

# Primary effusion lymphoma: current perspectives

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**Abstract:** Primary effusion lymphoma (PEL) is a rare and aggressive disease, affecting a unique population of patients who are often elderly or immunocompromised. PEL is associated with human herpesvirus type-8 infection and most commonly presents as malignant effusions of the body cavities. Patients diagnosed with PEL often have a compromised immune system from secondary conditions such as HIV. Chemotherapy has traditionally been the cornerstone of treatment for patients with a good performance status and no significant comorbidities. However, an optimal regimen does not exist. Most patients with PEL experience a relapse after frontline therapy within 6–8 months and subsequently require further treatment. In recent years, our understanding of the molecular drivers and environmental factors affecting the pathogenesis of PEL has expanded. This review will discuss the pathogenesis of PEL and various management approaches available in the frontline and relapsed setting as well as targeted agents that have shown promise in this disease.

**Keywords:** HIV-associated lymphomas, primary effusion lymphoma, HHV8-associated lymphomas

## Introduction

Originally referred to as body cavity lymphoma, primary effusion lymphoma (PEL) is a distinct B-cell non-Hodgkin lymphoma (NHL) with an aggressive phenotype. It is caused by human herpesvirus type 8 (HHV8), also referred to as Kaposi sarcoma-associated herpesvirus (KSHV).<sup>1</sup> This virus was initially described in association with AIDS-associated Kaposi sarcoma (KS) in 1994.<sup>2</sup> Subsequently, PEL was found to be associated with HHV8 in 1995 and was first reported as a unique neoplasm by the World Health Organization (WHO) classification in 2001.<sup>3</sup>

## Epidemiology

PEL is rare and accounts for ~4% of HIV-associated NHL and <1% of non-HIV-related lymphomas.<sup>4</sup> There is a male predominance of 6:1.<sup>5</sup> PEL typically presents in middle-aged patients infected with HIV or harboring other immunocompromised states, such as recipients of solid-organ transplants, patients with cirrhosis, and in the elderly, often in HHV8 endemic areas.<sup>6–10</sup> Epstein Bar virus (EBV) co-infection is commonly found (60%–90% of cases) although its role in the pathogenesis of PEL is not clear.<sup>11</sup> EBV-negative PELs are typically found in elderly HIV-negative patients from HHV8-endemic areas.<sup>12</sup>

## Pathogenesis

The gamma-herpesvirus HHV8 is found in association with a variety of malignancies including PEL, KS, a variant of Multicentric Castleman Disease, HHV8-positive

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diffuse large B-cell lymphoma (DLBCL), and germinotropic lymphoproliferative disease.<sup>4,13</sup> It is universally implicated with the oncogenesis of PEL, infecting the B-cell during its latent phase and replicating during the lytic phase.<sup>6,14</sup> In the latent phase of infection by HHV8, many viral transcripts are expressed promoting oncogenesis. These include latency-associated nuclear antigen (LANA), viral FLICE inhibitory protein (v-FLIP) and viral cyclin (vCyclin) and are implicated in the progression of HHV8-associated malignancies.<sup>3</sup> LANA maintains the latent phase of the virus, and additionally represses the tumor suppressor protein p53 and retinoblastoma protein, leading to cell growth and survival.<sup>15,16</sup> It also may contribute to NOTCH dysregulation and tumor progression.<sup>17</sup> vCyclin and v-FLIP contribute to tumor growth via constitutively activating cyclin-dependent kinase 6 and the transcription factor nuclear factor kappa B (NF- $\kappa$ B) pathway, respectively, leading to tumor proliferation and inhibition of apoptosis while maintaining viral latency.<sup>18</sup> HHV8 additionally produces interleukin IL-6 (vIL-6) which is found in a high concentration in PEL-related effusions and induces VEGF increasing vascular permeability and augmenting the formation of PEL-related effusions.<sup>19</sup> Additionally, vIL-6 prevents apoptosis by suppressing proapoptotic cathepsin D. Other HHV8 genes expressed during the latent phase of the viral life cycle affect oncogenesis via cell binding, proliferation, apoptosis, angiogenesis, cytokine production, B-cell proliferation all leading to tumor growth.<sup>4,13</sup> The lytic and reproductive phase of HHV8 leads to lysis and death of the infected cell therefore it behooves the disease and virus to remain in the latent phase to promote tumor growth and cell mortality.

