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HIV-associated lymphoma including Burkitt in the general population

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Abstract

Despite widely available antiretroviral therapy (ART), lymphoma remains the leading cause of death for HIV-infected persons in economically developed countries. Even a few months of drug interruptions can lead to drops in the CD4 cell count, HIV viremia and an increased risk of lymphoma. Currently, good HIV control facilitates intensive therapies appropriate to the lymphoma, including autologous and even allogeneic hematopoietic stem cell transplantation. Nonetheless, HIV-related lymphomas have unique aspects, including pathogenetic differences driven by the presence of HIV and often coinfection with oncogenic viruses. Future therapies might exploit these differences. Lymphoma subtypes also differ in the HIV-infected population, and the disease has a higher propensity for advanced-stabletage, aggressive presentation and extranodal disease. Other unique aspects include the need to avoid potential interactions between ART and chemotherapeutic agents and the need for HIV-specific supportive care such as infection prophylaxis. Overall, the care of these patients has progressed sufficiently that recent guidelines from the American Society of Clinical Oncology advocate the inclusion of HIV-infected patients alongside HIV-negative patients in cancer clinical trials when appropriate. This chapter will exam HIV lymphoma and include Burkitt lymphoma in the general population.

Keywords

HIV; AIDS; lymphoma; non-Hodgkin lymphoma; Hodgkin lymphoma; antiretroviral therapy; Burkitt

INTRODUCTION

Antiretroviral therapy (ART) for HIV has improved life expecting to 72 to 75 years, depending on CD4 count at HIV diagnosis.[1] Regardless, the lifetime cancer risk is 25% to 40%;[1–8] and cancer remains the leading cause of death in economically developed countries.[9] Non-Hodgkin lymphoma (NHL) is the most common cancer in the United States.

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Prior to ART HIV-infected persons had a 25- to 150-fold higher risk of NHL than in the general population. With ART, the risk of NHL remains 11- to 17-fold higher, depending on lymphoma subtype.[10] By age 75, the cumulative incidence of NHL in HIV-infected persons is 4.4% compared with 0.01% in HIV-negative persons.[11]

The HIV lymphomas also occur in the HIV-negative population, but their presentation, pathogenesis, and some treatment aspects treatments differ in the HIV-infected patient. Standard curative cancer therapy is the goal and is possible for most of these patients, and in general ART can continue during chemotherapy. Table 1 illustrates survival differences for lymphoma subtypes in the pre-ART and current era. Given the prevalence of Burkitt lymphoma in HIV, this chapter will also discuss Burkitt lymphoma as relevant to the general population.

LYMPHOMA RISK IN THE HIV-INFECTED POPULATION

Pathogenesis of HIV-associated lymphoma—The pathogenesis of HIV-associated lymphoma is multifactorial and includes aspects unique to HIV beyond that of general lymphoma pathogenesis. Immunosuppression, immune dysregulation, HIV itself, and coinfections with ongogenic viruses, primarily human herpes virus 8 (HHV8) and Epstein-Barr virus (EBV), vary by and within lymphoma subtype.[12]

Regarding immunosuppression, cohort studies show HIV viremia and depth of CD4 nadir increase lymphoma risk.[13] A randomized ART drug conservation trial showed ART interruptions until CD4 count dropped to low normal increased cancer risk 6-fold and lymphoma risk 3.7-fold.[14] Continuous ART is now the standard of care.

HIV related B-cell dysregulation precedes the diagnosis of lymphoma by years. For example, . elevated serum free light chains (SFLC) are associated with an 8-fold NHL risk, [15] while the ratio of SFLC, total immunoglobulin and immunofixation are not predictive of NHL. Interleukins (IL) including IL-10 and IL-6 also increase prior to a diagnosis of HIV lymphoma[16] and IL-10 single nucleotide polymorphisms may predispose to lymphoma[17] Despite these findings, screening is not currently recommended and findings are not considered actionable.

