Title

Serological Assessment of 18 Pathogens and Risk of AIDS-Associated Non-Hodgkin Lymphoma

Journal

JAIDS Journal of Acquired Immune Deficiency Syndromes, 80(3)

ISSN

1525-4135

Authors

Halec, Gordana
Waterboer, Tim
Brenner, Nicole
et al.

Publication Date

2019-03-01

DOI

10.1097/qai.0000000000001916

Peer reviewed

HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2020 March 01.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2019 March 01; 80(3): e53–e63. doi:10.1097/QAI.0000000000001916.

Serological Assessment of 18 Pathogens and Risk for AIDS-associated Non-Hodgkin Lymphoma

Gordana Halec[1], **Tim Waterboer**[2], **Nicole Brenner**[2], **Julia Butt**[2], **David W. Hardy**[3], **Gypsyamber D'Souza**[4], **Steven Wolinsky**[5], **Bernard J. Macatangay**[6], **Michael Pawlita**[2], **Roger Detels**[7], **Otoniel Martínez-Maza**[1], and **Shehnaz K. Hussain**[7,8]

[1]University of California Los Angeles (UCLA) AIDS Institute and Department of Obstetrics and Gynecology, UCLA David Geffen School of Medicine, Los Angeles, California, USA

[2]Infections and Cancer Epidemiology, Research Program Infection, Inflammation and Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany

[3]Clinical Investigations, Whitman-Walker Health, Washington, DC

[4]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

[5]Division of Infectious Diseases, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[6]Division of Infectious Diseases, Department of Medicine, University of Pittsburg School of Medicine, Pittsburgh, Pennsylvania, USA

[7]Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, California, USA

[8]Samuel Oschin Comprehensive Cancer Institute and Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, California, USA

Abstract

Background: HIV infection is associated with increased susceptibility to common pathogens which may trigger chronic antigenic stimulation and hyperactivation of B-cells, events known to precede the development of AIDS-associated non-Hodgkin lymphoma (AIDS-NHL).

Methods: To explore whether cumulative exposure to infectious agents contributes to AIDS-NHL risk, we tested sera from 199 AIDS-NHL patients (pre-NHL, average lead-time 3.9 years) and 199 matched HIV-infected controls from the Multicenter AIDS Cohort Study (MACS), for anti-IgG responses to 18 pathogens using multiplex serology. Odds ratios and 95% confidence intervals were estimated using conditional logistic regression models.

Corresponding author: Gordana Halec, UCLA AIDS Institute, David Geffen School of Medicine at UCLA, 615 Charles Young Drive, Los Angeles, CA, USA 90095-7363 GHalec@mednet.ucla.edu.

Conflicts of Interest and Source of Funding

Authors have no conflicts of interest to declare.

Results: We found no association between cumulative exposure to infectious agents and AIDS-NHL risk (OR 1.01, 95% CI 0.91–1.12). However, seropositivity for trichodysplasia spinulosa polyomavirus (TSPyV), defined as presence of antibodies to TSPyV capsid protein VP1, was significantly associated with a 1.6-fold increase in AIDS-NHL risk (OR 1.62, 95% CI 1.02–2.57). High Epstein-Barr virus (EBV) anti-VCA p18 antibody levels closer to the time of AIDS-NHL diagnosis (<4 years) were associated with a 2.6-fold increase in AIDS-NHL risk (OR 2.59, 95% CI 1.17–5.74). Additionally, high EBV anti-EBNA-1 and anti-ZEBRA antibody levels were associated with 2.1-fold (OR 0.47, 95% CI 0.26–0.85) and 1.6-fold (OR 0.57, 95% CI 0.35–0.93) decreased risk for AIDS-NHL, respectively.

Conclusions: Our results do not support the hypothesis that cumulative exposure to infectious agents contributes to AIDS-NHL development. However, the observed associations with respect to TSPyV seropositivity and EBV antigen antibody levels offer additional insights into the pathogenesis of AIDS-NHL.

Keywords

AIDS-NHL; HIV; infections; multiplex serology; antibodies

INTRODUCTION

Non-Hodgkin Lymphoma (NHL) is one of the most common AIDS-associated malignancies, and a common cause of death among HIV-infected individuals [1–3]. In fact, NHL incidence is 60- to 200-fold greater among HIV-infected people compared to the general population [2,4–6]. The introduction of highly active antiretroviral therapy (HAART) resulted in, among other benefits, up to 70% decrease of AIDS-NHL incidence compared to the pre-HAART era [7,8]. Nevertheless, NHL risk remains significantly higher in HIV-infected compared to immunocompetent individuals [8–10], and AIDS-NHL is still responsible for 23–30% of AIDS-related deaths in countries with widespread access to HAART [2,7,11–14]. Therefore, the identification and better understanding of risk factors contributing to AIDS-NHL immunopathogenesis remain of great importance.

AIDS-NHLs are a heterogeneous group of tumors that arise from B-cells in >90% of cases [15–17]. The pathogenic events leading to AIDS-NHL are complex and could involve chronic immune stimulation by multiple opportunistic infections [15,16,18–22]. Indeed, while progressive HIV infection itself is a known contributor to chronic B-cell hyperactivation and inflammation [16,23–25], it also provides a setting of increased susceptibility to potential deleterious effects of common pathogens that are mostly harmless in immunocompetent individuals [26]. For example, bacteremias are up to 20 times more prevalent among HIV-infected individuals compared to the general population [27], and opportunistic infections are frequently common cause of death in HIV-infected individuals [28,29].

The most common pathogens linked to AIDS-NHL development are two gamma-herpesviruses; Epstein-Barr Virus (EBV) and Kaposi Sarcoma-associated Herpesvirus (KSHV). Almost all primary central nervous system lymphomas (PCNSLs) are EBV-related, primary effusion lymphomas (PEL) are KSHV-related, and both EBV and KSHV are essential to the development of a subset of immunoblastic diffuse large B-cell lymphomas

(DLBCL) [15,30–34]. In addition, recent large cohort study reported that chronic co-infection with hepatitis B (HBV) and hepatitis C (HCV) viruses also contributes to the AIDS-NHL risk [35].

The association between infectious agents and NHL is not restricted to the setting of HIV, as some chronic infections have also been linked to the development of NHL in immunocompetent people. Chronic HBV infection increases risk for multiple NHL subtypes [36–38]; HCV infection can lead to development of marginal zone B-cell lymphoma (MZL) and DLBCL [39–41]; and chronic infection with *Helicobacter pylori* has been linked to the development of mucosa-associated lymphoid tissue (MALT) lymphoma [42–46].

While there is ample evidence that individual pathogens confer increased susceptibility to NHL with or without HIV infection, we sought to examine the effects of cumulative exposure to infectious agents in relation to AIDS-NHL risk. We hypothesized that such exposure could contribute to the chronic antigenic stimulation and hyperactivation of B-cells preceding AIDS-NHL development. To test this hypothesis, we measured the presence of antibodies to 38 different antigens of 18 distinct pathogens (14 viruses, 3 bacteria, and a protozoon). The selection of these pathogens was based on: a) previously reported associations with NHL [32,33,35,46–49], and/or b) higher frequency of pathogen or pathogen-associated disease in HIV-infected compared to immunocompetent individuals [50–60], respectively.

MATERIALS AND METHODS

Study population.

The Multicenter AIDS Cohort Study (MACS) is an ongoing prospective cohort study established in 1984 to study the natural and treated history of HIV and AIDS in men who have sex with men (MSM) recruited from four U.S. metropolitan areas (Baltimore/Washington, DC; Chicago; Los Angeles; and Pittsburgh) [61,62]. Study visits are held biannually and include face to face interviews, physical examination, specimen collection and laboratory testing. HIV seropositivity and $CD4^+$ T cell counts are measured at nearly all study visits, and sera are collected and stored in central repositories [63]. All protocols and questionnaires utilized in the MACS have been approved by the Institutional Review Board of each center.

Study Design.