## Clinical presentation

As its name describes, PEL presents with malignant lymphomatous effusions in body cavities (pleural space, peritoneal cavity, pericardium). The clinical presentation in PEL is based upon disease location and quantity of the effusion. A common presentation is an immunocompromised man who complains of shortness of breath, leading to an imaging finding of a pleural effusion. Increased abdominal girth, lower extremity edema, and increases in abdominal pressures may lead one to discover accumulation of ascitic fluid from PEL. Pericardial involvement may present with cardiac tamponade with symptoms of dizziness, low blood pressure, and electrocardiogram changes. Some patients may also present with typical B symptoms of fever, weight loss, and night sweats. More rarely, presentations such as an extracavitary mass have also been described. Areas of involvement include organs adjacent to a cavitory space, regional lymph nodes, bone marrow, skin, central nervous system, and the gastrointestinal tract.<sup>20–29</sup>

## Diagnostic testing

### Histopathological assessment

Initial diagnosis is made by hematopathologic assessment of the effusion at presentation. As morphologically described by the WHO, PEL cells bridge those of large-cell immunoblastic lymphoma, plasmablastic lymphoma, and anaplastic large-cell lymphoma<sup>30</sup> (Table 1). The cells are large, with moderate to abundant deeply basophilic cytoplasm, a large round to irregular nuclei, and prominent nucleoli. They express CD45, proving lymphoid origins, however, are a “null” lymphocyte phenotype as they do not exhibit typical B-cell or T-cell immunophenotype characteristics and are indeterminate

**Table 1** Pathologic features differentiating PEL from other aggressive lymphomas

	<b>DLBCL immunoblastic variant</b>	<b>PBL</b>	<b>ALCL</b>	<b>PEL</b>
Morphology	Diffuse sheets of large cells with prominent nucleoli and abundant cytoplasm, with plasmacytoid features	Diffuse large cells with abundant cytoplasm and eccentrically placed nuclei and smaller nucleoli resembling plasma cells	Pleomorphic nuclei with multiple (or single) prominent nucleoli with abundant cytoplasm	Variable morphology between large immunoblastic, plasmablastic or anaplastic large cell lymphoma
EBV positivity	90%–100%	>50%	Negative	60%–90%
HHV8 positivity	–	–	–	100%
Phenotype	BCL6–, CD138+, MUM1+	CD38+, CD138+, CD20–	CD30+, EMA+, CD4+, CD2+, TIA, Granzyme or Perforin+	CD30+, CD38+, CD138+, CD45+
Cellular origin	Mostly GC or post-GC B cells	Post-GC cells	Primitive T-cell origin	GC or post-GC B cells

**Abbreviations:** PEL, primary effusion lymphoma; EBV, Epstein Bar virus; HHV8, human herpes virus 8; GC, germinal center; DLBCL, diffuse large B cell lymphoma; PBL, plasmablastic lymphoma; ALCL, anaplastic large cell lymphoma.

by immunohistochemistry (IHC). CD30, a marker found in 70% of classical Hodgkin lymphoma. Reed-Sternberg cells are commonly observed in PEL, whereas CD15 is typically not expressed. Markers of plasma cell differentiation, including CD38 and CD138, are present; of note plasma-cell myeloma is typically CD45 negative.<sup>31</sup> human leukocyte antigen – antigen D related (HLA-DR), activation antigen, and epithelial membrane antigen are variably expressed.

Most importantly, the confirmation in diagnosis of PEL is dependent on identifying HHV8 viral infection in the nuclei of the malignant cells. This is evidenced via expression of LANA-1 by IHC stain or via DNA extraction and polymerase chain reaction amplification of HHV8.<sup>31</sup> This verification by itself can differentiate the null lymphocyte phenotype PEL from other lymphomas demonstrating strikingly similar clinical presentations and morphologic features.

### Cell of origin and genetic alterations in PEL

Gene expression profiling reveals the PEL cell of origin to be closely related to postgerminal center late-differentiating B-cells and likely of plasmablastic derivation.<sup>32</sup> While clonal rearrangement of the heavy immunoglobulin gene is detected, demonstrating B-cell derivation, a recurrent cytogenetic abnormality or PEL-specific driver mutation has not been identified.<sup>31</sup> Typical NHL-related gross rearrangements or mutations of BCL2, c-Myc, and TP53 are not identified in PEL.