HIV may drive lymphogenesis directly.[18] After HIV suppression, the HIV-1 matrix protein p17 persists in germinal centers and has pleotropic effects. Variants (vp17s) activate Akt signaling, promoting transformed B-cell growth, and possibly upregulate the EBV oncoprotein LMP-1 (latent membrane protein) in EBV-infected B-lymphocytes. Tat protein leads to aberrant expression of the gene coding for the activation-induced cytidine deaminase (AID), an enzyme required for switching from IgM to other immunoglobulin subclasses in the germinal center of the B-cell. [19] Tat protein injected into B-cells activates the nuclease-encoding RAG1 gene, leading to DNA damage and MYC gene translocation to the center of the nucleus, which is then colocalized with IgH 10 fold compared with normal controls. [20] This is relevant to myc driven DLBCL and Burkitt. Tat protein can lead to the generation of mitochondrial reactive oxygen species (ROS) by activating NADPH and spermine oxidases, increasing mitochondrial permeability and inactivating cytochrome C-oxidase in T-cells, possibly leading to DNA damage [21] Tat protein also

decreases antioxidant levels through the depletion of glutathione. [21] Tat may dysregulate the tumor suppressor genes pRb2/p130,37 increase activation of DNA repair b-polymerase. [22] increased cytokines levels, [23] and angiogenesis; [24] all of which could promote the development of lymphoma in HIV patients.

Co-virus infection varies by lymphoma subtype. For example, central nervous system (CNS) lymphoma is virtually always associated with EBV infection, and primary effusion lymphoma (PEL) is associated with HHV8 infection and often with EBV. About 40% of AIDS-Burkitt is associated with EBV. A distinct pathway for EBV has been elucidated through gene wide sequencing and transcriptome analysis in pediatric endemic and sporadic BL[25]. Similar data is not yet available in HIV BL. EBV-encoded nuclear antigens (EBNA) are expressed in all B cells infected with EBV [26] affecting the regulation of the cell cycle and their transformation into nonmalignant lymphoblastoid cell lines. [27] However, BL cells express fewer EBV proteins than nonmalignant infected cells. The primary viral protein in tumor cells is EBNA-1. Furthermore, as EBNA-1 has not been shown to induce B-cell lymphomas in mouse models, its exact role remains undefined.

All these factors contribute to genetic differences between HIV and non-HIV lymphoma. For example, interstitial deletions of fragile site-associated genes and others identified in genome-wide DNA profiling studies. [28]. Inherited genetic factors also play a role. For example, CCR5 is a major co-receptor for the entry of M-tropic variants of HIV-1. Homozygosity of a 32-base-pair (bp) deletion (CCR5-D32) (present in 1% of a Caucasian population) confers resistance to HIV-1.[29] In addition, HIV-infected patients *heterozygous* for the CCR5-D32 deletion are less likely to develop lymphoma. Finally, stromal-cell–derived factor-1 mutation increases lymphoma risk.[30]. Currently, we cannot currently exploit these differences clinically.

Subtypes of HIV-associated NHL—The World Health Organization Classification System categorizes HIV-NHL subtypes.[31] More than 95% are of B-cell origin, including diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, and plasmablastic lymphoma (PBL). Rare types include T-cell lymphomas and PELs, which lack B-, T-, and hematopoietic cell markers. Primary B cell CNS lymphoma, more commonly seen in the early years of the AIDS epidemic, is rarely diagnosed when ART is used consistently.

Across all subtypes of HIV-NHL patients predominantly present with stage III or IV disease, rapidly growing masses, and B symptoms (ie, fever, night sweats, and unexplained weight loss) [32]. Bone marrow (25% to 40% of cases), gastrointestinal tract (26%), and CNS (17% to 32%) are common. Leptomeningeal disease may be detected by cerebrospinal fluid (CSF) flow despite negative cytology at a higher frequency than in the immunocompetent population. In one study of four-parameter flow (CD3, CD19, kappa, and lambda) in 51 newly diagnosed DLBCL patients, 11 (22%) had leptomeningeal disease detected by flow cytometry alone and only 1 was detected by cytology.[33] Detection is likely higher now with ultrasensitive modern multiparameter flow cytometry.

LYMPHOMA TREATMENT STRATEGIES IN HIV-INFECTED PATIENTS

Diffuse large B-cell lymphoma—The most common aggressive lymphoma irrespective of HIV status is DLBCL. However, HIV-DLBCL is more commonly associated with the *myc* and *bcl-6* translocations and with proliferation indices >80%.[34, 35] Prior to ART, significant toxicity and shorter remissions with chemotherapy was related to advanced HIV infection.[36] Consequently, reduced-intensity chemotherapy became the standard of care, but is rarely appropriate with current ART.

