Management of aggressive lymphoma in HIV+ patients

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Disclosures

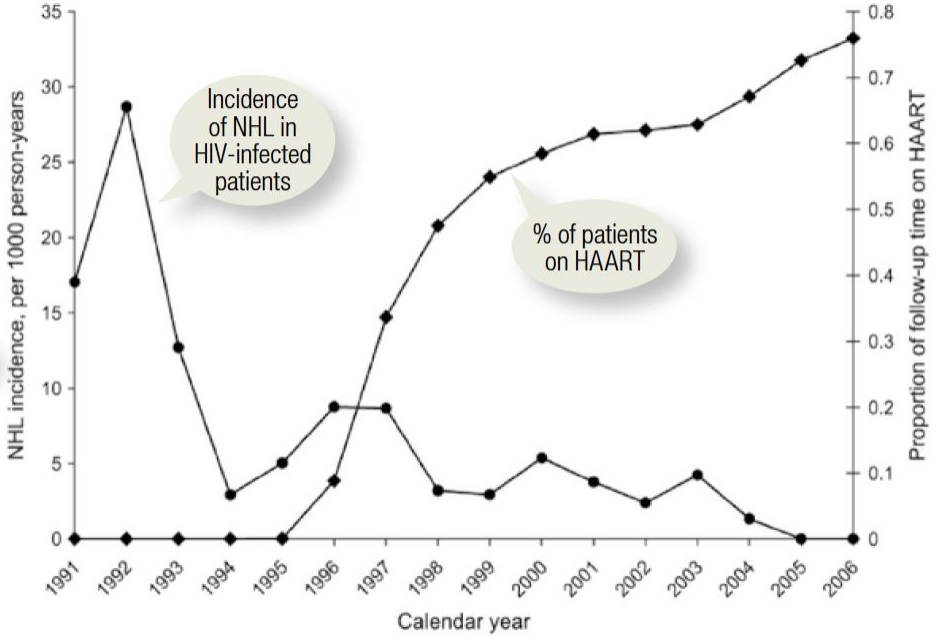
- **I have provided consultation, attended advisory boards and/or provided lectures for:**
- **Celgene, Mundipharma, Roche Pharma, and Janssen**

Incidence of lymphomas in HIV+ patients

The incidence of lymphoma is significantly increased in HIV patients: non-Hodgkin lymphoma (NHL) ≈100x and Hodgkin lymphoma (HL) ≈10-20x higher than in the general population.

The incidence of AIDS-related NHL is related to the low CD4 count in this population and hence has significantly decreased since the introduction of highly active antiretroviral therapy (HAART).

Cancer is the cause of death in one third of patients with HIV infection in the HAART era, NHL being the most common type.



Lymphomas, Essentials for Clinicians. Editors: Ghielmini M & Montoto S. p113, 2015

NHL is an AIDS-defining malignancy

Lymphoma also occurring in immunocompetent patients
Burkitt and Burkitt-like lymphomas
Diffuse large B-cell lymphomas
• Centroblastic
• Immunoblastic (including primary CNS lymphomas)
Extranodal MALT lymphoma (rare)
Peripheral T-cell cell lymphoma (rare)
Classical Hodgkin lymphoma
Lymphoma occurring more specifically in HIV-positive patients
Primary effusion lymphoma
Plasmablastic lymphoma of the oral cavity
Lymphoma also occurring in other immunodeficiency states
Polymorphic B-cell lymphoma (PTLD-like) (rare)

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Viral and genetic abnormalities in HIV–associated lymphomas

Histologic subtype	EBV +	KSHV/HHV-8+	Common recurring chromosomal abnormalities
Diffuse large B-cell lymphoma			*MYC* (10%); *BCL6* (20% of centroblastic DLBCL)[19,20] *TP53* (40%)[5,88]
Centroblastic	30%[2,10,11]	0	
Immunoblastic	80-90%[2,10,11]	0	
Plasmablastic lymphoma	>50%[2]	80%[81]	None
Primary effusion lymphoma	100%[2,8]	100%[2,8]	None
Burkitt lymphoma	30-50%[2,9]	0	*MYC* (100%)[2]; *TP53* (50-60%)[5,88]
Primary CNS lymphoma	100%[10]	0	*BCL6* (30-40%)[2]
Hodgkin lymphoma	80-100%[2]	0	None

EBV, Epstein-Barr virus; KSHV/HHV-8, Kaposi sarcoma herpes virus/human herpes virus 8; CNS, central nervous system.

