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Title

Hemophagocytic Lymphohistiocytosis in HIV-Related Lymphomas:

A Multicentre Retrospective Cohort Study

Running title

HLH in HIV-related lymphomas

Authors

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Statements and Declarations:

Author contributions:

The study was conceived and designed by PM, ADP and MB. PM, ADP, DD, MM, HS, AT, CF, AGL, KH, ND and MB collected and assembled the data. PM, ADP, MB and MH analysed and interpreted the data PM, ADP, DD, MM, HS, KH, CF and MB provided patients. ADP, PM, MH and MB wrote the manuscript. All authors reviewed the manuscript.

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The authors report no conflicts of interest.

Abstract and keywords

Abstract

Background: Hemophagocytic Lymphohistiocytosis (HLH) in adults is a rare, often fatal hyperinflammatory disorder triggered by infections, malignancies and autoimmune diseases. Lymphoma-associated HLH affects 0.6-3% of patients in HIV-negative cohorts. Limited data on HLH in People Living with HIV (PLWH) has been published.

Methods: Retrospective analysis of HRL patients treated at Chelsea and Westminster Hospital, London, UK and St. Joseph Hospital Berlin-Tempelhof, Germany from 2013-2024.

Results: 253 patients were enrolled; mean age 48.6 years. Median CD4 count 206/µL, with 49% having a CD4 cell count <200/µL. In 140 patients (56%) HIV-viral load was undetectable.

206 (81%) had advanced stage disease III (14%) or IV (67%). Median follow-up was 31 months. 5-year overall survival was 67%.

35 (14%) patients were diagnosed with HLH at the time of lymphoma diagnosis. HLH was most common in primary effusion lymphoma (4/16; 25%), followed by Burkitt lymphoma (8/30; 24%) and Hodgkin´s lymphoma (14/75; 18%). HLH patients were more often diagnosed with HIV and lymphoma concurrently (p=0.001), less likely to have suppressed HIV-VL (31% vs. 61%; p < 0.01) and had lower median CD4 count (102 vs. 239 cells/µL; p < 0.01). Patients with HLH demonstrated poorer outcome with 1-, 2-, and 5-year survival of 44%, 38% and 30% (p < 0.01) in comparison to patients without HLH with 81%, 79% and 73%.

Conclusions: HLH is more frequent in HRL. HLH in HRL is associated with lower CD4 count, detectable HIV viraemia and simultaneous diagnosis of HIV and lymphoma. Outcome of lymphoma-associated HLH in PLWH is poor.

Keywords:

HLH, HIV, HIV-associated Lymphomas, HScore, Hemophagocytic Lymphohistiocytosis

Article

Hemophagocytic Lymphohistiocytosis in HIV-Related Lymphomas: A Multicentre Retrospective Cohort Study

HLH in adults is characterized by fever, cytopenias, hepatosplenomegaly and hyperferritinemia, and carries a high mortality rate [1,2]. It can occur secondary to infections, autoimmune diseases or malignancies, most commonly of hematological origin [1,2]. Early identification of the underlying trigger is critical, but the sepsis-like presentation often delays diagnosis and worsens outcomes [3].

Common causes of secondary HLH in people living with HIV (PLWH) include various opportunistic infections, such as tuberculosis and disseminated histoplasmosis, as well as HIV-associated malignancies, especially lymphomas and HHV-8 related conditions such as multicentric Castleman disease [4]

Non-Hodgkin and Hodgkin lymphomas remain a leading cause of morbidity and mortality in PLWH in the modern antiretroviral therapy (ART) era. Although combination ART has reduced the incidence of certain HIV-associated lymphomas, the risk of lymphoma in PLWH remains significantly higher than in the general population [5]. Few studies have evaluated HLH in PLWH [6,7]. We previously reported HLH in 8% of HIV related Lymphomas (HRL) cases, with an associated increase in mortality [8]. In contrast, HLH complicates <1% of lymphomas in predominantly HIV-negative populations [9].

The aim of this study is twofold: firstly, to re-evaluate our findings in a larger multicentre cohort; secondly, to clarify the different clinical characteristics and outcome of lymphoma-associated HLH in HIV positive patients in comparison to published data in the general population.

Adult PLWH with histologically confirmed lymphoma diagnosed between 2013 and 2024 were retrospectively identified at two tertiary centres (National Reference Centre for HIV-Malignancies, Chelsea-Westminster Hospital London, UK and Department of Infectious

Diseases, St. Joseph Hospital Berlin, Germany). HLH diagnosis required an HScore ≥169 [10] or fulfilment of at least five of the eight HLH-2004 criteria [11]. Laboratory investigations included plasma HIV, EBV and HHV-8 viral loads when available.

