dysplasia in PWH is associated with a higher risk of recurrence compared to those without HIV.[205,217] Due to this, a randomized, double-blind, placebo-controlled trial investigated if HPV vaccination could prevent high-grade AIN recurrence in MSM living with HIV, but found no preventive effect.[221] 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.[222] The subgroup with perianal AIN appeared to respond better to imiquimod than those with intra-anal AIN. An AIDS Malignancy Consortium trial randomized 120 patients with high-grade AIN to ablation or active monitoring.[223] Complete or partial lesion clearance was more common in the treatment group (82% vs. 47%; 95% CI, 16%–50%; $P < .001$). Adverse events included mild or moderate anal pain and bleeding.

The multiple methods to treat anal dysplasia are associated with a decreased risk of progression to cancer. A recent phase III trial, the Anal Cancer/HSIL Outcomes Research (ANCHOR) study, included 4446 PWH ≥35 years with HSILs.[220] Participants were randomized into two groups: treatment of the HSIL or active monitoring of HSIL without treatment. Study results found that the rate of progression to cancer was lower in the treatment group than in the active monitoring group by 57% (95% CI, 6–80; $P = .03$). The observed rate of progression in the treatment group was 173 per 100,000 person-years (95% CI, 90–332), compared to 402 per 100,000 person-years (95% CI, 262–616) in the active monitoring group. Of note, the trial was not designed to compare the efficacy of the various methods of treatment of HSIL, but to provide data to support early screening and treatment of anal HSIL.

Furthermore, a systemic review of guidelines on screening, treatment, and follow-up for AIN found increasing consensus in recommending the treatment and follow-up of high-grade AIN.[224] However, most guidelines refrain from recommending a specific treatment modality.

Workup for Anal Cancer in PWH

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 PWH 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.[225,226] PWH 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 PWH should be performed as described in the NCCN Guidelines for Anal Carcinoma (available at www.NCCN.org). HPV-related disease in PWH is often multifocal. Therefore, PWH diagnosed with anal cancer should have colposcopic examination by a gynecologist to evaluate for the presence of vulvar, vaginal, or cervical disease. Non-malignant causes for lymphadenopathy and organ lesions should be considered, with referral for an infectious disease evaluation as indicated.

Management of Anal Cancer in PWH

Most evidence regarding outcomes in PWH with anal cancer comes from retrospective comparisons, a few of which found worse outcomes in PWH.[227-230] Most studies, however, have found outcomes to be similar in PWH and those without HIV.[140,141,147,148,226,231-234] 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 PWH compared with patients without HIV.[140] Furthermore, a population-based study of almost 2 million patients with cancer, 6459 of whom were living with HIV, found no increase in cancer-specific mortality for anal cancer in PWH.[29] Some phase II studies in anal cancer have included PWH.[235,236] Although the numbers of PWH 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 PWH 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 PWH 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 PWH, with referral for an infectious disease workup if suspicious/PET-avid nodes are seen (also see *Cancer Workup in PWH*, above). Poor performance status in PWH and anal cancer may be from HIV, cancer, or other causes. The reason for poor performance status should be considered when making treatment decisions. ART is recommended for all PWH and may improve performance status.

The phase II AIDS Malignancy Consortium 045 (AMC045) trial evaluated the safety and efficacy of cetuximab with cisplatin/5-FU and radiation in PWH with anal squamous cell carcinoma. Preliminary results from this trial and a similar trial in immunocompetent patients (Eastern Cooperative Oncology Group [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 PWH populations, respectively.[237] 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%).[238] The toxicities associated with the regimen in ECOG 3205 (patients who were immunocompetent) were substantial, with grade 4 toxicity occurring in 32% of the study population and 3 treatment-associated deaths (5%). In AMC045 (PWH), the 3-year locoregional failure rate was 20% (95% CI, 10%–37%) by Kaplan-Meier estimate.[239] 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 PWH or those without HIV with anal cancer at this time.

Surveillance and Survivorship in PWH Treated for Anal Cancer

Surveillance following treatment of anal cancer in PWH should be performed as described in the NCCN Guidelines for Anal Carcinoma (available at www.NCCN.org). A small retrospective study of 93 patients with anal cancer found that recurrence rates were not affected by HIV status.[233] 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.[225]

Regular anal cytology can also be considered for the detection of anal dysplasia in survivors of anal cancer 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.

