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Primary effusion lymphoma in people with and without HIV infection in the United States

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Abstract

Objective: Primary effusion lymphoma (PEL) is a rare non-Hodgkin lymphoma (NHL) subtype caused by Kaposi sarcoma (KS) herpesvirus. We describe PEL incidence and survival in people with HIV (PWH) and people without HIV in the US.

Design: Retrospective cohort study of PEL people with and without HIV.

Methods: PEL cases were identified in the HIV/AIDS Cancer Match (HACM) Study, a linkage of population-based cancer and HIV registries in 14 US regions. PEL incidence was examined using negative binomial regression and compared with the general population using a standardized incidence ratio. Survival was evaluated using Cox proportional hazard regression.

Results: During 2001–2019, 53% of 174 PEL cases identified in HACM data were among PWH. PWH had >700-fold higher PEL incidence than the general population. Compared to PEL cases without HIV, PWH were younger (median age: 44.8 vs. 77.7 years). Among PWH, prior KS was associated with 59-fold higher PEL incidence versus those without an AIDS diagnosis. PEL comprised 1.15% of the 8010 NHLs diagnosed among PWH in HACM during 2001–2019. HIV was not associated with mortality among PEL cases. Among PWH, Burkitt lymphoma and diffuse large B-cell lymphoma exhibited similar mortality to PEL but central nervous system lymphoma mortality was worse.

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Conflicts of Interest:

No potential conflicts of interest were disclosed by other authors.

Conclusions: There are two distinct subgroups of PEL cases in the US: younger patients with HIV and older patients without HIV. The proportion of PEL cases among PWH is highly disproportionate to the size of the HIV population, reflecting the greatly elevated incidence of PEL among PWH.

Keywords

lymphoma – primary effusion; herpesvirus 8 – human; lymphoma - non-Hodgkin; HIV; incidence; survival

INTRODUCTION

Primary effusion lymphoma (PEL) is a rare, B-cell non-Hodgkin lymphoma (NHL), often associated with immunosuppression due to human immunodeficiency virus (HIV) infection.¹ PEL typically presents as malignant effusions in the thoracic or abdominal cavities.¹ However, it can also manifest as lymphoid masses outside body cavities.² Historical median survival estimates for PEL range from 5 to 9 months;^{2–5} however, in settings where patients receive appropriate treatment survival estimates range from 10 to 40 months.^{6–8} Due to its rarity, there is no standard treatment for PEL, but treatment is generally extrapolated from other NHL subtypes using combination anthracycline-based chemotherapy.⁹

Kaposi sarcoma (KS) herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), is the causative agent of PEL and universally associated with it.^{10,11} Primarily transmitted via oral fluids, KSHV establishes lifelong latent infection in humans.¹¹ Globally, KSHV seroprevalence is estimated at 47% for people with HIV (PWH) and 24% for those without HIV, although there is marked geographic variability.^{12–14}

Three studies have described PEL incidence and survival in the United States (US).^{3,5,7} The most recent analysis of population-based data, including 105 patients with PEL diagnosed during 2004–2012, reported median survival of 4.8 months.³ Baidoun et al. examined survival among 219 PEL cases identified from the National Cancer Database (2004–2016) finding that HIV status was not associated with overall survival.⁵ In a study of 70 PEL cases from 10 US institutions, Hu et al. documented that approximately 90% PEL cases had HIV.⁷

There is an opportunity to extend reporting on PEL incidence in the US general population through 2021, and to compare characteristics of PEL cases by HIV status. In the present study, we use large population-based HIV and cancer registry databases to describe the incidence of PEL and survival after a PEL diagnosis in the US. Given the disproportionate incidence of this cancer among PWH, we focus on associations with HIV infection.

METHODS

PEL cases in people ≥ 20 years, were identified from two cancer registry data sources: the Surveillance, Epidemiology, and End Results (SEER) Program and the HIV/AIDS Cancer Match (HACM) Study. SEER 22 data, obtained from 22 cancer registries covering 48% of the US population, were used to describe PEL incidence in the US general population

during 2001–2021.¹⁵ The HACM Study is a population-based study linking HIV and cancer registries from 12 US states, Puerto Rico, and Washington, DC.¹⁶ HACM data were used to investigate PEL incidence and survival according to HIV status during 2001–2019. The study populations are described further in Appendix A.