Overall survival (OS) was defined from lymphoma diagnosis to death or last follow-up. Survival curves were estimated by the Kaplan–Meier method and compared by log-rank test. A multivariate Cox proportional hazards model was used to identify independent prognostic factors. The study was approved by the responsible review boards of both centres.

The cohort comprised 253 patients (median age 49, range 21-83 years; 83% male) from London (n=201) and Berlin (n=52). Patients baseline characteristics are shown in Table 1. The median CD4 count at lymphoma diagnosis was 206/µL (range 3-1610), 49% had CD4 <200/µL, and 56% of patients had an undetectable HIV viral load. The most common lymphoma subtypes were diffuse large B-cell lymphoma (DLBCL) (36%), Hodgkin lymphoma (HL) (30%) and Burkitt lymphoma (BL) (12%), followed by plasmablastic (PBL) (8%) and primary effusion lymphoma (PEL) (6%). Most patients (81%) had stage III/IV disease. After a median follow-up of 31 months, the 5-year OS of the entire cohort was 67% (Table 1).

HLH was diagnosed in 35 patients (14%) at lymphoma presentation. HLH occurrence was highest in Burkitt lymphoma (27%) and primary effusion lymphoma (25%), compared to 18% in Hodgkin lymphoma and <10% in other subtypes. Patients who developed HLH had significantly lower CD4 counts (median 102 vs. 239 cells/µL, $p<0.01$) and were less likely to have undetectable HIV viremia at lymphoma presentation (31% vs. 61%, $p<0.01$). HLH affected patients were also more frequently diagnosed with HIV and lymphoma concurrently (24% vs. 9%, $p<0.01$). Lymphomatous bone marrow involvement was more common in patients with HLH diagnosis (69% vs. 29%, $p<0.01$). Consistent with a hyperinflammatory state, HLH patients exhibited higher ferritin and LDH levels (median ferritin ~8850 vs. 440 ng/mL).

EBV DNA was detected in 72% of patients tested, with similar prevalence in those with and without HLH. HHV-8 viremia was present in 11% of patients; HLH developed in ~18% of patients with HHV-8-associated lymphomas.

Patients received first line lymphoma-specific systemic anticancer therapy according to subtype, in line with standard European guidelines (e.g., CHOP-based regimens for most DLBCL; ABVD for HL). HLH management was heterogeneous: Some patients received HLH-directed therapy - typically high-dose corticosteroids and, in selected cases, etoposide per HLH-94 or in accordance with recommendations of the Histiocyte Society [11-12] - concurrently with lymphoma treatment, whereas others were managed with supportive care and lymphoma-directed chemo(immuno)therapy alone. This variability mirrors the broader literature in adult HLH, where optimal regimens, especially in PLWH with malignancy, remain undefined.

As shown in Figure 1 survival was markedly worse for patients with HLH: 1-year OS 44% vs. 81% and 5-year OS 30% vs. 73% ($p<0.01$). Early mortality was prominent; approximately 20% of HLH patients died within the first month of lymphoma diagnosis.

In a multivariable Cox model adjusting for age, sex, HIV suppression, CD4 count, performance status and lymphoma stage, HLH remained an independent predictor of higher mortality (HR 2.4, $p=0.001$). Detectable HIV RNA was also independently associated with inferior survival (HR 1.8, $p<0.05$).

In this multicentre cohort of PLWH with lymphoma, the development of HLH was associated with markedly inferior survival. The 5-year survival rate was only 30% among patients with HLH, compared to 73% in those without HLH. This finding confirms HLH as a major adverse prognostic factor, in line with previous reports of high mortality in adult HLH [13;14]. For example, a population-based Swedish study documented only a ~25% two-year survival in patients with malignancy-associated HLH [9]. These outcomes stress the critical importance of early recognition and treatment of HLH in patients with HIV-related lymphoma, since even short delays can be lethal [3].

There is no clear consensus on optimal therapy for adult malignancy-associated HLH in PLWH. Current HLH treatment protocols, such as the HLH-94 etoposide/dexamethasone regimen are based on paediatric or mainly HIV-negative patient data [11-12], and their applicability to HIV-positive patients with lymphoma is uncertain. In practice, our cohort demonstrated a heterogeneous approach to HLH treatment – some patients received aggressive chemoimmunotherapy for HLH, while others did not – reflecting real-world challenges also noted in the literature where only about half of reported HIV-HLH cases receive specific HLH therapy [6]. Future studies are needed to determine how dedicated HLH therapies can be safely and effectively integrated with lymphoma treatment in this population.