PWH diagnosed with anal cancer should be counseled on infertility risks and referred for fertility counseling as appropriate. PWH 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 PWH

PWH are 5 to 14 times more likely to be diagnosed with Hodgkin lymphoma than individuals without HIV.[9,10,17,18] The incidence of Hodgkin lymphoma in PWH increased through 2002,[8,9] but studies that assessed the trends of incidence from 1996 through 2010 or 2012 found it to be decreasing.[11,18] Evidence regarding the role of immunosuppression in the development of lymphoma are conflicting.[3,17,240,241]

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.[242] PWH who develop Hodgkin lymphoma typically present with mixed cellularity or, less commonly, nodular sclerosis or lymphocyte-depleted histologies of classical disease.[243-247]

In contrast to individuals without HIV, nearly 90% of cases of Hodgkin lymphoma in PWH are EBV-associated.[242,248] PWH often present with more advanced disease, including extranodal disease and bone marrow involvement.[243,244,248,249] Bone-marrow-only presentations sometimes occur,[250] whereas CNS involvement is rare.[251] PWH 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 patients without HIV when they receive standard cancer treatment.[244,252,253]

Recommendations for the management of Hodgkin lymphoma are presented in the NCCN Guidelines for Hodgkin Lymphoma (available at www.NCCN.org) and the NCCN Harmonized Guidelines for Sub-Saharan Africa for Hodgkin Lymphoma (available at www.NCCN.org/harmonized).

Workup for Hodgkin Lymphoma in PWH

Approximately 4% of 22,355 patients with Hodgkin lymphoma in the SEER database from 2000 to 2010 were living with HIV at the time of diagnosis.[254] The NCCN Panel recommends that all patients with Hodgkin lymphoma be tested for HIV if not already known to have a documented HIV infection. PWH 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 PWH with Hodgkin lymphoma.[59,255]

Diagnosis and staging workup for Hodgkin lymphoma in PWH 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 PWH*, 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 PWH

Cancer mortality can be similar between PWH and those without HIV who have Hodgkin lymphoma.[29,31,244] However, disparities in treatment received results in increased mortality in PWH whose cancer is not treated.[40,41,256] In a population-based study of 2090 PWH, unadjusted 5-year overall survival was decreased in PWH compared to those without HIV (66% vs. 80%), whereas the difference disappeared in those who received chemotherapy.[256] One large database study, however, found that overall survival was decreased in PWH who have Hodgkin lymphoma (hazard ratio [HR], 1.47; 95% CI, 1.25–1.74), even though the population was matched by treatment characteristics.[257] 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 PWH who have Hodgkin lymphoma, with oncologic outcomes similar to those without HIV.[244,246,249,253] Favorable results have also been seen with Stanford V (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone).[258] 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.[259,260] Recent data demonstrate that combining brentuximab vedotin with AVD is highly active and safe in PWH.[261]

When using these regimens, ART with overlapping toxicities or direct interactions with chemotherapy should be avoided whenever possible (see *DDIs: Systemic Cancer Therapy and ART*, above). DDIs 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 and hematologic toxicity.[262] Similarly, brentuximab vedotin and ritonavir or cobicistat may be associated with excess hematologic toxicity.[126] These ARVs should therefore be avoided whenever possible; ISTI-based regimens are preferred. When possible, an HIV pharmacist and an oncology pharmacist should be consulted regarding chemotherapy in PWH who have Hodgkin lymphoma. Also see *Principles of Systemic Therapy and Drug-Drug Interactions* in the algorithm and *DDIs: Systemic Cancer Therapy and ART*, above.