We used the International Classification of Diseases for Oncology version 3 (ICD-O3) histology code 9678/3 to identify PEL cases in cancer registry data. Three physicians (RR, KL, JYS) reviewed clinical abstracts or pathology reports from 142 patients from five HACM cancer registries to determine if the available evidence supported a definitive diagnosis. As described in Appendix B, the clinical review confirmed the diagnosis in 64% of cases with the histology code 9678/3 overall, and this proportion increased to 100% when there was sufficient information to reach a confident diagnosis. The pathology review confirmed that 86% of cases with histology code 9678/3 were PEL. The HACM Study was exempt from ethics review at the National Cancer Institute but was approved, as required, by institutional review boards at participating registries.

Statistical analyses

We used SEER 22 data to calculate PEL incidence rates (IRs) in the US general population during 2001–2021. We employed negative binomial regression to estimate univariable and multivariable incidence rate ratios (IRRs) according to sex, 10-year age-group, race and ethnicity, and calendar year.

Remaining analyses used HACM data. We tabulated the characteristics of PEL cases with and without HIV (based on linkage to the HIV registries) and tested for differences using chi-square or Fisher exact tests. Since Florida provided data only on PEL cases with HIV, we excluded data from that state for these comparisons and for the survival analysis (described below).

To calculate PEL incidence among PWH, we followed individuals starting at the date their HIV infection was reported to the HIV registry, January 2001, or their 20th birthday, whichever occurred later. Follow-up ended at the earliest of PEL diagnosis, death, or end of cancer registry coverage (the last follow-up was in December 2019). We calculated IRRs from negative binomial regression models to assess risk factors for PEL among PWH, including sex and HIV risk group (i.e., men-who-have-sex with men [MSM], other males, females), age group, race and ethnicity, calendar year, and the presence of KS or another AIDS diagnosis (based on the 1993 surveillance definition).¹⁷

We estimated the proportion of NHL cases among PWH that were PEL using all NHL cases linked to PWH in HACM as the denominator. As a measure of relative risk for the association between HIV and PEL, a standardized incidence ratio (SIR) was computed by dividing the observed PEL cases in PWH by the expected PEL cases. Expected counts were based on general population rates from HACM cancer registries, stratified by sex, 10-year age-group, and calendar period (2001–2010 and 2011–2019). Since many PEL cases in the general population occur among PWH, expected rates are inflated;¹⁸ we therefore removed cases in PWH from the general population rates before calculating the SIR.

To evaluate overall survival among PEL cases by HIV status, we created Kaplan-Meier curves and performed Cox proportional hazards regression. PWH were followed from cancer diagnosis to either death or December 2019. We present unadjusted hazard ratios (HRs) for HIV status and HRs adjusted for sex, age group (<50, 50+), race and ethnicity, and calendar period. Among PWH, we compared PEL survival to that of other HIV-associated NHLs – diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, and primary central nervous system lymphoma.

During routine medical care, CD4 counts and HIV viral loads, are evaluated in PWH and reported to HIV registries. We summarize the proportion of patients with PEL with CD4 counts of <100, 100–199, 200–499, or ≥ 500 cells/mm³ and with detectable versus undetectable HIV viral loads (<200 copies/mL) during the five years leading to PEL diagnosis.¹⁹ When multiple assessments were available in a time interval, we averaged CD4 counts, and classified HIV viral load as detectable if at least one measurement was detectable.

We used a p-value cutoff of 0.05 for statistical significance, and all confidence intervals (CIs) were calculated at the 95% level. Data were analyzed in Stata 17 software (StataCorp).

RESULTS

During 2001–2021, 440 PEL cases were diagnosed among US adults in SEER 22 registry areas, corresponding to an incidence of 0.19 per million person-years (Supplementary Table 1). The majority (88.9%) of cases occurred in males, and males had nearly 10-fold higher PEL incidence compared to females (IRR: 9.76). PEL incidence increased strongly with age. Compared to 50–59-year-olds, people in their seventies had an IRR of 2.17 and people in their eighties had an IRR of 7.54. PEL incidence was elevated for non-Hispanic Black and Hispanic individuals compared to non-Hispanic White individuals (IRRs: 2.74 and 2.13, respectively). Relative to 2001–2005, PEL incidence was higher in subsequent calendar periods (IRRs: 1.72 for 2005–2010, 2.25 for 2011–2015, and 2.35 for 2016–2021).

During roughly the same period (2001–2019), 174 PEL cases were diagnosed among US adults in HACM registry areas, among which 52.9% (n=92) were in PWH (Table 1). A median of 6.9 years (interquartile range [IQR]: 0.75–10.8; range: 0–26.3 years) elapsed from HIV diagnosis to PEL diagnosis. PEL cases among PWH were significantly more likely to be male, younger, and non-Hispanic Black or Hispanic. The median age at PEL diagnosis was 45 years for PWH (IQR: 40–53, range: 21–79) versus 78 years for people without HIV (IQR: 63–88, range: 25–92). As a result, the majority (82.8%) of PEL cases in people under age 60 were among PWH, and 81% of cases aged ≥ 60 were among people without HIV. Almost a third (30.4%) of PEL cases in PWH also had a KS diagnosis, whereas only 12.2% of people without HIV had concomitant KS.

