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Immunologic and virologic predictors of AIDS-related non-Hodgkin lymphoma in the HAART era

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Abstract

HIV-infected persons treated with highly active antiretroviral therapy (HAART) continue to have elevated risk for non-Hodgkin lymphoma (NHL). We conducted a retrospective cohort study of NHL among patients at an urban HIV clinic (N=3025). Proportional hazards models identified immunologic and virologic predictors of NHL. Sixty-five NHLs arose during 1989-2006. NHL incidence declined over time. Nonetheless, 51 NHLs (78%) occurred within the HAART era (1996-2006). NHL risk increased with declining CD4 count (p-trend<0.0001) and increasing HIV viral load (p-trend=0.005). In a multivariable model, NHL risk was independently associated with both current CD4 count (hazard ratios 7.7 and 3.8, respectively, for CD4 counts 0-99 and 100-249 vs. 250+ cells/mm³; p-trend<0.0001) and prior time spent with a viral load above 5.00 log₁₀ copies/ml (hazard ratios of 3.4, 2.6, and 6.8, respectively, for 0.1-0.4, 0.5-1.4, and 1.5+ years vs. 0 years; p-trend=0.004). Although serum globulin levels were elevated compared to the general population, NHL risk was unrelated to this B-cell activation marker (p=0.39). Among HIV-infected individuals in the HAART era, NHLs are linked to immunosuppression and extended periods of uncontrolled HIV viremia. The association with high-level viremia could reflect detrimental effects on immune function related to incompletely effective HAART or direct effects on B-cells.

Keywords

non-Hodgkin lymphoma; acquired immunodeficiency syndrome; human immunodeficiency virus; immunosuppression; Epstein Barr virus; inflammation

Introduction

HIV-infected individuals have a markedly elevated risk for developing non-Hodgkin lymphoma (NHL) (1). Risk is especially increased for diffuse large B-cell lymphoma (DLBCL), Burkitt NHL, and central nervous system (CNS) NHL, and these NHL subtypes are considered AIDS-defining malignancies (2). Improvements in immune function attributable to highly active antiretroviral therapy (HAART), available in Western countries since 1996, have led to substantial declines in overall NHL risk in HIV-infected people (3).

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The pathogenesis of NHL in the setting of HIV infection has not been fully elucidated. Transformation of B-cells by Epstein Barr virus (EBV) likely plays a role in CNS NHL and DLBCL (4). These NHLs presumably arise due to loss of cell-mediated immune control of latent herpesvirus infection attributable to progressive HIV disease (5). In contrast, EBV does not appear to be involved in the development of AIDS-related Burkitt NHL (4), and the incidence of this NHL subtype has not changed during the HAART era (3).

While progressive loss of CD4 positive T-cells is important in AIDS lymphomagenesis (6), other immune mechanisms may also be relevant. One possibility is that the development of AIDS-related NHL is determined not solely by immune deficiency at a particular point in time (reflected, for example, by the current CD4 count), but in addition by the depth of prior immunosuppression (i.e., the nadir CD4 count) or duration of immunosuppression (i.e., previous time spent with a low CD4 count). HIV viral load may be an independent marker of immunosuppression among people with advanced HIV disease (7), and one recent study demonstrated that cumulative duration of HIV viremia is predictive of NHL (8). These alternative measures of immune status could be especially relevant in the HAART era, when therapy can halt inexorably declining immune function and allow manifestation of outcomes determined by events that occurred much earlier, before initiation of therapy.

Of interest, in a case-control study nested within an HIV clinic cohort during the pre-HAART era, Grulich et al. reported that high levels of serum globulins (mostly reflecting elevated IgG immunoglobulin) preceded the diagnosis and were predictive of AIDS NHL in a dose-response manner (9). B-cell dysfunction in HIV-infected people is characterized by production of abnormally low levels of antibodies to specific pathogens and poor immune responses to vaccines. Simultaneously, total serum levels of IgG are actually elevated, reflecting a non-specific polyclonal activation of B-cells (10-12).

