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Review Article

Hiv and Lymphoma: from Epidemiology to Clinical Management

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Abstract. Patients infected with human immunodeficiency virus (HIV) are at increased risk for developing both non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL). Even if this risk has decreased for NHL after the introduction of combination antiretroviral therapy (cART), they remain the most common acquired immune deficiency syndrome (AIDS)-related cancer in the developed world. They are almost always of B-cell origin, and some specific lymphoma types are more common than others. Some of these lymphoma types can occur in both HIV-uninfected and infected patients, while others preferentially develop in the context of AIDS. HIV-associated lymphoma differs from lymphoma in the HIV negative population in that they more often present with advanced disease, systemic symptoms, and extranodal involvement and are frequently associated with oncogenic viruses (Epstein-Barr virus and/or human herpesvirus-8). Before the introduction of cART, most of these patients could not tolerate the treatment strategies routinely employed in the HIV-negative population. The widespread use of cART has allowed for the delivery of full-dose and dose-intensive chemotherapy regimens with improved outcomes that nowadays can be compared to those seen in non-HIV infected patients. However, a great deal of attention should be paid to opportunistic infections and other infectious complications, cART-chemotherapy interactions, and potential cumulative toxicity. In the context of relatively sparse prospective and randomized trials, the optimal treatment of AIDS-related lymphomas remains a challenge, particularly in patients with severe immunosuppression. This paper will address epidemiology, pathogenesis, and therapeutic strategies in HIV-associated NHL and HL.

Keywords: HIV; Lymphoma; ARL.

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Introduction. Since the beginning of the acquired immune deficiency syndrome (AIDS) epidemic, in the early eighties, the association between lymphomas and the acquired immunodeficiency became evident and was reported before the discovery of human immunodeficiency virus (HIV) as the responsible agent for the syndrome. Diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL) and primary central nervous system lymphoma (PCNSL) were soon recognized as AIDS-defining event in patients who lived with HIV infection (PLWH).[1] Most of these patients could not tolerate the dosage of chemotherapy (CT) routinely employed in the HIV-negative population, and the majority died of these diseases. After the advent of combination antiretroviral therapy (cART) in 1996, the death rate from AIDS dramatically decreased as the risk of new opportunistic infections and the incidence of Kaposi's Sarcoma (KS). The incidence of lymphomas, however, did not decrease as sharply, and they became the most common AIDS-related cancer in the developed world.[2] The widespread use of cART has given PLWH the opportunity to receive and tolerate a standard dose

of CT and has increased the probability of cure. However, in the context of relatively sparse prospective and randomized trials, the optimal treatment of AIDS-related lymphomas (ARL) remains a challenge, particularly in patients with severe immunosuppression. In this review, we report the main information concerning epidemiology and pathogenesis of ARL and summarize the therapeutic strategies in Hodgkin (HL) and non-Hodgkin lymphoma (NHL), analyzing the lymphoma subtypes individually. We also briefly discuss some specific aspects of ARL clinical management, such as the use of concomitant cART, infectious prophylaxis, and prophylaxis of central nervous system (CNS) involvement by NHL. We also describe the main results with autologous (ASCT) and allogeneic stem cell transplantation (AlloSCT).

Epidemiology. ARL usually present with advanced-stage disease and follow an aggressive clinical course. They are almost always of B-cell origin, and some specific lymphoma types are more common than others.[3] Some of these lymphoma types can occur in both HIV-uninfected and infected patients, while others preferentially develop in the context of AIDS or in patients with other immunodeficiencies (**Table 1**).[4] In an early phase of the HIV epidemic, the relative risk to develop NHL for AIDS patients was >100-fold higher compared to the general population.[5,6] After entering the cART era, the incidence of ARL has substantially decreased; however, they remain clearly higher than in the general population.[7] In Italy, 500 fold higher risk to develop NHL than in the general population was reported in persons with AIDS between 1986-1996 and 90 fold higher between 1997-2004.[8] Actually, a wide range of increased risks for lymphoma has been reported in population-based studies, mainly depending on the population under observation and the calendar years examined. In the latest studies conducted in Switzerland and in the USA the relative increase in patients with HIV/AIDS appears lower, ranging between 10-20 fold higher than in the general population.[9,10] A consortium of North American cohorts estimated that the probability to develop NHL (i.e., cumulative incidence) among PLWH in the cART era is 4%, even if it appears declining across 96-2009.[11] However, the advent of cART had a different impact on the epidemiology of the various subtypes of NHL. While PCNSL dramatically decreased, the decline in DLBCL incidence was less impressive, and BL was not substantially affected.[7-10] The incidence of classical HL in PLWH is approximately 5 fold to 20 fold higher than in the general HIV negative population, and the risk of HL has remained stable or even increased since the introduction of cART.[12] Even in the cART era, it appears that people with AIDS and NHL or HL have a significantly reduced survival in comparison with an HIV-negative population with the same diseases.[13-15] Report from the Italian Cancer Registry showed, for the period 1996-2005, 5-year survival of 64% among HIV-uninfected patients with NHL, compared to 25% among AIDS patients with NHL, and respectively 86% vs. 42% among patients with HL.[13]

Pathogenesis. While it is clear that HIV increases the lymphoma risk, there is no evidence that HIV infection by itself leads to cell transformation.[16] Only recently a possible direct effect of HIV through secreted or transmitted viral proteins has been hypothesised: some experimental evidence support oncogenic functions of HIV Tat, and specific variants of HIV p17 has been found to be associated with the development of lymphoma.[17,18] However, HIV does not infect the lymphoma cells and is thought to have mainly an indirect role in lymphomagenesis, primarily causing immunosuppression, with the consequent attenuation of tumor surveillance. Indeed, an inverse association between CD4+ cell count and NHL onset has been demonstrated by several studies.[19,20] However, as the risk of lymphoma in PLWH remains high even after the widespread use of cART, the relationship between immune status and lymphoma development appears more complex. HIV-associated DLBCL and PCNSL

Table 1. Lymphomas associated with HIV infection (according to WHO classification of tumours of haematopoietic and lymphoid tissues, 2008) * (Ref.4).