For this present study, we designed a nested case-control study within the MACS. Cases included all participants with a diagnosis of pathologically confirmed AIDS-NHL following enrollment into the MACS and the availability of archival pre-NHL diagnostic serum. Based on these criteria, 200 AIDS-NHL cases were identified. For each case, one HIV-infected participant who did not develop AIDS-NHL up to November 2014 was selected. For cases, serum specimens were selected closest to 4 years prior to AIDS-NHL or any date preceding 4 years. For about half of the cases who did not have archival specimens at least 4 years prior to diagnosis, any pre-diagnosis specimens was utilized. For controls, specimen time-points were matched to each case by visit number. Additionally, controls were matched to

cases on: i) recruitment phase into the cohort (1984–1985, 1987–1991, or 2001+), ii) prior highly active antiretroviral drug use (HAART, ever versus never), and iii) CD4+ T cell counts at the time of AIDS-NHL diagnosis or matched time-point for controls (± 200/μl). In addition, cases who became HIV-infected after recruitment into the cohort were matched to controls by their seroconversion date, and cases treated with HAART were matched to controls on time since their first therapy. The definition of HAART was guided by the DHHS/Kaiser Panel [64] guidelines and defined as three or more antiretroviral (ART) drugs consisting of one or more protease inhibitors (PIs), or one non-nucleoside reverse transcriptase inhibitor (NNRTI), or the nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), or an integrase inhibitor (II), or an entry inhibitor (including fusion inhibitors; EI). One case/control set was excluded from analysis due to insufficient specimen volume leaving a total of 199 cases and 199 controls for the final analysis.

Serological Methods.

Frozen serum samples were shipped on dry ice to the German Cancer Research Center (Heidelberg, Germany) for serological testing for IgG antibodies to 38 previously well-defined and specific antigens of 18 pathogens (Supplementary Table S1). Analysis included: i) human herpesviruses: Herpes Simplex Virus 1 and 2 (HSV-1, −2), Epstein Barr Virus (EBV/HHV4), Human Cytomegalovirus (HCMV/HHV5), Human Herpesviruses 6 and 7 (HHV-6, −7), Kaposi's sarcoma-associated herpesvirus (KSHV/HHV8); ii) human hepatitis viruses: Hepatitis B Virus and Hepatitis C Virus (HBV and HCV); iii) human polyomaviruses (HPyV): BKPyV, JCPyV, Merkel cell polyomavirus (MCPyV), and Trichodysplasia spinulosa-associated polyomavirus (TSPyV); iv) Human Papillomavirus type 16 (HPV16); v) bacteria: Helicobacter pylori, Chlamydia trachomatis, and Mycoplasma genitalium; and iv) parasite Toxoplasma gondii. Antigen preparation and serological techniques have been previously described [65–69]. Briefly, serum samples (1:1000 dilutions) were incubated with antigen-loaded fluorescently labeled beads and analyzed on a Luminex 200 analyzer. As output, bead-bound fluorescence-stained human antibodies to each of the antigens of interest were quantified as median fluorescence intensity values (MFI) in a single reaction for each sample [69,70]. Following quantification, standard cut-offs for seropositivity were applied for each antigen by visual inspection of frequency distribution curves (percentile plots), as previously described [71–74]. Quality controls used on every tested plate included previously tested serum samples with known reactivity profiles. Coefficients of variation (CVs) for infection antibodies ranged from 6–29%, with a median of 18%. Eighty percent of markers tested had a CV less than 20%.

Statistical analyses.

Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression models. The case-control matching by design was incorporated into the models by adding a grouping variable for matched set. In addition to the matching factors, all models were adjusted for covariates selected *a priori* for their previously described associations with AIDS-NHL and included race/ethnicity (categorical: Hispanic white, non-Hispanic white, Hispanic black, non-Hispanic black, Asian/Pacific Islander) and age (continuous) at the date of serum collection for serological testing in this study.

To address our primary hypothesis, we examined the association between cumulative exposure to infectious agents and AIDS-NHL risk. This exposure was modeled as a continuous variable and defined as the number of pathogens found to be seropositive based on a predefined number of antigens testing positive, as well as a categorical variable (seropositive for 10–18 pathogens versus ≤9 pathogens). These categories were determined by the median number of seropositive pathogens in the control group (10 pathogens) and not by a *prior* biological rationale. Secondarily, we also examined the association between AIDS-NHL risk and seropositivity to each of the 18 pathogens individually (seropositive versus seronegative). We also examined quartiles of antibody levels to each antigen of the two herpesviruses that have been etiologically linked to AIDS-NHL (KSHV and EBV), among those participants who were seropositive for that antigen, using logistic regression models adjusting for the matching factors as covariates in the model. Quartiles of antibody levels to TSPyV VP1 antigen were also examined due to recent data suggesting influence on lymphoma pathogenesis [75]. Quartiles for antibody levels were determined by the distribution within the control group, and are presented as $<25^{th}$, 25^{th}-75^{th}, and $>75^{th}$ percentile for comparability with a prior study [76]. In addition, we examined patterns of AIDS-NHL risk associated with EBV antibody levels according to the time interval (or lead-time) between serum sample collection and AIDS-NHL diagnosis (<4 years or ≥4 years). The categories for lead-time were selected according to the natural distribution of the data and to ensure an approximately equal number of participants in each category. Due to the exploratory and hypothesis generating nature of these secondary aims, we did not correct for multiple-hypothesis testing.

Correlation matrix for all infections.

We have run a correlation matrix for all infections measured in our study (Supplementary Table S2). Bonferroni correction was applied for multiple comparisons. Significant positive correlation was found between seropositivity to HBV and HSV2, and HBV and KSHV, respectively; as well as between seropositivity to HSV2 and KSHV and HSV2 and Chlamydia trachomatis.

RESULTS

Study population.

Cases and controls were similar in their distributions by recruitment year, antiretroviral drug therapy, and CD4+ T-cell count, as expected based on the matching criteria (Table 1). The majority of cases and controls were enrolled into the MACS in the initial recruitment wave (1984–1986, 84.6% for each group), were HAART naïve (94.5% for each group) and had >400 CD4+ T-cells/mm^3 (46.2% of cases and 41.3% of controls, respectively). The majority of cases and controls were non-Hispanic white (70.9% and 79.9% respectively). Cases tended to be slightly older than controls; 35.2% of cases were 40 years or older, compared to 30.7% of controls.

Among the cases, the mean time from blood draw to NHL diagnosis was 3.9 years; ranging from 1 month to 12 years (standard deviation 1.6 years). The majority of cases were systemic lymphomas (69.8%), among which DLBCL was the most common subtype

(49.6%). For 82.4% of cases, AIDS-NHL was the first primary cancer. Kaposi sarcoma preceded AIDS-NHL in 32 out of the 35 cases where AIDS-NHL was a second primary cancer (Table 1).

Cumulative exposure to infectious agents.

Supplementary Table S1 lists the names of 18 pathogens and 38 antigens tested in this study. Cumulative exposure to infectious agents (defined as the number of pathogens found to be seropositive) was not associated with AIDS-NHL risk when examined as a continuous variable (OR 1.01, 95% CI 0.91–1.12) (Table 2). Seropositivity for a higher number of pathogens (10–18 versus ≤9), was not significantly associated with an increased AIDS-NHL risk (OR 1.35, 95% CI 0.78 – 2.32) (Table 2).

Individual pathogen seropositivity.

Seropositivity to trichodysplasia spinulosa polyomavirus (TSPyV) was significantly associated with AIDS-NHL (OR 1.62; 95% CI 1.02–2.57, Table 3). No other associations were observed regarding seropositivity of remaining 17 pathogens tested. Interestingly, when HCV and HBV were examined together, there was a suggestion of an increased risk of AIDS-NHL associated with seropositivity for both viruses compared to seronegativity for both (OR=1.51, 95% CI=0.63–3.61).

TSPyV, EBV- and KSHV-specific antigens.

Among 199 cases, 151 (76%) were defined as TSPyV seropositive compared to 134 (67%) of controls (p=0.037). Though seropositivity to TSPyV was significantly associated with AIDS-NHL risk (Table 3), we did not observe any significant associations between TSPyV antibody levels and AIDS-NHL risk (Table 4).

Seroprevalence of the four specific EBV antigens measured (VCA p18, EA-D, ZEBRA, and EBNA-1), was similar between cases and controls and ranged from 81–100% among cases and 86–100% among controls (data not shown). Among the EBV VCA p18 seropositives, high antibody levels (levels >75th percentile) were associated with a 2.6-fold increase in AIDS-NHL risk when measured within four years prior AIDS-NHL diagnosis (OR 2.59; 95% CI 1.17 – 5.74, Table 4). In contrast, EBV anti-ZEBRA and EBV anti-EBNA-1 antibody levels had significant inverse associations with AIDS-NHL risk, with 1.6 to 2.1-fold decreased risks associated with the 25^{th}-75^{th}, and $>75^{th}$ percentile categories, respectively, compared with those with levels in the $<25^{th}$ percentile category (OR 0.47; 95% CI 0.26 – 0.85 and OR 0.57; 95% CI 0.35 – 0.93, Table 4).