To a large extent, clinicians currently utilize the CD4 count to guide decisions about when to initiate HIV treatment (13), but additional markers might offer complementary information in capturing NHL risk and thus facilitate these decisions. In the present study, we evaluated immunologic and virologic predictors of NHL risk in a large urban clinic-based cohort of HIV-infected individuals. We sought to identify whether various markers of immune dysfunction (including current and nadir CD4 count, HIV viral load, serum globulin) were predictive of development of NHL. A sizeable fraction of the clinic follow-up occurred after 1996, so that our results reflect on the pathogenesis of AIDS-related NHL during the HAART era.

Methods

Study subjects and ascertainment of NHL outcomes

The Johns Hopkins Hospital Moore Clinic provides primary and specialty care to HIV-infected individuals living in Baltimore, Maryland. Clinic patients receive a detailed baseline evaluation, with collection of demographic and clinical data. Patients are routinely seen in the clinic at three-month intervals, with frequent measurement of HIV disease markers, i.e., CD4 counts and (beginning in 1996) HIV viral loads. Decisions regarding antiretroviral therapy are made by individual clinic providers following accepted practice guidelines. Since 1989, clinic records and hospital sources have been abstracted into an observational database (14). For the present study, data were complete through 2006. Institutional review boards at Johns Hopkins Hospital and the National Cancer Institute approved this study.

NHL events were ascertained through review of clinic charts and hospital records, and were confirmed by pathology reports and clinical history. HAART use was defined as therapy

with two nucleoside reverse transcriptase inhibitors and either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor. The clinic database contained information on start and stop dates for each medication, although detailed information on treatment interruptions and adherence was not available. Serum globulin levels were calculated as the difference between serum total protein and albumin levels, which were routinely measured at clinic visits. Among HIV-infected people, IgG comprises the majority of serum globulins, and serum globulin levels are correlated with IgG levels ($r=0.57$) (9).

Statistical analysis

We evaluated NHL risk beginning with the latter of date of entry into the clinic cohort or first measurement of CD4 count, HIV viral load, or serum globulin. Evaluation continued until the earliest of NHL, death, or loss to follow-up. We calculated NHL incidence as a function of calendar year and compared that to the proportion of follow-up time in each calendar year for which subjects were receiving a HAART regimen. We also calculated NHL incidence in HAART users and non-users.

To assess predictors of NHL risk, we constructed Cox models (SAS PHREG) that utilized calendar year as the time metric, in order to adjust optimally for secular trends in NHL incidence. This approach allowed subjects to have delayed entry on the calendar date when their follow-up started. HIV viral loads were routinely measured beginning in 1996 and so were only evaluated as an NHL risk factor in this period. On average, for each year of follow-up there were 2.2 CD4 count measurements (corresponding to 5.3 months between measurements), 3.6 serum globulin measurements (3.3 months) and, beginning in 1996, 2.3 HIV viral load measurements (5.1 months). We considered the most recent laboratory value to be “current” until the next measurement. Laboratory markers (current and nadir CD4 count, current HIV viral load, current serum globulin) were evaluated as time-dependent covariates in the Cox models. Based on the observed associations with NHL risk, we selected thresholds defining a low CD4 count (below 250 cells/mm³) or a high viral load (at least 5.0 log₁₀ copies/ml). We then evaluated the associations between NHL risk and cumulative duration with a low CD4 count or high viral load. These durations were measured since the start of follow-up and were modeled as time-dependent variables, calculated as the sums of separate time intervals considering the most recent laboratory values to be current until the next measurement was obtained. In univariate models, we assessed the proportional hazards assumption by incorporating an interaction between the variable of interest and calendar time, and by examining log-log survival plots. In additional models, we evaluated the effects of laboratory markers on NHL risk, adjusted for demographic factors that were significant predictors in univariate models.

As described below, we did not find HAART use to be protective against the development of NHL. One reason is that HAART use increased sharply after 1996, so that estimation of the effect of HAART on NHL risk was imprecise after we adjusted for calendar year trends. Also, we did not have detailed information on adherence and interruptions in treatment, so that some periods that we considered patients to be on HAART may not have corresponded to actual HAART use. In addition, observational studies can substantially underestimate the beneficial effect of HAART due to selection by clinicians of the most immunodeficient patients for its use (15). Although we thus could not reliably assess the effects of HAART on NHL risk, we included HAART use as a variable in adjusted and multivariable regression models to reduce the possibility of confounding of the other effects of interest.

