

Human immunodeficiency virus-associated Lymphomas: EHA–ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

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Highlights

- This EHA–ESMO Clinical Practice Guideline provides key recommendations for managing HIV-associated lymphomas.
- The guideline covers clinical, imaging and pathological diagnosis; staging and risk assessment; treatment and follow-up.

- The author group encompasses a multidisciplinary group of experts from different institutions and countries in Europe.
- Recommendations are based on available scientific data and the authors' collective expert opinion.

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INCIDENCE AND EPIDEMIOLOGY

Non-Hodgkin lymphoma (NHL) remains the most common type of cancer and a leading cause of mortality in people who are living with human immunodeficiency virus (HIV).¹ This is despite a marked decrease in the incidence of HIV-associated NHL (HIV-NHL) following the introduction of combination antiretroviral therapy (ART) in the mid-1990s.² In contrast, the incidence of Hodgkin lymphoma (HL) increased slightly but has remained stable since 2000.¹ Compared with the age- and gender-matched general population, the incidences of HIV-NHL and HIV-associated HL (HIV-HL) are increased ~10- to 20-fold.³

The most common histological types of HIV-associated lymphomas are diffuse large B-cell lymphoma (DLBCL; 37%), HL (26%) and Burkitt lymphoma (BL; 20%).⁴ Independent risk factors for DLBCL in people living with HIV (PLWH) include a low cluster of differentiation (CD)4 T-cell count and an uncontrolled HIV-1 viral load (VL).⁵ The availability of ART and better management of opportunistic infections allow PLWH to receive the same treatments as people without HIV, including intensive therapies, such as autologous stem-cell transplantation (ASCT), allogeneic stem-cell transplantation (allo-SCT) and chimeric antigen receptor T-cell (CAR-T) therapy. Patients with HIV-associated lymphomas should be enrolled in clinical trials whenever possible.

The aim of this guideline is to provide practical clinical guidance and recommendations to clinicians who manage HIV-associated lymphomas.

DIAGNOSIS, PATHOLOGY AND STAGING

Diagnostic procedures in patients with HIV-associated lymphoma generally mirror those recommended for lymphoma in the general population and those necessary to assess the severity and complications of HIV and its treatment (see Supporting Information S1: Table S1).

Lymphoma should be diagnosed via tumour biopsy, preferably excisional, that is evaluated by an expert haematopathologist using immunohistochemistry (IHC) and molecular techniques. In exceptional cases when no tumour mass can be biopsied, diagnosis can be made by cytology and flow cytometry.

Lymphoma staging should involve a contrast-enhanced computed tomography (CT) scan of the neck, chest, abdomen and pelvis and a bone marrow biopsy. A staging [¹⁸F]2-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET)-CT scan is more sensitive, especially for extranodal disease. FDG-PET-CT may, however, have a higher false-positive rate in PLWH due to immune deficiency-related lymphoid hyperplasia and non-suppressed HIV infection.⁶ Interim FDG-PET-CT (iFDG-PET-CT) results should, therefore, be interpreted cautiously if used to escalate treatment and when analysing end-of-treatment response; if there is doubt, FDG-avid lesions should be re-biopsied. Otherwise, response criteria do not differ from those used in immunocompetent individuals.

Magnetic resonance imaging (MRI) is the optimal method for staging and response assessment of central nervous system (CNS) lymphomas. Cerebral opportunistic infections may, however, mimic lymphoma in PLWH. Small case series suggest that FDG-PET-CT can differentiate between cerebral infections, such as toxoplasmosis,⁷ and CNS lymphoma, but biopsy (preferably stereotactic) remains the gold standard for diagnosis.

All additional investigations for patients with newly diagnosed HIV should follow the annually updated, evidence-graded European Acquired Immune Deficiency Syndrome Clinical Society guidelines, available at <http://www.eacsociety.org/guidelines/eacs-guidelines/>.

Recommendations

- Diagnostic work-up should follow recommendations for patients who are HIV-negative and those necessary to assess the severity and complications of HIV [V, A].
- Staging with FDG-PET-CT provides higher sensitivity than contrast-enhanced CT [III, A], but MRI is the optimal method for staging CNS lymphomas [III, A]. These techniques may, however, give false-positive results because of opportunistic infections or immune deficiency-related lymphoid hyperplasia and should be interpreted with caution [IV, C].
- Cytological and flow cytometry evaluation of cerebrospinal fluid (CSF) can be recommended in patients with aggressive NHL and when there is a high risk of CNS disease [IV, B].

CONCOMITANT THERAPIES

ART

All patients with HIV-related lymphoma should be treated with effective ART, even those with relatively preserved immune function. ART should be initiated and continued during chemotherapy (ChT) to ensure sustained viral suppression. Several prospective studies have shown that ChT tolerability, immune recovery and patient outcomes are improved with ART;⁸ however, pharmacokinetic and pharmacodynamic interactions between cytotoxic anticancer agents, ART and supportive medication [drug-drug interactions (DDIs)] must be carefully checked. A multidisciplinary approach is recommended and ART can be modified to avoid DDIs. Advice about specific ChT and ART DDIs is available at <http://www.hiv-druginteractions.org> and www.cancer-druginteractions.org.

Infection prophylaxis

When CD4 counts are <200 cells/μL, prophylaxis against *Pneumocystis jirovecii* pneumonia (PcP) and antiviral prophylaxis with acyclovir or valacyclovir in patients with a history of herpes simplex virus or varicella zoster virus infection is strongly recommended.⁹ They should also be offered at higher CD4 counts, as ChT in combination with prednisolone usually causes a profound fall in these cells. PcP prophylaxis also provides protection against toxoplasmosis and some bacterial infections.

Routine primary prophylaxis against mucosal candidiasis is not recommended; however, in severely immunosuppressed patients (e.g., CD4 counts <100 cells/μL), in those with anticipated prolonged neutropenia or in patients receiving high-dose (HD) methotrexate (MTX) or HD cytarabine (Ara-C)-containing regimens (most likely causing mucositis), antifungal prophylaxis with fluconazole may be considered, given its favourable DDI profile. Monitoring for cytomegalovirus is warranted if CD4 counts are <100 cells/μL.

Prophylactic fluoroquinolones are suggested for patients undergoing intensive ChT, who may experience prolonged neutropenia (>7 days) and mucositis.

Co-infection with hepatitis B and C

Two European cohort studies conducted in the modern ART era have shown a consistent increase in the risk of NHL in PLWH who are also affected by chronic hepatitis C virus (HCV) infection.^{10,11} HCV-associated DLBCL is a therapeutic challenge in terms of liver injury during immunochemotherapy (ICT) and long-term hepatic

complications. Immediate delivery of direct-acting antivirals (DAAs) is recommended during or after ICT. Concomitant treatment with ART, DAAs and ICT is feasible if particular attention is paid to DDIs.

The risk of reactivation of hepatitis B virus is markedly increased during and after treatment of HIV-associated lymphomas, increasing the risk of lethal liver failure; thus, patients should receive tenofovir (often already included in the ART regimen) or entecavir.

Recommendations

- Concomitant ART should be continued in patients receiving therapy for HIV-associated lymphoma [I, A].
- A multidisciplinary approach (including an HIV specialist) is strongly recommended to prevent DDIs [V, A].
- Prophylaxis against PcP could be offered to all patients [III, B] and is strongly recommended when CD4 counts are <200 cells/ μ L [I, A].
- Antiviral prophylaxis with acyclovir or valacyclovir should be offered to patients with a history of herpes simplex virus or varicella zoster virus infection and those with CD4 counts <200 cells/ μ L [I, A].
- In the context of HIV and HCV co-infection and DLBCL, DAAs can be recommended in patients established on ART [V, B].

DLBCL

Diagnosis, pathology and molecular biology

DLBCL is characterised by a diffuse infiltrate of large cells expressing the B-cell markers CD19 and CD20. DLBCL can be classified as germinal centre B-cell (GCB) or activated B-cell subtypes based on the cell of origin (COO) determined by gene expression profiling (GEP). Although COO classification based on GEP is preferred, IHC-based classification systems can be used if GEP is not available. The Hans algorithm is the most frequently used IHC-based classification; this classifies DLBCL as GCB or non-GCB subtypes, the latter being more frequent in HIV-associated DLBCL (HIV-DLBCL).¹²

Staging and risk assessment

The prognosis of HIV-DLBCL is determined by the International Prognostic Index (IPI).¹³ The predictive value of HIV-related factors such as CD4 count and VL on overall survival (OS) is not clear. Several tumour markers [i.e. proliferation index Ki-67, CD44, CD20, Epstein-Barr virus (EBV) positivity, MYC translocation, *BCL2* or *BCL6* translocation, *TP53* mutation and immunoglobulin (Ig) M expression] have shown prognostic value;¹⁴ however, with the exception of CD20 positivity (which is crucial for application of the anti-CD20 antibody rituximab), these markers currently have no impact on clinical management and need to be tested in prospective trials.

First-line management of HIV-DLBCL

Studies carried out in the pre-ART era suggest that patients with HIV-DLBCL tolerate standard ChT regimens poorly and have a poor prognosis. This changed with improvements in HIV therapy: phase II and real-world studies have demonstrated that PLWH can receive similar regimens to those used in patients who are HIV-negative.^{14,15}

Figure 1 shows a proposed treatment algorithm for patients with HIV-DLBCL.