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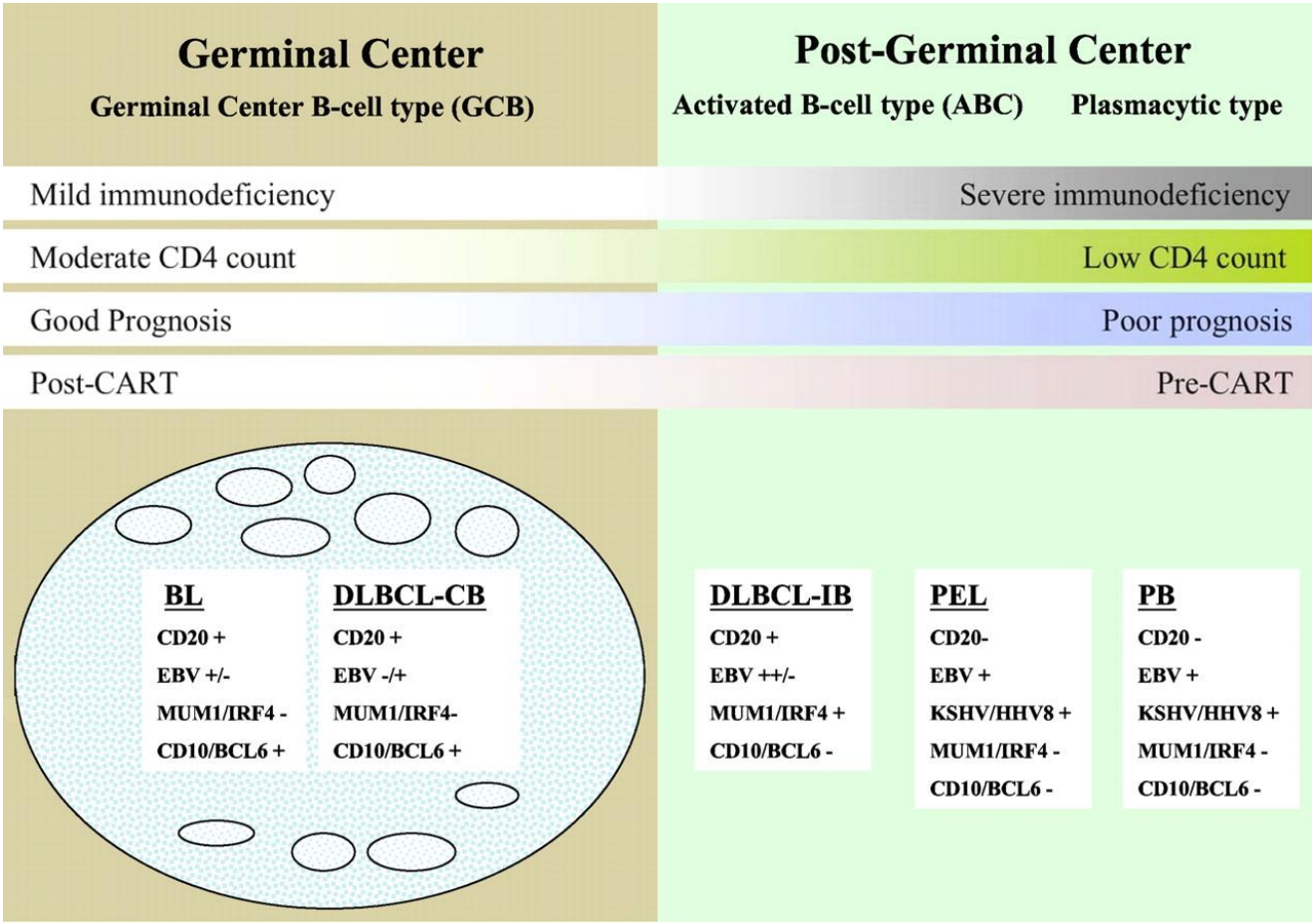
Kieron Dunleavy, and Wyndham H. Wilson. Blood 2012;119:3245-3255

Model of HIV-associated NHL – molecular and viral pathogenesis and DLBCL taxonomy



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Outcome of HIV patients in HAART era

In the HAART era, the outcome of HIV patients with NHL/HL has significantly improved, and it is similar to the outcome of NHL/HL in HIV-negative patients.

Patients with HIV and lymphoma should be managed in collaboration with the HIV team and receive HAART and prophylactic antibiotics during chemotherapy.

