How We Treat Classical Hodgkin Lymphoma in Patients Infected with Human Immunodeficiency Virus

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Abstract

HIV-associated classical Hodgkin lymphoma (HIV-cHL) is an important complication of HIV disease in the era of effective combination antiretroviral therapy (cART). Generally, newly diagnosed HIV-cHL should be managed with curative intent. With modern HIV therapeutics, HIV-cHL treatment outcomes are largely comparable to that of the background population with cHL (non-HIV-cHL). To achieve these outcomes, particular attention must be given to managing HIV. This includes understanding HIV as comorbid condition with a spectrum of impact that is unique to each patient. Meticulous attention to drug-drug interactions is required to avoid toxicity and pharmacokinetic effects that can undermine cure. Relapsed and refractory HIV-cHL poses additional therapeutic challenges. The standard management in this setting should also be based on that for non-HIV-cHL, and includes the use of salvage chemotherapy followed by autologous stem cell transplant (ASCT) in chemosensitive disease. The role of allogeneic hematopoietic stem cell transplant is less clear, but may be useful in select cases. Newer agents with activity in cHL are being tested as part of primary and salvage therapy, and are highly relevant for HIV-cHL as well.
Introduction

HIV-cHL is a serious complication of HIV. As with Kaposi sarcoma (KS) and non-Hodgkin lymphomas (NHL), cHL risk is substantially elevated by HIV infection. However, unlike those tumors, HIV-cHL does not confer a diagnosis of acquired immune deficiency syndrome (AIDS). HIV-cHL may present with extranodal involvement that can lead to life-threatening organ dysfunction. Nonetheless, outcomes comparable to that seen in the general population are possible with standard curative-intent therapy and modern cART. In this article, we discuss the epidemiology, pathobiology, and clinical management of HIV-cHL.

Case presentation

A 44 year-old man was referred with relapsed HIV-cHL. He initially presented 14 months prior with supraclavicular swelling, night sweats, and weight loss. Excisional lymph node biopsy demonstrated Epstein-Barr virus (EBV)-associated cHL, mixed cellularity (MC) subtype (Figure 1). HIV serology revealed previously undiagnosed infection. CD4+ count was 140 cells/mm³. He commenced tenofovir, lamivudine, and ritonavir-boosted atazanavir for HIV, as well as trimethoprim-sulfmethoxazole for Pneumocystis pneumonia (PCP) prophylaxis. He had no history of opportunistic infections (OIs). ¹⁸Fluorodeoxyglucose positron emission tomography (¹⁸FDG-PET) revealed ¹⁸FDG uptake in lymph nodes and bones (Figure 2a). He had advanced stage, unfavorable disease (stage IVB; International Prognosis Score [IPS] of 4, based on sex, stage, hemoglobin 10 mg/dL and albumin 2.0 mg/dL). He received doxorubicin, bleomycin, vinblastine,
and dacarbazine (ABVD) with pegfilgrastim and continued cART. His first cycle was complicated by Grade 4 neutropenic fever lasting 2 weeks. During subsequent cycles, vinblastine and dacarbazine were dose reduced by 50%. Additionally, there were dose delays during several cycles due to neutropenia, and the patient developed grade 2 neuropathy. $^{18}$FDG-PET after two cycles showed uptake in the left axilla. A solitary radiographic lymph node abnormality after six 28-day cycles was biopsied and showed reactive changes. He completed 8 cycles and achieved a complete response (CR). After therapy, CD4+ cell count was 173 cells/mm$^3$.

Twelve months after completing chemotherapy, a new axillary lymph node was palpated. Computerized tomography (CT) revealed a 2.5 cm axillary lymph node and other new smaller lymph nodes. Excisional biopsy revealed recurrent EBV+ cHL lymphoma, MC subtype. CD4+ count was 145 cells/mm$^3$ and HIV viral load remained undetectable. $^{18}$FDG-PET revealed no extranodal disease (Figure 2d). We reasoned that drug-drug interactions between HIV protease inhibitor (PI)-based therapy and vinblastine complicated his initial treatment, and that although he had recurrent disease at 12 months, it was likely chemosensitive owing to initial response despite prior dose reductions and cycle delays. Therefore, to reduce drug-drug interactions, we modified his cART, replacing ritonavir and atazanavir with efavirenz. Given his prior intolerance to therapy, we elected to employ dose–adjusted etoposide, doxorubicin, vincristine, cyclophosphamide and prednisone, and filgrastim (DA-EPOCH) rather than conventional cHL salvage.
We anticipated vincristine would be less affected by efavirenz than would be the case with vinblastine, and that dose-intensity could be adjusted based on the prior cycle. Due to the low-dose prolonged infusions, we anticipated minimal cardiac toxicity from additional doxorubicin. After 2 cycles, CT showed no disease, and he proceeded to autologous stem cell transplant following BEAM (BCNU, etoposide, cytarabine, melphalan) conditioning. CD4+ count 3 months post transplant was 186 cells/mm³. He has been followed on cART for 7 years with no relapse, undetectable HIV with CD4+ count rising to >500 cells/mm³, and resolution of his neuropathy.