Rituximab is beneficial if CD4 counts are ≥ 50 cells/ μ L and should be routinely combined with ChT.^{14,15} In contrast, in patients with CD4 counts <50 cells/ μ L, there is an increased risk of lethal infections with rituximab, and a large retrospective analysis reported no benefit on overall outcome.⁸ The most frequent regimens are rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone (R-CHOP) and infusional dose-adjusted (DA) rituximab-etoposide-prednisone-vincristine-cyclophosphamide-doxorubicin (R-EPOCH). A retrospective analysis of two consecutive phase II trials suggested that DA-R-EPOCH is more effective than R-CHOP; however, the patient populations differed,¹⁶ and a large retrospective pooled study did not report differences between the two regimens on multivariate analysis.⁸ Another infusional regimen is rituximab-cyclophosphamide-doxorubicin-etoposide (R-CDE); in a retrospective trial, both DA-R-EPOCH and R-CDE provided outcomes comparable with R-CHOP in patients with HIV-DLBCL, including those with MYC rearrangements.¹⁷ In a phase III trial, the combination of polatuzumab vedotin with rituximab-cyclophosphamide-doxorubicin-prednisone (Pola-R-CHP) demonstrated improved progression-free survival (PFS) versus R-CHOP in patients without HIV.¹⁸ Pola-R-CHP is used in patients who are HIV negative in some centres, but data in HIV-DLBCL are lacking. R-CHOP should be administered using the standard schedule of six cycles given every 3 weeks. Whilst a reduction in the number of cycles and addition of radiotherapy (RT) in the rare subgroup of patients with low-risk localised disease seems reasonable, there are no reliable data to support this approach. A National Cancer Institute study suggested that the number of DA-R-EPOCH cycles can be safely reduced to four in combination with two rituximab doses per cycle,¹⁹ but most centres administer six cycles. There are no published data on the use of alternative regimens [e.g., rituximab-doxorubicin-cyclophosphamide-vindesine-bleomycin-prednisone (R-ACVBP) and rituximab-cyclophosphamide-doxorubicin-vincristine-etoposide-prednisone (R-CHOEP14)] in the ART era, but some European centres use these in high-risk patients.

The incidence of subclinical leptomeningeal involvement in DLBCL seems higher than expected in risk-matched patients with HIV.²⁰ CNS prophylaxis with intrathecal (IT) MTX with or without Ara-C or intravenous (i.v.) MTX may be considered. The criteria used to determine whether patients require CNS prophylaxis should be the same as those used in people without HIV.

Management of relapsed or refractory HIV-DLBCL

There are no prospective randomised controlled trials for PLWH with relapsed or refractory (r/r) DLBCL. Indeed, HIV infection has been an exclusion criterion in most clinical trials of r/r DLBCL.

In general, if the HIV infection is well controlled with ART and there is no evidence of uncontrolled infections, transplant-eligible patients (i.e., aged ≤ 70 years and fit) should be offered salvage ICT followed by ASCT if the disease is chemosensitive. Standard platinum-based salvage regimens [e.g. rituximab-dexamethasone-Ara-C-cisplatin (R-DHAP), rituximab-ifosfamide-carboplatin-etoposide (R-ICE), rituximab-gemcitabine-dexamethasone-cisplatin (R-GDP) and rituximab-etoposide-methylprednisolone-Ara-C-cisplatin (R-ESHAP)] can be used, with response rates comparable to those observed in patients without HIV. Stem-cell mobilisation has been proven feasible. Data from 118 PLWH who received ASCT for different types of lymphoma (including 47% with DLBCL) were reported in a retrospective study by the European Group for Blood and Marrow Transplantation.²¹ The outcome after ASCT for HIV-associated lymphoma in this series was determined by lymphoma-dependent risk factors rather than

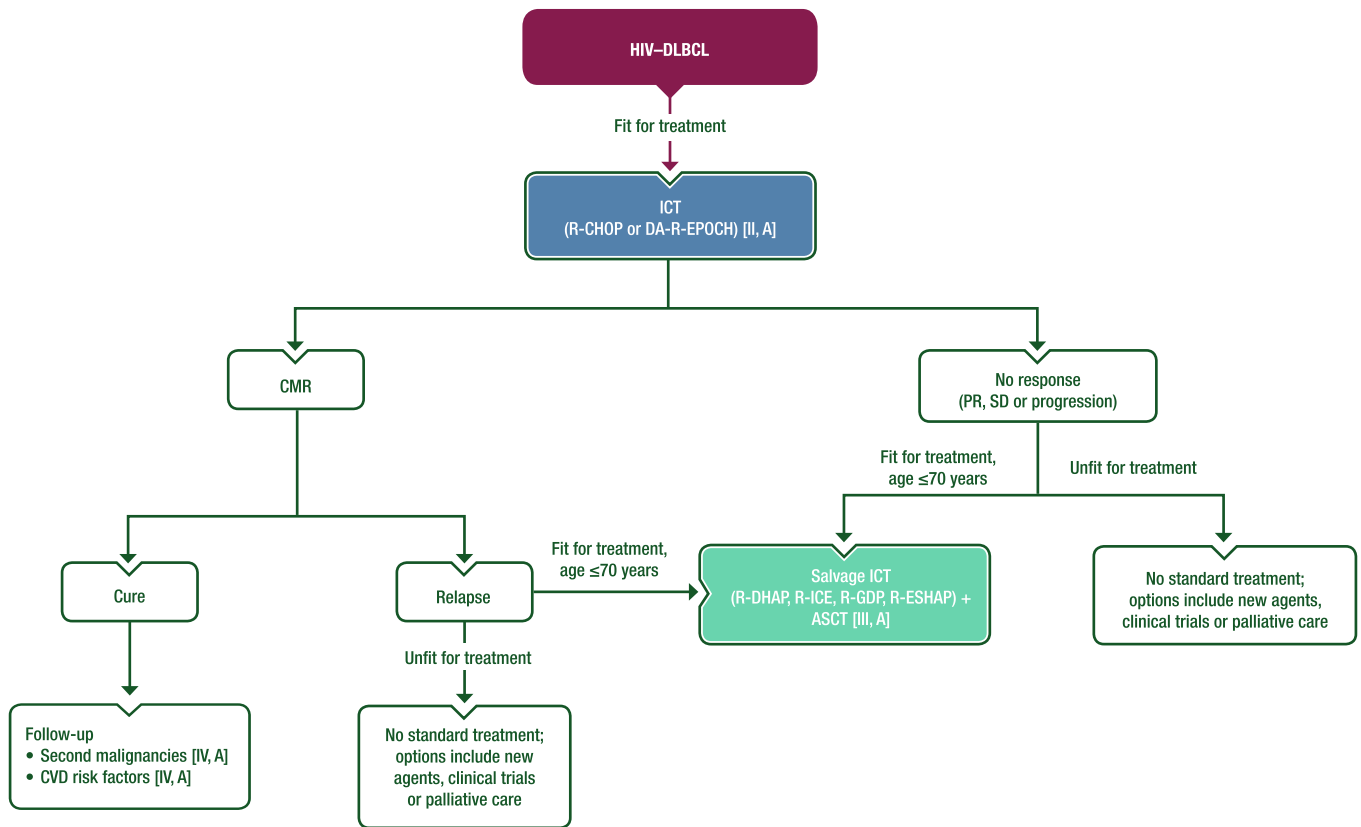


FIGURE 1 Management of HIV-DLBCL. Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects. ASCT, autologous stem-cell transplantation; CMR, complete metabolic response; CVD, cardiovascular disease; DA-R-EPOCH, dose-adjusted rituximab-etoposide-prednisone-vincristine-cyclophosphamide-doxorubicin; HIV-DLBCL, human immunodeficiency virus-associated diffuse large B-cell lymphoma; ICT, immunochemotherapy; PR, partial response; R-CHOP, rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone; R-DHAP, rituximab-dexamethasone-cytarabine-cisplatin; R-ESHAP, rituximab-etoposide-methylprednisolone-cytarabine-cisplatin; R-GDP, rituximab-gemcitabine-dexamethasone-cisplatin; R-ICE, rituximab-ifosfamide-carboplatin-etoposide; SD, stable disease.

HIV-related characteristics. When allo-SCT is indicated, a search for a matched donor who is homozygous for *CCR5-delta 32* deletion should be considered, following reports of long-term HIV control in a small number of patients.²² There is currently no standard of care (SoC) for non-transplant-eligible patients, but second-line regimens such as rituximab-gemcitabine-oxaliplatin (R-GemOx) can be used. There is limited evidence for novel agents such as polatuzumab vedotin, tafasitamab, brentuximab vedotin (BV), lenalidomide and proteasome inhibitors in this setting.

Based on randomised trials in patients without HIV, the use of CAR-T therapy in early relapsed DLBCL is associated with a better outcome than ASCT. CAR-T therapy is also approved following two lines of treatment. There is currently limited experience with this approach in HIV-DLBCL. Case reports have shown that anti-CD19 CAR-T therapy in PLWH is feasible, provided the VL is suppressed and CD4 counts are >200 cells/ μ L.^{23,24} Given the expanded approved indications for patients with r/r DLBCL, this strategy could be considered for selected r/r HIV-DLBCL cases.

Follow-up, long-term implications and survivorship

The OS of patients with HIV-DLBCL who are on ART and receive first-line therapy with standard ICT is approaching that of patients

who are HIV-negative and treated with similar regimens.²⁵ Around two-thirds of patients are cured with first-line therapy and are, therefore, susceptible to long-term complications. PLWH and NHL have an increased risk of second primary malignancies²⁶ and thus prevention of other risk factors is warranted. Likewise, the incidence of cardiovascular disease (CVD) is increased in patients with HIV infection²⁷ so regular screening and control of additional CVD risk factors is mandatory.

Recommendations

- Determination of COO by GEP or IHC may be recommended [IV, C].
- IPI should be used to evaluate prognosis [IV, A].
- Evaluation of *MYC* rearrangement may be carried out; if positive, investigation of *BCL2* and *BCL6* rearrangements may be carried out to exclude double- or triple-hit lymphoma [IV, C].
- Rituximab should be used routinely in combination with ChT if the CD4 count is ≥ 50 cells/ μ L [II, A].
- When using R-CHOP, six cycles every 3 weeks should be given [II, A].
- In low-risk patients, a reduction in the number of ChT cycles and addition of RT are optional [III, C].
- When using DA-R-EPOCH, six cycles should be given [II, A].

- Alternatively, four cycles of DA-R-EPOCH with two doses of rituximab per cycle can be given [III, B].
- IT MTX with or without Ara-C [III, C] or i.v. MTX [IV, A] are options for CNS prophylaxis.
- In the relapse setting, salvage ICT and ASCT should be offered to fit patients with well-controlled HIV infection [III, A].
- Lifestyle measures to reduce the risk of a secondary malignancy should be discussed [IV, A].
- CVD risk factors should be assessed and managed [IV, A].