Lymphomas also occurring in immunocompetent patients
Burkitt lymphoma
Diffuse large B-cell lymphoma
Hodgkin lymphoma
Other lymphomas (MALT lymphoma; peripheral T-cell and NK-cell lymphoma)
Lymphoma occurring more specifically in HIV+ patients
primary effusion lymphoma (PEL)
plasmablastic lymphoma
Lymphoma arising in HHV8-associated multicentric Castelmann Disease
Lymphomas occurring in other immunodeficiency states
Polymorphic lymphoid proliferations resembling PTLD

* Raphael M, Said J, Borish B, Ceserman E, Harris NL. Lymphomas associated with HIV infection. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: IARC Press; 2008.

are often associated with Epstein-Barr virus (EBV) infection and tend to occur when immunosuppression is more pronounced.

In contrast, HIV-associated BL tends to occur earlier in the course of the illness when CD4 counts are somewhat better preserved.[21] HL occurs with relatively high frequency during the first few months after initiation of cART as the CD4 cell counts are increasing, suggesting that HL may be driven by immune recovery rather than by cell count depletion, at least in some cases.[22] Anyway, while elimination of HIV from peripheral blood can be achieved with cART, viral replication can still occur in lymphoid tissues.[23] Moreover, the specific and direct role of other oncogenic viruses, such as EBV and human herpesvirus-8 (HHV-8), in ARL pathogenesis is well documented, and most lymphomas with excess risk among PLWH are associated with these virus infections (**Table 2**). The incidence of some EBV-associated lymphomas, including BL and HL, remains high in the cART era and rates of HHV8-associated primary effusion lymphoma (PEL) and multicenter Castleman's disease (MCD) are unaffected by the use of cART.[24] It is also known that chronic inflammation could contribute to lymphomagenesis; in clinical observation, even with long-term virological suppression, inflammatory biomarkers remain at high levels in HIV-infected people.[25] In conclusion, HIV creates an environment in which chronic antigen stimulation, cytokine dysregulation, and coinfection with oncogenic viruses, in the background of genetic abnormalities and disrupted immune surveillance to tumor antigens, can lead to the emergence of monoclonal B cells.[26,27]

Clinical Management. After a diagnosis of an ARL, in addition to the usual evaluation of lymphoid malignancy, assessment of HIV disease status including CD4 cell counts, HIV viral load, sensitivity of the virus to available antiretroviral drugs and prior history of AIDS-related complications is necessary. Understanding the prospects for successful long-term HIV management is essential. A patient with a high viral load and poor immune function, who is cART naïve, is likely to respond well to cART and have fewer complications of CT compared with a patient who has resistant HIV as a result of having had multiple cART regimens.

Combination of HIV treatment and chemotherapy. Several HIV medications and CT agents have overlapping side effects, such as renal and hepatic toxicity, myelosuppression and peripheral neuropathy.[28] In addition, many CT drugs and HIV medications are metabolized through the cytochrome p450 (CYP) enzyme system of the liver. The cART can augment or inhibit the clearance of CT agents and which can lead to either increased CT-associated toxicity or a decrease in treatment efficacy.[29,30] Notably, the HIV protease inhibitor ritonavir is a particularly potent inhibitor of the CYP system that can diminish the clearance of vinca alkaloids and should be avoided during ABVD therapy for HL.[29] Several authors propose antiretroviral discontinuation during lymphoma treatment.[31] However, a retrospective analysis of the trial AMC034 showed that in patients treated with concurrent cART dose adjusted-EPOCH + rituximab (R-DA-EPOCH) is well-tolerated and allows for faster recovery of immune function compared to consecutive CT and cART.[32] A meta-analysis of 1546 patients with HIV-associated NHL demonstrated that concurrent cART and CT was associated with statistically improved complete remission (CR) rates with a trend toward improved overall survival (OS).[33] Currently, it is suggested that all HIV-infected patients with malignancies should continue cART during CT.[29,30] There is some evidence of the detrimental effect of protease inhibitor (PI)-based cART, due to excess of toxicity and the use of integrase inhibitors might bring advantages concerning drug-drug interactions and allows for a faster decline of the viremia.[34]

Table 2. HIV-associated lymphomas and oncogenic viruses.

HIV-associated lymphomas	Associated oncogenic virus
DLBCL	Immunoblastic EBV 90% Centroblastic EBV 30% (Ref. 4)
Burkitt lymphoma	EBV 25-40% (Ref. 21)
PEL	EBV 80-100% HHV8 100% (Ref. 4,83)
PCNSL	EBV 80-100% (Ref. 94)
PBL	EBV 90-100% (Ref. 72)
Hodgkin lymphoma	EBV 90-100% (Ref. 4)
MCD	HHV8 100% (Ref. 105)

DLBCL (diffuse large B-cell lymphoma), PEL (primary effusion lymphoma), PCNSL (primary central nervous system lymphoma), PBL (plasmablastic lymphoma), MCD (multicenter Castelman's disease), EBV (Epstein-Barr virus), HHV8 (human herpesvirus 8)

Infection prophylaxis. No comparative studies exist, and only one guideline has been published for opportunistic infections (OI) prophylaxis in HIV-associated malignancies.[35] Cotrimoxazole prophylaxis against *P. jiroveci* pneumonia and toxoplasmosis should be administered during immuno-suppressive treatment regardless of the CD4 cell count.[36] Other infections' prophylaxis is generally recommended at least in

particular circumstances (low CD4 count, prolong and profound neutropenia, prolonged use of steroids).[37]