**Epidemiology**

*CHL in patients with HIV*

cHL incidence is approximately 50 per 100,000 person-years among HIV-infected individuals, 5-20 fold higher than in the background population¹⁻⁴. Nodular lymphocyte predominant Hodgkin lymphoma does not have an established association with HIV, although cases in HIV-infected people have been noted⁵. Unlike HIV-NHL, where incidence decreased by 50% after introduction of cART (mainly owing to decreases in immunoblastic histological types)⁵⁻⁶, HIV-cHL risk has remained stable and burden of disease has increased²⁻⁶⁻⁷. In the United States (US), cHL follows NHL, KS, lung cancer, and anal cancer as the fifth commonest tumor in the setting of HIV⁶. Median age is 40-44 years, which after correcting for age distribution of the at-risk population, is older than that of the general population⁸. Indeed, 14% of US cHL cases in this
age group are HIV-associated. Between 2000 and 2010, a large proportion of cHL in African Americans (17%) and Hispanics (10%) was attributed to HIV, reflecting shifting demographics of the US HIV epidemic. In Johannesburg, South Africa, where HIV seroprevalence is 20% in young adults, 60% of cHL cases are HIV-related. As with NHL, over time there has been a pathobiologic shift in cHL subtypes in patients with HIV. Prior to cART, MC was the commonest subtype. In the cART era, likely due to improved immunity among HIV-infected populations, the nodular sclerosis (NS) subtype now accounts for nearly 50% of cases.

**CD4+ T-cell counts, initiation of cART and HIV-cHL**

The association between HIV-cHL and CD4+ count is complex. Median CD4+ count at cHL diagnosis is between 150-250 cells/mm³. However, HIV-cHL risk is elevated at all CD4+ counts. Additionally, besides being a manifestation of untreated HIV, lymphocytopenia is also a common manifestation of cHL. In case-control studies of HIV patients matched for clinical features including time on cART, the median CD4+ count decrease for those who developed HIV-cHL was 100 cells/mm³ over 12 months prior to cHL diagnosis compared to a median increase of 35 cells/mm³ in controls. Indeed, a precipitous drop in CD4+ cells may be a heralding event of HIV-cHL. The period of highest risk of HIV-cHL diagnosis are the months after initiating cART. Data from a large Veteran’s Affair cohort suggests incidence may be
as high as 250 per 100,000 person-years during the first year of cART, with a slow decline over 10 years with controlled HIV, and a substantially lower risk thereafter\textsuperscript{21,23}. It has been speculated that a certain amount of immune competence is required for cHL to develop. Alternatively, with cART initiation and control of HIV viremia, an inflammatory condition may occur that promotes or unmasks existing cHL\textsuperscript{24}. It is not possible to identify those destined to develop HIV-cHL based on CD4+ dynamics alone\textsuperscript{23}. Vigilance for inflammatory, infectious, and malignant etiologies of immune reconstitution syndromes in all HIV patients initiating cART is recommended. Prompt evaluation may lead to improved outcomes.

**Pathobiology**

Hodgkin Reed-Sternberg cells (HRS), which make up a minority of tumor cells in cHL, are clonal mature B-cells that express activation markers CD15 and CD30\textsuperscript{25-28}. Distinct histologic patterns in the inflammatory background form the basis for cHL subcategorization. In HIV-cHL, HRS are usually EBV+. These EBV-infected HRS cells exhibit a type II latency pattern, in which expression of EBV-encoded genes is largely limited to Epstein-Barr nuclear antigen (EBNA1) and latent membrane proteins (LMP1, LMP2A, LMP2B). By *in situ* staining for EBV-encoded small RNA (EBER), up to 80% of NS and MC HIV-cHL cases are EBV-associated, compared to less than 40% of non-HIV-cHL\textsuperscript{16,26,29}. EBV-encoded genes modulate cellular signaling pathways, and contribute to pathogenesis. For example, LMP1\textsuperscript{25,28,30,31} is a constitutively active homologue of CD40 that
upregulates NF-KB signaling and is essential for B-cell transformation in vitro\textsuperscript{32}, while LMP2A mimics B-cell receptor signaling and also contributes to proliferation\textsuperscript{33}. EBNA1 appears to influence cytokine networks by stimulating production of chemokines such as CXCL10 and CCL20\textsuperscript{34,35}, thus attracting T-regulatory cells and inhibiting an immune response against the EBV+ cells.