Autologous stem cell transplantation also appears to be safe and effective in PWH 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 PWH with Hodgkin lymphoma.[263] In addition, a retrospective matched cohort analysis showed that relapse, overall survival, and PFS were similar in patients with Hodgkin lymphoma, who received autologous stem cell transplantation, regardless of their HIV status.[245] A retrospective, multicenter, registry-based study in Europe also found autologous stem cell transplantation to be a beneficial option in this population.[264] Most recently, autologous transplant was established as a standard of care for PWH who have relapsed/refractory HIV-related lymphomas in a study run jointly by the AMC and Blood and Marrow

Transplant Clinical Trials Network (the BMT CTN 0803/AMC 071 trial) that included 15 patients with Hodgkin lymphoma and 25 patients with diffuse large B-cell lymphoma.[265] Allogeneic HCT also appears to be safe in this population based on results of the phase II prospective multicenter BMT CTN-0903/AMC-080 trial, which included 17 PWH with acute leukemia, myelodysplasia, or lymphoma.[61]

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).[266,267]

Based on these data, the NCCN Panel recommends that PWH 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 PWH 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. ART is recommended for all PWH and may improve performance status. ABVD is less toxic than Stanford V or BEACOPP and therefore may be preferred in PWH. Extrapolating from randomized data in the general Hodgkin lymphoma population, bleomycin can be discontinued after 2 cycles in PWH who have advanced-stage Hodgkin lymphoma and a PET/CT scan showing response.[268] It is also reasonable to discontinue bleomycin in patients who have symptoms of pulmonary compromise or fall in diffusing capacity of the lungs for carbon monoxide (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 PWH 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 leukopenia with ABVD in the NCCN Guidelines for Hodgkin Lymphoma (available at www.NCCN.org), dose reductions in early cycles and or prophylactic antibiotics may be appropriate in PWH with advanced immunosuppression (CD4<200).

B symptoms, which include fever, drenching night sweats, and/or weight loss of greater than 10% body weight, are common in PWH who have Hodgkin lymphoma.[269] B symptoms may also indicate a concurrent opportunistic infection if CD4 counts are low.

Cervical Cancer in PWH

Persistent infection with high-risk HPV, the etiologic agent of cervical cancer, is more likely in PWH than individuals without.[270-272] Furthermore, the incidence of cervical cancer in PWH is about 3 to 6 times higher than that in those without HIV.[8,9,17,273-275] Some evidence suggests that ART lowers the risk of persistent HPV infection and the prevalence of cervical intraepithelial neoplasia (CIN), precursors of cervical cancer.[276-280] In addition, initiation of ART may reduce the progression of CIN and incidence of cervical cancer.[279] However, evidence that the incidence of cervical cancer in PWH has decreased significantly in the modern ART era is lacking.[8,10,12,18,166,281,282] In 2020, cervical cancer accounted for about 1% of cancers diagnosed in the HIV population.[164] This number is likely so low only because the U.S. HIV population is mostly male. Cervical cancer is a major health problem in low- and middle-income countries struggling with high HIV and HPV prevalence.

Recommendations for the management of cervical cancer in PWH are presented in the NCCN Guidelines for Cervical Cancer (available at www.NCCN.org). For recommendations for patients in sub-Saharan Africa, please see the NCCN Harmonized Guidelines for Sub-Saharan

Africa for Cervical Cancer (available at www.NCCN.org/harmonized). For recommendations for other lower-resource areas, please see the NCCN Framework for Resource Stratification of NCCN Guidelines for Cervical Cancer (available at www.NCCN.org/framework).

Management of Precancerous Cervical Lesions in PWH

Treatment options for CIN include cryotherapy, loop electrosurgical excision procedure (LEEP), and cold knife conization.[283,284] These options are generally safe and effective for PWH.[285-290] However, endocervical extension is more frequent among PWH.[291] Therefore, loop excision is less effective and recurrence rates are higher in PWH than in those without HIV.[291-294] A single-center randomized trial in Kenya, however, showed that LEEP for high-grade CINs (CIN2+) resulted in a significantly lower rate of cervical neoplasia recurrence over 24 months than cryotherapy in 400 PWH.[295] A secondary subgroup analysis of this randomized controlled trial also found that LEEP was more likely to clear high-risk HPV (hrHPV) infection compared to those undergoing cryotherapy.[296] Persistent hrHPV infection is strongly associated with recurrent CIN2+, indicating that the benefits of LEEP may be attributed to its effectiveness in clearing hrHPV infection. Additionally, a randomized, double-blind, placebo-controlled trial investigated if HPV vaccination prior to LEEP could prevent CIN2+ recurrence in PWH but found no preventive effect.[297]

Workup for Cervical Cancer in PWH

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, PWH should be referred to an HIV specialist (see *HIV Management During Cancer Therapy*, above).