Results

The study included 3025 HIV-infected subjects (Table 1) who began follow-up in 1989-2006 (median baseline year 1998). The majority were male and non-Hispanic black,

with a median baseline age of 38 years. The most common HIV risk factor was injection drug use (39.8%), while male-sex-with-males (MSM) activity was reported by 26.7%. At baseline, the median CD4 count was 285 cells/mm³ and median HIV viral load was 4.35 log₁₀ copies/ml, and only 28.0% of subjects were receiving HAART. The median serum globulin level at baseline was 4.2 g/dL.

During follow-up, 65 subjects developed NHL (2.1%, incidence 4.1 per 1000 person-years). The NHLs comprised 28 DLBCLs, 2 Burkitt NHLs, 28 CNS NHLs, and 7 NHLs of other/unknown subtype. As shown in Figure 1, NHL incidence was highest in 1992, with a steep decline beginning well before 1996. NHL incidence continued to decline throughout the late 1990s and 2000s. The decline in NHL incidence thus began before the sharp increase in HAART use during 1996-1999 (Figure 1).

Despite the marked decline in NHL incidence over time, 51 of the NHLs (78%) occurred in 1996 or after; among these cases, 25 (49%) were receiving HAART prior to development of NHL. NHL incidence was lower in HAART users than non-HAART users (3.0 vs. 5.2 per 1000 person-years). However, this association with HAART was not apparent in the proportional hazards regression model (hazard ratio 1.0, 95% CI 0.6-1.9), which fully accounted for calendar trends in NHL risk.

As shown in Table 2, NHL risk was significantly higher in MSM than in other males and females, although this difference attenuated over time ($p=0.05$ for test of non-proportional hazards). NHL risk was lower in non-Hispanic blacks than individuals of other race/ethnicity (hazard ratio 0.5) but did not vary by age. NHL risk increased with declining CD4 count ($p\text{-trend}<0.0001$) and increasing HIV viral load ($p\text{-trend}=0.005$), and was especially elevated in persons with HIV viral load of 5.00 log₁₀ copies/ml or higher (Table 2). Finally, NHL risk was unrelated to serum globulin level ($p=0.39$).

Table 3 presents associations between laboratory markers and NHL risk, adjusted for HAART use, sex and HIV risk group, race, and calendar year. Current CD4 count remained a strong predictor of NHL risk after adjustment ($p<0.0001$). Nadir CD4 count was also predictive, but appeared no better than current CD4 count, and only data from 1994 onward could be evaluated because of non-proportionality of hazards prior to this time point. NHL risk also increased with prior time spent with a CD4 count below 250 cells/mm³ (Table 3), but the amount of prior time was not a better predictor than the fact that any time was spent with a CD4 count below 250 cells/mm³ ($p=0.39$).

HIV viral load could be evaluated as an NHL risk factor only in 1996 and after. As shown in Table 3, NHL risk was significantly associated with elevated current HIV viral load (i.e., at least 5.00 log₁₀ copies/ml, adjusted hazard ratio 3.8). Furthermore, NHL risk rose with increasing prior time spent with a viral load of at least 5.00 log₁₀ copies/ml ($p<0.0001$), and this duration of time was a better predictor of NHL risk than was the mere presence of any prior viral load of at least 5.00 log₁₀ copies/ml ($p=0.05$). Current serum globulin level still did not predict NHL risk in an adjusted model ($p=0.70$, Table 3).

We constructed two multivariable models for NHL risk that included CD4 count and HIV viral load (Table 3). These models were restricted to 1996 and after because of availability of viral load data. In the first multivariable model that included both current CD4 count and current HIV viral load (model 1, Table 3), only current CD4 count independently predicted NHL risk. In contrast, in another multivariable model (model 2, Table 3) that considered prior time spent with an HIV elevated viral load (at least 5.00 log₁₀ copies/ml) instead of current viral load, both current CD4 count and prior time spent with an elevated HIV viral load were significant independent predictors of NHL risk ($p\text{-trend}<0.0001$ and $p\text{-trend}=0.004$, respectively).

Discussion

In this study of over 3000 HIV-infected patients followed at an inner-city hospital clinic in Baltimore, Maryland, we observed a substantial decline in NHL incidence over an 18-year period. In the HAART era (1996 onward), NHL risk was strongly elevated in subjects who had a low CD4 count or had previously spent several months or more with an elevated HIV viral load. We did not see an association between serum globulin levels and NHL risk.