Gaidano et al found a high frequency of BCL6 5' noncoding region nucleotide substitution mutations in PEL.<sup>33</sup> Bcl6 5' mutations are markers of B-cell transition through the germinal center. Therefore, these mutations suggest the origin as postgerminal-center B-cells.<sup>31</sup> In addition, a frequent occurrence of complete or partial trisomy 12, trisomy 7, and abnormalities of bands 1q21-25 have been noted.<sup>33</sup> Interleukin 1 receptor-associated kinase 1 (IRAK1), together with its binding partner MYD88, mediate toll-like receptor signaling and reactivate HHV8 leading to prolonged survival of PEL in culture. Via X chromosome targeted sequencing of PEL exudate cells, Yang et al found IRAK1 constitutively phosphorylated (mutated) in PEL and required for survival of these tumor cells.<sup>34</sup> Of note, the IRAK1 mutation is a common, essential driver for Kaposi sarcoma.

### Staging

As per the Lugano classification for NHL, all patients who present an effusion have stage IV disease at diagnosis.<sup>35</sup> Radiographic evaluation is akin to other aggressive NHL diagnoses including positron emission

tomography-computed tomography. Additionally, a bone marrow biopsy and/or lumbar puncture may be considered if clinically indicated.

### Prognosis

Given its resistance to cytotoxic therapies, treatment with PEL has generally been associated with a poor prognosis. Several factors have been evaluated as potential markers of prognosis. In a retrospective study of 28 HIV-positive patients with PEL, two independent predictors of decreased survival were identified by multivariate analysis: poor performance status and absence of combined antiretroviral therapy (c-ART) prior to PEL diagnosis.<sup>36</sup> In a different analysis of 104 patients with PEL, the number and location of affected cavities appeared to play a role in prognosis.<sup>5</sup> Specifically, the involvement of more than one body cavity was associated with an overall survival (OS) of 4 months in comparison to 18 months in patients with only one cavity involved.

### Management

Given the low incidence of PEL, there are no large-scale randomized studies to guide treatment and management decisions. Most of the evidence is based on retrospective studies, case reports, and preclinical data.

### Frontline treatment

Chemotherapy has traditionally been the cornerstone of treatment for patients with a good performance status and no significant comorbidities. However, an optimal regimen does not exist. As the majority of the PEL are diagnosed in the setting of HIV infection, the approach to their management is also based on HIV status.

### Chemotherapy

Although there is no one standard regimen that is universally accepted for the frontline treatment of PEL, an aggressive lymphoma regimen is typically used. Examples include dose-adjusted (DA) EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin) or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone).

The use of DA-EPOCH for PEL can be extrapolated from a study conducted at the National Cancer Institute in 39 patients with newly diagnosed AIDS-associated aggressive B-cell lymphoma.<sup>37</sup> The regimen produced an overall response rate (ORR) of 87%, 74% of which were complete remissions (CRs). At 52 months, the disease-free survival and OS were 92% and 60%, respectively. The treatment was well tolerated with grade 3 or 4 neutropenia, anemia, and thrombocytopenia

occurring in 30%, 17%, and 21% of the cycles, respectively. Serious constipation or stomatitis occurred in less than 3% of cycles, and grade 3 peripheral neuropathies occurred in two patients. Though no randomized controlled trials exist for PEL, there are case reports with the use of DA-EPOCH in combination with ART. In one case report, an HIV patient with extracavitary PEL received four cycles of EPOCH which led to a complete response after four cycles that lasted for 14 months after completing treatment.<sup>38</sup>

Simonelli et al conducted a retrospective analysis evaluating the efficacy of a CHOP-like regimen in which prednisone was omitted in the majority of the eight patients included in order to prevent the emergence or exacerbation of KS. Three patients achieved a CR (42%), and the median OS was 6 months.<sup>39</sup> Boulanger et al explored the efficacy of another multi-agent regimen, CHVp plus methotrexate, in another retrospective study of seven patients with AIDS-associated PEL. Patients received cyclophosphamide 650–700 mg/m<sup>2</sup>, doxorubicin 35–40 mg/m<sup>2</sup>, vincristine 0.8 mg/m<sup>2</sup>, or etoposide 80 mg/m<sup>2</sup> on day 1 followed by 4-hour intravenous infusion of methotrexate 2.5–3 g/m<sup>2</sup> on day 2 for 6–8 cycles every 21 days.<sup>40</sup> Three achieved a CR and remained in remission at 18, 26, and 78 months. Most of the patients had hematological toxicity with delayed clearance of methotrexate due to the presence of effusions. The use of methotrexate should be avoided as majority of the patients have an effusion that leads to decreased clearance and prolonged toxicity with methotrexate.