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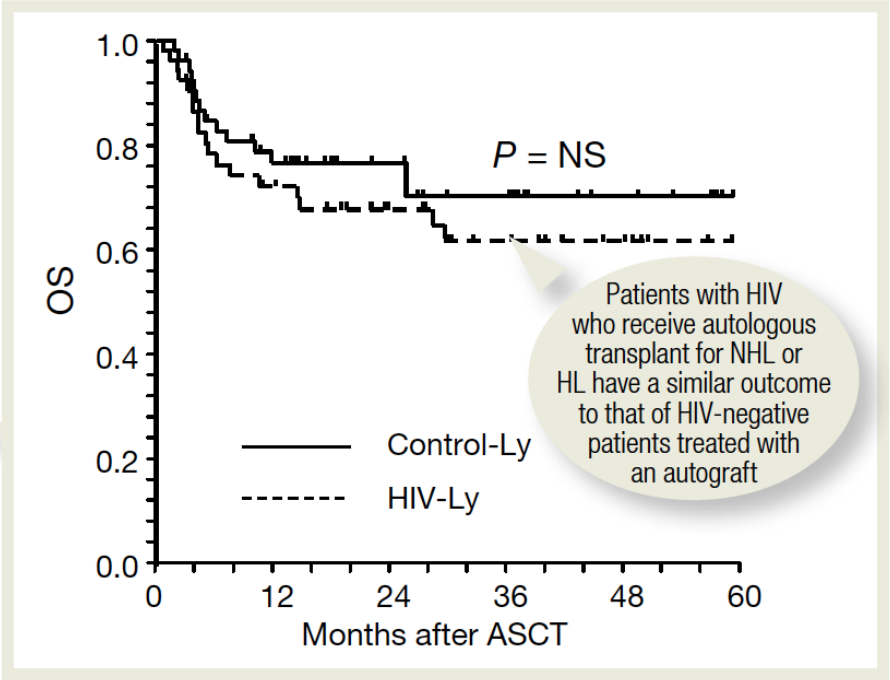
Outcome of HIV patients in HAART era

The most important prognostic factors for DLBCL in HIV patients are the IPI and the CD4 count. Rituximab ↑ treatment toxicity in patients with CD4 <50/μL.

The standard first-line therapy for DLBCL is R-CHOP, as in HIV-negative patients. Other protocols used are infusional regimens such as R-DA-EPOCH.

As in HIV-negative patients, the standard therapy for DLBCL at relapse or not in complete remission (CR) after first line is salvage chemotherapy followed by autologous stem cell transplantation (ASCT).



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Pivotal trials in HIV-associated lymphomas

Study	Study type	Study design	Results
Kaplan et al[53]	Prospective multicenter randomized phase III (n=192)	Randomization to standard-dose m-BACOD with GM-CSF versus low-dose m-BACOD without GM-CSF. No cART	Similar efficiacy of both regimens but less hematological toxicity with low-dose m-BACOD
Ratner et al[62]	Prospective multicenter sequential phase II (n=65)	First 40 patients received modified-dose (m) CHOP (50% cyclophosphamide and doxorubicin) and the next 25 patients received standard-dose CHOP. cART was administered	CR higher with full dose CHOP compared to mCHOP (48% vs 30%). Authors concluded that concomitant cART was safe but unable to conclude superiority of one regimen over another
Sparano et al[65]	Prospective multicenter sequential phase II (n=98)	First 43 patients received didanosine and the next 55 patients received cART with CDE	At 2 years, FFS and OS were 36% and 43%. Patients receiving concomitant cART had better survival and less toxicity
Mounier et al[56]	Prospective multicenter phase III study	485 patients were randomly assigned to different CHOP-based chemotherapy regimens according to an HIV score that was based on performance status, prior AIDS and CD4 count	Though HIV score, IPI score and cART affected survival, the intensity of CHOP-based chemotherapy had no effect on survival
Little et al[37]	Prospective single center phase II (n=39)	All patients received EPOCH and G-CSF with cART suspension	CR was 74%. At 53 months, DFS and OS were 92% and 60%. Patients in CR achieved CD4 recovery and HIV control following treatment. Conclusion that EPOCH with cART suspension is feasible and highly effective
Kaplan et al[58]	Prospective multicenter randomized phase III (n=150)	Randomization (2:1) to R-CHOP versus CHOP with concomitant cART. Some patients received maintenance rituximab.	CR rate higher with R-CHOP compared to CHOP (57.6% vs 47%). Increased infectious deaths with R-CHOP mostly in patients with low CD4 counts. Conclusion that rituximab does not improve clinical outcome
Boue et al[63]	Prospective multicenter phase II (n=61)	All patients received R-CHOP	CR in 77% of patients. Estimated 2 year OS was 75%
Spina et al[60]	Retrospective analysis of 3 phase II trials	Pooled results from 3 trials of CDE with rituximab	CR rate was 70%. At 2 years, FFS and OS were 59% and 64%. Conclusion that R-CDE is effective but rituximab may increase infections
Sparano et al[49]	Prospective multicenter phase II study	101 patients were randomized to receive either concurrent or sequential rituximab with DA-EPOCH	There was a superior outcome with concurrent rituximab and DA-EPOCH (CR rate 75%) and this was considerably better when compared to the previous ANC results with CHOP +/- R
Dunleavy et al[47]	Prospective single center phase II (n=33)	All patients received SC-EPOCH-RR with cART suspension	79% of patients needed only 3 cycles of treatment. At 5 year follow-up, PFS and OS were 84% and 68%. Outcome was better for GCB versus non-GCB DLBCL (5 year PFS of 95% versus 44%).

