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LONGER DURATION OF COMBINATION ANTIRETROVIRAL THERAPY REDUCES THE RISK OF HODGKIN LYMPHOMA: A COHORT STUDY OF HIV-INFECTED MALE VETERANS

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Abstract

Background—Hodgkin lymphoma (HL) incidence has increased since combined antiretroviral therapy (cART) introduction. It is unclear how different cART classes (e.g., protease inhibitors (PI), non-nucleoside reverse transcription inhibitors (NNRTI)) influence HL. This study aimed to determine the effects of cART duration on HL incidence among HIV-infected veterans.

Methods—We performed a retrospective cohort study utilizing the Veterans Affairs HIV Clinical Case Registry (1985–2010). HL cases were identified using ICD-9 codes (201.4-9). cART, PI, and NNRTI duration was the aggregate number of treatment days delivered. Incidence rates (IR) and rate ratios (IRR) were calculated from Poisson regression models to examine the effects of cART duration on HL.

Results—31,576 cART users contributed 288,736 person-years (PY) and 211 HL cases (IR=7.3/10,000 person-years). HL incidence decreased from 25.1/10,000 PY (95%CI=18.9–33.4) within the first year of cART to 0.6/10,000 PY (95%CI=0.3–1.6) after 10 years. In multivariable models, each additional year of cART was associated with decreased HL incidence (IRR=0.80; 95%CI=0.75–0.86); similar effects were observed in models assessing HL incidence by PI and NNRTI.

Conclusion—Our findings indicate long-term cART of any class is associated with decreased HL risk. High HL incidence directly following cART initiation supports a potential immune reconstitution mechanism in HIV-related HL. Further research is needed to evaluate the interaction between early cART, immune reconstitution, and HL.

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Keywords

Hodgkin lymphoma; HIV; non-AIDS defining cancer; epidemiology; combined antiretroviral therapy

BACKGROUND

Combination antiretroviral therapy (cART) for HIV infection has improved immune function and reduced the burden of opportunistic infections, prolonging survival for HIV-infected individuals in the United States.[1] However, since cART, the incidence of non-AIDS-defining malignancies (NADM), e.g. Hodgkin lymphoma (HL), has increased.[2–6] Although HIV-related HL has been strongly linked to the Epstein-Barr virus (EBV), the causes for the increased HL incidence in the cART era remain unclear.[7] Martis et al [8] have postulated several hypotheses, including 1) the alteration of the microenvironment secondary to CD4 repopulation, 2) HL Reed-Sternberg cells are not impacted by HIV and instead proliferate via pro-inflammatory signals, and 3) decreased competing risk with AIDS-defining events. However, one mechanism that requires additional investigation is the direct effect of cART use, and the class of treatment received, on cancer development.

Previous experimental studies have isolated several anticancer mechanisms directed by protease inhibitors (PI), e.g., induction of apoptosis[9] and cell cycle arrest[10], and non-nucleoside reverse transcriptase inhibitors (NNRTI), e.g., inhibition of downstream cell growth and differentiation in tumors.[11,12]. However, the direct effects of the different classes of cART on HL incidence have not been adequately evaluated in population-based studies of HIV-infected persons. Additionally, studies that have been conducted have reported largely inconsistent results. Powles et al [13] observed a 120% increased risk of HL among NNRTI users while Chao et al [14] reported no association between cART, PI, or NNRTI use and HL incidence.

Results from these studies highlight the contradictory findings from previous research. Furthermore, these and other studies have been limited by relatively small samples, particularly regarding the number of HL cases identified.[15,16,14,13] Previous studies have also measured treatment effects across cART users and non-users. However, due to the different disease and mortality patterns experienced by HIV-infected individuals who never received cART, results may be confounded by unmeasured factors making it difficult to derive accurate conclusions. The aim of the present study was to determine the effect of the duration of any cART, PI- and NNRTI-based regimens on HL incidence among a cohort of HIV-infected male US military veterans ever receiving cART.

METHODS

This study was approved by the Institutional Review Board of Baylor College of Medicine and the Committee for the Protection of Human Subjects at UTHealth (Houston, Texas).