Rarely, PEL are CD20 positive. As with other B-cell lymphomas, treatment should incorporate rituximab-based chemoimmunotherapy. Two single-patient case reports have demonstrated the efficacy of RCHOP in this population, resulting in durable CR lasting 22 and 30 months.<sup>41,42</sup> The use of R-EPOCH in an HIV-patient resulted in CR lasting 12 months.<sup>43</sup>

### Anti-retroviral therapy

Anti-retroviral treatment (ART) is an important component of the management in patients with lymphoproliferative malignancies in the setting of HIV. In a retrospective study of HIV-infected patients diagnosed with PEL, Boulanger et al demonstrated a shorter OS for patients with a poor performance status and untreated HIV infection prior to diagnosis.<sup>36</sup> Similarly, patients treated with a CHOP-like regimen without ART were unable to achieve a CR and had a shorter OS of 3 months.<sup>39</sup> ART given by itself can also lead to a CR, as evident by one case report in which a patient remained in CR at 14 months.<sup>44</sup>

Treatment with ART should therefore be the mainstay of HIV-positive patients with PEL. In terms of choice of antiretroviral agents, some agents have more activity in PEL than others based on preclinical studies. Azidothymidine has been shown to sensitize primary effusion lymphoma cells to Kaposi sarcoma associated herpesvirus-specific CD4+ T cells and inhibits proliferation in PEL cell lines.<sup>45</sup> Similarly, preclinical studies with the protease inhibitor Lopinavir has shown induction of apoptosis of PEL cells via suppression of the NF-κB pathway. Interestingly, this effect, though present, was not as significant with other protease inhibitors like Ritonavir and Darunavir.<sup>46</sup> Hence, involving the infectious disease specialist in managing these patients is crucial.

### Relapsed and refractory disease

Most patients with PEL experience a relapse after frontline therapy within 6–8 months and subsequently require further treatment.<sup>11</sup> Treatment options will depend upon the performance status, comorbidities, and goals of care based on the individual. Therapies that have been evaluated in patients include stem cell transplant, radiation, and targeted agents such as bortezomib.

### Stem cell transplant

Autologous stem cell transplant (ASCT) has been attempted in a handful of patients. Waddington et al published a case report of an HIV-positive patient with PEL who received high-dose chemotherapy followed by autologous stem cell transplant in PEL.<sup>47</sup> The patient had persistent disease prior to ASCT. The transplant was unsuccessful as he developed recurrent accumulation of pleural fluid consistent with persistent disease indicating failure of ASCT. Won et al demonstrated the effectiveness of ASCT in an HIV-negative patient who proceeded to ASCT after achieving a CR with salvage chemotherapy (ifosfamide, carboplatin, and etoposide).<sup>48</sup> The patient remained in CR 12 months after completion of ASCT.

As the majority of patients with PEL have concurrent HIV infection, there has been great apprehension regarding the use of allogenic stem cell transplant (allo-SCT) in this population. Nevertheless, Bryant et al successfully performed a reduced intensity conditioning regimen followed by allo-SCT in one HIV-positive patient with PEL.<sup>49</sup> The patient achieved a CR and remained in CR for a period of 31 months after transplantation. There have been no other reports of the use of allo-SCT in PEL, therefore, the role for this therapy remains uncharted.

## Radiation

When the goal of treatment shifts toward comfort in patients with refractory or relapsed disease, an important component is to identify if the site of disease is causing physical distress. Radiation by itself is inadequate in most instances for achieving a complete response as with other aggressive lymphomas; however, it can be useful to control the disease burden. In a case report by Cassoni et al, a multiply-refractory patient with PEL with a pleural-based mass was treated with localized radiation resulting in a sustained remission for 12 months.<sup>70</sup> Radiation can be considered for PEL with a solid component involved within one radiation field.