Gene expression profiling (GEP) has informed the pathogenetic role of the tumor microenvironment in EBV+ cHL\textsuperscript{36,37}. Furthermore, EBV+ cHL tends to group with high-risk gene expression profiles in cHL. While EBV infection of HRS cells is not the only factor leading to a high-risk molecular signature\textsuperscript{38}, modulation by EBV of host cellular pathways may promote high-risk features that typify the clinical presentation. Other unique features in HIV-cHL include decreased nodal CD4+ T-cells and lack of CD4+ rosetting around HRS cells as compared to non-HIV-cHL. This may parallel low circulating CD4+ cell counts. CD8+ cell infiltrates are preserved, however cytotoxic granzyme B expression is decreased compared to non-HIV-cHL\textsuperscript{25,28,39-42}, suggesting a role for defective EBV-specific immunity in disease pathogenesis\textsuperscript{43}. HIV itself may influence the nodal microenvironment and the CD4+ cell fluctuations after cART initiation, possibly contributing to HIV-cHL pathogenesis. Recruitment of reconstituted CCR4+CD4+ T-cells by HRS secretion of CCL17/TARC is one provocative possibility, but as yet the associations with EBV-infected HRS remain unclear\textsuperscript{44,45}. 
Tumor infiltrating macrophages (TAM), recruited in association with CD115/CSF1R expression by HRS cells\textsuperscript{37}, are increasingly recognized as important in the pathophysiology of cHL.\textsuperscript{46-48} TAM are prominent in EBV-associated cHL\textsuperscript{47,48}, including HIV-associated cases. Interestingly, the number of TAM in HIV-cHL does not appear to differ significantly with cART\textsuperscript{39} and among other factors may help explain why HIV-cHL risk does not appear to be substantially reduced by cART\textsuperscript{42}.

**Management**

*Clinical presentation, diagnosis and staging*

HIV-cHL often presents with advanced disease. Extranodal sites of disease, including bone marrow, liver, and spleen as well as B-symptoms are more common compared to the background population\textsuperscript{16,49}, and can occur in the absence of enlarged lymph nodes. Diagnosis is established by biopsy of involved tissue, usually a lymph node. HRS cells are identified by morphological characteristics and immunostaining demonstrates them to be CD15+, CD30+. PAX5+ and EBER+ HRS cells support the diagnosis.

Clinical evaluation includes history and physical, complete blood count with differential, albumin, liver and kidney function, baseline pulmonary function test for patients undergoing bleomycin-containing regimens, and \textsuperscript{18}FDG-PET with integrated or concurrent CT of the neck, chest, abdomen and pelvis\textsuperscript{50}. \textsuperscript{18}FDG-PET must be interpreted with caution, as HIV viremia and certain OIs can cause
18FDG-avid nodes51-53. Though not validated in the setting of HIV-cHL, 18FDG-PET is both sensitive and specific for detecting bone marrow involvement in cHL. Revised cHL staging criteria recommend omitting the bone marrow biopsy in non-HIV-cHL54 and we recommend omitting in most HIV-related cases as well. Nonetheless, bone marrow biopsy may be diagnostically useful in patients with cytopenias, since employing Occam’s razor to unify the clinical findings within a single diagnosis can lead to missed diagnoses in HIV-infected patients. For example, reactive hemophagocytic lymphohistiocytosis in HIV-infected patients can be attributed to HIV-cHL in up to 20% of cases55 and bone marrow biopsy in this setting can provide important information about the etiology of cytopenias. In the absence of specific risk stratification for HIV-cHL, patients should be classified as having early favorable, early unfavorable, or advanced disease using criteria for non-HIV-cHL.

*Evaluation of HIV status and co-morbidities*

Given the high proportion of cHL attributed to HIV, we recommend asking all adults with cHL for permission to test for HIV during the initial clinical evaluation. Treating cHL in a patient with unrecognized HIV infection introduces undue risk, including treatment-related death, while treating cHL and known HIV allows for optimal management of both diseases.

Comorbid HIV has a broad spectrum of severity that requires evaluation during initial treatment planning. CD4+ count, HIV viral load, and in some cases HIV
genotyping is integral to this assessment. Additional HIV-specific medical history includes duration of infection, HIV treatment history and response to therapy as measured by CD4+ counts and HIV viral load, and complications of HIV or its therapy. The state of health prior to cancer development provides critical information. At the healthy end, with high CD4+ cells and undetectable virus, HIV may be nearly inconsequential for initial cHL management. At the opposite, where there is HIV drug resistance and advanced CD4+ depletion, severe AIDS complications may render standard chemotherapy inadvisable. With improvements in HIV medicine, the latter scenario is increasingly rare and it is essential that this determination be based on expert knowledge.