Presence of antibodies to either LANA or K8.1 antigen was required to define the subject as KSHV seropositive. There was a non-significant dose-response between anti-LANA antibody levels and increased AIDS-NHL risk; high KSHV anti-LANA antibody levels ($>75^{th}$ percentile) was associated with a non-significant 1.9-fold increased risk for AIDS-NHL overall (OR 1.9; 95% CI 0.87 – 4.20, Table 4). Higher anti-K8.1 antibody levels also appeared to be modestly, but non-significantly associated with increased AIDS-NHL risk.

DISCUSSION

To explore the impact of common infections to the development of AIDS-NHL, we utilized multiplex serology approach and measured antibodies to 18 different pathogens commonly found at higher frequencies in HIV-infected compared to the non-HIV-infected individuals. Using sera collected prior to AIDS-NHL diagnosis, we found that cumulative exposure to pathogens we measured for was not associated with AIDS-NHL risk. However, novel observations include findings on seropositivity to TSPyV, and high antibody levels of EBV anti-VCA p18 antibodies, to be significantly associated with increased AIDS-NHL risk, whereas high levels of EBV anti-EBNA-1 and anti-ZEBRA antibodies were significantly associated with decreased AIDS-NHL risk.

Association of TSPyV with AIDS-NHL lymphoma is novel. TSPyV is a polyomavirus discovered in skin lesions of immunosuppressed patients which causes a rare skin disease trichodysplasia spinulosa [77,78]. In contrast to other polyomaviruses, TSPyV does not seem to be a part of the skin microbiome in healthy people [55], and Wieland and colleagues reported that TSPyV DNA was more frequently found on the skin of HIV-infected compared to non-HIV-infected men (3.8% vs. 0.8%) [55]. Indeed, when we stratified AIDS-NHL in our study into systemic and CNS lymphomas, we observed that the increased AIDS-NHL risk was restricted to systemic lymphomas (OR 2.03, 95% CI 1.17–3.53) and not to CNS lymphomas (OR 0.77, 95% CI 0.29–2.04). However, B-cell AIDS-NHL located in the skin are rare [79–81], and in our study only 3% (5/151) of TSPyV seropositive cases, and 2% (1/48) of TSPyV seronegative cases had skin-associated AIDS-NHL. Using the same multiplex serology assay for polyomaviruses, Teras and colleagues found no significant association between TSPyV seropositivity and NHL in immunocompetent people [82].

The observed associations between EBV antigens and AIDS-NHL risk may provide insight into pathogenic effects of EBV. EBV is a herpesvirus that causes lifelong infection and undergoes cycles of viral reactivation [83,84]. We found high levels of EBV anti-VCA p18 antibodies to be associated with increased AIDS-NHL risk, but only when measured closer to AIDS-NHL diagnosis date (<4 years). Detection of high EBV anti-VCA p18 IgG has been associated with high EBV loads in HIV carriers [85,86], and is thought to reflect an active EBV infection (loss of control of EBV infection) or EBV viremia [87]. Indeed, the loss of immunoregulatory control of EBV-infected B-cells, resulting from an impaired T-cell function, is one of the two major mechanisms underlying genesis of AIDS-NHL [22,31,88]. Modest positive associations of EBV VCA p18 and increased NHL risk were also found in immunocompetent people [76].

IgG antibodies to another EBV antigen, EBV EBNA-1, also persist throughout the lifetime among EBV-infected individuals. In contrast to anti-VCA p18, anti-EBNA-1 IgG antibodies are not present during the acute phase of EBV infection but develop in a later course of the infection [89]. EBNA-1, the EBV nuclear antigen, contains critical epitopes which can elicit cytotoxic T lymphocyte (CTL) responses to EBV infection, crucial for infection control [90,91]. In contrast to EBV VCA p18 findings, we found that high levels of anti-EBNA-1 IgG were associated with decreased AIDS-NHL risk, with associations being stronger when anti-EBNA-1 antibodies were detected >4 years prior diagnosis. We also observed an inverse

association between higher EBV anti-ZEBRA antibody levels and AIDS-NHL risk. The ZEBRA protein is one of the early encoded EBV proteins which activates a switch from the latent to the lytic viral gene expression [92,93]. We hypothesize that the observed inverse associations represent consumption of anti-EBNA-1 and anti-ZEBRA antibodies required to counteract chronic EBV viral infection preceding AIDS-NHL, possibly through antibody-dependent cell-mediated cytotoxicity [94]. Indeed, decreased anti-EBNA-1 antibody levels were shown to be associated with low CTL responses in children with chronic EBV infection, and in multiple diseases [95–98].

Our data on significant inverse association between high levels of antibodies to EBV ZEBRA and AIDS-NHL risk stand in contrast to increased NHL risk with high EBV ZEBRA antibodies observed in recent Western and Asian cohorts [75,76], respectively. These different findings might be reflective of different biology between NHL in immunosuppressed versus immunocompetent populations. Indeed, the observed positive association with EBV ZEBRA and EA_D in prior studies was specific for chronic lymphocytic leukemia/small lymphocytic (CLL/SLL) and follicular lymphoma (FL) NHL subtypes, which represented less than 1% of cases in our study [76].

Although the associations were not significant, there was a suggestive association of high levels of KSHV anti-LANA and anti-K8.1 antibodies and AIDS-NHL risk. KSHV is a causative agent of Kaposi sarcoma (KS) [34,99,100], and KS and AIDS-NHL represent the two most commonly occurring cancers among HIV-infected people [7]. KSHV is also the main cause of Primary Effusion Lymphoma (PEL) and Castleman's disease (CD), two rare AIDS-NHL subtypes [34,101]. The active role of KSHV has also been proposed in the immunoblastic variant of DLBCL [30,102–104]. We were unfortunately unable to define the DLBCL in our cohort further as immunoblastic, centroblastic or anaplastic [105] and therefore we could not confirm if it were the immunoblastic DLBCL variant that were KSHV seropositive. LANA, a latency-associated nuclear antigen, is one of the few KSHV encoded proteins that are highly expressed in latently infected tumor cells and acts as a regulator of viral transcription [106,107]. Its direct role in oncogenesis can be linked to binding and inactivation of the two major tumor suppressor proteins; p53 and pRb, respectively [108,109]. K8.1 glycoprotein is a structural component of KSHV expressed only during viral replication; therefore, it does seem plausible that the presence of KSHV K8.1 antibodies, or high levels of these, could indicate individuals who are at a greater risk for development of KSHV-associated malignancies [15,33,49,102].

NHL are a heterogeneous group of cancers both in general population, although less so in the setting of HIV. The two most common AIDS-NHL subtypes are DLBCL and BL. Also in our cohort DLBCL represented 69/139 (50%) and BL 23/139 (16%) of the systemic AIDS-NHL cases. Exploratory analysis in our cohort found that when these case groups were compared to one another, that there were not significant differences in antigen exposure. In addition, a fraction of AIDS-NHL in our study were second primary tumors (35/199, 18%). A subgroup analysis restricted to the 164 AIDS-NHL as a first primary cancer only, showed no significant differences in pathogen seropositivity or antibody levels to specific antigens compared to all AIDS-NHL.

In HIV infection, chronic antigenic stimulation (as in cases with multiple infections), and lack of CD4+ T-cell help, can lead to T-cell exhaustion, i.e. disruption of memory T-cell function and defects in memory T-cell responses necessary to combat and eliminate infectious agents [110–112]. Exhausted CD8+ T-cells exhibit a loss of cytotoxic function [113] and decreased mitogen-induced proliferation [114]. But, importantly, virus-specific CD8+ T-cell response can be restored, either through a period of rest from antigenic stimulation or through inhibition of the tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) apoptotic pathway. Also, antiretroviral therapy helps restore virus-specific CD8+ T cells [115,116]. Thus HAART in combination with strategies to reduce antigenic stimulation may help to reduce risk of AIDS-NHL. Indeed, association of EBV reactivation and T-cell exhaustion has been demonstrated in several diseases [98,117]. Further studies are required to investigate if reactivation of EBV or KSHV is associated with a T-cell exhaustion profile (upregulation of checkpoint inhibitors such PD-1, LAG-3, Tim-3, and CTLA-4 on T-cells), and AIDS-NHL risk.

Our study has few limitations. One limitation is the possibility that assessment of antibodies to different pathogens in HIV-infected people could be complicated by HIV-associated premature exhaustion of B-cells leading to impaired antibody responses [118–121]. Such impairment of serologic memory confers additional risk for HIV related opportunistic infections and mortality. Although premature exhaustion of immune cells can be reversed by antiretroviral therapy [115,116], a minority of cases and controls in out cohort received HAART. Another potential limitation is that our study consisted largely of white men who have sex with men, potentially limiting the generalizability of study findings. Also, 42/199 (21%) of the AIDS-NHL cases in our cohort were pathologically classified as “NHL not otherwise specified (NOS)”, making it difficult to evaluate NHL subtype-specific associations with seropositivity to certain pathogens or their antigens.