blood

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SC-EPOCH-RR drug doses and schedule.

	Dose mg/m^2/day	Treatment Days	
Infusional Agents			
Etoposide	50		
Vincristine	0.4	Days 1 to 4	
Doxorubicin	10		
Bolus Agents			
Cyclophosphamide	750	Day 5	Cycle 21 days
Prednisone	60 od	Days 1 to 5	
Biologic Agents			
G-CSF	300 mcg	Days 6 to 15	
Rituximab	375	Days 1 and 5	

od=once daily

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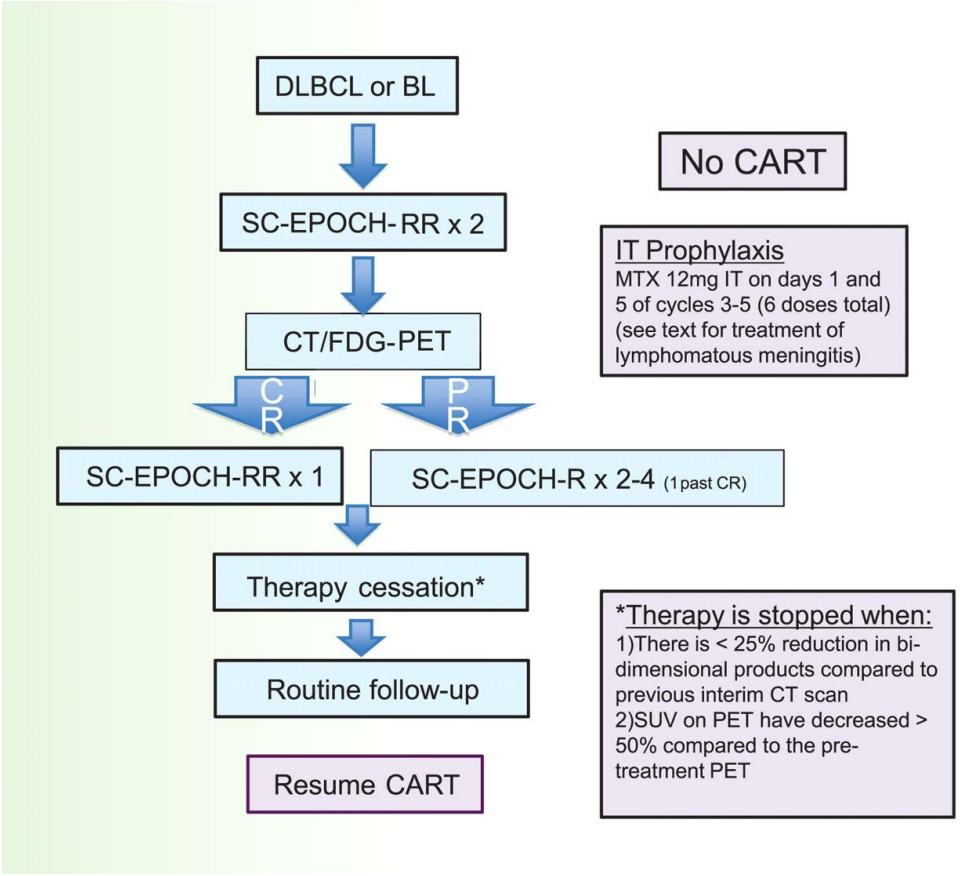
SC-EPOCH-RR treatment paradigm



