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## Cancer Clinical Trials in Persons with HIV Infection

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### Abstract

**Purpose of the review**—The era of modern HIV therapeutics is well under way. The cancer and infectious disease epidemiology of HIV disease has markedly altered as populations are availed to the benefits of antiretroviral therapy (ARV). The types of cancers occurring among those with HIV infection has broadened but the case burden in absolute numbers is very low relative to the background population. There are fewer incident cases of the AIDS-defining cancers (aggressive B-cell lymphomas, Kaposi's sarcoma, cervical cancer). There is an increased risk for certain non-AIDS-defining cancers, but these occur somewhat sporadically relative to clinical trial enrollment. The changing epidemiology of cancer in HIV poses challenges as well as opportunities for participation of persons with HIV in cancer therapy clinical trials.

**Recent Findings**—There are a excellent examples of cancer trials that inform cancer therapy for patients with HIV infection. Examples include those from HIV-specific trials and from trials mainly focused on the background population that included patients with HIV infection.

**Summary**—Interpretation of clinical trials to guide therapy for those with HIV infection and cancer largely depends on data that does not include HIV infected patients. The ability to extend clinical trials findings to populations not included in clinical trials remains problematic for a variety of populations, including those with HIV or AIDS. Careful prioritization of studies designed to bridge this gap is needed. However, there are published studies that serve as excellent examples bridging these gaps and the portfolio of cancer therapy trials underway will inform HIV and cancer better than at any time in the past.

### Keywords

Transplant; Immunotherapy; Pharmacokinetics

### Introduction

Treatment advances in cancer therapeutics are informed by clinical trials. The ability to interpret clinical trial results and apply the findings depends on myriad factors including the statistical design of the clinical trial and the criteria for selection of participants onto the study. Whenever a clinical trial is designed specifically for individuals with HIV and cancer, applying the study results to clinical practice depends primarily on the validity of the study

design itself. However, most clinical trials are not specific for persons with HIV and cancer, and most trials have historically excluded those with HIV. This creates challenges for interpreting and applying the results to persons with HIV infection. To apply the findings of trials to populations not represented in the conduct of in the clinical trial requires adoption of assumptions about the data from trials that may or may not actually transfer to populations beyond the data provided in the clinical trial.

Now that the modern era of HIV therapeutics is well underway, it has become clear that most individuals with HIV infection, who are meticulous in adhering to the medication requirements, avoid the opportunistic complications of HIV disease that characterized the earlier era. These patients tend to be relatively healthy, at least from the HIV disease perspective. It follows that there is no longer acceptable medical rationale for routine exclusion of persons with HIV from cancer clinical trials. Patients who are healthy can undergo cancer therapy in many cases just as any other patient and with very similar outcomes. HIV disease can be viewed as a comorbid condition and assessed for its potential to impact cancer therapy. Patients who have more advanced HIV disease and related complications may be more frail and the approach to cancer therapy must take this into account. Similarly, the decision to enroll patients on clinical trials, and the entry criteria for participation on clinical trials must take the HIV disease status into account. The routine inclusion of persons with well controlled HIV remains a work in progress and is not consistent across clinical trials, but clearly the fixed posture for routine exclusion on the basis of HIV infection is not medically justifiable and is coming to a close.

This review includes examples from the past several years of clinical trials that are specific for those with HIV and cancer and also some examples where participants with HIV were included in a clinical trial that was primarily focused on the background population. The advantages of both approaches to cancer therapy along with some of the challenges to accrual are discussed.

## **Are Cancer Clinical Trials Specific for Persons with HIV infection Still Necessary?**

Since it is possible to identify people who are healthy with comorbid HIV who can be included in HIV-non-specific cancer clinical trials, it can be asked whether it remains useful to continue conducting trials that enroll only those with HIV infection. The answer to this question is clear: such studies are essential for a number of reasons. The disease biology and natural history may differ from the background populations. There may be concerns for applying a given therapy or therapeutic modality, such as hematopoietic stem cell transplantation in those with HIV. There may be concerns that pharmacokinetic interactions with ARVs could alter the dose-response curves or therapeutic index of cancer therapeutics. It is also possible that the cancer drugs could adversely affect the pharmacokinetics of the ARVs. Intense study of HIV viral loads, viral reservoirs, immune dynamics and cancer biology can only be done on studies that are designed specifically to address these kinds of issues. While the occasional cancer patient with HIV infection is appropriate to enroll on

background trials, that approach will not lead to the important science queried in the instances just given. A number of studies illustrate the importance of this approach.