To our knowledge, this is the first comprehensive examination of seropositivity to multiple pathogens, including 14 different viruses, three bacteria, and a protozoon, in an attempt to better define cumulative pathogen exposures as well as individual pathogen/antigen associations with AIDS-NHL risk. Sensitive serological assays for detection of antibodies to infections can be a powerful tool for identification of cancer biomarkers [122]. In addition to the prior reports demonstrating that AIDS-NHL development is preceded by high serum levels of several inflammatory cytokines and chemokines indicative of B-cell hyperactivation [16,20,123], as well as microbial translocation [124], our results contribute data on association of well-known (KSHV and EBV) and potentially novel lymphomagenic agents (TSPyV) with AIDS-NHL risk. Therefore, a possible strategy to reduce underlying immune activation in HIV-infected persons as a strategy to reduce AIDS-NHL risk, may involve a multi-pronged approach including earlier access to HAART, use of anti-inflammatory agents to dampen immune activation, as well as treatment of co-infections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

We thank Larry Magpantay, Ute Koch and Claudia Brandel for excellent technical assistance.

This study was supported, in part, by a supplement to U01-AI-035040, by R01-CA-168482, and by the Pendleton Charitable Trust and the McCarthy Family Foundation.

Data in this manuscript were collected by the Multicenter AIDS Cohort Study (MACS). MACS (Principal Investigators): Johns Hopkins University Bloomberg School of Public Health (Joseph Margolick, Todd Brown), U01-AI35042; Northwestern University (Steven Wolinsky), U01-AI35039; University of California, Los Angeles (Roger Detels, Otoniel Martinez-Maza, Otto Yang), U01-AI35040; University of Pittsburgh (Charles Rinaldo, Lawrence Kingsley, Jeremy Martinson), U01-AI35041; the Center for Analysis and Management of MACS, Johns Hopkins University Bloomberg School of Public Health (Lisa Jacobson, Gypsyamber D'Souza), UM1-AI35043. The MACS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional co-funding from the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH). Targeted supplemental funding for specific projects was also provided by the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute on Deafness and Communication Disorders (NIDCD). MACS data collection is also supported by UL1-TR001079 (JHU ICTR) from the National Center for Advancing Translational Sciences (NCATS) a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH), Johns Hopkins ICTR, or NCATS. The MACS website is located at http://aidscohortstudy.org/.

Cancer incidence data were provided by the following state agencies: 1) Maryland Cancer Registry, Center for Cancer Prevention and Control, Department of Health and Mental Hygiene, Baltimore, MD 21201; 2) Illinois Department of Public Health, Illinois State Cancer Registry; 3) Bureau of Health Statistics & Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania; 4) Ohio Cancer Incidence Surveillance System (OCISS), Ohio Department of Health (ODH), a cancer registry partially supported in the National Program of Cancer Registries at the Centers for Disease Control and Prevention (CDC) through Cooperative Agreement # 5U58DP000795-05; and 5) California Department of Public Health pursuant to California Health and Safety Code Section 103885; CDC's National Program of Cancer Registries, under cooperative agreement 5NU58DP003862-04/DP003862; the National Cancer Institute's Surveillance, Epidemiology and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute. We acknowledge the State of Maryland, the Maryland Cigarette Restitution Fund, and the National Program of Cancer Registries of the CDC for the funds that support the collection and availability of the cancer registry data. The analyses, findings, interpretations and conclusions of this report are those of the authors. No endorsement by any of the states providing data, the National Cancer Institute, the CDC or their Contractors and Subcontractors is intended nor should be inferred.

REFERENCES

1. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer 2008;123(1):187–194. [PubMed: 18435450]
2. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 2007;370(9581):59–67. [PubMed: 17617273]
3. Hessol NA, Seaberg EC, Preston-Martin S, et al. Cancer risk among participants in the women's interagency HIV study. J Acquir Immune Defic Syndr 2004;36(4):978–985. [PubMed: 15220706]
4. Biggar RJ, Curtis RE, Cote TR, Rabkin CS, Melbye M. Risk of other cancers following Kaposi's sarcoma: relation to acquired immunodeficiency syndrome. Am J Epidemiol 1994;139(4):362–368. [PubMed: 8109570]
5. Rabkin CS. Epidemiology of AIDS-related malignancies. Curr Opin Oncol 1994;6(5):492–496. [PubMed: 7827152]
6. Cote TR, Biggar RJ, Rosenberg PS, et al. Non-Hodgkin's lymphoma among people with AIDS: incidence, presentation and public health burden. AIDS/Cancer Study Group. Int J Cancer 1997;73(5):645–650. [PubMed: 9398040]
7. Seaberg EC, Wiley D, Martinez-Maza O, et al. Cancer incidence in the multicenter AIDS Cohort Study before and during the HAART era: 1984 to 2007. Cancer 2010;116(23):5507–5516. [PubMed: 20672354]

8. Simard EP, Pfeiffer RM, Engels EA. Spectrum of cancer risk late after AIDS onset in the United States. Arch Intern Med 2010;170(15):1337–1345. [PubMed: 20696958]
9. Gibson TM, Morton LM, Shiels MS, Clarke CA, Engels EA. Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study. AIDS 2014;28(15):2313–2318. [PubMed: 25111081]
10. Shiels MS, Engels EA. Evolving epidemiology of HIV-associated malignancies. Curr Opin HIV AIDS 2017;12(1):6–11. [PubMed: 27749369]
11. Biggar RJ. AIDS-related cancers in the era of highly active antiretroviral therapy. Oncology (Williston Park) 2001;15(4):439–448; discussion 448–439. [PubMed: 11346932]
12. Bonnet F, Lewden C, May T, et al. Malignancy-related causes of death in human immunodeficiency virus-infected patients in the era of highly active antiretroviral therapy. Cancer 2004;101(2):317–324. [PubMed: 15241829]
13. Bonnet F, Balestre E, Thiebaut R, et al. Factors associated with the occurrence of AIDS-related non-Hodgkin lymphoma in the era of highly active antiretroviral therapy: Aquitaine Cohort, France. Clin Infect Dis 2006;42(3):411–417. [PubMed: 16392091]
14. Lewden C, Salmon D, Morlat P, et al. Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. Int J Epidemiol 2005;34(1):121–130. [PubMed: 15561752]
15. Cesarman E Pathology of lymphoma in HIV. Curr Opin Oncol 2013;25(5):487–494. [PubMed: 23942293]
16. Martinez-Maza O, Breen EC. B-cell activation and lymphoma in patients with HIV. Curr Opin Oncol 2002;14(5):528–532. [PubMed: 12192272]
17. Broder S, Karp JE. The expanding challenge of HIV-associated malignancies. CA Cancer J Clin 1992;42(2):69–73. [PubMed: 1311619]
18. Gaidano G, Carbone A, Dalla-Favera R. Genetic basis of acquired immunodeficiency syndrome-related lymphomagenesis. J Natl Cancer Inst Monogr 1998(23):95–100. [PubMed: 9709310]
19. Carbone A Emerging pathways in the development of AIDS-related lymphomas. Lancet Oncol 2003;4(1):22–29. [PubMed: 12517536]
20. Breen EC, Hussain SK, Magpantay L, et al. B-cell stimulatory cytokines and markers of immune activation are elevated several years prior to the diagnosis of systemic AIDS-associated non-Hodgkin B-cell lymphoma. Cancer Epidemiol Biomarkers Prev 2011;20(7):1303–1314. [PubMed: 21527584]
21. Epeldegui M, Thapa DR, De la Cruz J, Kitchen S, Zack JA, Martinez-Maza O. CD40 ligand (CD154) incorporated into HIV virions induces activation-induced cytidine deaminase (AID) expression in human B lymphocytes. PLoS One 2010;5(7):e11448. [PubMed: 20625427]
22. Epeldegui M, Vendrame E, Martinez-Maza O. HIV-associated immune dysfunction and viral infection: role in the pathogenesis of AIDS-related lymphoma. Immunol Res 2010;48(1–3):72–83. [PubMed: 20717742]
23. Lane HC, Masur H, Edgar LC, Whalen G, Rook AH, Fauci AS. Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. N Engl J Med 1983;309(8):453–458. [PubMed: 6224088]
24. Martinez-Maza O, Moody DJ, Rezai AR, et al. Increased spontaneous immunoglobulin secretion associated with cyclophosphamide-induced immune suppression. J Clin Immunol 1987;7(2):107–113. [PubMed: 3571433]
25. Breen EC, Rezai AR, Nakajima K, et al. Infection with HIV is associated with elevated IL-6 levels and production. J Immunol 1990;144(2):480–484. [PubMed: 2295799]
26. Coelho L, Veloso VG, Grinsztejn B, Luz PM. Trends in overall opportunistic illnesses, Pneumocystis carinii pneumonia, cerebral toxoplasmosis and Mycobacterium avium complex incidence rates over the 30 years of the HIV epidemic: a systematic review. Braz J Infect Dis 2014;18(2):196–210. [PubMed: 24275372]
27. Kovacs A, Leaf HL, Simberkoff MS. Bacterial infections. Med Clin North Am 1997;81(2):319–343. [PubMed: 9093231]