Although many patients will have undetectable HIV viral loads if on cART, some will have HIV viremia resulting from either ineffective therapy or no therapy. Patients continue to be diagnosed with HIV/AIDS after presenting late to medical attention for a variety of reasons, including lack of access to care, social stigma, and fear. HIV diagnosis made during a malignancy evaluation often presents an opportunity to successfully engage such patients in medical care, as illustrated in the case presentation. Treatment experienced patients may have uncontrolled HIV viremia for several reasons. HIV mutations, especially in patients with a complex history of cART use, may confer resistance to one or more antiretroviral agents. These are sometimes found in de novo infection as well. HIV resistance affects short-term and long-term management, and requires expert evaluation
including HIV genotyping\textsuperscript{56}. Lack of viral suppression due to cART non-adherence is important to recognize and address.

We evaluate degree of immunosuppression based on CD4+ count, history of OIs and CD4+ nadir. Patients with CD4+ counts higher than 350 cells/mm\textsuperscript{3} are less likely to have HIV-specific complications during chL therapy, those with CD4+ counts between 100-350 cells/mm\textsuperscript{3} have increased risk that can be mitigated with antimicrobial prophylaxis, and those with CD4+ counts under 100/mm\textsuperscript{3} are at highest risk, and require additional prophylaxis throughout treatment and follow-up (Table 1). A history of prior OIs or a low CD4+ nadir may indicate a more vulnerable immune status than reflected in contemporary CD4+ counts. We employ regular surveillance for treatment-related events (i.e. infections, mucositis) and have a low threshold to initiate evaluation for infectious complications in all HIV-infected patients, particularly those with prior OIs or a current or nadir CD4+ count less than 200 cells/mm\textsuperscript{3}. We evaluate CD4+ counts each cycle, then 3-monthly for the first year following chemotherapy.

We screen for Hepatitis B virus (HBV) and hepatitis C virus (HCV) with HBsAg, anti-HBc, anti-HBs and anti-HCV serology. Patients with a positive HBsAg require an HBV viral load and treatment of HBV. We monitor persons who are anti-HBc positive closely for signs of liver disease. For positive anti-HCV serology, we evaluate HCV RNA viral load. Sensitivity of HCV serology is suboptimal in HIV-infected patients, with 13% of seronegative patients having
evidence of HCV upon RNA testing. Therefore, HCV RNA testing is also advised in HCV seronegative patients with a history of intravenous drug use, AST/ALT abnormalities, and/or thrombocytopenia\textsuperscript{57}. Given advances in curative HCV therapy, we refer HCV infected patients for treatment after completion of chemotherapy.

**Primary chemotherapy for HIV-cHL**

Historically, absent cART, long-term HIV-cHL outcomes were poor. As with HIV-NHL, low-dose chemotherapy strategies were sometimes used\textsuperscript{58,59}. However, this strategy did not improve survival, and low-dose chemotherapy approaches are no longer appropriate. Adherence to chemotherapy dose and schedule in cHL therapy, even in the face of neutropenia (non-febrile), is critical for optimizing the probability of cure for both non-HIV\textsuperscript{60} and HIV-associated cHL\textsuperscript{61}.

High cure rates in HIV-cHL in the cART era have recently been demonstrated. The German HIV-related Lymphoma Study Group prospectively evaluated a stage-adapted approach. Patients with early stage favorable disease received 2-4 cycles of ABVD and involved-field radiation; patents with early unfavorable or advanced disease were largely treated with 6-8 cycles of standard BEACOPP (bleomycin, etoposide, cyclophosphamide, vincristine, procarbazine and prednisone). Most received concurrent cART. The complete response (CR) rates for patients with early favorable, early unfavorable, and advanced HIV-cHL were 96%, 100%, and 86%, respectively. Two-year disease-free survival (DFS) was
95% for early stage disease and 89% for advanced-stage disease. Two-year OS in the entire cohort was 90.7%\textsuperscript{62}. However, BEACCOPP was toxic; dose reductions and delays were common and treatment-related mortality was 7%. Our approach is to avoid BEACOPP in HIV-cHL, with the possible exception of response-adapted therapeutic escalation. This is consistent with US practice in non-HIV-cHL, where BEACOPP is generally viewed as more likely to contribute to late treatment-related myelodysplastic syndrome or leukemia. Likewise, concerns for late radiotherapy effects, such as secondary cancers and cardiovascular disease are also important for HIV-infected patients, a population potentially more vulnerable to these effects.