Diffuse large B cell lymphoma. DLBCL, the most frequent ARL, often presents at an advanced stage and with B symptoms and extranodal tissue is frequently involved, mainly in severely immunosuppressed patients. Prognosis is determined by patient-, lymphoma- and HIV-specific factors. The International Prognostic Index (IPI) has been extensively validated and remain a reliable predictor of outcomes. Low CD4 counts have been reported as predictors of poor survival in several studies, while others have not found such an association, especially in the cART era.[38,39] An AIDS-related lymphoma IPI has been recently developed, that employs the Age Adjusted-IPI and an HIV severity score incorporating CD4 count, viral load, and prior history of AIDS to risk-stratify ARL.[40] No consensus has emerged in the HIV setting for distribution and relation to outcome of biologically distinct subtypes of DLBCL, germinal center B-cell and activated B-cell[41-44] and the proportion and outcome of "double hit" (characterized by rearrangement of c-myc and either bcl-2 or bcl-6) and "double-expresser" DLBC lymphoma (overexpression of c-myc and bcl-2) has not been extensively studied. Treatment recommendations for DLBCL in HIV infected patients are mostly based on evidence from phase 2 trials, retrospective series or expert opinion. Interpretation of the literature is complicated by the fact that in many early studies patients with different subtypes of aggressive NHL were all treated with the same regimens and frequently composite outcomes were reported. A significant positive impact on outcomes for HIV-related DLBCL has been reported after the introduction of cART. North American and European cooperative group trials reported CR rates of 48-63% and 1-year overall survival (OS) of 60-80% with CHOP in the cART era.[45,46] Moreover, infusional regimens were explored; CDE results were in line with what seen with CHOP,[47] while 39 patients (79% with DLBCL and 18% BL) treated at National Cancer Institute (NCI) with DA-EPOCH, obtained a CR rate of 74%, and a median OS of 60%, comparable with HIV negative population treated with the same regimen at NCI at the same time.[31] After successful addition of the CD20-directed monoclonal antibody, rituximab to CHOP therapy in HIV negative patients, a direct comparison of CHOP vs. rituximab-CHOP (R-CHOP) in HIV-associated NHL have been conducted in the AMC010 trial. One hundred and fifty HIV-positive patients with intermediate and high-grade CD20-pos NHL (80% of patients had DLBCL) were randomized in a 1:2 fashion to receive either CHOP or R-CHOP followed by three-monthly rituximab maintenance. Despite higher CR/CR unconfirmed rate (58% vs. 47%), and less lymphoma-related deaths in the R-CHOP arm (14% vs. 29%), there were no statistical differences in progression-free survival (PFS) (median t10 months vs. 9) and OS (32 months vs. 25). A possible explanation for the lack of benefit from rituximab might be the high treatment-related mortality (14% in the rituximab arm vs. 2%; P=0.03), which was particularly high (36%) for pts with CD4 count < 50/mcL in R-CHOP arm. Moreover, 40% of the infectious deaths was during rituximab maintenance, and in this study routine neutropenic antibiotic prophylaxis was not employed.[48] Several phase 2 trials along with a pooled analysis from 19 trials demonstrated that the addition of rituximab to the CHOP regimen was beneficial (CR rate ranged between 58-77%) and did not lead to a higher rate of death from infectious complications.[33,49,50] Similarly, the addition of rituximab to CDE resulted in higher remission rate (RR) and improved survival.[51] Then, all trials in CD20 positive ARL nowadays include rituximab. Some trials exclude patients with CD4 < 50/mcL; however, rituximab has been used safely in patients with < 50/mcL CD4 count in many studies.[52,53] Several prospective trials combined rituximab with EPOCH. In AMC034, a randomized phase 2 trial, rituximab was given either consecutively with EPOCH or sequentially.[54] One hundred and 6 patients were enrolled (75% with DLBCL and 25% with BL or BL-like); CR was 73% in the concurrent arm (71% for DLBCL) vs. 55% in the sequential arm (46% for DLBCL). 2 years OS and PFS were 70% vs. 67% and 66% vs. 63% in the concurrent vs. sequential arm. The NCI explored short-course-EPOCH with dose-dense rituximab (SC-EPOCH-RR) in 33 patients, with rituximab given on day 1 and 5 of each cycle. Patients received one cycle after ^{18}fluorodeoxyglucose positron emission tomography (PET) negativity, with PET evaluated each cycle after the second. CR was 91% after a median of 3 cycles, with PFS and OS at five years 84% and 68% respectively.[43] Indirect evidence from retrospective analyses suggests that in ARL EPOCH might be more efficacious than CHOP. In DLBCL an improved OS was found in a retrospective analysis of pooled data with DA-EPOCH vs. CHOP; however, the difference between CHOP plus rituximab vs. EPOCH plus rituximab was not significant.[33] Moreover, no randomized trial comparing R-CHOP vs R-EPOCH has been performed in HIV positive patients and in HIV negative population a randomized prospective trial showed DA-R-EPOCH and R-CHOP to be equally effective.[53] **Table 3** shows the results of V the main studies investigating the first-line treatment of HIV-related DLBCL in the cART era. At present both regimens are considered a valid choice of CT for patients with HIV-associated DLBCL and outcomes approach those for HIV negative patients in the current era.[56,57]

Therapeutic options for relapsed/refractory (R/R) disease have been poorly investigated.

Table 3. Main reported series of front line therapy for HIV-associated aggressive B cell lymphoma in the cART era.

Therapy and study type	Number of patients	Histology	Complete Remission	Survival	Reference
Modified (m) CHOP and CHOP (phase II)	65 (mCHOP 40; CHOP 25)	Intermediate- and high-grade NHL	mCHOP: 30% CHOP: 48%	mCHOP: median DFS 16 ms CHOP: median DFS NR	Ratner (45)
DA-EPOCH (phase II)*	39	Aggressive B NHL	74%	PFS at 53 ms 73% OS at 53 ms 60%	Little (31)
CDE (phase II)*	98	Intermediate- and high-grade NHL	45%	2y-FFS 36% 2Y-OS 43%	Sparano (47)
R-CDE (pooled results of 3 phase II)	74	CD20+ NHL	70%	2y-PFS 59% 2y-OS 64%	Spina (52)
CHOP vs R-CHOP (phase III)	150 (CHOP 51; R-CHOP 99)	B-cell NHL	CHOP: 47% R-CHOP: 58%	CHOP: median PFS: 38 wks, OS: 110 wks R-CHOP: median PFS 45 wks, OS:139 wks	Kaplan (48)
CHOP (phase II)	72	Intermediate- and high-grade NHL	63%	Median OS 26.1 months	Weiss (46)
R-CHOP (phase II)	52	High-grade B-cell-NHL	77%	2y-PFS 69% 2y-OS 75%	Boué (49)
R-CHOP (phase II)	80	DLBCL	69%	3y-DFS 77% 3y-OS 56%	Ribera (50)
R-EPOCH (n=51) or EPOCH > R (n=55) (phase II randomized)	106 (R-EPOCH 51; EPOCH > R 55)	DLBCL, BL, BLL, aggressive CD20+ NHL	R-EPOCH: 69% EPOCH>R: 53%	R-EPOCH: 2y-PFS 66% 2y-OS 70% EPOCH>R: 2y-PFS 63% 2y-OS 67%	Sparano (54)
SC-EPOCH-RR (phase II)	33	DLBCL	91%	5y-PFS 84% 5y-OS 68%	Dunleavy (43)
DR-COP (phase II)	40	CD20 + aggressive NHL	48%	2y-PFS 52% 2y-OS 62%	Levine (52)