BL

Diagnosis, pathology and molecular biology

Translocation of *MYC* with the Ig heavy-chain loci (80%) or, less frequently, with kappa or lambda light chains, is the molecular hallmark of BL. In HIV-associated BL (HIV-BL), *TP53* mutations are present in a high percentage of patients.²⁸ Among cases with EBV infection, type I is the most common latency pattern. Some evidence suggests a direct role for HIV in the pathogenesis of HIV-associated lymphomas, including BL.²⁸

Staging and risk assessment

The usual staging procedures for HIV-BL follow the general recommendations for BL. Assessment of the biochemical parameters that define clinical and biological tumour lysis syndrome [lactate dehydrogenase (LDH), potassium, calcium, phosphate, uric acid and creatinine clearance] must also be included. According to the recently proposed BL-IPI, there are four variables [age ≥ 40 years, performance status (PS) ≥ 2 , serum LDH $> 3 \times$ upper limit of normal and CNS involvement] with independent prognostic value for PFS and OS.²⁹ Three risk groups were identified (see Supporting Information S1: Table S2). The index discriminated outcomes regardless of stage or first-line ChT and, importantly, HIV status was not a prognostic factor.

First-line management of HIV-BL

HIV-BL is now treated with the same multi-agent regimens used in the HIV-negative setting. These include rituximab-cyclophosphamide-vincristine-doxorubicin-MTX (R-CODOX-M) or rituximab-ifosfamide-etoposide-Ara-C (R-IVAC), rituximab-hyperfractionated cyclophosphamide-vincristine-doxorubicin-dexamethasone (R-hyper-CVAD), the German Multicentre Study Group for Adult Acute Lymphoblastic Leukaemia B-cell acute lymphoblastic leukaemia (GMALL-B-ALL) protocol³⁰⁻³² or equivalent regimens and the less intensive DA-R-EPOCH regimen (Figure 2).

Few prospective trials have been conducted in the rituximab era to assess the efficacy and toxicity of R-CODOX-M, R-IVAC or DA-R-EPOCH, with < 35 PLWH recruited.³³⁻³⁵ Two-year OS rates were $\sim 70\%$ and treatment-related mortality (TRM) rates were $< 5\%$ for these regimens.^{35,36} Short-course EPOCH with a double dose of rituximab (SC-RR-EPOCH) is a less intensive regimen used successfully in a small group of patients with HIV.³⁵ R-EPOCH has limited effect in the CNS and, therefore, is not recommended in HIV-BL with CNS involvement. In a retrospective series including 142 PLWH with BL in the United States, 19% had CNS involvement.³⁷ This was independently associated with HIV infection on multivariate analysis. DA-R-EPOCH had the highest CNS relapse rate when compared with other regimens, but only 45% of those

receiving IT ChT adhered to the strict administration schedule in the original protocol.³⁷ In a large international retrospective analysis, which included 249 PLWH with BL, 11% had CNS relapse. The highest relapse rates were seen with DA-R-EPOCH compared with R-hyper-CVAD and R-CODOX-M or R-IVAC (16%, 9% and 8%, respectively; $p = 0.032$).³³ Here, prognostic factors were associated with lymphoma characteristics rather than HIV control.

The phase II CARMEN study trialed a novel approach incorporating a dose-dense regimen with ASCT as first-line consolidation therapy for patients not achieving a complete response (CR) after induction.³⁸ Twenty PLWH were enrolled, with 5-year PFS and OS rates of 70% and 75%, respectively, although the TRM rate was 10%. Further studies are warranted.

Management of r/r HIV-BL

There are no clinical trials specifically in r/r HIV-BL. Similar to patients not infected with HIV, the prognosis of r/r HIV-BL is extremely poor, especially for those with primary refractory disease; in a series of 249 patients with HIV-BL from the United Kingdom and United States, 84 of whom had relapsed, the mortality rate was 87%.³³ HD salvage ChT followed by ASCT and/or allo-SCT is feasible in PLWH with DLBCL, but there is limited experience in BL.^{21,39} Enrolment in a clinical trial is advised, but most trials (e.g., with immunotherapy such as CD19-directed CAR-T therapy or bispecific antibodies) have excluded PLWH. The kinetics of BL, with rapidly progressive disease, may not allow for the 4- to 6-week waiting period during screening, apheresis and manufacturing necessary for CAR-T therapy.

Follow-up, long-term implications and survivorship

BL survivors should be screened periodically for long-term side effects related to the disease and its treatment, such as secondary malignancies, CVD, endocrine dysfunction, cognitive impairment and fatigue. A close collaboration with HIV teams is necessary. Cohort studies have not shown differences in survival rates between HIV-DLBCL and HIV-BL.^{40,41}

Recommendations

- Diagnostic work-up for HIV-BL should follow recommendations for patients who are HIV negative [IV, A].
- Baseline CSF flow cytometry plus one dose of IT MTX can be recommended for all patients [III, B].
- Weekly IT MTX should be given to CSF-positive patients until CSF is clear [III, B].
- In emergency situations, it is reasonable to give one cycle of R-CHOP to stabilise the patient [III, C; rituximab is not European Medicines Agency (EMA) or Food and Drug Administration (FDA) approved for BL].
- HIV-BL should be treated with the same multi-agent regimens utilised in the HIV-negative setting, noting that rituximab is not EMA or FDA approved for BL [III, A].
 - Treatment options for patients with BL-IPI low or intermediate and low-risk features:
 - Two cycles of DA-R-EPOCH (preferred, especially in those aged > 60 years) [III, A].
 - If iFDG-PET-CT negative: one cycle of DA-R-EPOCH [III, A].