Studies accessing potential pharmacokinetic interactions with chemotherapy, including novel agents, can only be accomplished with focused effort to address this problem. The National Cancer Institute and the AIDS Malignancy Consortium (AMC) have collaborated to prioritize agents and to conduct studies in order to insure that as novel agents are approved in cancer, those with HIV can be prescribed these medications with information on dosing and toxicity available according to ARV class. These trials have been designed to assess the PK and toxicity profiles of agents when paired with strong CYP3A4 inducers, such as the HIV protease inhibitors, or with the non-nucleoside reverse-transcriptase inhibitors expected to have less impact on pharmacokinetics. An important example of this type of clinical trials strategy was the AMC 061 that analyzed drug-drug interaction and toxicity of sunitinib given at various doses with the main ARV drug classes in persons with HIV and cancer. (1)\* The study suggested the need to reduce the dose of sunitinib to 37.5 mg/day when given with ritonavir-based ARV because of greater than expected myelosuppression. Similar studies have shown that ritonavir increases the toxicity of ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and thus reduces curative potential of the regimen in classical Hodgkin lymphoma (cHL) (2); ritonavir also increases the exposure to docetaxel thus raising the concern that alternate ARV components should be utilized when considering use of this antineoplastic drug. (3) Ongoing studies include those like AMC 078 (NCT01249443) assessing the combination of paclitaxel and carboplatin owing to interest of these agents in upper airway disease and the increased risk of head and neck cancers in HIV. AMC study 087 (NCT01822522) is evaluating ARV interactions with cabozantinib provides another important example of prioritizing this type of HIV-specific trial aimed at insuring safe use of novel cancer therapy agents in this population.

Clinical investigation of novel types of therapy such as immunotherapy, or for treatment modalities like hematopoietic cell therapeutics that have traditionally not been available to persons with HIV-infection, requires studies specific for HIV populations. There are several crucial reasons why this is so. First and foremost is the principled commitment to expand access to clinical trials for persons living with HIV. Therefore, clinical trials designed to show the feasibility of applying novel immunotherapeutics, including cellular therapy, must be conducted in the HIV-specific population to open the door to access to the broader portfolio of clinical trials. There are several important studies that have recently been completed or ongoing illustrative of this concept. The Blood and Marrow Clinical Trials Network (BMT CTN) in collaboration with the AMC completed a feasibility study and outcome estimate study enrolling 43 persons with HIV and hematologic malignancy who had recurrent disease following initial therapy. (4) \*\* This study demonstrated that persons with HIV benefit from autologous hematopoietic cell transplantation with treatment related mortality (5.2%), neutrophil and platelet recovery time (11 and 18 days respectively) that is similar to that seen in the background population. There was no loss of HIV disease control. Progression-free and overall survival were compared to matched case-controls from the Center for International Blood and Marrow Transplant Research (CIBMTR) database and no differences were observed between the HIV cases and the background cases. This study establishes autologous hematopoietic cell transplantation as a standard of care in relapsed

hematologic cancers and also informs appropriate inclusion criteria for HIV-infected persons on essentially all studies of autologous hematopoietic cell transplant for blood cancers. There are numerous gene therapy studies utilizing autologous hematopoietic cell transplantation aimed at providing this modality for cancer therapy but also assessing the potential effects on latent HIV reservoirs and subsequent HIV control (NCT02797470, NCT02378922). There is also a study being conducted of autologous gene modified HIV-resistant cells testing if engraftment can occur after combination chemotherapy, thus avoiding need for high-dose ablative chemotherapy, in previously untreated HIV-associated lymphomas (NCT02337985). An approach such as this, if ultimately successful, could expand cellular therapy to those where a high-dose conditioning regimen is not indicated or feasible to conduct.

There is also an ongoing trial of allogeneic hematopoietic cell transplant for persons with HIV and blood cancers (NCT01410344). Once this data is available it will inform how to consider inclusion of those with HIV onto clinical trials of allogeneic transplant, and may also suggest other HIV-specific studies that might include donors homologous for the 32 base pair deletion of the gene allele in the CCR5 HIV-1 co-receptor that could confer HIV resistance in the host. Gene modification of donor cells to make the host resistant to HIV is also an ongoing area of interest in cellular therapeutics and could potentially lead to improved outcomes for those with HIV infection.