Database

We conducted a retrospective cohort study of HIV-infected US military veterans diagnosed with HIV from 1985–2010 and cared for within the Veterans Health Administration, the largest integrated healthcare system and provider of comprehensive HIV care in the United States.[17] HIV-infected individuals were identified from the Department of Veterans Affairs (VA) HIV Clinical Case Registry (CCR), a nationwide registry containing health-related information on all known HIV-infected VA users.[17,18] The registry draws upon the electronic medical records of over 65,000 HIV-infected patients cared for by the VA since the registry's inception. The registry includes demographic, laboratory, pharmacy, outpatient clinic visit, hospitalization data, and dates of death.

Inclusion Criteria

The initial CCR population included 66,991 HIV-infected adult veterans (≥ 18 years) with an identifiable HIV diagnosis date between 1985 and 2010. Figure 1 describes selection criteria implemented to generate the final sample. HIV diagnosis was confirmed based on 1) the presence of multiple *International Classification of Diseases, Ninth Revision* (ICD-9) code for HIV, or 2) a combination of ICD-9 code for HIV, positive HIV-related test (e.g., ELISA, Western Blot, quantifiable HIV RNA measurement), or prescription delivery of antiretroviral therapy. Index HIV diagnosis date was defined as the earliest ICD-9 code, positive test, or prescription delivery. 6,769 individuals without adequate HIV diagnostics (i.e., only a single ICD-9 code for HIV and no lab or pharmacy records) or vital statistics were removed. Only men were included in our analyses due to the small number of HIV-infected female veterans (<2%). Additionally, we removed individuals whose date of death or censor was the same as their initial HIV diagnosis date. We only included veterans ever receiving cART. Additionally, cART users without quantifiable CD4 or HIV RNA measurements within 90 days of cART initiation were excluded. 31,576 HIV-infected veterans were included in the final sample.

Primary Outcome

The primary endpoint was incident HL, identified from the presence of at least one inpatient or outpatient ICD-9 code (201.4-9). Prevalent HL cases (i.e., individuals diagnosed before or within 6 months after the initial HIV diagnosis date) were excluded. The follow-up interval for longitudinal analyses spanned from the index HIV diagnosis date to HL diagnosis, death or December 31, 2010 (the final date of the current CCR iteration), whichever occurred first.

Calculating use of combined antiretroviral therapy

cART use was abstracted from electronic pharmacy records available in the CCR database, which included prescriptions dispensed at all Veterans Health Administration facilities. Use of cART among HIV-infected individuals was defined as any combination of 2 nucleoside reverse transcriptase inhibitors classes and 1 of either NNRTI or PI classes, integrase inhibitors, or CCR5 inhibitors and any combination of two classes. The durations of any cART, PI- and NNRTI-based regimens were defined as the aggregate number of therapy days delivered from the dispensed prescriptions. Estimates of treatment duration excluded

time intervals of discontinued use or nonadherence (i.e., treatment lapses based on timing of prescription refills).

Covariate definitions

Potential confounders included patient age at HIV diagnosis and race/ethnicity, illicit drug use, comorbid conditions captured during the follow-up interval using the Deyo modification of the Charlson comorbidity index (excluding points allotted for diagnosis of HIV infection) [19,20] and the era of HIV diagnosis (pre-cART <1996, early cART 1996–2001, late cART 2002–2010). Additional HIV disease factors were captured from the CCR laboratory database. Specifically, pretreatment immune function was estimated from the nadir CD4 count prior to cART initiation. Time-updated CD4 and HIV RNA measurements were also collected throughout the follow-up interval to monitor the effect of fluctuations in immune status throughout the follow-up period. CD4 variables were categorized as <200, 200–350, and >350 cells/ μ L. HIV RNA was modeled as the % time undetectable <20%, 20–39%, 40–59%, 60–79%, and 80%. For standardization of operational procedures at different contributing VA facilities over all study years, the value for undetectable HIV RNA was established as <500 copies/cell.

Statistical Analysis

All analyses were performed using SAS[®] version 9.1 (SAS Institute, Cary, NC). The distributions of patient characteristics among the study cohort were observed. We computed the crude incidence of HL by dividing the number of HL cases by person-years of follow-up. Incidence rates were estimated in the overall study cohort and in stratum defined by integer years of cART-based regimens.