PEL comprised 1.15% of the 8010 NHLs diagnosed among PWH in HACM during 2001–2019. The incidence of PEL among PWH was 1.37 cases per million person years (Table 2), corresponding to a more than 700-fold elevation compared with the expected incidence (SIR: 712, CI: 553–883). Among PWH, MSM and males with other modes of HIV

transmission had higher PEL incidence than females. PEL incidence in PWH was somewhat constant across age groups, except incidence was lower among those 50–59 versus those aged 60+ (IRR: 0.37). A prior KS diagnosis placed PWH at almost 60-fold higher risk of PEL (IRR: 58.9), whereas having another AIDS diagnosis without KS was associated with 1.8-fold higher risk of PEL (IRR: 1.82). PEL incidence among PWH was 2.2 to 3.4-fold times higher in recent years compared to 2001–2005.

Data on CD4 counts were available for 28 to 67 PWH in the five years before PEL diagnosis, with different individuals contributing depending on the time interval. There was an increase in the proportion of PWH with CD4 counts below 200 cells/mm³, reaching 68.7% in the six months before diagnosis (Figure 1). Viral load data were available for 27 to 64 of PWH in the corresponding time intervals. The proportion with detectible viral loads in each time interval ranged from 66.7% to 81.3% without a clear pattern (Supplementary Table 2).

In unadjusted survival analyses, PEL cases with HIV had lower mortality than those without HIV (unadjusted HR: 0.55, CI: 0.38–0.81) (**Figure 2a, Table 3**). Five-year overall survival was 44.5% for PWH and 15.2% for people without HIV, and median overall survival was 17 versus 8 months, respectively. However, after adjusting for age, the difference in mortality was not significant (age-adjusted HR: 0.77, CI: 0.49–1.21). In the multivariable model, no characteristics, including HIV status, were significantly associated with mortality (Table 3).

Among PWH, survival in PEL cases was similar to survival in those with Burkitt lymphoma or DLBCL; however, survival for primary central nervous system lymphoma was lower (Figure 2b). In a regression model adjusted for sex, age group, race/ethnicity, and calendar year of diagnosis, PWH with Burkitt lymphoma or PEL had similar risk of death compared to those with DLBCL (HR: 1.00, CI: 0.91–1.10, and 1.14, CI: 0.86–1.52, respectively), whereas PWH with primary central nervous system lymphoma had higher mortality (HR: 1.68, CI: 1.52–1.85). In an analysis restricted to PWH with PEL, survival was similar in 2011–2019 versus 2001–2010 (sex, age, and race/ethnicity adjusted HR: 1.62, CI: 0.80–3.30).

DISCUSSION

The present study comprehensively describes patterns in the incidence of PEL in the US over a period of two decades. This malignancy is extremely rare, with an incidence of 0.19 per million person-years. Our findings demonstrate two distinct and roughly equal-sized subgroups of PEL cases in the US: younger patients with HIV and older patients without HIV. Nonetheless, the proportion of PEL cases among PWH was highly disproportionate to the size of the HIV population. Indeed, the incidence of PEL among PWH was more than 700-fold higher than expected.

A close association between PEL and HIV has long been established on clinical grounds and arises due to the high prevalence of KSHV among PWH and poor immune control of this virus. Our study is the first to quantify the remarkable strength of this association as indicated by the greatly elevated SIR. Furthermore, among PWH, we demonstrated that PEL

incidence increased 59-fold after a KS diagnosis, highlighting the strong association with immune dysregulation and KSHV. In people without HIV, the association with advanced age may similarly reflect loss of immune control of KSHV due to other immune-related medical conditions or age-related immune dysfunction (i.e., immunosenescence).

Although it is frequently cited that the vast majority of PEL cases are among PWH,^{3,7} we found that about half of PEL cases in the US between 2001–2019 were among PWH. A global review of PEL case reports and series published from 1995 to 2019 found that 63% of PEL cases had HIV.² Our estimate is modestly lower than the prevalence of HIV in the global report (63%) and that reported in a recent US-based study (65%).^{2,5} It is possible that our estimate of the proportion of PEL cases with HIV is lower than prior estimates because our study is population-based, whereas PWH may be overrepresented in hospital and clinic-based studies. Among PWH, males, especially MSM, had the highest risk of PEL, likely due to a high prevalence of KSHV in this group.²⁰