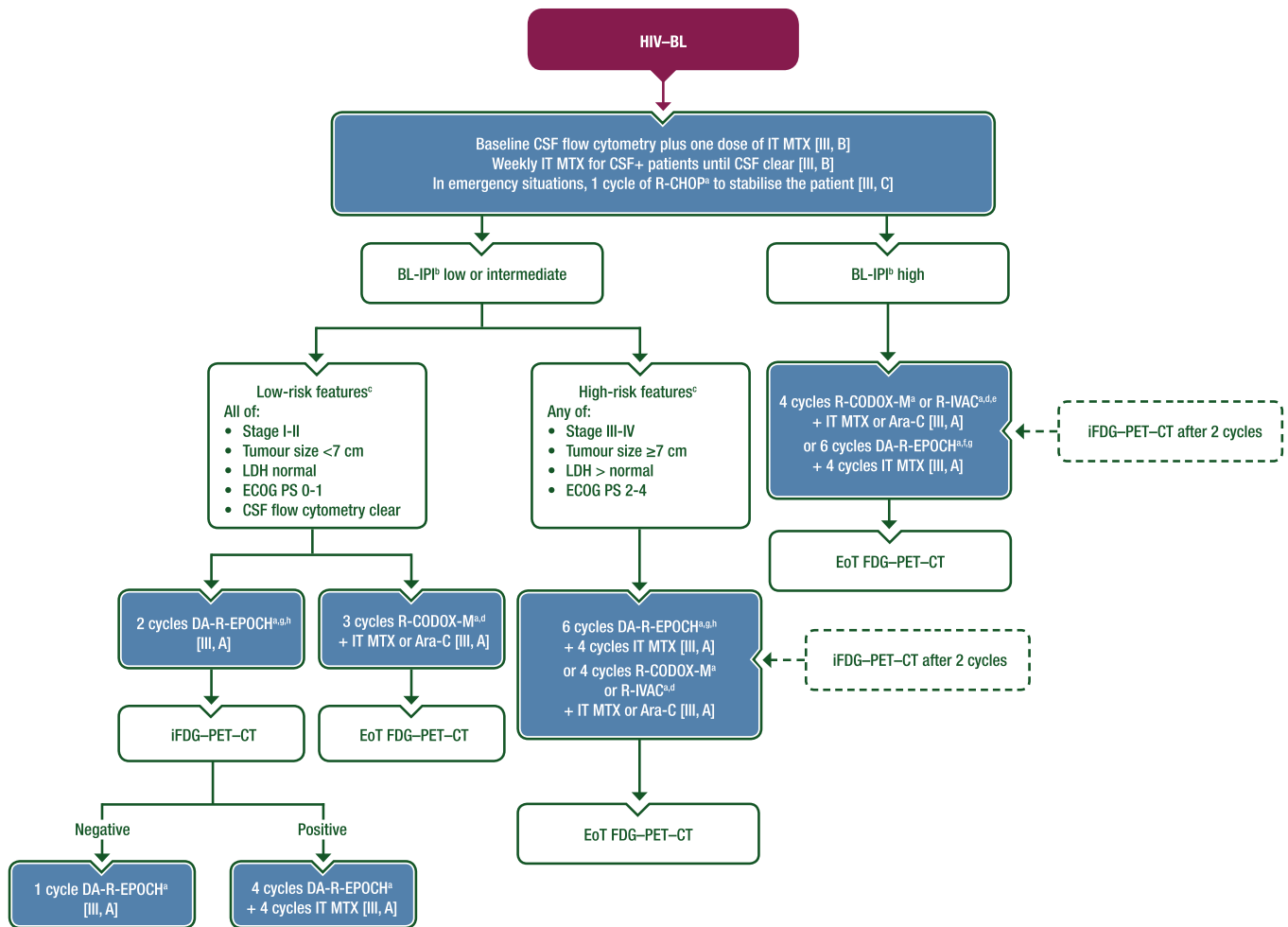


FIGURE 2 First-line management of HIV-BL. Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects; dashed lines: optional therapy. Ara-C, cytarabine; BL, Burkitt lymphoma; CALGB, Cancer and Leukemia Group B; CNS, central nervous system; CSF, cerebrospinal fluid; CSF+, cerebrospinal fluid positive; CT, computed tomography; DA-R-EPOCH, dose-adjusted rituximab-etoposide-prednisone-vincristine-cyclophosphamide-doxorubicin; ECOG, Eastern Cooperative Oncology Group; EMA, European Medicines Agency; EoT, end of treatment; FDA, Food and Drug Administration; FDG, [¹⁸F]2-fluoro-2-deoxy-D-glucose; GMALL-B-ALL, German Multicentre Study Group for Adult Acute Lymphoblastic Leukaemia B-cell acute lymphoblastic leukaemia; HIV-BL, human immunodeficiency virus-associated Burkitt lymphoma; i, interim; IPI, International Prognostic Index; IT, intrathecal; LDH, lactate dehydrogenase; LMB, lymphomes malins B; MTX, methotrexate; PET, positron emission tomography; PS, performance status; R-CHOP, rituximab-cyclophosphamide-doxorubicin-vincristine-prednisone; R-CODOX-M, rituximab-cyclophosphamide-vincristine-doxorubicin-methotrexate; R-IVAC, rituximab-ifosfamide-etoposide-cytarabine; ULN, upper limit of normal. ^aRituximab is not EMA or FDA-approved for the treatment of BL. ^bBL-IPI factors are age ≥40 years, ECOG PS 2-4, LDH >3 × ULN and CNS involvement, as per Olszewski et al.²⁹ ^cRisk definition as per Roschewski et al.³⁶ ^dOr equivalent regimens. Rituximab-containing regimens such as LMB, GMALL-B-ALL and CALGB protocols are valid alternatives to R-CODOX-M or R-IVAC. ^eR-CODOX-M or R-IVAC (or equivalent regimens) are preferred for patients with high-risk BL-IPI and for those with CNS disease at diagnosis. ^fDA-R-EPOCH is an alternative for less fit patients or those aged >60 years. ^gConsider R-CHOP plus immunotherapies for elderly and/or unfit patients with the aim of escalating if fitness improves. ^hDA-R-EPOCH may be preferred for patients with low- or intermediate-risk BL-IPI, especially those aged >60 years.

- If iFDG-PET-CT positive: four cycles of DA-R-EPOCH plus four cycles of IT MTX [III, A].
- Three cycles of R-CODOX-M plus IT MTX or Ara-C [III, A].
- Treatment options for patients with BL-IPI low or intermediate and high-risk features:
 - Six cycles of DA-R-EPOCH (preferred, especially for those aged >60 years) plus four cycles of IT MTX [III, A].
 - Four cycles of R-CODOX-M or R-IVAC plus IT MTX or Ara-C [III, A].
- Treatment options for patients with BL-IPI high:
 - Four cycles of R-CODOX-M or R-IVAC (preferred) plus IT MTX or Ara-C [III, A].
 - Six cycles of DA-R-EPOCH (alternative in less fit patients or those aged >60 years) plus four cycles of IT MTX [III, A].
- For patients not suitable for intensive therapy, DA-R-EPOCH should be considered, provided there is no CNS localisation [III, A].
- Rituximab-containing regimens, such as the lymphomes malins B (LMB), GMALL-B-ALL and Cancer and Leukemia Group B (CALGB) protocols are valid alternatives to R-CODOX-M or R-IVAC [III, B; rituximab is not EMA or FDA approved for BL].
- In the r/r setting, salvage ChT followed by ASCT or allo-SCT may be considered for chemosensitive disease [IV, C].

PLASMABLASTIC LYMPHOMA (PBL)

Diagnosis, pathology and molecular biology

PBL is a rare and aggressive entity with diffuse proliferation of large neoplastic cells, mostly resembling B immunoblasts or plasmablasts. PBL typically has a plasma-cell phenotype, which includes CD138, CD38, Vs38c and multiple myeloma 1/interferon regulatory factor 4 (MUM1/IRF4) expression and negativity or weak positivity for CD20 and paired box 5 (PAX5). The biological basis of PBL is not completely understood. In 75%-80% of HIV-positive cases, PBL is associated with EBV infection, which plays an anti-apoptotic role in B cells. Overexpression of the MYC protein is frequently reported. The most frequent genetic alterations are translocations and/or rearrangement of (IG)/MYC in ~50% of cases, together with amplifications of MYC. Other recurrent mutations involve *PRDM1* and the Janus kinase-signal transducer and activator of transcription (JAK-STAT) and RAS-mitogen-activated protein kinase (MAPK) signalling pathways.⁴²

Staging and risk assessment

PBL is unique in its predilection for the oral cavity, but nodal or extranodal involvement may occur, frequently at gastrointestinal sites. Most patients present with either stage I or stage IV disease. Oral primary location is inversely associated with the presence of B symptoms and advanced Ann Arbor stage.^{42,43} CSF analysis is advisable at initial staging.

First-line management of HIV-associated PBL

To date, there is no SoC for HIV-associated PBL (HIV-PBL) and treatment recommendations are based on case reports, small series and expert opinions. A clinically aggressive course and unsatisfactory results are usually described. A variety of ChT combinations have been reported, including cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP) or CHOP-like regimens, hyperfractionated cyclophosphamide-vincristine-doxorubicin-dexamethasone-MTX-Ara-C (hyper-CVAD-MA), cyclophosphamide-vincristine-doxorubicin-MTX (CODOX-M), ifosfamide-etoposide-Ara-C (IVAC) and etoposide-prednisone-vincristine-cyclophosphamide-doxorubicin (EPOCH).^{42,44} CHOP is most commonly used and although published literature suggests that it achieves suboptimal results, there are no data demonstrating superior outcomes with more intensive regimens.⁴³ In patients with disseminated disease, CR rates with polyChT are >50%, but ~70% of patients die due to progressive disease [median event-free survival (EFS) 22 months and OS 32 months].⁴³ Among 16 patients treated with bortezomib-EPOCH, 94% achieved a CR and the 5-year OS rate was 65%.⁴⁵ Patients with localised disease have a better prognosis and persistent disease control may be achieved with ChT plus local RT. Both CHOP and more aggressive regimens are acceptable approaches in HIV-PBL. Rituximab is not advised in the absence of CD20 expression. Consolidation ASCT may be considered for young patients with high-risk disease.⁴⁶ Bortezomib in combination with ChT is an option. In early-stage disease, doxorubicin-based ChT may be combined with RT. Consensus opinion is that IT therapy should be given as CNS prophylaxis. New approaches with the addition of novel agents are required and participation in clinical trials is highly encouraged. Figure 3 shows a proposed treatment algorithm for the first-line management of HIV-PBL.

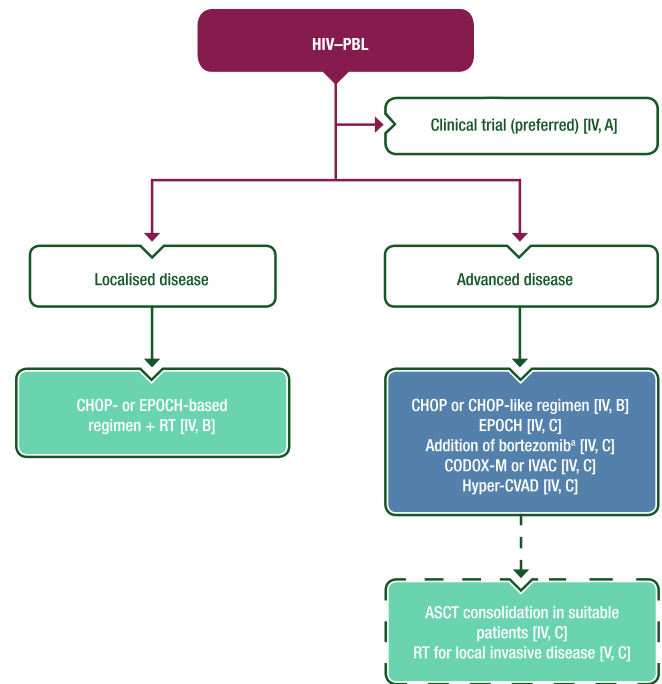


FIGURE 3 First-line management of HIV-PBL. Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects; dashed lines: optional therapy. ASCT, autologous stem-cell transplantation; CHOP, cyclophosphamide-doxorubicin-vincristine-prednisone; CODOX-M, rituximab-cyclophosphamide-vincristine-doxorubicin-methotrexate; EMA, European Medicines Agency; EPOCH, etoposide-prednisone-vincristine-cyclophosphamide-doxorubicin; FDA, Food and Drug Administration; HIV-PBL, human immunodeficiency virus-associated plasmablastic lymphoma; hyper-CVAD, hyperfractionated cyclophosphamide-vincristine-doxorubicin-dexamethasone; IVAC, ifosfamide-etoposide-cytarabine; PBL, plasmablastic lymphoma; RT, radiotherapy. *Not EMA or FDA approved for the treatment of PBL.

Management of r/r HIV-PBL

There is even less evidence on which to base advice for the management of r/r HIV-PBL. Treatment of r/r HIV-PBL does not usually differ from treatment of other types of HIV-NHL. ASCT may be an option for those who did not receive it in first line, at least for young patients who achieve response with salvage ChT (usually platinum-containing regimens). The use of antimyeloma agents, such as bortezomib and lenalidomide, alone or in combination with other treatments, has been attempted based on the plasmacytic differentiation of PBL cells, with some success in limited retrospective series.⁴⁷ Other agents with reported efficacy in case reports include BV and daratumumab. Figure 4 shows a proposed treatment algorithm for the management of r/r HIV-PBL.