Poisson regression models were constructed to evaluate the impact of the cumulative duration of cART use on the risk of HL incidence among users. To control for potential confounding, multivariate Poisson regression models were fit and adjusted for clinically-relevant covariates described previously (i.e., age at HIV diagnosis, race/ethnicity, illicit drug use, era of HIV diagnosis, Deyo comorbidity score, nadir and recent CD4, and % time undetectable HIV). Additional sensitivity analyses were conducted to verify study findings in separate, restricted cohorts excluding individuals who 1) died and were no longer at risk to develop HL, 2) were diagnosed with HIV before cART introduction in 1996 to account for the different treatments available to infected individuals during these time intervals, or 3) had <90 days of follow-up after initiating cART.

RESULTS

A total of 31,576 HIV-infected male US military veterans were included in the study. Participants contributed 288,736 person-years of follow-up from 1985–2010. Characteristics of the overall study cohort and in strata defined by years of total cART use are given in Table 1. The mean age of the study population at HIV diagnosis was 45 years (SD=10). Over one-half (62%) of the cohort were racial/ethnic minorities. Approximately one-third of individuals had documented use of illicit drugs (35%). The majority of individuals were diagnosed with HIV in the cART era (i.e., 1996–2010; 71%).

Less than one-half of individuals (45%) had nadir CD4 <200 cells/ μ L prior to initiating cART (mean=259 cells/ μ L). At the time of the last recorded follow-up measurement (either date of HL diagnosis, death, or censoring), over one-half of the cohort (55%) had a CD4 count above 350 cells/ μ L, while approximately one-fourth (26%) were below 200 cells/ μ L. Additionally, more than one-quarter of individuals (27%) had <20% time undetectable HIV RNA over their follow-up interval.

In this cohort of cART users, approximately 75% had ever received PI-based treatment, and a similar percentage had ever received NNRTI. The average cumulative duration of any cART use was 5 years (SD=4 years). The average cumulative duration of PI and NNRTI use was 3.1 years and 2.0 years, respectively. Average duration of use was shorter among individuals diagnosed with HL. Specifically, HL cases averaged 1.7 years of PI use (difference from non-cases=-1.4 years; $p<0.0001$), and 0.8 years of NNRTI use (difference from non-cases=-1.2 years; $p<0.0001$).

During the study interval, 211 HL cases were identified (0.7%). HL incidence among the entire cohort was 7.3/10,000 person-years (PY) (95%CI=6.3–8.3/10,000 PY). The crude incidence of HL per year of cART use is illustrated in Figure 2. According to the cumulative duration of any cART use, the HL incidence rate decreased from 25.1/10,000 PY (95%CI=18.9–33.4) within the first year of cART exposure to 0.6/10,000 PY (95%CI=0.3–1.6) after 10 or more years of use. There was a similar decrease in HL incidence observed with longer cumulative duration of PI and NNRTI use. According to duration of PI use, HL incidence decreased from 29.2/10,000 PY to 0.9/10,000 PY. For NNRTI's, HL incidence dropped from 24.2/10,000 PY to 0.6/10,000 PY with longer duration of use.

Approximately one-half of the study population had documented use of either PI (n=8221; 26%) or NNRTI (n=7571; 24%), but not both. HL cases were observed in each of these mutually-exclusive user groups. Among users only ever receiving PI's, 75 HL cases were observed (IR=12.1/10,000 PY; 95%CI=9.6–15.2/10,000 PY). There were 38 HL cases among NNRTI only users (IR=7.7/10,000 PY; 95%CI=5.6–10.6/10,000 PY).

In multivariable analysis examining the effect of cumulative duration of any cART, PI, and NNRTI use, longer duration of use was associated with decreased risk of developing HL. Figure 3 depicts the incidence rate ratio per additional year of cART exposure, adjusted for age at HIV diagnosis, race/ethnicity, illicit drug use, era of HIV diagnosis, non-AIDS comorbidities, nadir CD4 prior to treatment, recent CD4, and HIV RNA. With respect to duration of any cART use, each additional year of exposure was associated with a 20% decrease in HL incidence (IRR=0.80; 95%CI=0.75–0.86). Similar findings were observed in separate models assessing HL incidence by duration of PI and NNRTI use. Specifically, each additional year of PI exposure was associated with a nearly 15% decrease in HL incidence (IRR=0.86; 95%CI=0.80–0.91), and a 20% decrease in HL incidence was observed for each additional year of NNRTI use (IRR=0.80; 95%CI=0.73–0.89). Findings were robust to sensitivity analyses independently excluding deaths, HIV diagnosed in the pre-cART era, and individuals with <90 days of follow-up after initiating cART.