HLH occurred in 14% of our HIV-associated lymphoma patients – a substantially higher frequency than observed in predominantly HIV-negative lymphoma cohorts. In one nationwide study, HLH was identified in only 0.6% of lymphoma cases [9]. As clinical awareness of HLH has grown, an increase in reported incidence at the population level has been noted [13]. Our data underscore that lymphoma-associated HLH is a significant clinical problem in PLWH that should not be overlooked.

The strong association of HLH with uncontrolled HIV viremia and low CD4 counts in our study highlights the impact of severe immunosuppression. It is likely that PLWH with advanced disease harbour multiple risk factors for HLH. Opportunistic infections and HIV itself have been recognized as precipitants of secondary HLH [4,6-7], and our findings suggest that the immune dysregulation from untreated HIV contributes to the development of HLH in the setting of lymphoma.

Oncogenic co-infections may further promote hyperinflammation in this context. We observed a high rate of HLH in HHV-8-associated lymphomas and a trend toward higher HHV-8 viremia in those who developed HLH. In a prior study we found high HHV-8 viral loads to be associated with the occurrence of HLH in HIV-associated HHV-8 positive Multicentric Castleman Disease [14]. In contrast, EBV viremia was equally prevalent in patients with and without HLH, supporting the notion that EBV is often a bystander rather than the primary trigger for HLH in PLWH.

Notably, the predominance of male patients in our HLH cohort reflects the underlying demographics of the HIV population in our regions. The median age of patients with lymphoma-associated HLH (~45 years) was also younger than typically reported in HIV-negative HLH cohorts [9].

This analysis is limited by its retrospective design and the potential underestimation of HLH occurrences (only the first lymphoma presentation was analysed). Additionally, HLH specific laboratory data soluble IL-2 receptor, NK cytotoxic functional assays) were incomplete, which may have constrained further risk stratification. We were unable to analyse the specific causes of death due to a lack of standardised documentation. Finally, optimal management of HLH in this setting remains unclear. Whether incorporating HLH-directed therapies into lymphoma treatment can improve outcomes for patients with lymphoma-associated HLH warrants investigation in future studies.

In summary, HLH is substantially more frequent in PLWH with lymphoma than in the general population and is associated with profound immunosuppression, evidence of plasma HIV replication, concurrent HIV and lymphoma diagnoses, and marrow involvement. The combination of acquired immune dysfunction and oncogenic viral co-infections likely lowers the threshold for this fatal hyperinflammatory syndrome. Across subtypes, HLH portends strikingly worse survival and early mortality mirroring those in HIV negative patients. We advocate awareness of HLH risk at lymphoma presentation in PLWH - particularly in BL and PEL, and in those with low CD4 counts or detectable HIV RNA. Collaborative prospective studies are urgently needed to define safe, effective, and timely integration of HLH-directed therapies to specific anticancer therapies in this high-risk population.

1. Emile JF, Abla O, Fraitag S, Horne A, Haroche J, Donadieu J, et al. Revised classification of histiocytoses and neoplasms of the macrophage-dendritic cell lineages. Blood. 2016;127(22):2672-81.

2. Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet. 2014;383(9927):1503-16.

3. Abdelhay A, Mahmoud A, Mostafa M, Jain T, Elseidy S, Fahmawi S, et al. Delay in treatment of adult hemophagocytic lymphohistiocytosis is associated with worse in-hospital outcomes. Ann Hematol. 2023;102(11):2989-96.

4. Fardet L, Lambotte O, Meynard JL, Kamouh W, Galicier L, Marzac C, et al. Reactive haemophagocytic syndrome in 58 HIV-1-infected patients: clinical features, underlying diseases and prognosis. AIDS. 2010;24(9):1299-306.

5. Kimani SM, Painschab MS, Horner MJ, Muchengeti M, Fedoriw Y, Shiels MS, et al. Epidemiology of haematological malignancies in people living with HIV. Lancet HIV. 2020;7(9):e641-e51.

6. Tabaja H, Kanj A, El Zein S, Comba IY, Chehab O, Mahmood M. A Review of Hemophagocytic Lymphohistiocytosis in Patients With HIV. Open Forum Infect Dis. 2022;9(4):ofac071.

7. Migaud P, Drauz D, Dalla Pria A, Hosmann K, Muller M, Ghaeni L, et al. Hemophagocytic lymphohistiocytosis in people living with HIV-a single centre experience. Infection. 2025;53(5):2203-7.

8. Migaud P, Muller M, Arasteh K, Hentrich M, Stocker H. Hemophagocytic lymphohistiocytosis in HIV-associated lymphoproliferative disorders. Ann Hematol. 2022.