Our results showing that NHL risk rises sharply with declining CD4 count are in good accord with results from other studies (6,16,17). Although we had too few cases to analyze risk for separate NHL subtypes, prior work demonstrates that the relationship with CD4 count is apparent for the most frequent AIDS NHL subtypes, DLBCL and CNS NHL (6). EBV is commonly detected in tumor tissue from AIDS-related CNS NHLs (virtually 100% of cases) and DLBCLs (approximately 50%) but not in Burkitt NHL (4). As observed in our study, the current CD4 count (a marker of present immune status) appears to be as good a marker of NHL risk as nadir CD4 count (16), and the relationship between CD4 count and NHL risk continues to be important in the HAART era (6,16). Although we had no data on the EBV status of our NHL cases, the strong association with CD4 count supports the hypothesis that a major component of AIDS lymphomagenesis can be explained by severe HIV-induced immunosuppression, which allows for EBV reactivation and virus-driven transformation of lymphocytes (5).

The effect of HAART in reducing the risk of AIDS associated NHL has been dramatic, with declines of 40-80% comparing NHL incidence in the HAART era to that in the pre-HAART era (3,16,18,19). Prior studies have also described lower NHL risk in HAART users compared with non-users, with benefits apparent almost immediately and extending over years of HAART use (20). The mechanism underlying the effectiveness of HAART in reducing NHL risk is presumably related, at least in part, to its ability to lead to improved immune status (i.e., increases in CD4 count) and control of EBV.

As shown in Figure 1, NHL incidence in this HIV clinic cohort decreased dramatically well before HAART use climbed after 1996. The reason for a decline in NHL incidence before the introduction of HAART is unclear, but it has been noted previously in U.S. national trends among people with AIDS (3). The temporal decline could partly relate to increasing use by clinicians of moderately effective HIV therapy (i.e., dual nucleoside therapy). After we controlled for the calendar trend in NHL incidence in our proportional hazards model, we were unable to demonstrate a protective effect of HAART on the risk of developing NHL. Nonetheless, the close correlation between calendar year and HAART use led to wide confidence limits for the estimated HAART effect, including the possibility of substantial benefit (i.e., lower limit of 0.6 for the hazard ratio, corresponding to a 40% reduction in NHL risk). As noted above, we lacked detailed information on interruptions in HAART and subjects' adherence to their regimens. Also, in clinical practice, HAART was prescribed preferentially to patients with more severe immunodeficiency, as indicated by contemporaneous guidelines (e.g., reference (13)). This pattern of use could have attenuated the apparent benefits attributable to HAART (15).

Of note, we observed an increase in NHL risk with increasing prior duration of high-level viremia (i.e., HIV viral load of at least 5.00 log₁₀ copies/ml). NHL risk rose steeply even after only a few months of high-level viremia (multivariable hazard ratios = 2.6-3.4) and increased further with high-level viremia for 1.5 years or more (multivariable hazard ratio = 6.8). These results corroborate those recently reported by Zoufaly et al., who described increasing NHL risk to be independently associated with cumulative HIV viremia among individuals treated with HAART (8). In that study, the investigators measured cumulative

viremia as a product of the log-transformed HIV viral load (regardless of level) and duration. In contrast, we considered only time spent with an HIV viral load of at least 5.00 log₁₀ copies/ml, because our initial analyses indicated that only viremia of this magnitude was associated with elevated NHL risk (Table 2). The relationship between viremia and NHL risk could reflect detrimental effects on immune status associated with absence of treatment or incompletely effective HAART. Our analyses showed that this association between duration of high-level viremia and NHL risk was independent of CD4 count, and in general, the effect of HIV replication on AIDS risk is only partly explained by its association with future declines in CD4 count (7,21). The association of NHL risk with prolonged uncontrolled viremia may therefore reflect other disturbances of immune function, such as chronic immune activation or direct effects of HIV on B-cells (7,10,12).