cART: combination antiretroviral therapy, NHL: non-Hodgkin lymphoma, DLBCL: diffuse large B-cell lymphoma, BL: Burkitt lymphoma, BLL: Burkitt-like lymphoma, CHOP: Cyclophosphamide, vincristine, doxorubicin,and prednisone, CDE: cyclophosphamide, doxorubicin, and etoposide, DA-EPOCH: dose adjusted etoposide, prednisone, doxorubicin, cyclophosphamide, and vincristine, COMP: liposomal doxorubicin, cyclophosphamide, vincristine, and prednisone, R-CHOP: rituximab + CHOP, R-CDE: rituximab + CDE, R-EPOCH: rituximab concurrent with EPOCH, EPOCH > R: rituximab sequential after EPOCH, SC-EPOCH-RR: short-course EPOCH with dose-dense rituximab, DR-COP: pegylated liposomal doxorubicin, rituximab, cyclophosphamide, vincristine, and prednisone, DFS: disease free survival, FFS: failure free survival, PFS: progression free survival, OS: overall survival, NR: not reached, wks: weeks, ms: months.
* Not all patients were enrolled in the cART era

The standard of care in HIV-negative population is salvage therapy followed by high-dose CT and ASCT. The one year OS of patients with R/R ARL who did not undergo ASCT was only 37%, in a retrospective series of patients treated by several American institutions; patients who underwent ASCT as part of their salvage therapy lived longer (1 year OS 63.2%).[58] Since in the cART era several clinical trials have demonstrated that HIV-infected patients can safely and successfully undergo ASCT,[59] there is consensus to approach HIV positive patients with R/R DLBCL like immunocompetent patients. High dose salvage regimens such as ICE, DHAP, ESHAP, GDP, with rituximab appear to have similar efficacy, and patients with chemosensitive disease who are transplant eligible should proceed to ASCT (see dedicated paragraph on ASCT in the HIV setting). At present, we treat HIV positive patients with DLBCL in the first line with R-CHOP and consider consolidation with HDT in patients with high risk disease according to IPI, in cART responding patients with permissive immune status. In R/R disease we use conventional salvage CT (we prefer ESHAP) followed by ASCT in responding patients.

Burkitt lymphoma. BL, the second commonest subtype of ARL, occurs in individuals with relatively preserved CD4 counts. Patients typically present with poor Performance Status (PS) and high lactate dehydrogenase level**.** Extra-nodal involvement is common, and the incidence of CNS involvement ranges from 8 to 28%.[60] In the pre-cART era, HIV patients with BL were usually treated with the same non-intensive chemotherapy regimens as for DLBCL, with similar unsatisfactory results. After the advent of cART, survival in BL remained poor, with CHOP or M-BACOD-based therapies.[61] Spina et al. demonstrated that BL had a worse prognosis with R-CDE compared to DLBCL.[51] This led to the investigation of the intensive regimens commonly used in immunocompetent patients with BL (HyperCVAD, CODOX-M/IVAC, LMB-86), and several retrospective, and phase II studies showed their feasibility and efficacy in the HIV setting (CR rates 63-92% and OS 47-73%), even if they appeared more toxic than in the general population.[62-64] Moreover, several studies demonstrated the feasibility of adding rituximab to intensive regimens.[65-67] Ribera et al. reported the results of B-ALL/NHL2002 study, that showed comparable outcome in patients with and without HIV (CR 82% vs 87% and 4 years OS 63% vs 78%) in spite of a higher incidence of severe mucositis and infections in HIV positive patients, with 13% of patients who died in induction.[67] To reduce the toxicity of dose-intensive regimens, the AIDS Malignancy Consortium (AMC) conducted a study (AMC048) with a modified CODOX-M/IVAC-R regimen in 34 HIV-positive patients. A 2 years OS of 69% was reported with no severe mucositis and only one treatment-related death.[68] Dunleavy et al. treated 11 patients with SC-EPOCH-RR with an excellent OS 90% at 73 months of follow-up (69). Recently Ferreri AJM et al. reported the safety and activity of the Carmen Trial, a phase II trial including a dose-dense and short-term chemoimmunotherapy program, with ASCT as first-line consolidation for patients who did not achieve CR after induction.[70] **Table 4** shows the results of the main studies investigating the treatment of HIV-related BL in the cART era. We suggest treating HIV positive patients with the regimens specifically designed for HIV-positive subjects with BL.[68-70] As an alternative, the same intensive regimens commonly used for immunocompetent patients in a specific center, including rituximab, can be used; however, dose-adjustment might be required, at least in patients with advanced HIV disease.

Plasmablastic lymphoma. PBL was initially described in the late nineties as a rare variant of DLBCL, with plasmacytoid appearance, affecting primarily mucosal sites, particularly the oropharynx, and occurring predominantly in HIV positive patients.[71] Median CD4 count at presentation ranges from 87-206 cells/ml. It is characterized by loss of the mature B cell markers including CD20, and an elevated proliferation index. It is almost always associated with EBV, and up to 50% of the cases carry a translocation involving c-MYC, which might have a negative prognostic impact.[72,73] No prospective trials have been conducted in patients with PBL, and the majority of the studies report poor OS (5-17 months) with a variety of regimens, including CHOP, CHOP-like regimens, EPOCH, CDE, CODOX-M/IVAC.[74-76] Castillo et al. reported no OS benefit of intensive regimens like CODOX-M/IVAC vs. CHOP or CHOP-like regimens.[75] Ibrahim et al. reported a single institution experience on 25 patients showing improved OS with DA-EPOCH vs. CHOP (17 vs. 7 months).[77] More encouraging results have been recently reported in a small series by Ariela Noy et al. (CR 70% achieved with either CHOP- or EPOCH-based regimens and one year OS 67%).[78] Reasons for different outcomes reported by different authors are not clear. Cattaneo et al. reported their single institution experience, showing 67% three years OS in 13 patients with PBL treated during the cART era.[79] In this series treatment strategy included CHOP-14 regimen and extensive use of radiotherapy (RT); moreover, five patients received ASCT as consolidation, an approach that seems promising in this setting.[80] We suggest treating PBL patients with intensive chemotherapy (CHOP-14 as an option) followed by RT, at least in a localized stage. Early consolidation with ASCT might be an option for advanced stage patients and the cART should be concurrently used.[33]