The backbone of ongoing clinical trials at the AIDS Malignancy Consortium (AMC) is a 5 day infusional combination therapy rituximab (R)-EPOCH (etoposide, prednisone vincristine, cyclophosphamide, and doxorubicin–cyclophosphamide dose-adjusted to CD4 count). Rarely, patients present with stage I low-risk DLBCL and may receive rituximab (R)-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and radiation. In advanced stage paitents the choice of R-EPOCH is admittedly not based on randomized trials. Various combination therapies studied in HIV-DLBCL include ACVB (doxorubicin, cyclophosphamide, vindesine, bleomycin, methylprednisolone, and methotrexate) and CHOP in a risk-adapted trial[37] and the infusional regimen CDE (cyclophosphamide, doxorubicin, and etoposide).[38, 39] EPOCH emerged as the predominant approach after a 2003 US National Cancer Institute (NCI) study showed a 79% complete remission (CR) rate.[40] Building on EPOCH, AMC trial AMC-034 favored the addition of concurrent over sequential rituximab, the anti-CD20 antibody.[41] Febrile neutropenia was 12% and any grade 3/4 infection 28%. Two year PFS and OS were in the range of 70%. A meta-analysis of 1546 patients in 19 clinical trials strongly favored R-EPOCH over R-CHOP[42] for event-free survival (EFS) (hazard ratio [HR]: 0.40; 95% confidence interval [CI]: 0.23–0.69; $P <$ .001) and overall survival (OS) (HR for death: 0.38; 95% CI: 0.21–0.69; $P <$ .01). R-EPOCH may overcome the high proliferation index (>80%) in HIV-related lymphoma. In fact, Ki-67 >90% predicted a better survival in a comparison of R-EPOCH and R-CHOP in two AMC phase 2 studies (AMC-010 and AMC-034),[43] although changes in ART over time (neither study mandated ART) and differences in baseline CD4 counts are possible confounders. In contrast, in a recent French retrospective study R-CHOP and R-EPOCH were equivalent, but the study included only 52 patients.[44] Moreover, in the general population R-EPOCH and R-CHOP were equivalent in a 2016 randomized trial, though subset analysis is pending.[45]

Central nervous system prophylaxis in diffuse large B-cell lymphoma—CNS prophylaxis in HIV-DLBCL follows the same indications as in the general population. Most HIV-DLBCL patients receive CNS prophylaxis because of the prevalence of extranodal disease. Intrathecal (IT) or systemic strategies are not prospectively compared. As noted earlier, flow cytometry should be used at least on the initial CSF sample to rule out cytologically negative occult disease. Patients with occult disease treated with prophylactic schedules alone did not do well[33] and treatment approaches for active CNS involvement apprear warranted.

Anti-CD20 monoclonal antibody therapy in B-cell lymphoma—Rituximab is a necessary component of B-cell NHL therapy in the general population, but initial phase 2 studies suggested safety issues in HIV. These have been discounted, and it is now widely

used.[46–48] A 2005 phase 3 study failed to demonstrate any added benefit of rituximab added to CHOP and suggested it increased toxicity when patients had CD4 counts <50 cells/μL.[49] However, a pooled analysis of AMC studies suggested rituximab was safe in all other patients. Specifically treatment-related mortality (TRM) was 37% TRM in patients with CD4 count <50 cells/μL compared with only 6% TRM in the remaining patients (P < .01).[50] Non-comparison trials have also contributed to the general consensus to use rituximab while monitoring for infection, using prophylactic hematopoietic growth factors in all patients and antibiotic prophylaxis in those at highest risk.[48, 51–53]

The role of immune status in diffuse large B-cell lymphoma—An HIV-specific DLBCL outcome score lymphoma score consists of three components: age-adjusted International Prognostic Index score, number of involved extranodal sites, and an HIV score that incorporates baseline CD4 count, HIV viral load, and prior history of AIDS.[54] Additional prognostic tumor markers include cMYC, Ki-67, CD44, EBV, SKP2, BCL6, p53, CD20, and IgM. Patients who are ART at lymphoma diagnosis may do well, however, if ART facilitates immune reconstitution during or subsequent to chemotherapy (see discussion of concurrent ART in Infection prophylaxis section).[55, 56] In contrast profoundly low CD4 counts and multidrug-resistant HIV, the hall marks of advanced HIV infection are associated with poor lymphoma outcomes.