An elevated level of total serum globulin is thought to reflect hypergammaglobulinemia and therefore generalized B-cell activation (11). In accord with expectation, serum globulin levels in our HIV-infected subjects were higher than observed in healthy individuals (i.e., median 4.2 g/dL vs. 2.0-3.5 g/dL in the general population) (22). It is difficult to reconcile our null findings relating serum globulin results and NHL risk with those reported by Grulich et al. (9). However, supporting our negative results, a case-control study found no association between the risk of AIDS NHL and levels of IgG, IgM, IgA, and IgE measured in pre-diagnostic serum specimens (23). While the inconsistency in association between globulin levels and NHL risk might suggest that B-cell activation is irrelevant in the pathway to NHL, another explanation could be that B-cell activation is important only for some NHL subtypes, or that alternative markers of B-cell activation are required. Along these lines, serum levels of soluble CD30 (a lymphocyte surface molecule) or free immunoglobulin light chains may provide more sensitive methods for assessing B-cell activation (23,24).

We found additional associations between demographic characteristics and NHL risk. Among HIV-infected individuals, higher NHL risks are generally observed in males compared to females, whites compared to non-whites, and with increasing age (16,20,25-27). Some studies (16,20,26), but not all (8,28), have reported an especially elevated risk for NHL among HIV infected MSM. These associations could reflect accumulation of genetic damage with age, differences in exposures to environmental cofactors or socioeconomic status, or the variable presence of an additional causative infectious agent. For example, human herpesvirus 8 is implicated in a minority of DLBCLs (29), and coinfection with this virus is especially common in HIV-infected MSM. NHL risk could also have been affected by duration of HIV infection or polymorphisms in host immune genes, but we did not have data on these factors. The availability of longitudinal data for a large clinic population, extending into the HAART era, was a strength of our study. We also had access to repeated laboratory measurements over time, which allowed us to thoroughly examine associations between relevant laboratory markers and NHL risk.

In conclusion, our results highlight the continued importance of immunosuppression in the development of NHL among HIV-infected individuals during the HAART era. The increased NHL risk observed with prolonged HIV viremia may reflect the effects of chronic immune activation and could support earlier initiation of HAART to prevent development of this malignancy. Studies utilizing additional markers of B-cell activation would be informative.

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References

- (1). 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; 370:59–67. [PubMed: 17617273]
- (2). 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR*. 1992; 41:1–19.
- (3). Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, Biggar RJ. Trends in cancer risk among people with AIDS in the United States 1980–2002. *AIDS*. 2006; 20:1645–54. [PubMed: 16868446]
- (4). International Agency for Research on Cancer. Epstein-Barr virus and Kaposi's sarcoma herpesvirus/human herpesvirus. Lyon; France: 1997. p. 8
- (5). 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; 18:444–48. [PubMed: 16894291]
- (6). Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EA. AIDS-related cancer and severity of immunosuppression in persons with AIDS. *J Natl Cancer Inst*. 2007; 99:962–72. [PubMed: 17565153]
- (7). Engels EA, Rosenberg PS, O'Brien TR, Goedert JJ. Plasma HIV viral load in patients with hemophilia and late-stage HIV disease: a measure of current immune suppression. *Ann Intern Med*. 1999; 131:256–64. [PubMed: 10454946]
- (8). Zoufaly A, Stellbrink HJ, Heiden MA, Kollan C, Hoffmann C, van Lunzen J, Hamouda O. Cumulative HIV Viremia during Highly Active Antiretroviral Therapy Is a Strong Predictor of AIDS-Related Lymphoma. *J Infect Dis*. 2009; 200:79–87. [PubMed: 19476437]
- (9). Grulich AE, Wan X, Law MG, Milliken ST, Lewis CR, Garsia RJ, Gold J, Finlayson RJ, Cooper DA, Kaldor JM. B-cell stimulation and prolonged immune deficiency are risk factors for non-Hodgkin's lymphoma in people with AIDS. *AIDS*. 2000; 14:133–40. [PubMed: 10708283]
- (10). de Milito A. B lymphocyte dysfunctions in HIV infection. *Curr HIV Res*. 2004; 2:11–21. [PubMed: 15053337]
- (11). 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; 309:453–58. [PubMed: 6224088]
- (12). Moir S, Fauci AS. Pathogenic mechanisms of B-lymphocyte dysfunction in HIV disease. *J Allergy Clin Immunol*. 2008; 122:12–19. [PubMed: 18547629]
- (13). Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. U.S. Department of Health and Human Services; [Accessed December 24, 2008]. November 32008 Available at <http://aidsinfo.nih.gov/2008>
- (14). Moore RD. Understanding the clinical and economic outcomes of HIV therapy: the Johns Hopkins HIV Clinical Practice Cohort. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998; 17:S38–S41. [PubMed: 9586651]
- (15). Ahdieh L, Gange SJ, Greenblatt R, Minkoff H, Anastos K, Young M, Nowicki M, Kovacs A, Cohen M, Munoz A. Selection by indication of potent antiretroviral therapy use in a large cohort of women infected with human immunodeficiency virus. *Am J Epidemiol*. 2000; 152:923–33. [PubMed: 11092434]
- (16). Bhaskaran K, Brettle R, Porter K, Walker AS. Systemic non-Hodgkin lymphoma in individuals with known dates of HIV seroconversion: incidence and predictors. *AIDS*. 2004; 18:673–81. [PubMed: 15090773]
- (17). Stebbing J, Gazzard B, Mandalia S, Teague A, Waterston A, Marvin V, Nelson M, Bower M. Antiretroviral treatment regimens and immune parameters in the prevention of systemic AIDS-related non-Hodgkin's lymphoma. *J Clin Oncol*. 2004; 22:2177–83. [PubMed: 15169806]
- (18). International Collaboration on HIV and Cancer. Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. *J Natl Cancer Inst*. 2000; 92:1823–30. [PubMed: 11078759]

