Evolving Paradigms in HIV Malignancies: Review of Ongoing Clinical Trials

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Abstract

This review highlights current interventional clinical trials for HIV-associated malignancies (HIVAMs), with emphasis on 4 mechanistic areas: immunomodulatory therapies and gene therapies, including immune checkpoint inhibitors; cytotoxic therapies; novel tumor-targeted and virally targeted therapies in both AIDS-defining and non-AIDS-defining cancers (NADC); and other screening or topical/ablative interventions. A search on ClinicalTrials.gov located 35 trials, including 12 immunomodulatory or gene therapy trials, 6 cytotoxic therapy trials, 10 trials of therapies with tumor or viral molecular targets, and 7 trials evaluating screening interventions or topical or ablative therapies. Study drugs, mechanisms, and outcomes of interest, including future directions, are discussed. Targeted therapies and immunotherapies address not only the tumor but underlying viral oncogens, including possible benefits on HIV-specific immunologic control. The resulting science from the trials listed in this review will provide important translational breakthroughs for people living with HIV (PLWH) and cancer. We highlight disease-specific challenges that could be addressed in future studies, including testing the safety and efficacy of cutting-edge immunotherapy and targeted treatments used in the general cancer population, and improving gaps in knowledge and practice for cancer screening and its treatment, especially in low-resource regions. Additional important considerations include identification of novel therapies for virally mediated tumors that disproportionately present in PLWH, how to treat persons with HIVAM and advanced immunosuppression, and how to comanage both diseases in antiretroviral therapy-naïve persons and those receiving care in settings where supportive therapies for hematologic toxicities and infections are limited. Current and future clinical trials should address needs of both resource-replete and -limited regions, as well as cancers that are uncommon in or respond differently to HIV-negative populations (eg, Kaposi sarcoma or anal cancer), in addition to an increased focus on NADCs not traditionally linked with HIV, such as lung or gastrointestinal tumors.

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Since the advent of combination antiretroviral therapy (ART), malignancies have become among the leading causes of death in persons living with HIV (PLWH).¹ As treatment outcomes for PLWH and malignancies have improved in the past 2 decades, clinical trials for HIV-associated malignancies (HIVAMs) have also tremendously evolved. Until recently, most cancer-specific treatment trials excluded PLWH. For example, the Friends of Cancer Research HIV Working Group reviewed eligibility criteria from studies supporting 46 new drug applications of agents in patients with cancer

that led to FDA approval from 2011 to 2015 and found that 74% of these studies had HIV-specific or general infection exclusion criteria, likely excluding PLWH. However, they also reported on 13 studies that specifically included PLWH, and from these studies summarized several potential approaches for including PLWH in future cancer trials. They concluded that although HIV infection should no longer be an exclusion criterion for most cancer trials, concurrent ART therapy and immune status should be considered in the development of trial eligibility criteria.²

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Study of ART use with HIVAM treatment is particularly important, because the WHO only recently began to strongly recommend initiating ART for all PLWH regardless of CD4-positive T-cell count (CD4 count) after 2 large randomized trials demonstrated overall benefit, especially in terms of non-AIDS-defining morbidity and mortality.³⁻⁵ Further understanding of the role of chronic immune activation and exhaustion in both HIV and cancer has also supported the idea that ART and cancer-directed therapies must go hand-in-hand.⁶⁻⁹ Thus, in cancers common in non-HIV-infected populations, many trials have had to focus on safety and pharmacokinetic studies in persons on ART, simply to prove that the regimen can be tolerated immunologically and that these regimens do not cause drug-drug interactions with strong inducers or inhibitors of cytochrome P450 enzymes (eg, efavirenz or protease inhibitors, respectively).

In addition, the burden of cancer is now being seen in sub-Saharan Africa (SSA) and other resource-limited regions, where longer life expectancy on ART and higher burden of viral oncogens has caused HIVAMs to become the second-leading cause of death, after tuberculosis, in PLWH. Thus, current and future clinical trials will need to address the needs of both resource-replete and resource-limited areas, as well as cancers that are uncommon or respond differently in HIV-negative populations, such as Kaposi sarcoma (KS) or anal cancer. This review summarizes and highlights current HIVAM clinical trials, with emphasis on 4 mechanistic areas: immunomodulatory therapies and gene therapies, including immune checkpoint inhibitors (ICIs); cytotoxic therapies; novel tumor-targeted and virally targeted therapies in both AIDS-defining cancers (eg, KS, AIDS-defining lymphomas, and cervical cancer) and non-AIDS-defining cancers (NADCs); and other screening or topical/ablative interventions.

Process

We initiated a search on ClinicalTrials.gov using the following search terms: “HIV” or “AIDS” or “acquired immunodeficiency syndrome” plus “malignancy,” “cancer,” “squamous intraepithelial lesions,” or “Kaposi sarcoma.” We limited trials to interventional treatment and screening trials, and included only those listed as active, recruiting, enrolling, or not yet recruiting. A total of 35 trials were found, including 12

immunomodulatory or gene therapy trials, 6 cytotoxic therapy trials, 10 trials of therapies with tumor or viral molecular targets, and 7 trials evaluating screening interventions or topical or ablative therapies.

ICIs, Gene Therapy, and Other Immunotherapies

Among the immunomodulatory or gene therapy trials, most were phase I or I/II (n=9; Table 1). Most of the trials focused on lymphoma (n=6), 2 on KS, 1 on non-small cell lung cancer, 1 on multiple tumor types, and 1 on human papillomavirus (HPV)-related cancers. There were only 3 phase II studies, all of which involved a PD-1 inhibitor alone or in combination with a CTLA-4 inhibitor. In addition, 5 of the lymphoma studies evaluated gene-modified stem cell trials with or without cytotoxic chemotherapy, with 1 phase I/II allogeneic Epstein-Barr virus (EBV)-specific cytotoxic T-cell transplant trial for EBV-associated lymphoproliferative disorders. Lastly, there were 2 studies of pomalidomide, a thalidomide analog and immunomodulatory drug (IMiD) that augments T-cell- and NK-cell-mediated immunity and exerts antiangiogenic and antineoplastic effects.¹⁰ These trials evaluated pomalidomide in combination with liposomal doxorubicin for advanced or refractory KS, and pomalidomide alone in individuals with high-grade squamous intraepithelial lesions (HSIL).

Immunomodulatory Agents and Effects on HIV-1 Replication and Latency

Blocking of both PD-1 and CTLA-4 in HIV-1-specific, CD4- and CD8-positive T cells leads to a recovery of cell proliferation and cytokine production *in vitro*.¹¹ Furthermore, CTLA-4 blockade also increases CD4-positive T-cell proliferation and augments HIV-specific CD4-positive T-cell function.^{12,13} In a simian immunodeficiency virus (SIV)-infected macaque model, blockade of PD-1 by a monoclonal antibody increased the number of virus-specific CD4-positive T cells and memory B cells and levels of envelope-specific antibodies. These immunologic effects were associated with the lack of side effects and significantly increased overall survival of the treated SIV-infected macaques.¹⁴

Given these promising data, several ICI trials, including the AMC-095 study of combined CTLA-4/PD-1 blockade, featured laboratory end points, in-

Table 1. Immune Checkpoint Inhibitors, Gene Therapy, and Other Immunotherapies for HIV-Associated Malignancy

Clinical Trial Title (ClinicalTrials.gov Identifier)	Study Interventions	Trial Design ^a and Mechanisms	Diseases
Phase I Study to Evaluate the Safety, Feasibility and Immunologic Correlatives of Intra-Lesional Nivolumab Therapy for Limited Cutaneous Kaposi Sarcoma (NCT03316274) Location: United States Sponsor: University of California, San Francisco	Biologic: Intralesional injection of nivolumab	Phase I: Safety, feasibility, immunologic correlatives in treated HIV-infected or HIV-uninfected persons Mechanism: Anti-PD-1 antibody	Limited cutaneous KS
A Phase I Trial of Pomalidomide in Combination With Liposomal Doxorubicin in Patients With Advanced or Refractory Kaposi Sarcoma (NCT02659930) Location: United States Sponsor: NCI	Drugs: Liposomal doxorubicin, pomalidomide	Phase I: Safety, tolerability of liposomal doxorubicin, pomalidomide combinations in 2 groups: (1) KS requiring systemic therapy; (2) KS with concurrent KSHV-associated MCD or KICS; HIV+/-	KS
Phase I Study of MK-3475 (Pembrolizumab) in Patients With Human Immunodeficiency Virus (HIV) and Relapsed/Refractory or Disseminated Malignant Neoplasm (NCT02595866) Location: United States Sponsor: NCI	Biologic: Pembrolizumab	Phase I: Safety, feasibility, tolerability, efficacy Secondary outcomes: HIV reservoir, anti-HIV cytotoxicity Mechanism: Anti-PD-1 antibody	cHL and NHL Advanced, recurrent/refractory, or metastatic neoplasms: melanoma, hepatocellular carcinoma, KS, NSCLC
An Evaluation of the Toxicity and Therapeutic Effects of Epstein-Barr Virus-Immune T-Lymphocytes Derived From a Normal HLA-Compatible or Haplotype-Matched Donor in the Treatment of EBV-Associated Lymphoproliferative Diseases or Malignancies and Patients With Detectable Circulating Levels of EBV DNA Who Are at High Risk for EBV-Associated Lymphoproliferative Diseases (NCT0002663) Location: United States Sponsor: Atara Biotherapeutics	Biologic: Allogeneic EBV-specific cytotoxic T lymphocytes	Phase I/II: Dose finding and side effects/safety in PLWH or other immunodeficiency, history of organ or hematopoietic transplant, or with existing EBV-associated malignancy Mechanism: Increases killing of cells latently infected with EBV	EBV-induced lymphomas, EBV-associated malignancies, transplant patients with EBV viremia at high risk of developing a recurrent EBV lymphoma
A Clinical Trial of Gene-Modified Stem Cells to Generate HIV-Resistant Cells in Conjunction With Standard Chemotherapy for Treatment of Lymphoma in Patients With HIV Infection (NCT02343666) Location: United States Sponsor: Fred Hutchinson Cancer Research Center (FHCRC)	Biologic: C46/CCR5/P140K lentiviral vector-transduced autologous HSPCs Drugs: Carmustine, O6-benzylguanin	Phase I pilot: Side effects and dose-finding of HIV-resistant gene-modified stem cells Mechanism: C46 is an HIV entry inhibitor, mutation of the CCR5 coreceptor blocks HIV binding, and P140K allows chemoselection of transduced cells	Stage I-IV HL and NHL requiring autologous HSPS
AMC-097: Stem Cell Gene Therapy for HIV Mediated by Lentivector Transduced, Pre-Selected CD34+ Cells (NCT02797470) Location: United States Sponsor: AIDS Malignancy Consortium (AMC)	Biologic: Lentivirus vector CCR5 shRNA/TRIM5alpha/TAR decoy-transduced autologous hematopoietic progenitor cells Drugs: Carmustine, cytarabine, etoposide, melphalan	Phase I/II: Dose-finding and safety Mechanism: CCR5 shRNA knocks down CCR5 receptors, TRIM5a blocks HIV preintegration/postentry, and TAR decoy scavenges HIV Tat to prevent transcription	Recurrent adult HL, NHL, and Burkitt lymphoma
Safety and Feasibility of Stem Cell Gene Transfer Following R-EPOCH for Non-Hodgkin Lymphoma in AIDS Patients Using Peripheral Blood Stem/Progenitor Cells Treated With a Lentivirus Vector-Encoding Multiple Anti-HIV RNAs (NCT02337985) Location: United States Sponsor: City of Hope	Biologics: Lentivirus vector rHIV7-sh1-TAR-CCR5RZ-transduced hematopoietic stem/progenitor cells, rituximab Drugs: EPOCH	Phase I pilot: Single-arm, 6 cycles of R-EPOCH followed by infusion of gene therapy stem cells. rHIV7: shRNA targets an HIV exon, blocks Tat/rev transcription. TAR decoy: binds to HIV Tat to prevent transcription. CCR5RZ: ribozyme catalyzes CCR5 to prevent coreceptor use by HIV	NHL requiring autologous HCT
AMC-095: A Phase I Study of Ipilimumab and Nivolumab in Advanced HIV-Associated Solid Tumors With Expansion Cohorts in HIV-Associated Solid Tumors and a Cohort of HIV-Associated Classical Hodgkin Lymphoma (NCT02408861) Location: United States, Australia Sponsor: AMC/NCI	Biologic: Ipilimumab, nivolumab	Phase I: Side effects and optimal dose of nivolumab when combined with ipilimumab ^b Mechanism: Ipilimumab: monoclonal antibody against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) Nivolumab: anti-PD-1 antibody	Unresectable, advanced, and metastatic solid neoplasms; anal carcinoma; KS; lung carcinoma; cHL
Immunotherapy by Nivolumab After Prior Chemotherapy for HIV+ Patients With Advanced Non-Small Cell Lung Cancer (NSCLC): IFCT-CHIVA2 Phase IIa Trial (NCT03304093) Location: France Sponsor: Intergroupe Francophone de Cancerologie Thoracique	Biologic: Nivolumab	Phase II: Single-arm, open-label trial of nivolumab given in patients with progression after primary cytotoxic therapy Secondary outcomes: HIV reservoir and herpesvirus replication Mechanism: Anti-PD-L1 antibody	Stage IIIB/metastatic NSCLC
A Phase II Exploratory Study of Durvalumab (MEDI4736) in HIV-1 Patients With Advanced Solid Tumors (NCT03094286) Location: Spain Sponsor: Spanish Lung Cancer Group	Biologic: Durvalumab	Phase II: Feasibility, efficacy in PLWH and CD4 count >350 cells/mm ³ Secondary outcomes: Anticancer and anti-HIV immunity Mechanism: Anti-PD-L1 antibody	Advanced/Metastatic solid tumors
Study of Pomalidomide in Anal Cancer Precursors (SPACE): A Phase 2 Study of Immunomodulation in People With Persistent HPV-Associated High Grade Squamous Intraepithelial Lesions (NCT03113942) Location: Australia Sponsor: Kirby Institute	Drug: Pomalidomide	Open-label phase II: Efficacy of pomalidomide in persistent HPV-associated HSILs in patients with and without HIV Mechanism: Cereblon inhibition (IMiD), antiangiogenesis, antiproliferative effects	Anal HSILs
Optimized Antiretroviral Therapy During Allogeneic Hematopoietic Stem Cell Transplantation in HIV-1-Infected Individuals (NCT01836068) Location: United States Sponsor: Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins	Drug: Enfuvirtide (T-20)	Phase I: Feasibility of maintaining uninterrupted ART with enfuvirtide monotherapy post-HCT if oral ART not tolerated Secondary outcome: Cell-associated HIV DNA Mechanism: HIV fusion inhibitor	Any underlying hematologic malignancy requiring allogeneic HCT

Abbreviations: ART, antiretroviral therapy; cHL, classic Hodgkin lymphoma; EBV, Epstein-Barr virus; EPOCH, etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin; HCT, hematopoietic cell transplant; HL, Hodgkin lymphoma; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; HSPS, hematopoietic stem and progenitor cell; IMiD, immunomodulatory drug; KICS, Kaposi sarcoma-associated herpesvirus inflammatory cytokine syndrome; KS, Kaposi sarcoma; KSHV, Kaposi sarcoma-associated herpesvirus; MCD, multicentric Castleman disease; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung cancer; PLWH, persons living with HIV; shRNA, short hairpin RNA.

^aUnless otherwise noted, trials include only persons with treated HIV infection (ie, on ART and/or virologic control). Noted studies include persons without HIV infection.

^bUntreated HIV allowed as long as the participant is either stable while on or not on ART for 4 weeks before and then during the study.

cluding quantitation of the replication-competent viral reservoir in peripheral blood mononuclear cells, and measurement of anti-HIV-specific T cells. The French ANRS CO24 OncoVIHAC cohort will prospectively follow all available PLWH who receive ICI as part of routine cancer care to evaluate their safety and effects on the HIV reservoir (ClinicalTrials.gov identifier: NCT03354936). The Cancer Immunotherapy Trials Network (CITN) trial of pembrolizumab in solid tumors and Hodgkin lymphoma will also address these questions through longitudinal analysis of the replication-competent HIV reservoir (ClinicalTrials.gov identifier: NCT02595866).

Hematopoietic Cell Transplant and Gene Therapy Trials

Current allogeneic and autologous hematopoietic cell transplant (HCT) trials focus on safely increasing the aggressiveness of conditioning regimens, as well as leveraging clinical indications for autologous HCT to investigate gene therapies for functional HIV cure. City of Hope is currently testing the safety and impact of high-dose conditioning with carmustine, etoposide, and cyclophosphamide followed by autologous HCT on HIV-specific immune reconstitution in patients with HIV-associated lymphoma (NCT02337985). Preliminary results of the CTN 0903/AMC-080 trial showed that overall survival in myeloablative/nonablative transplant recipients with HIV was similar to historical results for non-HIV-infected persons (82% at 6 months, 57% at 1 year), with no deaths attributable to HIV.¹⁵ Another ongoing study is evaluating the feasibility and efficacy of subcutaneous enfuvirtide monotherapy as a bridge for patients who are unable to take oral ART following HCT (ClinicalTrials.gov identifier: NCT01836068).

Several active trials leverage clinically indicated HCT to test gene-edited autologous hematopoietic cells targeted at HIV. Each study is using a lentivirus vector with 3 gene targets in different combinations. AMC-097 is evaluating transduced autologous CD34-positive cells with short hairpin RNA (shRNA) CCR5 that causes interference to transcription of this gene, preventing expression of one crucial coreceptor required for HIV-1 cell entry. TRIM5 α prevents proviral integration by blocking uncoating of HIV capsids in the cytosol, which is thought to be one of the factors that render rhesus monkeys resistant to HIV infection.

The last component is a TAR decoy oligonucleotide, which outcompetes HIV *Tat* to prevent transcription at the promoter.¹⁶ The study from Fred Hutchinson Cancer Research Center (NCT02343666; Table 1) pairs a mutated CCR5 sequence with an HIV entry inhibitor (C46) and a chemoselection agent (P140K). P140K causes cellular resistance to O6-benzylguanine, a highly toxic suicide inhibitor, thus enriching the population of transduced cells while depressing both nontransformed HCT and malignant cell lines. The last study tests a rHIV7-shI-TAR-CCR5RZ combination, again targeting TAR and CCR5, this time through a ribozyme that catalyzes CCR5, added to a different shRNA (rHIV7), which blocks transcription of HIV *Tat/Rev* (NCT02337985).

Cytotoxic Chemotherapy

Of the 6 trials evaluating novel cytotoxic therapeutic trials, 5 are accruing PLWH with Hodgkin's or non-Hodgkin lymphomas (Table 2). Early findings from the only phase I/II safety and efficacy trial evaluating substitution of the CD30 monoclonal antibody brentuximab vedotin for bleomycin has demonstrated safety in 7 patients.¹⁷ Other studies evaluating cytotoxic therapy are phase II studies determining the safety and efficacy of other novel therapies for HIV-associated lymphoma, including short-course EPOCH (etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin) and the addition of ibrutinib in dose-adjusted EPOCH as frontline treatment (NCT00006436 and NCT03220022, respectively). One trial is evaluating the safety and efficacy of rituximab plus CHOP (prednisone/vincristine/cyclophosphamide/doxorubicin) in Malawi, a resource-limited setting (NCT02660710), and another is determining the efficacy of methotrexate/leucovorin/rituximab in primary central nervous system lymphoma (NCT00267865). The only currently open phase III trial in this group is evaluating the novel modulated electrohyperthermia (mEHT; Oncothermia) plus standard chemoradiotherapy for locally advanced cervical cancer in South Africa (NCT03332069). Previous studies have shown that the addition of hyperthermia to conventional cytotoxic therapy improves treatment efficacy.¹⁸ mEHT utilizes the principles of extracellular hyperthermia using low frequency modulated direct electroic field, but not temperature-dependent, effects of electromagnetic fields and special modulation, the effect of

Table 2. Cytotoxic Chemotherapy Trials for HIV-Associated Malignancy

Clinical Trial Title (ClinicalTrials.gov Identifier)	Study Interventions	Trial Design ^a and Mechanisms	Diseases
A Pilot Trial of AVD and Brentuximab Vedotin (SGN-35) in the Treatment of Stage II-IV HIV-Associated Hodgkin Lymphoma (NCT01771107) Location: United States, France Sponsor: NCI	Drugs: Brentuximab vedotin + dacarbazine, doxorubicin hydrochloride, vinblastine	Pilot phase I/II: Dose finding, side effects, efficacy Mechanism: Chimeric monoclonal antibody to CD30 conjugated to the antimitotic agent monomethyl auristatin E (MMAE or vedotin)	AIDS-related stage II-IV HL
Short-Course EPOCH-Rituximab in Untreated CD-20+ HIV-Associated Lymphoma (NCT00006436) Location: United States Sponsor: NCI	Biologics: Rituximab, filgrastim Drugs: EPOCH	Nonrandomized phase II: Dose-deescalation study; treatment every 3 weeks with combination of EPOCH + rituximab for 1 cycle beyond complete response by CT of all detectable tumors for a minimum of 3 and maximum of 6 cycles	AIDS-related NHL, DLBCL
LCCC 1335: A Single-Arm Phase I/II Clinical Trial of Rituximab Plus CHOP Chemotherapy for Diffuse Large B-cell Lymphoma in Malawi (NCT02660710) Location: Malawi Sponsor: UNC Lineberger Comprehensive Cancer Center	Biologic: Rituximab Drugs: Cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone (R-CHOP)	Nonrandomized phase II: 40 adult patients aged 18–60 years (20 HIV-infected with CD4 count ≥100 cells/mm ³ , 20 HIV-uninfected) will receive a maximum of 6–8 cycles of R-CHOP Outcome: To establish the safety of R-CHOP in the Malawi population	DLBCL, HIV
Phase I and Dose-Expansion Study of Ibrutinib and R-da-EPOCH for Front Line Treatment of AIDS-Related Lymphomas (NCT03220022) Location: United States Sponsor: NCI	Drugs: Cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, etoposide, prednisone, ibrutinib Biologic: Rituximab	Phase I: Side effects, dose finding of ibrutinib in combination with R-EPOCH in stage II-IV DLBCLs	AIDS-related NHL
Chemotherapy and HAART to Treat AIDS-related Primary Brain Lymphoma (NCT00267865) Location: United States Sponsor: NCI	Drugs: Methotrexate, leucovorin Biologic: Rituximab	Nonrandomized phase II: Induction with rituximab, high-dose methotrexate, leucovorin every 2 weeks x 6 cycles. Consolidation with high-dose methotrexate alone	Primary central nervous system lymphomas
Modulated Electro-Hyperthermia Plus Chemoradiation for Locally Advanced Cervical Cancer Patients in South Africa (NCT03332069) Location: South Africa Sponsor: National Research Foundation of South Africa, NTP Radioisotopes SOC Ltd	Device: mEHT Radiation: External-beam radiation, brachytherapy Drug: Cisplatin	Phase III: Standard chemoradiotherapy with or without mEHT for locally advanced cervical cancer. End points: (1) local disease control at 6 months on imaging, (2) progression-free survival	Cervical carcinoma

Abbreviations: AVD, doxorubicin/vincristine/dacarbazine; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; DLBCL, diffuse large B-cell lymphoma; EPOCH, etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin; HL, Hodgkin lymphoma; mEHT, modulated electrohyperthermia; NHL, non-Hodgkin's lymphoma.
^aUnless otherwise noted, trials include only persons with treated HIV infection (ie, on ART and/or virologic control).

which may exceed that of the overall heating (macroscopic temperature elevation) by 3- to 4-fold.¹⁹ mEHT does not require hyperthermia-range temperature and may be performed safely, without invasive thermal control.²⁰

Targeted and Molecular Therapies

We identified 10 active trials of therapies targeted at viral oncogenes or other molecular targets, most of which are phase I or II (Table 3). Four trials include antiviral drugs for KS-associated herpesvirus (KSHV) activity in KS or KSHV-associated lymphoproliferative disorders. An NCI-sponsored study is evaluating 5 different oncolytic virotherapy approaches to multicentric Castleman's disease and/or KSHV-associated inflammatory cytokine syndrome (KICS), including combinations of zidovudine and ganciclovir, IMiDs, sirolimus, rituximab, and interferon- α , with or without cytotoxic chemotherapy per underlying disease (NCT00092222). AMC-098 is studying nelfinavir, an early-generation HIV protease inhibitor once abandoned for its off-target effects, and more recently found to directly inhibit KSHV replication in vitro and in vivo (NCT03077451).^{21–23} This trial uses higher-than-

standard nelfinavir dosing to parlay the well-known “off-target” effects on NF κ B, VEGF, HIF-1- α , and PI3K/Akt pathways. A Mexican government-sponsored study is evaluating the impact of 4 weeks of valganciclovir on KICS in ART- and treatment-naïve persons with limited KS (NCT03296553). Finally, a Brazilian study is evaluating the safety and maximum tolerated dose of using a class I histone deacetylase inhibitor (HDAC) “kick” followed by valganciclovir to “kill” latently infected KSHV-infected cells (NCT03397706).

Three additional KS trials target tumor angiogenesis. The first (AMC-096) uses recombinant soluble Ephrin B4 fusion protein (sEphB4-HSA) inhibition of the EphB2-VEGF pathway (NCT02799485). The second study is from the United Kingdom evaluating the safety and tolerability of selumetinib, an orally active, ATP-independent inhibitor of the mitogen-activated protein kinase kinase (MEK/ERK 1/2) pathway (NCT01752569). The third study (AMC-087) is a multitumor phase I dose-finding study evaluating the safety of the c-MET/multi-tyrosine kinase inhibitor cabozantinib in PLWH, including patients with KS and several other cancers (NCT01822522).

Finally, 3 studies are evaluating antiviral approaches for HPV-related neoplasia. The first is an open-label

HIV Malignancies: Ongoing Studies Review

Table 3. Targeted and Molecular Therapies for HIV-Associated Malignancy

Clinical Trial Title (ClinicalTrials.gov Identifier)	Study Interventions	Trial Design ^a and Mechanisms	Diseases
AMC-098: A Pilot Study of Nelfinavir for the Treatment of Kaposi Sarcoma (NCT03077451) Location: United States and Uganda Sponsor: AMC	Drug: Nelfinavir	Phase II: Intra-person dose-escalation to high-dose nelfinavir. Efficacy against tumor and herpesvirus replication; HIV+ and HIV- study arms Mechanism: Antiviral protease inhibitor	Endemic, classic, and HIV-associated KS
Valganciclovir for Suppression of HHV-8 Four Weeks Prior to Initiation of cART in Patients With Disseminated Kaposi Sarcoma Compare With Standard Therapy, Its Impact on the Development of IRIS and Attributable Mortality (NCT03296553) Location: Mexico Sponsor: National Institute of Cancerologia	Drugs: Valganciclovir + cART	Phase II: Randomized open-label: valganciclovir x 4 weeks followed by ART initiation with valganciclovir maintained until KSHV DNA undetectable in blood vs cART initiation alone in KS Main outcome: Immune reconstitution inflammatory syndrome-related mortality Mechanism: Antiviral, DNA polymerase inhibition	KS
Targeted Oncolytic Virotherapy and Natural History Study of KSHV-Associated Multicentric Castleman's Disease With Laboratory and Clinical Correlates of Disease Activity (NCT00922222) Location: United States Sponsor: NCI	Drugs: (1) High-dose zidovudine + ganciclovir (2) High-dose zidovudine, ganciclovir + bortezomib (3) Sirolimus (4) Rituximab + liposomal doxorubicin, interferon-alpha (5) Rituximab + EPOCH	Phase II: Natural history, comparison of outcomes treatment in 1 of 5 parallel comparator arms depending on clinical course in HIV+/- Main outcome: Evaluate natural history and clinical correlates of multicentric Castleman's disease treatments	KSHV-associated lymphoproliferative disorders
AMC-096: sEphB4-HSA in Treating Patients With Kaposi Sarcoma (NCT02799485) Location: United States Sponsor: AMC	Biologic: Recombinant EphB4-HSA fusion protein	Phase II: Efficacy and safety, evaluate effects on the (VEGF)-Notch-EphrinB2 angiogenic pathway in HIV+/- Main outcome: Clinical response and toxicity of recombinant EphB4-HSA fusion protein (sEphB4-HSA) (at initial dosing of 15 mg/kg every 2 weeks) Mechanism: Inhibition of EphA3 and EphB4 (antiangiogenesis)	KS
A Study of Selumetinib in Patients With Kaposi's Sarcoma (SCART) (NCT01752569) Location: United Kingdom Sponsor: Sheffield Teaching Hospitals NHS Foundation Trust	Drug: Selumetinib	Phase I: Completed, identified optimal dose. Phase II: Safety and efficacy with ART Mechanism: Mitogen-activated protein kinase kinase (MEK/ERK 1/2)	KS
A Phase 1b/2 Open-Label, Dose Escalation & Expansion Study of Orally Administered VRx-3996 & Valganciclovir in Subjects With Epstein-Barr Virus-Associated Lymphoid Malignancies (NCT03397706) Location: United States, Brazil Sponsor: Viracta Therapeutics, Inc.	Drugs: VRx-3996 (tractinostat), valganciclovir	Phase 1b/II: Safety and maximally tolerated dose of VRx-3996 in combination with valganciclovir, in HIV+/- Mechanism: Class I histone deacetylase inhibitor "kick" with valganciclovir "kill" of latently EBV-infected cells	EBV-associated lymphoma lymphoproliferative disorders
AMC 087: Phase I Trial of Cabozantinib (XL184) for Advanced Solid Tumors in Persons With HIV Infection (NCT01822522) Location: United States Sponsor: NCI	Drug: Cabozantinib S-malate	Phase I: To determine the safety and maximally tolerate dose of cabozantinib-s-malate ^b Mechanism: Multiple tyrosine kinase inhibitor of VEGFR-2, c-MET, RET	Advanced/Recurrent/ Metastatic/ Unresectable solid neoplasms
Open-Label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Doses of Topical ABI-1968 in Subjects With Anal High-Grade Squamous Intraepithelial Lesions (aHSIL) (NCT03202992) Location: United States, Australia Sponsor: Antiva Biosciences	Drug: ABI-1968	Phase I: To evaluate topical ABI-1968, in treatment of anal precancerous lesions in HIV+/- Mechanism: Acyclic nucleoside phosphate with direct anti-HPV activity. Induces apoptosis only of HPV-infected cells	Anal canal HSIL
AMC-099: A Randomized, Placebo-Controlled Trial of HPV Vaccination to Reduce Cervical High-Grade Squamous Intraepithelial Lesions Among HIV-Infected Women Participating in an HPV Test-and-Treat Program (COVENANT) (NCT03284866) Location: Kenya, Malawi, South Africa, Tanzania, Uganda, Zimbabwe Sponsor: AMC	Biologic: Recombinant HPV nonvalent vaccine vs placebo	Phase III, randomized: Determine whether 9-valent vaccine prevents HSIL and cervical cancer in HIV-positive women on ART who have high-risk HPV but no lesions at baseline	Women with HIV/AIDS at risk for cervical cancer
HPV Vaccine to Interrupt Progression of Vulvar and Anal Neoplasia (VIVA) Trial: A Randomized, Double-Blind, Placebo-Controlled Trial (NCT03051516) Location: United States Sponsor: Fred Hutchinson Cancer Research Center	Biologic: Recombinant HPV nonvalent vaccine	Phase IV, randomized: Efficacy of adding HPV vaccine to ablative therapy for HSIL vulvar or anal lesions to decrease in HSIL recurrence, in HIV+/-	Anal canal HSIL, vulvar HSIL

Abbreviations: ART, antiretroviral therapy; EBV, Epstein-Barr virus; EPOCH, etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin; HPV, human papillomavirus; HSA, human serum albumin; HSIL, high-grade squamous intraepithelial lesion; KS, Kaposi sarcoma; KSHV, Kaposi sarcoma-associated herpesvirus.

^aUnless otherwise noted, studies include only persons with treated HIV infection (ie, on ART and/or virologic control).

^bUntreated HIV allowed as long as the participant is either stable while on or not on ART for 4 weeks before and then during the study.

phase I trial to determine the safety and tolerability of an acyclic nucleoside phosphate with direct anti-HPV activity for HSIL of the anal canal (NCT03202992). The others are phase III/IV randomized controlled trials evaluating the FDA-approved 9-valent Gardasil

HPV vaccine as a therapeutic strategy, including one for preventing HSIL in women coinfecting with HIV and high-risk HPV (COVENANT), and the other for preventing recurrence of HSIL after local ablative therapy for a first vulvar or anal HSIL lesion.

Interventional Screening Practices and Topical Therapies

We found 7 trials evaluating screening and treatment practices, all of which are aimed at detecting or treating HPV-associated squamous cell tumors or precursor lesions of cervical, oropharyngeal, or anal cancer (Table 4). One diagnostic trial in the cervix is evaluating the use of HPV screening plus either cytology or visual inspection with acetic acid for the detection of HSIL (NCT03324009). The second diagnostic test pairs carbon monoxide testing with a visual inspection of the oral cavity for malignancies and premalignancies and incorporates smoking cessation with patient follow-up (NCT02823847).

Of the remaining trials, 1 is evaluating the efficacy of topical curcumin in cervical HSIL (NCT02944578), and 4 are focusing on topical or ablative treatments of early invasive anal cancer or HSIL (Table 4). There is no standard of care for treating anal dysplasia, although electrocautery or argon plasma coagulation are both common first-line treatments, and previously documented recur-

rence rates have ranged from 0% to 79%. AMC-A01 (ANCHOR; NCT02135419) is investigating whether multimodal treatment of HSIL reduces incidence of anal carcinoma compared with observation in PLWH. AMC-092 (NCT02437851) is evaluating the efficacy of surgical excisional treatment alone for superficially invasive squamous cell carcinoma, and AMC-088 (NCT02059499) is an ongoing randomized study of intra-anal imiquimod 2.5% versus topical 5-FU 5% versus observation for the treatment of anal HSIL in PLWH. Finally, a phase II study is evaluating the safety and efficacy of radiofrequency ablation for anal HSIL (NCT03302858).

Future Directions

There are a broad range of active and soon-to-be-activated trials for HIVAM. Increasingly, as is the case for oncology clinical trials in general, the focus is on immunotherapy and targeted therapy, with lesser emphasis on cytotoxic therapy alone. Although the resulting science from the trials discussed provide

Table 4. Interventional Screening Practices and Topical Therapy for HIV-Associated Malignancy			
Clinical Trial Title (ClinicalTrials.gov Identifier)	Study Interventions	Trial Design ^a and Mechanisms	Diseases
Non-Invasive Oral Cancer Screening Among Individuals Who Have HIV Infection (NCT02823847) Location: United States Sponsor: The University of Texas MD Anderson	Procedures: Visual and direct fluorescent oral screening examination, oral biopsy Device: Carbon monoxide test	Diagnostic: Evaluate positive predictive value of these procedures to detect premalignant and malignant oral lesions in HIV-infected smokers; ART not specified	Malignant neoplasms of mesothelial and soft tissue
Development of a Two-Stage Cervical Cancer Screening Algorithm for Botswana (NCT03324009) Location: Botswana Sponsor: Beth Israel Deaconess Medical Center	Procedures: HPV screen followed by either Papanicolaou test or VIA	Diagnostic: Determine receiver operating characteristics for either HPV/Papanicolaou test or HPV/VIA algorithms; ART not specified	Women with HIV/AIDS at risk for cervical cancer
Biomolecular Effects of Topical Curcumin in HSIL Cervical Neoplasia (NCT02944578) Location: United States Sponsor: Emory University	Drug: Intravaginal administration of topical curcumin	Randomized phase II: Curcumin vs placebo prior to loop electrosurgical excision procedure in HIV+/-	Cervical neoplasia
AMC-A01: ANCHOR Study: Anal Cancer/HSIL Outcomes Research Study (NCT02135419) Location: United States (including Puerto Rico) Sponsor: AMC	Drugs: Imiquimod, fluorouracil Devices: Laser therapy, infrared photocoagulation therapy, thermal ablation therapy	Phase III: Compare topical or ablative treatment vs active monitoring in preventing anal cancer in patients with HSIL; ART not specified	Anal HSIL
AMC-092: A Multicenter Observational and Feasibility Study of Excision of Superficially Invasive Squamous Cell Carcinoma (SISCCA) of the Anal Canal and Perianus in HIV-Infected Persons (NCT02437851) Location: United States Sponsor: AMC	Observational: Following therapeutic conventional local surgery	Phase II: Persons who have had complete local excision of superficially invasive squamous cell cancer followed for 3 years for recurrence, survival, risk of colostomy, toxicities; CD4 >350 cells/mm ³ or on ART	Stage 0-I anal squamous cell cancer
AMC-088: A Randomized, Phase III Study of Intra-Anal Imiquimod 2.5% vs. Topical 5-Fluorouracil 5% vs. Observation for the Treatment of High-Grade Anal Squamous Intraepithelial Lesions in HIV-Infected Men and Women (NCT02059499) Location: United States (including Puerto Rico) Sponsor: AMC	Drugs: Imiquimod, fluorouracil	Phase III, randomized: Efficacy of (1) intra-anal imiquimod 2.5% and (2) intra-anal topical 5-fluorouracil (fluorouracil) 5% for treatment of anal HSIL vs observation alone for both medications; CD4 >200 cells/mm ³ and/or virologic control	Anal intraepithelial neoplasia, HSIL
A Safety and Efficacy Trial of Circumferential Anal Canal Radiofrequency Ablation for High-Grade Anal Intraepithelial Neoplasia Using the BARRX Anorectal Wand (NCT03302858) Location: United States Sponsor: Stephen E. Goldstone	Device: BARRX anorectal wand	Phase II: Safety, effectiveness of circumferential radiofrequency ablation to the anal canal using the BARRX ablation system to destroy anal HSIL in HIV+/-	HSIL HPV-related squamous cell carcinoma

Abbreviations: ART, antiretroviral therapy; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; VIA, visual inspection with acetic acid.
^aUnless otherwise noted, studies include only persons with treated HIV infection (ie, on ART and/or virologic control).

important translational breakthroughs for PLWH, the following disease-specific challenges need to be addressed in future studies.

Kaposi Sarcoma

Ongoing challenges in KS include suboptimal efficacy and attendant toxicities of cytotoxic chemotherapy, especially regions that bear the burden of this disease, such as SSA. Given the benefit of ICIs on reversing immune exhaustion, one of the key hypotheses being addressed is that these agents may have synergistic benefit for both HIV and herpesvirus infections, in contrast to other modalities that risk worsening virologic control. However, in addition to the risk of severe immunologic reactions,²⁴ cost and requirement for intravenous administration provide barriers to use of these therapies in low-resource settings. Additionally, given lower-than-expected efficacy of targeted therapies, future KS trials could consider combining multiple, ideally orally available agents with different mechanisms to target redundant KSHV and tumor-promoted angiogenesis and cell survival pathways.^{25–27}

HPV-Related Malignancies

Limited prospective outcome studies are available in HIV-associated cervical cancer, and retrospective studies have demonstrated that PLWH have decreased tolerability to chemoradiotherapy (chemoRT) compared with persons without HIV.^{28,29} Hematologic toxicity, particularly, often results in dose reductions or elimination of concurrent chemotherapy during RT. Future planned studies will examine the toxicities of outback carboplatin/taxol in ART-treated PLWH for 4 cycles after standard chemoRT for locally advanced cervical cancer. In addition, nelfinavir inhibits the phospho-AKT pathway and decreases oxygen consumption.^{30–32} As such, it has been investigated as a radiation sensitizer in a variety of cancers in HIV-negative patients. Compared with common radiation sensitizers, such as platins, potential benefits of nelfinavir include oral administration, relatively manageable side effects, and ease of delivery without refrigeration or handling precautions in low-resource regions.

Lymphoma

There are many new horizons, including gene therapy, for treatment of lymphoma in higher-resource

settings. Most of these could and should include PLWH routinely, and may simultaneously be able to evaluate strategies for HIV cure concurrent with need for cancer treatments. However, with the burden of AIDS-related lymphoma in SSA, and no current standard-of-care in this setting, future trials should focus on moving care toward accepted standards for resourced settings, where HIV infection may no longer be an independent predictor of death, once risk score and receipt of rituximab are taken into account.³³ Establishing the safety of rituximab in PLWH has been important, as will be ensuring access to this drug, including in the United States, where it is less commonly offered to PLWH.³⁴

NADCs and General Considerations

Most ongoing trials focus on cancers and precancers that are virally mediated and have a higher incidence among PLWH. Only a few phase I studies are investigating appropriate dosing and tolerability of agents among PLWH for NADC, such as anal, lung, hepatocellular, and oropharynx cancers. Future trials will need to determine the dosing and safety of novel cancer therapies for PLWH, as new therapies for cancers that are common in HIV-negative persons begin to be used to treat HIVAMs. This is of particular importance, given that PLWH have been shown to be less likely to receive cancer therapy³⁴ and to have poorer outcomes.³⁵

Additionally, increasing evidence shows that a robust immune system is critical to cancer control, as evidenced by improved outcomes with immunotherapy for multiple disease sites.^{36–39} Further work identifying and exploiting immunologic and molecular characteristics of cancers in PLWH may also improve treatment outcomes for PLWH.

Summary

Recently completed trials overall support the position by the Friends of Cancer Research HIV Working Group that, barring specific concerns, PLWH should be treated similar to individuals without HIV infection and should be included in similar trials and standard of care, assuming ART is carefully managed.⁴⁰ However, more research is needed to address several themes in HIVAM. Future trials should focus on not only testing safety and efficacy of cutting-edge immunotherapy and targeted treat-

ments being used in the general cancer population, but also improving the gaps in knowledge and practice for cancer screening and treatment, especially in low-resource regions. Additional important considerations include identifying novel therapies for virally mediated tumors that disproportionally pres-

ent in PLWH, treating persons with HIVAM and advanced immunosuppression, and optimizing co-management of both diseases in ART-naïve persons and those receiving care in settings where supportive therapies for hematologic toxicities and infections are limited.⁴⁰

References

- Vandenhende MA, Roussillon C, Henard S, et al. Cancer-related causes of death among HIV-infected patients in France in 2010: evolution since 2000. *PLoS One* 2015;10:e0129550.
- Uldrick TS, Ison G, Rudek MA, et al. Modernizing clinical trial eligibility criteria: recommendations of the American Society of Clinical Oncology–Friends of Cancer Research HIV Working Group. *J Clin Oncol* 2017;35:3774–3780.
- World Health Organization. Guideline on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV. Geneva, Switzerland; World Health Organization; 2015.
- Lundgren JD, Babiker AG, Gordin F, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015;373:795–807.
- TEMPRANO ANRS 12136 Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015;373:808–822.
- Vali B, Jones RB, Sakhdari A, et al. HCV-specific T cells in HCV/HIV co-infection show elevated frequencies of dual Tim-3/PD-1 expression that correlate with liver disease progression. *Eur J Immunol* 2010;40:2493–2505.
- Moir S, Fauci AS. B-cell exhaustion in HIV infection: the role of immune activation. *Curr Opin HIV AIDS* 2014;9:472–477.
- Yanik EL, Napravnik S, Cole SR, et al. Relationship of immunologic response to antiretroviral therapy with non-AIDS defining cancer incidence. *AIDS* 2014;28:979–987.
- Jones RB, Ndhlovu LC, Barbour JD, et al. Tim-3 expression defines a novel population of dysfunctional T cells with highly elevated frequencies in progressive HIV-1 infection. *J Exp Med* 2008;205:2763–2779.
- Polizzotto MN, Uldrick TS, Wyvill KM, et al. Pomalidomide for symptomatic Kaposi's sarcoma in people with and without HIV infection: a phase I/II study. *J Clin Oncol* 2016;34:4125–4131.
- Trautmann L, Janbazian L, Chomont N, et al. Upregulation of PD-1 expression on HIV-specific CD8+ T cells leads to reversible immune dysfunction. *Nat Med* 2006;12:1198–1202.
- Kaufmann DE, Kavanagh DG, Pereyra F, et al. Upregulation of CTLA-4 by HIV-specific CD4+ T cells correlates with disease progression and defines a reversible immune dysfunction. *Nat Immunol* 2007;8:1246–1254.
- Zaunders JJ, Ip S, Munier ML, et al. Infection of CD127+ (interleukin-7 receptor+) CD4+ cells and overexpression of CTLA-4 are linked to loss of antigen-specific CD4 T cells during primary human immunodeficiency virus type 1 infection. *J Virol* 2006;80:10162–10172.
- Velu V, Titanji K, Zhu B, et al. Enhancing SIV-specific immunity in vivo by PD-1 blockade. *Nature* 2009;458:206–210.
- Ambinder RF, Wu J, Logan B, et al. Allogeneic hematopoietic cell transplant (alloHCT) for hematologic malignancies in human immunodeficiency virus infected (HIV) patients (pts): Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0903)/AIDS Malignancy Consortium (AMC-080) trial [abstract]. *J Clin Oncol* 2017;35(15 Suppl):Abstract 7006.
- Podsakoff GM, Engel BC, Carbonaro DA, et al. Selective survival of peripheral blood lymphocytes in children with HIV-1 following delivery of an anti-HIV gene to bone marrow CD34(+) cells. *Mol Ther* 2005;12:77–86.
- Rubinstein PG, Moore PC, Rudek MA, et al. Brentuximab vedotin with AVD shows safety, in the absence of strong CYP3A4 inhibitors, in newly diagnosed HIV-associated Hodgkin lymphoma. *AIDS* 2018;32:605–611.
- Skitzki JJ, Repasky EA, Evans SS. Hyperthermia as an immunotherapy strategy for cancer. *Curr Opin Investig Drugs* 2009;10:550–558.
- Andocs G, Rehman MU, Zhao QL, et al. Comparison of biological effects of modulated electro-hyperthermia and conventional heat treatment in human lymphoma U937 cells. *Cell Death Discov* 2016;2:16039.
- Pang CLK, Zhang X, Wang Z, et al. Local modulated electro-hyperthermia in combination with traditional Chinese medicine vs. intraperitoneal chemoinfusion for the treatment of peritoneal carcinomatosis with malignant ascites: a phase II randomized trial. *Mol Clin Oncol* 2017;6:723–732.
- Gantt S, Carlsson J, Ikoma M, et al. The HIV protease inhibitor nelfinavir inhibits Kaposi's sarcoma-associated herpesvirus replication in vitro. *Antimicrob Agents Chemother* 2011;55:2696–2703.
- Gantt S, Casper C, Ambinder RF. Insights into the broad cellular effects of nelfinavir and the HIV protease inhibitors supporting their role in cancer treatment and prevention. *Current Opin Oncol* 2013;25:495–502.
- Gantt S, Cattamanchi A, Krantz E, et al. Reduced human herpesvirus-8 oropharyngeal shedding associated with protease inhibitor-based antiretroviral therapy. *J Clin Virol* 2014;60:127–132.
- Postow MA, Hellmann MD. Adverse events associated with immune checkpoint blockade. *N Engl J Med* 2018;378:1165.
- Rudek MA, Moore PC, Mitsuyasu RT, et al. A phase I/pharmacokinetic study of sunitinib in combination with highly active antiretroviral therapy in human immunodeficiency virus-positive patients with cancer: AIDS Malignancy Consortium trial AMC 061. *Cancer* 2014;120:1194–1202.
- Bender Ignacio RA, Lee JY, Rudek MA, et al. A phase Ib/pharmacokinetic trial of PTC299, a novel post-transcriptional VEGF inhibitor, for AIDS-related Kaposi's sarcoma: AIDS Malignancy Consortium trial 059. *J Acquir Immune Defic Syndr* 2016;72:52–57.
- Uldrick TS, Wyvill K, Peer C, et al. Phase I and pharmacokinetic study of sorafenib in Kaposi sarcoma [abstract]. *J Clin Oncol* 2013;31(Suppl):Abstract 10588.
- Simonds HM, Wright JD, du Toit N, et al. Completion of and early response to chemoradiation among human immunodeficiency virus (HIV)-positive and HIV-negative patients with locally advanced cervical carcinoma in South Africa. *Cancer* 2012;118:2971–2979.
- Ferreira MP, Coghill AE, Chaves CB, et al. Outcomes of cervical cancer among HIV-infected and HIV-uninfected women treated at the Brazilian National Institute of Cancer. *AIDS* 2017;31:523–531.
- Gupta AK, Li B, Cerniglia GJ, et al. The HIV protease inhibitor nelfinavir downregulates Akt phosphorylation by inhibiting proteasomal activity and inducing the unfolded protein response. *Neoplasia* 2007;9:271–278.
- Pore N, Gupta AK, Cerniglia GJ, et al. Nelfinavir down-regulates hypoxia-inducible factor 1alpha and VEGF expression and increases tumor oxygenation: implications for radiotherapy. *Cancer Res* 2006;66:9252–9259.
- Lin A, Maity A. Molecular pathways: a novel approach to targeting hypoxia and improving radiotherapy efficacy via reduction in oxygen demand. *Clin Cancer Res* 2015;21:1995–2000.
- Cingolani A, Cozzi Lepri A, Teofili L, et al. Survival and predictors of death in people with HIV-associated lymphoma compared to those with a diagnosis of lymphoma in general population. *PLoS One* 2017;12:e0186549.
- Rositch AF, Jiang S, Coghill AE, et al. Disparities and determinants of cancer treatment in elderly Americans living with HIV/AIDS [published online ahead of print]. *Clin Infect Dis*, doi: 10.1093/cid/ciy373
- Suneja G, Shiels MS, Melville SK, et al. Disparities in the treatment and outcomes of lung cancer among HIV-infected individuals. *AIDS* 2013;27:459–468.
- Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017;377:1919–1929.
- Eggermont AM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. *N Engl J Med* 2018;378:1789–1801.
- Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018;378:2078–2092.
- Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 Blockade with pembrolizumab in advanced Merkel-cell carcinoma. *N Engl J Med* 2016;374:2542–2552.
- Alvarnas JC, Zaia JA, Forman SJ. How I treat patients with HIV-related hematological malignancies using hematopoietic cell transplantation. *Blood* 2017;130:1976–1984.