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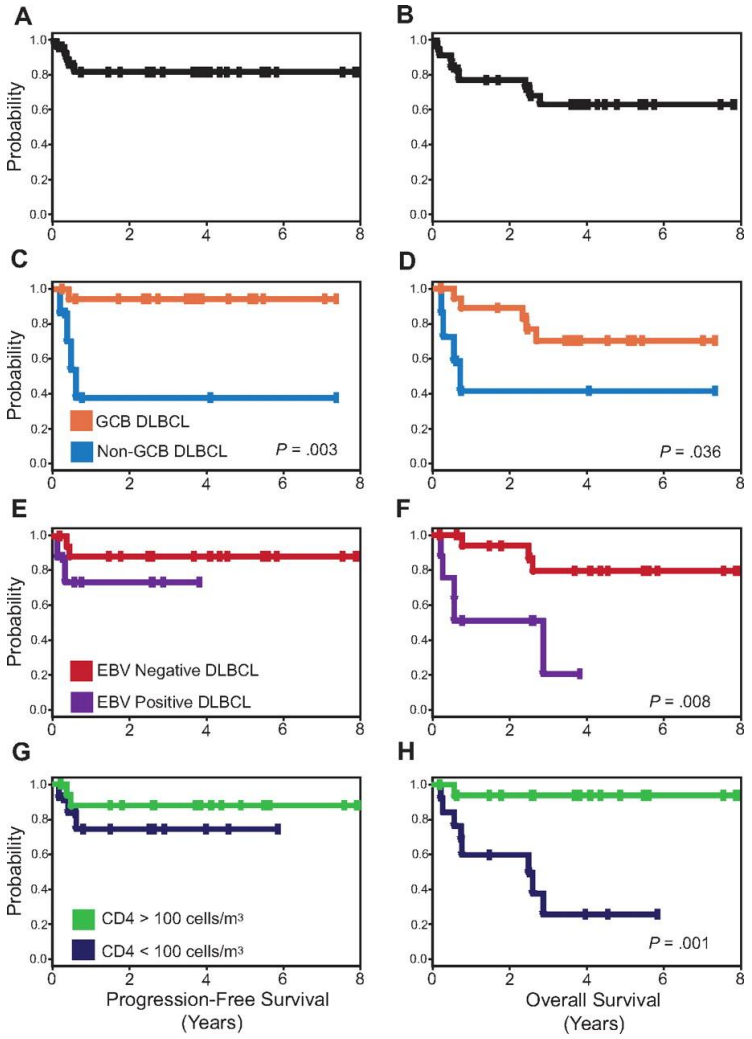
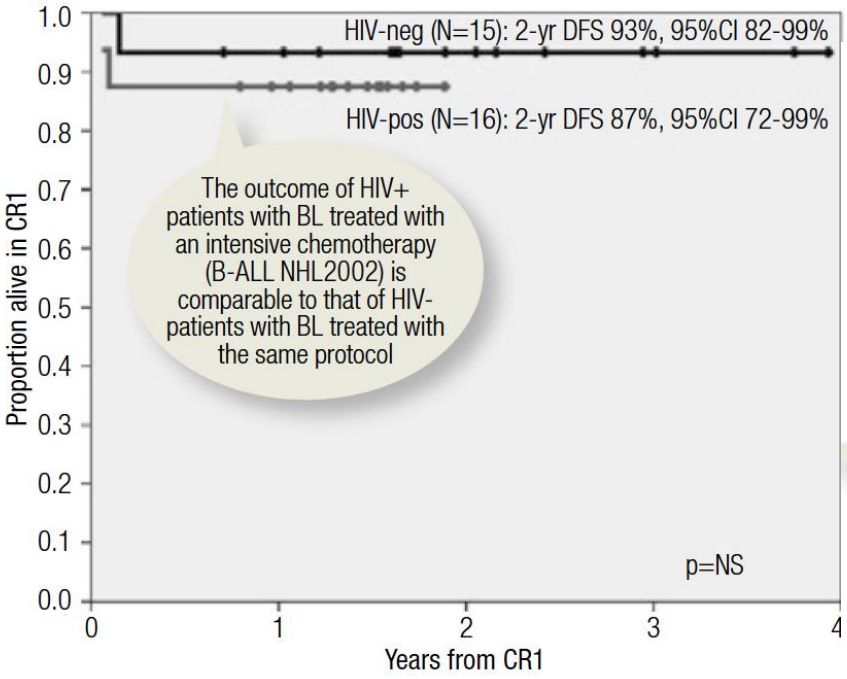
PFS and OS Kaplan-Meier curves



Kieron Dunleavy et al. Blood 2010;115:3017-3024

Burkitt`s lymphoma in HIV patients



BL is diagnosed in patients with a relatively high CD4 count who frequently present with extranodal disease.

The outcome of patients with HIV and BL is comparable to that of HIV-negative patients when treated with the same intensive chemotherapy.

There are some suggestions that infusional regimens, such as R-DA-EPOCH, achieve excellent results in patients with HIV-BL.

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Thank you

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