- (19). Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, Holmberg SD, Brooks JT. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. *Ann Intern Med.* 2008; 148:728–36. [PubMed: 18490686]
- (20). Polesel J, Clifford GM, Rickenbach M, Dal Maso L, Battegay M, Bouchardy C, Furrer H, Hasse B, Levi F, Probst-Hensch NM, Schmid P, Franceschi S. Non-Hodgkin lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. *AIDS.* 2008; 22:301–6. [PubMed: 18097233]
- (21). Mellors JW, Margolick JB, Phair JP, Rinaldo CR, Detels R, Jacobson LP, Munoz A. Prognostic value of HIV-1 RNA, CD4 cell count, and CD4 Cell count slope for progression to AIDS and death in untreated HIV-1 infection. *JAMA.* 2007; 297:2349–50. [PubMed: 17551128]
- (22). Kratz A, Ferraro M, Sluss PM, Lewandowski KB. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Laboratory reference values. *N Engl J Med.* 2004; 351:1548–63. [PubMed: 15470219]
- (23). Breen EC, Fatahi S, Epeldegui M, Boscardin WJ, Detels R, Martinez-Maza O. Elevated serum soluble CD30 precedes the development of AIDS-associated non-Hodgkin's B cell lymphoma. *Tumour Biol.* 2006; 27:187–94. [PubMed: 16651853]
- (24). Gottenberg JE, Aucouturier F, Goetz J, Sordet C, Jahn I, Busson M, Cayuela JM, Sibilia J, Mariette X. Serum immunoglobulin free light chain assessment in rheumatoid arthritis and primary Sjogren's syndrome. *Ann Rheum Dis.* 2007; 66:23–27. [PubMed: 16569685]
- (25). Coté TR, Biggar RJ, rosenberg PS, Devesa SS, Percy C, Yellin FJ, Lemp G, Hardy C, Goedert JJ, Blattner WA. Non-Hodgkin's lymphoma among people with AIDS: incidence, presentation and public health burden. *Int J Cancer.* 1997; 73:645–50. [PubMed: 9398040]
- (26). Franceschi S, Dal Maso L, La Vecchia C. Advances in the epidemiology of HIV-associated non-Hodgkin's lymphoma and other lymphoid neoplasms. *Int J Cancer.* 1999; 83:481–85. [PubMed: 10508483]
- (27). Kirk O, Pedersen C, Cozzi-Lepri A, Antunes F, Miller V, Gatell JM, Katlama C, Lazzarin A, Skinhoj P, Barton SE. Non-Hodgkin lymphoma in HIV-infected patients in the era of highly active antiretroviral therapy. *Blood.* 2001; 98:3406–12. [PubMed: 11719381]
- (28). Pedersen C, Barton SE, Chiesi A, Skinhoj P, Katlama C, Johnson A, van Lunzen J, Hirschel B, Maayan S, Lundgren JD, AIDS in Europe Study Group. HIV-related non-Hodgkin's lymphoma among European AIDS patients. *Eur J Haematol.* 1995; 55:245–50. AIDS in Europe Study Group. [PubMed: 7589342]
- (29). Engels EA, Pittaluga S, Whitby D, Rabkin C, Aoki Y, Jaffe ES, Goedert JJ. Immunoblastic lymphoma in persons with AIDS-associated Kaposi's sarcoma: a role for Kaposi's sarcoma-associated herpesvirus. *Mod Pathol.* 2003; 16:424–29. [PubMed: 12748248]

Figure 1.