Follow-up, long-term implications and survivorship

Although the prognosis of PBL is generally reported as poor, long-term survival can be achieved. In an analysis of 135 patients,

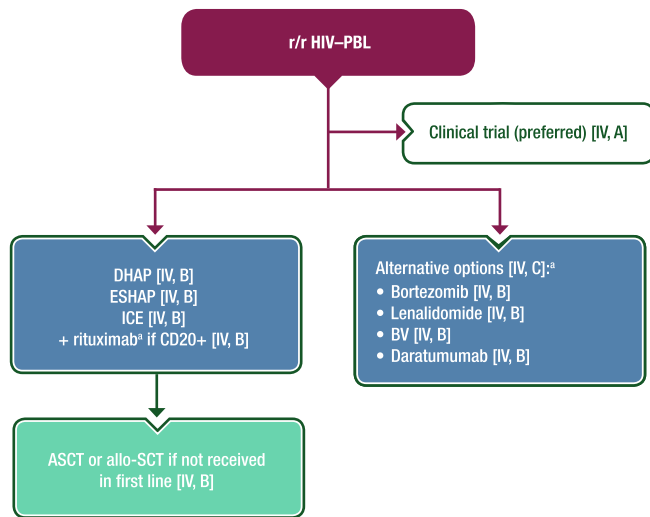


FIGURE 4 Management of r/r HIV-PBL. Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other management and non-treatment aspects. Allo-SCT, allogeneic stem-cell transplantation; ASCT, autologous stem-cell transplantation; BV, brentuximab vedotin; CD, cluster of differentiation; DHAP, dexamethasone-cytarabine-cisplatin; EMA, European Medicines Agency; ESHAP, etoposide-methylprednisolone-cytarabine-cisplatin; FDA, Food and Drug Administration; HIV-PBL, human immunodeficiency virus-associated plasmablastic lymphoma; ICE, ifosfamide-carboplatin-etoposide; PBL, plasmablastic lymphoma; r/r, relapsed or refractory. ^aNot EMA or FDA approved for the treatment of PBL.

OS was better in PLWH than in HIV-negative patients, which may be due to beneficial effects of ART on immune reconstitution.⁴³

Recommendations

- Patients with HIV-PBL should be enrolled in clinical trials whenever possible [IV, A].
- Patients with localised HIV-PBL should receive a CHOP- or EPOCH-based regimen plus RT [IV, B].
- Patients with disseminated HIV-PBL should receive polyChT (e.g., a CHOP-based regimen) [IV, B].
 - The addition of bortezomib is an option [IV, C; not EMA or FDA approved for PBL].
 - Alternative regimens include EPOCH [IV, C], CODOX-M or IVAC [IV, C] and hyper-CVAD [IV, C].
- Consolidation with ASCT may be considered in suitable patients with advanced disease [IV, C].
 - RT for local invasive disease may also be considered [V, C].
- In the relapse setting, platinum-based salvage therapy [dexamethasone-Ara-C-cisplatin (DHAP), etoposide-methylprednisolone-Ara-C-cisplatin (ESHAP) or ifosfamide-carboplatin-etoposide (ICE)] plus rituximab if CD20 positive (not EMA or FDA approved for PBL), followed by ASCT or allo-SCT (if not used in the first line) should be discussed [IV, B].
- If the treatment above is not feasible, antimyeloma agents (bortezomib [IV, B], lenalidomide [IV, B], BV [IV, B] or daratumumab [IV, B], noting that none are EMA or FDA approved for PBL) are an option [IV, C].

PRIMARY EFFUSION LYMPHOMA

Diagnosis, pathology and molecular biology

The discovery of Kaposi sarcoma (KS) herpesvirus, or human herpesvirus 8 (HHV-8), led to the recognition of primary effusion lymphoma (PEL) as a distinct lymphoproliferative disorder. PEL usually presents as serous effusions (ascites, pleuritis and/or pericarditis) without detectable tumour mass (60%–70% of cases) or as an extracavitary mass (extracavitary PEL, 30%–40% of cases). Diagnosis is based on cytological examination of serous fluid or pathological examination of a tumour biopsy specimen (see Supporting Information S1: Figure S1). Tumoural cells are polymorphic with immunoblasts, plasmablasts or anaplastic features. These cells are positive for the latency-associated nuclear antigen (LANA) of HHV-8 and are frequently (>70%) co-infected by EBV (EBV-encoded small RNAs), suggesting lymphomagenesis involves interplay between the two herpesviruses. The cells lack expression of most B-cell markers except for a few terminal B-cell differentiation markers (see Supporting Information S1: Table S3). The frequent aberrant expression of T-cell markers may lead to misdiagnosis. In EBV-negative cases, the differential diagnosis with HHV-8-positive large B-cell lymphoma may be difficult.

Staging and risk assessment

As well as classical staging for lymphoma, staging of HIV-associated PEL (HIV-PEL) should include evaluation of possible pericardial effusion (echocardiography and/or MRI). CSF analysis is also advisable.

Association with other HHV-8-related diseases, such as multicentric Castleman disease (MCD) and KS should be considered.

First-line management of HIV-PEL

HIV-PEL is highly aggressive with a dismal prognosis and there is no established SoC. Based on retrospective studies and small case series, treatment options include ChT regimens used in other types of NHL in conjunction with ART. Figure 5 shows a proposed algorithm for the first-line treatment of HIV-PEL.

CHOP-based regimens and EPOCH provide similar CR rates (55%–57%), both with a median OS of <18 months.^{48,49} Rituximab is not usually indicated, but some clinicians use it to treat concurrent MCD or to deplete the KS- or EBV-associated herpesvirus-infected B-cell reservoir.⁴⁹

More aggressive ChT regimens or consolidation with ASCT might be considered in young patients with good HIV control, even in the absence of controlled studies.⁵⁰

Management of r/r HIV-PEL

r/r HIV-PEL is associated with a particularly poor prognosis. There is even less evidence in this setting than for first-line treatment and no drug has been approved yet by the EMA or FDA. ASCT may be an option for patients who did not receive it in first line, as may allo-SCT for those patients who respond to second-line ChT.^{51,52} Bortezomib and lenalidomide have been used alone or in combination with conventional ChT with some positive results.⁵³ Monoclonal antibodies directed at programmed death-ligand 1, CD30 and CD38 are promising options and OS is expected to improve in the future. In a

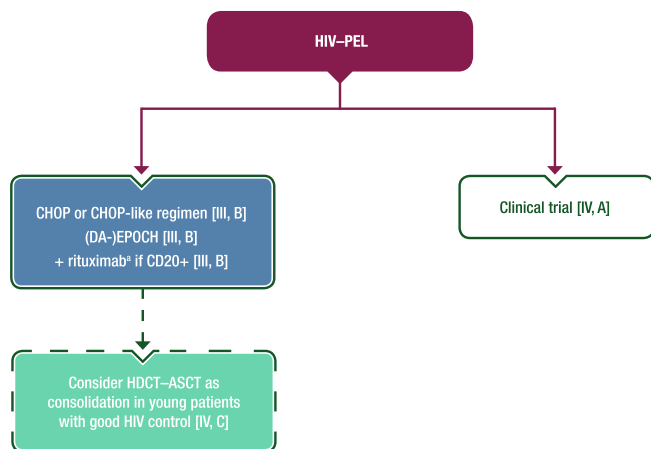


FIGURE 5 First-line management of HIV-PEL. Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other management and non-treatment aspects; dashed lines: optional therapy. ASCT, autologous stem-cell transplantation; CD, cluster of differentiation; CHOP, cyclophosphamide–doxorubicin–vincristine–prednisone; DA, dose-adjusted; EMA, European Medicines Agency; EPOCH, etoposide–prednisone–vincristine–cyclophosphamide–doxorubicin; FDA, Food and Drug Administration; HDCT, high-dose chemotherapy; HIV, human immunodeficiency virus; HIV-PEL, human immunodeficiency virus-associated primary effusion lymphoma; PEL, primary effusion lymphoma. *Not EMA or FDA approved for the treatment of PEL.

retrospective study, three of five patients with r/r HIV-PEL had a response with pembrolizumab with or without pomalidomide, including one CR and long-term disease control.⁵⁴ Figure 6 shows a proposed algorithm for the treatment of r/r HIV-PEL.

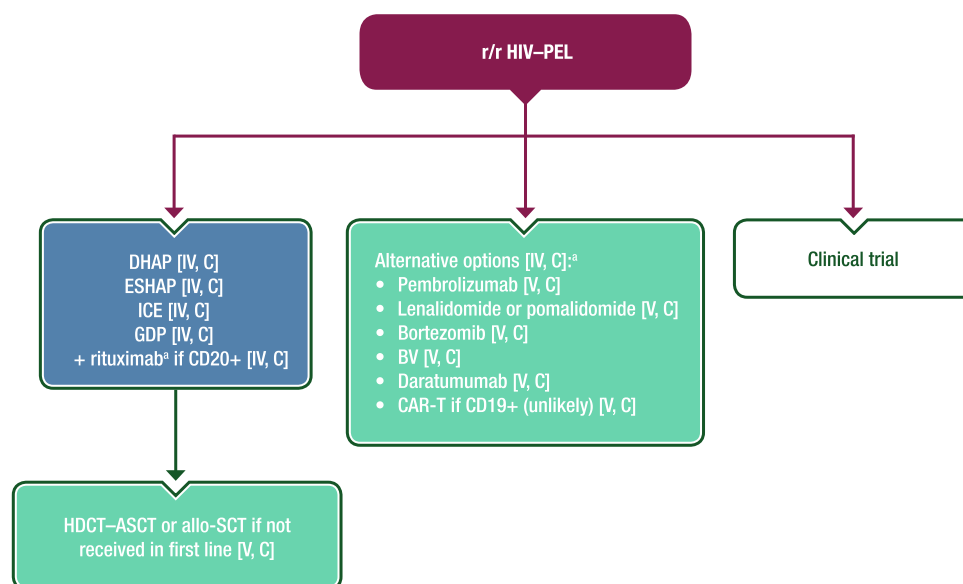


FIGURE 6 Management of r/r HIV-PEL. Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects. Allo-SCT, allogeneic stem-cell transplantation; ASCT, autologous stem-cell transplantation; BV, brentuximab vedotin; CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; DHAP, dexamethasone–cytarabine–cisplatin; EMA, European Medicines Agency; ESHAP, etoposide–methylprednisolone–cytarabine–cisplatin; FDA, Food and Drug Administration; GDP, gemcitabine–dexamethasone–cisplatin; HDCT, high-dose chemotherapy; HIV-PEL, human immunodeficiency virus-associated primary effusion lymphoma; ICE, ifosfamide–carboplatin–etoposide; PEL, primary effusion lymphoma; r/r, relapsed or refractory. *Not EMA or FDA approved for the treatment of PEL.