However, new therapies seem advisable to improve outcomes and should be investigated in first and/or salvage setting. Bortezomib is of particular interests as

Table 4. Main reported series of front line therapy for HIV-associated Burkitt lymphoma in the cART era.

Therapy and study type	Number of patients	Complete remission	Survival	Treatment- related mortality	Reference
HyperCVAD (phase II)*	13	92%	2y-OS 48% 2y-DFS 52%	15%	Cortes (62)
CODOX-M/IVAC (retrospective)	8	63%	2y-EFS 60%	12.5%	Wang (63)
LMB-86 (phase II)*	63**	70%	4y-EFS 35% 4y-OS 38%	11%	Galicier (64)
SC-EPOCH-RR (phase II)	11	100%	FFP 95% OS 100% at 73 ms	0%	Dunleavy (69)
B-ALL/NHL2002 (phase II)	38	82%	4y-OS 63% 4y-DFS 80%	13%	Ribera (67)
B-ALL/NHL2002 (post-hoc analysis of 2 parallel series)	81	80%	4y-PFS 71% 4y-OS 72% 4y-DFS 89%	11%	Xicoy (65)
Modified CODOX-M/IVAC (phase II)	34	Not reported	1y-PFS 69% 2y-OS 69%	3%	Noy (68)
Carmen trial (phase II)	20	80%	3y-PFS 70% 3y-OS 77%	10%	Ferreri (70)

cART: combination antiretroviral therapy, HyperCVAD: cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine, CODOX-M/IVAC: cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, and cytarabine, LMB-86: cyclophosphamide, vincristine, prednisone, doxorubicin, methotrexate, etoposide, and cytarabine, SC-EPOCH-RR: short-course EPOCH (etoposide, prednisone, doxorubicin, cyclophosphamide, and vincristine) with dose-dense rituximab, B-ALL/NHL2002: cyclophosphamide, prednisone, rituximab, vincristine, dexamethasone, teniposide, doxorubicin, methotrexate, ifosfamide, etoposide, and cytarabine, Modified CODOX-M/IVAC: CODOX-M/IVAC + rituximab, with reduced and/or rescheduled cyclophosphamide and methotrexate, and capped vincristine, DFS: disease free survival, EFS: event free survival, FFP: freedom from progression, PFS: progression free survival, OS: overall survival, ms: months.
* Not all patients were enrolled in the cART era. ** All stage IV.

it is also particularly effective against multiple myeloma, which shares many molecular and immunohistochemical features with PBL; several reports have documented activity of bortezomib in PBL.[81] Moreover, lenalidomide as a single agent has been used with some success in relapsed/refractory PBL and in combination with CT in the first-line setting.[82]

Primary effusion lymphoma. PEL is a rare B-cell lymphoma characterized by effusions involving the pleura, pericardium, and/or peritoneum; however, a rare solid extra-cavitary variant has been described. Severe immunosuppression with low CD4+ cell counts is common. Most PELs have lymphocyte activation markers (CD30 and CD38) without normal B-cell markers (CD19 and CD20). HHV8 has a pathogenetic role and is present in almost 100% of cases. Other HHV8-related complications such as KS or MCD may precede or occur concurrently with PEL.[83,84] The most used CT regimen is CHOP that allows achieving CR rate of 40-50%, with median survival around six months.[84-86] However, some patients do achieve long-term remissions, but predictive factors have not been identified. Reports of outcomes using more intensive CT are controversial and seem to indicate that intensifying CT is of limited benefit.[87] Anecdotal reports of cases responding to cART alone have been reported. The effect of anti-HHV-8 therapy remains unproven.[88] Bortezomib has been used in combination with conventional CT with promising results.[89] A case report describes sustained remission in an HIV negative patients treated with single-agent lenalidomide.[90] Recently, Shah NN et al. has reported the successful use of daratumumab, a CD38-directed human IgG1κ monoclonal antibody, to treat a case of HIV-related PEL.[91] Anti-CD30 directed treatment also showed promise.[92]

In conclusion, the optimal first-line treatment for HIV-related PEL is undefined. Standard CHOP therapy or more intensive CT regimens in young patients with advanced disease are acceptable approaches. Even if newer therapies are advocated, no specific strategy can be recommended at present.

Primary central nervous system lymphoma. PCNSL is a subtype of DLBCL with a post-germinal center

phenotype. The immunophenotype of PCNSL in HIV positive subjects differs from immunocompetent patients; EBV is almost always detectable in lymphoma cells and cerebrospinal fluid, while it is rarely present in PCNSL in the HIV negative population.[93,94] Clinical findings and standard radiological investigations cannot provide a definitive diagnosis, that usually requires brain biopsy; however, the combination of detectable EBV in cerebrospinal fluid (CSF) and consistent radiological findings in a severely immunosuppressed HIV positive patients may be sufficient in selected cases. HIV positive patients with PCNSL usually have advanced immunosuppression and CD4 count < 50/mmc, making impossible the administration of high dose (HD) methotrexate (MTX) and cytosine arabinoside, as employed in immunocompetent patients (95), in a high proportion of patients. Whole brain RT was used extensively as the only therapy in the pre-cART era, but with dismal outcomes and survival of a few months. The advent of cART led to a modest improvement in survival.[96-99] Anecdotal literature suggests that the prompt implementation of cART in patients with HIV-PCNSL could result in long-term remission; however, this procedure should be reserved for carefully selected patients, not eligible for intensive CT.[100] At least two retrospective study showed the feasibility and efficacy of combined cART plus HD-MTX, at least in selected patients.[101,102] Moulignier et al. analyzed 51 patients consecutively treated in France with HD-MTX (3 gr/ms) and cART and reported a median OS of 5.7 years. No one died of acute treatment-related toxicity.[102] Gupta et al. reported on 20 patients treated with cART plus MTX-based regimens from several centers in the US; median OS was not yet reached after a median follow-up of 27 months. In this experience CD4 reconstitution with cART administered during HD-MTX correlates with long-term survival; rituximab did not add untoward toxicity while the addition of other agents to HD-MTX did not improve outcome and was associated with an increased rate of neutropenic complications and a more attenuated rate of CD4 recovery.[101] Thus, in the absence of prospective studies, we suggest treating cART responding patients with HD MTX and rituximab. If induction treatment is well tolerated and a response is documented, consolidation with HDT and ASCT could be considered in selected patients. Indeed, ASCT seems to have a beneficial role in HIV positive PCNSL patients, and which deserves further evaluation.[103]