Using both SEER and HACM data, we found that 89% of PEL cases in the US general population were in males, similar to prior estimates from the literature (86–96%).^{2,5,7} In our study, 83% of cases in people under age 60 arose in PWH, and like Hu et al., we found that PEL cases in PWH were much younger than those without HIV (median age at diagnosis here: 45 vs. 78 years; Hu: 45 vs. 75 years),⁷ reflecting both the young age of the PWH population in general and the strongly immunosuppressive effects of HIV. No prior study has reported on PEL incidence in the US general population by race and ethnicity. We found that PEL incidence was more than 2-fold higher in Hispanic and non-Hispanic Black and individuals compared to non-Hispanic White individuals in the general population. This finding is probably explained by the higher prevalence of HIV infection in minoritized racial/ethnic groups in the US. Indeed, race and ethnicity were not associated with PEL incidence in our analyses of HACM data restricted to PWH.

PEL is an uncommon NHL subtype among PWH in the US, comprising just 1.15% of NHL diagnosed among PWH in our study. This proportion is lower than that reported in Germany and Austria (3.0% of NHLs diagnosed 2005–2018), Italy (4.0% during 1987–2002) and France (8.6% during 1996–2019).^{21–23} After 2001–2005, PEL incidence increased in the US general population and especially among PWH. This increase may reflect greater recognition of PEL by clinicians and pathologists and higher uptake of the ICD-O3 histology code specific to PEL (first introduced in 2001). It is difficult to be certain of a diagnosis of PEL without an expert review of all clinical and pathological information, and possibly additional testing of tumor tissue. Such an evaluation was not possible using the retrospective information available to us through cancer registries, which was in some cases limited. Nonetheless, based on the available information, our clinical and review demonstrated that this ICD-O3 histology code had a reasonable positive predictive value of 61.1% (both clinical reviewers classified 22 of the 36 records as PEL). Additionally, at least one clinical reviewer was very confident/confident of the diagnosis of PEL for 30 of the 36 (83.3%) cases. Similarly, based on a review of pathology reports, we confirmed PEL diagnoses for 6 of 7 cases (85.7%). We also considered the possibility that the linkage between HIV and cancer registries would have missed some HIV diagnoses. During our review of 82 clinical abstracts provided by three HACM cancer registries, we identified three

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PEL cases with HIV that had not been linked to a HACM HIV registry, suggesting that the linkage had 97% sensitivity (these three cases were then added to the cases in PWH; see Appendix B).

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Several findings in our study support that long-term immunosuppression or immune dysregulation among PWH contribute to the development of PEL. We found a median time from HIV diagnosis to PEL diagnosis of 6.9 years. In our study, 68% of PWH had CD4 counts of <200 cells/mm³ in the six months leading to PEL diagnosis. Similarly, Hu et al. reported that 71% of 35 PWH had CD4 counts <200 cells/mm³ at PEL diagnosis.⁷ We also observed that 76% of PWH with PEL had a prior diagnosis of AIDS, and AIDS (even in the absence of KS), was a risk factor for PEL. The proportion of PWH with detectible viral load was high (~70–80%) in the years preceding PEL diagnosis, indicating a lack of effective HIV treatment.

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HIV status did not statistically significantly influence survival among patients with PEL after adjustment for age at diagnosis. Among PWH, survival for patients with PEL was similar to those with DLBCL and Burkitt lymphoma. In contrast, survival was worse for patients with primary central nervous system lymphoma, a lymphoma subtype occurring in the setting of very advanced HIV and that has especially poor prognosis.^{25,26} Due to better HIV treatment and cancer management, we expected PEL survival among PWH to improve in more recent years; however, survival was unchanged during 2011–2019 versus 2001–2010. This pattern may reflect gaps in referral of PWH with PEL to expert cancer care, as treatment of this malignancy is complex and patients frequently have other comorbidities.⁹

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A key strength of our study is our use of large population-based cancer datasets, including ascertainment of HIV status for many cases by linkage with HIV registries. This permitted us to include a sizeable number of cases of this rare malignancy and to compare incidence and survival by HIV status. Our study is the first to quantify the elevation in PEL risk experienced by PWH and to examine PEL incidence according to race/ethnicity, concurrent KS diagnoses, and HIV risk group. A limitation of our study is that data on CD4 counts and HIV viral loads among PWH were incomplete, preventing us from evaluating these HIV disease markers as risk factors for PEL. There are challenges with the central pathology review, which is based on appropriate coding and local pathology review. Finally, we lacked clinical details on PEL cases, such stage of disease, KSHV-specific measurements, and HIV and cancer treatment.