Drug-drug interactions must be taken into consideration when managing HIV-cHL. In a retrospective analysis, Spanish study groups GESIDA and GELCAB found potentially life-threatening adverse events with co-administration of the HIV PI, ritonavir, the backbone of many commonly used PI-based cART regimens. Of 61 patients treated with ABVD and ritonavir-based cART, 10% died of treatment-related infections and 41% required dose delays\textsuperscript{63}. Subsequently, ritonavir, through strong CYP3A4 inhibition, has been demonstrated to exert pharmacokinetic effects on vinblastine resulting in severe neutropenia and neuropathy\textsuperscript{64,65}. In contrast, a recent retrospective comparison of 93 HIV-infected and 131 HIV-unrelated patients treated with ABVD from 1997 to 2010 found similar outcomes in the two populations. What distinguishes this report from the previous is that 92% of HIV-infected patients received a PI-sparing cART
regimen. Both groups received comparable cHL treatment. HIV-infected patients also received appropriate OI prophylaxis. Only one toxic death was noted among HIV-infected patients. Five-year DFS and OS in HIV-infected and uninfected patients respectively were 85% versus 87% and 81% versus 88%, with no statistically significant differences between groups. HIV was not a predictor for OS after correcting for IPS\textsuperscript{59}.

Taken together, we currently recommend treating HIV-cHL as one would treat non-HIV-cHL, with careful management of HIV. The optimal care for the patient with HIV-cHL should be guided by current approaches for early favorable, early unfavorable, and advanced disease in the non-HIV setting. Accordingly, in the US, ABVD remains the general standard-of-care first line therapy for both early and advanced non-HIV-cHL, and existing evidence, though limited, generally supports ABVD as a standard in HIV-cHL\textsuperscript{66,67}. For bulky stage I and II disease in non-HIV-cHL, radiotherapy is commonly employed, although there is interest in reducing or eliminating radiotherapy for at least some of these patients\textsuperscript{68}, which is the focus of ongoing NCI sponsored trials. In our opinion, granulocyte colony stimulating factors (G-CSF)\textsuperscript{69}, especially for those with CD4+ count less than 200 cells/mm\textsuperscript{3}, should be used more liberally than in HIV-unrelated cases, where primary neutropenic fever prophylaxis is not recommended.
Approach to cART and supportive care

We either continue cART or initiate cART as early as possible when managing patients with HIV-cHL. This practice is informed by experience, as there is no prospective data to inform optimal timing of cART initiation in this setting. Available data raise the possibility of inadequate CR rates when concurrent cART is not employed. Nonetheless, if the only option is to use cART that negatively impacts ability to administer curative intent chemotherapy, we will defer cART until completion of treatment for HIV-cHL based on experience in treating HIV-NHL. With increasing availability of antiretroviral agents, and several cHL regimens, this tactic has become increasingly unnecessary. In the setting of hepatic or renal dysfunction we consider temporarily suspending or deferring cART to minimize polypharmacy. Drug-drug interactions may be particularly complicated in patients with low CD4+ counts and concurrent infections requiring treatment or those with limited cART options.

For symptomatic patients with advanced HIV-cHL, starting chemotherapy as soon as possible is usually desired, and often leads to improvement in performance status and tumor associated organ dysfunction. An appropriate cART regimen can be started after initial administration of ABVD. Occasionally, unanticipated adverse events occur when administering chemotherapy and concurrent cART. In such cases we prioritize cHL in treatment decisions and avoid chemotherapy delays. If necessary, cART can be suspended. After chemotherapy, we may modify cART based on patient and HIV-related factors. In
addition to managing HIV, monitoring for OIs, especially oral candidiasis, as well as select use of OI prophylaxis (Table 1) is required in treating HIV-cHL. Optimal outcomes are fostered by collaborative teams with expertise in infectious disease, pharmacology, social support and patient education. Additional specialists may be required.

A basic principle we follow is to eliminate where possible concomitant medications, including antiretroviral drugs, that constrain ability to administer full-dose and on-schedule chemotherapy for cHL. Facilitating this are more than thirty-five US Food and Drug Administration (FDA)-approved antiretroviral drugs and combined-pill combinations (Table 2). Regimens generally include a three-drug combination of 2 nucleoside reverse transcriptase inhibitors (NRTI) and one drug from another class. We avoid older NRTI due to their excess toxicity and believe ritonavir, used alone or as a pharmacologic booster as well as other strong CYP3A4 inhibitors such as cobicstat are essentially contraindicated for co-administration during ABVD. We also avoid other PIs due to CYP3A4 inhibitory properties. Preferred cART regimens have minimal expected CYP3A4 effects and employ agents with low stand-alone toxicity. At present, a regimen of an integrase strand transfer inhibitor (INSTI) (dolutegravir or raltegravir) or certain non-nucleoside reverse transcriptase inhibitors (NNRTI) (rilpivirine) along with a NRTI combination of emtricitabine and tenofovir (Truvada®) or abacavir and lamivudine (Epzicom®), is likely to have minimal clinically relevant adverse effects on cancer therapy for HIV-cHL. Additional regimens are feasible, but
require consideration of agents or combinations not listed in Table 2. In patients treated with cART, adherence should be assessed each cycle. We use a simple 7-day recall tool\textsuperscript{74,75}, which entails asking the number of missed cART doses over the last 7 days. For those reporting less than 100\% adherence, evaluation of the underlying reasons for non-adherence is required. We recommend HIV viral load monitoring each cycle until viral suppression is documented in patients initiating or changing cART, and in those with possible non-adherence.