28. Bonnet F, Lewden C, May T, et al. Opportunistic infections as causes of death in HIV-infected patients in the HAART era in France. Scand J Infect Dis 2005;37(6–7):482–487. [PubMed: 16089023]
29. Louie JK, Hsu LC, Osmond DH, Katz MH, Schwarcz SK. Trends in causes of death among persons with acquired immunodeficiency syndrome in the era of highly active antiretroviral therapy, San Francisco, 1994–1998. J Infect Dis 2002;186(7):1023–1027. [PubMed: 12232845]
30. Deloose ST, Smit LA, Pals FT, Kersten MJ, van Noesel CJ, Pals ST. High incidence of Kaposi sarcoma-associated herpesvirus infection in HIV-related solid immunoblastic/plasmablastic diffuse large B-cell lymphoma. Leukemia 2005;19(5):851–855. [PubMed: 15744337]
31. Epeldegui M, Widney DP, Martinez-Maza O. Pathogenesis of AIDS lymphoma: role of oncogenic viruses and B cell activation-associated molecular lesions. Curr Opin Oncol 2006;18(5):444–448. [PubMed: 16894291]
32. Engels EA, Pfeiffer RM, Landgren O, Moore RD. Immunologic and virologic predictors of AIDS-related non-hodgkin lymphoma in the highly active antiretroviral therapy era. J Acquir Immune Defic Syndr 2010;54(1):78–84. [PubMed: 20418723]
33. Engels EA. Infectious agents as causes of non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 2007;16(3):401–404. [PubMed: 17337646]
34. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. N Engl J Med 1995;332(18):1186–1191. [PubMed: 7700311]
35. Wang Q, De Luca A, Smith C, et al. Chronic Hepatitis B and C Virus Infection and Risk for Non-Hodgkin Lymphoma in HIV-Infected Patients: A Cohort Study. Ann Intern Med 2017;166(1):9–17. [PubMed: 27750294]
36. Kim JH, Bang YJ, Park BJ, et al. Hepatitis B virus infection and B-cell non-Hodgkin's lymphoma in a hepatitis B endemic area: a case-control study. Jpn J Cancer Res 2002;93(5):471–477. [PubMed: 12036441]
37. Engels EA, Cho ER, Jee SH. Hepatitis B virus infection and risk of non-Hodgkin lymphoma in South Korea: a cohort study. Lancet Oncol 2010;11(9):827–834. [PubMed: 20688564]
38. Ulcickas Yood M, Quesenberry CP, Jr., Guo D, et al. Incidence of non-Hodgkin's lymphoma among individuals with chronic hepatitis B virus infection. Hepatology 2007;46(1):107–112. [PubMed: 17526021]
39. Peveling-Oberhag J, Arcaini L, Hansmann ML, Zeuzem S. Hepatitis C-associated B-cell non-Hodgkin lymphomas. Epidemiology, molecular signature and clinical management. J Hepatol 2013;59(1):169–177. [PubMed: 23542089]
40. Khaled H, Abu-Taleb F, Haggag R. Hepatitis C virus and non-Hodgkin's lymphomas: A minireview. J Adv Res 2017;8(2):131–137. [PubMed: 28149648]
41. de Sanjose S, Benavente Y, Vajdic CM, et al. Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. Clin Gastroenterol Hepatol 2008;6(4):451–458. [PubMed: 18387498]
42. Morgner A, Miehlke S, Fischbach W, et al. Complete remission of primary high-grade B-cell gastric lymphoma after cure of Helicobacter pylori infection. J Clin Oncol 2001;19(7):2041–2048. [PubMed: 11283137]
43. Morgner A, Bayerdorffer E, Neubauer A, Stolte M. Helicobacter pylori associated gastric B cell MALT lymphoma: predictive factors for regression. Gut 2001;48(3):290–292. [PubMed: 11171813]
44. Schreuder MI, van den Brand M, Hebeda KM, Groenen P, van Krieken JH, Scheijen B. Novel developments in the pathogenesis and diagnosis of extranodal marginal zone lymphoma. J Hematop 2017;10(3–4):91–107. [PubMed: 29225710]
45. Park JB, Koo JS. Helicobacter pylori infection in gastric mucosa-associated lymphoid tissue lymphoma. World J Gastroenterol 2014;20(11):2751–2759. [PubMed: 24659867]
46. Wotherspoon AC. Gastric MALT lymphoma and Helicobacter pylori. Yale J Biol Med 1996;69(1):61–68. [PubMed: 9041690]
47. Chang PY, Detels R, Martinez-Maza O, et al. Comment on "characteristics of B-cell lymphomas in HIV/HCV-coinfected patients during the combined antiretroviral therapy era: an ANRS CO16

LYMPHOVIR cohort study". J Acquir Immune Defic Syndr 2014;67(2):e84–86. [PubMed: 24820108]

48. Marcucci F, Spada E, Mele A, Caserta CA, Pulsoni A. The association of hepatitis B virus infection with B-cell non-Hodgkin lymphoma - a review. Am J Blood Res 2012;2(1):18–28. [PubMed: 22432084]
49. Cesarman E, Knowles DM. The role of Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) in lymphoproliferative diseases. Semin Cancer Biol 1999;9(3):165–174. [PubMed: 10343068]
50. Deshmukh AA, Chiao EY, Cantor SB, et al. Management of precancerous anal intraepithelial lesions in human immunodeficiency virus-positive men who have sex with men: Clinical effectiveness and cost-effectiveness. Cancer 2017;123(23):4709–4719. [PubMed: 28950043]
51. D'Souza G, Wiley DJ, Li X, et al. Incidence and epidemiology of anal cancer in the multicenter AIDS cohort study. J Acquir Immune Defic Syndr 2008;48(4):491–499. [PubMed: 18614927]
52. Wiedinger K, Bitsaktsis C, Chang S. Reactivation of human polyomaviruses in immunocompromised states. J Neurovirol 2014;20(1):1–8. [PubMed: 24481784]
53. Tada H, Rappaport J, Lashgari M, Amini S, Wong-Staal F, Khalili K. Trans-activation of the JC virus late promoter by the tat protein of type 1 human immunodeficiency virus in glial cells. Proc Natl Acad Sci U S A 1990;87(9):3479–3483. [PubMed: 2159152]
54. Pulitzer MP, Amin BD, Busam KJ. Merkel cell carcinoma: review. Adv Anat Pathol 2009;16(3): 135–144. [PubMed: 19395876]
55. Wieland U, Silling S, Hellmich M, Potthoff A, Pfister H, Kreuter A. Human polyomaviruses 6, 7, 9, 10 and Trichodysplasia spinulosa-associated polyomavirus in HIV-infected men. J Gen Virol 2014;95(Pt 4):928–932. [PubMed: 24421113]
56. Munawwar A, Singh S. Human Herpesviruses as Copathogens of HIV Infection, Their Role in HIV Transmission, and Disease Progression. J Lab Physicians 2016;8(1):5–18. [PubMed: 27013807]
57. Dang T, Jaton-Ogay K, Flepp M, et al. High prevalence of anorectal chlamydial infection in HIV-infected men who have sex with men in Switzerland. Clin Infect Dis 2009;49(10):1532–1535. [PubMed: 19848599]
58. Winstanley P Drug treatment of toxoplasmic encephalitis in acquired immunodeficiency syndrome. Postgrad Med J 1995;71(837):404–408. [PubMed: 7567731]
59. Weiss H Epidemiology of herpes simplex virus type 2 infection in the developing world. Herpes 2004;11 Suppl 1:24A–35A.
60. Griffiths PD. CMV as a cofactor enhancing progression of AIDS. J Clin Virol 2006;35(4):489–492. [PubMed: 16413825]
61. Detels R, Jacobson L, Margolick J, et al. The multicenter AIDS Cohort Study, 1983 to. Public Health 2012;126(3):196–198. [PubMed: 22206985]
62. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR, Jr. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. Am J Epidemiol 1987;126(2):310–318. [PubMed: 3300281]
63. Giorgi JV, Cheng HL, Margolick JB, et al. Quality control in the flow cytometric measurement of T-lymphocyte subsets: the multicenter AIDS cohort study experience. The Multicenter AIDS Cohort Study Group. Clin Immunol Immunopathol 1990;55(2):173–186. [PubMed: 1969782]
64. DHHS/Henry J. Kaiser Family Foundation Panel on Clinical Practices for the Treatment of HIV infection [Accessed November 3 R. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. http://aidsinfonihgov/contentfiles/AdultandAdolescentGLpdf 2008.
65. Dondog B, Schnitzler P, Michael KM, et al. Hepatitis C Virus Seroprevalence in Mongolian Women Assessed by a Novel Multiplex Antibody Detection Assay. Cancer Epidemiol Biomarkers Prev 2015;24(9):1360–1365. [PubMed: 26169147]
66. Michel A, Waterboer T, Kist M, Pawlita M. Helicobacter pylori multiplex serology. Helicobacter 2009;14(6):525–535. [PubMed: 19889070]
67. Waterboer T, Neale R, Michael KM, et al. Antibody responses to 26 skin human papillomavirus types in the Netherlands, Italy and Australia. J Gen Virol 2009;90(Pt 8):1986–1998. [PubMed: 19386782]