Multicentric Castleman's Disease. Even if a polyclonal disease, MCD is an aggressive B-cell lymphoproliferative disorder with an increased incidence in PLWH, that can be life-threatening, either through multiple organ failure or the development of NHL.[104] It presents with various clinical features and lymph nodes and spleen enlargements, with usually B symptoms, weakness, and malaise. A hemophagocytic syndrome may complicate the clinical course in a non-negligible number of cases.[105] Almost all MCD cases in HIV positive subjects are associated with lytically active HHV-8 infection. HHV-8 encodes a viral IL-6 that plays a major role in the pathophysiology of the disease and the level of plasma HHV8 DNA is a helpful biomarker to monitor disease activity and response to therapy.[106] A variety of treatment strategies have been reported, and there is no widely accepted standard of care. Usually, the treatment approach is designed according to the severity of the disease. The prognosis has improved in recent years, mainly after the introduction of cART (even if MCD can occur or worsen soon after initiation of cART) and treatment with rituximab.[107] Rituximab showed its efficacy in 2 prospective trials,[109] and there is evidence that rituximab decreases the risk of subsequent development of NH.[110] Notably, an association with KS has been reported up to 70% of cases, and KS may reactivate during treatment with rituximab. Cytotoxic CT as a single agent (etoposide seems to give the best results) or in combination are effective and are considered the therapy of choice in patients with severe disease.[101] The utility of antiherpes agents in MCD has not been demonstrated. We usually treat patients with a combination of cART, rituximab, and antiviral therapy such as valganciclovir, reserving combination CT (such as CHOP) + rituximab in severe or not responding disease. Targeting IL-6 and IL6 receptor with monoclonal antibodies appears as an attractive approach and could be considered at least in selected patients.[112]

Hodgkin lymphoma. HL in PLWH frequently presents with unfavorable features such as advanced-stage, extranodal disease, and bone marrow involvement, and is associated with EBV in 80-100% of cases. The mixed cellularity subtype is the most commonly observed. Median CD4 counts at HL diagnosis ranges between 150 and 260 cells/mcL, and its incidence has remained stable or may have even increased after the advent of cART.[12] Before the introduction of cART, the prognosis was poorer compared to the general population, mainly for poor tolerance of CT, with high rates of OI and toxic deaths.[113,114] CR and OS rates improved significantly in patients responding to cART; indeed, the low CD4 count remains an independent adverse prognostic factor.[115,116] While a prospective study with Stanford V and concomitant cART resulted in 3-year OS 51%,[117] higher cure rates have been reported with ABVD and cART. Three large retrospective studies reported CR rate of 74-87% and five years OS of 76-81%. Notably, in two of these studies, a comparison was made with HIV negative patients, and the HIV status, which did not result to affect the outcome.[118-120] A relatively large prospective study on a stage- and risk-adapted treatment strategy, including ABVD, baseline BEACOPP, and

involved field RT has been reported by Hentrich et al. CR rates were respectively 96%, 100%, and 86% for early favorable-, early unfavorable-, and advanced-stage disease and 2 years OS 95.7%, 100%, and 86.8%. However, BEACOPP was toxic, dose delays and dose reductions were common, and treatment-related mortality was 7% in patients with advanced disease.[121] Then, nowadays prognosis for patients with HL and HIV infection approaches that of patients without HIV infection, and a stage adapted treatment appears feasible. ABVD with or without RT (with the same indication for RT as in HIV negative population) is now seen as the standard of care for front-line therapy. However, a higher incidence of toxicity might be expected compared to the general population. The role of BEACOPP is not clear as the experience are very limited and contrasting results have been reported.[122] **Table 5** shows the results of the main studies investigating the first-line treatments of HIV-related HL in the cART era.

Patients who relapse or have primary refractory disease should be considered for conventional salvage CT followed by ASCT as several experiences have reported the feasibility and efficacy of this approach in the HIV setting (see dedicated paragraph). Only limited evidence on the role of PET scans in the diagnosis of HL, and interim evaluation is available in HIV positive patients. As a general rule, PET scan results should be interpreted with caution as PET can be falsely positive in particular in cART- naïve or viremic patients. A recent Intergroup Cooperative trial that used FDG-PET after cycle 2 of ABVD to guide further therapy included 12 pts with HIV infection; even if based on a very small experience, the investigators concluded that it might be appropriate to include HIV patients in further studies of response-adapted therapy.[123] Novel agents, such as the CD30-directed immunoconjugate brentuximab vedotin (BV), are under evaluation in the HIV setting.[124]
The combination of BV with doxorubicin, vinblastine, and dacarbazine showed safety in newly diagnosed HIV-associated HL in a phase I study (no dose-limiting toxicity was found and six patients who completed therapy achieved CR);[125] the phase II portion of this trial is ongoing (NCT01771107). Immunomodulatory approaches, such as checkpoint inhibition with anti-PD-1 agents, may also be investigated in future studies, with some cautions due to the peculiarity of the HIV setting.[126]

We treat HIV positive patients in the first line with ABVD +/- RT in a stage- and risk-adapted strategy,

Table 5. Main reported series of front line therapy for HIV-associated Hodgkin lymphoma in the cART era.