\textit{Treatment of relapsed and refractory HIV-associated cHL}

The standard of care for relapsed cHL in HIV-uninfected patients is salvage therapy followed by high-dose chemotherapy and autologous peripheral stem cell transplant (ASCT). HIV-infected patients have been shown to successfully undergo this modality\textsuperscript{76-79}. Treatment-related mortality is 3-5\% across several conditioning regimens, and long-term outcomes in reported series appear comparable to HIV-negative patients\textsuperscript{76-80}. It is unclear whether late toxic events, such as secondary myelodysplastic syndrome, are different than in the background population\textsuperscript{79}.

We continue to individualize relapsed therapy according to the treatment history. The case presented illustrates this philosophy. Currently, two clinical trials being conducted by the Blood and Marrow Clinical Trials Network (co-sponsored the NCI and the National Heart, Lung, and Blood Institute) for HIV-infected patients with hematologic cancers should be strongly considered for a patient such as the
one presented. One is evaluating ASCT, and the other allotransplant using preferentially, but not required, homologous CCR5-Δ32 HIV co-receptor donors, possibly rendering the new immune system impervious to HIV. These studies will provide feasibility data and insights into transplant options for HIV-cHL and other hematologic malignancies. Insights may also be gained into HIV reservoirs important toward efforts in HIV eradication. Given near universal EBV-association, we consider allogeneic donor searches early for patients with relapsed or refractory HIV-cHL to expedite potential enrollment in allotransplant studies.

**Future Directions**

On-going efforts to decrease toxicity and improve survival in non-HIV-cHL and HIV-cHL are likely to lead to therapeutic advances for both populations. We strongly recommend inclusion of HIV-cHL patients in clinical trials of novel agents and allogeneic transplant to promote advances in the field\(^81\). In HIV-cHL, it is not yet possible to identify those for whom ABVD is likely to fail. Improved prognostic and predictive markers are needed. Response-adapted therapy based on early \(^{18}\)FDG-PET has been the subject of recent study in non-HIV-cHL. Negative and positive interim \(^{18}\)FDG-PET scans after 2 cycles of ABVD in advanced stage non-HIV-cHL have been associated respectively with 95% and 12% 2-year progression free survival\(^82-84\). The \(^{18}\)FDG-PET can be falsely positive in HIV sometimes necessitating confirmation of positive findings. Cycle 1 negative PET scans may be even more useful in identifying those for whom more limited
therapy can be given\textsuperscript{85}. Although FDG-PET imaging in HIV-cHL has not been validated, preliminary data suggests a high negative predictive value\textsuperscript{86}. Potentially increased false positive rates in HIV-cHL may lead to less useful predictive values for positive interim scans. Therefore, strategies using negative \textsuperscript{18}FDG-PET for treatment reduction may be the more fruitful research undertaking in HIV-cHL.

Novel therapeutics in primary and second-line cHL therapy is an area of active investigation. Brentuximab vedotin, a CD30 directed immunoconjugate of the antimitotic agent monomethyl auristatin E was FDA approved for refractory cHL\textsuperscript{87}. Phase III studies evaluating the combination of brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine\textsuperscript{88} as upfront therapy are underway in non-HIV-cHL. The AMC in collaboration with the NCI Cancer Therapy Evaluation Program is also testing this combination HIV-cHL (NCT01771107). It is hopeful that outcomes of these studies will advance therapy regardless of HIV serostatus. Many additional immune modulatory (i.e. checkpoint inhibition with anti-PD1 agents) and epigenetic approaches are currently being evaluated in cHL. Advances in these areas and improved understanding of disease biology will likely lead to future paradigm shifts in both non-HIV-cHL and HIV-cHL.

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Authorship:
Thomas S. Uldrick wrote the manuscript, cared for patient, reviewed the case presented, compiled the clinical data, and performed the literature review.
Richard F. Little wrote the manuscript, cared for patient, reviewed the case presentation and clinical data, and performed the literature review.
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Table 1. Suggested opportunistic infection prophylaxis in patients with HIV and classic Hodgkin lymphoma undergoing chemotherapy