68. Sehr P, Muller M, Hopfl R, Widschwendter A, Pawlita M. HPV antibody detection by ELISA with capsid protein L1 fused to glutathione S-transferase. J Virol Methods 2002;106(1):61–70. [PubMed: 12367730]
69. Waterboer T, Sehr P, Michael KM, et al. Multiplex human papillomavirus serology based on in situ-purified glutathione s-transferase fusion proteins. Clin Chem 2005;51(10):1845–1853. [PubMed: 16099939]
70. Waterboer T, Sehr P, Pawlita M. Suppression of non-specific binding in serological Luminex assays. J Immunol Methods 2006;309(1–2):200–204. [PubMed: 16406059]
71. Karagas MR, Nelson HH, Sehr P, et al. Human papillomavirus infection and incidence of squamous cell and basal cell carcinomas of the skin. J Natl Cancer Inst 2006;98(6):389–395. [PubMed: 16537831]
72. Michael KM, Waterboer T, Sehr P, et al. Seroprevalence of 34 human papillomavirus types in the German general population. PLoS Pathog 2008;4(6):e1000091. [PubMed: 18566657]
73. Antonsson A, Green AC, Mallitt KA, et al. Prevalence and stability of antibodies to the BK and JC polyomaviruses: a long-term longitudinal study of Australians. J Gen Virol 2010;91(Pt 7):1849–1853. [PubMed: 20219899]
74. Carter JJ, Paulson KG, Wipf GC, et al. Association of Merkel cell polyomavirus-specific antibodies with Merkel cell carcinoma. J Natl Cancer Inst 2009;101(21):1510–1522. [PubMed: 19776382]
75. Bassig BA, Willhauck-Fleckenstein M, Shu XO, et al. Serologic markers of viral infection and risk of non-Hodgkin lymphoma: A pooled study of three prospective cohorts in China and Singapore. Int J Cancer 2018;143(3):570–579. [PubMed: 29574937]
76. Teras LR, Rollison DE, Pawlita M, et al. Epstein-Barr virus and risk of non-Hodgkin lymphoma in the cancer prevention study-II and a meta-analysis of serologic studies. Int J Cancer 2015;136(1):108–116. [PubMed: 24831943]
77. van der Meijden E, Janssens RW, Lauber C, Bouwes Bavinck JN, Gorbalenya AE, Feltkamp MC. Discovery of a new human polyomavirus associated with trichodysplasia spinulosa in an immunocompromized patient. PLoS Pathog 2010;6(7):e1001024. [PubMed: 20686659]
78. Kazem S, van der Meijden E, Feltkamp MC. The trichodysplasia spinulosa-associated polyomavirus: virological background and clinical implications. APMIS 2013;121(8):770–782. [PubMed: 23593936]
79. Burg G, Kempf W, Cozzio A, et al. WHO/EORTC classification of cutaneous lymphomas 2005: histological and molecular aspects. J Cutan Pathol 2005;32(10):647–674. [PubMed: 16293178]
80. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105(10):3768–3785. [PubMed: 15692063]
81. Corti M, Carolis LD, Solari R, et al. Non Hodgkin's lymphoma with cutaneous involvement in AIDS patients: report of five cases and review of the literature. Braz J Infect Dis 2010;14(1):81–85. [PubMed: 20428660]
82. Teras LR, Rollison DE, Pawlita M, et al. Prediagnostic circulating polyomavirus antibody levels and risk of non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev 2015;24(2):477–480. [PubMed: 25488906]
83. Kraus RJ, Mirocha SJ, Stephany HM, Puchalski JR, Mertz JE. Identification of a novel element involved in regulation of the lytic switch BZLF1 gene promoter of Epstein-Barr virus. J Virol 2001;75(2):867–877. [PubMed: 11134300]
84. Laichalk LL, Thorley-Lawson DA. Terminal differentiation into plasma cells initiates the replicative cycle of Epstein-Barr virus in vivo. J Virol 2005;79(2):1296–1307. [PubMed: 15613356]
85. Stevens SJ, Blank BS, Smits PH, Meenhorst PL, Middeldorp JM. High Epstein-Barr virus (EBV) DNA loads in HIV-infected patients: correlation with antiretroviral therapy and quantitative EBV serology. AIDS 2002;16(7):993–1001. [PubMed: 11953465]
86. Stevens SJ, Verschuuren EA, Verkuujlen SA, Van Den Brule AJ, Meijer CJ, Middeldorp JM. Role of Epstein-Barr virus DNA load monitoring in prevention and early detection of post-transplant lymphoproliferative disease. Leuk Lymphoma 2002;43(4):831–840. [PubMed: 12153173]

87. Gulley ML, Tang W. Laboratory assays for Epstein-Barr virus-related disease. J Mol Diagn 2008;10(4):279–292. [PubMed: 18556771]

88. Bibas M, Antinori A. EBV and HIV-Related Lymphoma. Mediterr J Hematol Infect Dis 2009;1(2):e2009032. [PubMed: 21416008]

89. Draborg AH, Jorgensen JM, Muller H, et al. Epstein-Barr virus early antigen diffuse (EBV-EA/D)-directed immunoglobulin A antibodies in systemic lupus erythematosus patients. Scand J Rheumatol 2012;41(4):280–289. [PubMed: 22646970]

90. Rickinson AB, Moss DJ. Human cytotoxic T lymphocyte responses to Epstein-Barr virus infection. Annu Rev Immunol 1997;15:405–431. [PubMed: 9143694]

91. Hislop AD, Taylor GS, Sauce D, Rickinson AB. Cellular responses to viral infection in humans: lessons from Epstein-Barr virus. Annu Rev Immunol 2007;25:587–617. [PubMed: 17378764]

92. Countryman J, Miller G. Activation of expression of latent Epstein-Barr herpesvirus after gene transfer with a small cloned subfragment of heterogeneous viral DNA. Proc Natl Acad Sci U S A 1985;82(12):4085–4089. [PubMed: 2987963]

93. Rooney CM, Rowe DT, Ragot T, Farrell PJ. The spliced BZLF1 gene of Epstein-Barr virus (EBV) transactivates an early EBV promoter and induces the virus productive cycle. J Virol 1989;63(7): 3109–3116. [PubMed: 2542618]

94. Iwatsuki K, Yamamoto T, Tsuji K, et al. A spectrum of clinical manifestations caused by host immune responses against Epstein-Barr virus infections. Acta Med Okayama 2004;58(4):169–180. [PubMed: 15551754]

95. Xing Y, Song HM, Wei M, Liu Y, Zhang YH, Gao L. Clinical significance of variations in levels of Epstein-Barr Virus (EBV) antigen and adaptive immune response during chronic active EBV infection in children. J Immunotoxicol 2013;10(4):387–392. [PubMed: 23418935]

96. Wakiguchi H, Fujieda M, Matsumoto K, Ohara Y, Wakiguchi A, Kurashige T. Defective immune response to Epstein-Barr virus in patients with acute lymphocytic leukemia. Acta Paediatr Jpn 1989;31(2):144–149. [PubMed: 2560606]

97. Savoldo B, Huls MH, Liu Z, et al. Autologous Epstein-Barr virus (EBV)-specific cytotoxic T cells for the treatment of persistent active EBV infection. Blood 2002;100(12):4059–4066. [PubMed: 12393655]