Additional workup for cervical cancer in PWH should be performed as described in the NCCN Guidelines for Cervical Cancer (available at www.NCCN.org). In addition, PWH with CIN or invasive cervical cancer should also be evaluated for field effects of HPV oncogenesis, namely anal and vulvar cancer. Non-malignant causes for lymphadenopathy and organ lesions should be considered, with referral for an infectious disease evaluation as indicated.

Management of Cervical Cancer in PWH

A systematic review published in 2015 identified only 8 studies (3 prospective and 5 retrospective) addressing the management of cervical cancer in PWH.[298] Hematopoietic grade 1 and 2 toxicity rates were higher in PWH than in patients without HIV. Grade 3 and 4 events that differed by HIV status were anemia (4% in PWH vs. 2%) and gastrointestinal reactions (5% in PWH vs. 2%). This systematic review also found that PWH who started ART early were more likely to complete cancer treatment. Additional data following the 2015 systematic review also suggest that PWH who have cervical cancer are more likely to experience hematologic toxicity and less likely to complete a full course of chemotherapy than patients without HIV.[299]

A prospective cohort study of 348 patients with cervical cancer in Botswana compared outcomes between the 66% who were living with HIV and those who were not.[36] The PWH had a 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 patients (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 those 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 these patients, regardless of their HIV

status, was lower than would be expected in the United States. Another study in Botswana included 143 patients with and without HIV, who were treated with radiation therapy for cervical cancer.[300] No differences were seen in 2-year overall survival or on acute toxicities between the participants with and without HIV. Other African studies have also shown that chemoradiation therapy is safe in PWH who have cervical cancer.[301,302]

Based on these limited data, the NCCN Panel recommends that PWH 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 PWH who have cervical cancer, with referral for an infectious disease workup if suspicious/PET-avid nodes are seen (also see *Cancer Workup in PWH*, above). Poor performance status in PWH 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. ART is recommended for all PWH and may improve performance status.

Management of Cancer in PWH in Lower Resource Settings

Low- and middle-income countries (LMIC) have been disproportionately affected by HIV. In fact, there were over 20 million PWH in East and Southern Africa and almost 5 million in West and Central Africa in 2019, together accounting for 67% of global HIV incidence.[303] As ART has become more accessible in LMIC, PWH have a decreased risk of AIDS development, improved survival, a decline in AIDS-defining cancers, and an increase in non–AIDS-defining cancers, much like higher resource regions experienced previously.[304] Despite these declines, the burden of cervical cancer and Kaposi sarcoma has remained high in LMIC.[304-306]

Cancer treatment in LMIC, however, is constrained by limited resources.[307] In fact, cancer mortality is higher in Africa than in high-income countries.[308] Research into effective cancer treatments that are more cost-effective and readily available in lower-resource regions are needed, but conducting clinical trials in these areas can be challenging.[309]

Overall, the panel believes that most PWH who develop cancer in LMIC should be offered the same cancer therapies as individuals without HIV, and modifications to cancer treatment should not be made solely on the basis of HIV status. The NCCN Harmonized Guidelines for Sub-Saharan Africa, NCCN Guidelines that have been adapted for regions such as Latin America and the Middle East/North Africa, and the NCCN Framework for Resource Stratification of NCCN Guidelines (all available at www.NCCN.org) are resources that can help PWH who have cancer worldwide to receive the best care available.

Summary

Cancer treatment is generally as safe and effective for PWH as it is for patients without HIV, and the NCCN Panel recommends that most PWH who develop cancer should be offered the same cancer therapies as individuals without HIV. Modifications to cancer treatment should not be made solely based on HIV status. However, PWH who have cancer require special considerations, including the possible need to modify ART or cancer therapy based on the potential for DDIs, potential modifications to supportive care, 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 PWH who have 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 ART is recommended for all PWH and may improve performance status. The panel strongly recommends that an HIV specialist be involved in the care of PWH during cancer treatment.

Unfortunately, data on the treatment of PWH 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 American Society of Clinical Oncology (ASCO) and Friends of Cancer Research HIV Working Group, PWH should not be excluded from cancer clinical trials if they meet specified criteria.[310] Clinicians who work with PWH 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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