Non-Hodgkin lymphoma incidence and HAART use in HIV-infected patients followed in the Johns Hopkins Hospital Moore Clinic. Non-Hodgkin lymphoma (NHL) incidence is indicated with the solid line and filled circles, using the left vertical axis. The proportion of follow-up time during which HIV-infected people received highly active antiretroviral therapy (HAART) is displayed with the solid line and filled diamonds, using the right vertical axis. Data are not shown for 1989 and 1990, when there were no NHL events but little follow-up time.

Table 1
Baseline characteristics of patients followed in Johns Hopkins Hospital HIV clinic
(N=3025)

Characteristic	Summary measure
Sex, n (%)	
Male	2009 (66.4)
Female	1016 (33.6)
Age in years, n (%)	
17-32	775 (25.6)
33-37	705 (23.3)
38-43	808 (26.7)
44+	737 (24.4)
Median age in years	38
Race/ethnicity, n (%)	
Non-Hispanic black	2313 (76.5)
Non-Hispanic white	652 (21.6)
Hispanic or other/unknown	60 (2.0)
HIV risk group, n (%)	
Men-who-have-sex-with-men*	808 (26.7)
Injection drug users	1205 (39.8)
Other/unknown	1012 (33.5)
CD4 count (cells/mm ³), n (%)	
0-99	616 (20.4)
100-249	558 (18.5)
250-499	812 (26.8)
500+	601 (19.9)
Missing	438 (14.5)
Median CD4 count	285
HIV viral load (log ₁₀ copies/ml), n (%)	
Below 3.00	431 (14.3)
3.00-3.99	291 (9.6)
4.00-4.99	592 (19.6)
5.00+	469 (15.5)
Missing	1242 (41.1)
Median HIV viral load	4.35
Receiving HAART, n (%)	
No	2179 (72.0)
Yes	846 (28.0)
Serum globulin level (g/dL), n (%)	
Below 3.5	495 (16.4)

Characteristic	Summary measure
3.5-4.4	1031 (34.1)
4.5-5.4	565 (18.7)
5.5+	349 (11.5)
Missing	585 (19.3)
Median serum globulin level	4.2

Abbreviations: HAART highly active antiretroviral therapy

* This group includes 117 subjects who were both men-who-have-sex-with-men and injection drug users.

Table 2
Associations of demographic characteristics and laboratory markers with NHL among patients with HIV infection

Characteristic	NHL cases, n	Incidence*	HR (95%CI)	p-value
Sex and HIV risk group [†]				<0.0001
Men-who-have-sex-with-men	34	8.2	1.0	
Other males	19	3.1	0.2 (0.1-0.5)	
Females	12	2.1	0.2 (0.1-0.4)	
Age at baseline, years				0.78
17-32	23	5.0	1.0	
33-37	18	4.6	1.0 (0.5-1.9)	
38-43	13	3.1	0.7 (0.4-1.4)	
44+	11	3.3	0.9 (0.4-1.8)	
Race/ethnicity				0.01
Non-Hispanic black	42	3.4	0.5 (0.3-0.9)	
Other	23	6.2	1.0	
Current CD4 count, cells/mm ³				<0.0001 [‡]
0-99	35	14.3	1.0	
100-249	13	4.0	0.3 (0.1-0.5)	
250-499	9	1.6	0.1 (0.0-0.2)	
500+	3	0.7	0.0 (0.0-0.1)	
Current HIV viral load, log ₁₀ copies/ml				0.005 [‡]
Below 3.00	13	2.2	1.0	
3.00-3.99	1	0.5	0.2 (0.0-1.5)	
4.00-4.99	9	2.7	1.0 (0.4-2.5)	
5.00+	15	8.1	3.2 (1.5-6.7)	
Current serum globulin level, g/dL				0.39
Below 3.5	16	4.5	1.0	
3.5-4.4	17	2.8	0.6 (0.3-1.1)	
4.5-5.4	12	3.7	0.7 (0.4-1.6)	
5.5+	5	2.9	0.6 (0.2-1.6)	

Abbreviations: NHL non-Hodgkin lymphoma, HR hazard ratio, CI confidence interval.