DISCUSSION

To our knowledge, this represents the largest study conducted to investigate the impact of the type and duration of cART use on HL incidence. In this study of 31,576 HIV-infected male US military veterans with documented cART use, we identified 211 HL cases. We observed HIV-related HL incidence was highest in the first year of cART exposure and declined steadily with each additional year of use. The effect of cART on HL incidence was not specific to the class of treatment received. In multivariable models, longer durations of PI and NNRTI use were independently associated with decreased HL incidence.

Our findings suggest the effects of cART use can be conceptualized broadly in terms of early and long-term use. Considering this approach, findings related to early cART use fit well within the postulated immunologic framework driving HL development, specifically that HIV-related HL development may be impacted by an immune reconstitution mechanism. The highest incidence rates for HL were observed within the first year of cART exposure, irrespective of cART class. HL incidence rates declined significantly with increasing exposure to cART, and few HL cases were observed among individuals with long-term cART use. It is likely that multiple factors act in combination during the early treatment interval. However, HIV-related HL is known to be associated with the EBV herpesvirus[21,22]. Results from the current study support the intriguing hypothesis that an EBV-mediated immune reconstitution mechanism, in a similar fashion to other herpesviruses (e.g., KS-associated herpesvirus, cytomegalovirus, varicella zoster virus and herpes simplex virus) that have all been demonstrated to have common immune reconstitution inflammatory syndrome presentations, may promote the development of HL among HIV-infected patients initiating cART.[7,23]

Immune reconstitution inflammatory syndrome (IRIS) in HIV-infected individuals treated with cART describes an adverse reaction resultant from the repopulation of highly-activated, highly-differentiated, polyfunctional CD4 cells specific to the underlying IRIS-associated antigen, accompanied by increased levels of proinflammatory cytokines. Over the interval following cART initiation, as host antigen-specific immune responses are restored, previously subclinical infections emerge, also referred to as “unmasking IRIS”. Although CD4 repopulation following cART may provide added protection against HIV replication, repopulation of B cells and specific subsets immediately subsequent to cART initiation may also present new targets for viral infection and activation (i.e., EBV).[24,25] The frequency of IRIS varies dependent on the population and pathogen. However, estimates have shown as many as 25% of cART users experience at least one IRIS-related episode.[26,27]

In the context of EBV infection and HL development, EBV-specific CD4 cell responses rapidly decline with HIV co-infection, dampening EBV clearance. Subsequent repopulation of EBV-specific CD4 cells under poorly regulated, proinflammatory immune conditions may yield an environment conducive to HRS cell activation and HL development. Additional research is needed to confirm the detailed mechanisms impacting immune reconstitution and HL development after cART.

While careful examination of HL incidence rates by duration of cART use indicate elevated risk in the early interval of cART use, our findings from multivariable analyses also reveal that long-term cART use is associated with protection against HL development. Previous studies have reported conflicting findings regarding the effect of cART on HL risk. For example, Powles et al [13] reported increased HL risk among NNRTI users. More recently, Chao et al [14] conducted a study of nearly 13,000 HIV-infected individuals and assessed the effect of antiretroviral therapy duration on the risk for several different cancers. The authors found no association between antiretroviral therapy duration and HL risk, based on 29 identified HL cases. However, these studies were restricted by various limitations including the classification of cART use as ever compared to never use, which could be confounded by the issue of competing causes of mortality among those who never received cART, and the utilization of relatively small samples. In the current study of more than 200 HL cases, we observed a significant protective association between the duration of cART use and HL incidence, robust to multivariable adjustment.