Cell of origin in diffuse large B-cell lymphoma—As in the general population HIV-negative DLBCL can be classified according to its COO (germinal center B cell-like [GCB] or activated B cell-like [ABC] type) by gene expression profiling[57] and approximated by immunohistochemistry (IHC) into GCB and non-GCB, where the Hans model predominates.[58] GCB vs non GCB analyses in HIV have shown conflicting results regarding prognosis. . For example, 3 cycles of RR-EPOCH in GCB subtypes led to a is 95% EFS compared with only 44% in non-GCB subtypes in HIV-DLBCL.[59] However, this approach for advanced-stage HIV-DLBCL has not been rigorously investigated in another trial. In contrast, a retrospective analysis of several AMC trials that used 6 cycles of R-EPOCH showed the same survival in GCB and non-GCB subtypes.[43] Analyzed by protein expression, AIDS-related DLBCL shared features of both germinal center and non-germinal subtypes, suggesting a distinctive pathophysiology from HIV-negative DLBCL.[60] The reason for this difference is unclear, although it is possible that pathogenetic differences noted above play a role.

Burkitt lymphoma—Burkitt lymphoma is highly overrepresented in patients living with HIV. The mutations found in AIDS-related Burkitt lymphoma include those also found in sporadic Burkitt lymphoma: activating mutations in the *cMYC* proto-oncogene, frequent inactivation of *p53*, and point mutations in *BCL-6*. Epstein-Barr virus is discussed above.

In the general population, rituximab improved BL 3 year EFS (75% [95% CI 66–82]) compared with (62% [53–70]; log-rank p stratified by treatment group=0·024). [61] However, the chemotherapy backbone has not been compared in randomized trials and remains an area of active investigation. The less toxic R-EPOCH regimen is described below.

Prior to ART, intensive therapies now standard in the general population were avoided in HIV-related cases because of fears of TRM. However, a retrospective study of CODOX-M/IVAC (cyclophosphamide, vincristine, doxorubicin, methotrexate/ifosfamide, etoposide, cytarabine) given with ART showed a 2-year EFS of 80%.[62] A prospective study of 13 patients treated with hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) plus methotrexate and high-dose cytarabine with ART showed a 92% complete response rate but only 38% 2-year OS,[63] results similar to those reported by others.[64, 65] The largest prospective study dedicated to HIV-Burkitt lymphoma, AMC 048, studied 34 patients, added rituximab, and modified the dosing and schedules of CODOX-M/IVAC to reduce toxicity.[66] The 2-year overall survival was 69% with only one treatment-related death. Modifications of the CODOX-M/IVAC regimen resulted in a grade 3 to 4 toxicity rate of 79%, lower than the 100% rate of the parent regimen, and without grade 3 to 4 mucositis. Despite a 68% protocol completion rate, the 1-year survival rate compared favorably with studies that excluded HIV-positive patients. Notably, patients with parenchymal CNS disease were eligible, but none enrolled. Other prospective studies included small numbers of HIV patients with similar results: hyper-CVAD in 13 patients [63] and B-ALL/NHL2002 in 19 patients. [67]

The NCI reported favorable results with dose-adjusted R-EPOCH for both HIV-infected and HIV-negative patients with Burkitt lymphoma, as well as less toxicity than prior intensive regimens.[68] A confirmatory multicenter trial included 28 (25%) HIV-infected patients, supporting this regimen in patients without parenchymal CNS disease, a study exclusion.[69] HIV status did not affect the projected 2-year EFS of 85%. The cytotoxic agents in R-EPOCH do not cross the blood–brain barrier and this regimen *should not* be used in the setting of evident brain metastases. Regimens incorporating CNS treatment are preferable. Leptomeningeal was present in 25% of patients. However, leptomeningeal disease, peripheral blood or bone marrow involvement at diagnosis predicted a 1-year EFS of 65%, compared with 98% when no factor was present. A direct comparison of this trial to R-CODOX-M/IVAC is not possible. However, the primarily outpatient R-EPOCH regimen is associated with less hematologic toxicity by design and the absence of a randomized trial is a reasonable strategy for patients without parenchymal central nervous system involvement. Stichting Hemato-Oncologie voor Volwassenen Nederland (HOVON) is conducting a randomized trial in Europe to compare R-CODOX-M/IVAC and R-EPOCH.