9. Lofstedt A, Jadersten M, Meeths M, Henter JI. Malignancy-associated hemophagocytic lymphohistiocytosis in Sweden: incidence, clinical characteristics, and survival. Blood. 2024;143(3):233-42.

10. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014;66(9):2613-20.

11. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48(2):124-31.

12. La Rosee P, Horne A, Hines M, von Bahr Greenwood T, Machowicz R, Berliner N, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood. 2019;133(23):2465-77.

13. Abdelhay A, Mahmoud AA, Al Ali O, Hashem A, Orakzai A, Jamshed S. Epidemiology, characteristics, and outcomes of adult haemophagocytic lymphohistiocytosis in the USA, 2006-19: a national, retrospective cohort study. EClinicalMedicine. 2023;62:102143.

14. Migaud P, Dalla Pria A, Hosmann K, Kelleher P, Fulgenzi CAM, Stocker H, et al. Haemophagocytic lymphohistiocytosis in HIV-associated HHV-8-positive multicentric Castleman disease. AIDS. 2025;39(5):519-25.

Table 1: Characteristics of patients with HIV-associated lymphomas with or without Hemophagocytic lymphohistiocytosis

Figure 1: Kaplan-Meier curve showing the overall survival of 35 patients with HLH vs. 218 patients without HLH.