98. Pender MP, Csurhes PA, Burrows JM, Burrows SR. Defective T-cell control of Epstein-Barr virus infection in multiple sclerosis. Clin Transl Immunology 2017;6(1):e126. [PubMed: 28197337]

99. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 1994;266(5192):1865–1869. [PubMed: 7997879]

100. Cesarman E, Moore PS, Rao PH, Inghirami G, Knowles DM, Chang Y. In vitro establishment and characterization of two acquired immunodeficiency syndrome-related lymphoma cell lines (BC-1 and BC-2) containing Kaposi's sarcoma-associated herpesvirus-like (KSHV) DNA sequences. Blood 1995;86(7):2708–2714. [PubMed: 7670109]

101. Soulier J, Grollet L, Oksenhendler E, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood 1995;86(4):1276–1280. [PubMed: 7632932]

102. Engels EA, Rosenberg PS, Frisch M, Goedert JJ. Cancers associated with Kaposi's sarcoma (KS) in AIDS: a link between KS herpesvirus and immunoblastic lymphoma. Br J Cancer 2001;85(9): 1298–1303. [PubMed: 11720464]

103. Engels EA, Pittaluga S, Whitby D, et al. Immunoblastic lymphoma in persons with AIDS-associated Kaposi's sarcoma: a role for Kaposi's sarcoma-associated herpesvirus. Mod Pathol 2003;16(5):424–429. [PubMed: 12748248]

104. Chadburn A, Hyjek E, Mathew S, Cesarman E, Said J, Knowles DM. KSHV-positive solid lymphomas represent an extra-cavitary variant of primary effusion lymphoma. Am J Surg Pathol 2004;28(11):1401–1416. [PubMed: 15489644]

105. Harris NL, Stein H, Coupland SE, et al. New approaches to lymphoma diagnosis. Hematology Am Soc Hematol Educ Program 2001:194–220. [PubMed: 11722985]

106. Fukumoto H, Kanno T, Hasegawa H, Katano H. Pathology of Kaposi's Sarcoma-Associated Herpesvirus Infection. Front Microbiol 2011;2:175. [PubMed: 21904536]

107. Sun Q, Tsurimoto T, Juillard F, et al. Kaposi's sarcoma-associated herpesvirus LANA recruits the DNA polymerase clamp loader to mediate efficient replication and virus persistence. Proc Natl Acad Sci U S A 2014;111(32):11816–11821. [PubMed: 25071216]
108. Friborg J, Jr., Kong W, Hottiger MO, Nabel GJ. p53 inhibition by the LANA protein of KSHV protects against cell death. Nature 1999;402(6764):889–894. [PubMed: 10622254]
109. Radkov SA, Kellam P, Boshoff C. The latent nuclear antigen of Kaposi sarcoma-associated herpesvirus targets the retinoblastoma-E2F pathway and with the oncogene Hras transforms primary rat cells. Nat Med 2000;6(10):1121–1127. [PubMed: 11017143]
110. El-Far M, Halwani R, Said E, et al. T-cell exhaustion in HIV infection. Curr HIV/AIDS Rep 2008;5(1):13–19. [PubMed: 18417030]
111. Bucks CM, Norton JA, Boesteanu AC, Mueller YM, Katsikis PD. Chronic antigen stimulation alone is sufficient to drive CD8+ T cell exhaustion. J Immunol 2009;182(11):6697–6708. [PubMed: 19454664]
112. Khaitan A, Unutmaz D. Revisiting immune exhaustion during HIV infection. Curr HIV/AIDS Rep 2011;8(1):4–11. [PubMed: 21188556]
113. Wherry EJ, Blattman JN, Murali-Krishna K, van der Most R, Ahmed R. Viral persistence alters CD8 T-cell immunodominance and tissue distribution and results in distinct stages of functional impairment. J Virol 2003;77(8):4911–4927. [PubMed: 12663797]
114. Zajac AJ, Blattman JN, Murali-Krishna K, et al. Viral immune evasion due to persistence of activated T cells without effector function. J Exp Med 1998;188(12):2205–2213. [PubMed: 9858507]
115. Kostense S, Otto SA, Knol GJ, et al. Functional restoration of human immunodeficiency virus and Epstein-Barr virus-specific CD8(+) T cells during highly active antiretroviral therapy is associated with an increase in CD4(+) T cells. Eur J Immunol 2002;32(4):1080–1089. [PubMed: 11920575]
116. Wilson EM, Sereti I. Immune restoration after antiretroviral therapy: the pitfalls of hasty or incomplete repairs. Immunol Rev 2013;254(1):343–354. [PubMed: 23772630]
117. Loebel M, Strohschein K, Giannini C, et al. Deficient EBV-specific B- and T-cell response in patients with chronic fatigue syndrome. PLoS One 2014;9(1):e85387. [PubMed: 24454857]
118. Moir S, Ogwaro KM, Malaspina A, et al. Perturbations in B cell responsiveness to CD4+ T cell help in HIV-infected individuals. Proc Natl Acad Sci U S A 2003;100(10):6057–6062. [PubMed: 12730375]
119. Moir S, Ho J, Malaspina A, et al. Evidence for HIV-associated B cell exhaustion in a dysfunctional memory B cell compartment in HIV-infected viremic individuals. J Exp Med 2008;205(8):1797–1805. [PubMed: 18625747]
120. De Milito A B lymphocyte dysfunctions in HIV infection. Curr HIV Res 2004;2(1):11–21. [PubMed: 15053337]
121. Hu Z, Luo Z, Wan Z, et al. HIV-associated memory B cell perturbations. Vaccine 2015;33(22): 2524–2529. [PubMed: 25887082]
122. Beachler DC, Gellert LL, Jacobson LP, et al. Kaposi sarcoma-associated herpesvirus serum DNA and antibodies not associated with subsequent non-Hodgkin lymphoma risk. J Acquir Immune Defic Syndr 2011;56(2):188–192. [PubMed: 21116187]
123. Vendrame E, Hussain SK, Breen EC, et al. Serum levels of cytokines and biomarkers for inflammation and immune activation, and HIV-associated non-Hodgkin B-cell lymphoma risk. Cancer Epidemiol Biomarkers Prev 2014;23(2):343–349. [PubMed: 24220912]
124. Epeldegui M, Magpantay L, Guo Y, et al. A prospective study of serum microbial translocation biomarkers and risk of AIDS-related non-Hodgkin lymphoma. AIDS 2018.

Table 1.

Selected characteristics of the 199 AIDS-NHL cases and 199 matched HIV-infected controls from the Multicenter AIDS Cohort Study

	AIDS-NHL cases (N = 199)	HIV-infected controls (N = 199)
	N *(%)*	**N *(%)***
Recruitment Cohort		
1984–1985	168 *(84)*	168 *(84)*
1987–1991	24 *(12)*	24 *(12)*
2001+	7 *(4)*	7 *(4)*
Race		
White, non-Hispanic	161 *(81)*	159 *(80)*
Black, non-Hispanic	17 *(8)*	23 *(11)*
Hispanic	21 *(11)*	16 *(8)*
Asian or Pacific Islander	0 *(0)*	1 *(1)*
Age[1]		
< 30	28 *(14)*	31 *(15)*
30 – 39	83 *(42)*	93 *(47)*
40 – 49	70 *(35)*	61 *(31)*
≥ 50	18 *(9)*	14 *(7)*
CD4+ T-cells/mm3[1]		
< 200	44 *(22)*	40 *(20)*
200 – 399	63 *(32)*	57 *(29)*
≥400	92 *(46)*	102 *(51)*
Prior HAART exposure[1]		
No	188 *(95)*	188 *(95)*
Yes	11 *(5)*	11 *(5)*
Time from serum date until NHL diagnosis, years (mean ± SD)	3.9 ± 1.6	N/A
NHL Site / ICD-O-3 code[2]		
Systemic / all beside 71.0–71.9 and 72.0–72.9	139 *(70)*	
Central Nervous System / 71.0–71.9, 72.0–72.9	60 *(30)*	
NHL Subtype (systemic only) / ICD-O-3 code[3]		
Diffuse large B-cell lymphoma / 9680.3, 9684.3	69 *(50)*	
Burkitt Lymphoma / 9687.3	23 *(16)*	
Lymphoplasmacytic lymphoma / 9671.3	1 *(1)*	
Mature T-cell lymphoma / 9702.3	2 *(1)*	
Primary effusion lymphoma / 9678.3	1 *(1)*	

	AIDS-NHL cases (N = 199)	HIV-infected controls (N = 199)
Follicular lymphoma / 9691.3	1 *(1)*	
NHL, NOS / 9590.3, 9591.3	42 *(30)*	
Cancer diagnosis prior to NHL[4]		
NHL is first primary cancer	164 *(82)*	
NHL is second primary cancer	35 *(18)*	
Tumor EBV status		
Negative	28 *(14)*	
Positive	60 *(30)*	
Unknown	88 *(44)*	

Abbreviations: AIDS, Acquired Immunodeficiency Syndrome; NHL, non-Hodgkin lymphoma; SD, standard deviation; HAART, highly active antiretroviral therapy; EBV, Epstein-Barr virus

[1]The reference date for these variables is the collection date of a blood sample used for testing in this study

[2]ICD-O-3 topographical codes: http://codes.iarc.fr/topography

[3]ICD-O-3 morphological codes: http://codes.iarc.fr/codegroup/2, here for systemic NHLs only

[4]Kaposi sarcoma preceded AIDS-NHL in 32 out of the 35 cases where AIDS-NHL was a second primary cancer

Table 2.