CNS prophylaxis via IT treatment is mandatory in Burkitt lymphoma irrespective of HIV status unless the patient has low-risk disease.[69] The multicenter R-EPOCH trial omitted IT prophylaxis in low-risk patients defined as having a single site of disease <10 cm in diameter and normal lactate dehydrogenase (LDH), or complete resection and a negative pre-chemotherapy CSF by flow cytometry and cytology. These patients had no CNS relapses.

Plasmablastic lymphoma (PBL)—PBL was first described in the pre-ART era as nearly exclusively associated with HIV and almost entirely incurable.[70] This very rare CD20-negative variant of HIV-DLBCL has myeloma markers (including CD38 and CD138) and a proliferation index typically >90%. A stage I jaw mass is common, though disseminated disease can include numerous bone lesions. Retrospective studies in the ART era show cures

in both HIV-infected and HIV-negative patients,[71, 72] although a dedicated prospective study has not been conducted because of the rarity of the disease. By default most experts use EPOCH to treat PBL with some anecdotal reports adding bortezomib to EPOCH because of its activity in myeloma.[73] A recent prospective AMC study included 15 PBL patients; 10 had CD4 counts <200 cells/μL, and the rate of both complete response and 1-year OS using EPOCH alone was 67%.[74] The AMC is studying daratumumab, anti-CD38 antibody approved in myeloma, added to EPOCH. [75] The disease must be differentiated from myeloma, which has a different therapeutic approach.

Primary central nervous system lymphoma—Primary CNS NHL (PCNHL)is extremely rare in patients receiving ART typically as it affects patients with CD4 counts <50 cells/μL. PCNHL is typically diffuse large B-cell lymphomas, EBV-associated, and multifocal. [76] EBV in the CSF can assist in making the diagnosis when biopsy is infeasible, especially when combined with thallium-201 single-photon emission computed tomography. Patients present with confusion, memory loss, lethargy, and other focal neurologic findings.[77] In the pre-ART era, palliative treatment with steroids and whole-brain radiation (3000 Gy to 5400 Gy) lead to response rates of 75% and a median OS of 2 to 4 months regardless of CD4 count. [78] A pilot study using only zidovudine (1.5 g twice daily), ganciclovir (5 mg/kg twice daily), and interleukin-2 (2,000,000 U twice daily) had 2 of 5 patients remaining in complete remission at 28 months and 52 months, but closed early because of low patient accrual.[79] Induction regimens are generally based on high-dose methotrexate, and retrospective studies of AIDS-related primary CNS lymphoma include 14 ART-era patients with a 60% 5-year OS[80] and 51 patients with a 48% 5 year OS.[81] Several novel approaches are available for HIV-negative PCNHL, but have not been studied in HIV. For example, sequential multiagent induction and upfront autologous stem cell transplant demonstrated a 2-year OS of 81% in PCNSL, suggesting that this approach could be attempted in the appropriate HIV-patient setting.[82]

Primary effusion lymphoma (PEL)—PEL comprises approximately 1% to 5% of AIDS-related lymphoma cases. Typically, diagnosis is made in the absence of nodal disease on by pericardiocentesis, thoracentesis, or paracentesis with cytology and immunohistochemistry. PEL cells harbor gene rearrangements but are pleomorphic and lack expression of B-cell–associated genes, including surface immunoglobulin. The gene expression profile of PEL cells suggests plasmablastic derivation.[83] HHV8 is nearly universal and latent gene products contribute to pathogenesis.[84–88] Concurrent infection with EBV is frequent. PEL may also involve the omentum, lymph nodes, mediastinum, and lung. In a retrospective analysis of 11 PEL patients treated with doxorubicin, vincristine, and prednisone, the CR rate was 42% but median survival was only 6 months.[89] As with other lymphomas, the outcome may be better in the ART era,[90] although prospective studies do not exist. A report of antiviral therapy alone leading to sustained remission has been documented,[91] but this treatment is not the standard of care.