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Combining data from large population-based studies allowed us to provide a comprehensive overview of PEL in the US. We found that there are two distinct groups of people with PEL, young people with HIV and older people without HIV. Some of the patterns in the general population reflect the prevalence of HIV; specifically, the higher frequency of cases among males and minoritized groups. PWH had enormously elevated risk of PEL compared with the general population. Among PWH, a diagnosis of KS was a strong risk factor for PEL, highlighting the key roles played by KSHV infection and immunosuppression in the etiology of this cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability statement:

Data use agreement restrictions preclude sharing HACM Study data with external researchers however SEER data are accessible at <https://seer.cancer.gov/data/access.html>

REFERENCES

1. Shimada K, Hayakawa F, Kiyoi H. Biology and management of primary effusion lymphoma. *Blood*. 2018;132(18):1879–1888. doi:10.1182/blood-2018-03-791426 [PubMed: 30154110]
2. Aguilar C, Laberiano C, Beltran B, Diaz C, Taype-Rondan A, Castillo JJ. Clinicopathologic characteristics and survival of patients with primary effusion lymphoma. *Leuk Lymphoma*. 2020;61(9):2093–2102. doi:10.1080/10428194.2020.1762881 [PubMed: 32449626]
3. El-Fattah MA. Clinical characteristics and survival outcome of primary effusion lymphoma: A review of 105 patients. *Hematol Oncol* 2017;35(4):878–883. doi:10.1002/hon.2372 [PubMed: 27859456]
4. Castillo JJ, Shum H, Lahijani M, Winer ES, Butera JN. Prognosis in primary effusion lymphoma is associated with the number of body cavities involved. *Leuk Lymphoma*. 2012;53(12):2378–82. doi:10.3109/10428194.2012.694075 [PubMed: 22591071]
5. Baidoun F, Moustafa MA, Tun HW, Hill BT. Clinical Characteristics and Survival Outcomes of Primary Effusion Lymphoma: A National Cancer Database Study. *Clin Lymphoma Myeloma Leuk* 2022;22(7):e485–e494. doi:10.1016/j.clml.2022.01.006 [PubMed: 35110006]
6. Guillet S, Gerard L, Meignin V, et al. Classic and extracavitary primary effusion lymphoma in 51 HIV-infected patients from a single institution. *Am J Hematol* 2016;91(2):233–7. doi:10.1002/ajh.24251 [PubMed: 26799611]
7. Hu Z, Pan Z, Chen W, et al. Primary Effusion Lymphoma: A Clinicopathological Study of 70 Cases. *Cancers (Basel)*. 2021;13(4)doi:10.3390/cancers13040878
8. Lurain K, Polizzotto MN, Aleman K, et al. Viral, immunologic, and clinical features of primary effusion lymphoma. *Blood*. 2019;133(16):1753–1761. doi:10.1182/blood-2019-01-893339 [PubMed: 30782610]
9. Patel R, Lurain K, Yarchoan R, Ramaswami R. Clinical management of Kaposi sarcoma herpesvirus-associated diseases: an update on disease manifestations and treatment strategies. *Expert Rev Anti Infect Ther* 2023;21(9):929–941. doi:10.1080/14787210.2023.2247161 [PubMed: 37578202]
10. Surveillance Epidemiology and End Results (SEER) Program. Neoplasm information: Primary effusion lymphoma. Accessed August 12, 2024. <https://seer.cancer.gov/seertools/hemelymph/51f6cf57e3e27c3994bd5378/>
11. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Biological Agents. Vol. 100 B. 2012. IARC monographs on the evaluation of carcinogenic risks to humans. <http://monographs.iarc.fr/ENG/Monographs/vol100B/mono100B.pdf>
12. Rohner E, Wyss N, Heg Z, et al. HIV and human herpesvirus 8 co-infection across the globe: Systematic review and meta-analysis. *Int J Cancer*. 2016;138(1):45–54. doi:10.1002/ijc.29687 [PubMed: 26175054]
13. Begre L, Rohner E, Mbulaiteye SM, Egger M, Bohlius J. Is human herpesvirus 8 infection more common in men than in women? Systematic review and meta-analysis. *Int J Cancer*. 2016;139(4):776–83. doi:10.1002/ijc.30129 [PubMed: 27062038]
14. Pfeiffer RM, Wheeler WA, Mbisa G, Whitby D, Goedert JJ, de The G, Mbulaiteye SM. Geographic heterogeneity of prevalence of the human herpesvirus 8 in sub-Saharan Africa: clues about etiology. *Ann Epidemiol* 2010;20(12):958–63. doi:10.1016/j.annepidem.2010.07.098 [PubMed: 21074111]
15. Surveillance, Epidemiology, and End Results (SEER) Program. Data from: (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Limited-Field Data, 22 Registries, Nov 2023 Sub (2000–2021) - Linked To County Attributes - Time Dependent (1990–2022) Income/Rurality, 1969–2022 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2024, based on the November 2023 submission.
16. National Cancer Institute. HIV/AIDS Cancer Match Study. Accessed June 25, 2024. <https://dceg.cancer.gov/research/who-we-study/cohorts/hiv-aids-cancer-match-study#:~:text=The%20HIV%20FAIDS%20Cancer%20Match,regions%20of%20the%20United%20States.>

17. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992;41(RR-17):1–19.
18. Chaturvedi AK, Mbulaiteye SM, Engels EA. Underestimation of relative risks by standardized incidence ratios for AIDS-related cancers. Ann Epidemiol 2008;18(3):230–4. doi:10.1016/j.annepidem.2007.10.005 [PubMed: 18083545]
19. Centers for Disease Control and Prevention. HIV treatment as Prevention. Accessed June 24, 2024. <https://www.cdc.gov/hiv/risk/art/index.html#:~:text=HIV%20medicine%20can%20even%20make,called%20an%20undetectable%20viral%20load>.
20. Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, Kedes DH. Sexual transmission and the natural history of human herpesvirus 8 infection. N Engl J Med 1998;338(14):948–54. doi:10.1056/NEJM199804023381403 [PubMed: 9521982]
21. Calvani J, Gerard L, Fadlallah J, et al. A Comprehensive Clinicopathologic and Molecular Study of 19 Primary Effusion Lymphomas in HIV-infected Patients. Am J Surg Pathol 2022;46(3):353–362. doi:10.1097/PAS.0000000000001813 [PubMed: 34560683]
22. Hentrich M, Muller M, Wyen C, et al. Characteristics and outcome of human immunodeficiency virus (HIV)-associated primary effusion lymphoma as observed in the German HIV-related lymphoma cohort study. Br J Haematol 2021;194(3):642–646. doi:10.1111/bjh.17515 [PubMed: 33959944]
23. Simonelli C, Spina M, Cinelli R, et al. Clinical features and outcome of primary effusion lymphoma in HIV-infected patients: a single-institution study. J Clin Oncol 2003;21(21):3948–54. doi:10.1200/JCO.2003.06.013 [PubMed: 14581418]
24. Bhattacharya R, Uddin MM, Patel AP, et al. Risk factors for clonal hematopoiesis of indeterminate potential in people with HIV: a report from the REPRIEVE trial. Blood Adv 2024;8(4):959–967. doi:10.1182/bloodadvances.2023011324 [PubMed: 38197863]
25. Howlader N, Shiels MS, Mariotto AB, Engels EA. Contributions of HIV to Non-Hodgkin Lymphoma Mortality Trends in the United States. Cancer Epidemiol Biomarkers Prev 2016;25(9):1289–96. doi:10.1158/1055-9965.EPI-16-0273 [PubMed: 27418269]
26. Vargas JC, Marques MO, Pereira J, et al. Factors associated with survival in patients with lymphoma and HIV. AIDS 2023;37(8):1217–1226. doi:10.1097/QAD.0000000000003549 [PubMed: 36939075]