Recommendations

- Detection of HHV-8 and EBV using IHC, in situ hybridisation or quantitative PCR should be carried out on all specimens from patients with a suspected diagnosis of HIV-PEL [II, A].
- CHOP-based regimens and (DA-)EPOCH can both be recommended with the addition of rituximab if CD20 positive (not EMA or FDA approved for PEL) [III, B].
- HDCT-ASCT consolidation might be considered in young patients with good HIV control [IV, C].
- In the relapse setting, salvage therapy [DHAP, ESHAP, ICE or gemcitabine–dexamethasone–cisplatin (GDP)] plus rituximab if CD20 positive (not EMA or FDA approved for PEL) [IV, C], followed by ASCT or allo-SCT (if not used in first line) [V, C] could be discussed.
- If the treatment above is not feasible, alternative options include pembrolizumab, lenalidomide or pomalidomide, bortezomib, BV, daratumumab or CAR-T therapy if CD19 positive (unlikely) [V, C]; noting that none are EMA or FDA approved for PEL].

CNS LYMPHOMA

Diagnosis, pathology and molecular biology

HIV-associated primary CNS lymphoma (HIV-PCNSL) occurs in patients who are severely immunocompromised and differs in pathogenesis, natural history and treatment from primary CNS lymphoma (PCNSL) of the immunocompetent host. Nearly all PCNSLs are of B-cell origin. In PLWH, the most frequent histology is DLBCL. Unlike PCNSL in immunocompetent hosts, EBV infection is essential to the pathobiology of HIV-PCNSL. Gene expression profiles in PCNSL are also different in PLWH compared with immunocompetent individuals.⁵⁵ PCNSL presents with acute or subacute neurological signs and symptoms depending on location, size of lesions and surrounding

oedema; B symptoms are rare. Full medical and neurological evaluation and Mini-Mental State Examination should be carried out alongside investigations including serum LDH, CSF analysis for EBV DNA using quantitative PCR, cytology and flow cytometry if lumbar puncture can be safely carried out, and contrast-enhanced brain MRI. PCNSL can be multifocal or solitary and most commonly affects deep structures and white matter.⁵⁶ FDG-PET-CT scans support the diagnosis of PCNSL by excluding systemic involvement.

Staging and risk assessment

Ophthalmology assessment is essential as lymphomatous involvement may be identified in 5%–20% of cases.⁵⁷ In addition to FDG-PET-CT, testicular ultrasound is recommended in men to exclude occult systemic disease (present in $\leq 8\%$ of cases), in which case the diagnosis is revised to secondary CNS lymphoma (SCNSL).

First-line management of HIV-PCNSL

There is increasing evidence that HD-MTX and ART can be used with curative intent, without whole brain RT (WBRT) or other consolidation. A retrospective study of 51 patients with HIV-PCNSL receiving a median of six infusions of HD-MTX (3 g/m²) and ART demonstrated a median OS of 5.7 years and a 5-year OS rate of 48%.⁵⁸ The only prospective trial conducted in this setting enrolled 12 patients treated with rituximab-HD-MTX, with an estimated 5-year OS rate of 67%.⁵⁹ Concurrent ART is essential for immune reconstitution and may contribute to long-term disease control.

In the uncommon scenario of HIV-PCNSL in patients established on ART with well-controlled HIV where the lymphoma pathogenesis and natural history resemble that of the immunocompetent host, clinicians should consider rituximab-MTX-Ara-C-thiotepa (MARIx)⁶⁰ or a similar multi-agent induction regimen and consolidation ASCT.

A proposed algorithm for first-line treatment of HIV-PCNSL is shown in Figure 7.

Management of r/r HIV-PCNSL

Both WBRT and HD-MTX have been used in r/r HIV-PCNSL. WBRT remains a reasonable option in patients with chemorefractory disease, those who cannot tolerate HD-MTX and for palliative intent in patients with poor functional status. Lenalidomide or Bruton tyrosine kinase inhibitors may also be considered if available.⁶¹ Thiotepa-ICT, followed by ASCT if the disease is chemosensitive, is also an option.

Follow up, long-term implications and survivorship

Brain MRI with contrast is the gold standard to assess treatment response 4–8 weeks after ChT. Thereafter, symptom-driven investigations without routine rescanning are a reasonable approach as there is little evidence to support MRI brain surveillance in PLWH. Data on neurocognitive sequelae are scant.^{59,62}

Management of HIV-associated SCNSL

Historically, SCNSL has been characterised by negative outcomes in both early (de novo presentation) and late (relapsed disease) settings. In the ART era, the frequency of CNS involvement in systemic HIV-associated lymphomas is similar to that in patients who are HIV negative;⁶³ for this reason, treatment of secondary CNS DLBCL should not

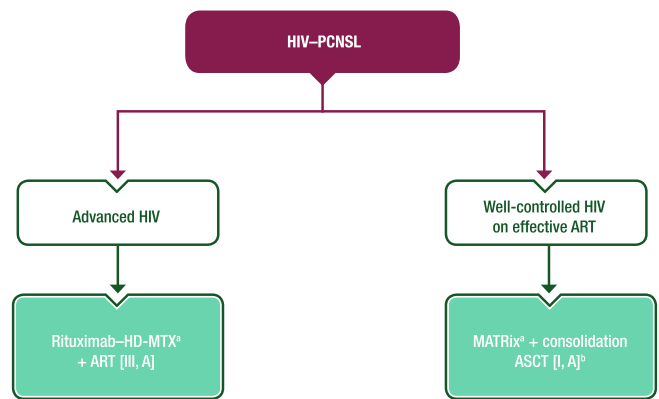


FIGURE 7 First-line management of HIV-PCNSL. Purple: algorithm title; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects. ART, combination antiretroviral therapy; ASCT, autologous stem-cell transplantation; EMA, European Medicines Agency; FDA, Food and Drug Administration; HD-MTX, high-dose methotrexate; HIV, human immunodeficiency virus; HIV-PCNSL, human immunodeficiency virus-associated primary central nervous system lymphoma; MARIx, rituximab-methotrexate-cytarabine-thiotepa; PCNSL, primary central nervous system lymphoma. ^aRituximab is not EMA or FDA approved for the treatment of PCNSL. ^bWhen the lymphoma resembles that of the immunocompetent host.

differ from that in the HIV-negative population. Despite the exclusion of PLWH from the International Extranodal Lymphoma Study Group 42/MARIETTA study, the authors recommend consideration of the MARIETTA approach, which incorporates three courses of MARIx followed by three courses of R-ICE and consolidation with carmustine-thiotepa and ASCT, for chemosensitive HIV-associated SCNSL (HIV-SCNSL).⁶⁴ In patients with a first presentation of SCNSL, the 2-year PFS rate (71%) was significantly improved compared with patients with CNS involvement at relapse (28%). CAR-T therapy should also be considered in this setting, based on encouraging responses described in the HIV-negative population.^{65,66}

Recommendations

HIV-PCNSL

- Rituximab-HD-MTX (≥ 3 g/m²) and fully active ART is recommended [III, A; rituximab is not EMA or FDA approved for PCNSL].
- A multi-agent induction regimen (e.g., MARIx) and consolidation ASCT should be considered for patients already established on effective ART, when the lymphoma resembles that of the immunocompetent host [I, A; rituximab is not EMA or FDA approved for PCNSL].
- In the relapse setting, WBRT can be considered in patients who are chemorefractory or not suitable for ChT [III, B]. Thiotepa-ICT, followed by ASCT if the disease is chemosensitive, can also be considered [III, B].

HIV-SCNSL

- Treatment for patients with HIV-SCNSL can be similar to that used for the HIV-negative population and the MARIETTA approach or CAR-T therapy should be considered [II, B].

HL

The main risk factor for HL in the HIV setting is a moderately lowered CD4 count.⁵ In a recent study, the hazard ratio for HL was highest (6.36) among patients with CD4 counts of 100–200 cells/ μ L compared with the reference group (CD4 counts >500 cells/ μ L).⁵ In contrast, higher HIV-1 VL (>50 copies/mL) was not associated with an increased risk of HL compared with a VL of \leq 50 copies/mL.⁵

Diagnosis, pathology and molecular biology

HL is characterised by a small neoplastic infiltration of Hodgkin and Reed–Sternberg (HRS) cells against an inflammatory background of lymphocytes, histiocytes, plasma cells, eosinophils and neutrophils. The neoplastic HRS cells are typically CD30 and CD15 positive, with B-cell markers such as CD20 and CD79a expressed in a minority of cells. EBV infection is almost universal in HIV–HL with a latency II type, expressing Epstein–Barr nuclear antigen 1, latent membrane protein 1 and 2 and EBV-encoded RNA. Subtypes most frequently diagnosed in PLWH are mixed cellularity followed by nodular sclerosis.⁶⁷

Staging, risk assessment and response evaluation

In the ART era, initial staging and risk and response assessments are similar to those in the non-HIV setting. Although PLWH display frequent adverse prognostic factors, HIV does not adversely affect OS per se. The Ann Arbor classification is used for initial staging and to subdivide patients according to the absence or presence of disease-related symptoms. FDG–PET–CT is the gold standard for baseline and response assessments. A bone marrow aspirate or biopsy is no longer routinely required.⁶⁸ As in the non-HIV setting, high metabolic tumour volume on initial FDG–PET–CT is associated with a worse prognosis.⁶⁹

FDG–PET–CT should be used for response assessment using the 5-point scale. As in the non-HIV setting, iFDG–PET–CT is prognostic in patients with HIV–HL treated with doxorubicin–bleomycin–vinblastine–dacarbazine (ABVD).⁷⁰ The Lymphoma Response to Immunomodulatory Therapy Criteria introduced the term ‘indeterminate response’ to describe lesions requiring biopsy or subsequent imaging to confirm pseudoprogression versus true progression.⁷¹ These patterns deserve further evaluation in the HIV setting.

First-line management of HIV–HL

Advanced-stage disease is diagnosed in 66%–80% of HIV–HLs. As in the HIV-negative setting, stage-adapted treatment is recommended. A proposed treatment algorithm for HIV–HL is shown in Figure 8.