Therapy and study type	Number of patients	Stage III/IV (or risk-group)	Complete remission	Survival	Reference
Stanford V (phase II)	59	71%	81%	3y-OS 51% 3y-FFP 60%	Spina (117)
BEACOPP ** (phase II)	12	92%	83%	3y-OS 75%	Hartmann (122)
ABVD (retrospective)	62	100%	87%	5y-EFS 71% 5y-OS 76%	Xicoy (118)
VEBEP (phase II)	73	70%	67%	3y-OS 66%	Spina (116)
ABVD (retrospective)	93	80%	74%	5y-EFS 59% 5y-OS 81%	Montoto (119)
ABVD/BEACOPP (phase II)	23 14 71	Early favourable Early unfavourable Advanced	96% 100% 86%	2y-OS 96% 2y-OS 100% 2y-OS 87%	Hentrich (121)
ABVD* (retrospective)	68	76%	Not reported	2y-PFS 89% 2y-OS 94%	Besson (120)
AVD-BV (phase I)	6	83%	100%	PFS 100% (median f-up 25 months)	Rubinstein (125)

cART: combination antiretroviral therapy, ABVD: doxorubicin, bleomicine, vinblastine, and dacarbazine, Stanford V: doxorubicin, vinblastine, mecloretamine, etoposide, vincristine, bleomycin, and prednisone, BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, VEBEP: vinblastine, epirubicin, bleomycin, etoposide, and prednisone, AVD-BV: Brentuximab Vedotin, doxorubicin, vinblastine, and dacarbazine. EFS: event free survival, FFP: freedom from progression, PFS: progression free survival, OS: overall survival.
*Only 96% of patients of the series received ABVD
** Not all patients were enrolled in the cART era.

according to standard guidelines we use for HIV negative population. We perform the PET-2 evaluation and evaluate case by case if PET-2 is positive. In R/R disease we use conventional salvage CT (we prefer BeGEV) followed by ASCT in responding patients.

Prophylaxis of CNS involvement by NHL. CNS involvement by systemic NHL has been reported up to 25% in HIV positive patients, and the use of intrathecal (i.t.) prophylaxis with MTX and/or ARA-C has been long considered a mandatory part of the systemic treatment of all HIV infected patients with aggressive NHL,[6,127] even if any formal studies to evaluate the role of i.t. prophylaxis have been conducted.[128] However, the CNS involvement has decreased since the introduction of cART and the widespread use of rituximab.[129,130] A recent retrospective review of pooled data from 886 patients was recently published by Barta et al.[131] At presentation CNS involvement was found in 13% of patients, and CNS relapses were rare, but occurred early and had poor outcomes (median OS 1.6 months). More than 90 % of patients had received i.t. MTX prophylaxis. Then, the use of i.t. prophylaxis in all HIV positive patients with NHL in an era of better systemic lymphoma control remains to be defined. Most experts recommend that CNS prophylaxis, in the context of an effective cART, should be given following the same criteria as in HIV negative patients, according to different sites of involvement, stage, and histological subtype.

Autologous stem cell transplant. High dose therapy (HDT) and ASCT has been considered prohibitive in HIV positive patients for several years, at least until the introduction of cART, when groups from Europe and USA began to offer ASCT to HIV positive patients with R/R lymphoma.[132,133] Then, ASCT has been demonstrated to be feasible and efficacious in several series of HIV positive patients with NHL and HL.[59,132-134] Patients were sent to the ASCT mainly because of R/R and in few cases of high risk first CR. The results of the main series of ARL receiving ASCT are shown in **Table 6**.[135-141] These studies showed low transplant-related mortality and durable remissions. After variable follow-up periods, PFS varied from 29-85% and OS from 36-87%, with results that mainly depended on the status of disease at the time of transplantation and an overall outcome comparable to their HIV negative counterparts. The HIV positive patients seem to experience more infectious complications in the first few months after transplant than patients without HIV that didn't translate into a significant difference in survival, while the risk of relapse showed a trend in favor of HIV positive patients.[140,142,143] However, these studies were mainly retrospective or recruited patients at the time of stem cell collection. In the Italian study,[138] patients with relapsed or refractory lymphoma were recruited at the time of treatment failure, before salvage CT. 54% of the entire series of 50 patients could proceed to ASCT, with satisfactory outcome in patients who actually received transplantation (overall survival 75%) as well as good results in the entire series, with 50% of patients alive after a median follow-up of 45 months (**Figure 1**). A recent prospective trial from Italy analyzed the use of ASCT as upfront consolidation after R-CHOP, in patients with aggressive B cell lymphoma at high risk according to the IPI, and reported promising results. Of 27 enrolled patients, 15 patients received ASCT according to the protocol, and 14 are alive and relapse-free after several years from the transplant.[144] Nowadays, HIV infection should not preclude lymphoma patients from undergoing ASCT. The same eligibility criteria as established for HIV negative lymphoma patients should be adopted for patients with HIV and the second-line therapy as induction before ASCT should consist of the same salvage regimens used for the HIV-negative population.

Allogeneic stem cell transplant. Reports of alloSCT for HIV infected patients date back to the early eighties. However, prior to effective antiretroviral therapy, alloSCT outcomes were extremely poor, with patients dying because of treatment-related toxicity or relapse. After the advent of cART, single-institution, retrospective studies with a small number of patients suggest that alloSCT may be feasible and beneficial in HIV positive patients with hematologic malignancies.[145] A Center for International Blood & Marrow Transplant Research (CIBMTR), a registry study, reported outcomes of 23 patients receiving alloSCT (including matched related or unrelated donor transplants) for several different hematologic disorders and found that 4 of 9 patients survived in the cART era.[146] Cumulative incidences of acute and chronic graft versus host disease (GVHD) did not appear much different than would be expected from HIV negative patients. Major causes of death were regimen-related toxicities and infections. Ten patients of this series had an NHL; however, the outcomes were not analysed separately.