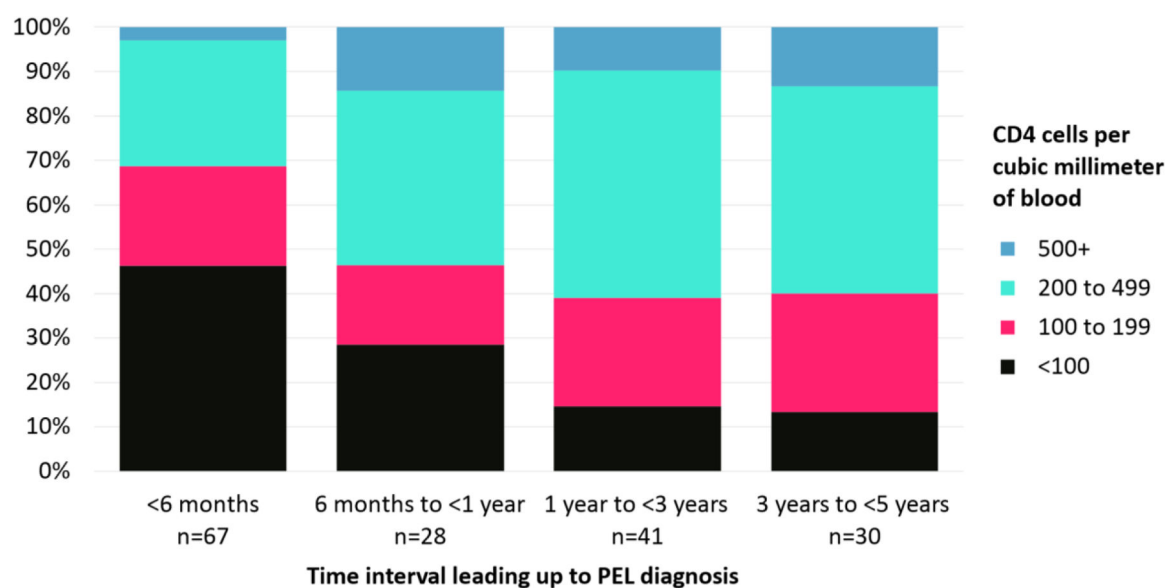


Figure 1. Distribution of CD4 counts among people with HIV in the five years leading to primary effusion lymphoma diagnosis

HIV human immunodeficiency virus, PEL primary effusion lymphoma

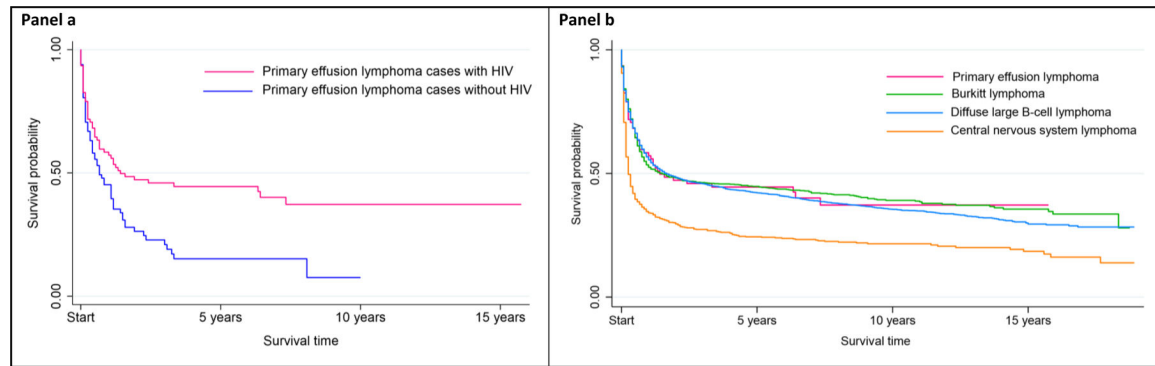


Figure 2. Overall survival after a diagnosis of primary effusion lymphoma or another non-Hodgkin lymphoma subtype

The Kaplan-Meier curves show overall survival following lymphoma diagnosis. Panel a depicts survival among primary effusion lymphoma cases with (pink) and without HIV (blue). Panel b is restricted to people with HIV and depicts survival for four different types of non-Hodgkin lymphoma.

Table 1. Demographic characteristics of 174 primary effusion lymphoma cases captured in HIV/AIDS Cancer Match Study registries, 2001–2019

Characteristic	PEL cases in PWH		PEL cases in people without HIV		p-value	Proportion of PEL cases among PWH Row %
	n	Col %	n	Col %		
Overall	92 ^a		82			52.9
Sex					0.002	
Female	4	4.3	16	19.5		20.0
Male	88	95.7	66	80.5		57.1
Age-group (years)					<0.001	
20 to 29	7	7.6	2	2.4		77.8
30 to 39	18	19.6	5	6.1		78.3
40 to 49	38	41.3	4	4.9		90.5
50 to 59	14	15.2	5	6.1		73.7
60 to 69	12	13.0	11	13.4		52.2
70 to 79	3	3.3	21	25.6		12.5
80 or older	0	0.0	34	41.5		0.0
Race and ethnicity					0.005	
Non-Hispanic White	34	37.0	47	57.3		42.0
Non-Hispanic Black	26	28.3	15	18.3		63.4
Hispanic	30	32.6	14	17.1		68.2
Other ^b	2	2.2	6	7.3		25.0
Calendar period at diagnosis					0.417	
2001 to 2005	5	5.4	8	9.8		38.5
2006 to 2010	24	26.1	14	17.1		63.2
2011 to 2015	38	41.3	37	45.1		50.7
2016 to 2019	25	27.2	23	28.0		52.1
Kaposi sarcoma prior to or at PEL diagnosis					0.006	
No	64	69.6	72	87.8		47.1
<1 year before	14	15.2	1	1.2		93.3
1 to <3 years before	6	6.5	4	4.9		60.0
3 or more years before	8	8.7	5	6.1		61.5

col column, PEL primary effusion lymphoma, PWH people with HIV

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PEL cases from Florida were excluded because the corresponding people without HIV were not included from Florida.
Includes any race and ethnicity not already listed and missing/unknown.