Limited-stage HL

Patients with limited-stage HIV–HL, as defined by the German Hodgkin Study Group, should receive two cycles of ABVD followed by 20 Gy involved-site RT (ISRT).⁷² In a prospective study that included 23 patients with limited-stage HIV–HL, two cycles of ABVD followed by 20 Gy involved-field RT (IFRT) resulted in a CR rate of 96% and a 2-year OS rate of 95.7% [95% confidence interval (CI) 87.7%–100%].⁷³ As the use of 20 Gy and 30 Gy doses of RT proved equally effective in limited-stage HL in the HIV-negative setting, the lower dose should be preferred in limited-stage HIV–HL. Moreover,

there is accumulating evidence of excellent disease control with smaller ISRT fields.⁷⁴

If the long-term risks of RT are thought to outweigh the benefit of improved PFS (e.g., in women \leq 21 years of age with breast tissue in the radiation field), RT may be omitted or substituted with one or two additional cycles of ABVD in patients with a negative FDG–PET–CT scan after two cycles of ChT (i.e., PET2-negative), although no data are available on the use of this approach in HIV–HL.⁷⁴

In patients who are HIV negative and have limited-stage HL and a positive iFDG–PET–CT scan after two cycles of ABVD, the use of two cycles of escalated bleomycin–etoposide–doxorubicin–cyclophosphamide–vincristine–procarbazine–prednisone (BEACOPP_{escalated}) before ISRT results in a reduced relapse rate.⁷⁵ This approach cannot, however, be generally recommended for limited-stage HIV–HL as it has not been investigated in PLWH.

Intermediate-stage HL

Limited data are available on the treatment of intermediate-stage HIV–HL. Two-year PFS and OS rates in 14 patients treated with four cycles of ABVD or bleomycin–etoposide–doxorubicin–cyclophosphamide–vincristine–procarbazine–prednisone (BEACOPP_{baseline}), followed by 30 Gy IFRT were 88% (95% CI: 67.3%–100%) and 100%, respectively.⁷³

In the HIV-negative setting, the SoC for patients with intermediate-stage HL is either four cycles of ABVD followed by 30 Gy ISRT or the 2 + 2 approach (two cycles of BEACOPP_{escalated} followed by two cycles of ABVD), followed by 30 Gy ISRT if patients are PET4-positive.^{74,76} In patients initially treated with ABVD who have a positive FDG–PET–CT scan after two cycles, escalating treatment to two cycles of BEACOPP_{escalated} (instead of ABVD) before ISRT results in significantly improved PFS.⁷⁵ As there is no data on these approaches in PLWH, they cannot be generally recommended for patients with intermediate-stage HIV–HL.

Advanced-stage HL

In a prospective trial including 71 PLWH with advanced-stage HL, treatment with six to eight cycles of BEACOPP_{baseline} or ABVD was associated with a 2-year PFS rate of 87.5% (95% CI: 79.1%–96.8%) and a 2-year OS rate of 86.8% (95% CI: 79.0%–95.2%).⁷³ Four toxicity-related deaths (5.6%) were reported among patients who received BEACOPP_{baseline}, three of which occurred after the seventh and eighth cycles. Thus, no more than six cycles of BEACOPP_{baseline} should be applied and caution is advised, especially in patients with low CD4 counts. This strategy is also supported by a retrospective study including 85 PLWH treated with six cycles of ABVD; there was no adverse effect of HIV infection on OS or EFS compared with patients who were HIV negative and treated with the same regimen.⁷⁷ A more recent report based on 12 patients with HIV–HL treated within the Southwest Oncology Group S0816 phase II trial showed that ABVD-based FDG–PET–CT-adapted therapy is feasible.⁷⁸ Patients with a negative PET2 subsequently received four additional cycles of ABVD, while those with a positive PET2 received six cycles of BEACOPP_{baseline}. Eleven of the 12 patients received six cycles of ABVD and three patients developed progressive disease (all PET2 negative), with an estimated 2-year PFS rate of 83% (95% CI: 46.1%–95.3%). Data on the use of BEACOPP_{escalated} in advanced-stage HIV–HL are not available.

Based on prospective trials in the HIV-negative setting, RT after ChT for advanced HL is restricted to patients with FDG–PET–CT-positive residual disease; this approach is therefore also recommended

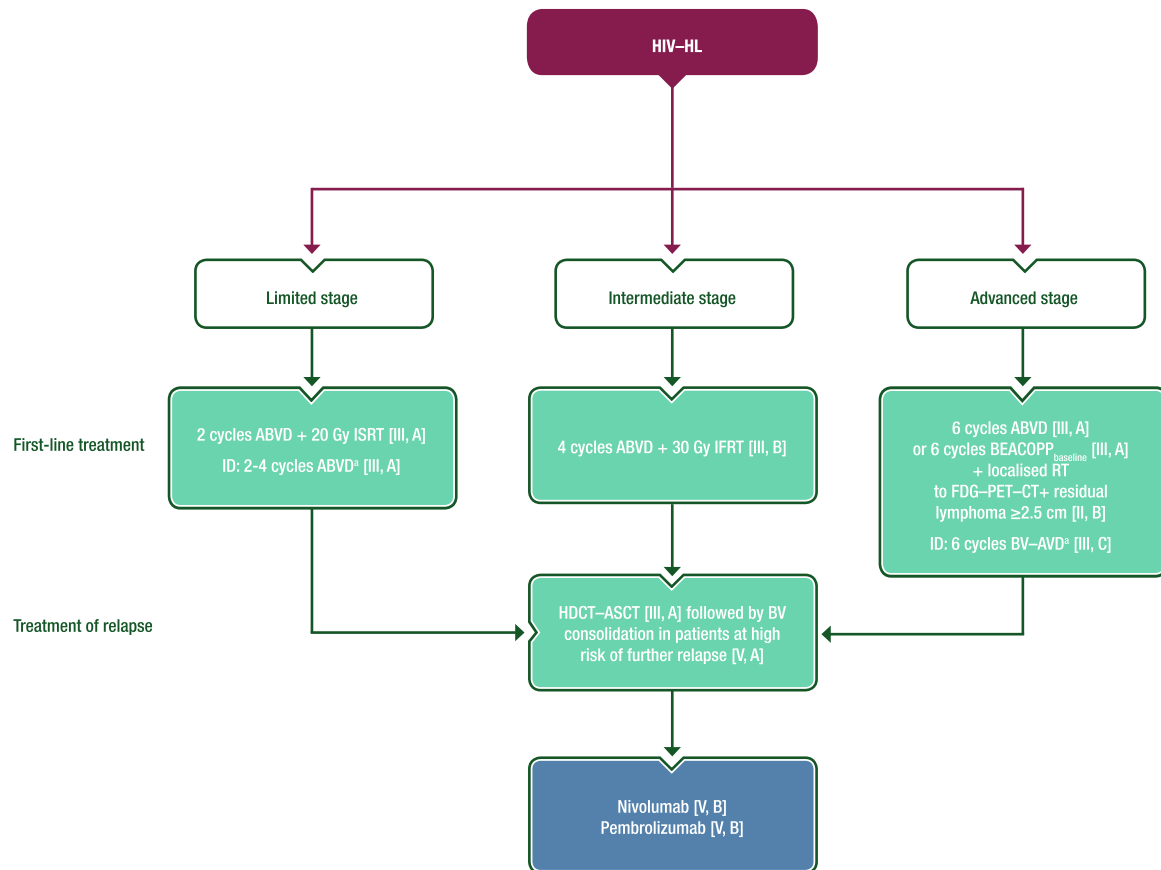


FIGURE 8 Management of HIV-HL. Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects. ABVD, doxorubicin-bleomycin-vinblastine-dacarbazine; ASCT, autologous stem-cell transplantation; AVD, doxorubicin-vinblastine-dacarbazine; BEACOPP, bleomycin-etoposide-doxorubicin-cyclophosphamide-vincristine-procarbazine-prednisone; BV, brentuximab vedotin; CT, computed tomography; FDG, [¹⁸F]2-fluoro-2-deoxy-D-glucose; FDG-PET-CT+, positive findings on FDG-PET-CT; HDCT, high-dose chemotherapy; HIV-HL, human immunodeficiency virus-associated Hodgkin lymphoma; ID, individual decision; IFRT, involved-field radiotherapy; ISRT, involved-site radiotherapy; PET, positron emission tomography; RT, radiotherapy. *No data in HIV-HL.

in patients who are HIV positive.⁷⁴ BV is EMA and FDA approved in combination with doxorubicin-vinblastine-dacarbazine (AVD) in newly diagnosed stage IV HL, and six cycles of BV-AVD resulted in a 2-year PFS rate of 87% in a phase I/II trial of patients with stage II-IV HIV-HL.⁷⁹ In this study, patients requiring ART that included strong cytochrome P450 3A4 inhibitors were excluded and there was a 10% incidence rate of grade 3-4 peripheral sensory neuropathy.

There is increased use of BV-etoposide-doxorubicin-cyclophosphamide-dacarbazine-dexamethasone (BrECADD) instead of BEACOPP in patients without HIV aged ≤60 years, based on its more favourable toxicity profile,⁸⁰ however, data on BrECADD in HIV-HL are limited at this time.

Management of r/r HIV-HL

HD ChT (HDCT) followed by ASCT is SoC for r/r HL in the HIV-negative setting and its feasibility in PLWH has been demonstrated in prospective trials and retrospective analyses.^{21,81} PLWH with r/r HL who have a response to ART, adequate organ function and no active infections should, therefore, be treated with salvage ChT followed by HDCT-ASCT according to guidelines for the HIV-negative setting.⁷⁴ Consolidation with BV following HDCT-ASCT was shown to improve

tumour control in HIV-negative patients with an increased risk of relapse.⁸² Owing to the poor prognosis of patients with relapse after HDCT, BV consolidation should also be considered in PLWH with high-risk r/r HL.