Our results highlight a broad effect of long-term treatment with cART, non-specific to the class of treatment received. The significant protective effect observed in multivariable models adjusted for immune-related HIV factors (e.g., CD4 cell count and HIV RNA) suggests that cART may provide direct long-term anticancer benefits. However, the effect of other, more nuanced forms of immune reconstitution and re-organization not captured in the current models cannot be discounted. *In vitro* and *in vivo* studies have isolated several cell cycle anticancer mechanisms directed by PI and NNRTI therapies.[28,9,10] Specifically, in one experimental study, Gills et al evaluated the effect of 6 different PI therapies on cell proliferation in 60 cancer cell lines derived from 9 different tumor types.[28] Nelfinavir provided the most potent inhibition of cell proliferation. Further examination revealed that several of the PIs tested induced apoptotic cell death. Additionally, even when apoptosis was blocked, the authors observed non-apoptotic cell death related to induction of endoplasmic reticulum stress and autophagy.

NNRTIs have also been observed to induce cellular changes that restrict DNA polymerization and inhibit downstream cell growth and differentiation in tumors.[11,29] Evidence from experimental models has shown that expression of endogenous reverse transcriptase is upregulated in tumor cells, but silenced in well-differentiated tissues.[30] However, several previous studies have confirmed that reverse transcriptase inhibitors, such as NNRTIs demonstrate the ability to restore cell differentiation in different human cancer models through reprogramming gene expression.[11,31] Further population-based research is required to verify the direct effects of different combinations of long-term PI and NNRTI use in reducing HL development.

The findings from the current study should be viewed within the context of the study design. Data for the present retrospective cohort study was extracted from a national, system-wide VA registry of HIV-infected veterans. Certain limitations are inherent in large registry-based observational analyses. First, ICD-9 diagnostic codes for HL have not been previously validated in this database. Therefore, we cannot rule out potential misclassification. However, diagnostic codes for other malignancies have been successfully validated within the VA.[32,33] Second, this study was conducted exclusively on a population of

considerable public health interest, male military veterans, which may have implications on the generalizability of findings to other populations. Despite these limitations, our study is strengthened by the large number of HIV-infected individuals contributing data on cART exposure. Additionally, the number of HL cases identified in our sample delivers requisite statistical power to include important covariates in regression models.

CONCLUSION

Our findings indicate that long-term cART use confers protection against the risk of HL development. The effect of the duration of cART use was not different for PI- and NNRTI-based therapy regimens. The high incidence of HL within the first two years of cART exposure supports previous indications that an immune reconstitution mechanism may play a key role in HIV-related HL development. Further research is needed to evaluate the interaction between early cART use, EBV replication, immune reconstitution, and HL development to improve potential screening and treatment opportunities.

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REFERENCES

1. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2000; 30(Suppl 1):S5–S14. [PubMed: 10770911]
2. Herida M, Mary-Krause M, Kaphan R, et al. Incidence of non-AIDS-defining cancers before and during the highly active antiretroviral therapy era in a cohort of human immunodeficiency virus-infected patients. *J Clin Oncol*. 2003; 21(18):3447–3453. [PubMed: 12972519]
3. Engels EA, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States 1980–2002. *AIDS*. 2006; 20(12):1645–1654. [PubMed: 16868446]
4. Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. *J Natl Cancer Inst*. 2011; 103(9):753–762. [PubMed: 21483021]
5. 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]
6. Shiels MS, Cole SR, Kirk GD, Poole C. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. *J Acquir Immune Defic Syndr*. 2009; 52(5):611–622. [PubMed: 19770804]
7. Engels EA. Non-AIDS-defining malignancies in HIV-infected persons: etiologic puzzles, epidemiologic perils, prevention opportunities. *AIDS*. 2009; 23(8):875–885. [PubMed: 19349851]
8. Martis N, Mounier N. Hodgkin lymphoma in patients with HIV infection: a review. *Curr Hematol Malig Rep*. 2012; 7(3):228–234. [PubMed: 22547166]
9. Gills JJ, Lopiccolo J, Dennis PA. Nelfinavir, a new anti-cancer drug with pleiotropic effects and many paths to autophagy. *Autophagy*. 2008; 4(1):107–109. [PubMed: 18000394]
10. Jiang W, Mikochik PJ, Ra JH, et al. HIV protease inhibitor nelfinavir inhibits growth of human melanoma cells by induction of cell cycle arrest. *Cancer Res*. 2007; 67(3):1221–1227. [PubMed: 17283158]