Association between pathogen burden and AIDS-NHL risk

	AIDS-NHL cases	HIV-infected controls	OR	95% CI
	N *(%)*	N *(%)*		
Risk per seropositive antigen	199 *(100)*	199 *(100)*	1.01	0.91–1.12
Categories of seropositive pathogens				
≤ 9	36 *(18)*	44 *(22)*	1	
10 – 18	163 *(82)*	155 *(78)*	1.35	0.78–2.32

Table 3.

Associations between seropositivity for each of the 18 pathogens and subsequent AIDS-NHL risk in pre-diagnostic sera from 199 AIDS-NHL cases and 199 HIV-infected matched controls from the Multicenter AIDS Cohort Study

	AIDS-NHL cases N *(%)*	HIV-infected controls N *(%)*	OR	95% CI
Human papillomaviruses				
HPV16 L1 negative	158 *(79)*	165 *(83)*	1	
HPV16 L1 positive	41 *(21)*	34 *(17)*	1.33	0.75 – 2.37
Human polyomaviruses				
BKPyV VP1 negative	32 *(16)*	32 *(16)*	1	
BKPyV VP1 positive	167 *(84)*	167 *(84)*	1.10	0.61 – 2.01
JCPyV VP1 negative	145 *(73)*	140 *(70)*	1	
JCPyV VP1 positive	54 *(27)*	59 *(30)*	0.85	0.52 – 1.38
TSPyV VP1 negative	48 *(24)*	65 *(33)*	1	
TSPyV VP1 positive	151 *(76)*	134 *(67)*	**1.62**	**1.02 – 2.57**
MCPyV VP1 negative	64 *(32)*	71 *(36)*	1	
MCPyV VP1 positive	135 *(68)*	128 *(64)*	1.20	0.76 – 1.90
Human hepatitis viruses				
HBV negative	48 *(24)*	44 *(22)*	1	
HBV positive	151 *(76)*	155 *(78)*	1.00	0.60 – 1.65
HCV negative	174 *(88)*	181 *(91)*	1	
HCV positive	25 *(12)*	18 *(9)*	1.23	0.25 – 5.98
Human herpesviruses[1]				
HSV1 negative	47 *(24)*	53 *(27)*	1	
HSV1 positive	152 *(76)*	146 *(63)*	1.11	0.69 – 1.79
HSV2 negative	64 *(32)*	60 *(30)*	1	
HSV2 positive	135 *(68)*	139 *(70)*	0.81	0.51 – 1.27
EBV negative	0 *(0)*	1 *(1)*	1.0	
EBV positive	199 *(100)*	198 *(99)*	NE	
HCMV negative	0 *(0)*	1 *(1)*	1.0	
HCMV positive	199 *(100)*	198 *(99)*	NE	
HHV6 negative	96 *(48)*	80 *(40)*	1	
HHV6 positive	103 *(52)*	119 *(60)*	0.71	0.46 – 1.10
HHV7 negative	52 (26)	44 *(22)*	1	
HHV7 positive	147 *(74)*	155 *(78)*	0.76	0.47 – 1.24
KSHV negative	81 *(41)*	90 *(45)*	1	
KSHV positive	118 *(59)*	109 *(55)*	1.18	0.76 – 1.83
Bacterial infections				
H. pylori negative	165 *(83)*	166 *(83)*	1	
H. pylori positive	34 *(17)*	33 *(17)*	1.02	0.55 – 1.88
C. trachomatis negative	26 (13)	31 *(16)*	1	

	AIDS-NHL cases N *(%)*	HIV-infected controls N *(%)*	OR	95% CI
C. trachomatis positive	173 *(87)*	168 *(84)*	1.18	0.63 – 2.18
M. genitalium negative	113 *(57)*	105 *(53)*	1	
M. genitalium positive	86 *(43)*	94 *(47)*	0.80	0.52 – 1.22
Parasitic infections				
Toxoplasma gondii negative	182 *(91)*	185 *(93)*	1	
Toxoplasma gondii positive	17 *(9)*	14 *(7)*	1.22	0.55 – 2.72

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2020 March 01.

Table 4.

Association between antibody levels of TSPyV, EBV, KSHV antigens in seropositive AIDS-NHL cases and HIV-infected matched controls from the Multicenter AIDS Cohort Study overall, and stratified by lead-time

	All AIDS-NHL				< 4 year lead-time				≥ 4 years lead-time			
	AIDS-NHL cases (N)	HIV-infected controls (N)	OR	95% CI	AIDS-NHL cases (N)	HIV-infected controls (N)	OR	95% CI	AIDS-NHL cases (N)	HIV-infected controls (N)	OR	95% CI
TSVPyV VP1												
< 25th	49	34	1		26	16	1		23	18	1	
25th - 75th	75	67	0.84	0.47–1.50	38	37	0.55	0.16–1.82	37	30	1.89	0.54–6.60
≥ 75th	27	33	0.59	0.29–1.20	14	18	0.29	0.05–1.57	13	15	1.40	0.22–8.50
EBV EA-D												
< 25th	48	43	1		19	18	1		29	25	1	
25th - 75th	64	85	0.63	0.37 – 1.07	35	50	0.56	0.25 – 1.26	29	35	0.70	0.33 – 1.45
≥ 75th	51	42	1.02	0.56 – 1.86	28	20	1.22	0.50 – 2.96	23	22	0.90	0.39 – 2.08
EBV VCA p18												
< 25th	39	50	1		19	31	1		20	19	1	
25th - 75th	102	100	1.31	0.78 – 2.12	48	48	1.73	0.84 – 3.53	54	52	0.85	0.39 – 1.81
≥ 75th	58	49	1.49	0.84 – 2.65	36	24	**2.59**	**1.17 – 5.74**	22	25	0.74	0.31 – 1.78
EBV ZEBRA												
< 25th	66	47	1		26	23	1		40	24	1	
25th - 75th	76	92	**0.57**	**0.35 – 0.93**	41	54	0.66	0.33 – 1.34	35	38	0.56	0.28 – 1.12
≥ 75th	42	46	0.63	0.36 – 1.13	25	20	1.10	0.48 – 2.53	17	26	0.39	0.17 – 0.89
EBV EBNA-1												
< 25th	66	48	1		31	26	1		35	22	1	
25th - 75th	94	96	0.71	0.44 – 1.15	51	53	0.78	0.40 – 1.51	43	43	0.62	0.31 – 1.24
≥ 75th	31	48	**0.47**	**0.26 – 0.85**	17	21	0.67	0.29 – 1.56	14	27	**0.32**	**0.13 – 0.75**
KSHV LANA												
< 25th	19	26	1		9	12	1		10	14	1	
25th - 75th	57	52	1.46	0.72 – 2.98	27	30	1.24	0.43 – 3.60	30	22	1.86	0.68 – 5.09
≥ 75th	38	26	1.91	0.87 – 4.20	22	14	2.01	0.64 – 6.30	16	12	1.88	0.60 – 5.92
KSHV K8.1												

	All AIDS-NHL				< 4 year lead-time				≥ 4 years lead-time			
	AIDS-NHL cases (N)	HIV-infected controls (N)	OR	95% CI	AIDS-NHL cases (N)	HIV-infected controls (N)	OR	95% CI	AIDS-NHL cases (N)	HIV-infected controls (N)	OR	95% CI
< 25th	14	13	1		8	6	1		6	7	1	
25th - 75th	42	24	1.78	0.70 – 4.49	18	13	1.03	0.28 – 3.78	24	11	3.15	0.76 – 13.4
≥ 75th	18	12	1.31	0.44 – 3.91	11	5	1.70	0.37 – 7.72	7	7	0.87	0.16 – 4.80