<table>
<thead>
<tr>
<th>Opportunistic Infection</th>
<th>Threshold for prophylaxis</th>
<th>Prophylactic regimens</th>
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<tbody>
<tr>
<td>Pneumocystis jirovici</td>
<td>All patients during chemotherapy, continue after therapy until CD4 sustained over 200 cells/mm³ for 3-6 months</td>
<td>Preferred:</td>
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<tr>
<td>(Pneumocystis pneumonia; PCP)</td>
<td></td>
<td>• Trimethoprim-sulfmethoxazole 800/160 mg tablet (Bactrim DS®) Monday, Wednesday, Friday</td>
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<td></td>
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<td>• OR trimethoprim-sulfmethoxazole 400/80 mg tablet daily</td>
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<td></td>
<td>Alternatives:</td>
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<td></td>
<td></td>
<td>• Pentamidine 300 mg in 6 mL sterile water via nebulizer inhaler, once monthly</td>
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<td></td>
<td></td>
<td>• Atovaquone 1500 mg suspension one daily</td>
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<td></td>
<td></td>
<td>• Dapsone 100 mg tablet daily. Mild hemolysis may be seen in patients with G-6-P-D deficiency</td>
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<td></td>
<td></td>
<td>Trimethoprim-sulfmethoxazole and atovaquone may also prevent toxoplasmosis</td>
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<tr>
<td>Herpes simplex virus (HSV) 1/2</td>
<td>All patients with history of oral or anogenital HSV. Follow general recommendations for HSV.</td>
<td>• Valacyclovir 1000 mg tablet daily</td>
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<tr>
<td></td>
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<td>• Famciclovir 500 mg tablet twice daily</td>
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secondary prophylaxis starting 3-6 months after completion of therapy.

- Acyclovir 400 mg tablet twice daily
  These agents may also provide prophylaxis against varicella zoster reactivation.

- Fluconazole 200 mg tablet once daily (or three times/week). Also prevents cryptococcal disease in HIV-patients with CD4+ counts < 100 cells/mm³. Do not administer the day before or the day of chemotherapy.

- Nystatin oral suspension 5mL “swish and swallow” 2-4 times daily (may be included in oral mouthwashes used for management of mucositis)

- Azithromycin 1200 mg weekly

*Candida albicans* (especially oral thrush)
Consider primary prophylaxis if CD4+ count < 100 cells/mm³, or secondary prophylaxis if history of mucosal candidiasis. Alternatively, can be treated upon earliest symptoms, especially if CD4+ count > 200 cells/mm³.

Atypical mycobacteria, i.e.
- *mycobacterium avium* complex or *mycobacterium intracellulare*
  CD4+ count < 100 cells/mm³. Consider a higher current CD4+ threshold in patients with a recent history of a nadir < 100 cells/mm³ or history of atypical mycobacterial infection
### Table 2. Antiretroviral therapy: select agents with level A1 evidence for treating HIV, potential CYP3A4 interactions, and other considerations for concurrent use with chemotherapy

<table>
<thead>
<tr>
<th>Class/Drugs</th>
<th>Dose</th>
<th>CYP3A4 Interactions</th>
<th>Side Effects</th>
<th>Other Considerations</th>
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<td>Dual-nucleoside reverse transcriptase inhibitors</td>
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<tr>
<td>emtricitabine/tenofovir (Truvada®)</td>
<td>1 tablet (200mg/300mg) daily</td>
<td>-</td>
<td>• Nephrotoxicity (&lt;3%)</td>
<td>• Dose adjust for creatinine clearance &lt; 50 mL/min</td>
</tr>
</tbody>
</table>
<pre><code>                                                                                 |                   | • Dual anti-HBV activity, preferred in HBV co-infected patients |                                                               |
                                                                                 |                   | • AI* NRTI in several NNRTI, PI and INSTI based regimens |                                                                 |
</code></pre>

Appropriate HIV therapy generally consists of an INSTI, NNRTI or PI combined with two-agent NTRI combination tablet.

First choice antiretroviral agents in combination with chemotherapy regimens containing CYP3A4 substrates are those that are not metabolized via CYP3A4 system, and are listed below.

**Dual-nucleoside reverse transcriptase inhibitors**
abacavir/lamivudine (Epzicom®)
1 table (600mg/300mg) daily

• Life threatening hypersensitivity reactions in patients with HLA-B*57*01 allele
• Pharmacogenomic testing for HLA-B*57-01 required before use of abacavir
• Avoid Epzicom® if creatinine clearance <50 mL/min, instead use renally dosed individual agents
• AI* NRTI in combination with dolutegravir

Integrase strand transfer inhibitors
dolutegravir (Tivicay®)
1 tablet (50 mg) daily

• Metabolized by UGT1A1; dose increase required with efavirenz, rifampin or select ritonavir-based combinations, and possibly other UGT1A1 inducers
• Increase dose to 50 mg twice daily for patients with certain INSTI-related mutations
• AI in combination with dual NRTIs
raltegravir (Isentress®) 1 tablet (400 mg) twice daily - • Elevated AST/ALT • Elevated creatine phosphokinase • Metabolized by UGT1A1; dose increase required with rifampin • AI* in combination with emtricitabine/tenofovir

Additional second choice options. Use somewhat more likely to be limited by potential drug-drug interactions (underlined) during chemotherapy