Hodgkin lymphoma—HIV infection markedly increases the risk of HL, although it is not an AIDS-defining diagnosis. Paradoxically, ART and immune reconstitution increase the incidence of HL, while ART decreases the incidence of NHL.[92] HIV-HL is associated

with B symptoms, mixed cellularity subtype more commonly than nodular sclerosis subtype, and extranodal disease.[93] Unlike in HIV-negative HL, noncontiguous spread of disease is common and mediastinal involvement is less common.[94] Cytopenias due to bone marrow involvement in 40% to 50% may be the first indication of HIV-HL. Like AIDS-NHL, HIV-HL is characterized by a high frequency of EBV infection. The pathologic role of EBV in HL is evidenced by the Reed-Sternberg cell expression of EBV-transforming proteins.

Similar to HIV-NHL, response to ART correlates with outcome in antiviral-naive HIV-HL patients.[95] Prior to ART, response to standard chemotherapy ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and overall survival (median 1.5 years) were lower in HIV-infected patients with HL. With ART HIV-HL outcomes are comparable to those in the general population: a French study showed 2-year OS and PFS of 94% and 89%, respectively;[93] and a US intergroup study (S0816) showed similar results in a small cohort.[96] A German study of 108 patients using a stratified treatment approach including BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone) for the advanced-stage patients showed CR rates for early-stage favorable HL, early-stage unfavorable HL, and advanced-stage HL of 96%, 100%, and 86%, respectively. The study reported a 2-year PFS rate of 92% and a 2-year OS rate of 91% after a median follow-up of 26 months.[97] However, BEACOPP is rarely used in frontline therapy in the US because of its toxicity. The antibody-drug conjugate brentuximab vedotin (BV) in combination with AVD for stage III and stage IV HL in the general population, showed 2-year modified PFS rates of 82.1% and 77.2% ($P = .04$) for the BV plus AVD and ABVD arms, respectively, [98] leading to US FDA approval. The BV combination decreased the risk of disease progression and death (HR: 0.770; $P = .035$). OS was the same. The AMC has reported the safety of AVD-BV in untreated stage II–IV HIV-HL. [99] HIV-specific concerns include the increased risk of neuropathy with this combination compared with ABVD.

Multicentric Castleman disease—Though not a malignancy, Multicentric Castleman disease (MCD) presents similarly to lymphoma, with multifocal adenopathy, effusions, and lymphoma type systemic symptoms.[100] HHV8 viral IL-6 secreted by infected plasmablasts drives the pathogenesis and distinguishes it from idiopathic MCD, in which endogenous IL-6 is elevated. Moreover, in HIV MCD plasmablasts retain CD20 expression in HIV-related disease, enabling therapeutic targeting with rituximab. Intermittent therapy for relapsing disease is favored over prolonged maintenance.[101] MCD can morph into HHV8-related DLBCL, and repeat biopsy is indicated for relapsed or refractory disease.

CONSIDERATIONS FOR SPECIFIC THERAPIES IN THE COMORBID SETTING

Transplantation and CAR-T cells for Hodgkin lymphoma and non-Hodgkin lymphoma—Myeloablative autologous transplants have been performed in both NHL and HL patients. The first prospective study was a the City of Hope, with 9 of 12 NHL patients beyond first CR alive at 18.5 months.[102] Other pilot studies included 8 patients[103] and 6 patients.[104] The European Cooperative Study Group on AIDS and Tumors (GICAT) reported the only study enrolling patients before second-line therapy, with 27 of 50 eligible lymphoma patients receiving autologous transplant and a median 33 month OS.[105] In

addition, 3 retrospective case-control studies showed outcome after autotransplant was equivalent irrespective of HIV status.[106–108] These trials laid the groundwork for the AMC and Blood and Marrow Transplant Clinical Trials Network (BMT CTN) multicenter study demonstrating a 1-year TRM of 5.2% and a 2-year OS of 87% for HIV-infected patients.[109] Outcomes were similar to 153 case matched HIV negative controls from the Center for International Blood and Marrow Transplant Research database, leading to the conclusion that HIV patients should receive autologous transplantation when appropriate to the management of their lymphoma.