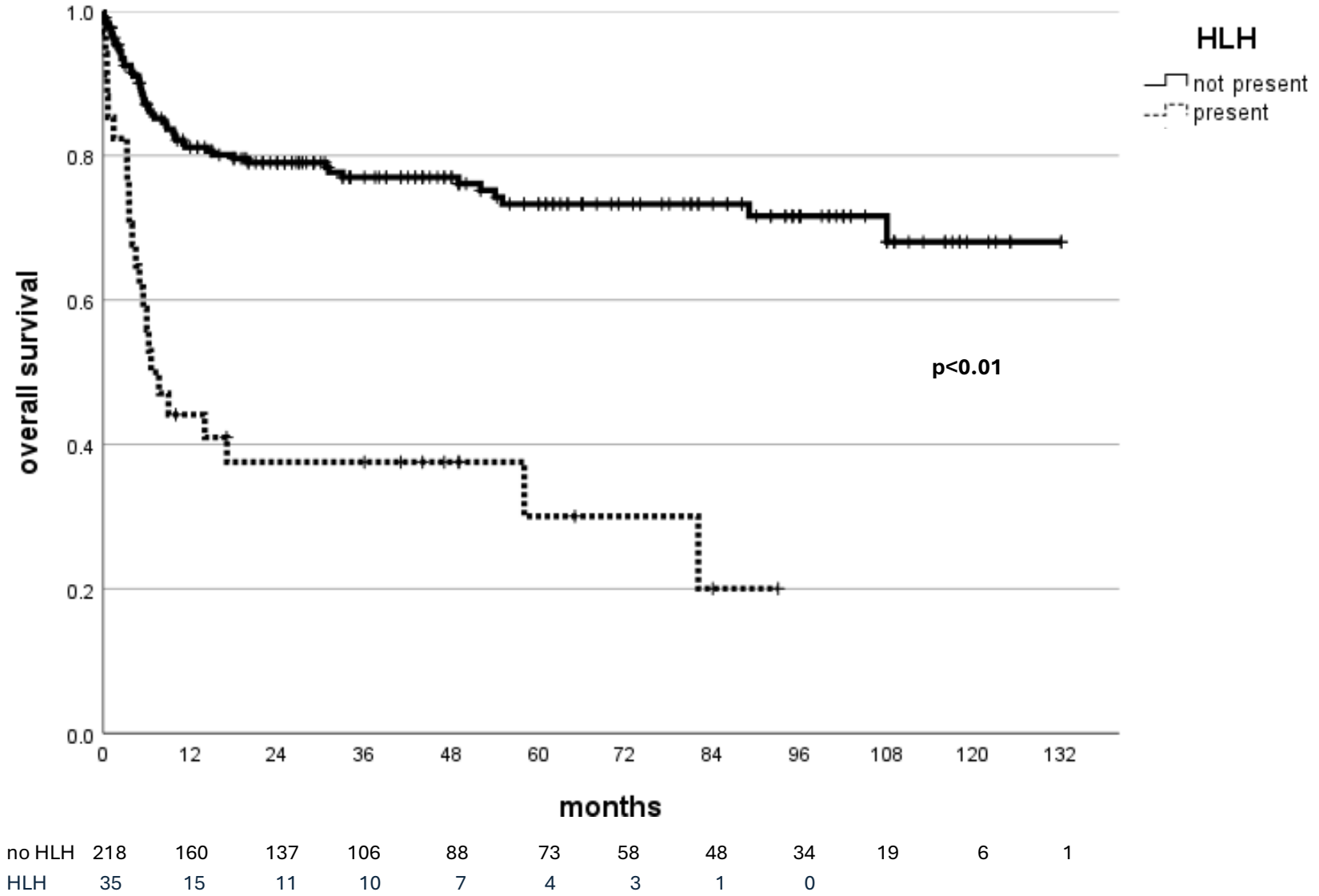


Figure 1: Kaplan-Meier curve showing the overall survival of 35 patients with HLH vs. 218 patients without HLH.

Table 1: Characteristics of patients with HIV-associated lymphomas with or without Hemophagocytic lymphohistiocytosis

	Total *(n= 253)*	With HLH *(n=35;13.8%)*	Without HLH *(n=218; 86.2%)*	P-value
Female *n* (%)	44 (17.4)	5 (14.3)	39 (17.9)	
Age [years]; median (range)	48.6 (21-83)	46 (23-64)	49 (21-83	
Ferritin [ng/mL]; median (range)	579 (4-106,246)	8004 (159-106,246)	436 (4-32,723)	<0.01
HLH-criteria, median (range)	1 (0-6)	5 (5-7)	1 (0-4)	
Hscore [points]; median (range)	81 (18-256)	207 (142-256)	70 (18-161)	
HIV				
CD4-count baseline [/µL]; median (range)	206 (3-1,610)	102 (12-352)	239 (3-1,610)	<0.01
CD4-count baseline <200/µL ; n (%)	124 (49.2)	27 (77.1)	97 (44.5)	
Viral load undetectable; (<50cop/mL) *n* (%)	140 (56.5)	11 (31.4)	133 (61)	<0.01
Viral load baseline in detectable patients [cop/mL]; median (range)	42.115 (0-5,150,422)	29.757 (0-1,150,650)	58.170 (0-5,150,422)	
Interval HIV diagnosis to Lymphoma diagnosis [months]; median(range)	55 (0-480)	7.6 (0-312)	65 (0-480)	0.01
HIV first diagnosed in context of Lymphoma *n* (%)	70 (27.7)	17 (48.6)	53 (24.3)	0.02
On ART at time of Lymphoma diagnosis *n* (%)	170 (67.2)	16 (45.7)	154 (70.6)	
ART-class during treatment of Lymphoma *n* (%)				
INSTI-based	202 (79.8)	33 (94.3)	169 (77.5)	
PI-based	10 (4)	0	10 (4.6)	
NNRTI-based	29 (11.5)	1 (2.9)	28 (12.8)	
other/none	12 (4.7)	1 (2.9)	11 (5)	
Lymphoma				
Stage III	38 (15)	1 (2.9)	37 (17)	
Stage IV	168 (66.4)	33 (94.3)	135 (61.9)	
B-symptoms	190 (75.1)	34 (97.1)	156 (71.6)	
Subtypes n (%)				
DLBCL	91 (36)	6 (17.1)	85 (38.9)	
HL	75 (29.6)	14 (40)	61 (28)	
BL	30 (11.9)	8 (22.9)	22 (10.1)	
PBL	21 (8.3)	2 (5.7)	19 (8.7)	
PEL	16 (6.3)	4 (11.4)	12 (5.5)	
T-Cell-Lymphoma	8 (3.2)	1 (2.9)	7 (3.2)	
Mantle/Marginal-Cell Lymphoma	7 (2.8)		7 (3.2)	
CNS-Lymphoma	5 (2.0)		5 (2.3)	
Outcome				
Follow up [months]; median (range)	31 (0-132)	7.7 (0.1-93)	34 (0-132)	
1 year survival *n* (%)	174 (75.9)	15 (44.1)	160 (81.1)	<0.01
2 years survival *n* (%)	148 (73.2)	11 (37.6)	137 (79)	<0.01
5 years survival *n* (%)	77 (67.4)	4 (30)	73 (73.3)	<0.01

ART Antiretroviral Therapy*; BL Burkitt Lymphoma; CNS Central Nervous System; DLBCL Diffuse-Large-B-Cell-Lymphoma; HL Hodgkin´s Lymphoma; HLH* Hemophagocytic Lymphohistiocytosis*;*

INSTI Integrase Inhibitor; NNRTI Non-Nucleoside reverse transcriptase inhibitors; PBL Plasmablastic Lymphoma; PEL Primary Effusion Lymphoma; PI Protease Inhibitor