*Non-nucleoside reverse transcriptase inhibitors*

rilpivirine (Endurant®) 1 tablet (25 mg) daily Weak induction • Depressed mood, insomnia (<10%) • Contraindicated in combination with strong CYP3A4 inducers or proton pump inhibitors • AI* in combination with emtricitabine/tenofovir (once-a-day combination, Complera®) in patients with HIV viral load < 100,000 copies/mL and CD4+ count > 200
efavirenz (Sustiva®, also included in once-a-day combination with emtricitabine/tenofovir (Atripla®) 1 tablet (600 mg) daily (in Atripla®; 600/300/200 mg tablet once daily)

Strong

- Depressed mood (5%)
- CYP3A4 metabolized. Dose adjust if used in combination with voriconazole or rifampin

Induction

- Nervous system symptoms, (headache, insomnia, dizziness) <30%, general resolve within 2-4 weeks
- Rash (10-15%)

• AI* as Atripla®, or in combination with abacavir/lamivudine in patients with HIV viral load < 100,000 copies/mL

Contraindicated in combination with vinblastine and other chemotherapy drugs heavily dependent on CYP3A4 metabolism. May be useful after completion of chemotherapy.

Protease inhibitors

Darunavir (Prezista®) 1 tablet (800 mg) daily combined with ritonavir 1

Strong

- Gastrointestinal symptoms (10-20%)
- A1* in combination with emtricitabine/tenofovir

Inhibition

- Dyslipidemia (20-25%)
- Increased dose recommended for
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dose/Regimen</th>
<th>Interactions</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir (Reyataz®)</td>
<td>1 tablet (300 mg) daily combined with ritonavir 1 tablet (100 mg) daily</td>
<td>Strong Inhibition</td>
<td>AST/ALT abnormalities (12%)</td>
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<td>Rash (6%)</td>
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<td>cART experienced patients or those with specific HIV mutations</td>
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<td>Contraindicated with strong CYP3A4 inducers</td>
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<td>Hyperbilirubinemia (44%)</td>
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<td>Gastrointestinal symptoms (&lt;5%)</td>
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<td>Dyslipidemia (24%)</td>
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<td>Rash (5-7%)</td>
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<tr>
<td>Cobicstat boosted once-a-day regimens</td>
<td>Elvitegravir/cobicstat/emtricitabine/tenofovir (Stribild®) 1 tablet (150mg/150mg/200mg/300mg) daily</td>
<td>Strong Inhibition</td>
<td>Gastrointestinal symptoms (10-20%)</td>
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<td></td>
<td></td>
<td></td>
<td>Headache (7%)</td>
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<td>Nephrotoxicity (10%)</td>
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<td>Take with food</td>
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<td></td>
<td>Do not initiate if creatinine clearance &lt; 70 mL/min</td>
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<td></td>
<td>Concurrent strong CYP3A4 inducers contraindicated</td>
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<td></td>
<td></td>
<td>Atazanavir is strong UGT1A1 inhibitor, contraindicated with irinotecan</td>
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</tbody>
</table>
NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transfer inhibitors

* AI, strong level of evidence in antiretroviral naïve patients based on randomized controlled trials; recommendations in concordance with Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents.56
Figure Legends

Figure 1. 40X histopathology and immunohistochemistry of HIV-associated classical Hodgkin lymphoma. (A) Hematoxylin and eosin stain showing classical Hodgkin lymphoma, mixed cellularity subtype (B) CD15 (C) CD30 and (D) EBV latent membrane protein-1 demonstrating immunostaining of Reed Sternberg cells (E) CD68 staining showing many (>>5%) macrophages and (F) hematoxylin and eosin stain at time of relapse showing classical Hodgkin lymphoma, mixed cellularity subtype.

Figure 2. 18Fluorodeoxyglucose Positron Emission Tomography (18FDG-PET) in HIV-associated classic Hodgkin Lymphoma (A) Baseline 18FDG-PET, volumetric image, bulky intensely hypermetabolic cervical, mediastinal and axillary lymph nodes and multiple focal bone lesions (representative vertebral lesion, red arrow). (B) Interim 18FDG-PET at the end of cycle 2, coronal image focused on small suspicious lesion in left axilla (red arrow); diffuse bone uptake attributable to peg-filgrastim also noted. After cycle 6, a biopsy of residual abnormalities in the left axilla was performed that showed reactive changes and no evidence of classic Hodgkin lymphoma. (C) End of therapy 18FDG-PET, volumetric image, resolution of 18FDG avid nodes (D) Relapse 18FDG-PET, volumetric image, left axillary avid lymph node (red arrow), as well as other small nodes above the diaphragm.
Figure 1
Figure 2
How we treat classical Hodgkin lymphoma in patients infected with human immunodeficiency virus

Thomas S. Uldrick and Richard F. Little