Nonmyeloablative allogeneic transplantation has been used in select patients with refractory disease and produced short-term remissions (12 months) with little toxicity, including few opportunistic infections.[110] A retrospective study of 23 patients suggested outcomes would improve in the ART era.[111] The AMC and BMT CTN reported allogeneic transplant in a wide variety of hematologic malignancies.[112] with myeloablative (n = 8) or reduced intensity (n = 9) conditioning. ART was continued throughout the transplant process whenever possible, and at 100 days TRM was zero. Complete chimerism was achieved by 8 patients by 100 days and by 1 additional patient by 6 months. HIV was detected by a viral outgrowth assay for very low viremia in the 2 patients with mixed chimerism but not detected in either of the 2 who achieved 100% donor status. Median follow-up of survivors was 24 months (range, 7–27 months). The cumulative incidence of grades II–IV acute graft-versus-host disease (GVHD) was 41%, 1-year OS was 59%, and the causes of death were relapsed/progressive disease (5), acute GVHD (1), adult respiratory distress syndrome (1), and liver failure (1). Infections were reported in 11 patients (3 grade 2; 8 grade 3).

One patient with acute myelogenous leukemia—Timothy Brown, also known as The Berlin Patient—received a transplant from a donor with a CCR5homozygous deletion and has probably been cured of HIV.[113] As noted above, CCR5 is a major co-receptor for the entry of M-tropic variants of HIV-1. Thus, a donor homozygous for a 32-bp deletion (CCR5-D32) could theoretically repopulate the bone marrow with cells resistant to HIV.[113] To date, large scale trials exploring HIV-resistant donors have not been feasible.

Notably, HIV patients were excluded from trials of autologous chimeric antigen receptor (CAR) T cell against CD19. Case reports identify two patients received this treatment successfully without unexpected toxicity. [114] The AMC is planning a study to explore what level of immunity is necessary to support this approach.

Infection prophylaxis—Hematopoietic growth factor support to prevent neutropenia and secondary infection is necessary in HIV. The treatment intensity and the immune status dictated dosing. Neutropenia should be avoided if possible in patients with a CD4 count <50 cells/μL because it increases their risk of septic shock.[49, 50]

NCCN guidelines outline other infection prophylaxis based on known risks associated with varying degrees of immunosuppression.[115] Pneumocystis prophylaxis is needed regardless of CD4 count. Systemic prophylaxis rather than inhaled pentamidine is preferable. With intensive regimens, prophylaxes for herpes simplex and varicella are required. All patients with a CD4 count <100 cells/μL should be considered for quinolone prophylaxis during

nadir, especially if rituximab is employed, because of excess sepsis-related deaths. Fluconazole may be given for thrush but should be avoided 1 day before and after chemotherapy as it interferes with clearance of drugs metabolized through cytochrome P450 3A4 (CYP3A4).[116]

HIV-infected patients have an increased prevalence of viral hepatitis B and hepatitis C. Rituximab can lead to reactivation of latent hepatitis B virus or exacerbation of low-level infection, both leading to fulminant hepatic failure. Patients who screen positive for hepatitis B must be on antiviral therapy for hepatitis B, often accomplished with drugs that overlap with anti-HIV therapy. Hepatitis B prophylaxis without HAART can lead to outgrowth of resistant HIV strains. Typically, anti-hepatitis B therapy is continued for at least a year after rituximab exposure.[117]

Combining chemotherapy and antiviral therapy—Most oncologists continue ART during chemotherapy. In early ART days concerns arouse regarding drug–drug interactions and increased toxicities. Concurrent chemotherapy and ART is supported by six randomized studies in opportunistic infections showed immune recovery within the first month of ART decreases infection mortality.[118] Thus, discontinuing or postponing ART initiation during chemotherapy could be detrimental.

Concurrent ART leads to more rapid immune reconstitution within a month of chemotherapy completion: T .[119] In AMC-034, R-EPOCH ART was at physician discretion.[120] A retrospective analysis showed concurrent ART therapy showed no impact on infection rates or lymphoma-specific outcomes, but did accelerate immune recovery particularly post-chemotherapy.

New ART medications avoid specific ART components to minimize drug–drug interaction (see known interactions and considerations in Table 2). Neurotoxicity and myelosuppression can be minimized. National Comprehensive Cancer Network (NCCN) Guidelines provide additional details (www.nccn.org). Practitioners should consult with pharmacologists and other resources about new drugs. Generally, integrase inhibitors are combinable with chemotherapy.