Patients relapsing after HDCT-ASCT should be treated with nivolumab or pembrolizumab,⁸³ and those not eligible for HDCT should be treated according to the recommendations for patients with HL who are HIV negative, favouring pembrolizumab over BV as data for pembrolizumab are available from a prospective phase III trial.⁸⁴

Recommendations

- Patients with limited-stage HIV-HL should receive two cycles of ABVD followed by 20 Gy ISRT [III, A].
- Patients with intermediate-stage HIV-HL can be treated with four cycles of ABVD followed by 30 Gy IFRT [III, B].
- Patients with advanced-stage HIV-HL should be treated with six cycles of ABVD or six cycles of BEACOPP_{baseline} [III, A] followed by RT for patients with FDG-PET-CT-positive disease (residual lymphoma ≥2.5 cm) [II, B].
- Six cycles of BV-AVD may be an individual option in newly diagnosed stage IV HIV-HL [III, C].

- In the relapse setting, salvage ChT followed by ASCT is recommended in PLWH who are suitable for stem-cell transplantation [III, A].
- BV consolidation should be considered in patients with high-risk r/r HIV-HL [V, A].
- Patients relapsing after HDCT-ASCT can be treated with nivolumab [V, B] or pembrolizumab [V, B].

MCD

HHV-8-associated MCD (HHV-8-MCD) is a rare lymphoproliferative disorder that is predominantly associated with HIV infection. Incidence does not correlate with CD4 count or HIV plasma viraemia.

Diagnosis, pathology and molecular biology

A combination of B symptoms, specific histopathological findings and detectable blood HHV-8 is sufficient for diagnosis.⁸⁵ HHV-8-MCD is characterised by episodic exacerbations and remissions. HHV-8 encodes a viral homologue of interleukin (IL)-6, the effects of which mirror those of its mammalian counterparts. Untreated HHV-8-MCD can progress to a febrile, life-threatening, acute illness with a rapid fatal course via multiple organ failure, haemophagocytic syndrome or evolution to NHL. The histological characteristics of affected lymph nodes include the presence of IgM lambda-restricted plasmablasts with positive HHV-8-associated LANA staining.

Staging and risk assessment

Baseline CT or FDG-PET-CT is useful to identify affected nodes and to assess organ involvement. Eastern Cooperative Oncology Group PS, end-organ involvement, haemophagocytic syndrome or haemolytic anaemia are helpful in defining severe cases for a risk-stratified treatment approach.⁸⁶

First-line management of HHV-8-MCD

Although HHV-8-MCD occurs mainly in patients with undetectable HIV RNA, ART should always be administered. Symptomatic HHV-8-MCD usually requires prompt therapeutic intervention. Treatment evidence is based on two prospective studies^{87,88} and a retrospective multicentre analysis,⁸⁹ which showed that rituximab is useful as monotherapy. In several cohort studies, OS and disease-free survival improved with rituximab compared with historical controls.⁸⁷⁻⁸⁹ High levels of HHV-8 viraemia, serum C-reactive protein, IL-6 and IL-10 rapidly decline after rituximab therapy. In severe cases, including those with haemophagocytic syndrome, etoposide can be added to first-line rituximab to control the consequences of the cytokine storm. If KS is present at MCD diagnosis, the combination of rituximab with cytotoxic ChT, including etoposide or liposomal doxorubicin, is also considered as initial therapy for severe cases.⁹⁰ Other approaches such as antivirals, immunomodulators and IL-6-blocking agents are of limited value. In cases with severe refractory anaemia and thrombocytopenia, splenectomy could be considered despite providing only short-term symptom resolution.

A proposed treatment algorithm for first-line management of HHV-8-MCD is shown in Figure 9.

Management of r/r HHV-8-MCD

With control of HHV-8 VL, sustained CRs are often observed, but HHV-8-MCD relapses are not infrequent and may occur after recovery of B-cell counts. In case of relapse, multiple rechallenges with rituximab-based ICT are safe and efficacious.⁸⁶ More aggressive ChT regimens (e.g., CHOP) can be considered in rituximab-refractory disease.

Follow-up, long-term implications and survivorship

Clinical, virological and biochemical responses should be regularly monitored during acute episodes. Radiological response should be evaluated using CT or FDG-PET-CT after completion of ICT. Besides prolonged B-cell depletion, the main serious adverse effect of rituximab is reactivation or progression of concomitant KS. In these settings, combination with liposomal doxorubicin should be considered.

NHL incidence is reduced with rituximab but remains high, especially for HHV-8-associated NHL (PEL, DLBCL). These entities should be considered during follow-up.^{86,91} Clinical follow-up is recommended every 3–6 months. Patients should be made aware of the risk of relapse and should seek medical attention at the specialist centre if symptoms recur.

Recommendations

- ART can be initiated or optimised [IV, B].
- Rituximab is recommended as first-line therapy [III, A; not EMA or FDA approved for MCD].
- In severe cases, etoposide can be added to first-line rituximab to control the consequences of the cytokine storm [III, B].
- Combinations of rituximab with cytotoxic ChT, including etoposide or liposomal doxorubicin if KS is present at MCD diagnosis, are also considered as first-line therapy for severe cases [III, B].
- Antivirals, immunomodulators and IL-6-blocking agents are of limited value [IV, D].
- In cases with severe refractory anaemia and thrombocytopenia, splenectomy could be considered [IV, C].
- In case of relapse, multiple rechallenges with rituximab-based ICT are safe and efficacious [III, B].
- More aggressive ChT regimens (e.g., CHOP) can be considered in rituximab-refractory disease [IV, B].

METHODOLOGY

This Clinical Practice Guideline (CPG) was developed in accordance with the ESMO standard operating procedures for CPG development (<https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>). The relevant literature has been selected by the expert authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. Levels of evidence and grades of recommendation have been applied using the system shown in Supporting Information S1: Table S4. Statements without grading were considered justified standard clinical practice by the authors. The guideline uses people-first terminology. For future updates to this CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website: <https://www.esmo.org/guidelines/guidelines-by-topic/haematological-malignancies>.

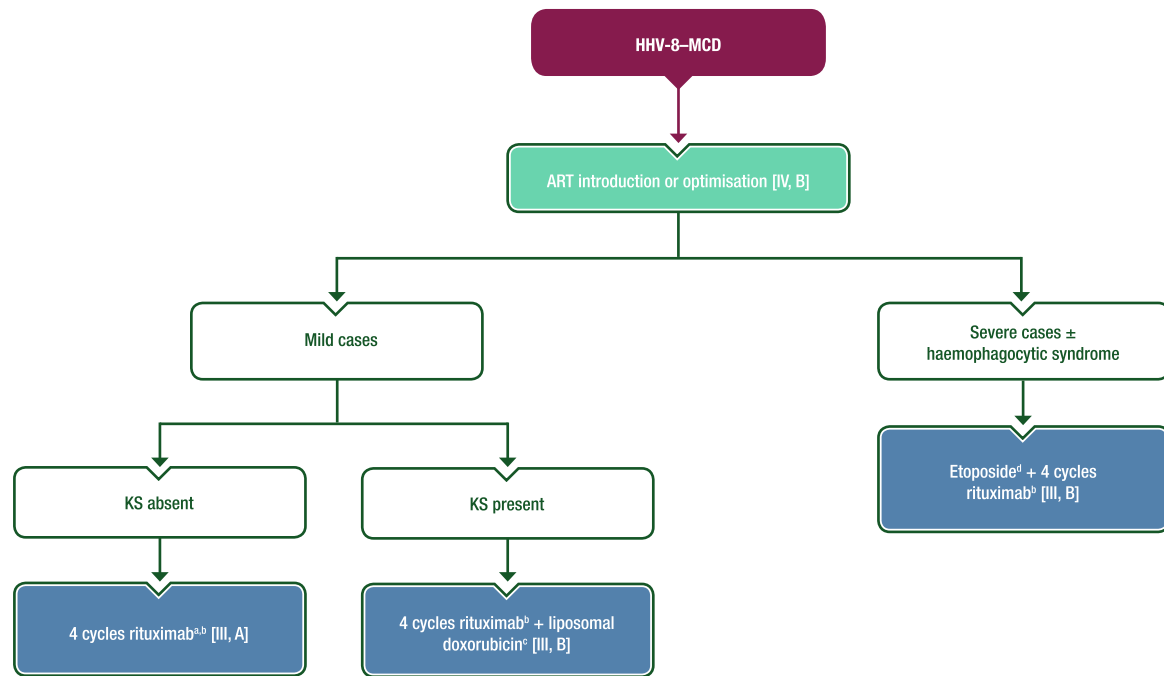


FIGURE 9 First-line management of HHV-8-MCD. Purple: algorithm title; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other management and non-treatment aspects. ART, combination antiretroviral therapy; CD, cluster of differentiation; EMA, European Medicines Agency; FDA, Food and Drug Administration; HHV-8-MCD, human herpesvirus 8-associated multicentric Castleman disease; i.v., intravenous; KS, Kaposi sarcoma; MCD, multicentric Castleman disease. ^aEtoposide can be added to the first cycle to avoid a possible flare. ^bNot EMA or FDA approved for the treatment of MCD. Rituximab should be used with caution in patients with a CD4 count <50 cells/μL and/or delayed after a few courses of etoposide, but may be considered as it is associated with improved outcome in MCD and reduces the risk of lymphoma development. ^cThe number of liposomal doxorubicin cycles depends on the burden of KS disease, but the minimum number is four. ^dEtoposide can be administered orally or by i.v. injection; the i.v. route optimises bioavailability.

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All authors conceptualised, wrote and approved the final version.

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KH reports personal fees for advisory board membership from Gilead, Hexal, Incyte, Miltenyi, Novartis, Recordati and Roche; personal fees as an invited speaker from BeiGene, Bristol Myers Squibb (BMS), Novartis, Recordati, Roche and Servier; personal fees for a writing engagement from Hexal; institutional fees as coordinating Principal Investigator (PI) from Incyte and Roche; a non-remunerated role as working group chair of the German Society of Hematology and Medical Oncology (DGHO); non-remunerated advisory role for the European Hematology Association (EHA) Education Committee; and a non-remunerated leadership role for the German Lymphoma Alliance. MB reports personal fees as an invited speaker from BMS, EUSA Pharma, Gilead, Janssen, Merck and Viiv Healthcare. IA reports personal fees for advisory board membership from AbbVie,

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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