## Antiviral therapies

As the malignant cells in PEL are infected with HHV8 virus, they theoretically can be targeted through antiviral therapy. Unfortunately, since the HHV8 virus is in a latent state, it is resistant to most antiviral agents. Klass and Offermann proposed a potential solution whereby induction of the HHV8 virus into the lytic phase via valproate followed by treatment with a lytic-phase effective anti-herpetic drug may lead to apoptosis of the infected cell.<sup>50</sup> Using an HHV-8 positive PEL cell line, they found lytic replication to be sensitive to ganciclovir, foscarnet and cidofovir, and resistant to acyclovir.<sup>50,51</sup>

The effectiveness of antiviral therapy in PEL has been demonstrated in a handful of case reports. An HIV patient who was refractory to frontline chemotherapy regimen of bortezomib, cyclophosphamide, Adriamycin, and prednisone experienced a CR with valganciclovir while continuing to receive c-ART.<sup>52</sup> The patient received treatment for 12 months but had achieved a CR by 6 months with eradication of the HHV8 virus. Seven months after completion of therapy, the patient continued on c-ART and remained disease free. Cidofovir has also been used in combination with ART and interferon. Hocqueloux et al published a case report of a patient with HIV-associated PEL treated with cidofovir and interferon (IFN)- $\alpha$ : cidofovir 5 mg/kg every 15 days in combination, IFN- $\alpha$  3 million units 3 times a week.<sup>53</sup> A CR was achieved after 2 months of treatment; cidofovir was stopped at 3 months, whereas IFN- $\alpha$  was continued for 7 months. The patient remained in a complete remission for 24 months. The inferior activity of cidofovir is postulated to be due to poor penetration of the drug into the effusion.<sup>54,55</sup> It has been shown to be highly active as a single agent when administered directly into the affected cavity. Luppi et al successfully treated three patients with HIV-negative, HHV8+ PEL with intracavitary cidofovir 2.5–5 mg/kg every week.<sup>55</sup>

The first patient achieved a CR with two doses of intrapleural cidofovir and maintained a remission for 10 months. The second patient achieved a CR after 3 doses of intraperitoneal cidofovir, maintaining a remission for 5 months. The third patient achieved a CR after three doses of intrapleural cidofovir and remained treatment free for 15 months. This approach is limited to disease involving only one cavity but may be extrapolated to HIV-positive patients as well. There are no data for the use of intracavitary cidofovir injection in multiple cavities.

## Talc pleurodesis

When PEL presents solely as an effusion, palliative approaches to decrease accumulation of fluid can be performed. One commonly utilized approach in other malignancies including malignant mesothelioma is pleurodesis. In this procedure, the visceral and parietal pleural layers are fused together so that there is no accumulation of fluid. Talc is a sclerosant which has been effectively used in this process. In addition to causing a fusion of the visceral and parietal pleura, it also has an apoptotic effect on mesothelioma cells by regulating the surface expression of the proto-oncogene c-myc and enhancing apoptosis.<sup>56</sup> A case series has shown that it is possible to achieve and maintain long-term remissions in patients with HIV-negative HHV8-associated PEL with video-assisted talc pleurodesis.<sup>57</sup> Remissions were achieved instantaneously after the procedure and lasting 50–60 months in the three patients evaluable. This is a reasonable option for elderly, frail individuals who have limited treatment options and are unable to tolerate aggressive treatments.

## Targeted therapies

### Proteasome inhibitors

Proteasomal activity is required for the survival of PEL cells and viral replication of KSHV cells. Preclinical data have shown that proteasome inhibitors reduce cell proliferation and induce apoptosis in KSHV-positive, EBV-positive and KSHV-positive, EBV-negative PEL cell lines.<sup>54</sup> As described previously, HHV8 viral latent transcripts also constitutively activate the NF- $\kappa$ B pathway, leading to tumor cell proliferation and survival. Bortezomib is a proteasome inhibitor currently approved in multiple myeloma and mantle cell lymphoma.<sup>58</sup> While single-agent bortezomib was not shown to be active in a small case series of three HIV-infected patients with relapsed/refractory PEL, it has promise in combination with other agents.<sup>8</sup> Siddiqi et al administered a combination of bortezomib, PEGylated liposomal doxorubicin, and rituximab to an HIV-negative patient with CD20

positive PEL, which resulted in a durable CR lasting at least 2 years.<sup>59</sup> Bortezomib has also been studied with the histone deacetylase inhibitor, vorinostat, in a murine PEL xenograft model. The combination of bortezomib and vorinostat led to KSHV lytic replication and cell death, thus demonstrating the synergy of vorinostat and bortezomib.<sup>60</sup>