Gene therapy—Patients undergoing autologous stem cell transplants for relapsed and refractory lymphoma have been studied in an early trial of gene therapy to engineer reinfused stem cells resistant to HIV.[121] A lentivirus vector with 3 RNA-based anti-HIV moieties (tat/rev short hairpin RNA, TAR decoy, and CCR5 ribozyme) showed low levels of transcripts in four patients were at 24 months. Newer vectors with anticipated higher rates of transduction are currently in clinical trials (AMC-097 ClinicalTrials.gov Identifier: NCT02797470). Future trials could explore similarly transduced autologous hematopoietic stem cells in HIV patients without malignancy to cure HIV infection.

ELIGIBILITY IN GENERAL POPLUATION CLINICAL TRIALS

The American Society of Clinical Oncology has issued policy statements on clinical trial eligibility in underserved populations including HIV-infected patients.[122] HIV patients who are healthy and at low risk for AIDS-related outcomes should be included in general

population patient studies. HIV-related eligibility criteria should be straightforward and focus on current and past CD4 and T-cell counts, history (if any) of AIDS-defining conditions, and status of HIV treatment. HIV-infected patients should be treated using the same standards as other patients with comorbidities, and ART should be considered a concomitant medication. Notably, the immune status of general population patients on the trial should be compared to avoid discrimination based on CD4 count alone. Finally, ART-chemotherapy interactions should be evaluated on a trial-by-trial basis.

HIV-LYMPHOMA IN LIMITED RESOURCE SETTINGS

The AIDS epidemic in sub-Saharan Africa has led to a marked increase in the burden of HIV/AIDS-related malignancies. Treatment of lymphoma is constrained by limited resources that effect the availability of intravenous chemotherapy and the supportive care of complications. For example, in Burkitt lymphoma intravenous systemic therapy is associated with mortality rates between 20% and 66%.[123–125] A study in Uganda and Kenya used modified oral chemotherapy to treat HIV-DLBCL.[126] Only 4 febrile neutropenia episodes and 3 treatment-related deaths (6% mortality rate) occurred. While the median survival was only 12 months, 33% of patients survived 5 years. Only 18 of 49 patients (37%) had access to ART, and those patients had nearly a 3-fold increase in survival ($P = .035$). An AMC has an ongoi ng randomized study in sub-Saharan Africa comparing standard CHOP with an oral chemotherapy regimen (AMC-068) was closed due to low accrual.

CONCLUSION

HIV-infected persons on ART have a life expectancy approaching that of the general population. The largest source of mortality are AIDS-defining and non-AIDS-defining cancers including lymphoma . Interruptions in HIV treatment lead to increased cancer risk. Current therapies include standard of care treatment and transplant strategies in the setting of relapsed and refractory lymphoma. CAR-T cells need to be explored. Future directions include exploiting biologic differences to therapeutic advantage; for example, targeting EBV and/or HHV8 coinfection, engineering hematopoietic stem cells with anti-HIV vectors, transplanting naturally occurring HIV-resistant hematopoietic stem cells, and enrolling appropriate HIV-infected patients alongside HIV-negative lymphoma patients in clinical trials.

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Table 1.

Overall survival of HIV lymphoma subtypes according to pre and post ART

	Pre-ART	**Current ART era**
DLBCL	40%[127]	70–80% [40] [41]
Burkitt	10–40%[40] [62] [63] [127]	70–80%[66] [68]
Hodgkin	55%[87]	80–90%[93] [87]
PEL	33%[89]	40%[82]
PBL	6%[70]	75%[128]
PCNS	20%[76]	60%[80] [81]

DLBCL: diffuse large B cell lymphoma. PEL: primary effusion lymphoma. PBL: plasmablastic lymphoma. PCNS: primary central nervous system lymphoma.

Table 2.

Examples of chemotherapy and antiviral interactions

Drug	Effect	Recommendation
Zidovudine	Myelosuppression	Contraindicated with chemotherapy
Ritonavir	Strong CYP3A4 inhibitor that will increase chemotherapy toxicity	Avoid with chemotherapy such as doxorubicin or vinca alkaloids
Cobicistat	Strong CYP3A4 inhibitor that will increase chemotherapy toxicity	Avoid with chemotherapy such as doxorubicin or vinca alkaloids
Fluconazole	CYP3A4 inhibitor that will increase chemotherapy toxicity	Avoid before and during doxorubicin or vinca alkaloids