All hazard ratios are adjusted for calendar year through use of calendar year as the time scale in the proportional hazards regression model.

* Incidence is in cases per 1000 person-years.

[†] The hazard ratios shown in the table are for the risk in 1996. The proportional hazards assumption was not met for this variable (p=0.05). As a result, the hazard ratio for other males changed by a factor of 1.2 per calendar year, and the hazard ratio for females changed by a factor of 1.2 per calendar year.

[‡] P-value is for test of trend.

Table 3
Associations of laboratory markers with NHL risk, adjusted for demographic characteristics and HAART use

Characteristic	Adjusted models *		Multivariable model 1 †		Multivariable model 2 ‡	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Current CD4 count, cells/mm ³		<0.0001 [‡]		<0.0001 [‡]		<0.0001 [‡]
0-99	13 (6.6-26)		13 (4.9-34)		7.7 (2.6-23)	
100-249	3.5 (1.6-7.8)		4.2 (1.5-12)		3.8 (1.2-12)	
250+	1.0		1.0		1.0	
Nadir CD4 count, cells/mm ³ §		<0.0001 [‡]				
0-99	9.2 (3.5-24)					
100-249	3.5 (1.2-10)					
250+	1.0					
Prior years with CD4 count below 250 cells/mm ³		0.0001 (0.39)**				
0	1.0					
0.1-0.7	4.0 (1.5-11)					
0.8-2.4	4.4 (1.6-12)					
2.5+	6.9 (2.5-19)					
Current HIV viral load, log ₁₀ copies/ml		<0.0001		0.33		
Below 5.00	1.0		1.0			
5.00+	3.8 (2.0-7.4)		1.4 (0.7-2.9)			
Prior years with HIV viral load at or above 5.00 log ₁₀ copies/ml		<0.0001 (0.05)**				0.004 [‡]
0	1.0				1.0	
0.1-0.4	6.3 (2.3-17)				3.4 (1.2-9.6)	
0.5-1.4	5.5 (1.8-18)				2.6 (0.8-8.6)	
1.5+	18 (6.2-54)				6.8 (2.1-22)	
Current serum globulin level, g/dL		0.70				
Below 3.5	1.0					

Characteristic	Adjusted models*		Multivariable model 1†		Multivariable model 2‡	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
3.5-4.4	0.7 (0.3-1.4)					
4.5-5.4	1.0 (0.4-2.3)					
5.5+	0.8 (0.3-2.4)					

* All adjusted models contain only the indicated variable from the table, and are adjusted for sex and HIV risk group (men-who-have-sex-with-men, other male, female), the interaction of sex and HIV risk group with calendar year (to account for non-proportionality), race, HAART, and calendar year (used as the time scale and thus incorporated into the baseline hazard).

† Multivariable model 1 includes CD4 count and current HIV viral load, as well as adjustment for sex and HIV risk group (men-who-have-sex-with-men, other male, female), the interaction of sex and HIV risk group with calendar year (to account for non-proportionality), race, HAART, and calendar year (baseline hazard). Multivariable model 2 includes CD4 count and prior years with elevated HIV viral load (at or above 5.00 log10 copies/ml), as well as adjustment for sex and HIV risk group (men-who-have-sex-with-men, other male, female), the interaction of sex and HIV risk group with calendar year (to account for non-proportionality), race, HAART, and calendar year (baseline hazard). Because of availability of HIV viral load data, these models are restricted to follow-up time in 1996 and after.

‡ P-value is for test of trend.

§ The model for nadir CD4 count is for follow-up time in 1994 and after, because the proportional hazards assumption was not met for follow-up time prior to 1994.

** The first p-value is a test of trend across categories of duration of low CD4 count or elevated HIV viral load. The second p-value (in parentheses) is a test comparing the indicated model against a model with only one term for low CD4 count or elevated HIV viral load, regardless of duration.