### Brentuximab vedotin (BV)

BV is an antibody drug conjugate against CD30, currently approved in previously treated classical Hodgkin lymphoma and anaplastic large cell lymphoma.<sup>61</sup> As PEL is typically CD30 positive, Bhatt et al evaluated the role of BV in CD30 positive UM-PEL-1 and UM-PEL-3 cell lines and xenograft models.<sup>62</sup> BV induced G2 phase cell cycle arrest with intracellular delivery of the drug monomethyl auristatin E, inducing apoptosis of both the CD30 expressing cells and intratumoral cells lacking the target antigen. This effect was also observed in xenograft models inoculated with UM-PEL-1 and UM-PEL-3 cells. While there have been no clinical trials of BV in PEL, it has shown promise in other CD30+ lymphomas. Jacobsen et al administered BV to patients with CD30+ non-Hodgkin lymphoma patients, resulting in notable activity among the different histologies.<sup>63</sup> The ORR in DLBCL was 44%, including 17% complete remissions and a median duration of response of 16.6 months (range 2.7–22.7 months). Responses were also seen in patients with gray zone and posttransplant lymphoproliferative disorders. While the true efficacy in PEL is unclear, BV may be considered in select patients.

### Preclinical studies

Preclinical data have provided insight into targeted therapies that may have efficacy in PEL. The mammalian target of rapamycin (mTOR), its activator AKT, and the target p70S6 kinases are frequently phosphorylated in PEL. Rapamycin, an inhibitor of mTOR, has been tested in a variety of PEL cell lines (BC-1, BC-3, JSC-1, BCBL-1, BCP-1, and VG-1), proving its ability to inhibit proliferation and induce apoptosis.<sup>64</sup> It has also been studied in xenograft models, confirming its ability to inhibit PEL tumor growth. PEL cell lines also secrete high levels of VEGF and L-6.<sup>65</sup> Given these findings, the VEGF inhibitor, bevacizumab, and the IL-6 inhibitor, tocilizumab, have also been studied in PEL cell lines (BCBL-1, BC-1, BC-3, TY-1) and xenograft mouse models.<sup>66</sup> Neither bevacizumab or tocilizumab were able to inhibit proliferation in the cell line studies, however, both agents were able to inhibit the development of malignant pleural effusion and

provide a survival benefit in the xenograft models. These data support the exploration of the agents' utility in the clinical setting.

The immunomodulatory agent, lenalidomide, was initially approved in multiple myeloma but has also shown activity in other lymphoid malignancies including mantle cell lymphoma.<sup>67</sup> It has been evaluated with arsenic trioxide, a potent agent in acute promyelocytic leukemia.<sup>68</sup> The combination resulted in inhibition of growth in PEL cell lines (BC-1 and BC-3) by upregulating p53 and inducing apoptosis.<sup>69</sup> Reduction of the expression of latent viral transcripts (LANA-1, LANA-2, v-FLIP, and v-Cyclin) and proteins (LANA-1/LANA-2) was also noted. In PEL xenograft models, lenalidomide and arsenic trioxide induced greater responses and OS than lenalidomide alone. These preclinical studies provide a rationale for the use of these agents in the clinical setting. Unfortunately, given the rarity of this disease and the comorbidities associated with it, it is difficult to develop readily accessible trials for patients.

## Conclusion

PEL is an uncommon and aggressive disease affecting a unique population of patients who are often elderly or immunocompromised. Most of the patients diagnosed with PEL have significant other comorbidities, such as HIV, along with a poor performance status which limit their enrollment in clinical trials. For the fit and healthy patients, intensive chemotherapy remains the preferred choice, however, the availability of various targeted agents may alter this approach. For the unfit individuals, palliative treatments or newer targeted agents should be considered. With the improvement in our understanding of PEL, the treatment landscape is evolving and promising. Despite our advances, for now the use of ART for HIV-positive patients will continue to remain the backbone of treatment.

## Disclosure

The authors report no conflicts of interest in this work.

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