The first prospective cooperative group trial of matched related or unrelated alloSCT[147] has been recently reported. Myeloablative or nonmyeloablative regimen were used at the investigator's discretion. Seventeen patients underwent alloSCT for treatment of acute myeloid leukemia (9), acute lymphoblastic leukemia (2), myelodysplasia (2) or lymphoma (4). There was no non-relapse mortality at 100 days. Grade II-IV GVHD developed in 41% of patients. At 24 months of median follow-up, one year OS was 57%; cause of death included disease relapse (5), acute GVHD (1), liver failure (1), and adult respiratory distress syndrome (1).

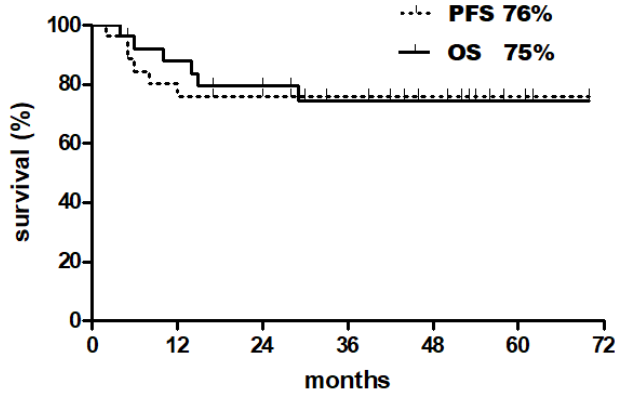
Even if data supporting the use of alloSCT are limited, most authors conclude that alloSCT should be

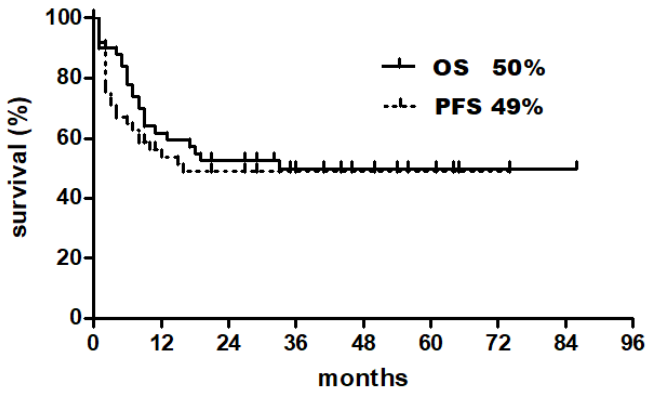
Table 6. Main reported series of ASCT as salvage treatment in HIV-positive patients with lymphoma.

Reference	n. of pts	Median age (range)	Histology (n.of pts)	Conditioning regimen (n.of pts)	PFS*	OS*	Follow-up (range)
Gabarre (137)	14	37 ys (27-53)	HL (6) DLBCL (5) BL (2) PEL (1)	BEAM (5) Bu/Ara-C/Mel (1) TBI-based (8)	4 pts alive in CR	5 pts alive	32 ms (14-49)
Krishnan (136)	20	44 ys (11-68)	HL (2) DLBCL (10) BL (6) ALCL (2)	CBV (28) TBI/Cy/Eto (4)	85%	85%	32 ms (6-70)
Re (138)	27	39 ys (31-59)	HL (8) DLBCL (13) BL (1) PBL (2) ALCL (2) PEL (1)	BEAM	76%	75%	44 ms (4-70)
Serrano (141)	33	42 ys (28-61)	HL (10) DLBCL (10) BL/BLL (6) PBL (3) ALCL (3) PTCL (1)	BEAM (27) BEAC (3) TBI-based (3)	53% at 61 ms	61% at 61 ms	58 ms (2-114)
Balsalobre (135)	68	41 ys (29-62)	HL (18) DLBCL (31) BL/BLL (8) PBL (4) ALCL (3) PTCL (3)	BEAM and variants (65) TBI-based (3)	56%	61%	32 ms (2-81)
Spitzer (139)	20	42 ys (33-60)	HL (5) DLBCL (12) BL/BLL (3)	Dose reduced Bu/Cy	49%	74%	6 ms (1-30)
Alvarnas (140)	40	47 ys (22-62)	HL (15) DLBCL (16) BL/BLL (7) PBL (2)	BEAM	80%	82%	25 ms (3-28)

DLBCL: diffuse large B-cell lymphoma, BL: Burkitt lymphoma, BLL: Burkitt-like lymphoma, HL: Hodgkin lymphoma, PBL: plasmablastic lymphoma, PEL: primary effusion lymphoma, ALCL: anaplastic large cell lymphoma, PTCL: peripheral T-cell lymphoma, TBI: total Body irradiation, Cy: cyclophosphamide, Mel: melphalan, Bu: busulfan, Ara-C: cytarabine, Eto: etoposide, BEAM: BCNU, etoposide, cytarabine, melphalan, BEAC: BCNU, etoposide, cytarabine, cyclophosphamide, CBV: cyclophosphamide, BCNU, etoposide. TBI: total body irradiation, n.: number, pts: patients, ms: months, ys: years, PFS: progression free survival, OS: overall survival, CR: complete remission.
* PFS and OS are reported at median follow-up unless otherwise stated

Figure 1a*. Overall survival and progression-free survival of 27 patients with HIV-related lymphoma after ASCT (Ref. 138).
Figure 1b*. Overall survival and progression-free survival of the entire series of 50 patients with HIV-related lymphoma eligible for the study (Ref. 138).





*This research was originally published in Blood. Re A, Michieli M, Casari S, et al.n High-dose therapy and autologous peripheral blood stem cell transplantation as salvage treatment for AIDS-related lymphoma: long-term results of the Italian Cooperative Group on AIDS and Tumors (GICAT) study with analysis of prognostic factors. Blood. 2009;114:1306-13.

considered for HIV patients with evidence of treatable HIV infection and standard indications for alloSCT.

Conclusions. Safer, more convenient, and better-tolerated cART options and improved supportive care strategies have all contributed to improvements in overall survival and decrease in therapy-associated toxicity in HIV patients with lymphoma. Treatment should principally be the same as in HIV negative lymphoma patients. Indeed, several large clinical series demonstrated that patients with HIV and lymphoma receiving the same treatment, or included in the same protocols, may have a similar outcome of HIV negative patients. This has been demonstrated for DLBCL, BL, and HL. However, a great deal of attention should be paid to OI and other infectious complications, cART-chemotherapy interactions, and potential cumulative toxicity.

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