11. Sciamanna I, Landriscina M, Pittoggi C, et al. Inhibition of endogenous reverse transcriptase antagonizes human tumor growth. *Oncogene*. 2005; 24(24):3923–3931. [PubMed: 15806170]
12. Landriscina M, Bagala C, Piscazzi A, et al. Nevirapine restores androgen signaling in hormone-refractory human prostate carcinoma cells both in vitro and in vivo. *Prostate*. 2009; 69(7):744–754. [PubMed: 19152342]
13. Powles T, Robinson D, Stebbing J, et al. Highly active antiretroviral therapy and the incidence of non-AIDS-defining cancers in people with HIV infection. *J Clin Oncol*. 2009; 27(6):884–890. [PubMed: 19114688]
14. Chao C, Leyden WA, Xu L, et al. Exposure to antiretroviral therapy and risk of cancer in HIV-infected persons. *AIDS*. 2012; 26(17):2223–2231. [PubMed: 22951631]
15. Bohlius J, Schmidlin K, Boue F, et al. HIV-1-related Hodgkin lymphoma in the era of combination antiretroviral therapy: incidence and evolution of CD4(+) T-cell lymphocytes. *Blood*. 2011; 117(23):6100–6108. [PubMed: 21368291]
16. Guiguet M, Boue F, Cadranet J, Lang JM, Rosenthal E, Costagliola D. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol*. 2009; 10(12):1152–1159. [PubMed: 19818686]
17. Backus L, Mole L, Chang S, Deyton L. The Immunology Case Registry. *J Clin Epidemiol*. 2001; 54(Suppl 1):S12–S15. [PubMed: 11750204]
18. Backus LI, Gavrilov S, Loomis TP, et al. Clinical Case Registries: simultaneous local and national disease registries for population quality management. *J Am Med Inform Assoc*. 2009; 16(6):775–783. [PubMed: 19717794]
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987; 40(5):373–383. [PubMed: 3558716]
20. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *Journal of clinical epidemiology*. 1992; 45(6):613–619. [PubMed: 1607900]
21. Dolcetti R, Boiocchi M, Gloghini A, Carbone A. Pathogenetic and histogenetic features of HIV-associated Hodgkin's disease. *Eur J Cancer*. 2001; 37(10):1276–1287. [PubMed: 11423259]
22. Kutok JL, Wang F. Spectrum of Epstein-Barr virus-associated diseases. *Annu Rev Pathol*. 2006; 1:375–404. [PubMed: 18039120]
23. Jaffe HW, De Stavola BL, Carpenter LM, et al. Immune reconstitution and risk of Kaposi sarcoma and non-Hodgkin lymphoma in HIV-infected adults. *AIDS*. 2011; 25(11):1395–1403. [PubMed: 21572307]
24. Douek DC, Roederer M, Koup RA. Emerging concepts in the immunopathogenesis of AIDS. *Annu Rev Med*. 2009; 60:471–484. [PubMed: 18947296]
25. Moir S, Malaspina A, Ho J, et al. Normalization of B cell counts and subpopulations after antiretroviral therapy in chronic HIV disease. *The Journal of infectious diseases*. 2008; 197(4):572–579. [PubMed: 18240953]
26. French MA, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. *HIV Med*. 2000; 1(2):107–115. [PubMed: 11737333]
27. Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis*. 2005; 5(6):361–373. [PubMed: 15919622]
28. Gills JJ, Lopiccolo J, Tsurutani J, et al. Nelfinavir, A lead HIV protease inhibitor, is a broad-spectrum, anticancer agent that induces endoplasmic reticulum stress, autophagy, and apoptosis in vitro and in vivo. *Clin Cancer Res*. 2007; 13(17):5183–5194. [PubMed: 17785575]
29. Landriscina M, Altamura SA, Roca L, et al. Reverse transcriptase inhibitors induce cell differentiation and enhance the immunogenic phenotype in human renal clear-cell carcinoma. *Int J Cancer*. 2008; 122(12):2842–2850. [PubMed: 18351578]
30. Martin SL. Ribonucleoprotein particles with LINE-1 RNA in mouse embryonal carcinoma cells. *Mol Cell Biol*. 1991; 11(9):4804–4807. [PubMed: 1715025]