There is also a continuing need to conduct disease-specific studies that are open only to those with HIV infection, or at least are designed to accrue sufficient numbers of persons with HIV for a primary analysis. Some cancers, such as those caused by the Kaposi's sarcoma herpes virus (also known as human herpes virus 8) are so tightly bound with HIV as part of the pathobiology of the disease, that specific study is essential. KSHV-related multicentric Castleman disease (MCD) occurs mainly in those with HIV infection, and study of this disease has yielded interesting finding relevant to therapy of those with high KSHV viral loads who are manifesting fevers, cytopenias and other laboratory abnormalities in the absence of overt Kaposi's sarcoma or even apparent MCD.(5, 6)\* This potentially lethal syndrome has been termed the KSHV Inflammatory Cytokine Syndrome (KICS) and it would likely not have been recognized except through intensive study of persons with HIV-related malignancies. Novel therapeutic approaches targeted to vulnerabilities in KSHV itself have been developed by focusing exclusively in the HIV population (7, 8). Additionally strategies to target interleukin-6 (IL-6), a prime mediator of KSHV-related Castleman, have yielded promising results utilizing the anti-IL-6 monoclonal antibody siltuximab in this setting (9).

In addition to the rare cancers associated with HIV infection, specific study of novel agents in the more commonly seen tumors associated with HIV are important to conduct. The new immuno-conjugate brentuximab approved for use in multiply relapsed Classical Hodgkin lymphoma or as maintenance therapy after autologous transplant is being studied by the AMC in collaboration with French investigators of the Lymphoma Academic Research Organization (LYSARC) (NCT01771107). There are several reasons for conducting an HIV specific study with the agent. There are drug-drug interactions with the monomethyl auristatin E component of brentuximab vedotin and with vinblastine with which it is often

co-administered. There is the potential for enhanced neurotoxicity when combining the agent with vinblastine. The black box warning for progressive multifocal leukoencephalopathy (PML) is of concern in this population and requires evaluation. Although there is very low likelihood that more definitive trials defining the use of brentuximab vedotin in the HIV population will be conducted, this trial will inform its safety profile and provide information for its feasibility when combined with AVD (doxorubicin, vinblastine, and dacarbazine). The use of brentuximab in those with HIV can then be informed by extrapolation from the treatment-defining trials that led to the labeling indications for the agent.

The AMC is conducting a number of studies of HPV infection and preventive strategies for cervical and anal cancer in persons with HIV. This programmatic approach to viral induced cancers among those with HIV represents both a clinical imperative and a rich scientific opportunity. The ANCHOR study (NCT02135419) is a large clinical trial of anal cancer prevention in persons with HIV. Other clinical trials in development in this arena have important public health implications as well and are strong examples for the need for HIV specific trials.

Recent advances in immunotherapy have also centered around checkpoint inhibition. Agents such as ipilimumab, nivolumab, pembrolizumab and others are creating opportunities for clinical research based on immunologic control of cancer. The overlap between immune evasion by HIV and cancer are intriguing. Two network studies have been launched in the US to study these agents. One is led by the NCI CCR in collaboration with the Cancer Immunotherapy Network (CITN) and another study being conducted by the AMC. The CITN trial (NCT02595866) is evaluating the safety of pembrolizumab in those with HIV and cancer, while the AMC study (NCT02408861) is evaluating the safety of ipilimumab and nivolumab in this setting. Each of these studies includes intensive study of HIV latent reservoirs and immune function that could not be done without specific HIV enrollment. Additionally, since the variety of tumors targeted on these studies would be difficult or impossible to accrue onto separate disease-specific studies, the feasibility data will provide needed information as the agents become available in the non-HIV setting for specific tumors. At the same time, the NCI-sponsored disease-specific studies of these agents are not excluding those with HIV infection.

### **Is there any utility to including persons with HIV onto cancer therapy clinical trials not specific to HIV?**

Access to clinical trials for those with HIV infection has traditionally been very limited. Prior to the advent of modern ARVs, this was rational because patients with HIV and cancer had short life expectancy. The typical rationale provided for exclusion of persons with HIV in the earlier era is no longer medically justifiable. It is incorrect to state that patients with HIV are more likely to have myelosuppression and lethal complications of chemotherapy. As demonstrated in the HIV-autologous transplant trial mentioned above (4), those with HIV and cancer who undergo intensive therapy have similar outcomes to the background population. Multiple other studies and retrospective analyses show this to be the case in

diffuse large B-cell lymphoma, classical Hodgkin lymphoma (cHL), and Burkitt lymphoma (10). Therefore, inclusion of those with HIV who are relatively healthy from the HIV perspective onto clinical trials who are otherwise eligible for the trial should be adopted as the contemporary standard. Exclusion should be based on evidence not speculation and habit.

Several trials have included those with HIV onto studies primarily focused on the background population and serve to illustrate both the importance of including this population and the feasibility of doing so. The SWOG 0816 study (conducted by the NCI National Clinical Trials Network (NCTN) in collaboration with the AMC) of response-adapted therapy in cHL using early interim fluorodeoxyglucose–positron emission tomography (FDG-PET) imaging was mainly focused on the background population but included those with HIV infection with specific eligibility criteria that allowed enrollment of those whose comorbid HIV status was unlikely to pose a risk either for the trial participant or for the study endpoints. (11)\*\* Of the three hundred thirty-six patients enrolled, 12 with HIV infection received treatment on the study (12). The study conclusions confirmed ABVD as highly effective in patients with advanced stage poor-risk HIV-cHL when administered in a multicenter non-HIV specialty setting and showed that PET-negative responses were seen at a similar rate as the background population in the trial. Moreover, there was no undue added toxicity as compared to non-HIV patients. This main finding of the trial supports the use of response-adapted therapy which is evolving to be a standard approach for HIV-negative patients with advanced stage HL. The inclusion of persons with HIV infection on the S0816 support the utilizing the response adapted approach in patients with HIV-HL, with the goal of reducing long-term toxicity. Given the relative rarity of HIV-cHL, inclusion of HIV on this study helped advance the clinical science relative to all individuals with cHL, regardless of HIV status.

The NCI Center for Cancer Research led study (conducted in collaboration with the NCTN and the AMC) of dose-adjusted EPOCH-R in previously untreated Burkitt lymphoma, C-Myc positive diffuse large B-cell lymphoma and plasmablastic Lymphoma was launched as a national study that includes both HIV-positive and negative individuals. The single institution setting for Burkitt lymphoma showed similar outcomes regardless of HIV status (13). The preliminary findings for first 77 patients receiving therapy on the national trial, 20 of whom were HIV positive, showed no effect of HIV status on outcomes. (14)\*\* Inclusion of persons with HIV onto this clinical trial served to strengthen the trial findings overall, and helped overcome accrual barriers by enlarging the overall eligible population in this rare disease.

Finally, the ECOG-ACRIN lead NCI-MATCH trial (Molecular Analysis for Therapy Choice) includes individuals with HIV infection.(15) This national study is agnostic to tumor type, but instead assigns treatment according to molecular findings relevant to an agent that has evidence of activity for the mutation. Inclusion of individuals with HIV infection onto this study is a clear demonstration of the commitment to apply the best science and clinical trials to designs to all persons with cancer.



## Summary

Strategies to advance cancer therapeutics for persons with HIV infection include a variety of clinical trials approaches. Clinical trials that are specific to those with HIV are essential, but it is also imperative to include persons with HIV in clinical trials not specific to HIV. The important questions that can be asked must be carefully prioritized to enhance efficient utilization of resources. Since the absolute number of individuals with HIV and any specific cancer is relatively low, strategies that provide dosing, toxicity, and feasibility data are crucial. Although not perfect, these data provide information vital to extrapolating from the larger clinical trials and allows treatment decisions for those with HIV that are not completely based on assumption. When persons with HIV are included on the background studies, comparison to the background population is more relevant since the patients are all contemporaneously enrolled. Historical comparison with all of its caveats can also serve to reassure that those treated on HIV specific trials have similar outcomes to the background population. The era of modern HIV therapeutics has revolutionized the approach to persons with HIV and cancer and the consideration for participation on clinical trials.

## References

1. Rudek MA, Moore PC, Mitsuyasu RT, Dezube BJ, Aboulafia D, Gerecitano J, et al. A phase 1/ 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(8):1194–1202. [PubMed: 24474568] \*Example of approach to HIV-specific populations to define drug-drug interactions and toxicity of novel cancer agents to provide evidence for using for specific indications.
2. Corona G, Vaccher E, Spina M, Toffoli G. Potential hazard drug-drug interaction between boosted protease inhibitors and vinblastine in HIV patients with Hodgkin's lymphoma. *AIDS*. 2013; 27(6): 1033–1035. [PubMed: 23698067]
3. Rudek MA, Chang CY, Steadman K, Johnson MD, Desai N, Deeken JF. Combination antiretroviral therapy (cART) component ritonavir significantly alters docetaxel exposure. *Cancer Chemother Pharmacol*. 2014
4. Alvarnas JC, Le Rademacher J, Wang Y, Little RF, Akpek G, Ayala E, et al. Autologous hematopoietic cell transplantation for HIV-related lymphoma: results of the (BMT CTN) 0803/ (AMC) 071 Trial. *Blood*. 2016 \*\*Example of a HIV-specific trial that demonstrates feasibility of high-dose chemotherapy and stem cell rescue. This trial provides compelling evidence that HIV does not prevent aggressive curative intent cancer therapy and can be used as evidence to include persons with HIV onto background clinical trials.
5. Uldrick TS, Wang V, O'Mahony D, Aleman K, Wyvill KM, Marshall V, et al. An interleukin-6-related systemic inflammatory syndrome in patients co-infected with Kaposi sarcoma-associated herpesvirus and HIV but without Multicentric Castleman disease. *Clin Infect Dis*. 2010; 51(3):350–358. [PubMed: 20583924]
6. Polizzotto MN, Uldrick TS, Wyvill KM, Aleman K, Marshall V, Wang V, et al. Clinical Features and Outcomes of Patients With Symptomatic Kaposi Sarcoma Herpesvirus (KSHV)-associated Inflammation: Prospective Characterization of KSHV Inflammatory Cytokine Syndrome (KICS). *Clin Infect Dis*. 2016; 62(6):730–738. [PubMed: 26658701] \*Example of why clinical research in HIV-specific population is important. Without such research these rare findings would not be uncovered and important disease features left unaddressed.
7. Uldrick TS, Polizzotto MN, Aleman K, O'Mahony D, Wyvill KM, Wang V, et al. High-dose zidovudine plus valganciclovir for Kaposi sarcoma herpesvirus-associated multicentric Castleman disease: a pilot study of virus-activated cytotoxic therapy. *Blood*. 2011; 117(26):6977–6986. [PubMed: 21487108]

8. Uldrick TS, Polizzotto MN, Aleman K, Wyvill KM, Marshall V, Whitby D, et al. Rituximab plus liposomal doxorubicin in HIV-infected patients with KSHV-associated multicentric Castleman disease. *Blood*. 2014; 124(24):3544–3552. [PubMed: 25331113]
9. van Rhee F, Wong RS, Munshi N, Rossi JF, Ke XY, Fossa A, et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2014; 15(9):966–974. [PubMed: 25042199]
10. Barta SK, Samuel MS, Xue X, Wang D, Lee JY, Mounier N, et al. Changes in the influence of lymphoma- and HIV-specific factors on outcomes in AIDS-related non-Hodgkin lymphoma. *Ann Oncol*. 2015; 26(5):958–966. [PubMed: 25632071]
11. Press OW, Li H, Schöder H, Straus DJ, Moskowitz CH, LeBlanc M, et al. US Intergroup Trial of Response-Adapted Therapy for Stage III to IV Hodgkin Lymphoma Using Early Interim Fluorodeoxyglucose–Positron Emission Tomography Imaging: Southwest Oncology Group S0816. *Journal of Clinical Oncology*. 2016 \*\*Shows advantages of including HIV and non-HIV participants in the same trial. Improves accraul and informs boths subsets of patients.
12. Danilov AV, Li H, Press OW, Shapira I, Swinnen LJ, Noy A, et al. Feasibility of Interim PET-Adapted Therapy in HIV-Positive Patients with Advanced Hodgkin Lymphoma (HL): Sub-Analysis of SWOG S0816 Phase 2 Trial. *Blood*. 2015; 126(23):1498.
13. Dunleavy K, Pittaluga S, Shovlin M, Steinberg SM, Cole D, Grant C, et al. Low-intensity therapy in adults with Burkitt's lymphoma. *N Engl J Med*. 2013; 369(20):1915–1925. [PubMed: 24224624]
14. Dunleavy K, Noy A, Abramson JS, LaCasce AS, Link BK, Parekh S, et al. Risk-Adapted Therapy in Adults with Burkitt Lymphoma: Preliminary Report of a Multicenter Prospective Phase II Study of DA-EPOCH-R. *Blood*. 2015; 126(23):342. \*\*Shows advantages of including HIV and non-HIV participants in the same trial. Improves accraul and informs boths subsets of patients.
15. Conley BA, Chen AP, O'Dwyer PJ, Arteaga CL, Hamilton SR, Williams PM, et al. NCI-MATCH (Molecular Analysis for Therapy Choice) - a national signal finding trial. *ASCO Meeting Abstracts*. 2016; 34(15 suppl):TPS2606.



**KEY POINTS**

- Clinical trials exclusively for those with HIV focus on intensive study to provide information on tumor biology, HIV disease parameters, and feasibility
- Clinical trials for those exclusively with HIV intended to demonstrate feasibility and/or drug-drug interactions are essential tools for extending cancer therapy to those with HIV
- Clinical trials for the background population that include persons with HIV are an efficient way to gain information relevant to both populations and can help reduce accrual barriers in rare diseases.