Table 2.
Incidence of primary effusion lymphoma among people with HIV captured in HACM Study registries, 2001–2019

Characteristic	No. of PEL cases	Col %	Incidence rate per million person-years	Univariable IRR (95% CI)	Multivariable IRR ^a (95% CI)
Overall	102	100.0	1.37	...	...
Sex and HIV risk group					
MSM	70	68.6	2.34	[Referent]	[Referent]
Male: other	18	17.6	1.08	0.32 (0.16–0.65)	0.68 (0.39–1.16)
Female	4	3.9	0.20	0.05 (0.02–0.15)	0.14 (0.05–0.38)
Unknown	10	9.8	1.37	0.35 (0.15–0.84)	0.78 (0.39–1.53)
Age-group (years)					
20 to 29	8	7.8	12.2	0.60 (0.24–1.51)	0.93 (0.39–2.22)
30 to 39	25	24.5	16.2	0.95 (0.46–1.95)	1.09 (0.58–2.06)
40 to 49	36	35.3	14.7	0.75 (0.39–1.45)	0.81 (0.45–1.45)
50 to 59	15	14.7	7.77	0.36 (0.17–0.78)	0.37 (0.19–0.74)
60 or older	18	17.6	21.3	[Referent]	[Referent]
Race and ethnicity					
Non-Hispanic White	38	37.3	1.98	[Referent]	[Referent]
Non-Hispanic Black	27	26.5	0.86	0.40 (0.23–0.71)	0.66 (0.39–1.11)
Hispanic	26	25.5	1.36	0.59 (0.33–1.06)	0.73 (0.44–1.21)
Other	11	10.8	2.52	1.08 (0.51–2.27)	1.48 (0.75–2.92)
Prior AIDS diagnosis					
No AIDS diagnosis	23	22.5	0.76	[Referent]	[Referent]
Diagnosed with Kaposi sarcoma	28	27.5	54.9	74.6 (41.7–134)	58.9 (33.3–104)
Diagnosed with AIDS without Kaposi sarcoma	49	48.0	1.18	1.53 (0.92–2.56)	1.82 (1.09–3.03)
Unknown ^b	2	2.0	1.15	1.47 (0.34–6.32)	1.47 (0.34–6.32)
Calendar period of PEL diagnosis					
2001 to 2005	7	6.9	5.52	[Referent]	[Referent]
2006 to 2010	24	23.5	11.7	2.37 (0.95–5.91)	2.27 (0.98–5.30)
2011 to 2015	43	42.2	17.3	3.28 (1.38–7.83)	3.42 (1.52–7.67)
2016 to 2019	28	27.5	17.4	3.54 (1.44–8.70)	3.33 (1.43–7.75)

AIDS Acquired immunodeficiency syndrome, CI confidence interval, Col column, dx diagnosis, HACM HIV and Cancer Match, HIV human immunodeficiency virus, MSM men who have sex with men, PEL primary effusion lymphoma, No. number

^a Adjusted for all characteristics listed in the table.
^b Data on this variable were missing for one registry (Massachusetts).

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Table 3.
Mortality among primary effusion lymphoma patients in HACM Study registries, 2001–2019

Characteristic	No. of deaths	Univariable HR (95% CI)	Multivariable HR ^a (95% CI)
HIV status			
Negative	64	[Referent]	[Referent]
Positive	48	0.55 (0.38–0.81)	0.76 (0.47–1.23)
Sex			
Female	14	[Referent]	[Referent]
Male	98	0.96 (0.55–1.68)	1.25 (0.69–2.28)
Age group, years			
<50	34	[Referent]	[Referent]
50+	78	2.12 (1.41–3.19)	1.59 (0.95–2.67)
Race and ethnicity			
Non-Hispanic White	61	[Referent]	[Referent]
Non-Hispanic Black	23	0.55 (0.34–0.89)	0.64 (0.39–1.07)
Hispanic	22	0.51 (0.31–0.83)	0.63 (0.37–1.07)
Other	6	0.81 (0.35–1.87)	0.78 (0.33–1.82)
Calendar period at PEL diagnosis			
2001 to 2005	11	[Referent]	[Referent]
2006 to 2010	25	0.65 (0.32–1.32)	0.75 (0.36–1.58)
2011 to 2015	47	0.75 (0.39–1.44)	0.83 (0.42–1.67)
2016 to 2019	29	0.91 (0.45–1.83)	0.94 (0.45–1.96)

CI confidence interval, HR hazard ratio, No. number

^a Adjusted for all characteristics listed in the table.