31. Landriscina M, Fabiano A, Altamura S, et al. Reverse transcriptase inhibitors down-regulate cell proliferation in vitro and in vivo and restore thyrotropin signaling and iodine uptake in human thyroid anaplastic carcinoma. *J Clin Endocrinol Metab.* 2005; 90(10):5663–5671. [PubMed: 16030158]
32. Kramer JR, Giordano TP, Soucek J, Richardson P, Hwang LY, El-Serag HB. The effect of HIV coinfection on the risk of cirrhosis and hepatocellular carcinoma in U.S. veterans with hepatitis C. *Am J Gastroenterol.* 2005; 100(1):56–63. [PubMed: 15654781]
33. Chiao EY, Giordano TP, Richardson P, El-Serag HB. Human immunodeficiency virus-associated squamous cell cancer of the anus: epidemiology and outcomes in the highly active antiretroviral therapy era. *J Clin Oncol.* 2008; 26(3):474–479. [PubMed: 18202423]

Figure 1.

Flow chart of selection criteria generating final cohort of HIV-infected veterans

Figure 2.
Crude incidence rate for Hodgkin lymphoma by cumulative duration of cART use

Figure 3.
Adjusted incidence rate ratio for Hodgkin lymphoma by cumulative duration of cART use

Table 1

Characteristics of 31,576 HIV-infected cART users, stratified by years of cART use

	Total cART use, in years			
	Overall	<2	2–5	>5
	N(%)	n(%)	n(%)	n(%)
Age at HIV diagnosis (Mean [SD])	45 (10)	45 (11)	45 (10)	44 (10)
Race/ethnicity				
White	12043 (38)	3246 (31)	2925 (35)	5872 (46)
Black	15610 (49)	5746 (56)	4381 (53)	5465 (42)
Hispanic	2396 (8)	731 (7)	581 (7)	1084 (8)
Unknown/ Other	1527 (5)	661 (6)	400 (5)	466 (4)
Year of HIV Diagnosis				
Pre-cART era 1985–1995	9200 (29)	2627 (25)	2069 (25)	4504 (35)
Early cART era 1996–2001	9672 (31)	2612 (25)	2071 (25)	4989 (39)
Late cART era 2002–2010	12704 (40)	5163 (50)	4147 (50)	3394 (26)
Illicit Drug Use				
No	20681 (65)	6552 (63)	5164 (62)	8965 (70)
Yes	10895 (35)	3850 (37)	3123 (38)	3922 (30)
Deyo Score without AIDS				
0	16600 (53)	6556 (63)	4336 (53)	5708 (44)
1	9222 (29)	2428 (23)	2435 (29)	4359 (34)
2 and above	5754 (18)	1418 (14)	1516 (18)	2820 (22)
Nadir CD4 count prior to cART				
CD4 < 200	14300 (45)	4681 (45)	3684 (44)	4935 (46)
CD4 200 – 350	8701 (28)	2671 (26)	2404 (29)	3626 (28)
CD4 > 350	8575 (27)	3050 (29)	2199 (27)	3326 (26)
CD4 count at time of event/censor				
CD4 < 200	8179 (26)	4263 (41)	2280 (28)	1636 (13)
CD4 200 – 350	5895 (19)	2019 (19)	1686 (20)	2190 (17)
CD4 > 350	17493 (55)	4112 (40)	4320 (52)	9061 (70)
% time undetectable HIV RNA				
<20%	8463 (27)	5439 (52)	1935 (23)	1089 (8)
20–39%	4936 (16)	1400 (13)	1594 (19)	1942 (15)
40–59%	4971 (16)	961 (9)	1305 (16)	2705 (21)
60–79%	5136 (16)	985 (9)	1259 (15)	2892 (23)
80%	8070 (25)	1617 (16)	2194 (27)	4259 (33)
cART use, by therapy class *				
PI	23730 (75)	6691 (64)	6075 (73)	10964 (85)
NNRTI	23026 (73)	6097 (59)	6241 (75)	10688 (83)

* Categories are not mutually exclusive and do not sum to 100;

cART=combination antiretroviral therapy; PI=Protease inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor